Dana-Farber Cancer Institute

The Jimmy Fund

September 29, 2020

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 pediatric oncologists and research scientists at Dana-Farber Cancer Institute, I am pleased to share the enclosed update with you. Despite the temporary shutdown of all laboratories across our campus and the Harvard system briefly from March through June due to COVID-19, we have made many advances, and our trailblazing work to combat pediatric low grade astrocytomas and improve patient care and outcomes would not be possible without the continued support from generous donors like Lauren's First and Goal Foundation. We are grateful for the Foundation's steadfast partnership and hope that you might consider a renewed gift of $50,000 to help us achieve our shared goal of eventually finding a cure.

We cannot and will not let the COVID-19 crisis slow our momentum as we work to give children and adolescents diagnosed with brain tumors more and better targeted treatment options. While we have made strides to better understand, diagnose and treat PLGAs, there is still much to do to help children who suffer from this insidious disease and the harsh side effects of treatments. Low-grade gliomas are still devastating because children face a lifetime of debilitation from the tumors and treatments. More than any other cancer, brain tumors can have lasting and life-altering physical, cognitive, and psychological impacts. But our unique team of multidisciplinary clinical and research experts is working passionately every day to change the trajectory for these patients.

If you have any questions about the 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 commitment to PLGA research and consideration of our current request during these challenging times.

Best regards,

Amy Trapasso

Amy E. Trapasso
Senior Director, Corporate & Foundation Relations

PROGRESS UPDATE FALL 2020

Lauren's First and Goal

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Pratiti (Mimi) Bandopadhayay, MBBS, PhD

Introduction

Pediatric low-grade gliomas collectively are the most common childhood brain tumors. The Pediatric Low-Grade Astrocytoma (PLGA) Program at Dana-Farber Cancer Institute was established in 2007 to find more effective, less toxic treatments for children with these brain tumors. It is the only multidisciplinary clinical and research program dedicated to pediatric low-grade gliomas.

In August 2020, Dana-Farber became a member of the **Pediatric Brain Tumor Consortium (PBTC).** Founded by the National Cancer Institute, the PBTC is composed of 16 academic medical centers and children's hospitals, which were competitively selected for their scientific excellence and clinical expertise.

Under the direction of **Pratiti (Mimi) Bandopadhayay, MBBS, PhD,** research scientists and clinicians work to identify targetable vulnerabilities in PLGAs and other low-grade gliomas and to develop new, more effective therapies that attack only cancer cells and leave healthy cells unharmed. She and her colleagues are assisted by an advisory committee that includes **Scott Armstrong, MD, PhD, Rameen Beroukhim, MD, PhD, Michael Eck, MD, PhD, Daphne Haas-Kogan, MD,** and **Katherine Warren, MD**. Your generous support helps this world-class team make trailblazing advances in research and care for our youngest patients. Thank you for your partnership.

Genetic Alterations

The PLGA Program is leading ongoing studies to understand the mechanisms through which the most common genetic alterations drive pediatric low-grade gliomas and develop strategies to overcome them. These efforts are focused on three common families of genes that are affected—BRAF, FGFR, and MYB.

BRAF

A **fusion gene** is a gene made by joining to parts of different genes.

Unlike high-grade gliomas, which usually have multiple driver genes, the most common kind of pediatric low-grade glioma, called pilocytic astrocytoma, exhibits just a single genetic alteration—a rearrangement that generates the KIAA1549: BRAF fusion gene (see sidebar), the most common BRAF alteration in PLGAs. These tumors may be successfully treated with surgery and sometimes standard chemotherapy; however, patients receiving chemotherapy often have long-term side effects.

Using single-cell sequencing on low-grade astrocytomas—a technique that enables researchers to isolate individual cells to determine their function and behavior—Bandopadhayay, Beroukhim, and their colleagues found that only one cell type causes these cancers to grow. Researchers are now developing drugs that specifically target these cancer-causing progenitor cells, which are precursors to more specialized cells. This would spare normal, healthy cells and decrease side effects.

Rameen Beroukhim, MD, PhD

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

Michael Eck, MD, PhD

Patient-derived xenografts, surgical grafts of human tissue onto mouse models, faithfully recapitulate the genetic and biological complexity of human cancers and offer an elegant platform to study disease and test new therapeutic agents.

FGFR

FGFR is the second-most common mutated gene in pediatric low-grade gliomas, occurring in up to 20% of patients. Many low-grade gliomas have a specific mutation in the FGFR1 gene, which is involved in cellular functions such as proliferation, maturation, survival, and the development of new blood vessels. In a new initiative, Bandopadhayay and Beroukhim, along with **Keith Ligon, MD, PhD,** are teaming with Dana-Farber chemical biologists **Sara Buhrlage, PhD, Nathanael Gray, PhD,** and Eck to understand how FGFR mutations and rearrangements can be targeted in low-grade gliomas. These studies are also helping clinicians decide which patients with low-grade gliomas need further treatment after surgery and evaluate outcomes in those who receive additional treatment and those who do not.

MYB

An important tool in cancer research is studying the disease and the effects of potential treatments on cells and tissues taken from patients. Under Ligon's direction, the Center for Patient Derived Models creates models, including cell lines and patient-derived xenografts (see sidebar), for drug sensitivity testing in lab research and clinical trials.

Bandopadhayay, Beroukhim, and Ligon have developed multiple models of low-grade gliomas that harbor rearrangements in the MYB or MYBL1 genes. Ligon and Beroukhim have introduced MYBL1 mutations, which occur only in pediatric low-grade gliomas and a type of salivary gland cancer, in mice to study how these alterations affect brain development and the behavior of low-grade gliomas. MYBL1 plays an important role in the control of cell proliferation and the differentiation of cells from an immature to a mature state. When MYBL1 is rearranged, one end of the gene gets chopped off and reattaches to a different portion of the chromosome, fueling tumor formation.

In another approach, Bandopadhayay's lab has introduced MYB and MBL1 alterations in neural stem cells to understand the mechanisms through which they induce tumor formation and is applying methods to identify new therapeutic targets. The lab has also generated neural stem cell models that express BRAF, MYB, and FGFR alterations to reproduce their effects in low-grade glioma. The researchers are using these models to find genes upon which the models are dependent, with the goal of finding new drugs that may be used to treat children with low-grade gliomas. In addition, Beroukhim and Ligon are using specialized mouse models to study drugs that might control low-grade glioma growth.

Studying Cancer's Escape Routes

Dana-Farber investigators are leading efforts to understand how malignant brain tumors harboring many mutations manage to evade treatment—a question with significant practice-altering implications. In the April 2020 *Nature*, an international team of scientists led by Bandopadhayay, Beroukhim, and Ligon published an analysis of more than 10,000 gliomas, including pediatric and adult low- and high-grade gliomas, the world's largest such dataset to date. The study utilized data from Profile, Dana-Farber's comprehensive patient-based cancer genomics project, and other sources to examine the molecular signatures of tumors and clinical outcomes of patients treated with a variety of therapies.

Pediatric high-grade gliomas more commonly become **hypermutated** than pediatric low-grade gliomas.

The team made multiple discoveries, including demonstrating the two pathways by which gliomas become "hypermutated," leading to disease that is more aggressive and difficult to treat (see sidebar). This process of hypermutation stems from an interplay between the standard treatment for glioma—the chemotherapy drug temozolomide—and genetic changes that occur in isolated glioma cells.

While temozolomide can benefit patients, it can also cause hypermutated cells to emerge that can resist the drug, and the surviving glioma cells can cause the tumors to progress. Surprisingly, in some patients who developed this form of treatment-related resistance, switching to another chemotherapy called lomustine still seemed to be effective, suggesting further study of the treatment is warranted in this patient population.

Critically, the investigators found that patients with hypermutated glioma tumors saw no significant benefit when treated with immune checkpoint inhibitors. This finding was somewhat unexpected, as immune checkpoint blockers have been shown to be effective in other types of cancers if their cells are hypermutated.

Bandopadhayay, Beroukhim, Ligon, and their colleagues noted that the absence of an immune response is likely linked to several complex factors, including the immunosuppressive environment surrounding brain tumors and the specific types of genetic mutations that are found in hypermutated gliomas. This finding suggests that future efforts to treat gliomas with checkpoint inhibitors should explore using them in combination with other immune-boosting therapies.

Eric Fischer, PhD

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

Karen Wright, MD, MS

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

Antibodies are proteins produced by the immune system in response to an antigen. Each antibody can bind to only one antigen, a substance that provokes an immune response. Antibodies can be used to both detect and treat cancer.

Altogether, the discoveries in this landmark study provide fundamental insights into the underlying causes of hypermutation in gliomas and justify expanding the use of genomics to help identify patients at risk of resistance and those most likely to respond to certain therapies.

Degrading Proteins

Researchers are examining another way to destroy cancer cells—through degradation, which breaks down proteins, rather than impairing their activity. 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 called ubiquitination. Deubiquitinating enzymes, known as DUBs, however, reverse this process in many oncoproteins, fueling malignancy.

In the lab, Buhrlage is developing novel strategies and prototype drugs that target aberrant proteins that contribute to low-grade gliomas. Specifically, she is investigating USP28 as a novel target for protein degradation of MYB fusion proteins, as well as pursuing approaches to find vulnerabilities that will open up new treatment options. **Eric Fischer, PhD,** is working on the other end of the pathway, developing small molecules that trick ubiquitin ligases into recognizing cancer-driving fusion proteins such as KIAA1549: BRAF, leading to ubiquitination and degradation of these oncogenes.

Clinical Trials

Pediatric subspecialists in the PLGA Program collaborate to launch groundbreaking clinical trials that result from years of painstaking lab research. These trials determine whether new treatments are safe and effective and work better than current treatments.

TARGETING BRAF FUSION GENES

In the lab, **Rosalind Segal, MD, PhD,** is engineering antibodies (see sidebar) that bind to the KIAA1549: BRAF fusion and may be used to reduce the turnaround time for diagnosis of PLGA's from four weeks to two days. In a multicenter phase I clinical trial through the Pediatric Neuro-Oncology Consortium, **Karen Wright, MD, MS,** and Haas-Kogan are studying whether the investigational drug DAY101 (previously known as TAK-580) can effectively target and destroy the KIAA1549: BRAF fusion as well as BRAF V600E, another key mutation in low-grade gliomas.

Kee Kiat (Aaron) Yeo, MD

Susan Chi, MD, Deputy Director, Pediatric Neuro-Oncology

The **Children's Oncology Group** is an organization composed of leading pediatric cancer research institutes that collaborate to enroll patients in clinical trials.

INHIBITING MEK

Findings by Eck and his colleagues on the close interplay between BRAF and MEK support the use of the inhibitor MEK162, for which Wright co-leads a phase II clinical trial in patients with low-grade gliomas. The drug targets the MEK1 and MEK2 proteins in a chain of molecules along the BRAF pathway that tells cells to grow and divide. Inhibiting the activity of these proteins may slow down the growth of cancerous cells.

Bandopadhayay, Haas-Kogan, Ligon, and **Sanda Alexandrescu, MD,** are contributing to a phase II trial evaluating the role of MEK inhibitors for children with newly diagnosed or recurrent pediatric low-grade gliomas as part of the Children's Oncology Group (see sidebar). Haas-Kogan is leading the trial for recurrent gliomas, while Ligon and Alexandrescu are reviewing the pathology for children being considered for enrollment in the trial. Bandopadhayay is coordinating efforts to evaluate the genomic predictors of response. More than 500 children are expected to enroll across both studies, providing an unprecedented opportunity to understand the response of pediatric low-grade gliomas to MEK inhibition.

While many pediatric low-grade gliomas can be cured with surgical removal, others require additional therapy. Traditional chemotherapy has long been the standard-of-care treatment for these children and, while effective, the agents can be associated with significant side effects. In a study led by **Kee Kiat (Aaron) Yeo, MD,** and **Susan Chi, MD,** researchers found that trametinib, another MEK inhibitor, appears to be effective in pediatric patients with recurrent or progressive low-grade gliomas. The study was published in the August 2020 *Journal of Neuro-Oncology*. An early phase clinical trial of trametinib for pediatric low-grade gliomas is currently underway to evaluate how tumors respond to the drug and to assess its toxicity.

The Impact of Your Philanthropy

Thank you for your commitment to Dana-Farber, which helps investigators lead pioneering projects that advance our understanding of pediatric low-grade gliomas. These discoveries strengthen our ability to uncover and deliver new therapeutic options for patients, keeping Dana-Farber at the forefront of pediatric cancer research and care. Thank you for your generous support of these critical efforts and for your dedication to our lifesaving mission.

Report written by Scott Edwards.

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.

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