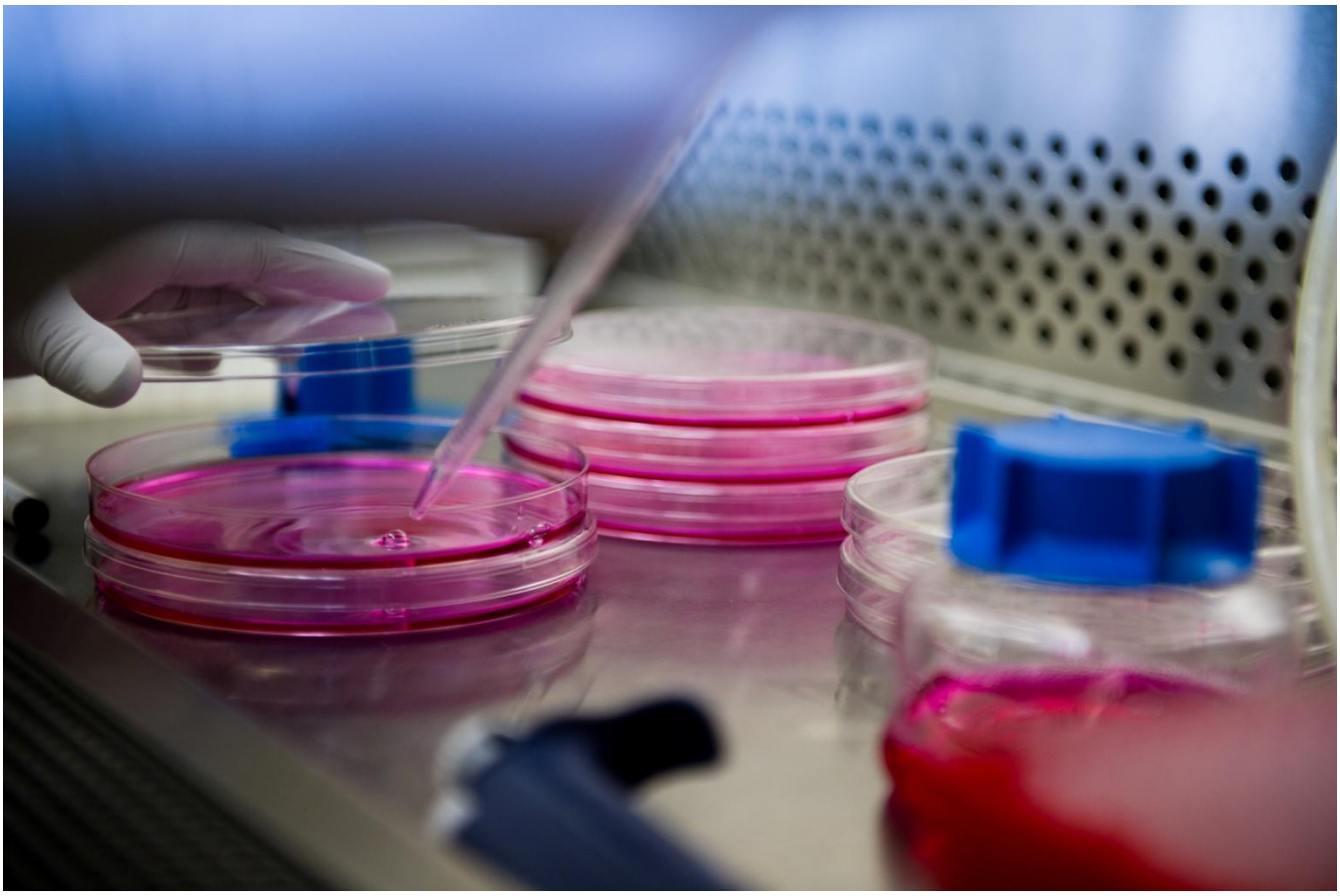
DANA-FARBER
CANCER INSTITUTE



PROGRESS UPDATE

Evan T. Mandeville DIPG Research Fund

August 2016

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CANCER 2015-16

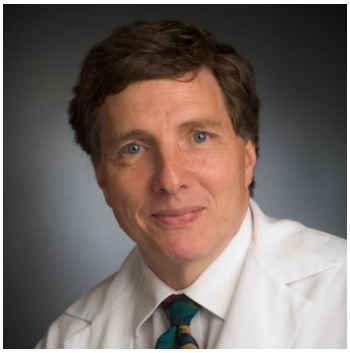
BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT CANCER 2015-16

Dana-Farber Cancer Institute has been the top ranked cancer hospital in New England by U.S. News and World Report for 15 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 a global leader in discovery science and patient care for pediatric brain tumors, including rare tumors such as diffuse intrinsic pontine glioma (DIPG). Under the direction of **Mark Kieran, MD, PhD,** Director of Pediatric Medical Neuro-Oncology, **Keith Ligon, MD, PhD,** Director of Neuro-Oncologic Pathology, and **Rameen Beroukhim, MD, PhD,** Dana-Farber physician-scientists are spearheading a breadth of innovative research projects to uncover the biological underpinnings of DIPGs and develop more effective therapies for patients with this aggressive tumor.

Over the past year, researchers have completed a groundbreaking clinical trial to biopsy newly diagnosed patients, identified promising therapeutic targets, and created sophisticated laboratory models of DIPG to identify new treatments. Your generous support has played an important role in bolstering this research and advancing discoveries that will benefit patients. Thank you for your dedication to these critical efforts.



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

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

Rameen Beroukhim, MD, PhD

DIPG BIOPSIES: HISTORY OF ADVOCACY AND A NEW TRIAL

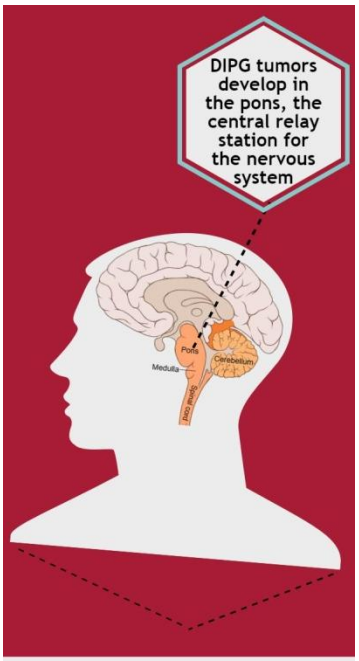
In 2002, Dr. Kieran began campaigning for biopsies for patients with DIPG, a procedure that was once considered to be too risky due to the location of these tumors in the brain. Scientists rely on tumor biopsies to accurately diagnose disease, identify genetic drivers, and test the most promising therapies. Without biopsies, the scientific community struggled to learn more about this cancer. Dr. Kieran argued that new surgical techniques would allow for safe removal of tissue and that innovative molecular biology advances could glean information from even tiny DIPG samples. By 2007, a medical team in France conducted more than 20 successful biopsies.

Leadership in DIPG biopsy clinical trials

In 2010, after Dr. Kieran had proof that this procedure was safe to perform, he developed a large-scale clinical trial to biopsy newly diagnosed DIPGs at Dana-Farber and 24 sites throughout the country. Through this trial—the first of its kind in North America—Dr. Kieran and his collaborators aimed to explore whether patients with DIPG could benefit from precision medicine, a

form of care through which investigators strive to select targeted treatments based on each patient's tumor genetics. The team collected and sequenced DIPG samples to learn more about which alterations were causing disease, and uncovered key details about the previously mysterious driver mutations. They found that this knowledge could inform some of their treatment decisions and the selection of more targeted therapies.

Building on the success of this initial study, Dr. Kieran is developing a new national clinical trial to further understand how best to deliver precision medicine to patients. Through this trial, researchers will collect DIPG biopsy samples at the time of diagnosis, conduct genetic sequencing, and analyze the resulting data to pinpoint the alterations driving each specific tumor. The investigators will then select the appropriate therapies for each patient based on their genomics, and test the efficacy of these targeted drugs in addition to standard radiation treatment. As new therapies are discovered and developed, they will also be incorporated into the trial.

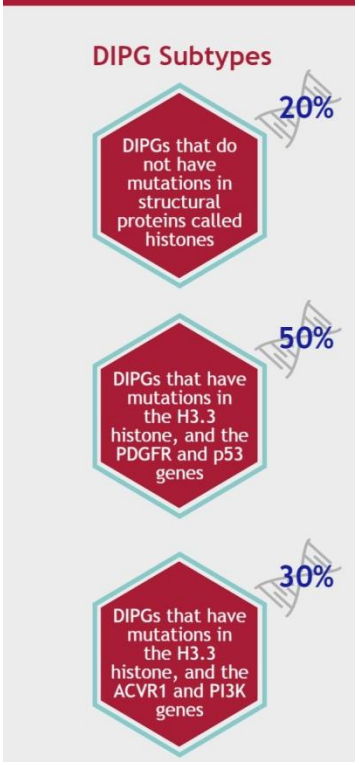


PURSUING NEW AND MORE EFFECTIVE THERAPIES

Identifying the drivers of DIPG through genomics

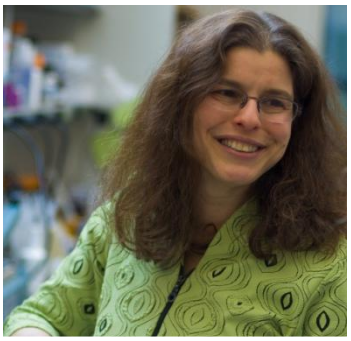
Thanks to increased access to DIPG samples, investigators can conduct more advanced genetic sequencing than ever before. These studies are revealing key information about the biological mechanisms driving DIPG growth, which could represent potential places to intervene with therapy.

Dana-Farber researchers and their collaborators have identified several mutations that drive DIPG tumors and three subtypes of disease (see sidebar). Since existing drugs block some of these targets, Drs. Kieran and Ligon are exploring the most promising therapies for patients with each of these subtypes. For instance, the Dana-Farber team has access to the only available ACVR1 inhibitor that can cross the blood-brain barrier, which has demonstrated efficacy in pre-clinical research and might offer an important new therapeutic option.



Developing sophisticated laboratory models

To leverage expanding information about the drivers of DIPG and potential therapies, Dana-Farber investigators are developing a range of research models. These tools play a critical role in enabling investigators to better understand the biology behind tumors and test drugs in the laboratory before they can be used in patients. Dr. Beroukhim is also working with **Pratiti Bandopadhayay, MBBS, PhD**, to use models to study resistance and learn more about why certain tumors stop responding to treatment. Dana-Farber has one of only a handful of existing models of DIPG, and Drs. Beroukhim and Bandopadhayay are working with their colleagues to develop additional resources.



Rosalind Segal, MD, PhD, Ted Williams Chair; Co-Chair of the Department of Cancer Biology

In addition, the team is collaborating with **Rosalind Segal, MD, PhD,** to develop new models that better reflect the real-world population of patients. The tumor microenvironment—the area surrounding a tumor—can play a major role in the development, progression, and treatment of brain tumors, including DIPG. The complex interactions between tumor and environment make it challenging to develop accurate research systems that recapitulate patient tumors.

There are more than 300 cases of DIPG in the Untied States each year

Dr. Segal discovered an innovative method to overcome this issue that allows tumors to progress in the laboratory as they would in patients. This pioneering strategy enables investigators to closely study the growth of brain tumors and explore the effect of various drugs. Drs. Kieran and Ligon are now working with Dr. Segal to use this method to develop DIPG models and test drugs of interest. Through collaboration with other research centers, the team is also expanding access to DIPG tissue samples and research models to ensure that scientists learn as much as possible about this rare cancer. Combined, these resources are helping investigators to expedite the identification of the most promising therapeutic candidates for further study and lead more informed clinical trials.

The blood-brain barrier is formed by tightly packed cells lining vessel walls that keep toxins and bacteria out of the brain

Breaking through the blood-brain barrier

As Drs. Kieran and Ligon and their colleagues test new drug candidates in preclinical studies, they must also learn whether these therapies can pass through the blood-brain barrier (see sidebar). While this layer protects the brain, it can also prevent certain drugs from entering—presenting a

challenge for investigators hoping to send therapeutic compounds to the brain. **Nathalie Agar, PhD,** has developed a sophisticated method for determining whether drugs can break through the blood-brain barrier, as well as how and where these therapies function once they arrive. Using novel technology, Dr. Agar is able to trace drugs as they travel through the body and develop clear images showing their movement out of the brain blood vessels and into the brain.

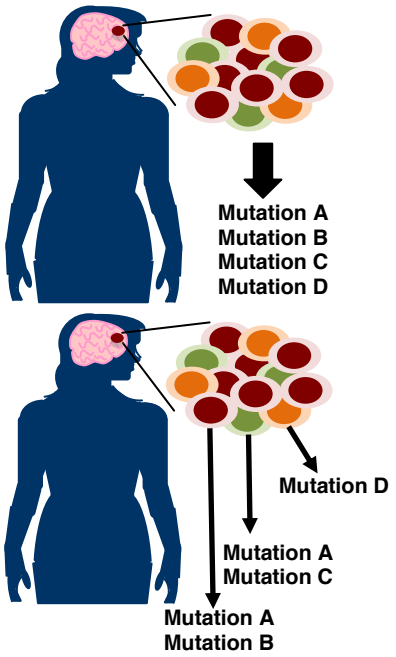
By preclinically screening potential drugs for their ability to cross the blood-brain barrier, investigators can learn which compounds should undergo further testing in clinical trials. This technique is more efficient and accurate than previous strategies, and produces clearer images due to a number of advances by Dr. Agar and her team. Drs. Kieran and Ligon are working with Dr. Agar to use this unique strategy to test drugs before incorporating them into patient-based studies such as the new biopsy trial.

Nathalie Agar, PhD

SINGLE CELL SEQUENCING: UNDERSTANDING HETEROGENEITY

As genomic studies are revealing, DIPG tumors have high genetic variability. In addition to different subtypes, scientists have discovered that cancer cells within one DIPG might contain different driver mutations. This diversity can make DIPGs challenging to treat: When adjacent cancer cells are caused by different alterations, multiple drugs are likely needed to destroy all types of tumor cells. Treatment with a single drug might only impact that particular cell type and allow others to continue growing.

To understand more about the specific mutations within individual DIPG tumors, Drs. Beroukhim and Bandopadhayay are applying a single cell sequencing method (see sidebar) that was developed at Dana-Farber by Drs. Ligon and Beroukhim in collaboration with **Matthew Meyerson, MD, PhD**. The team first tested this technique in glioblastoma, a brain tumor with similar complexities and treatment challenges as DIPG. Drs. Beroukhim and Bandopadhayay are now adapting this strategy to learn how DIPG cells work together to cause tumor growth, and to pinpoint combinations of treatments that might be more effective against these diverse cells.



Top: **Bulk analysis may reveal the presence of multiple mutations within a sample, but it does not reveal how those mutations are distributed in sub-populations of cancer cells within the tumor.**

Bottom: **Single-cell analyses allow scientists to identify tumor sub-populations bearing distinct combinations of mutations.**

THE POWER OF PHILANTHROPY

Your generous support is empowering Drs. Kieran and Ligon to lead innovative scientific and clinical studies to advance our understanding of DIPGs. Discoveries made in Dana-Farber laboratories are advancing the field and enabling our investigators to uncover novel therapeutic targets and evaluate potential treatment strategies. As we continue to make progress against this disease, we thank you for your partnership.

Report written by Brittany Flaherty.

FOR MORE INFORMATION

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