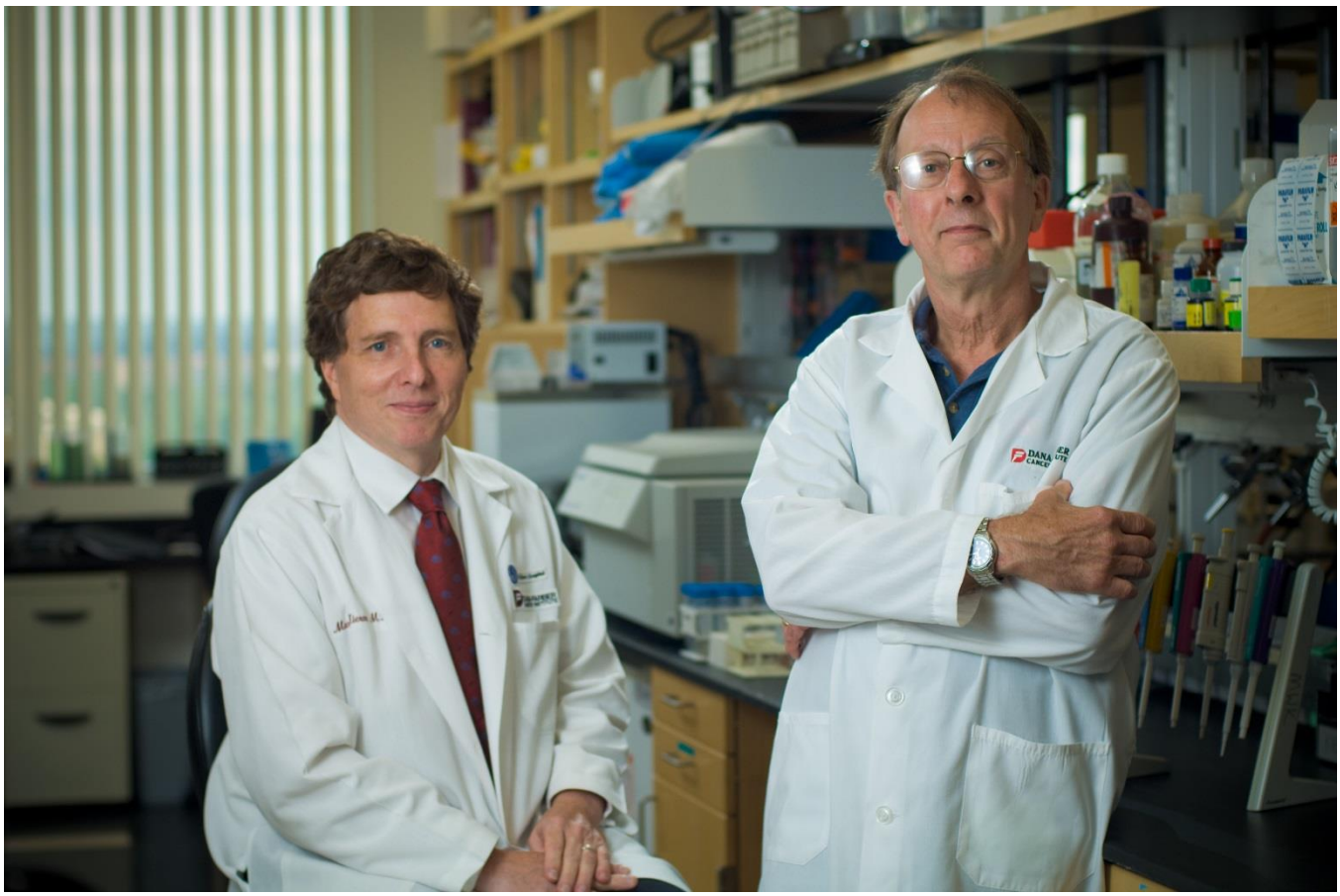
DANA-FARBER
CANCER INSTITUTE



PROGRESS UPDATE

PLGA Foundation

October 2017

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

Dana-Farber Cancer Institute is home to the only dedicated pediatric low-grade glioma program in the world. Over the past year, the talented physician-scientists in the Pediatric Low-Grade Astrocytoma (PLGA) Program have initiated landmark research initiatives, marshalling the combined efforts of institutions all over the country. Under the leadership of **Mark Kieran, MD, PhD,** Director of Pediatric Neuro-Oncology, and **Charles Stiles, PhD**, a multidisciplinary team of investigators are leading research collaborations and pioneering clinical trials to better understand and treat pediatric PLGAs.

This year has seen several advancements, including a new technique that helps researchers study pediatric brain tumors in the laboratory, a finding that could help physicians test the most promising treatment options for patients. Investigators are also probing the biological underpinnings of PLGAs, uncovering new targets and resistance mechanisms that could inform future drug development. As the most common form of pediatric brain tumor, discoveries made in the PLGA Program have significant impact, and we thank you for your commitment to this important work.

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

Charles Stiles, PhD

LEVERAGING THE POWER OF GENOMIC PROFILING

Dr. Kieran and **Peter Manley, MD**, participated in the largest genomic analysis to date of pediatric brain tumors, which opened in 2012. Along with a multidisciplinary group of Dana-Farber investigators—including Dr. Stiles, **Pratiti Bandopadhayay, MBBS, PhD, Rameen Beroukhim, MD, PhD,** and **Karen Wright, MD, MS**—the researchers performed clinical testing on 203 pediatric brain tumors, including low-grade gliomas, to determine whether genomic sequencing could uncover clinically significant abnormalities.

As published in the January 2017 *Neuro Oncology*, after analyzing subset of these samples, the researchers found that 55 percent of pediatric patients with low-grade tumors (and 56 percent of pediatric patients with all tumor types) had mutations that could both influence diagnosis and potentially be targeted using therapies that are already approved or available through clinical trials. Their work affirmed that genomic analysis could be used clinically to influence the diagnosis and treatment of pediatric brain tumors.

Peter Manley, MD, Director, Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic

PRECISION MEDICINE TAKES CENTER STAGE

BRAF: A new drug targets two mutations

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

While PLGAs are largely curable, the treatments can cause significant side effects. Precision medicine, therapy tailored to a cancer's molecular profile, sends drugs directly to tumor cells, reducing potential side effects. To this end, Dr. Kieran is focusing on BRAF, a mutation seen in approximately 75 percent of PLGA tumors.

PLGA malignancies are driven by one of two BRAF mutations: V600E or a fusion gene called KIAA1549:BRAF. This latter mutation causes uncontrolled cell growth and does not respond to traditional BRAF inhibitors. Dr. Kieran worked with **Rosalind Segal, MD, PhD**, and a team of collaborators to launch a multi-center study to test a new drug called TAK580 in preclinical models, theorizing it would act against both mutations. Their findings, published in the June 2017 *Neuro-Oncology*, found that the drug could penetrate the blood-brain barrier and was effective against both the fusion gene and V600E. Dr. Kieran is working to open a clinical trial to test the drug's efficacy in patients.

FDA-approved drug shows promise against V600E

Dr. Kieran is running a phase II clinical trial testing the BRAF inhibitor dabrafenib in patients with a range of advanced tumors carrying V600E mutations. This drug, already approved by the Food and Drug Administration for melanoma, was highly effective against pediatric low-grade gliomas: Of 32 patients treated with dabrafenib, 23 (72%) saw their tumors either shrink or stop growing. Dr. Kieran presented these promising early findings at the 2016 European Society for Medical Oncology meeting in Copenhagen.

In a follow-up study, Dana-Farber investigators are studying dabrafenib in combination with MEK inhibitor trametinib, which has been shown to last longer and produce fewer side effects than other therapeutic options. In fact, this combination is so favorable that the combination has become the standard of treatment in adult patients with V600E-mutated melanoma. A phase II trial testing the efficacy and safety of dabrafenib alongside trametinib in patients with advanced V600E-mutated tumors, including pediatric low-grade gliomas, is currently underway.

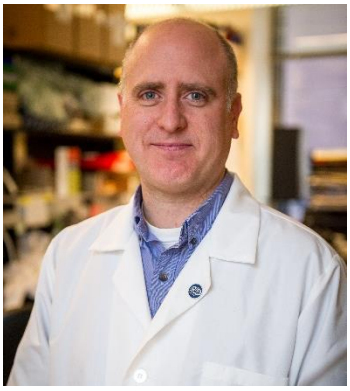
Exploring the unique profile of MYB-QKI

Recent genomic analysis by Dana-Farber investigators led to a landmark discovery in angiocentric gliomas, a rare low-grade brain tumor about which little was previously known. Drs. Bandopadhayay, Beroukhim, and **Keith Ligon, MD, PhD**, studied 249 pediatric low-grade gliomas, including 19 angiocentric gliomas, and discovered an unusual genetic abnormality. Through a glitch in DNA segments, two separate genes—MYB and QKI—became fused. Though harmless on their own, the combination of these genes leads to tumor development. Their findings were published in the February 2016 *Nature Genetics.*

Now that the biological drivers of angiocentric gliomas are better understood, Drs. Ligon and Beroukhim are developing mouse models to study the specific mechanisms behind MYB-QKI, which might help them to identify the pathways it disrupts and, ultimately, pinpoint novel drug targets.

Pratiti Bandopadhayay, MBBS, PhD

Rameen Beroukhim, MD, PhD



Keith Ligon, MD, PhD

INNOVATING MODELS THAT DRIVE RESEARCH

Low-grade gliomas are notoriously hard to culture, only lasting a few days in the laboratory. Unlike hardier high-grade tumors, which remain aggressive and fast-growing in a laboratory setting, low-grade gliomas are more dependent on their microenvironment. Historically, this has made the preclinical study of novel treatments for PLGAs a challenge.

In 2015, Dr. Segal was part of a groundbreaking study that resulted in the development of an innovative method for creating models that better reflected the tumor microenvironment. This strategy kept low-grade tumors alive in the laboratory for up to two weeks. Building on this advancement, Dr. Segal, in collaboration with a team of bioengineering experts, developed even longer lasting models, called hydrogel cocultures. These hydrogel cocultures have unique properties that make them malleable and durable, allowing primary tumor cells to grow for up to a month in the laboratory.

PEDIATRIC NEURO-ONCOLOGY: SUPPORTING SURVIVORS

Under the leadership of Dr. Manley, the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic is committed to addressing the unique challenges that face survivors of pediatric brain tumors. Through supportive programs and wide-ranging research initiatives, Dr. Manley and his team aim to reduce treatment side effects and provide multi-faceted care that addresses the physical, emotional, and psychosocial well-being of their patients. They provide families with the resources they need to navigate pediatric brain tumor treatment, as well as ongoing assistance to the growing population of survivors.

In one study, Dr. Manley and his team looked at the use of MRIs in patients with low-grade gliomas to see if the process could be optimized. Primarily, they aimed to determine whether the number of images could be reduced, given that children receive anesthesia for the scan. Traditionally, these patients receive approximately 15 MRIs over a 10-year period, which is both burdensome and costly. Initial findings suggest that fewer scans yield similar results as more frequent scanning, indicating that recurrences would not be missed in patients who did not present with symptoms, despite the reduction in imaging.

THE POWER OF PHILANTHROPY

Your philanthropy has fueled advancements in PLGA research, empowering Dana-Farber investigators to develop and deliver cutting-edge treatments to patients. Discoveries made here are advancing therapeutic strategies for pediatric patients, helping our physicians promote their long-term health and well-being. Your contribution furthers the Institute's mission to provide first-rate care, and we thank you for your meaningful partnership in these important efforts.

Report written by Caroline de Lacvivier

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