

USC BRAIN TUMOR CENTER

Report

Volume 3 • Issue 2

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From the Directors: GO GRAY IN MAY!!!

Almost everyone knows someone who has been affected by a brain tumor, either directly or as a caregiver. This Spring Issue of the USC Brain Tumor Center Newsletter coincides with **Brain Tumor Awareness Month** in May. Bringing Awareness about brain tumors is vital to everyone in the brain tumor and cancer community.

In this issue we wanted to take a moment and share a unique patient story that highlights the importance of our collaborative work at the USC Brain Tumor Center.

Our multi-disciplinary team continues to assess what more we can do for our patients and caregivers, and to drive towards a cure for brain tumors.

At the USC Brain Tumor Center, we are relentlessly striving to offer our patients access to new technologies that are safe and revolutionizing the way brain tumors are treated.

As we continue to make progress in our research and treatment efforts, we are proud to announce that **Dr. Josh Neman**, Scientific Director of the BTC received the **Fight Like the Averys FLAG Grant** from the **Uncle Kory Foundation**. This \$50,000 yearly grant is dedicated to funding pediatric brain cancer research.

The USC Brain Tumor Center will continue to offer access to expanding clinical trials and to further strengthen and hone our portfolio. Our patient caregiver support group is offered monthly via Zoom, and our team remains committed to providing and investigating the best possible care and treatment options for our patients. But we can't do it alone. Brain Cancer Awareness Month is an opportunity for all of us to come together to raise awareness about this devastating disease.

Whether it's through sharing our patients' stories, participating in a fundraising event, or simply talking to your friends and family about the importance of brain cancer research, every effort counts.

Thank you for your continued support of the USC Brain Tumor Center, and let's work together to make a difference in the fight against brain cancer

Heal on!

David D. Tran, MD, PhD
Co-Director, USC Brain Tumor Center

Gabriel Zada, MD, MS, FAANS, FACS
Co-Director, USC Brain Tumor Center

Josh Neman, PhD
Scientific Director, USC Brain Tumor Center



Brain Story

By Anna Zaich

My husband, Jon, has a nickname for me - **"BRAIN"**. The name is not for my brilliant intellect, but apparently stems from our UCLA pedigree as classmates, especially when I was discouraged or apprehensive about some horrendous paper or upcoming final exam.

Many, many years later, one of my family members suffered a stroke and it turned out to be caused by a congenital condition in the carotid arteries. So being the **"BRAIN"**, I decided to explore whether I might have this condition.

In the spring of 2009, I had my first ever MRI. It seemed to take forever, and my husband asked, "Why did you take so long?" As a novice

and not a medical **"BRAIN"**, I said, "I have no idea."

But two days later in our shared Irvine office, we found out why it took so long. The doctor told us that the good news was that I didn't have the family condition, but the bad news was that I had a brain mass and a lung mass inadvertently discovered during the MRI. Not a good combination and a total shock!

The next three weeks were a whirlwind of appointments, lung biopsy, memory and breathing tests and seeing if I could hop on one foot. At the conclusion of those three weeks, I was fortunate enough to consult with **Dr. Steven Giannotta**, Chair of Neurological Surgery

Continues on page 2

“Brain Story...” continued

at USC Keck. Thirty minutes before we saw Dr. Giannotta, we had just received the news that my lung mass was benign but would require surgical removal.

Dr. Giannotta’s demeanor changed dramatically upon that piece of news. My “BRAIN” tumor was a **meningioma** (non-malignant) but located in a tricky spot near my brain stem. He advised me to get MRIs on a quarterly basis to watch for any further tumor growth and that I could be followed by the local neurosurgeon.

So, the “BRAIN”’s life went merrily along, I never had any symptoms such as difficulty walking, lack of balance, talking or swallowing among other things. I regularly did my MRIs and was always told that there was no change in tumor size, so Jon nicknamed it “THE ROCK”. In 2017, after an MRI, my life changed with the news that the meningioma had grown and was now significantly pushing against the brain stem.

We headed back to USC Keck, as all UCLA “BRAINS” do, to see Dr. Giannotta for his opinion on this most recent news. I still had the gift of no symptoms as

the brain is quite remarkable in adapting to foreign objects apparently, but Dr. Giannotta said that there was no more waiting and watching. Action needed to be taken immediately.

A few weeks later after consults with **Dr. Eric Chang**, Radiation Oncology, and many others of the soon to be named USC Brain Tumor Center, we moved forward with getting me fitted with a mask and the “BRAIN” underwent five, approximately 60 minute, **CyberKnife** treatments over two weeks. The first four I was well dressed in my four brand new Bruin t-shirts, and Jon was busy passing around blue and gold UCLA stickers to all the Keck cast of support advisors, including the Keck pastoral chaplain.

Humor and prayer helped Jon and me to navigate the uncertain road including asking the physicist, who had to calculate the very sophisticated calculations, to ensure that the CyberKnife hit the “ROCK” and not the “BRAIN Stem”. I asked him not to pull an all-nighter before that math calculation.

Upon the last treatment, I wore full USC “regalia”. The CyberKnife had successfully converted my

“BRAIN” to be a **Trojan! Fight On!** Now we had to wait three months to see what was happening to the “ROCK”. My 3-month MRI came with the good news that **Dr. Cheng Yu**, the physicist, had done the math correctly and the CyberKnife hit the “ROCK” in the bullseye and was withering. The radiation didn’t hit my brain stem and the pressure on the brain stem no longer existed. The “BRAIN” no longer had to fear of any future body motor symptoms from a damaged brain stem.

As many years have gone by, we have enjoyed our many relationships with Keck and as a result, we have seen the birth of the USC Brain Tumor Center. I have become a member of the **Brain Tumor Advisory Council** as what I have termed my membership as a “**Patient Alum**”.

The passion, dedication, and collaboration of all the BTC professionals is amazing to experience. The compassion and guidance to all patients enduring a brain tumor diagnosis is to be praised.

This “BRAIN” and husband, Jon, are truly thankful!

USC Brain Tumor Center promotes Brain Tumor Awareness throughout the year

At the USC Brain Tumor Center our staff understands the worries that brain tumor patients and their families often face. To help make the journey easier, the center partners to provide multiple options that care for the whole patient — not just their diagnosis. It is our mission to provide unsurpassed clinical care to patients from all over the world and to cure brain tumors. An important part of our mission is to promote awareness. **Brain Tumor Awareness Month** is nationally recognized in the United States during the month of May, but raising awareness about brain tumors/brain cancer is our mission year-round.

The USC BTC raises awareness throughout the entire year, and we do it in various ways.

- The BTC partners with organizations who are involved in supporting the brain tumor community across the United States. These organizations include: **Brain Tumor Companion, The American Brain Tumor Association (ABTA)** and **Uncle Kory Foundation’s Tour de Pier**, to name a few.
- During the month of May our Center’s social media channels focus on promoting brain tumor awareness.
- During this important month we also partner with businesses in the community that provide support toward our mission of finding a cure, while promoting our cause.
- On the **USC Day of Support**, our University’s main community fundraising event (on May 4th), there is a dedicated spotlight for the USC BTC.
- We offer **Brain Health talks** throughout the community in person, via television and radio.

- On a quarterly basis we publish the **USC BTC Newsletter** which reaches over 1,000 readers that include, our patients, donors, physicians and partners and provides a summary of the latest advancements in research, clinical trials, and patient care
- Our Center offers a **monthly Patient Caregiver Support Group**.
- Our **Annual Research Retreat** is held in December. This retreat showcases the latest research, technologies, clinical trials, and treatments for all types of brain tumors, from leading scientists and clinicians from **Keck Medicine, Norris Comprehensive Cancer Center, Children’s Hospital Los Angeles** and **USC Keck School of Medicine**. This year the retreat will invite Brain Tumor Programs and Centers throughout Southern California. The retreat is followed by a poster session and a celebration of the work that has been done throughout the year.
- The USC BTC is supported by our **Advisory Council** that is comprised of dedicated and resourceful individuals with a primary focus on promoting the growth of the USC Brain Tumor Center. These amazing volunteers – many of whom have personal testimony with our incredible team – help lift the Center to new heights by offering their advice, their time, talents, and support in advancing the established goals of the Center.

Join us in the fight against Brain Cancer by raising awareness and bringing attention to the critical need to find and provide effective brain treatment options for those impacted by a brain tumor diagnosis.

Make a gift to the USC BTC today
<https://giveteto.usc.edu/?fundid=9251541035>

Cutting Cancer's Communication Cord in the Youngest Patients

USC Neuroscientist Josh Neman Receives \$50,000 Grant to Help Cure Pediatric Brain Tumors

By By Janice O'Leary

Four years ago when the **Scientific Director of the USC Brain Tumor Center Josh Neman, PhD**, gave a talk in Santa Monica for the **Pediatric Brain Tumor Foundation**, he met **Nohea Avery**, the mother of two children, **Kalea** and **Noah**, diagnosed with medulloblastoma—the deadliest kind of pediatric brain cancer, the very kind he studies. He had no idea then as he spoke to a room full of concerned parents and caregivers just how significant the Avery family would become to his work.

This past winter, a small but mighty charitable organization in Southern California called the **Uncle Kory Foundation (started by Mandy and Heath Gregory, a USC Marshall School of Business alum)** announced that Neman had won its first **FLAG award—its Fight Like the Averys Grant**, named for that same family he'd met—to support his research into **medulloblastoma**. The \$50,000 merit-award came as a surprise to Neman because he and his colleagues had applied for one of the organization's seed grants, not knowing the FLAG award was just being established.

"It's bittersweet to receive this grant," Neman said. "I'm so happy to get the award to do the work, but sad that it's under such unfortunate circumstances."

The ravages of medulloblastoma are especially devastating; the five-year survival rate is low, and for those pediatric patients who do make it, the chemotherapy and radiation used on their developing brains typically does permanent damage. Unfortunately, Kalea and Noah succumbed to the cancer, though they—and their parents—fought hard for years.

"I want to thank the Uncle Kory Foundation and the families who have made this funding possible," Neman said.

"We're a small organization," said **Renee Vachon, Director of Operations at Uncle Kory**. "So that means we must be very disciplined and thoughtful about the programs we support. We think funding innovative early research, which can lead to much larger awards, is the best way for us to make a difference."

Uncle Kory's scientific advisory board independently reviews all grants and, based on scientific and clinical potential, fund meritorious and promising projects. When Nohea Avery then reviewed the list of funded grants, she chose Neman to be the recipient of this first FLAG award. "Josh's research really intrigued her," Vachon said. "She is very passionate about funding research that will lead to better, safer treatments, specifically designed for children."

Neman understands the urgency to find novel, more precise treatments to battle medulloblastoma, both to improve the survival rate as well as to protect young brain tissue. To get there, he studies tumors' microenvironment in the brain and how the very nature of the brain can sometimes encourage and promote tumors to spread.

"We're finding out the normal and healthy cells of the body actually contribute a lot to tumor growth," he said. "Cancer cells hijack the

body and appear as a wolf in sheep's clothing, asking other cells to help them out."

In the case of medulloblastoma, rogue cancer cells left over after surgical resection of the tumor develop resistance to radiation and chemotherapy and become even more aggressive in their growth. They trick one of the brain's main chemical neurotransmitters and use that as fuel to then spread down the spinal cord, where any kind of treatment becomes especially risky.

As smart and tricky as medulloblastoma seems, that particular kind of tumor might have met its match in Neman and the USC Brain Tumor Center team, especially with the power of the Uncle Kory FLAG award to back their pilot study. His lab figured out which protein and chemical neurotransmitter the cancer manipulates and has identified a **new potential inhibitor of that protein called NEO216**, developed by USC neurosurgeon **Tom Chen**. Essentially, they hope to use NEO216 to sever the line of communication between the brain and the cancer cells' protein. No communication equals no hijacking of fuel, and thus, no growth. The rogue tumor cells would die out.

As a bonus, Neman hopes they can also use NEO216 to target and reduce the main tumor, making for a much safer and effective therapy, ultimately decreasing the suffering for pediatric patients on several fronts, increasing survival, and preserving their sensitive brains.

The grant will fund the pilot study to first test NEO216 in mice. If the results look as promising as Neman expects, then he and his team will take the next step of going into Phase I of human clinical trials, ultimately seeking FDA approval for this as a new treatment for medulloblastoma.

"Our preliminary data shows that this drug works, and that it really works," Neman said. He anticipates a Phase I trial could be as near as three to four years away. "We've made significant inroads, but we have to prove it still."

Vachon and the Uncle Kory Foundation believe in his work as well. "If we fund these early ideas," she said, "they lead to more grants and get to the bedside faster."

One way the organization raises its funds is through its **annual Tour de Pier bike ride in Manhattan Beach**. It has raised \$10.5 million to date through the event, which takes place this year on May 21. Neman plans to be there.

He's grateful for the collaboration of Chen and others in the USC Brain Tumor Center, including then-graduate student Vahan Martirosian, who was integral in the initial studies of the drug and gaining the grant funding.

While he's clearly passionate about his work at the center and is indeed fighting like the Averys against medulloblastoma, Neman said, "As a cancer researcher, I can't wait to be out of a job."



SELECTED PUBLICATIONS



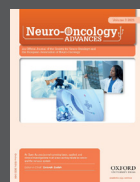
Executive summary from American Radium Society's appropriate use criteria on neurocognition after stereotactic radiosurgery for multiple brain metastases.

Milano MT, Chiang VLS, Soltys SG, Wang TJC, Lo SS, Brackett A, Nagpal S, Chao S, Garg AK, Jabbari S, Halasz LM, Gephart MH, Knisely JPS, Sahgal A, Chang EL. *Neuro Oncol.* 2020 Dec 18;22(12):1728-1741. doi: 10.1093/neuonc/noaa192.

Background: The American Radium Society (ARS) Appropriate Use Criteria brain malignancies panel systematically reviewed (PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses]) published literature on neurocognitive outcomes after stereotactic radiosurgery (SRS) for patients with multiple brain metastases (BM) to generate consensus guidelines.

Methods: The panel developed 4 key questions (KQs) to guide systematic review. From 11 614 original articles, 12 were selected. The panel developed model cases addressing KQs and potentially controversial scenarios not addressed in the systematic review (which might inform future ARS projects). Based upon quality of evidence, the panel confidentially voted on treatment options using a 9-point scale of appropriateness.

Conclusions: For patients with 2-10 BM, SRS alone is an appropriate treatment option for well-selected patients with good performance status. Future study is needed for those scenarios in which there was disagreement among panelists.



Clinical utility of comprehensive genomic profiling in central nervous system tumors of children and young adults.

Ji J, Kaneva K, Hiemenz MC, Dhall G, Davidson TB, Erdreich-Epstein A, Hawes D, Hurth K, Margol AS, Mathew AJ, Robison NJ, Schmidt RJ, Tran HN, Judkins AR, Cotter JA, Biegel JA. *Neurooncol Adv.* 2021 Feb 25;3(1):vdab037. doi: 10.1093/oaajnl/vdab037.

Background: Recent large-scale genomic studies have revealed a spectrum of genetic variants associated with specific subtypes of central nervous system (CNS) tumors. The aim of this study was to determine the clinical utility of comprehensive

genomic profiling of pediatric, adolescent and young adult (AYA) CNS tumors in a prospective setting, including detection of DNA sequence variants, gene fusions, copy number alterations (CNAs), and loss of heterozygosity.

Methods: OncoKids, a comprehensive DNA- and RNA-based next-generation sequencing (NGS) panel, in conjunction with chromosomal microarray analysis (CMA) was employed to detect diagnostic, prognostic, and therapeutic markers. NGS was performed on 222 specimens from 212 patients. Clinical CMA data were analyzed in parallel for 66% (146/222) of cases.

Conclusions: Our results demonstrate the significant clinical utility of integrating genomic profiling into routine clinical testing for pediatric and AYA patients with CNS tumors.



Medulloblastoma uses GABA transaminase to survive in the cerebrospinal fluid microenvironment and promote leptomeningeal dissemination.

Martirosian V, Deshpande K, Zhou H, Shen K, Smith K, Northcott P, Lin M, Stepanosyan V, Das D, Remsik J, Isakov D, Boire A, De Feyter H, Hurth K, Li S, Wiemels J, Nakamura B, Shao L, Danilov C, Chen T, Neman J. *Cell Rep.* 2021 Jun 29;35(13):109302. doi: 10.1016/j.celrep.2021.109302.

Medulloblastoma (MB) is a malignant pediatric brain tumor arising in the cerebellum. Although abnormal GABAergic receptor activation has been described in MB, studies have not yet elucidated the contribution of receptor-independent GABA metabolism to MB pathogenesis. We find primary MB tumors globally display decreased expression of GABA transaminase (ABAT), the protein responsible for GABA metabolism, compared with normal cerebellum. However, less aggressive WNT and SHH subtypes express higher ABAT levels compared with metastatic G3 and G4 tumors. We show that elevated ABAT expression results in increased GABA catabolism, decreased tumor cell proliferation, and induction of metabolic and histone characteristics mirroring GABAergic neurons. Our studies suggest ABAT expression fluctuates depending on metabolite changes in the tumor microenvironment, with nutrient-poor conditions upregulating ABAT expression. We find metastatic MB

cells require ABAT to maintain viability in the metabolite-scarce cerebrospinal fluid by using GABA as an energy source substitute, thereby facilitating leptomeningeal metastasis formation.



Radiation Therapy for Brain Metastases: A Systematic Review.

Garsa A, Jang JK, Baxi S, Chen C, Akinniranye O, Hall O, Larkin J, Motala A, Hempel S. *Pract Radiat Oncol.* 2021 Sep-Oct;11(5):354-365. doi: 10.1016/j.prro.2021.04.002.

Purpose: This evidence report synthesizes the available evidence on radiation therapy for brain metastases.

Methods and materials: The literature search included PubMed, EMBASE, Web of Science, Scopus, CINAHL, clinicaltrials.gov, and published guidelines in July 2020; independently submitted data, expert consultation, and contacting authors. Included studies were randomized controlled trials (RCTs) and large observational studies (for safety assessments), evaluating whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) alone or in combination, as initial or postoperative treatment, with or without systemic therapy for adults with brain metastases due to lung cancer, breast cancer, or melanoma.

Results: Ninety-seven studies reported in 189 publications were identified, but the number of analyses was limited owing to different intervention and comparator combinations as well as insufficient reporting of outcome data. Risk of bias varied, and 25 trials were terminated early, predominantly owing to poor accrual. The combination of SRS plus WBRT compared with SRS alone or WBRT alone showed no statistically significant difference in overall survival (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.69%-1.73%; 4 RCTs) or death owing to brain metastases (relative risk [RR], 0.93; 95% CI, 0.48%-1.81%; 3 RCTs). We did not find systematic differences across interventions in serious adverse events, number of adverse events, radiation necrosis, fatigue, or seizures.

Conclusions: Despite the substantial research literature on radiation therapy, comparative effectiveness information is limited. There is a need for more data on patient-relevant outcomes such as quality of life, functional status, and cognitive effects.

**CLINICAL TRIALS:
Now Enrolling at the USC Brain
Tumor Center**

Have you or someone you know recently been diagnosed with a brain tumor? Choosing the right treatment can be challenging. To find out more about our breakthrough treatments, contact our specialized brain tumor team at **(844) 33-BRAIN (844-332-7246)** or email frances.chow@med.usc.edu.

A Phase 1/2 Trial of Selinexor and Temozolomide in Recurrent Glioblastoma

Selinexor is a novel first-in-class XPO1 inhibitor with potent anti-tumor activity. Preclinical studies demonstrate that selinexor blocks nuclear export, impairs DNA repair, and triggers tumor cell death. Through the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program, Dr. Frances Chow led a team of cancer biologists, pharmacists, and translational scientists to develop a clinical trial to evaluate the safety and efficacy of temozolomide in combination with selinexor in recurrent glioblastoma.

This study is supported by the National Institutes of Health (NIH) and is currently enrolling at USC and across the Experimental Therapeutics Clinical Trials Network (ETCTN).

| Trial | Interventions | Phase | |
|-------------------------|---|---|-------------------|
| Brain Metastasis | | | |
| 1 | Stereotactic Radiosurgery (SRS) Compared with Collagen Tile Brachytherapy | <ul style="list-style-type: none"> • GammaTile • Stereotactic radiosurgery | Phase 1 |
| Glioblastoma | | | |
| 2 | A Phase 1/2 Study of Selinexor and Temozolomide in Recurrent Glioblastoma | <ul style="list-style-type: none"> • Selinexor + Temozolomide • Temozolomide | Phase 1/2 |
| 3 | An Open-Label, Phase 1/2A Dose Escalation Study of Safety and Efficacy of NE0100 in Recurrent Grade IV Glioma | <ul style="list-style-type: none"> • Perillyl alcohol (inhaled) | Phase 1/2A |
| 4 | A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Glioblastoma or Other Primary Central Nervous System Tumors Harboring Activating FGFR 1-3 Alterations (FIGHT-209). | <ul style="list-style-type: none"> • Pemigatinib | Phase 2 |
| 5 | Testing the Addition of the Immune Therapy Drugs, Tocilizumab and Atezolizumab, to Radiation Therapy for Recurrent Glioblastoma (BN010) | <ul style="list-style-type: none"> • Radiation + Tocilizumab + Atezolizumab • Radiation + Tocilizumab | Phase 2 |
| 6 | Enzastaurin Plus Temozolomide During and Following Radiation Therapy in Patients with Newly Diagnosed Glioblastoma with or Without the Novel Genomic Biomarker, DGM1 | <ul style="list-style-type: none"> • Enzastaurin + Standard therapy • Standard therapy | Phase 3 |
| 7 | GammaTile and Stupp in Newly Diagnosed GBM (GESTALT) | <ul style="list-style-type: none"> • GammaTile + Standard therapy • Standard therapy | Phase 4 |
| 8 | Pivotal, Randomized, Open-label Study of Optune® Concomitant with RT & TMZ for the Treatment of Newly Diagnosed GBM (EF-32) | <ul style="list-style-type: none"> • Optune + Standard therapy • Standard therapy | N/A |
| Meningioma | | | |
| 9 | A Phase 1/2 Study of Nivolumab Plus or Minus Ipilimumab in Combination with Multi-Fraction SRS for Recurrent High-Grade Radiation-Relapsed Meningioma | <ul style="list-style-type: none"> • SRS+Nivolumab+Ipilimumab • SRS+Nivolumab | Phase 1/2 |
| 10 | An Open-Label, Phase 2 Study of NE0100 in Participants with Residual, Progressive or Recurrent High-grade Meningioma | <ul style="list-style-type: none"> • Perillyl alcohol (inhaled) | Phase 2 |
| 11 | Observation or Radiation Therapy in Patients with Newly Diagnosed Grade II Meningioma That Has Been Completely Removed by Surgery (NRG-BN003) | <ul style="list-style-type: none"> • Radiation • Standard therapy | Phase 3 |

USC Brain Tumor Center

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Patient referrals, (844) 33-BRAIN (844-332-7246)

At the USC Brain Tumor Center, our mission is to provide exceptional, comprehensive and innovative concierge-style treatment plans for adults and children with all types of brain tumors and related conditions. Giveto.USC.edu

We Are the USC Brain Tumor Center

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For more information about brain tumor clinical trials, please contact **Aida Lozada**, Clinical Trials Manager, at Aida.Lozada@med.usc.edu

Please email us with your questions at BTC@med.usc.edu



Learn more at: BTC.keckmedicine.org