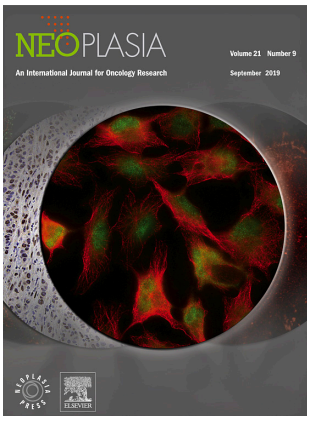
Spring 2023

Peer-Reviewed Article Published in Neoplasia

CBTP Team Studies the Nature of Leptomeningeal Dissemination Across Rare Pediatric Brain Tumor Types



A much-anticipated article led by Children's Brain Tumor Project (CBTP) postdoctoral fellows Carolina Cocito and Brice Martin, Principal Investigators Dr. Nadia Dahmane, Dr. Jeffrey Greenfield, and Dr. Mark Souweidane, in collaboration with partners at New-York Presbyterian/ Columbia University, was recently published in the April special issue on pediatric brain tumors of *Neoplasia*. The paper, "Leptomeningeal Dissemination in Pediatric Brain Tumors," explores the nature of leptomeningeal dissemination (LMD) across various rare pediatric brain tumor types.

Leptomeningeal metastasis, or leptomeningeal dissemination (LMD), is the presence of cancer cells along the meninges, which are the thin layers of tissue that cover and protect the brain and spinal cord. LMD in pediatric brain cancer patients is a poorly understood phenomenon that is inadequately categorized. Incidence rates, as well as prognosis, treatment, and screening practices, vary greatly depending on the primary tumor pathology. Although LMD is encountered most frequently in patients with medulloblastoma, reports of LMD have been described across a wide variety of pediatric brain tumor pathologies, which the paper addresses in detail.

Leptomeningeal metastasis may be present at the time a primary tumor is diagnosed, at the time of recurrence, or as primary LMD without the presence of a primary lesion.

The presence of LMD poses a great challenge in the treatment of almost every brain tumor type in children. Tumor cells in the cerebral spinal fluid develop select environmental advantages to survive the harsh, nutrient-poor, and turbulent environment of the CSF and leptomeninges, meaning the surviving tumor cells in the resulting LMD are difficult to address and more resistant to treatment.

This review comprehensively examines the state of LMD in all pediatric brain tumors, including medulloblastoma, craniopharyngioma, atypical teratoid rhabdoid tumors (ATRT), choroid plexus tumors, diffuse midline glioma (DMG), ependymoma, germ cell tumors, and diffuse leptomeningeal glioneuronal tumors. It emphasizes incidence, clinical presentation, and therapeutic management with the goal of providing novel insights into this therapeutically challenging disease. This review also highlights the crucial need for additional studies to better understand the mechanisms underlying LMD in all pediatric brain tumors along with improved diagnostic and treatment approaches, will help to improve the prognosis of children affected by primary brain tumors.

Pre-clinical Research on Choroid Plexus Carcinoma Published in May Issue of Journal of Controlled Release

Choroid plexus carcinoma (CPC) is a rare infantile brain tumor with an aggressive clinical course that often leaves children with debilitating side effects due to aggressive and toxic chemotherapies. Development of novel treatments for this disease has been extremely limited.

Dr. Souweidane's lab team conducted preclinical research on CPC led by post-doc Brice Martin, and in collaboration with Dr. Craig Thomas' group at NIH-NCI. They conducted the first high-throughput screen (HTS) on a human patient-derived CPC cell line and identified 427 hits highlighting key molecular targets in CPC. Furthermore, a combination screen with a wide variety of targets revealed multiple synergistic combinations that may pave the way for new therapeutic strategies against CPC.

Based on *in vitro* efficiency, drug ability to penetrate the central nervous system, and potential to translate into clinical applications, several drug combinations were selected and extensive experiments both *in vitro* and *in vivo* validated two combinations. The pharmacokinetic properties, meaning the processes by which drugs are absorbed, distributed, localized in the different organs, and excreted, were also studied to prove increased brain penetration with intra-arterial (IA) delivery over intra-venous (IV) delivery and demonstrated a higher CNS penetrance for the combination melphalan/elimusertib.

Upon the establishment of melphalan/elimusertib as the preferred combination, transcriptome analyses showed dysregulation of key oncogenic pathways (e.g. MYC, mammalian target of rapamycin mTOR, p53) and activation of critical biological processes (e.g. DNA repair, apoptosis, hypoxia, interferon gamma). Importantly, IA administration of melphalan combined with elimusertib led to a significant increase in survival in a CPC genetic mouse model.

In conclusion, this study is, to the best of our knowledge, the first that identifies multiple promising combinatorial therapeutics for CPC and emphasizes the potential of IA delivery for the treatment of CPC. We are now pursuing this study with the *in vitro* and *in vivo* validation of additional drug combinations.

Read an update on enrollment in the correlating clinical trial on page 3.

Dr. Jeffrey Greenfield Promoted to Professor of Neurosurgery in Pediatrics

We are thrilled to share that Jeffrey Greenfield, MD, PhD, has recently been promoted to Professor of Neurosurgery in Pediatrics. Dr. Greenfield is a board-certified neurosurgeon who specializes in pediatric neurosurgery and believes that compassionate clinical care, research, and continued education are all central to being the best possible neurosurgeon and physician.

As co-director of the Children's Brain Tumor Project, Dr. Greenfield led the development of novel precision medicine-guided brain tumor therapy. Dr. Greenfield's lab explores the potential of targeted oncologic therapy and discoveries based upon precision medicine techniques such as whole exome, whole genome, and RNA sequencing. Part of this research has been spearheading institutional biobanking efforts and centralizing the collection of rare tumor specimens. Collaborations with Craig Thomas, PhD at the National Institute of Health and the New York Genome Center have yielded exciting results from our comprehensive biobank of rare pediatric brain cancers, and his lab team is translating these findings into rapid high-throughput screening techniques to personalize care for children with rare brain tumors. Xenograft and organoid capabilities are being developed to ensure complete operating room to therapeutic continuity of all personalized medicine applications. His lab is also participating in an international effort to sequence rare pediatric brain tumors and define molecular signatures within this cohort of poorly understood tumors.

Teaching and education are also central to Dr. Greenfield's career in neurosurgery. As associate program director for the residency program in neurological surgery, he has won multiple teaching awards from the residents, and recently designed a novel curriculum to augment their seven-year training. He directs the medical student interest groups and the rotations for medical students on the neurosurgery service. Finally, he recently co-edited a textbook with a pediatrician designed to facilitate the education of primary care providers of children with the common neurosurgical conditions they may see in their practice.

2023 Broncos Field Hockey, Section 1 Champions

DO SOMETHING SPOTLIGHT

"The Good Hood" Demonstrates Continued Community Support

In the fall of 2022, the Bronxville varsity field hockey team collaborated with the Good Hood Club to fundraise for the Children's Brain Tumor Project at Weill Cornell Medicine. The Good Hood Club is a loungewear company that donates 50% of profits to children's oncology research initiatives.

The team raised a total of $4400 through its charity game fundraising event, which included proceeds from the sales of Good Hood Club specialty hoodies, a "Dollars for Goals" activity that collected donations for each of the seven goals scored during the charity game, and proceeds from a series of varsity and JV sponsored bake sales.

"The close-knit town of Bronxville has been directly impacted by pediatric brain cancer in many ways, and I continue to be inspired by how this incredible community continues to support the research at the Children's Brain Tumor Project," said Dr. Jeffrey Greenfield. "As a Bronxville resident myself, it is quite heartwarming to see another generation and group of inspired students thinking broadly and choosing this cause.

GC Conference Comes to New York

Weill Cornell Medicine is proud to host the fourth International Congress on Gliomatosis Cerebri Research on September 14-15, 2023. Gliomatosis cerebri (GC) is a rare pattern of brain tumor dissemination, for which there is no cure. Dr. Jeffrey Greenfield will chair the event, along with co-chairs Dr. Mariella Filbin, Boston Children's Hospital; Dr. Chris Jones, Institute for Cancer Research UK; and Dr. Andrés Morales, SJD Hospital, Barcelona.

The congress is organized by a dedicated event committee with the purpose of fueling research collaboration to address this rare disease type amongst global research leaders who share the goal of improving outcomes for GC patients. The two-day conference is financially supported by a united group of family-founded associations from around the world who have been impacted by this disease.

Several international research centers will be represented at the conference to continue the coordinated investigation of the characteristics of this rare disease with the goal of improving patient care and outcomes. These efforts were first set into motion in 2012 when the international congress on gliomatosis cerebri research first met at Curie Institute in Paris, France, and it continues to gain promising momentum.

Copyright 2023, Weill Cornell Medical College. All Rights Reserved.

Dr. Mark Souweidane Treats First Patient on Phase 1 Trial for CPC

Based on the pre-clinical findings highlighted on page one, Dr. Mark Souweidane recently designed the first-ever phase 1 clinical trial specifically for children with choroid plexus carcinoma (CPC), a rare brain tumor that often results in severe side effects from the current standard of care.

The trial adopts a surgical approach called intra-arterial (IA) drug delivery, in which Souweidane's team delivers a novel drug combination directly into the tumor bed of the choroid plexus (lining of ventricles) by using a catheter threaded through a major artery that provides direct access to the diseased tissue through this complex yet minimally invasive procedure.

The trial requires enrollment of six children to prove safety, the first of whom received treatment on May 4th. The procedure was a great success.

"Asking parents to allow their child to be the very first participant in a new clinical trial weighs on me tremendously," said Dr. Souweidane. "I felt like I couldn't breathe again until seeing this child come out of the procedure without complications, and thankfully I couldn't be more optimistic about the results."

Colleen Sanders Joins the Team in Critical New Role as Nurse Navigator

Colleen Sanders, MSN, RN, CNL, is the new Brain Care Clinical Coordinator in Pediatric Neurosurgery. The role is that of a navigator who helps guide our young neurosurgery patients and their families through the complexities of pediatric brain tumor care among other conditions. With deep knowledge of the care systems across both NewYork-Presbyterian/Weill Cornell and NewYork-Presbyterian/Columbia University, she provides a bridge across all resources and unparalleled clinical and emotional support to families.

In this new role, Colleen is provided with the resources and protected time needed to offer extraordinary care throughout a patient's journey. As a direct point of contact for patient families, she helps advocate for and educate them on what they need to know throughout the process.

"I'm a new mom myself, which has made my role in pediatric care even more purposeful," said Sanders. "I can relate to how difficult it must be for our patient families to navigate the reality of pediatric brain tumor care, and in this new role it is rewarding to have the opportunity to provide support and guidance during such a challenging experience for patients and their families. We never want anyone to feel lost as they are trying to seek care, and my hope is that I can be there for them and do my best to fill that gap."

Save the Dates - Upcoming Events in Support of the CBTP

OCTOBER 12 - "NO LAUGHING MATTER" COMEDY NIGHT, HONORING MERYL WITMER

After an incredibly successful event in 2022, our annual "No Laughing Matter" comedy night fundraiser will be held on Thursday, October 12th, returning to the New York Athletic Club, 180 Central Park South. This year, the Children's Brain Tumor Project is proud to honor Meryl Witmer, founder of Eagle Capital Management, LLC and mom to brain tumor survivor, Andrew.

The annual comedy night fundraiser draws 300 attendees from New York City and the surrounding areas to enjoy performances by famous comedians, including Jim Gaffigan in 2018. Other memorable performances included special Tony-Award winner, Freestyle Love Supreme in 2021, Jordan Klepper and Roy Wood Jr. from The Daily Show in 2022, and many more. This event is critical to the success of the lab.

Visit **nolaughingmatter2023.org** for more information.

NOVEMBER 15 - FOURTEENTH ANNUAL CRISTIAN RIVERA FOUNDATION CELEBRITY GALA

The Cristian Rivera Foundation (CRF) has donated more than $2 million to doctors and families of DIPG patients. CRF takes pride in the work they do, but they can't do this alone. They need your help.

We hope you will take the first step by joining CRF on November 15th when their highly-anticipated gala returns to Capitale in New York City to fundraise for DIPG research. We encourage you to support this important event by considering a ticket or table purchase. 100% of the donations you raise in support of your participation will go to medical facilities that conduct innovative research and clinical trials, increase public awareness of DIPG, and provide financial support to families.

For more information, visit **cristianriverafoundation.org/14thannualcrfgala.**

Make a donation today at ChildrensBrainTumorProject.org

From left: Brice Martin, Irene Bhuiyan, Carolina Cocito, Esteban Uceda, Rachel Yan, Corinne Smith, Valentina Del Pozzo, and Christopher Padilla

Interview with Summer Student Irene Bhuiyan

How did you hear about the Children's Brain Tumor Project?

I live in Atlanta, and I first heard about the CBTP through The Joshua Bembo Project (TJBP), a nonprofit organization dedicated to finding a cure for Gliomatosis Cerebri. I was inspired by the organization's purpose and their dedication to finding a cure for children's brain cancer.

Can you share some information about your education/career goals?

I am a third-year undergraduate student majoring in neuroscience. I am also in an accelerated degree program to get my master's degree in neuroscience. My primary goal is to become a research scientist, and I have an immense interest in medical and behavioral research.

Why did you decide to volunteer for the lab after your initial experience?

During my initial experience, I was able to develop a DNA extraction protocol. Ever since then, I fell in love with devising experiments and learning more about the research process. Along with this, I grew an interest in pediatric oncology research and I want to explore further and contribute more to the cause.

Please share one or two things that you learned during your time in the lab, so far.

Most of my experience in the lab surrounded the PCR (polymerase chain reaction) process. I became proficient in DNA extraction, PCR with a variety of primers, and gel electrophoresis. I also shadowed the research team and learned about a variety of crucial research techniques like western blots and cryostat sectioning.

Would you recommend this experience to others?

I would definitely recommend this experience to others. This experience taught me so much about the realm of scientific research beyond what can be taught in the classroom. Hands-on experience and learning from professionals in the field provided me with a lot of insight and knowledge that have proven to be invaluable.

Six CBTP Abstracts Accepted

Pediatric Neurooncology Research Conference

The CBTP will have six publication abstracts highlighted at the Society for Neurooncology's (SNO) 7th Biennial Pediatric Neuro-Oncology Research Conference June 22-24, in Washington, D.C. This conference encourages the sharing of ideas and offers attendees a state-of-the-art update in the field of pediatric brain tumor research. Our team has been selected to present their work through oral presentations and scientific posters selected by the abstract review committee, including:

1. Development of novel preclinical models and therapeutic strategies for ETMR.
2. Preclinical Validation of a Novel Therapeutic Strategy for Choroid Plexus Carcinoma.
3. Influence of low-intensity focused ultrasound on locoregional drug delivery to the brain.
4. Non-invasive diagnosis of brainstem gliomas in pediatric, adolescent, and young adult patients through cerebrospinal fluid cell-free DNA sequencing.
5. Minimally invasive diagnosis of diffuse leptomeningeal glioneuronal tumor (DLGNT) using cerebrospinal fluid cell-free DNA sequencing in pediatric and young adult patients.
6. Diffuse Midline Glioma with Extracranial Metastasis.

These abstract selections validate the importance and breadth of the great scientific work underway in our lab.

Undergrad Student Summer Research Program Funded

At the onset of 2023, the CBTP Foundation was presented with an unmet need, which was to increase the number of eager scientists working not only here in our lab at Weill Cornell Medicine, but in the greater field of pediatric brain tumor research. To that end, the CBTP Foundation made a five-year commitment in support of a designated educational fund for emerging leaders in research. The Children's Brain Tumor Project Summer Undergraduate Research Fellowship in Pediatric Neurooncology will take applications Nov 1, 2023 - February 15, 2024.

Each year, this new program will provide two undergraduate students enrolled in U.S. universities the opportunity to experience eight weeks of hands-on research experience working on projects related to basic neuroscience and pediatric neuro-oncology.

The main purpose of this program is to nurture the interest of students to pursue a PhD, specifically in neuroscience and pediatric brain tumor research. Providing support for student employment over the summer months is an important way to enhance the progress being made in the lab, while giving young minds the opportunity to learn under the mentorship of neuroscientists at Weill Cornell Medicine.

The competitive program requires a CV, student transcripts, 2-3 letters of recommendation, and a personal statement indicated previous research experience and long-term goals of the student. Applicants will be notified with a decision by mid-March 2024. For more information and to apply, visit **childrensbraintumorproject.org/summerinternship**.

Copyright 2023, Weill Cornell Medical College. All Rights Reserved.

CBTP wins "Accelerating Impact for Hard-to-Treat Cancers" Award from Childhood Cancer Research Fund in Recognition of Work on ETMR

The Children's Cancer Research Fund (CCRF) has recently awarded Dr. Jeffrey Greenfield and his team a competitive grant to study embryonal tumors with multiple rosettes (ETMR), a rare pediatric brain tumor that is difficult to treat and desperately needs more attention in the research landscape. The two-year project entitled, "The Development of Novel Preclinical Models and Therapeutics for ETMR," aims to generate unique ETMR preclinical models for testing novel drug combinations that will be identified in collaboration with Dr. Craig Thomas (NCI), with the goal of identifying targets that will lead to the design of new, safe, and efficient therapies for children with ETMR.

Currently, the cellular and molecular mechanisms underlying ETMR development is poorly understood. In fact, only one patient-derived ETMR cell line exists, and targeted therapeutics have not been developed due to absence of preclinical models. To expand knowledge of ETMR biology and accelerate novel therapeutics for ETMR, it is essential to develop preclinical models.

Our lab has successfully generated a novel patient-derived ETMR cell line from a resected patient tumor sample and created two patient-derived xenograft models. This exciting project will allow us to leverage our unique patient-derived cell lines in the identification of mechanisms driving ETMR development and progression, and to propose new therapeutic strategies that show more efficacy in addressing those mechanisms. Collaborators on this project are: Dr. Craig Thomas (NCI), Dr. David Pisapia (WCM Pathology), and Dr. Xi Kathy Zhou (WCM Population Health Sciences).

A Warm Welcome Coupled with a Bittersweet Farewell

Corinne Smith (left), and Charli Hertz (right)

Corinne Reflects on Her Time at the Lab

This fall, I will begin pursuing a PhD in neuroscience at The Icahn Medical School at Mount Sinai. I was drawn to the program for its focus on translational research and the rare opportunity to do clinical work with patients as a PhD student.

Because of my love of science and deep curiosity around development, I have always wanted to pursue a career in research and a PhD. I am fascinated by the nature versus nurture debate. How does our environment affect the way we biologically develop? How does our development affect us? What happens when these things go awry? I was given the opportunity to explore these questions in the context of brain development and pediatric brain tumors during my time with the Children's Brain Tumor Project (CBTP) as a research technician in Dr. Nadia Dahmane's lab. This opportunity has allowed me to develop foundational research skills and scientific reasoning. It solidified my passion for developmental biology as a means to approach questions surrounding diseases and disorders and allowed me to see this as an area of research I want to continue to pursue.

My involvement with the CBTP has expanded my knowledge and passion for translational research and largely influenced the type of PhD program I wanted to be a part of. I was especially touched during last year's family council meeting. It reinforced the *why* of what we do. It was inspiring to meet with so many of the family members, hear their stories, and see their deep interest and support in the work that we do. It became apparent to me the importance of translational research. As a scientist, it is easy to get lost in the day-to-day management of experiments. The experience served as a powerful reminder of the direct impact research can have on real peoples' lives and put translation research at the forefront for me.

I cannot wait to take this passion and energy inspired by the Dahmane Lab and the CBTP into my PhD. I am so grateful for my experience here and the way it has both impacted my scientific career and me personally.

— written by Corinne Smith

Why Charli Hertz Joined the CBTP

My name is Charli Hertz and I am the new Senior Research Technician in the lab of Dr. Jeffrey Greenfield, working for the Children's Brain Tumor Project (CBTP) laboratories at Weill Cornell Medicine. Although I was born in New York, I grew up in Miami Beach. I returned to Manhattan as soon as I could; completing my undergraduate degree at Barnard College in 2019.

Since an early age, I knew I wanted to help children with cancer. In Kindergarten my school participated in a St. Jude Math-a-thon fundraiser to help raise money for a cousin of our classmate who had just been diagnosed with Leukemia. I remember feeling a great sense of accomplishment being a part of a team, whose goal was to help someone in need. Our class received updates from St. Jude Hospital, where we got to meet patients, doctors, and virtually tour hospital rooms and MRI suites. After discovering an additional interest in the brain in a high school psychology class, I chose to attend Barnard College and major in Neuroscience. At Barnard, I learned the fundamentals of Neuroscience and explored cutting-edge research techniques during my laboratory experiences. Yet, I longed for the feeling I experienced as a kid, knowing that I was contributing to a greater goal of helping others. After graduation, I combined my technical neuroscience skills with this desire and began working at Memorial Sloan Kettering Cancer Center (MSKCC) studying adult glioma in the lab of Dr. Ingo Mellinghoff.

At the CBPT I will be assisting some of our post-doctoral fellows in on-going research projects and independently establishing research protocols that will benefit CBTP in the years to come.

I am honored to be a part of the CBTP. I am amazed at the more than forty families whose hard work and generosity made such a unique scientific endeavor possible. I am thrilled to be a part of a collaborative group harnessing a multi-faceted research approach, one in which the standard of care for rare and inoperable pediatric brain tumors can be changed.

— written by Charli Hertz

Make a donation today at ChildrensBrainTumorProject.org

Walk Don't Run. Life is a Journey.
Previous Patient Celebrates Bar Mitzvah!

Walker Lipton was only six years old when he was diagnosed with a brain tumor. Dr. Jeffrey Greenfield and Dr. Mark Souweidane were Walker's neurosurgeons who shared in his journey toward healing from medulloblastoma.

On April 29, 2023, Walker became a bar mitzvah. Addressing hundreds of family members and friends who came to celebrate this incredible milestone, Walker bravely reflected on his life journey in his own words.

"I feel very blessed that I am able to be here today with each and every one of you," he said. "I don't typically spend time dwelling on the past and why certain things happened to me, it is just something that I was chosen to face. I know when I do think about it, I wouldn't wish it on anyone. However, it is part of who I am and who I will always be."

Walker went on to say, "[My life journey] has taught me that I can overcome any obstacle. I should be proud of my accomplishments no matter how big or small they are. It taught me that I should never assume or take anything for granted."

All of us at the Children's Brain Tumor Project are indeed proud of everything Walker has accomplished. His mom, Tara Lipton, addressed his brave life journey beautifully in the letter she included in the event program, excerpts from which are included below.

"Facing difficult circumstances at a very young age with a level of courage and determination that still has me awestruck, my little ninja warrior learned just how precarious life can be. Walker knows that life is a gift that must be lived to the fullest, each and every day. Whether he is playing his heart out on the basketball court, studying the Torah as he prepared for his Bar Mitzvah, holding court at a table at Benihana, or passionately (aka stubbornly) arguing his point of view on any given topic, I am filled with pride as I witness Walker living life to the fullest, each and every day."

"This is a joy-filled milestone in Walker's life. I hope everyone who has been touched by his story will take with them a little bit of Walker's amazing spirit, by embracing his motto, 'Walk don't run. Life is a journey.'"

Dr. Souweidane Presents on DIPG/DMG in May

May is Brain Tumor Awareness Month, and it's no coincidence that Dr. Mark Souweidane has been very busy. On May 12 and 13, Dr. Souweidane participated in the **ChadTough Scientific Retreat** in Michigan, which is a forum for DIPG/DMG researchers to collaborate, especially on unpublished work. There he was paired with Dr. Sabine Mueller, Pediatric Neruo-oncologist at UCSF, to lead two breakout sessions on existing DIPG clinical studies and mapping out a future for additional clinical studies. On May 19 and 20, Dr. Souweidane arrives in Lexington, Kentucky, to participate in the **DIPG/DMG symposium**, an international medical research conference focusing on DIPG and DMG. This event brings together 200 researchers, doctors, foundations, and families in a collaborative environment to create and fund exciting new and innovative research initiatives specific to DIPG/DMG.

Copyright 2023, Weill Cornell Medical College. All Rights Reserved.