A Proposal
to
Gray Matters Brain Cancer Foundation

for Support of Brain Cancer Research

at Dana-Farber Cancer Institute

Rameen Beroukhim, MD, PhD

Dana-Farber Cancer Institute

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Introduction

We are living through one of the most remarkable scientific revolutions in history. Advances in genomics and other technologies offer investigators unprecedented opportunities to understand fully the genetic mutations that cause cancer. Dana-Farber, because of its unique 50-50 balance of research and clinical care, is in the optimal position to make the next scientific breakthroughs. This powerful integration of research and care fuels the translation of laboratory discoveries into clinical applications for patients. The following details one such opportunity in glioblastoma research.

Accelerating and Advancing Research in Brain Cancer

An important revelation in glioblastoma research over the last decade is that what we think of as a single entity called glioblastoma is actually a collection of diseases. Each tumor arises through the acquisition of a series of changes in its DNA. The cumulative result of these changes is the uncontrolled and invasive growth that is cancer. However, tumors in different patients take different paths to become cancer, and the specific mutations these tumors undergo can vary dramatically. The result is that tumors in different patients, which arose due to different sets of mutations, behave very differently. In particular, they respond differently to the treatments we offer.

In principle, a comprehensive description of the genome of an individual tumor should largely determine which therapeutic agents it will respond to. In recognition of this fact, extensive efforts are being made at the Dana-Farber and elsewhere to transition to a "personalized medicine" model in which each patient's tumor is comprehensively characterized, so that the optimal treatment for that tumor can be determined from its genomic profile. Indeed, in August 2011 the Dana-Farber implemented genomic profiling of tumors of all consenting, newly-diagnosed patients, to enable the transition to a personalized care model.

A major obstacle to the implementation of such personalized care is identifying which tumors are likely to respond to which therapeutic agents. One approach is to treat a variety of patients with each agent and see who responds. However, this necessarily implies treating patients who will not respond. We propose to inform clinical trials going forward with data from preclinical models of glioblastoma, so that treatments can be focused on patients most likely to benefit from them.

In particular, we propose to screen existing and experimental drugs against a panel of "neurosphere" cell lines that represent human glioblastomas with a variety of genomic profiles. Over the last several years, Dr. Keith Ligon has generated a panel of approximately 40 cell lines grown from glioblastomas resected from patients treated at the Dana-Farber. These cell lines can be grown easily in the laboratory and assessed using a variety of standard measures, such as their proliferative capacity and ability to form tumors in mice. Dr. Ligon has taken great care to grow these cell lines under conditions that enable them to retain the genomic features of the primary tumors from which they were obtained. Indeed, he has confirmed their similarity to the tumors from

which they were grown through comprehensive genomic characterization of each cell line. We propose to treat each line with several dozen drugs including standard-of-care agents, compounds entering clinical trials, and "tool" compounds known to inhibit important pathways in glioblastoma. We will determine the extent to which each cell line dies when treated with each compound, and identify genomic features that predict which tumors are likely to be responsive to which drugs.

This project will accomplish two aims. First, it will identify therapeutic agents that are in principle effective against at least some glioblastomas. Second, it will identify features of those glioblastomas that predict their response to these agents. These results will guide the design of further preclinical studies and of clinical trials using these agents to treat patients who are most likely to respond.

A gift of $70,000 would provide immediate support to this evolving research and propel it closer to clinical trials that have the potential to benefit patients with this disease.

Thank you

Dana-Farber divides its resources equally between providing care for patients today and researching cures for tomorrow. This balance results in extraordinary collaboration between investigators and caregivers so that more patients can overcome brain tumors and lead healthier lives post-treatment, fulfilling Dana-Farber's mission of ensuring a better future for all cancer patients. The faculty, including Dr. Rameen Beroukhim, in DFCI's Center for Neuro-Oncology, are committed to improving the lives of patients stricken with these diseases, and philanthropy drives these endeavors. Your support would allow us to bring novel, exciting treatments to the medical community and establish new standards of care, both through our own efforts and by establishing collaborations around the country. Your commitment will allow us to accelerate our pace of discovery while speeding the translation of these findings from the laboratory into clinical application, transforming novel scientific techniques into bedside therapies. 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.