DANA-FARBER
CANCER INSTITUTE

PROGRESS UPDATE

Evan T. Mandeville DIPG Research Fund

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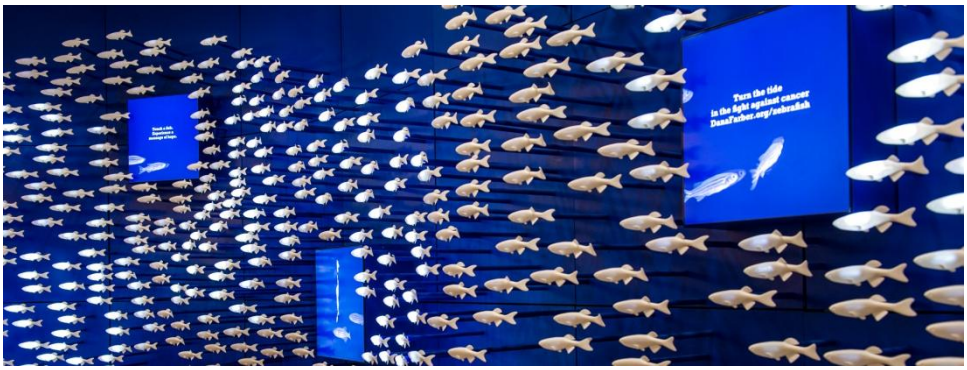
EXECUTIVE SUMMARY

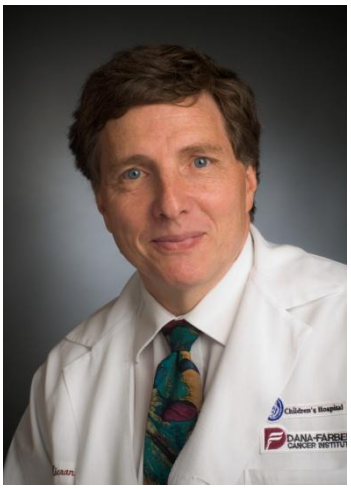
Since its founding in 1947, Dana-Farber Cancer Institute has been dedicated to advancing pediatric cancer research and providing the finest, cutting-edge care. Thanks to new opportunities afforded by genomic analysis and other advances, novel treatments have dramatically increased childhood cancer cure rates, representing one of the major success stories in cancer treatment. Our physician-scientists are continuing to leverage recent innovations to propel groundbreaking research, with the ultimate goal of improving outcomes and minimizing the potential long-term effects of treatment for pediatric neuro-oncology patients.

Mark Kieran, MD, PhD, director of the Pediatric Neuro-Oncology Center, is leading exemplary research in the Stop & Shop Family Pediatric Brain Tumor Clinic to uncover the genetic underpinnings of these malignancies and expose new opportunities for targeted therapeutic intervention. In parallel, **Peter Manley, MD,** director of the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic, is conducting an array of unique studies aimed at helping survivors manage the late effects of cancer treatment and improve their quality of life.

This report highlights the Center's exciting recent progress, including the development of a zebrafish model of AT/RT (page 3), the discovery of novel mutations in diffuse intrinsic pontine gliomas (page 5), and a study of long-term survivorship in low-grade gliomas (page 8). Your investment in this work is accelerating critical discovery science and clinical investigations, and we thank you for your support.



Scientists have determined that the gene functionality of zebrafish (above) is remarkably similar to that of a human gene. Dana-Farber researchers use this excellent model of human disease to identify the genes responsible for many forms of cancer and potential strategies to develop targeted therapies.



Mark Kieran, MD, PhD, director of the Pediatric Neuro-Oncology Center

Peter Manley, MD, director of the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic

ADVANCING RESEARCH FOR RARE PEDIATRIC BRAIN TUMORS

New clinical trials and collaborations in AT/RT

Dana-Farber investigators are global leaders in the effort to improve the understanding and treatment of atypical teratoid rhabdoid tumors (AT/RT). **Susan Chi, MD,** director of Dana-Farber's Pediatric Brain Tumor Clinical Trials Program, is leading important AT/RT studies that are helping to inform critical treatment advances. In 2009, Drs. Chi and Kieran helped to test a novel, intensive treatment regimen for children with AT/RT that resulted in the highest ever survival rates. Building on this work, Dr. Chi is designing a new, international clinical trial to examine the impacts of high dose chemotherapy on newly diagnosed AT/RT patients.

Susan Chi, MD, director of Dana-Farber's Pediatric Brain Tumor Clinical Trials Program

Working with **Charles Roberts, MD, PhD,** director of Dana-Farber's Research Program in Solid Tumors and an international leader in AT/RT research, Dr. Chi also recently launched an early phase clinical trial at Dana-Farber to test an inhibitor called LEE011. Children from the United States, France, and the United Kingdom are enrolled in the study, which aims to reveal the efficacy of this first potential targeted therapy for AT/RT.

For rare cancers like AT/RT, it is particularly important for Dana-Farber investigators to collaborate with other leaders in the field to expedite discoveries. In December 2013, Dr. Chi led an international meeting in Paris focused on advances in rhabdoid tumor research, which drew more than 70 basic and clinical investigators to inspire new solutions. Dr. Chi is also collaborating with other hospitals in Denver and Philadelphia to develop a national rhabdoid tumor registry. This tumor bank would provide researchers with access to more samples of AT/RT to expedite the development of novel therapeutic strategies.

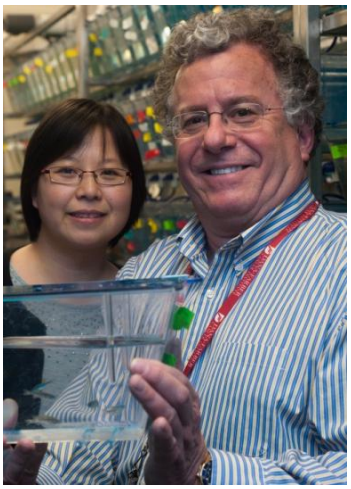
Charles Roberts, MD, PhD, director of Dana-Farber's Research Program in Solid Tumors

Developing a zebrafish model of AT/RT

Drs. Kieran and Chi are also working with **A. Thomas Look, MD,** and his team to develop a new research model of AT/RT in zebrafish. These tiny, translucent fish grow and reproduce quickly and are easy to study in large numbers, allowing researchers to translate preclinical studies into potential therapeutic strategies efficiently and effectively.

Cancer biologist **Felix Oppel, PhD,** recently joined Dr. Look's laboratory to take on the challenge of developing a zebrafish model of AT/RT. He aims specifically to uncover the role of the gene SMARCB1 in AT/RT development, building on work led by Dr. Roberts. Dr. Roberts, who has studied the biological mechanisms driving pediatric rhabdoid tumors for more than a decade, discovered that SMARCB1 is the singular mutation driving the development of AT/RT tumors. The zebrafish model will help researchers study the cellular origin—the mutated cells that initiate tumor formation—in AT/RT and unravel the precise mechanisms through which SMARCB1 leads to malignant tumor growth.

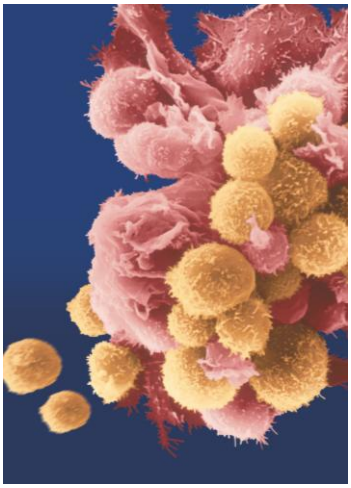
This new model may help to reveal potential targets and strategies for therapeutic intervention, broadening the options available for AT/RT patients. In addition, the SMARCB1 gene encodes a protein that is part of a specific cellular complex that regulates gene expression and has been implicated in 20 percent of all cancers. This work will, therefore, likely have important implications for other types of cancer. Furthermore, the successful development of a zebrafish model of AT/RT would also lay the foundation for novel preclinical models of other central nervous system cancers.



A. Thomas Look, MD, and his colleague with a zebrafish.

Leveraging the immune system to treat glioblastoma

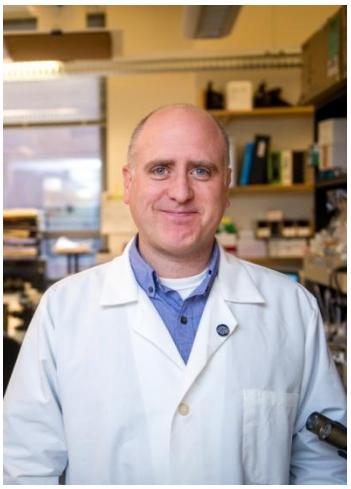
In the emerging field of cancer immunotherapy, which was named the 2013 Breakthrough of the Year by the esteemed journal *Science*, Dana-Farber is an international leader. Since the brain interacts with the immune system in a unique way, most immunotherapy advances in other types of cancer do not directly translate to treatments for neuro-oncology patients. Dr. Kieran is spearheading efforts to learn how leveraging the body's immune system can benefit pediatric brain tumor patients. Dr. Kieran is currently leading a clinical trial to test a promising immunotherapy vaccine in patients with glioblastoma multiforme, as well as anaplastic astrocytoma and ependymoma. This study could help to reveal immunotherapy's potential to treat brain cancer and inspire additional research focused on harnessing the power of the immune system.



Immune system cells (in yellow) attack a cancer cell.

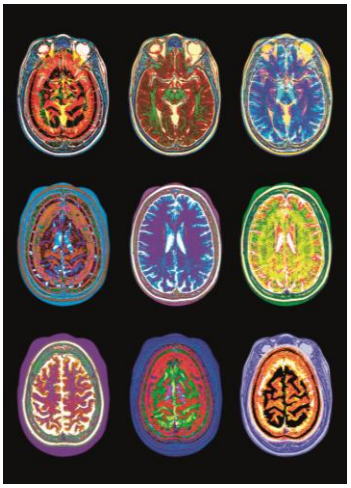
Uncovering new drivers of diffuse intrinsic pontine gliomas

Diffuse intrinsic pontine gliomas (DIPG) are the most aggressive brain tumors in children. Due to the difficulty of performing biopsies in the brainstem where DIPGs develop, researchers have historically had limited means to study the drivers of this disease. Dr. Kieran is currently leading studies to reassess the utility of taking biopsies in this region due to cutting-edge advancements in imaging, neurosurgery, and genetic profiling techniques. Dr. Kieran and his collaborators recently presented findings at the June 2014 International Symposium on Pediatric Neuro-Oncology from a national trial that demonstrated the increased safety of pretreatment biopsy for DIPG patients. This strategy may allow researchers to better understand the genetic underpinnings of DIPG and tailor therapies to each individual patient's cancer.



Keith Ligon, MD, PhD

Dr. Kieran also recently collaborated with pathologist **Keith Ligon, MD, PhD,** and published results in the April 2014 *Nature Genetics* about their discovery of several novel mutations that drive DIPG and other pediatric high-grade astrocytomas, aggressive tumors that have proven resistant to treatment thus far. Drs. Ligon and Kieran, in conjunction with their collaborators at McGill University in Montreal, Canada, sequenced 40 tumor biopsy samples—many of which were from patients with DIPG—and uncovered novel cancer-causing mutations, including mutations in the genes ACVR1, FGFR1, and P13K.



Digitally enhanced brain scans, acquired using magnetic resonance imaging.

Since promising drugs exist that may successfully target these mutations in other diseases, researchers may be able to repurpose these drugs to treat DIPG. Repurposing drugs across disease areas can expedite the development of new treatments since the drugs are less expensive to develop and are more likely to pass through clinical trials. The identification of these novel mutations with potential corresponding drugs expands the number of promising therapeutic targets for DIPG and other high-grade astrocytomas. This work also further justifies the importance of pretreament biopsies for delivering tailored therapies.

Developing targeted therapies for medulloblastoma patients

Even tumors that arise in the same type of tissue and look identical under a microscope may have important genetic differences that dictate their response to treatment. Building upon this knowledge, Dana-Farber investigators have identified several different subtypes of medulloblastoma, a fast-growing tumor that typically arises in the cerebellum. Because of the tumor's molecular heterogeneity, Dr. Kieran is leading several investigations to test drugs that target the specific mutations driving these subtypes, which could help improve patient outcomes and reduce toxicity.

Pratiti Bandopadhayay, MBBS, PhD

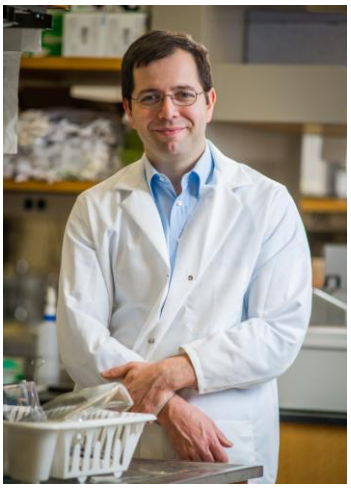
For instance, approximately 35 percent of medulloblastomas are caused by amplification of the gene Myc, and are highly aggressive and challenging to treat. Dr. Kieran recently collaborated with cancer biologists **Pratiti Bandopadhayay, MBBS, PhD,** and **Rameen Beroukhim, MD, PhD,** as well as chemical biologist **James Bradner, MD,** to test whether a compound developed by Dr. Bradner called JQ1 could help suppress Myc activity in medulloblastoma. They published findings in the February 2014 *Clinical Cancer Research* that demonstrated that JQ1 suppresses Myc expression in medulloblastoma cell lines and mouse models, reducing the growth of these cancer cells. They presented this promising data at the 2014 International Symposium on Pediatric Neuro-Oncology, and Dr. Kieran is preparing to launch a clinical trial to test a JQ1 prototype's efficacy in patients with Myc-amplified medulloblastoma.

Rameen Beroukhim, MD, PhD

Another 30 percent of medulloblastomas are characterized by the activation of the sonic hedgehog gene. Dr. Kieran is currently leading an international trial of the investigational drug LDE225, which has shown promise in targeting this gene. Dr. Kieran also published findings in the March 2014 *Cancer Cell* from a study that not only identified the key mutations driving this form of cancer, but also determined which mutations respond to a type of drug called a smoothened inhibitor. This study generated the first-ever validated test to identify patients who are most likely to benefit from these inhibitors. Dr. Kieran is now focusing on developing combination therapies to help to treat medulloblastomas that harbor the sonic hedgehog gene and are resistant to existing treatments.

Uncovering the drivers of craniopharyngioma

Pathologist **Sandro Santagata, MD, PhD,** studies the basic mechanisms of growth in slow-growing pediatric brain tumors. One subtype, craniopharyngioma, has proven particularly tenacious and difficult to treat due to its location near the optic system and the risk of damaging normal structures during surgery. These challenges have prevented major treatment advances for this disease for more than 30 years. As published in February 2014 in *Nature Genetics*, Drs. Santagata, Manley, and Kieran and their collaborators recently uncovered the key mutations driving adult and pediatric craniopharyngiomas. These discoveries may inform the development of more effective, targeted therapies and expand treatment options for patients.



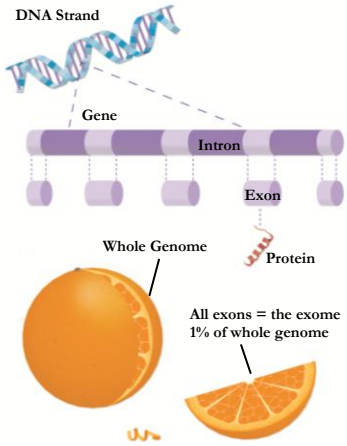
Sandro Santagata, MD, PhD

Using whole exome sequencing, the team discovered that a mutated gene called CTNNB1 is the primary driver of the subtype of craniopharyngioma that typically occurs in children. While inhibitors for CTNNB1 are not yet clinically available, researchers are testing compounds that may target this mutation. This study also identified a different mutant gene, BRAF, as the sole driver of 95 percent of craniopharyngiomas that typically arise in adults. Dr. Santagata and his collaborators are now testing existing BRAF inhibitors to see if they effectively reduce these tumors preoperatively. This important work has revealed two potential therapeutic targets, and could lead to new treatment options for adults and children with craniopharyngioma.

Identifying the genetic drivers of disease through Profile

For the first time, investigators can quickly scan entire tumor genomes to unveil the underlying causes of cancer. Dana-Farber scientists are leveraging these advances to test each patient's tumor for hundreds of cancer-driving mutations as a part of *Profile*—one of the most comprehensive patient-based cancer genomics projects in the world.

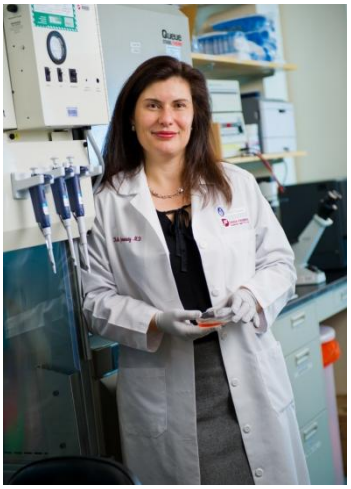
Profile, which was initially open to adult patients, expanded in 2013 to include pediatric patients. Already, more than 90 percent of the samples acquired thus far have come from patients with pediatric brain tumors, giving faculty in the Stop & Shop Family Pediatric Brain Tumor Clinic a unique opportunity to learn about the origins of these tumors. The ultimate goal of this flagship program is to help inform treatment decisions and tailor therapies based on



Since exons, collectively known as "the exome," make up the portion of the human genome that codes for proteins and contains most disease-causing variants, whole exome sequencing can be faster and more cost effective than genome sequencing.

Illustration by Meaghan Harrigan.

the precise genetic alterations of each child's cancer to help improve outcomes. Drs. Chi and Bandopadhayay and their colleague, **Katherine Janeway, MD,** presented their progress and early success in developing an Institute-wide precision cancer medicine initiative for pediatric neuro-oncology patients at the 2014 International Symposium on Pediatric Neuro-Oncology.



Katherine Janeway, MD

NEURO-ONCOLOGY OUTCOMES AND SURVIVORSHIP

As scientific advances yield more successful outcomes for pediatric patients, investigators are increasingly focused on the late effects of treatment and ways to improve long-term health in survivors. The Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic is one of the few survivorship programs dedicated exclusively to pediatric brain tumor survivors. Our physician-researchers are focused on supporting patients' long-term health and providing expert care to promote their emotional, social, and medical well-being. Investigators in this program—who specialize in neuro-oncology, neurology, and psychosocial oncology—are examining treatment plans and outcomes to help fine-tune care, minimize late effects, and ensure the best possible quality of life for survivors.

Long-term survivorship in low-grade gliomas

Previous studies have demonstrated that patients treated for pediatric low-grade gliomas (PLGG) have high 5-year and 10-year survival rates. Building on this work, Drs. Manley and Bandopadhayay recently led the first comprehensive study to examine longer-term outcomes in adult survivors of PLGG by examining data from more than 4,000 patients diagnosed between 1973 and 2008. The results, published in the January 2014 *Pediatric Blood & Cancer*, confirmed that former PLGG patients have excellent survival rates, even after 20 years. However, patients who received radiation as part of their treatment had lower long-term survival rates than those who did not. These findings, which have generated significant interest among pediatric low-grade glioma researchers, indicate that clinicians should exhaust other strategies before using radiation to treat this illness. Dr. Manley's work suggests that minimizing radiation will help reduce toxicities and improve long-term survivorship in patients treated for PLGG. Retrospective studies

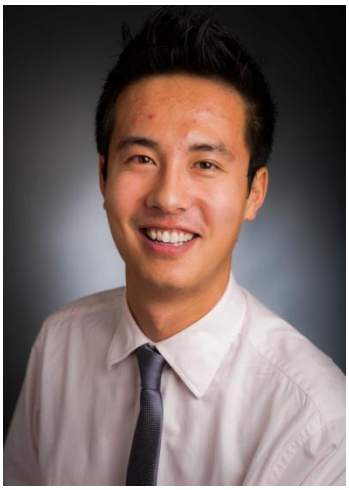
like this help to ensure that Dana-Farber is both pursuing new treatments as well as refining existing practices to continually improve outcomes.

Project REACH study alleviates insomnia and fatigue

Project REACH (Research Evaluating After-Cancer Health) is an ongoing project that involves conducting research surveys of cancer survivors to learn more about the long-term impacts of treatment. Under the leadership of **Christopher Recklitis, PhD, MPH,** director of research at the Perini Family Survivors' Center, Project REACH is currently examining the occurrence and impact of sleep dysfunction and fatigue on brain tumor survivors. Results to date have indicated that patients with certain tumor subtypes are more at risk for developing insomnia and other sleep-related issues, which can significantly impact quality of life in survivors.

Christopher Recklitis, PhD, MPH, director of research at the Perini Family Survivors' Center

Working with clinical psychologist **Eric Zhou, PhD,** Dr. Recklitis helped to adapt a cognitive behavioral program that helps young cancer survivors combat insomnia. The program requires adjustments to the survivor's sleep schedule, relaxation practices, and other behaviors related to sleep. Drs. Zhou and Recklitis shared their early results at the Canadian Cancer Research Conference in November 2013, which demonstrated that participating patients experienced a measurable decline in the severity of their insomnia.



Eric Zhou, PhD

STEPS program provides critical psychosocial support

Another important initiative at Dana-Farber that supports pediatric brain tumor survivors and their families is the Success through Education and Psychosocial Support (STEPS) program. Under the direction of **Cori Liptak, PhD,** the STEPS program connects survivors to their peers and alleviates the social isolation reported among many brain tumor survivors. Research conducted through this program suggested that this isolation is related to the long-term medical, cognitive, and psychosocial effects of treatment. The goal of STEPS is to help patients improve their mood and social skills, and learn ways to apply these changes to their lives and careers. Since its inception four years ago, the program has grown and now attracts as many as 60 participants at each monthly meeting, which includes dinner, team-building activities, and a support group or guest speaker.

HEARTFELT THANKS FOR YOUR SUPPORT

Your meaningful commitment in support of Stop & Shop Family Pediatric Brain Tumor and Neuro-Oncology Outcomes Clinics has helped to propel the progress described in this report. As we continue to pursue the finest treatments and deliver holistic care for our pediatric brain tumor patients and survivors, we are incredibly grateful for your partnership. On behalf of our patients and their families, thank you for your generous support of Dana-Farber's lifesaving mission.

Report written by Brittany Flaherty.

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