Dana-Farber Cancer Institute | The Jimmy Fund

PROGRESS UPDATE 2025

Stop & Shop Family Pediatric Brain Tumor Clinic and the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic

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Introduction

The Stop & Shop Family Pediatric Brain Tumor Clinic at Dana-Farber Cancer Institute delivers cutting-edge care to infants, children, adolescents, and young adults with brain and spinal cord tumors. Our dedicated clinicians and researchers are advancing innovative approaches to diagnosis and treatment that preserve survivors' quality of life. Your continued generosity fuels this work, empowering both the Stop & Shop Family Brain Tumor Clinic and the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic to provide exceptional care that meets the urgent challenges of cancer while supporting the long-term health and well-being of our patients.

Infant Brain Tumor Center

Led by **Susan Chi, MD**, the Infant Brain Tumor Program is driving ambitious research to deliver urgently needed therapies to our youngest patients.

TARGETING ATRT

Atypical teratoid rhabdoid tumor (ATRT), the most common malignant brain tumor in children younger than one year of age, remains difficult to treat. ATRTs are highly aggressive, and current treatment regimens employ intensive, multimodal approaches that include surgery, high-dose chemotherapy, autologous stem cell rescue, and/or radiotherapy. Despite these approaches, the odds of long-term survival remain under 50%, with survivors experiencing significant treatment-related side effects. At recurrence or progression, chances of cure are extremely limited, and no standard of care exists.

The **blood-brain barrier** is a layer of cells that separates the brain from surrounding blood vessels. It protects the brain by allowing only certain molecules, such as oxygen, to pass through—keeping out toxins and pathogens, but also blocking many cancer drugs that could otherwise treat brain tumors.

A major obstacle to treatment is the **blood-brain barrier**, which blocks many potentially effective therapies, while those that do cross it can also damage healthy brain tissue. Nanoparticle-based therapies, which have the potential to carry drugs across this barrier and deliver them directly to tumor cells, offer a promising solution for pediatric brain tumors.

Chi and **Pratiti (Mimi) Bandopadhayay, MBBS, PhD**, are leveraging advances in diffuse midline glioma (DMG), another aggressive brain tumor, to develop nanoparticle therapies for ATRT. They are identifying genes that promote nanoparticle uptake in tumor cells and testing a repurposed nanoparticle drug—liposomal doxorubicin—for safety and efficacy in ATRT models—laying the foundation for future trials.

Platform trials evaluate multiple treatments for a single disease under one overarching trial structure.

Additionally, **Tom Rosenberg, MD**, in partnership with Chi and the Pediatric Neuro Oncology Consortium (PNOC), has designed a **platform trial** to expedite the development of new therapies for ATRT. Rosenberg will lead the study's first arm, testing a novel combination of gemcitabine (IV chemotherapy) and paxalisib (oral targeted therapy) for patients with recurrent ATRT. This combination has already shown efficacy and synergy in ATRT cell lines and animal models.

The team is also investigating ways to make current chemotherapy agents for ATRT and other infant brain tumors more effective. In collaboration with international researchers, they are studying the mechanisms of resistance to existing therapies and identifying new drug combinations that could enhance and extend treatment responses in patients.

USING CEREBROSPINAL FLUID TO GUIDE TREATMENT

A **liquid biopsy** is a laboratory test that uses a sample of blood, urine, or another body fluid to look for cancer cells or small fragments of DNA, RNA, or other molecules released by a tumor. Because it does not require surgery, a liquid biopsy is less invasive than a traditional tissue biopsy.

Cerebrospinal fluid (CSF), which surrounds the brain and spinal cord, can carry fragments of tumor DNA—called circulating tumor DNA (ctDNA). With this in mind, Dana-Farber researchers are testing how **liquid biopsies** using CSF can improve diagnosis and monitor disease more precisely in pediatric brain tumors such as medulloblastoma and ATRT. Tracking ctDNA in CSF over time can help clinicians evaluate treatment response, detect residual disease, and identify recurrence earlier.

Currently, CSF from patients with malignant brain tumors is often examined for whole tumor cells. Although reliable and accurate, this approach has low sensitivity, meaning it can miss disease if too few tumor cells are present in the sample. However, liquid biopsies offer much greater sensitivity and may improve diagnostic accuracy, as well as real-time treatment decisions.

To evaluate this approach, Rosenberg and his team analyzed 120 samples from more than 50 pediatric patients with various malignant brain and spine tumors collected during routine clinical testing. Using state-of-the-art molecular assays to detect ctDNA, preliminary analyses showed accurate detection in most samples across a wide range of central nervous system (CNS) tumors. These findings suggest a more sensitive, less invasive, actionable strategy that could improve diagnosis, enable earlier detection of spread or recurrence, and inform real-time treatment decisions.

Mariella Filbin, MD, PhD
Research Co-Director, Pediatric Neuro-Oncology Program at Dana-Farber/Boston Children's Hospital

Karen Wright, MD, MS

Updates on High-Grade Gliomas

High-grade gliomas are the leading cause of cancer-related deaths in children and adolescents. There are few effective targeted therapies for these cancers and only about a fifth of children diagnosed with high-grade gliomas live more than five years.

AVAPRITINIB SHOWS POTENTIAL FOR PEDIATRIC HIGH-GRADE GLIOMAS

An international team of clinical collaborators, led by **Mariella Filbin, MD, PhD**, performed the first-ever clinical test of avapritinib—a targeted therapy already approved for use in treating certain adult cancers—in pediatric and young adult patients with a form of high-grade glioma. The results, published in *Cancer Cell*, showed that the drug was generally safe and resulted in tumor reduction visible on brain scans and clinical improvement in three of seven patients—all of whom had relapsed after multiple rounds of chemotherapy and radiation.

Avapritinib, a small molecule that can cross the blood-brain barrier, targets platelet-derived growth factor alpha (PDGFRA)—a protein overactive in some pediatric high-grade gliomas that leads to uncontrolled cancer cell growth. Preclinical research conducted by Filbin's team found that avapritinib reduced tumor growth in patient-derived tumor and animal models, inspiring a collaboration with clinical partners to treat a small group of patients with PDGFRA-altered high-grade glioma with avapritinib.

Building on promising results, the team is designing a larger clinical trial, led by Filbin and **Karen Wright, MD, MS**, to evaluate avapritinib treatment in pediatric patients newly diagnosed with PDGFRA-altered high-grade gliomas. Filbin's team will also investigate which genetic alterations within tumors can predict response to avapritinib, advancing efforts toward more personalized treatment strategies. In parallel, the team is developing combination therapies that pair avapritinib with other Food and Drug Administration (FDA)-approved drugs to enhance therapeutic benefit and prevent resistance.

CDK4/6 inhibitors are drugs that block two proteins (CDK4 and CDK6) that drive cell division. By slowing this "growth" signal, they help stop tumor cells from multiplying, and are often used alongside hormone therapy for certain types of breast cancer.

ADOLESCENT GLIOMA SUBTYPE RESPONDS TO CDK4/6 INHIBITOR

In another study, Filbin and collaborators found early signs that a class of existing cancer drugs called **CDK4/6 inhibitors** could work against a specific

Robbie Majzner, MD

CRISPR is 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.

subtype of pediatric high-grade glioma: H3G34R/V-mutant diffuse hemispheric glioma (DHG-H3G34). This aggressive cancer typically occurs during adolescence and accounts for approximately 15–20% of all childhood high-grade gliomas.

By closely examining tumor cells, Filbin discovered that these cancers resemble abnormal, immature neurons more than previously thought. Using a **CRISPR** screen to systematically deactivate genes across the human genome, the researchers identified several vulnerabilities unique to these neuron-like tumor cells—most notably CDK6, a key regulator of cell growth. In lab models, three CDK4/6 drugs were able to cross the blood-brain barrier, with ribociclib showing the strongest effect at slowing tumor growth and extending survival. Because no public repositories exist for this rare form of brain cancer, all patient-derived samples tested were obtained from patients treated at Boston Children's Hospital and at partner hospitals in Vienna, London, Rome, Hamburg, and Munich.

These findings, published in *Cancer Cell*, have already translated to patient care: a 13-year-old with twice-relapsed disease who had no remaining options experienced 18 months without tumor progression on ribociclib. A global clinical trial is now being planned to test ribociclib earlier, at the time of diagnosis. While this drug alone is unlikely to be curative—it can sometimes slow tumor growth rather than eliminate it—researchers are developing combination treatments to boost its effectiveness.

"We are at a time when we are starting to see positive effects with one drug," said Filbin. "As with leukemia decades ago, where there was only little effect with one drug, we started layering on multiple drugs, and now we have a very high cure rate in kids with leukemia—that's our hope with these cancers."

CAR T-cell therapy is an immunotherapy approach in which immune cells are removed from a patient's blood, reprogrammed in the lab, and infused back into the patient to attack and destroy cancer cells. Dana-Farber is one of only a few cancer centers in the country certified to offer CAR T-cell therapy, which is approved to treat pediatric acute lymphoblastic leukemia and aggressive B cell lymphoma and mantle cell lymphoma in adults.

CAR T-CELL THERAPY COLLABORATION

For many pediatric patients with high-grade gliomas, traditional treatments like surgery, radiation, and chemotherapy alone are not effective, and immunotherapies that unleash the immune system have so far shown limited success. To advance new options, Filbin is partnering with **Robbie Majzner, MD**, to explore combination approaches using **CAR T-cell therapy** and targeted therapies. Filbin's lab provides expertise in target selection, surgical tissue procurement, and assay development, while Majzner's team guides CAR T-cell engineering and preclinical testing. This interdependence enables a robust translational pipeline from foundational biology through preclinical validation and clinical application.

Building on initial data, the team is planning a sequence of clinical trials to test CAR T-cell therapy in patients with high-grade gliomas. This upcoming trial, led by Majzner and Chi, will use an established therapeutic target, while subsequent trials will originate directly from the team's in-house preclinical discoveries—representing a fully translational bench-to-bedside pathway.

"Dana-Farber's capacity to execute this bench-to-bedside model is uncommon in pediatric oncology," said Filbin. "Few pediatric centers can match this depth, underscoring the distinctiveness and potential high impact of investing in this effort."

MAPPING THE BIOLOGY OF EPENDYMOMAS

Supratentorial ependymomas are aggressive childhood brain tumors that comprise several subtypes with very different behaviors, making them difficult to treat. In a comprehensive study, recently accepted for publication in *Nature*, Filbin and her team analyzed thousands of cells from multiple patient tumors using advanced tools that reveal the activity of individual cells, their location within the tumor, and their growth dynamics in real time.

Ependymal cells are specialized glial cells in the central nervous system that line the brain's ventricles and the central canal of the spinal cord. They play a key role in producing and circulating cerebrospinal fluid, which cushions and nourishes the brain. By forming a barrier between the brain and this fluid, ependymal cells help protect the brain while still allowing essential exchanges to occur.

They found that, across tumor subtypes, cancer cells often resemble two kinds of very early brain cells and then branch toward either nerve-like or **ependymal**-like paths. The tumors also displayed distinct internal structures, including organized regions shaped by low-oxygen zones and local "neighborhoods" where similar cell types clustered together.

Filbin discovered that normal brain cells in the tumor's surroundings can influence cancer cells to adopt more neuron-like characteristics. These neuron-like cancer cells mimic immature nerve cells in both appearance and movement patterns—traits that enable them to migrate more easily and be better able to invade nearby brain tissue. This subgroup of tumor cells was both fast-growing and mobile, suggesting it may drive spread and expansion. Another cell type was more stationary but divided fast.

By linking what cancer cells are, where they live in the tumor, and how they behave, the study provides a clearer picture of why these tumors differ from one child to another. These insights point to new treatment strategies—such as targeting low-oxygen zones and the signals exchanged between tumor and normal brain cells—and support more precise diagnoses and personalized therapies based on each tumor's unique biology.

Updates on Low-Grade Glioma Tumors and Rare Tumors

Pediatric low-grade gliomas are the most common brain tumors in children. Each year, thousands of children across the world are diagnosed with low-grade gliomas and face challenges—both from the tumors and the therapies used to treat them. Led by Bandopadhayay, the Pediatric Low-Grade Astrocytoma (PLGA) Program is exploring more effective, less toxic treatments for children with low-grade brain tumors.

FGFR ALTERATIONS IN LOW-GRADE GLIOMAS

Led by Chi and Bandopadhayay, researchers studied over 11,000 brain tumors (gliomas) across children and adults and found that changes in FGFR genes, which help control cell growth, are relatively common. About 5% of all gliomas and nearly 9% of pediatric gliomas carry these FGFR alterations. The types of FGFR changes vary by patient age, tumor grade, and tumor type, with FGFR1 changes particularly linked to certain mixed nerve-and-glial tumors. In lab models engineered to include FGFR1 alterations, these changes activated major growth pathways (MAPK and mTOR), promoted tumor formation, and triggered nerve cell–related gene programs.

Importantly, these FGFR1-driven tumor cells were sensitive to broad FGFR inhibitors and drugs that block the MAPK pathway. Among pediatric patients treated with currently available FGFR-targeted medicines, most had disease that remained stable rather than shrinking. Together, these findings, published in *Nature Communications*, suggest that testing for FGFR changes could guide targeted treatments in pediatric gliomas, while also highlighting the need for better drug combinations or next-generation therapies to achieve stronger, more durable responses.

BREAKTHROUGH IN ETMR BIOLOGY

A groundbreaking study led by Filbin and **Volker Hovestadt, PhD**, has uncovered critical insights into the biology of embryonal tumor with multilayered rosettes (ETMR), a rare and aggressive brain tumor affecting young children.

ETMRs are driven by a unique genetic alteration known as the C19MC microRNA cluster, which keeps tumor cells in an immature and aggressive state. Through single-cell and spatial analysis of patient tumors, the research team discovered that ETMR cells mimic early brain development, forming a

hierarchy of stem-like and neuron-like cells. This cellular cooperation is crucial for tumor growth, with more mature cells providing signals that help stem-like cells thrive. Blocking either the signals or the receptors could exploit a key weakness in ETMR and may offer a new treatment approach.

Antisense therapies are short, lab-made pieces of DNA or RNA that bind to a cell's messenger RNA to block or adjust the instructions for making a protein—reducing harmful proteins or correcting faulty messages.

The study, published in *Nature Cancer*, calls for further clinical trials to test FGFR and NOTCH inhibitors—key signaling routes the tumor uses to grow—in ETMR patients and explores **antisense therapies** that turn off C19MC microRNAs. These findings offer a powerful rationale for more effective targeted therapies, potentially transforming the treatment landscape for children with ETMR. Early lab results are encouraging, and if confirmed in patients, these approaches could lead to more effective targeted treatments and better outcomes for children with this devastating disease.

Ana Aguilar-Bonilla, MD

MIRDAMETINIB FOR CERTAIN NF1-ASSOCIATED TUMORS

Neurofibromatosis type 1–associated plexiform neurofibromas (NF1-PNs) are painful, slow-growing nerve tumors with few treatment options. **Ana Aguilar-Bonilla, MD**, led Dana-Farber's participation in a large, mid-stage clinical trial at multiple hospitals to test an oral drug called mirdametinib, a **kinase** inhibitor, in 58 adults and 56 children whose tumors were causing significant problems. Tumor size was tracked by MRI, and a response meant the tumor shrank by at least 20% on two scans in a row.

Kinase is a type of enzyme that is commonly targeted in cancer therapy.

During the main treatment period, 41% of adults and 52% of children met this response goal. On average, tumors shrank by about 40%, with some patients seeing very large reductions. Importantly, both adults and children reported early and lasting improvements in pain, manageable side effects, and overall enhanced quality of life. As the largest trial of its kind in NF1-PN to date, these results, published in the *Journal of Clinical Oncology*, suggest mirdametinib can meaningfully shrink tumors and reduce pain in both adults and children, pointing to a promising treatment option where few currently exist.

MEK inhibitors are a type of targeted therapy that block proteins called MEK1 and MEK2, which help control cell growth and survival. By blocking these proteins, the drugs can slow cancer cell growth and, in some cases, cause cancer cells to die.

Next, Aguilar-Bonilla is developing a clinical trial for patients with NF1-PNs using a combination of **MEK inhibitors** and cabozanitib—drugs that block different tumor growth signals—to determine if they may shrink tumors more effectively, slow regrowth, and relieve symptoms like pain, pressure, and limited movement—improving daily function compared with one drug alone.

Psychosocial Support and Advocacy

Dana-Farber's **Pediatric Neuro-Oncology Outpatient Psychosocial Care Program** offers pediatric patients and their families a range of personalized, integrated services from diagnosis and treatment into survivorship, ensuring that they feel supported mentally, emotionally, and socially at all stages.

EXPANSION TO MEET THE NEEDS OF MORE PATIENTS

The team, which consists of two psychologists—including full-time neuropsychologist **Emily Warren, PhD**—has expanded over the past year to include two social workers, **Marcella Mazzenga, MSW, LCSW**, and **Julianna Brody-Fialkin, LICSW, MSW, MPH**. This interdisciplinary team, which is also supported by two psychiatrists, meets weekly for case conferences, and this expansion and collaboration have improved access and satisfaction among the medical team, psychosocial staff, and families.

The team is engaged in quality improvement and research, including a grant proposal to develop group psychoeducation and connection for patients transitioning from surgery to surveillance, a historically under-followed cohort. Overall, expanded staffing and standardized processes are enabling comprehensive, timely, and coordinated psychosocial care for pediatric neuro-oncology patients and their families.

STANDARDIZED ASSESSMENT OF ALL PATIENTS

The program is moving toward psychosocial assessment for all patients on active treatment, with earlier engagement in the outpatient setting and closer collaboration across institutions, including Boston Children's Hospital. Standardized assessments are being implemented across disease teams to screen for behavioral health needs, such as suicide risk, mood, and anxiety, as well as to address sibling concerns, connect families to internal and community resources, facilitate peer connections, and link patients to disease-specific foundations. The approach emphasizes comprehensive care and regular reassessment, with intensity highest in the first one to two months post-diagnosis. Every patient on active treatment receives initial contact, and ongoing involvement is tailored to family preference, while a survivorship clinic provides psychosocial assessment annually.

As one example, a single social worker has managed 25 active follow-ups and a total caseload of 110 patients across active treatment and surveillance since January 2025.

SCHOOL ADVOCACY AND REENTRY

Another focus of the program is school advocacy and reentry. Social workers and other team members collaborate to attend school meetings, facilitate individualized education plans and symptom management, address bullying concerns, advise on school placement, and support communication with educators and peers. The team also advocates for safe school attendance when appropriate, emphasizing its importance for social and emotional well-being.

For needs beyond oncology care, such as pre-existing anxiety, autism spectrum disorder, or the need for intensive or in-home therapy, families are referred to community providers. Coordination is tailored to geographic constraints, with out-of-state patients linked to local services when telehealth options are limited.

The Impact of Your Philanthropy

Treating childhood brain tumors demands precision—therapies must target cancer while protecting a child's development and long-term quality of life. Achieving that balance requires deep insight into each tumor's biology. Dana-Farber physician-scientists are rapidly advancing targeted, less toxic approaches tailored to these complexities. Additionally, our efforts to address patients' psychosocial needs from diagnosis through treatment and survivorship are critical to the resilience and well-being of patients and families. Your support makes this work possible. We thank you on behalf of our patients and families for making these advances possible.

Report written by Caitlin Henault.

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