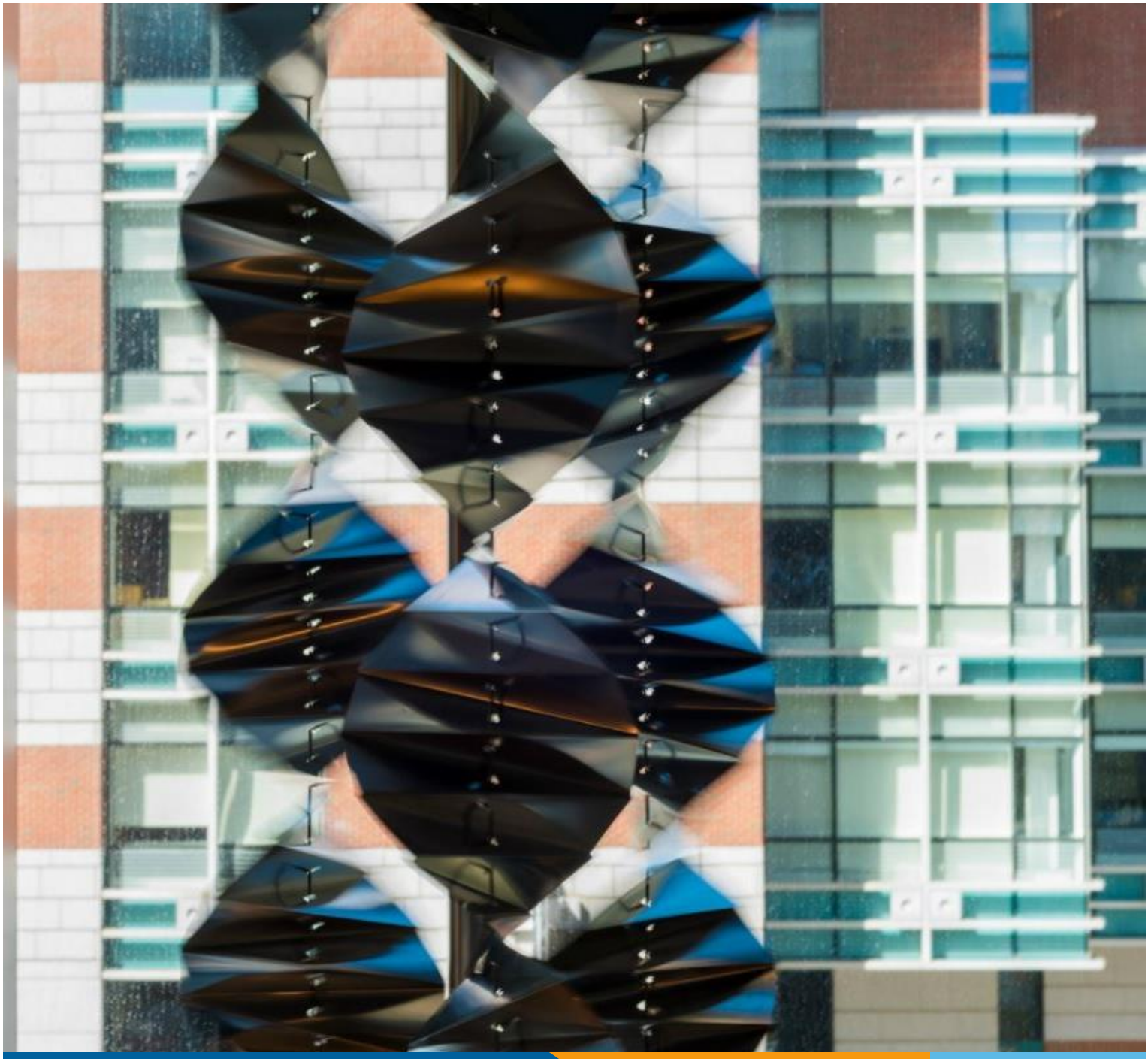

PROGRESS UPDATE FALL 2020

Evan T. Mandeville DIPG Research Fund

Dana-Farber Cancer Institute | The Jimmy Fund

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Introduction

Investigators at Dana-Farber Cancer Institute are global leaders in pediatric brain tumor research and patient care, including for rare brain tumors such as diffuse intrinsic pontine glioma (DIPG). Under the leadership of **Katherine Warren, MD,** and **Mariella Filbin, MD, PhD,** a team of physician-scientists pursues ambitious research initiatives to better understand the biological complexities of DIPG and uncover targetable genetic mutations in the hope of providing better treatment options for this disease.

This past year has seen a number of advances, including the development of innovative research models to help investigators delve deeper into the genetics of DIPG, with the goal of testing targeted therapies against these abnormalities and ultimately moving toward delivering more effective treatments. In addition to the genetic complexity of the disease, researchers are studying ways to enlist the immune system, the body's natural defense system, to mount an attack on these aggressive tumors. Thank you for your partnership in this important work.

Expanding Expertise

Dana-Farber's expertise in research and clinical care has been recognized by membership in two nationwide research and clinical programs for childhood brain tumors. In December 2019, Dana Farber spearheaded the launch of the first DIPG Clinical Consortium in partnership with several pediatric hospitals across the country, including Lucile Packard Children's Hospital Stanford, Seattle Children's Hospital, Lurie Children's Hospital of Chicago, Texas Children's Hospital, and the University of Florida. The consortium is using extensive preclinical information from DIPG tumor cell lines and animal models to optimize clinical trial design, determine effective dosing and scheduling, and translate these findings into comprehensive clinical trials.

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

Understanding NTRK Fusions

A **fusion gene** is made by joining two parts of different genes. NTRK fusions are found in a broad range of pediatric cancers, including high-grade gliomas and certain DIPGs.

In a study published in the July 2020 *Acta Neuropathologica Communications*, Filbin and her colleagues described the clinical and molecular features of a novel fusion involving the NTRK gene that drives a variety of adult and pediatric tumors, including GBM and a subset of DIPGs. This fusion gene can lead to cell proliferation and resistance to natural cell death. Filbin is now conducting single-cell analyses—techniques that enable researchers to isolate individual cells to study their function and behavior—of NTRK-fused GBM and DIPG cells to gain a greater understanding of how these cells promote tumor growth. In 2018, the Food and Drug Administration approved larotrectinib as one of the first approved targeted therapies for NTRK-fused gliomas.

Examining the Microenvironment

Because DIPG tumors contain few immune cells relative to other cancers, the disease is considered immunologically "cold"—meaning that it is difficult to stir up an immune response against these tumors. In the lab, Filbin and her colleagues are studying how DIPG cells communicate with the normal brain and how this is different among age groups. For example, the developing brain of a baby may have different mechanisms that feed a tumor compared to an adolescent or adult. They are examining how DIPG cells interact with normal nerve cells in the brain, called neurons, and cells that form the scaffolding of the brain to determine how the DIPG cells keep the immune system at bay. The findings could lead to novel immunotherapies that spur an immune response against DIPG tumors.

Targeting Cell Differentiation

In 2018, Filbin made pioneering strides in characterizing the cellular architecture of DIPG, finding, through single-cell sequencing studies, that tumors fueled by H3K27M mutations could be sensitive to therapies that alter cell types by forcing them into more mature stages of development, a process known as differentiation. She also identified the LSD1 gene as a promising candidate to target to sensitize DIPG cells to differentiation therapy.

As a next step, she and her colleagues tested a dual HDAC and LSD1 inhibitor in mouse models and found that the combination treatment induced differentiation and slowed DIPG cell growth. This promising discovery, published in the October 2019 *Cancer Cell*, could be a compelling treatment

Pratiti (Mimi) Bandopadhayay, MBBS, PhD

Rameen Beroukhim, MD, PhD

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

strategy for H3K27M-mutated DIPG. She is now testing the drug in a larger cohort of mouse models to determine optimal dosing.

In addition, H3K27M is an epigenetic regulator for which current drugs do not exist. Filbin is collaborating with **Jun Qi, PhD,** to design novel epigenetic therapies that target the unique drivers of DIPG. Epigenetics is a biological mechanism that turns genes on and off without changing the underlying genetic sequence. Epigenetic changes are potentially reversible, raising the possibility that drugs capable of returning epigenetic marks to their normal setting could be effective in treating cancer.

Modeling MYC

Pratiti (Mimi) Bandopadhayay, MBBS, PhD, Rameen Beroukhim, MD, PhD, and **Keith Ligon, MD, PhD,** have developed mouse models of pediatric high-grade gliomas such as DIPG and glioblastoma multiforme (GBM) that are driven by rearrangements in the MYC gene, which signals cells to grow and prevents them from maturing. With these models, they discovered changes in regions of DNA that are distant from MYC and activate cellular regulators of MYC to increase production of the gene and its proteins. They are now using the mouse models to discern the precise location and function of these cellular regulators, and whether they work only in concert with MYC or with other genes as well. These models will help physician-scientists learn more about how MYC rearrangements drive the growth of these brain tumors and aid in the development of new therapies for patients.

Elucidating PPM1D's Role

Bandopadhayay and Beroukhim have made strides in illuminating the genomic makeup of high-grade tumors like DIPG and GBM. Their ongoing efforts have revealed a number of potential therapeutic targets, including the PPM1D gene, which may play a role in fostering the growth of these tumors. They have introduced PPM1D mutations into cell lines and mouse models to observe how the gene functions and interacts with surrounding proteins. Early findings suggest that the gene may help trigger the malignancy's initial formation. They are now testing the efficacy of PPM1D inhibitors in both cell lines and mouse models and running drugs screens on DIPG and GBM cell lines to identify interventions that may warrant further investigation.

Identifying Combination Therapies

Panobinostat inhibits the activity of an enzyme called HDAC that is overexpressed in cancer cells. Inhibiting its activity may cause cell death.

Marizomib is a proteasome inhibitor that blocks the activity of molecular structures that rid cells of unwanted proteins.

In a study published in the November 2019 *Science Translational Medicine*, Warren and her colleagues screened more than 2,700 approved and investigational drugs to determine which might be suitable for treating DIPG. They identified a combination that includes panobinostat and marizomib as a promising therapeutic option (see sidebar).

Under Warren's leadership, Dana-Farber has opened a phase I clinical trial of this drug combination to treat patients with DIPG, using a novel study design. Normally, for a phase I study, most patients receive one drug and continue until their disease progresses or they no longer tolerate the drug. Given the lack of treatment options for DIPG, however, this study, which is expected to enroll 39 patients, is designed to allow patients to eventually receive the combination of drugs and to continue for as long as they receive clinical benefit from them.

In another study, Warren and her colleagues found that panobinostat itself has difficulty penetrating the blood-brain barrier, the physical separation of the brain from the rest of the body, in preclinical models of DIPG. The findings were published in the April 2020 *Cancer Chemotherapy and Pharmacology*. She is now working with colleagues who are using mass spectrometry imaging, a tool used to study molecular structures, to better understand how drugs penetrate the blood-brain barrier, as well as studying the use of nanoparticles to improve drug delivery to brain tumors.

The Impact of Your Philanthropy

Dana-Farber researchers collaborate across disciplines and beyond institutional walls to bring novel treatments to children with DIPG. Thanks to your generosity and the generosity of others, our physician-scientists are leveraging new technologies to answer fundamental questions about these malignancies. Thank you for your critical investment in Dana-Farber's DIPG initiatives and for your commitment to our mission to improve care and outcomes for children with this terrible disease.

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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