DECEMBER 2025

Clinical Trials at Weill Cornell Medicine

Recent, Current, and in the Pipeline

The Children's Brain Tumor Project is strongly committed to translate our lab breakthroughs into safe and life-saving therapeutic options for children battling brain cancer today. However, many clinical trials are stuck in the pipeline due to recent federal funding cuts and the administration's decision to dismantle the Pediatric Brain Tumor Consortium (PBTC), a vital research collaboration in which our team held leadership roles for more than a decade. Now more than ever, we rely on donor support to continue to drive and advance these important studies and provide new treatment options to children with brain tumors. Many of whom may otherwise have none.

TRIAL TITLE	STATUS	FOCUS/DESCRIPTION
Convection-Enhanced Delivery for Diffuse Intrinsic Pontine Glioma (DIPG)	COMPLETED AND PUBLISHED	Direct drug infusion into the brainstem to bypass the blood-brain barrier and improve precision therapy without systemic toxicity.
Tumor Biobanking for Drug Screening and Bioanalysis (ClinicalTrials.gov ID: NCT04852354)	ENROLLING	Biobanking study to enhance understanding of pediatric central nervous system (CNS) tumors, with the goal of developing improved treatments and identifying new therapeutic targets.
Intra-Arterial Drug Delivery for DIPG and Choroid Plexus Carcinoma (CPC) (ClinicalTrials.gov ID: NCT04994977)	ENROLLING	Targeted drug delivery through the brain's arterial system to maximize tumor impact and minimize side effects.
Laser Interstitial Thermal Therapy (LITT) for Low-Grade Glioma (PBTC ID: 062)	APPROVED BY NCI/CTEP	Minimally invasive, image-guided laser therapy that ablates tumor tissue while preserving healthy brain tissue.
Radioimmunotherapy for DIPG (Phase 1A/1B)	PIPELINE	Next phase for the previous successful trial using convection-enhanced delivery to release radioimmunotherapy agents directly into the tumor. SEE MORE ON PAGE 2.
Direct Drug Delivery of Unique CAR-T Cells for DMG	PIPELINE	Direct drug infusion of novel CAR-T cells into the brainstem to bypass the blood-brain barrier and improve precision therapy without systemic toxicity.
Targeted Drug Delivery for Craniopharyngioma	PIPELINE	Noninvasive ultrasound approach to open the blood-brain barrier using ultrasound, allowing drugs to get through with minimal systemic toxicity.
Focused Ultrasound for Low-Grade Glioma (LGG)	PIPELINE	Localized therapy designed to protect critical structures in the brain during treatment for this non-cancerous but persistent brain tumor.
Sonobiopsy for Diffuse Midline Glioma	PIPELINE	A novel diagnostic method that uses ultrasound to release tumor biomarkers for non-invasive testing.

TO LEARN MORE VISIT CHILDRENSBRAINTUMORPROJECT.ORG/CLINICALTRIALS

A Major Milestone for the Children's Brain Tumor Project: A First-in-Kind Therapy for Children with Diffuse Midline Glioma (DMG)

This year, our team reached a remarkable milestone: our new clinical trial evaluating 177Lu-DTPA-omburtamab delivered by convection-enhanced delivery (CED) in children with diffuse midline glioma (DMG) is now advancing to scientific review, the final step before regulatory submission.

This study builds directly on the pioneering work of Dr. Mark Souweidane's Phase 1 CED trial in DIPG, which proved that targeted, catheter-based delivery of therapy directly into the brainstem is both feasible and safe. The new Phase 1A/1B trial represents the next generation of that work by introducing a theranostic approach that uses the same tumor-specific antibody (B7-H3) with a modern, lower-toxicity radiation isotope, Lutetium-177, to deliver tumor-killing radiation precisely where it is needed.

Through a tiny surgically placed catheter, the theranostic radioimmunoconjugate will be infused directly into the tumor, with the study assessing safety, optimal dosing, and early efficacy in children whose tumors have not progressed after radiation therapy.

If successful, this trial has the potential to reshape the treatment landscape for DMG and offers new hope to families facing one of the most challenging pediatric brain tumors. We are proud to highlight this effort as one of the major achievements of the year and a critical step forward in bringing innovative therapies to children with brain cancer.

Right: Remembering Chad Carr. Dr. Souweidane talking with Chad, a beloved patient who participated in the original CED trial.

Federal Funding to the Pediatric Brain Tumor Consortium (PBTC) Comes to an End Resulting in Halted Clinical Trials

In March 2026, The National Cancer Institute (NCI) will end funding for the Pediatric Brain Tumor Consortium (PBTC), a network that has led groundbreaking early-phase clinical trials for children with brain tumors since 1999.

The PBTC has been the engine behind studies of novel therapies for the deadliest pediatric brain cancers, including diffuse midline glioma (DMG), ependymoma, and other high-risk tumors with almost no effective treatments. With funding cuts, enrollment in several critical trials has already been halted, including CAR T-cell therapy for ependymoma and a new minimally invasive laser ablation trial, both of which give great hope to families who may otherwise have no treatment options.

The consortium, an association of 16 academic centers and children's hospitals dedicated to pioneering trials for novel treatments for pediatric brain cancer, has directed its members to stop enrolling new patients and announced that it would not be eligible to apply for funding beyond March. The tragedy lies not only in the immediate disruption to clinical trials, but also the loss of the collaborative ecosystem that drives discovery. Pediatric brain tumor research is already severely underfunded and faces enormous barriers; dismantling a proven infrastructure like the PBTC will slow progress, fragment efforts, and ultimately cost lives.

Dr. Souweidane was recently quoted in the New York Times stating, "The thing that's intangible, that will never be able to be monitored, is the cross-fertilization, the collaboration, the idea making that happens in these groups."

This is a tremendous step backward. Children with brain tumors deserve more trials, more collaboration, and more innovation — not less.

We urge our community of families, advocates, policymakers, and donors to raise their voices, demand solutions, and support efforts that keep this momentum alive.

PEER-REVIEWED PUBLICATIONS IN 2025

Peer-reviewed papers that are accepted for publication are the gold standard for demonstrating merit for scientific findings. Before any results are shared with the world, they're examined line-by-line by independent experts who challenge the methods, pressure-test the data, and make sure the conclusions track accurately. It's a slow process, which can be frustrating, but it protects the integrity of the work and the progress that depends on it. Our 2025 peer-reviewed publications not only validate the significance and quality of our work, but also enhance our impact and contribution to the advancement of science.

- **NATURE BIOTECHNOLOGY - OCTOBER 2025** Pooled CRISPR screens with joint single-nucleus chromatin accessibility and transcriptome profiling. Yan RE, Corman A, Katgara L, Wang X, Xue X, Gajic ZZ, Sam R, Farid M, Friedman SM, Choo J, Raimondi I, Ganesan S, Katsevich E, Greenfield JP, Dahmane N, Sanjana NE.Nat Biotechnol. 2025 Oct;43(10):1628-1634. doi: 10.1038/s41587-024-02475-x. Epub 2024 Nov 21.
- **CHILD'S NERVOUS SYSTEM - OCTOBER 2025** Diffuse midline glioma with extra central nervous system metastases in the pediatric, adolescent, and young adult population. Giantini-Larsen AM, Garton ALA, Rivera M, Han R, Pisapia DJ, Sait SF, Karajannis MA, Greenfield JP, Bilsky MH, Newman WC, Souweidane MM. Childs Nerv Syst. 2025 Oct 7;41(1):306. doi: 10.1007/s00381-025-06903-4.PMID: 41055765
- **NEUROONCOLOGY PEDIATRICS - AUGUST 2025** MODL-10. Two novel patient-derived xenograft models for pediatric pineal tumors allow for the detection of cell therapy candidates. Carolina Cocito, Christopher Padilla, Alexandra Backlund, David Pisapia, Benjamin Liechty, Mark Souweidane, Nadia Dahmane, Jeffrey Greenfield Neuro-Oncology Pediatrics, Volume 1, Issue Supplement_1, ABSTRACTS FROM 2025 SNO PEDIATRIC NEURO-ONCOLOGY CONFERENCE August 2025, wuaf001.299
- **SCIENTIFIC REPORTS - JULY 2025** Single-dose radiotherapy is more effective than fractionation when combined with anti-PD-1 immunotherapy in glioblastoma. Cocito C, Branchtein M, Zhou XK, Gongora T, Dahmane N, Greenfield JP.Sci Rep. 2025 Jul 2;15(1):22910. doi: 10.1038/s41598-025-06909-7.PMID: 40596223
- **FRONTIERS IN IMMUNOLOGY - JULY 2025** Checkpoint antibody receptor modified ARMed CAR T circumvents the suppressive immunome in GBM. Cook DR, Boesteanu AC, Yin Y, Reid R, Roccograndi L, Dahmane N, Martinez-Lage M, O'Rourke DM, June CH, Johnson LA.Front Immunol. 2025 Jul 31;16:1579925. doi: 10.3389/fimmu.2025.1579925. eCollection 2025.PMID: 40821779
- **NEURO-ONCOLOGY ADVANCES - JULY 2025** Patterns of relapse in diffuse intrinsic pontine glioma after convection-enhanced delivery of 124I-omburtamab. Bander ED, Garton ALA, Pasquini L, Reiner AS, Yildirim O, Ilica AT, Donzelli M, Haque S, Souweidane MM. Neurooncol Adv. 2025 Jul 19;7(1):vdaf128. doi: 10.1093/noajnl/vdaf128. eCollection 2025 Jan-Dec.PMID: 40709014
- **NEUROONCOLOGY - MAY 2025** Designing a time-dependent therapeutic strategy using CDK4/6 inhibitors in an intracranial ATRT model. Martin B, Guadix SW, Sathian R, Laramee M, Pandey A, Ray I, Wang A, Davuluri R, Thomas CJ, Dahmane N, Souweidane M.Neuro Oncol. 2025 May 15;27(4):1076-1091. doi: 10.1093/neuonc/noae262.PMID: 39657117
- **JOURNAL OF NEUROONCOLOGY - MAY 2025** Financial toxicity in pediatric and adolescent neurosurgical oncology. Giantini-Larsen AM, Brown S, Reiner AS, Giandalone SD, Zappi K, Abou-Mrad Z, Khakoo Y, Dunkel IJ, Karajannis MA, Sait SF, Hoffman CE, Greenfield JP, Souweidane MM, Newman WC.J Neurooncol. 2025 May 12. doi: 10.1007/s11060-025-05056-3.
- **NEUROONCOLOGY - MAY 2025** Phase 2 trial of veliparib, local irradiation, and temozolomide in patients with newly diagnosed high-grade glioma: a Children's Oncology Group study. Karajannis MA, Onar-Thomas A, Lin T, Baxter PA, Boué DR, Cole BL, Fuller C, Haque S, Jabado N, Lucas JT Jr, MacDonald SM, Matsushima C, Patel N, Pierson CR, Souweidane MM, Thomas DL, Walsh MF, Zaky W, Leary SES, Gajjar A, Fouladi M, Cohen KJ.Neuro Oncol. 2025 May 15;27(4):1092-1101. doi: 10.1093/neuonc/noae247.
- **BIORxIV - APRIL 2025** Machine learning-predicted chromatin organization landscape across pediatric tumors. Gjoni K, Zhang S, Yan RE, Zhang B, Miller D, Resnick A, Dahmane N, Pollard KS. bioRxiv [Preprint]. 2025 Apr 2:2025.03.28.645984. doi: 10.1101/2025.03.28.645984.
- **COMMUNICATIONS MEDICINE - MARCH 2025** The radiogenomic and spatiogenomic landscapes of glioblastoma and their relationship to oncogenic drivers. Fathi Kazerooni A, Akbari H, Hu X, Bommineni V, Grigoriadis D, Toorens E, Sako C, Mamourian E, Ballinger D, Sussman R, Singh A, Verginadis II, Dahmane N, Koumenis C, Binder ZA, Bagley SJ, Mohan S, Hatzigeorgiou A, O'Rourke DM, Ganguly T, De S, Bakas S, Nasrallah MP, Davatzikos C.Commun Med (Lond). 2025 Mar 1;5(1):55. doi: 10.1038/s43856-025-00767-0.PMID: 40025245
- **NEUROONCOLOGY - FEBRUARY 2025** Phase 1 dose-escalation trial using convection-enhanced delivery (CED) of radio-immunotheranostic 124I-Omburtamab for diffuse intrinsic pontine glioma (DIPG). Souweidane MM, Bander ED, Zanzonico P, Reiner AS, Manino N, Haque S, Carrasquillo JA, Lyashchenko SK, Thakur SB, Lewis JS, Donzelli M, Cheung NV, Larson SM, Kramer K, Pandit-Taskar N, Dunkel IJ.Neuro Oncol. 2025 Feb 19:noaf039. doi: 10.1093/neuonc/noaf039. Online ahead of print.PMID: 39969230
- **SCIENTIFIC REPORTS - FEBRUARY 2025** Immunoglobulin superfamily 3 (Igsf3) function is dispensable for brain development. Cocito C, Xiang C, Huang M, Gongora T, Surana P, Davuluri R, Dahmane N, Greenfield JP.Sci Rep. 2025 Feb 23;15(1):6526. doi: 10.1038/s41598-024-79349-4.PMID: 39988603 Free PMC article.
- **NEUROONCOLOGY ADVANCES - JANUARY 2025** Therapeutic manipulation and bypass of the blood-brain barrier: powerful tools in glioma treatment. Giantini-Larsen AM, Pandey A, Garton ALA, Rampichini M, Winston G, Goldberg JL, Magge R, Stieg PE, Souweidane MM, Ramakrishna R.Neurooncol Adv. 2025 Jan 15;7(1):vdae201. doi: 10.1093/noajnl/vdae201. eCollection 2025 Jan-Dec.PMID: 39877748

Conferences and Awards

Presenting at and participating in research conferences are critical to fostering the exchange of ideas, enabling collaborations, and providing attendees with timely and significant updates in the field of pediatric brain tumor research.

Care for Rare ETMR and ATRT Strategy Forum
Presenter: Carolina Cocito–New Combinatorial Strategies for the Treatment of Embryonal Tumor with Multilayered Rosettes

Gliomatosis Cerebri International Conference
Co-Chair and Presenter: Dr. Jeffrey Greenfield–GC Registry and the Future of International Collaboration
Presenter: Michael Farid–Diffuse Gliomas

Pediatric Brain Tumor Research Network (PBTRN) hosted by Weill Cornell Medicine
Presenter: Dr. Taha Merghoub–Rewiring the Immune Response: A New Path for Pediatric Brain Tumors
Presenter: Michael Farid–Molecular Insights into Glioma

Congress of Neurological Surgeons (CNS) Annual Meeting
Presenter/Panelist: Dr. Mark Souweidane–Intro, Q&A, and Cases for Discussion during session on Advances in the Management of Pineal and Intraventricular Pathology in Children

14th International Pediatric Conference in Dubai hosted by KidsHeart Medical Center in affiliation with NewYork-Presbyterian Kids/Morgan Stanley Children's Hospital
Presenter: Dr. Mark Souweidane

Building a Robust, Multidisciplinary Clinical and Research Team

The greatest return on the investment from our donors, is in the people who are driving our research forward at the Children's Brain Tumor Project. Over 80% of our lab expenses go directly toward brainpower by compensating our employees and fostering an environment where innovation thrives. This investment pays dividends in multiple ways: the stability and longevity of our team, the volume and quality of groundbreaking science they produce, and the programs we build to inspire the next generation of neuroscientists.

This year, two of our long-time postdoctoral fellows were promoted to faculty (Instructor) positions—an achievement made possible by the years of dedication and expertise they cultivated in our lab. Our commitment to mentorship also continues through our summer programs, which now include a highly competitive internship for undergraduates and a unique week-long shadowing experience for outstanding high school students. These opportunities ignite curiosity and provide early exposure to the field.

Our team consists of three renowned principal investigators, two experienced instructors with a long track-record specific to pediatric brain tumors, a dedicated program director, a clinical trials manager, two department MDs working on research portfolios, two post-doctoral scientists, a research associate, three lab technicians, and a student fellow in computational biology. This doesn't include our clinical team who serve our patient population, nor does it include our partners. The reach of our team is wider than the confines of our own laboratory because most of our research projects are collaborative. We work closely with research teams in other departments at Weill Cornell, teams at the Weill Cornell Meyer Cancer Center, and multiple teams at other academic research institutions around the world.

Updates on Tumor Banking and Analysis

From June 25, 2020, through August 19, 2025, we consented and collected tissue from more than 250 pediatric patients affected by a variety of brain tumors. In 2024 alone, we collected tissue from 56 patients, 47 of which were from surgical biopsies or tumor resections, and 9 were from autopsies.

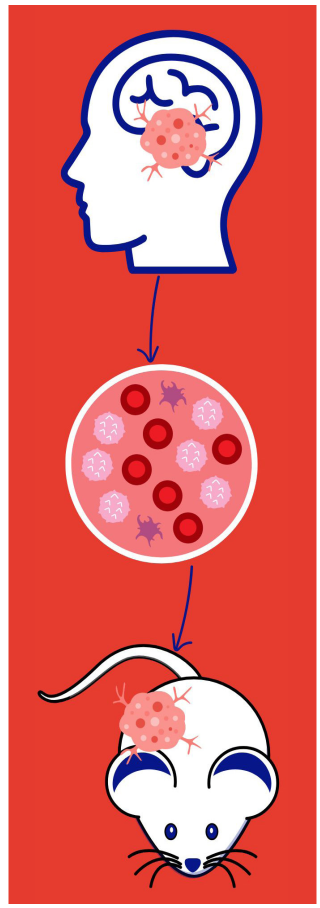
Having access to such tumor banking has given the lab the opportunity to develop numerous projects and collaborations which drive critical discoveries that lead to a better understanding of rare pediatric brain cancers. These insights are critical for developing more effective therapies for these devastating, often fatal diseases.

All our studies are built on strong and productive collaborations between our team, clinicians, and pharmacologists, with the goal of creating unique and powerful preclinical tools to tackle the most difficult-to-treat brain tumors.

In conjunction with our in-house CBTP tumor bank, we share with other labs including the Children's Brain Tumor Network (CBTN)—the largest biorepository of pediatric brain tumors in the world. We also integrate analyses with external datasets including the CBTN and public references such as GTEx, BrainSpan, and ENCODE—to produce robust, generalizable findings, validate signals across cohorts, benchmark against normal tissue, and prioritize therapeutic targets at scale. The following pages include various lab activities made possible by the extensive volume of tumor tissue collected and processed by our lab team, all of which constitutes the foundation for innovation and progress.

Working with Preclinical Models of Rare Pediatric Brain Tumors

With our brain tumor collection protocol, the CBTP lab generates novel and unique preclinical models including patient-derived cell lines and xenografts (PDXs) to model extremely rare pediatric brain tumors. Specifically, our team has generated three new cell lines for **Gliomatosis Cerebri (GC)**, a rare subtype of infiltrative high-grade glioma.



We have also generated PDXs for several rare embryonal tumors that will be essential tools to test toxicity and efficacy of novel therapeutical approaches both *in vitro* and *in vivo*. Embryonal tumors are very aggressive tumors often arising in very young children and include tumors such as **medulloblastoma, Atypical Teratoid Rhabdoid Tumor (ATRT), pineoblastoma,** and **Embryonal Tumor with Multilayered Rosettes (ETMR)**. For example, our lab generated two new stable ETMR cell lines, and three new PDX mouse models.

Over the past two years, we have collected tissue from three patients with high grade pineal tumors (pineoblastoma) and successfully established *in vivo* PDX models from the tissue, a feat that, to the best of our knowledge, no other lab has documented.

Furthermore, in the past year, the lab also successfully generated a PDX model and a cell line from a **high-grade glioma with a rare MN1:PATZ1 gene fusion**. The generation of preclinical models containing this specific fusion will likely help further our understanding of these gliomas and how to treat them.

For all the preclinical models we are developing, we also generate variants expressing luciferase to allow for *in vivo* monitoring of tumor growth, which is especially critical when testing for efficacy of therapeutical approaches.

ABOUT THE PEDIATRIC BRAIN TUMOR RESEARCH NETWORK

Despite the sheer size and strength of New York City's scientific community, research labs still end up working in silos. The Pediatric Brain Tumor Research Network (PBTRN) was established to change that by bringing every NYC-based academic institution to the same table to share major findings openly and collaboratively on a quarterly basis. The network consists of more than 100 invitees from Columbia University, Mount Sinai, Montefiore Children's Hospital, Memorial Sloan Kettering Cancer Center, New York University, and Weill Cornell Medicine. Weill Cornell was thrilled to host this event again on October 23, 2025.

Creating Organoids

Aligned with cell lines and *in vivo* PDX generation, we are currently working on incorporating the development of pediatric brain tumor organoids into our biobanking protocol. Organoids are a sophisticated form of cell culture with added potential; they are essentially miniature replicas of their source tissue.

Organoids allow for 3D structural modeling of the tumors in question, more accurately reflecting the degree of complexity and levels of interaction seen in real tissues and pathologies. These models bridge the gap between two-dimensional cell studies and trials in animals. These organoids can also be supplemented with additional cells that are contained in the tumor microenvironment such as endothelial or immune cells thus mimicking the more complex environment in which pediatric brain tumors arise and develop.

Questions that can be difficult to answer in non-human animal systems can be pursued with higher integrity in organoids. Organoids can be screened and tested for different treatment modalities, with results more closely reflecting response patterns in the patient from whom the organoids have been derived. Additionally, studies of the organoid unit itself can give insight into disease mechanisms, some of which may be targetable.

Using CRISPR-Based Screens

By leveraging CRISPR technology, a powerful gene-editing tool, we can identify modulators and target specific vulnerabilities in pediatric brain tumors. In essence, the technology allows us to identify which genes are required and sufficient for the survival of pediatric brain tumor cells, then CRISPR provides the tools to turn those genes "on and off" in brain tumor cells both *in vitro* and *in vivo* according to those findings.

Our lab has been working in partnership with Dr. Neville Sanjana's lab at Rutgers University to test methods that combine CRISPR screens with single cell sequencing readouts to identify the genetic perturbations that lead to transcription profiles linked to differentiated cells. This work was published late last year. (Yan et al, Nature Biotechnology 2024).

As a next critical step, the CBTP will integrate CRISPR technology into our robust precision medicine workflows, launching a new wave of functional screening that can inform individualized therapy and impact pediatric brain tumor patient outcomes.

Leveraging High Throughput Drug Screening

In addition to CRIPSR-based functional screens, we are continuing our collaborative projects with Dr. Craig Thomas (National Institutes of Health, National Center for Advancing Translational Sciences or NCATS); one of these projects for Choroid Plexus Carcinoma (CPC) has been published (see: https://doi.org/10.1016/j.jconrel.2023.04.016). As a result of this work, the first-ever Phase 1 clinical trial to treat children with CPC is now open for enrollment with a promising drug combination and innovative drug-delivery design (intra-arterial).

More recently we have tested 2,800 different drugs by high throughput drug screening (HTDS) on the new ETMR cell lines that we have generated, identifying promising candidates that may be used as single agents or in combination. Our screen discovered several FDA approved drug combinations which are effective against ETMR, and the best candidates were provided to our neurooncologist colleagues. We discovered a novel FGFR inhibitor to be effective when used both as single agent, and in combination with Topoisomerase and CDK inhibitors. The data obtained from this study were presented at the "ETMR and ATRT Strategy Forum" in Cancun in February 2025. This project was also partially funded by a grant from the Children's Cancer Research Fund (CCRF). The results are currently in preparation for publication. We have also collaborated with other institutions such as Quellos High Throughput Screening Core in Seattle to perform a drug screening on a case of a recurrent ependymoma tumor.

LOW-INTENSITY FOCUSED ULTRASOUND

Evaluating Risk of LIFU-MB in DMG

Low-Intensity Focused Ultrasound (LIFU) is a non-invasive technique using gentle sound waves to modulate brain activity, distinct from High-Intensity Focused Ultrasound, which uses stronger, higher energy levels. LIFU is very precise in targeting specific brain regions. Our team at the CBTP is particularly interested in exploring the potential benefits of LIFU in enhancing drug delivery to the brain by temporarily opening the blood-brain barrier (BBB) to allow larger drug molecules to reach inoperable brain tumors.

By combining the use of LIFU with microbubbles (MB)—a well-established technique using tiny gas-filled spheres that are safely injected into the bloodstream—we can temporarily increase the permeability of the blood-brain barrier. When the LIFU is applied to a specific area of the brain, the microbubbles in that targeted region expand and contract in response to the sound waves, creating tiny openings in the tight junctions of the blood vessel walls that allow therapeutic agents in the bloodstream to pass into the brain tissue temporarily.

This year, we have completed strong preclinical studies on the safety limitations and ideal parameters within which LIFU-MB can be leveraged in the treatment of diffuse midline gliomas (DMG), a devastating diagnosis with no proven therapeutic options.

LIFU-MB Liquid Biopsy Platform

The team also developed an LIFU-MB platform in patient-derived DMG mouse models that integrated timed blood and CSF sampling after opening the blood brain barrier (BBB). This allowed them to assess whether LIFU-MB can increase the detection of tumor-derived DNA and other biomarkers. Improving the accuracy of liquid biopsy findings via this sonobiopsy approach has the potential to provide great benefits. It may enable us to monitor tumor genetics, treatment response/resistance, and early detection of recurrence in real-time. Coupled with scans, these findings can help drive decisions on surgeries and allow for personalized, timely treatment adjustments, especially for hard-to-access tumors.

These favorable results have great potential to be leveraged in translational projects. We are sharing results from this LIFU-MB preclinical foundation to support multiple grant submissions and to define a clear path toward clinical translation for children with DMG.

COLLABORATING ON IMMUNOTHERAPY

CAR T-Cell Immunotherapy

CAR T-cell therapy reprograms a child's own immune cells (T-cells) to recognize and destroy tumor cells. For pediatric brain tumors, it offers hope by targeting cancer precisely, potentially improving outcomes while reducing the short- and long-term side effects of traditional treatments.

In 2025, in collaboration with the groups of Drs Jedd Wolchok and Taha Merghoub (respectively Director and Deputy Director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine) and Dr. Mohamed Hamieh (Department of Pediatrics, Weill Cornell Medicine), the CBTP conducted a series of preclinical survival studies with different CAR T cells to help identify effective drug delivery approaches for immunotherapy in the treatment of pediatric brain tumors such as Diffuse Midline Glioma (DMG). The study examined the results of systematically varied CAR T doses delivered intravenously and compared those results against the same doses delivered via locoregional methods including convection-enhanced delivery (CED).

This generated strong preliminary data regarding trafficking, efficacy, and neurotoxicity in the brainstem. The team is currently leveraging the preliminary findings to inform the design of a non-invasive, FUS-enhanced CAR T delivery strategy.

Expansion of Computational Analyses

As our precision medicine program continues to expand, computational analysis will remain at the core of translating complex biological data into actionable insights for patients. To illustrate this important and central aspect of our laboratory research, we present here one of these projects aiming at better understanding (and in the future targeting) the 3D genome organization in pediatric brain tumors.

Mechanisms initiating and driving childhood are complex and remain poorly understood. One potential mechanism may be attributed to variations in the genome including structural variants (SVs)—large scale changes in the genome—which are increasingly recognized as key drivers of oncogenesis by disrupting the organization of the 3D genome.

Although DNA is often depicted as a long, linear sequence; in reality, the genome is folded into a highly organized 3D architecture. This structure brings distant regulatory elements into physical proximity with their target genes, which is essential for precise gene expression during brain development. Disruption of this architecture by SVs can disrupt regulatory networks, leading to activation of cancer-causing genes or silencing of tumor suppressors. Sequencing to profile SVs and pinpoint the variants that influence genome folding and tumorigenesis has traditionally required extensive resources and time-consuming lab work.

To accelerate this effort, we collaborated with Dr. Katherine Pollard (UCSF-Gladstone Institutes) and Dr. Adam Resnick (Children's Hospital of Philadelphia and Childhood Brain Tumor Network) to identify and prioritize SVs most likely to disrupt 3D genome organization and contribute to tumorigenesis. Dr. Pollard's group developed Akita, an advanced machine-learning model that predicts genome structure disruptions caused by somatic SVs. In collaboration with the CBTN, we applied Akita to pediatric brain tumors, including ATRT, medulloblastoma, and diffuse midline glioma.

Our findings reveal that duplications and deletions cause the greatest disruptions to 3D genome architecture, and repeatedly affected regions were enriched for tumor-associated genes and transcriptional regulators.

Machine learning has given us a powerful roadmap that helps researchers prioritize focus on the variants that alter genome folding and gene regulation. This framework identifies high-confidence loci for experimental validation and provides a foundation for linking SV-driven regulatory changes to cancer pathogenesis that can lead to more precise targeted therapies.

The computational analyses project was supported by an NIH R03 grant (N. Dahmane, K. Pollard, and A. Resnick) and the Love4Lucas Foundation (N. Dahmane).

Collaboration with Biotech to Develop Novel Therapies for Pediatric Brain Tumors

Our team at the CBTP, led by Dr. Nadia Dahmane, continues to collaborate on a groundbreaking project with Dr. Neil Goldstein at SkunkWorx-Bio to develop peptide-drug conjugates (PDCs) as a novel therapeutic strategy for pediatric brain tumors. PDCs have emerged as a promising class of therapeutics due to their ability to deliver highly targeted, tumor-specific effects with exceptional precision.

Unlike conventional chemotherapies, which often cause systemic toxicity, PDCs concentrate the drug within tumor cells while sparing healthy tissue. This targeted approach not only enhances efficacy but also reduces adverse effects. Importantly, peptide-based therapeutics can outperform traditional small molecules, monoclonal antibodies, and even antibody-drug conjugates (ADCs), positioning them as next-generation biomolecules capable of overcoming long-standing challenges in cancer treatment.

Our current project focuses on novel PDCs targeting MYC and HDAC activity, two critical drivers of pediatric brain tumor biology, with a particular emphasis on Atypical Teratoid/Rhabdoid Tumor (ATRT). Early results are highly encouraging: PDCs designed to inhibit MYC effectively suppress MYC function and significantly reduce viability in ATRT cells, as well as in other tumor models characterized by MYC or NMYC overexpression and/or amplification.

Furthermore, preclinical *in vivo* studies in mouse models of human ATRT demonstrate promising activity in inhibiting tumor growth, underscoring the therapeutic potential of this approach. These findings suggest that PDCs could represent a transformative strategy for targeting oncogenic pathways that have long been considered "undruggable."

Given that MYC proteins are also deregulated in other aggressive pediatric brain tumors, including medulloblastoma and diffuse midline glioma, the potential impact of our discoveries extends well beyond ATRT, offering broad therapeutic relevance across multiple tumor types.

This work has been supported by an NIH STTR-R41 grant (to Drs. Goldstein and Dahmane) and a Childhood Cancer Research Seed Grant from the Pablove Foundation (awarded to Valentina Dal Pozzo, a postdoctoral fellow at CBTP).

Celebrating Ten Years of the Rudin Fellowship

Mentoring the Next Generation of Scientists in Neurosurgery and Neurooncology

"There are very few year-long research opportunities in neurosurgery, and this program offers a unique chance to immerse fully in translational science. I have always been driven to study cancer and hope to become a surgeon scientist. The fellowship is allowing me to explore that path in a meaningful way."

—Michael Farid, Third-year medical student at Weill Cornell and current Rudin Fellow.

FELLOWSHIPS ARE CRITICAL TO ADVANCING RESEARCH

Mentorship and hands-on study inspires careers in pediatric neurooncology, where there is a great unmet need.

Appointments allow students to achieve professional and independent success in driving research forward.

Work may result in peer-reviewed publications, findings from which may support new clinical applications for children in treatment for brain tumors.

FELLOWSHIP ADVISORY PANEL

Dr. Mark Souweidane – Program Director (Department of Neurological Surgery, Weill Cornell Medicine)

Dr. Ira Dunkel (Department of Pediatrics, MSK)

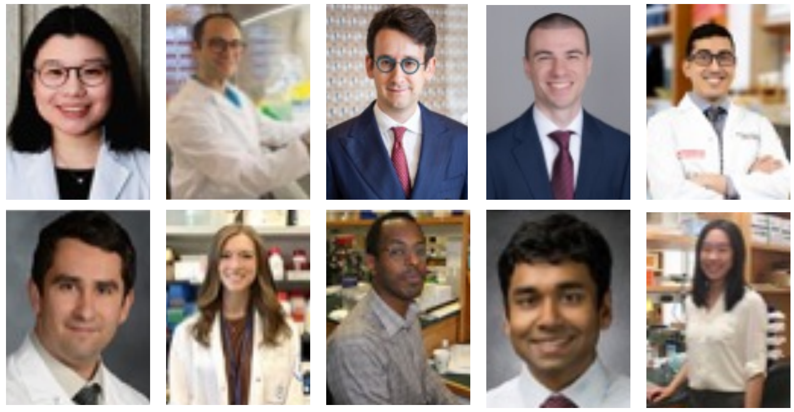
Dr. Jeffrey Greenfield (Department of Neurological Surgery, Weill Cornell Medicine)

Dr. Nadia Dahmane(Department of Neurological Surgery, Weill Cornell Medicine)

Dr. David Pisapia (Department of Pathology, Weill Cornell Medicine)

Dr. Rohan Ramakrishna (Department of Neurological Surgery, Weill Cornell Medicine)

Dr. Vivian Tabar (Department of Neurological Surgery, MSK)



The Weill Cornell Medicine Medical Student Research Fellowship in Pediatric Neuro-Oncology was established in 2015 through the generous support of the Jack and Susan Rudin Foundation and the Louis and Rachel Rudin Foundation. For ten years, the Children's Brain Tumor Project has selected one exceptional medical student annually to join our team and immerse themselves in research at the intersection of science and clinical care—an ideal pathway for exploring a career in pediatric neuro-oncology.

Each fellow takes a one-year leave from medical school to pursue intensive research on pediatric central nervous system (CNS) tumors. The program offers projects in basic, translational, and clinical research, with mentorship from faculty at Weill Cornell Medical College, Memorial Sloan Kettering Cancer Center, or The Rockefeller University.

Through hands-on investigation, interdisciplinary collaboration, and training in advanced methods, fellows develop the skills needed to bridge bench and bedside and to pursue careers that unite clinical practice with innovative research.

Since 2015, the fellowship has supported ten outstanding medical students from leading institutions, including Weill Cornell, Boston University, and Rutgers. Their work has led to peer-reviewed publications, conference presentations, and new collaborative initiatives. Seven alumni have pursued—or are applying for—neurosurgery training, and one has completed a Ph.D. in pediatric brain tumor research.

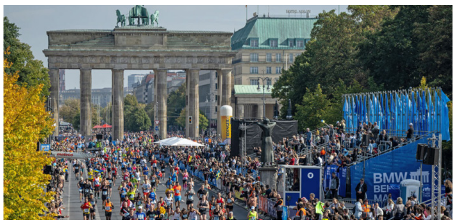
Year-long research fellowships in neurosurgery and neuro-oncology are exceedingly rare for medical students. Ours remains the only program dedicated specifically to pediatric neuro-oncology, and we aim to grow it to offer unparalleled opportunities, mentorship, and exposure to more students, strengthening the pipeline of future clinician-scientists committed to improving outcomes for children with brain tumors.

We are seeking renewed support to expand this transformative initiative, amplify its impact, and accelerate progress toward better treatments and cures. To explore partnership opportunities for you or your organization, please contact Cindy Campbell via email at cic2008@med.cornell.edu.

2025 News Highlights from the CBTP

"NO LAUGHING MATTER" FUNDRAISER HONORING NANCY GOODMAN RAISES $750,000

The seventh annual comedy night fundraiser honoring Nancy Goodman and featuring comedians Chris Distefano and Josh Johnson from the Daily Show, raised critical funds totaling more than $750,000 for the Children's Brain Tumor Project Lab. Visit nolaughingmatter2025.org.



TEAM CBTP EXPANDS ITS REACH

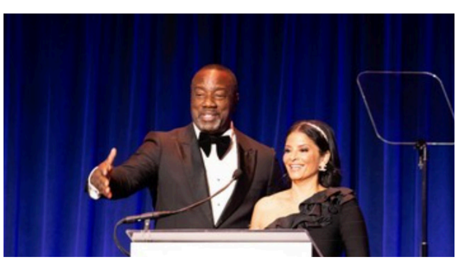
Our nonprofit continues to be a designated charity partner in the United Airlines NYC Half and the TCS NYC Marathon. In 2025, we expanded our race team access to include the World Major Marathons in Berlin and Tokyo! Visit teamcbtp.org.

TCS MARATHON TEAM AND UNITED AIRLINES HALF MARATHON BREAK RECORDS IN 2025

This year's marathon team raised more than $98,000, setting a new record for our organization since we first became an official charity partner of the TCS NYC Marathon in 2018. The United Airlines half marathon team also broke records raising almost $80,000!

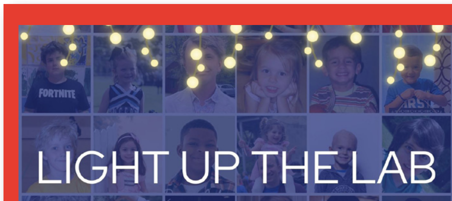
CBTP HELPS PREVIOUS PATIENT CREATE PEER-BASED SUPPORT PROGRAM

Founded by previous patient Isabelle Melnick, the Brain Tumor Patient Companionship Program is an independent program that provides support to pediatric brain tumor patients by pairing them with other patients who have had similar experiences.



CRISTIAN RIVERA FOUNDATION HOSTS 16TH ANNUAL CELEBRITY GALA AT CIPRIANI WALL STREET

Pictured here are hosts Darlene Rodriguez and Malik Yoba at the 16th Cristian Rivera Foundation (CRF) Celebrity Gala. The event celebrated hope, honored leadership, and fueled groundbreaking research for children facing DIPG. Our longest and largest donor, we are forever grateful to CRF.



LIGHT UP THE LAB WITH US

As 2025 comes to a close, the lab's annual "Light up the Lab" initiative **needs to raise $100,000** in support of the critical research underway at the CBTP lab. With every donation received, we light candles and string lights in honor of those who have been impacted by a brain or spinal tumor. LightuptheLab.org.