Dana-Farber Cancer Institute

The Jimmy Fund

September 30, 2021

BY E-MAIL
Ms. Marianne Loose
Lauren´s First and Goal Foundation, Inc.
1002 B Bartlett Loop
West Point, NY 10996

Dear Ms. Loose:

On behalf of the multidisciplinary researchers within the PLGA Program at Dana-Farber Cancer Institute, I am pleased to share the enclosed update. Dana-Farber is leading the way in revealing the causes of pediatric brain cancer and uncovering new treatment strategies to help children battling pediatric low grade astrocytomas (PLGAs). Our advancements would not be possible without the continued support from generous donors like Lauren's First and Goal Foundation. We are grateful for your steadfast partnership and hope that you might consider a renewed gift of $50,000 to help us continue our innovative work.

When Dana-Farber Cancer Institute opened its doors more than 70 years ago and began treating children with cancer, pediatric leukemia was an aggressive and formidable foe. Today, brain tumors are now the most common cancer and cause of cancer-related death in children less than 15 years of age. They are the most common solid tumor in children – accounting for approximately 25% of all childhood cancers. While children with low-grade tumors often survive, they can face serious side effects from the disease as well as from the treatments currently available. As you'll read in our report, our team has expanded its collaborations to better understand the genetics, improve our model systems for research, and explore the potential of new targeted therapies to improve outcomes for young patients with these brain tumors, for whom better treatments are desperately needed.

If you have any questions about the PLGA Program or report, you can reach me at AmyE_Trapasso@dfci.harvard.edu. On behalf of the entire program, and especially the patients who will ultimately benefit from your investment, thank you for your unwavering commitment to PLGA research and consideration of our request.

Best regards,

Amy E Trapasso

Amy E. Trapasso
Senior Director, Foundation Relations

PROGRESS UPDATE FALL 2021

Lauren's First And Goal Foundation

The Dana-Farber Campaign *Defy Cancer*

Dana-Farber Cancer Institute

The Jimmy Fund

Pratiti (Mimi) Bandopadhayay, MBBS, PhD, Director, PLGA Program

Rameen Beroukhim, MD, PhD

Introduction

Pediatric-low grade gliomas, which originate in glial cells that support and nourish neurons in the brain, are the most common childhood brain tumors. Under the leadership of **Pratiti (Mimi) Bandopadhayay, MBBS, PhD,** Dana-Farber Cancer Institute's Pediatric Low-Grade Astrocytoma (PLGA) Program, one of the world's only multidisciplinary clinical and research program for pediatric low-grade gliomas, studies these tumors and develops desperately needed therapies. Thank you for your partnership in this critical work, which is providing hope for our youngest patients and their families.

Understanding Low-Grade Glioma Genetics

Pediatric low-grade gliomas are collectively made up of many different tumor types, with different underlying processes that make them grow. As described below, PLGA Program physician-scientists have found mutations in a number of different genes that can be used as new treatment targets in these cancers.

A SINGLE-CELL MAP OF LOW-GRADE GLIOMAS

Tumors are made up of millions of different cells, each of which has unique features and properties. **Rameen Beroukhim, MD, PhD,** and Bandopadhayay have joined forces with investigators in Germany, Australia, and Canada to apply cutting-edge technology to generate a single-cell atlas of low-grade gliomas. These findings should help researchers understand how different cells help drive tumor growth, revealing vulnerabilities that can be therapeutically targeted.

GENETIC DEPENDENCIES OF PEDIATRIC CANCERS

Genetic dependencies refer to the genes required for cancer cell survival and proliferation. Recently, Bandopadhayay helped create a computational overview of pediatric dependency data, which revealed that, despite conventional wisdom, pediatric cancers—including childhood brain tumors—have as many dependencies as adult cancers. Importantly, many of these potential drug targets are unique to pediatric cancers. This finding challenges the current model of repurposing adult drugs for pediatric cancers, which may not sufficiently address the complex biology of these malignancies. As published in the April 2021 *Nature Genetics,* these results illuminate the need for developing novel drugs designed specifically for pediatric cancer.

Keith Ligon, MD, PhD, Director, Center for Patient Derived Models

Eric Fischer, PhD

Michael Eck, MD, PhD

All human cells tag proteins with ubiquitin, a small protein that marks unneeded or abnormal proteins for degradation by the proteasome, the body's cellular disposal system, in a process known as ubiquitination. **Protein degradation** breaks down and eliminates proteins rather than impairing their activity.

Following on this theme, Bandopadhayay is working to define the genetic dependencies of neural stem cells that have been scientifically engineered to express cancer-driving mutations. Her lab has generated models of pediatric low-grade gliomas that express MYB, BRAF, and FGFR alterations, which are being used to better understand the biology of these mutations and identify new therapeutic targets by creating a low-grade glioma specific dependency map.

FGFR MUTATIONS AND SECONDARY GENETIC ABNORMALITIES

FGFR1 is second most commonly mutated gene in pediatric low-grade gliomas. Bandopadhayay and **Keith Ligon, MD, PhD,** are using research models to determine whether FGFR1 mutations alone can trigger glioma development or whether co-occurring genetic abnormalities are also needed. After studying their preliminary data, they discovered that alternative alterations in the MAPK pathway could serve as a potential secondary driver of FGFR-mutant gliomas. Alongside this work, the researchers are also trying to determine if secondary MAPK alterations help to drive cancer cells' resistance to FGFR inhibitors. Their findings may help determine if FGFR and MAPK inhibitors can be used as combination treatments for these tumors.

In the lab, **Eric Fischer, PhD,** is testing whether protein degradation (see sidebar and page 6) might work against pediatric low-grade gliomas driven by FGFR mutations or gene fusions (genes made by joining two parts of two genes). Previously, Fischer and his colleagues demonstrated that a degrader they developed, known as DGY-09-192, degraded the FGFR2 fusion protein in research models. He is now investigating if DGY-09-192 can be used to treat FGFR1-mutant low-grade gliomas.

BRAF: A PRIMARY DRIVER OF PLGAS

The BRAF gene is part of a signaling pathway that controls several important cellular functions. Pilocytic astrocytoma, the most common type of pediatric low-grade glioma, exhibits only a single genetic alteration—a rearrangement that generates the KIAA1549: BRAF fusion gene. Another specific mutation in BRAF, called BRAF V600E, increases the growth and spread of cancer cells.

In order to develop drugs that target BRAF, **Michael Eck, MD, PhD,** is studying the structure of the gene to understand how it is normally regulated and how this is lost in the context of the KIAA1549: BRAF fusion in pediatric low-grade gliomas. Using machine learning, Eck and his colleagues have developed further insights into the fusion gene, which may help researchers develop new therapeutic strategies to counteract it. In addition, Fischer is developing small

Kee Kiat (Aaron) Yeo, MD

Karen Wright, MD, MS

Because **BRAF** is required for normal cell function, inhibiting the pathway causes harmful side effects for patients, forcing doctors to use lower doses of drugs, limiting their effectiveness. Eck and his colleagues aim to design a drug that inhibits BRAF V600E specifically, without inactivating the normal version of the gene. They are preparing to rapidly screen hundreds of thousands of small molecules for their ability to inhibit BRAF V600E specifically.

molecules that trick ubiquitin enzymes into recognizing the KIAA1549:BRAF fusion, leading to the ubiquitination and degradation of these cancer-promoting genes.

Eck is also working to find better drugs for BRAF-mutant pediatric low-grade gliomas (see sidebar). His search includes inhibitors that are specific to BRAF and not other RAF mutations (such as ARAF and CRAF). Working with **Jianwei Che, PhD,** he screened more than 100 compounds, identifying a series of related compounds with activity specifically against BRAF V600E. These BRAF-selective compounds may be better tolerated than ones that indiscriminately hit all RAF proteins.

Nika Danial, PhD, recently discovered that the main cancer-causing pathway in PLGAs alters their capacity to obtain and process nutrients, which is needed to generate energy and the cellular "building blocks" that produce new cancer cells to fuel tumor growth. In collaboration with **Nathalie Agar, PhD,** Danial is using tumor biopsies and cellular models to define and identify metabolic profiles of PLGAs and associated vulnerabilities.

Now, they are analyzing and comparing data sets of KIAA1549: BRAF metabolic patterns to those in BRAF V600E. These analyses will enable them to examine how the tumor microenvironment—the cells, molecules, and blood vessels that surround a tumor—organizes and processes nutrients, as well as determine how these metabolic patterns produce liabilities that can be targeted to block these tumor's fuel supply, including combination therapies with MAPK pathway inhibitors.

IDH MUTATIONS COMMON AMONG ADOLESCENT GLIOMAS

While many pediatric low-grade gliomas are driven by alterations in the BRAF pathway, a significant proportion of older children and young adolescents have "adult-type" gliomas with IDH1/2 mutations. These mutations typically lead to more aggressive tumors and poorer prognosis. While IDH1/2 mutations were previously thought to be rare in pediatric glioma, recent data suggests these may occur at a significantly higher frequency, especially among adolescents. Importantly, the prognostic significance of IDH1/2 mutation in children remains unclear.

Kee Kiat (Aaron) Yeo, MD, and **Karen Wright, MD,** in collaboration with other physician-scientists across the country, led a study that systematically evaluated the rate of IDH1/2 mutation among patients with pediatric gliomas and described current treatment approaches and patient outcomes. They found that approximately 10% of all pediatric gliomas—and 20% in those ages

Rosalind Segal, MD, PhD,
Edward J. Benz Jr., MD, Chair

Epigenetics is a set of gene regulatory mechanisms that control how genes are expressed but do not make permanent changes in their DNA code.

Patient-derived xenografts, surgical grafts of human tissue onto mouse models, reliably recapitulate the genetic and biological complexity of human cancers and offer a strong platform to test new treatments.

15-21—bear IDH mutations. The study was presented at the 19th International Symposium on Pediatric Neuro-Oncology in December 2020 and virtually at the American Society of Pediatric Hematology and Oncology Conference in April 2021.

AN ALTERNATIVE MECHANISM FOR GLIOMA DEVELOPMENT

Because most pediatric cancers, including low-grade gliomas, have fewer genetic mutations than adult tumors, other mechanisms, such as epigenetics (see sidebar), may play important roles in their development and growth. Previously, **Volker Hovestadt, PhD,** found that profiling genome-wide DNA methylation, an epigenetic mechanism that regulates the expression of genes, can be used to classify pediatric high-grade gliomas into molecular subgroups.

Hovestadt is now developing methods to investigate the regulatory landscape of low-grade gliomas, including new ways to efficiently profile DNA methylation in single tumor cells and to distinguish different types of malignant cells (i.e., tumor stem cells and differentiated tumor cells) and cells in the tumor microenvironment. His work may improve scientists' ability to accurately classify and diagnose low-grade gliomas and lead to the identification of novel targets for precision cancer treatment.

Modeling Low-Grade Gliomas

Cancer studies rely on strong research models that can be used to better understand tumor biology and to develop effective, non-drug-resistant therapies. Under Ligon's direction, the Center for Patient Derived Models creates patient-derived cells lines, patient-derived xenografts (see sidebar), and novel models for rapidly testing drugs using fresh patient tumors.

Researchers rely on patient tissue samples to create these innovative models. In the past year, through patient donations and Ligon's efforts, Dana-Farber now has a tissue bank with a collection of 583 pediatric low-grade gliomas, the majority of which are accompanied by genomic or molecular profiling data. With an additional 699 low-grade glioma samples from PLGA consortium and other sites, the PLGA Program now has tissue and data from more than 1,200 PLGAs with which to conduct research.

In her lab, **Rosalind Segal, MD, PhD,** is establishing new model systems for growing and studying PLGAs based on the tissue microenvironment of regions at the base of the brain, where these tumors typically arise. Developing a better understanding of this microenvironment will improve

Sara Buhrlage, PhD

Immune checkpoint inhibitors alter on/off switches on cells to enable the immune system to recognize and attack cancer cells.

DUBs, which reverse the ubiquitination process in many cancer-causing proteins, are an emerging class of drug targets. Recent studies describing highly potent inhibitors of DUBs, including USP7, have led to increased interest in DUBs as targets for drug discovery.

scientists' ability to develop more faithful PLGA models for future research and provide a biological basis for the development of novel targeted therapies.

In a study using one new model system, Segal and her colleagues found that DAY101, an experimental BRAF inhibitor (see page 7), reduced the proliferation of primary juvenile pilocytic astrocytoma cells compared to a control group. The study supports using this model system to study pediatric low-grade gliomas and to evaluate new therapies on patient tumor cells.

Exploring Potential New Drugs

Dana-Farber has an extensive history of studying new drugs with the potential to become safe and effective cancer treatments. But, before experimental drugs can be given to patients, they must be created and tested extensively in the lab to ensure they function as expected, are safe, and show promise for further study in patients.

MSI TO GUAGE THE EFFECTIVENESS OF CHECKPOINT INHIBITORS

Immunotherapy approaches, which harness the power of the immune system to fight cancer, are being investigated for several brain tumors, including immune checkpoint inhibitors (see sidebar) for the treatment of PLGAs. Immune checkpoint proteins act as molecular brakes that are exploited by cancer cells to suppress the body's defensive response by T cells against tumors.

Many drugs are unable to reach tumors in the brain because they are too large to penetrate the blood-brain barrier, the physical separation between the brain and the rest of the body. In her lab, Agar is using mass spectrometry imaging (MSI), a tool used to study molecular structures, to determine whether inhibitors of CD73, a checkpoint protein that suppresses immune system activation, effectively reach their target in PLGA tumors. Visualizing the penetration of these drugs in the brain may allow for improved immunotherapy strategies and patient prognosis.

DUB INHIBITORS MAY PROMOTE PROTEIN DEGRADATION

Sara Buhrlage, PhD, is developing novel strategies and prototype drugs that target aberrant proteins that contribute to pediatric low-grade gliomas. Specifically, she is developing small molecule inhibitors that override the activity of deubiquitinating enzymes (DUBs; see sidebar) and restore cells' standard ubiquitination and degradation functions.

Daphne Haas-Kogan, MD, Chair, Department of Radiation Oncology

Registration trials are designed to obtain sufficient data and results to support the filing of an application for FDA approval.

Targeted protein degradation is rapidly gaining traction; however, there are currently no Food and Drug Administration (FDA)-approved DUB-targeting drugs. Buhrlage and her team have developed potent and selective chemical probes—important components of drug discovery—for USP7 and USP28, and are now supporting pharmacological investigations of these DUBs across subsets of pediatric gliomas.

Bringing Lab Discoveries to the Clinic

PLGA Program researchers are testing new types of low-grade glioma treatments through innovative clinical trials that move lab findings to the patient's bedside. In a national phase I trial led by Wright and her colleagues, preliminary data suggests safety and tolerability of DAY101, as well as early efficacy, for tumors with alterations in the mTOR pathway. The study has led to a registration trial (see sidebar), as well as FDA Breakthrough Therapy Designation, which may speed its formal approval. The findings were presented virtually at the 25th Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology in November 2020.

Wright is also co-leading a phase II clinical trial of MEK162, a drug that targets the MEK1 and MEK2 proteins along the mTOR, which instruct cells to grow and divide. **Daphne-Hass Kogan, MD,** leads a phase II trial of MEK inhibitors for recurrent pediatric low-grade gliomas across 44 sites (see sidebar).

Everolimus is an inhibitor of the mTOR pathway that blocks genes that regulate cancer cell proliferation and reduces levels of certain growth factors, such as VEGF, involved in the development of new blood vessels. In the February 2021 *Pediatric Blood & Cancer*, Wright and colleagues from children's hospitals throughout the United States described the efficacy of everolimus as an alternative treatment for patients with recurrent or progressive low-grade glioma.

The Impact of Your Philanthropy

Discoveries made through the PLGA Program are shining new light on the molecular and genetic underpinnings of low-grade pediatric brain cancers, expanding treatment options and improving quality of life for patients. Thank you for your meaningful partnership in this important work and for your commitment to Dana-Farber's lifesaving mission.

Report written by Scott Edwards.

The Dana-Farber Campaign

Defy Cancer

In May 2021, Dana-Farber announced **The Dana-Farber Campaign,** our ambitious, multiyear $2 billion fundraising initiative to prevent, treat, and Defy Cancer by accelerating **revolutionary science, extraordinary care, exceptional expertise, and essential opportunities.**

Dana-Farber Cancer Institute has been the top ranked cancer hospital in New England by U.S. News and World Report for 20 consecutive years, and is the only cancer center in the country ranked in the top 6 for both adult and pediatric cancer programs.

Dana-Farber Cancer Institute was named the #3 cancer center in the world by Newsweek in its World's Best Specialized Hospitals ranking.

The Dana-Farber Campaign *Defy Cancer*

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450 Brookline Avenue, Boston, MA 02215 | dana-farber.org

10% of all designated gifts will support our Faculty Research Fund to advance Dana-Farber's research mission.