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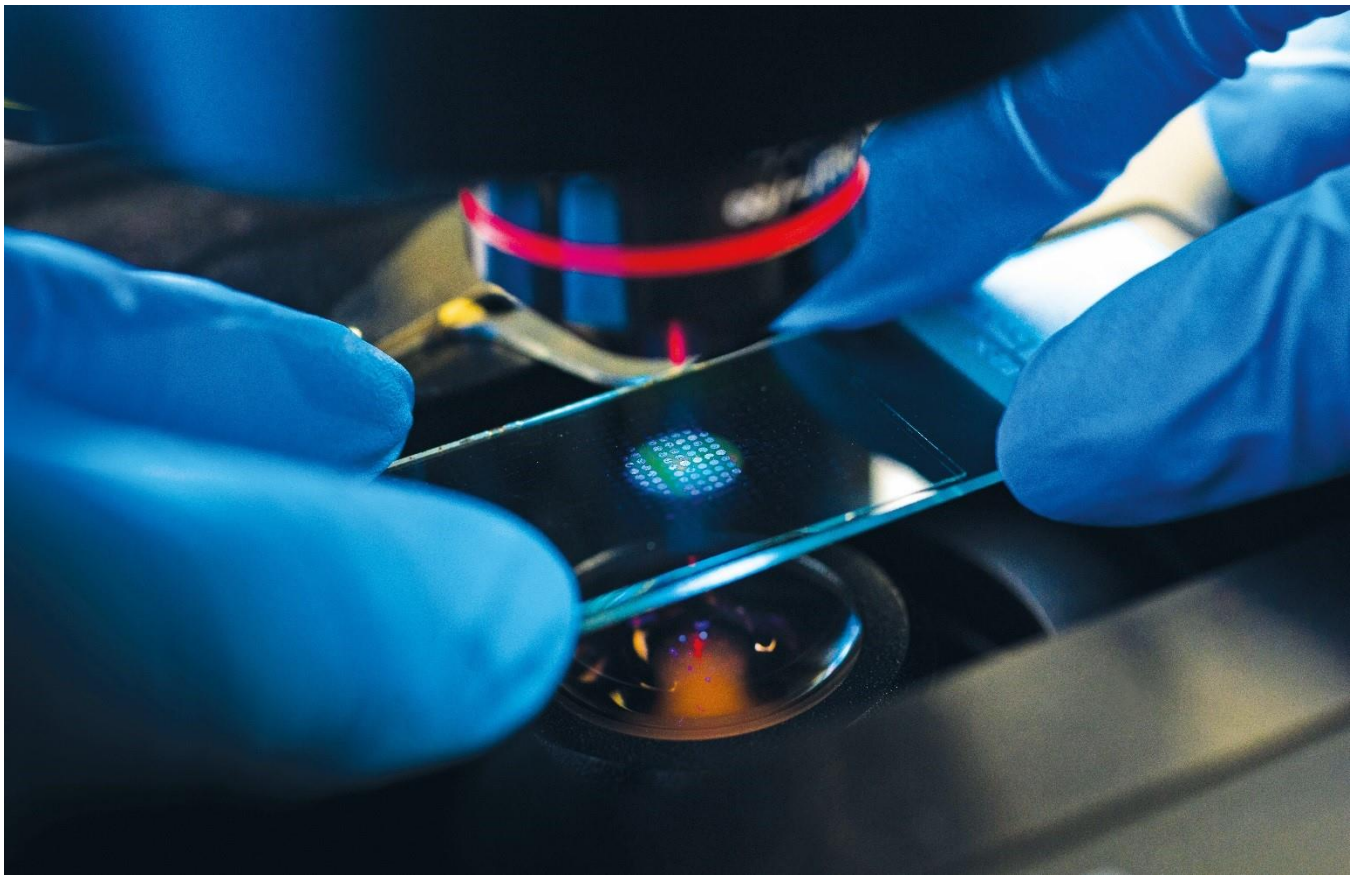

PROGRESS UPDATE

Evan T. Mandeville DIPG Research Fund

December 2018

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CANCER 2018-19

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT CANCER 2018-19

Dana-Farber Cancer Institute has been the top ranked cancer hospital in New England by U.S. News and World Report for 18 consecutive years, and is the only cancer center in the country ranked in the top 4 for both adult and pediatric cancer programs.

MAGNET RECOGNIZED
AMERICAN NURSES CREDENTIALING CENTER

EXECUTIVE SUMMARY

As a top-ranked pediatric cancer center, Dana-Farber Cancer Institute combines first-rate patient care with groundbreaking research to expedite drug discovery for childhood diseases. Neurologists, neuro-oncologists, neurosurgeons, and pediatric subspecialists collaborate to launch groundbreaking clinical trials and translational studies that bring novel treatments to patients with diffuse intrinsic pontine glioma (DIPG). Under the leadership of **Susan Chi, MD,** a team of physician-scientists have made several landmark advancements, including launching the largest genomic study to date of DIPGs.

As you will read, our multi-disciplinary team of experts are leading ambitious studies in gene discovery, chemical biology, model system development, and clinical research so that innovative findings flow from bench to bedside. Your philanthropy has been central to fueling this discovery engine, which is expediting DIPG research and bringing novel therapies to patients. Thank you for your partnership.

Susan Chi, MD, Interim Director, Pediatric Medical Neuro-Oncology; Director, Pediatric Brain Tumor Clinical Trials Program

Pratiti Bandopadhayay, MBBS, PhD

Rameen Beroukhim, MD, PhD

WHOLE GENOME SEQUENCING SHEDS NEW LIGHT

DIPGs are fast-growing tumors found at the base of the brain. They arise in the brain's glial tissues—tissues made up of cells that help support and protect the brain's neurons. Both due to the tumor's sensitive location on the brainstem and its relative rarity, until recently, investigators have been unable to obtain biopsies that could help to shed light on the malignancy's genomic makeup.

Thanks to a biopsy effort launched at Dana-Farber, physician-scientists have collected enough tissue samples to open a large-scale screening initiative aimed at identifying the drivers of DIPG and other high-grade gliomas. After sequencing the whole genomes of 174 tissue samples—the largest study of its type to date—**Pratiti Bandopadhayay, MBBS, PhD, Rameen Beroukhim**, **MD, PhD,** and **Keith Ligon MD, PhD**, discovered several previously unknown drivers of DIPG. Their findings could help researchers better understand the regulatory elements underlying tumor growth and ultimately lead to new treatments.

Unveiling the mechanisms that cause resistance

Drs. Bandopadhayay, Beroukhim, Ligon, and their collaborators are sequencing DIPG tumor samples before and after treatment to learn more about how treatment alters the tumor microenvironment. Their findings could offer potential insights into the mechanisms that help tumors evolve over time to become resistant to therapy and how this process might be overcome. As part of this effort, Dr. Bandopadhayay is now partnering with **Benjamin Ebert, MD, PhD,** to characterize mutations in a gene called PPM1D, which are found in both DIPGs and leukemias. Ultimately, they hope to identify potential targeted therapies.

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

Analyzing DIPG cell-by-cell

Drs. Bandopadhayay, and Beroukhim, are partnering with Dr. Ligon and **Mariella Filbin, MD, PhD**, on a single-cell RNA sequencing project that will compare pediatric low-grade gliomas and DIPGs at a single-cell level. This process reveals the code contained in RNA, a messenger that carries the instructions from DNA to create proteins. Unlike standard methods that measure gene expression in large numbers of cells, this approach enables researchers to isolate and study individual cells**,** painting a richer portrait of the molecular drivers of malignancy.

Benjamin Ebert, MD, PhD, Chair of Medical Oncology; George P. Canellos, MD, and Jean S. Canellos Professor of Medicine, Harvard Medical School

BRINGING IMMUNOTHERAPY TO THE CLINIC

Vaccines, drugs, and modified human cells that activate the immune system against cancer have improved outcomes and prolonged lives in some types of cancer. These interventions are known as immunotherapy, an approach that uses the body's own immune system to treat cancer. To bring this advancement to DIPG, Dana Farber is participating in an international phase II clinical trial comparing nivolumab, a type of immunotherapy that targets PD-1, used alone to nivolumab in combination with ipilimumab, an immunotherapy that blocks a protein known as CTLA-4, in patients with high-grade central nervous system malignancies, including DIPG. Researchers aim to learn more about which of these immunotherapy approaches is better tolerated and more effective. The study opened in spring 2017 and is currently enrolling patients.

Marielle Filbin, MD, PhD

INNOVATIVE MODELS ADVANCE PRECLINICAL RESEARCH

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

Rosalind Segal, MD, PhD, is collaborating with bioengineering experts at the Massachusetts Institute of Technology (MIT) to develop an innovative modeling method called hydrogels, which allow investigators to replicate the complexities of the tumor microenvironment. These malleable synthetic matrixes present new opportunities for researchers to study DIPG growth and the efficacy of potential therapies in the laboratory, and Dr. Segal and her team have begun testing drugs in these models. Dana-Farber investigators are working to adapt the model to study invasive mechanisms of brain malignancies, which could ultimately help shine a light on innovative ways to stop metastasis.

EXPLORING ALTERNATIVE BIOPSY METHODS

Making strides in DNA barcoding

Because DIPG grows in a sensitive part of the brain, biopsies cannot be undertaken more than once; as a result, alternate methods are needed to monitor the tumor's development. To this end, Dr. Bandopadhayay and Beroukhim continue to contribute to a multi-center initiative to design a type of DNA barcoding technology called EvoSeq. Using this technology, researchers are able to observe cells as they undergo treatment, gaining insight into which cells survive intervention. This technology can be used to investigate the biological mechanisms underlying resistance. Also, by treating the barcoded cells with different drugs, investigators can identify combinations that might boost anti-tumor effects. Dr. Bandopadhayay presented on this technology at the November 2017 Society of Neuro-oncology Annual Meeting.

Cell-free DNA: a new method for tracking tumors

With the aim of establishing an alternative means to diagnose and track pediatric brain tumors, Drs. Bandopadhayay, Beroukhim, and Wright are partnering with MIT and the Broad Institute of MIT and Harvard to explore the potential of cell-free DNA, which occurs when cancer cells shed their DNA into the bloodstream. This phenomenon can be detected and analyzed using

sophisticated technologies and may offer the same information as traditional biopsies. Further, cell-free DNA can be extracted with greater ease and with minimal risk to the patient, representing a new frontier in cancer science.

The team has collected samples from more than 100 patients and generated a sequencing assay (see sidebar) specific to pediatric brain tumors. This work was recently presented at the June 2018 ISPNO. Over the next year, the investigators will test the technology and analyze the data in order to both validate cell-free DNA as a diagnostic platform and as a potential method to study and overcome treatment resistance.

Sequencing assay: an investigative approach to identify the presence of a target substance. In the case of liquid biopsy, the assay will test blood for the presence of cell-free DNA

THE POWER OF PHILANTHROPY

Your support is helping Dana-Farber physician scientists to bring urgently needed therapies to pediatric patients with DIPG. Discoveries made at Dana-Farber are shining new light on the molecular underpinnings of high-grade brain tumors such as DIPG, advancing diagnostics, and expanding treatment options in an ongoing effort to improve outcomes for these difficult diseases. Your contribution is integral to the Institute's mission to provide this first-rate care, and we thank you for your meaningful commitment to these important causes.

Report written by Caroline de Lacvivier.

FOR MORE INFORMATION

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