DANA-FARBER
CANCER INSTITUTE

PROGRESS UPDATE

Evan T. Mandeville DIPG Research Fund

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BEST HOSPITALS U.S.News NATIONAL CANCER 2017-18

BEST CHILDREN'S HOSPITALS U.S.News CANCER 2017-18

Dana-Farber Cancer Institute has been the top ranked cancer hospital in New England by U.S. News and World Report for 17 consecutive years, and is the only cancer center in the country ranked in the top 4 for both adult and pediatric cancer programs.

EXECUTIVE SUMMARY

Investigators at Dana-Farber Cancer Institute are global leaders in pediatric brain tumor research and patient care, including rare brain tumors such as diffuse intrinsic pontine giloma (DIPG). Under the leadership of **Mark Kieran, MD, PhD,** Director of Pediatric Medical Neuro-Oncology, and **Keith Ligon, MD, PhD,** Director of Neuro-Oncologic Pathology, our team of physician-scientists are pursuing ambitious research initiatives to better understand the biological complexities of DIPG and uncover targetable mutations in the hope of providing better treatment options for this disease.

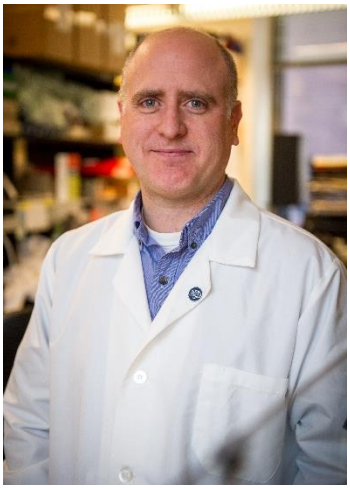
This past year has seen a number of advancements, including the development of innovative DIPG models to help investigators test new drugs in the laboratory, a finding that could propel therapeutic development and provide insights into the mechanisms that drive this malignancy. We thank you for your support of this important work.

Mark Kieran, MD, PhD, Director of Pediatric Medical Neuro-Oncology

DEMONSTRATING THE POWER OF GENOMIC PROFILING

This year, Dr. Kieran and **Peter Manley, MD**, continued their participation in the largest genomic analysis to date of pediatric brain tumors, an initiative that first launched in 2012. Along with their collaborators—including **Pratiti Bandopadhayay, PhD, MBBS; Rameen Beroukhim, MD, PhD; Susan Chi, MD; Keith Ligon, MD, PhD; Charles Stiles, PhD;** and **Karen Wright, MD, MS**—the researchers performed clinical testing on 203 pediatric brain tumors, including high grade gliomas, to determine whether genomic sequencing could uncover clinically significant abnormalities.

Their results, published in the January 2017 *Neuro Oncology*, found that 56 percent of patients had mutations that could influence their diagnosis and help identify potential therapies that are already federally approved or available through clinical trials. Their work affirmed that genomic analysis could be used in the clinic to influence the diagnosis and treatment of pediatric brain tumors.



Keith Ligon, MD, PhD, Director of Neuro-Oncologic Pathology

DIPG: A PIONEERING BIOPSY EFFORT OFFERS INSIGHTS

DIPG is a rare and aggressive pediatric brain tumor located in the brain stem that affects approximately 300 children in the United States each year. Historically, physicians had considered this region to be too risky to biopsy, a roadblock that kept scientists in the dark about the genetic makeup of this difficult disease.

Building on years of research indicating that such biopsies could be conducted safely and effectively, Dr. Kieran led a pioneering clinical trial in 2011 to collect DIPG biopsy samples at the time of diagnosis, resulting in an unprecedented resource bank that investigators have been able to use to examine the biological workings of this complex malignancy. Now, Dr. Kieran and his team are in the process of analyzing 130 DIPG tissue samples collected as part of this groundbreaking clinical trial.

DIPG and gliomatosis cerebri: a comparative study

In one genomic analysis, Dr. Kieran and his collaborators will compare data from the DIPG tissue samples to the genomic profile of gliomatosis cerebri, a rare and aggressive malignancy that shares many molecular characteristics with DIPGs. The tumors differ in one notable way, however: DIPGs begin as a mass, while gliomatosis cerebri tumors have no localized core. As a result, investigators have struggled to collect enough tissue to study this rare disease. Dr. Kieran's approach offers the opportunity to build a resource bank that can illuminate the biological underpinnings of each malignancy while shining a light on the potential differences between the two tumors.

THERAPEUTIC INNOVATIONS

ACVR1: targeting a new mutation

With access to greater numbers of biopsy samples, Dana-Farber researchers have been able to perform in-depth genomic analyses, uncovering new mutations that could inform future drug development. For example, Dr. Kieran and his team discovered abnormalities in the H3F3A gene in a large percentage of pediatric high-grade astrocytomas. While they have not yet been able to effectively zero in on this mutation, other abnormalities that appear alongside

H3F3A could represent potential new targets. To this end, Dr. Kieran plans to test a drug that targets the abnormal gene ACVR1, which is present in a subtype of DIPG but has never been identified in cancer before now. He plans to combine the therapy with an immunotherapy (see sidebar) to see how they interact in cell lines.

Developing preclinical models that last

Leveraging emerging data on DIPG, **Rosalind Segal, MD, PhD**, and her colleagues have developed an innovative research model that can be used to test potential therapies. These models, called hydrogels, closely mimic the tumor microenvironment in patients, and have unique properties that make them malleable and long-lasting. Additionally, the models' composition can be altered to fit a wide variety of tumors, giving the finding wide applicability. Dr. Segal and her collaborators will begin using the hydrogels for drug testing in late 2017.

PROBING THE EPIGENETIC ROOTS OF DIPG

Approximately 80 percent of DIPG tumors are driven by epigenetic errors—corruptions in the processes that turn genes on or off—which cause unregulated tumor growth. In a multi-center study, Drs. Beroukhim and Bandopadhayay are conducting RNA sequencing and methylation profiling (see sidebar), two screening methods that could provide a deeper understanding of the epigenetic events driving DIPG.

Drs. Beroukhim and Bandopadhayay are also performing whole genome sequencing of DIPG tumor tissue, both before and after radiation treatment, to reveal the mechanisms behind resistance. They aim to use this data to identify biomarkers that could help predict treatment outcomes, establishing molecular subgroups of DIPGs that could explain why some patients respond better than others to radiation.

Immunotherapy: Treatments that harness the power of the immune system to identify and attack cancer cells.

RNA Sequencing: The process used to reveal the code contained in RNA, a messenger that carries the instructions from DNA for how to create proteins.

Methylation Profiling: The study of how DNA methylation, an epigenetic mechanism that regulates gene expression, drives disease.

A NEW KIND OF BIOMARKER

Dana-Farber investigators are actively looking for better ways to track DIPG tumor progression. Physicians cannot perform a DIPG biopsy on a patient more than once, given the invasiveness of the procedure, so alternate methods are needed to monitor the tumor's development. To this end, Dr. Bandopadhayay is participating in a multi-center initiative to design DNA barcoding technology that would allow investigators to track individual DIPG cells in the lab. Using this tool, researchers will be able to observe the evolution of single cells as they undergo treatment, which could provide investigators with a more personalized genetic profile of a patient's tumor and help them to design targeted treatment plans.

THE POWER OF PHILANTHROPY

Your philanthropy has fueled the work of Dr. Kieran and his colleagues as they execute large-scale studies that elucidate the biological complexities of DIPGs. Their advancements are continuing to inform clinical practice and therapeutic interventions, uncovering potential targets for future drug development. Your commitment to Dana-Farber has kept the Institute at the forefront of its field in pediatric brain tumor research and care, and we thank you for your meaningful contribution to these important efforts.

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FOR MORE INFORMATION

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