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PROGRESS UPDATE

Evan T. Mandeville DIPG Research Fund

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BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CANCER 2019-20

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT CANCER 2019-20

Dana-Farber Cancer Institute has been the top ranked cancer hospital in New England by U.S. News and World Report for 19 consecutive years, and is ranked in the top 5 nationally for both adult and pediatric cancer programs.

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EXECUTIVE SUMMARY

Dana-Farber Cancer Institute brings together the brightest minds in pediatric neuro-oncology to advance diffuse intrinsic pontine glioma (DIPG) treatment and care. Their work is shining new light on the complex biology driving this malignancy and opening new avenues for future drug discovery. This year brings a number of significant developments, including a change in leadership: In June 2019, **Katherine Warren, MD,** was named the Clinical Director for Pediatric Neuro-Oncology. Warren is an internationally recognized expert in pediatric neuro-oncology, and she is a leading innovator in developing new means of drug delivery for children with brain tumors and ensuring that effective therapies reach the tumor site in sufficiently potent concentrations. Your generous support helps Warren and her colleagues make game-changing advances in research and care for our youngest patients, and we are grateful for your dedicated support of our important mission.

Katherine Warren, MD, Clinical Director, Pediatric Neuro-Oncology

Mariella Filbin, MD, PhD

DIPG SEQUENCING REVEALS NEW THERAPEUTIC STRATEGY

DIPG is a rare pediatric brain tumor with no known cure. Because tissue samples are scarce, little is known about the tumor's molecular makeup. To overcome this challenge, **Mariella Filbin, MD, PhD**, is leveraging new single-cell genetic sequencing technologies (see sidebar) to analyze exactly how DIPG develops and discover potential drug targets.

Using single-cell sequencing, researchers can analyze every cell in a given tumor sample, gaining a more granular picture of the dependencies and interactions between tumor cells in their larger context. Filbin performed single-cell sequencing on more than 3,000 individual brain cells from six gliomas with H3K27M mutations, an alteration typically found in DIPGs. This mutation is only found in brainstem tumors of pediatric patients, suggesting that tumor growth could be triggered during the brain's development.

Filbin and her collaborators found that cells driven by H3K27M resemble oligodendroglial precursor cells (OPC), a subtype of glial cell that has not

Single-cell sequencing: 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.

yet undergone differentiation, the natural process by which cells transform from one cell type to another. In this pre-differentiated state, glioma cells behave like stem cells, proliferating out of control without ever reaching maturity.

Further, Filbin and her collaborators found that a subpopulation of tumor cells are able to mature beyond their stem cell state despite harboring the H3K27M mutation. These findings, published in the April 2018 *Science,* suggest that H3K27M-driven gliomas could be sensitive to therapies that induce differentiation, thus forcing them out of their stem cell state and halting tumor growth.

As a next step, Filbin is leading a study of the DIPG microenvironment—a collection of tumor cells, blood vessels, structural elements, and specialized immune cells that surrounds the tumor and protects it from immune attack—with the aim of learning how DIPG tumor cells use normal neural cells to infiltrate the brain. Insights from her work could reveal how normal cells conspire with tumor cells to drive DIPG, thus presenting new possibilities for therapeutic intervention.

In addition, Warren and her collaborators are translating results from high throughput drug screens in children with DIPG. In concert with Filbin, Warren will oversee extensive preclinical testing of drugs found to have activity against DIPG tumor cells in the laboratory to optimize clinical trial design for these children, targeting adequate, effective drug levels at the tumor site.

PPM1D: INVESTIGATING A KEY MUTATION

Pratiti Bandopadhayay, MBBS, PhD, and **Rameen Beroukhim, MD, PhD,** have made pioneering strides into characterizing the genomic makeup of high-grade tumors like DIPG and glioblastoma, a rare central nervous system tumor. Their ongoing biopsy efforts have revealed a number of potential therapeutic targets, including the gene PPM1D, which is mutated in a subtype of DIPGs and glioblastomas. Bandopadhayay and Beroukhim are now working with **Prasidda Khadka**, along with a team of cross-institutional collaborators, to see how PPM1D may contribute to the formation and proliferation of these cancers.

Pratiti Bandopadhayay, MBBS, PhD, Director, PLGA Program

Rameen Beroukhim, MD, PhD

Prasidda Khadka

The investigators have introduced this mutation into cell lines and mouse models in order to observe PPM1D's primary functions and how it interacts with surrounding proteins. Early findings suggest that this gene may play a role in the malignancy's initial formation. To validate this discovery, as well as identify alternative drug targets that may partner with PPM1D to fuel cancer growth, Bandopadhayay, Beroukhim, and their collaborators are using advanced CRISPR technology (see sidebar) to more deeply investigate PPM1D-mutated cells and their potential dependencies.

As a next step, physician-scientists are testing the efficacy of PPM1D inhibitors in both cell lines and mouse models. They are also running concurrent drug screens, testing more than 6,000 therapies to identify interventions that may merit further investigation.

EPIGENETICALLY TARGETING DIPG

As scientists map the epigenetic (see sidebar) disruptions that occur in cancer, the implications for cancer therapy are becoming increasingly evident. Unlike genetic mutations, epigenetic changes are potentially reversible. This raises the possibility that drugs capable of returning epigenetic markers to their normal settings could be effective in cancer. A few of these drugs—including some that were developed in partnership with Dana-Farber scientists—have already been approved by the Food and Drug Administration (FDA) to treat certain cancer types, and dozens more are currently being tested in clinical trials.

Recent studies have shown that the majority of DIPGs are driven by mutations in epigenetic regulators (see sidebar) like H3K27M, for which current drugs do not exist. To address this need, Filbin is partnering with **Jun Qi, PhD**, to design novel epigenetic therapies that target the unique drivers of this malignancy. Their collaboration promises to influence future treatment options for DIPGs and could drive drug discovery in a broad range of cancers driven by mutations in the H3 family.

CRISPR: a state-of-the-art genome editing tool that enables scientists to modify the genetic makeup of living cells with astonishing speed and efficiency, facilitating experiments that would not have been feasible using previous techniques.

Epigenetics: the study of inherited changes that are not due to alterations in the DNA code. Epigenetic phenomena can be attributed to changes in the way DNA is packaged in the nucleus. DNA packaging influences which genes are ultimately expressed as proteins have been feasible using previous techniques.

Epigenetic regulators: agents that control gene expression and DNA replication.

THE POWER OF PHILANTHROPY

Dana-Farber researchers collaborate across disciplines and beyond institutional walls to bring novel treatments to patients with rare and aggressive diseases. Thanks to your generosity, our physician-scientists are leveraging new technologies to answer fundamental questions about DIPG. Your commitment is integral to the Institute's mission to provide first-rate care and to our investigators' ongoing efforts to improve outcomes for high-grade brain tumors. We thank you for your critical investment in Dana-Farber's DIPG research initiatives.

Report written by Caroline.

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