

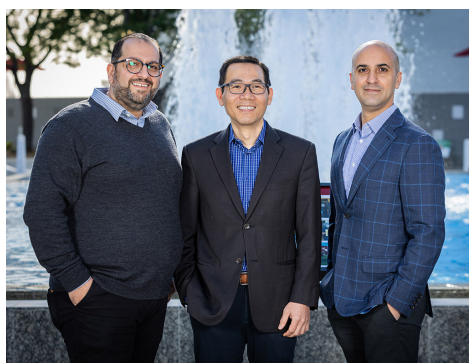
USC BRAIN TUMOR CENTER

Report

Volume 4 • Issue 2

SPRING 2024

From the USC BTC Directors: WE GO GRAY IN MAY!



May is **Brain Tumor Awareness Month** and at the USC Brain Tumor Center we always **Go Gray in May!** In this Spring Issue of the USC Brain Tumor Center Newsletter, we want to emphasize the importance of collaboration and promoting awareness about brain tumors and why it is vital to everyone in the healthcare and brain tumor community.

Increasing awareness and research funding is vital to improve diagnostic techniques, develop more effective treatments and ultimately increase survival rates for patients affected by a brain tumor diagnosis. The USC Brain Tumor Center is always working on advancing research on behalf of our brain tumor community.

In this issue of the USC BTC Newsletter, we would like to highlight one of our most distinguished colleagues, **Dr. Thomas Chen**, who has been in the Department of Neurological Surgery since 1997. He is the **Director of the Glioma Research Group**, a translational research group focused on novel ways of delivering drugs to brain tumors and developing new drugs with novel mechanisms of action. The USC Brain Tumor Center offers patients two current investigator-initiated clinical trials that have emerged from his research.

Providing unsurpassed care for our patients is part of the mission of the USC BTC. In this issue we want to take a moment and share a wonderful patient story that highlights the importance of our collaborative work at the USC Brain Tumor Center. We offer translational medicine or what we call “bench to

bedside” medicine. We want to share with you how we are advancing precision oncology by integrating drug screening and genomic profiling to rapidly advance personalized brain tumor treatment.

It is with great excitement that we announce the date of the **2nd Annual Southern California Brain Tumor Conference**, hosted at the USC Health Science Campus and the Keck School of Medicine of USC. Save the date for December 6, 2024 and join eight prominent Southern California institutions who will come together to discuss the latest advancements and breakthroughs in brain tumor research and care.

The USC Brain Tumor Center offers access to clinical trials and is constantly working to further strengthen and expand our portfolio. We care deeply for our patients and their caregivers- Our patient’s caregiver support group is offered via Zoom monthly and we remain committed to providing the best possible care for our patients.

But we can’t do it alone. **Brain Tumor 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. We are grateful to our donors and to our community partners for bringing attention to the critical need to find and provide effective brain tumor treatment options for those impacted by a brain tumor diagnosis.

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.

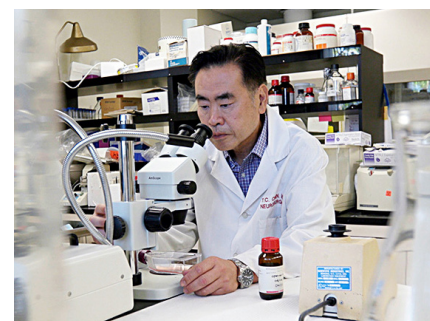
Fight on!

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

Meet Dr. Thomas Chen



Dr. Thomas Chen is a tenured professor of neurosurgery, orthopedics surgery, and pathology. He has been with the Department of Neurological Surgery since 1997.

He operates and treats patients with central nervous system (CNS) malignancies (both brain and spine). He is the **Director of the Glioma Research Group**, a translational research group focused on novel ways of delivering drugs to brain tumors, and developing new drugs with novel mechanisms of action. The novel ways of delivering drugs include **nasal brain delivery**, and disrupting the **blood brain barrier** directly via direct intra-arterial disruption of the blood brain barrier. The research has resulted in **135 new patents** that are filed through USC.

Dr. Chen’s goal is to develop USC specific trials that can benefit patients with malignant brain and spine tumors. He has four current trials that have been approved by the FDA for IND testing (2 Phase II, 2 Phase I). The two Phase II trials are using NEO100 for intranasal delivery for patients with Grade III or IV recurrent IDH1 mutant gliomas, and for using NEO100 for intranasal delivery for malignant or atypical meningiomas. The two Phase I trials include NEO212, a temozolomide conjugate, for **primary and metastatic brain cancer**; and NEO100 for **pediatric brain cancers**.

Dr. Chen is currently funded by the NIH for a R21, STTR grant; Department of Defense, and CIRM grant for a replication competent retrovirus.

When Gabriel Zada, MD, performed brain surgery on Felicitas Gonzales, no one expected that, eight days later, Dr. Zada would be operating on her daughter Margarita as well.

By Candace Pearson



(Left to right) Margarita, Dr. Zada, and Felicitas.

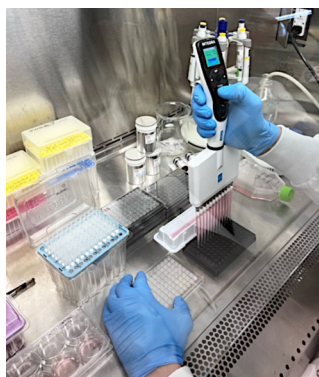
Neurosurgeon Gabriel Zada, MD, entered the operating room at Keck Hospital of USC on June 22, 2023, prepared to remove a noncancerous pituitary tumor from his 64-year-old patient, Felicitas Gonzales. An expert in brain, skull base and pituitary tumor surgery, Dr. Zada had performed such a procedure many times before.

He knew Felicitas' daughters, Margarita, 37, and Betsy, 27, and other relatives were waiting to hear the outcome. What he couldn't know was he would be performing a different brain surgery on Margarita only eight days later.

The unusual occurrence marked the first time Dr. Zada, director of the USC Brain Tumor Center, part of Keck Medicine of USC, has operated on two such close relatives. It brought him the thanks of a whole family.

"Undergoing a neurosurgical operation can be one of the most frightening and life-changing experiences a person will ever have," Dr. Zada says. "I was very privileged and honored they entrusted me with both of their lives."

This extraordinary family story will be included in the spring issue of USC Health magazine. Visit www.keckmedicine.org/magazine in mid-May to read the full story.



Advancing Precision Oncology: Integrating Drug Screening and Genomic Profiling for Personalized Brain Tumor Treatment

As the **USC Brain Tumor Center Tissue Core**, having successfully established cell lines from patients' tumor samples procured from the operating room, we initiated our drug screening efforts in the summer of 2023.

Utilizing FDA-approved chemotherapy drugs capable of penetrating the blood-brain barrier, we conducted screenings patient-derived brain metastatic cell originating from lung, breast, and melanoma, as well as primary brain tumors –such as

glioblastoma, pituitary, and meningioma.

Our goal is to merge these drug screening outcomes with genomic data through RNA sequencing to facilitate personalized medicine practices at USC.

Our forthcoming endeavor involves the development of **3-dimensional human organoids** and **xenograft models** utilizing these patient-derived brain tumor cell lines, enabling us to assess the efficacy of identified drugs in the lab.

By leveraging this comprehensive approach, treatment decisions concerning chemotherapy drugs and regimens for individual patients will be meticulously tailored based on their genomic profiles and drug screening results.

This advancement empowers our neuro-oncologists with precise therapeutic options, representing a significant stride toward



Saman Sedighi, MD



Josh Neman, PhD

personalized care and enhanced outcomes in the treatment of brain tumors.

This advancement holds the potential to revolutionize the paradigm of brain tumor treatment, offering the promise of personalized care and improved patient outcomes.

USC Brain Tumor Center Development

Thank you to all our donors, big and small, whose contributions this year helped fuel the mission of our USC Brain Tumor Center team. Every dollar raised goes to advancing the research that will improve the lives of brain tumor patients today and in the future.

Our BTC team works tirelessly to get ahead of disease and to better predict the most effective and compassionate treatments.

We are grateful for our loyal donors who support the BTC year after year, and we welcome our

newest donors, including **12-year-old Nick Viola** whose thoughtful gift came via his grandmother, Carole, as his Christmas request.

We look forward to sharing the Center's achievements and goals with anyone interested in learning more and hope that it will inspire others to join us in partnership. This month, we are honored to be the recipient of the proceeds from the **STRIDE** fitness fundraiser, hosted by **STRIDE Pasadena** and **Kelly Self**. Thank you to all those who are participating and providing wonderful support to the BTC, all while getting in a fantastic and fun workout!

A thank you to all as we look forward to continuing this upward trajectory to propel the USC BTC mission forward.

If you would like to explore how you can make an impact, or discuss joining our Advisory Council, please feel free to contact:

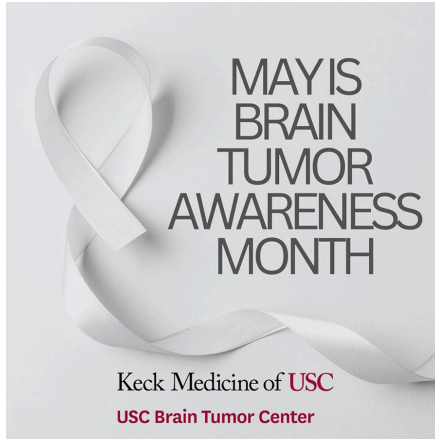
Nicole Measles
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Nicole Measles

Brain Tumor Awareness Month

Brain Tumor Awareness Month is nationally recognized in the United States during the month of May. At the USC Brain Tumor Center raising awareness about brain tumors/brain cancer is our mission year-round. Almost everyone knows someone who has been affected by a brain tumor either directly or as a caregiver.



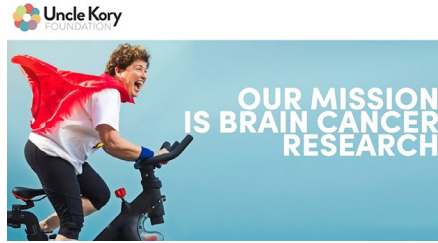
“Increasing awareness and research funding is vital to improve diagnostic techniques, develop more effective treatments and ultimately increase survival rates for those affected by a brain tumor diagnosis” says Dr. Gabriel Zada (Surgical Director, USC Brain Tumor Center).

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, we focus on 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.



The USC Brain Tumor Center raises awareness throughout the year in various ways:

- We partner with other organizations that support the brain tumor community across the country. This year the USC BTC sponsored the **National Brain Tumor Society - Southern California's Tumor Walk/Race**. Our team will be riding in the



Tour the Pier in support of the **Uncle Kory Foundation** (<https://www.unclekory.org/tour-de-pier>) in May. The USC BTC is also sponsoring the **American Brain Tumor Association National Conference** in September (<https://www.abta.org/national-conference/>) and their **Los Angeles BT5K In October** (<https://give.abta.org/event/2024-bt5k-los-angeles/e551059>).

- We publish a quarterly newsletter for our community, physicians and partners that provides a summary of the latest for brain tumor care.
- We will host the **Second Annual Southern California Brain Tumor Conference** on December 6th, 2024, in collaboration with top 8 institutions in Southern California.
- We are supported by an Advisory Council that is comprised of dedicated individuals whose primary goal is to support advancing the established goals of the Center.



- We partner with businesses in the community that provide support toward our mission of finding a cure while promoting our cause.

The USC Brain Tumor Center is extremely grateful to the **Smith Brothers Restaurants (Parkway Grill, Arroyo Chop House, Smitty's)** for their commitment to supporting the USC Brain Tumor Center during the month of May. Their support during Brain Tumor Awareness

month promotes awareness and supports crucial cutting-edge clinical, research and educational efforts of the USC BTC. “The partnership with Smith Brothers is extremely meaningful. They are a great example of what it means to give back to important causes in the community.



We are tremendously appreciative for their commitment to supporting Brain Cancer Research” says Paola Mork, Manager, USC Brain Tumor Center. Visit any of the Smith Brothers Restaurants any Thursday in May so that a portion of your proceeds will enable the USC BTC to accelerate brain cancer research.

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

SMITH BROTHERS RESTAURANTS

Dinner with Purpose

In support of...

Keck Medicine of USC
USC Brain Tumor Center

Smith Brothers Restaurant Corporation and Keck Medicine of USC Brain Tumor Center invite you to join us in the fight against brain cancer.

Dine with us at all three of the Smith Brothers Restaurants: Smitty's Grill, Parkway Grill, and Arroyo Chop House on every Thursday in May, and a percentage of the proceeds will be donated to support the invaluable research being done at Keck Medicine of USC Brain Tumor Center.

Thursday, May 2
Thursday, May 9
Thursday, May 16
Thursday, May 23
Thursday, May 30

ARROYO CHOP HOUSE

626.377.7462
arroyochophouse.com
638 S. Arroyo Parkway, Pasadena

Smitty's

626.792.9899
smittysgrill.com
110 S. Lake Ave., Pasadena

Parkway Grill

626.795.1001
theparkwaygrill.com
510 S. Arroyo Parkway, Pasadena



Save the Date!

2ND ANNUAL

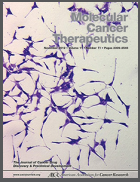
Southern California

BRAIN TUMOR CONFERENCE

Friday, December 6, 2024

HSC Conference Center, USC Health Sciences Campus

SELECTED PUBLICATIONS



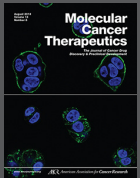
Perillyl alcohol for the treatment of temozolomide-resistant gliomas.

Cho HY, Wang W, Jhaveri N, Torres S, Tseng J, Leong MN, Lee DJ, Goldkorn A, Xu T, Petasis NA, Louie SG,

Schönthal AH, Hofman FM, Chen TC.

Mol Cancer Ther. 2012 Nov;11(11):2462-72. doi: 10.1158/1535-7163.MCT-12-0321.

■ Perillyl alcohol (POH) is a monoterpene that has been used orally for the treatment of systemic cancer. However, when used orally significant gastrointestinal side effects and lack of overall efficacy were documented. Recently, in a phase II trial in Brazil for the treatment of temozolomide (TMZ)-resistant malignant gliomas, POH was well tolerated when administered intranasally. The present study explores the effects and mechanisms of POH on TMZ-sensitive and TMZ-resistant glioma cells. To show whether intranasal delivery of POH was effective for the treatment of TMZ-resistant gliomas, animals bearing intracranial tumors were given POH intranasally. Animals treated through intranasal administration of POH exhibited a decrease in tumor growth and an increase in survival. Our data show that POH is an effective anti-glioma cytotoxic agent for TMZ-resistant gliomas when administered intranasally.



NEO212, temozolomide conjugated to perillyl alcohol, is a novel drug for effective treatment of a broad range of temozolomide-resistant gliomas.

Cho HY, Wang W, Jhaveri N,

Lee DJ, Sharma N, Dubeau L, Schönthal AH, Hofman FM, Chen TC.

Mol Cancer Ther. 2014 Aug;13(8):2004-17. doi: 10.1158/1535-7163.MCT-13-0964.

■ Patients with glioblastoma multiforme (GBM), a malignant primary brain tumor, inevitably develop resistance to standard-of-care chemotherapy, temozolomide. This study explores the effects of the novel agent NEO212, a conjugate of temozolomide to perillyl alcohol, on temozolomide-resistant gliomas. NEO212 was tested for cytotoxic activity on three human temozolomide-resistant glioma cell lines, which were resistant to temozolomide based on overexpression of the base excision repair (BER) pathway, mismatch repair (MMR) deficiency, or overexpression of O(6) methyl-guanine-DNA methyltransferase (MGMT). BER expression was evaluated by Western blotting and PARP activity. MMR deficiency was determined by Western blotting and microsatellite instability. MGMT overex-

pression was evaluated by Western blotting and O(6)-benzylguanine (O(6)BG) inhibition. For in vivo evaluation of NEO212, temozolomide-resistant glioma cells were implanted into immune-incompetent mice, and NEO212 was administered. NEO212, at equimolar concentrations of temozolomide, was more cytotoxic for temozolomide-resistant cells than temozolomide and not toxic to normal cells. NEO212-induced cell death in temozolomide-resistant glioma cells was independent of such mechanisms of resistance as high levels of MGMT, MMR deficiencies, or overexpression of BER proteins. NEO212 functions as a DNA alkylating agent, similar to temozolomide; however, this novel conjugate is unique for it may induce endoplasmic reticulum (ER) stress and inhibits autophagy. In vivo studies show that NEO212 reduces intracranial tumor growth and increases animal survival without significant toxicity. These results demonstrate that NEO212 is an effective drug against malignant gliomas that can be used for a broad range of newly diagnosed and temozolomide-resistant gliomas.

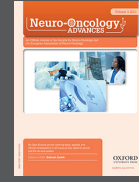


NEO212 Inhibits Migration and Invasion of Glioma Stem Cells.

Marín-Ramos NI, Thein TZ, Cho HY, Swenson SD, Wang W, Schönthal AH, Chen TC, Hofman FM.

Mol Cancer Ther. 2018 Mar;17(3):625-637. doi: 10.1158/1535-7163.MCT-17-0591.

■ Glioblastoma multiforme is a malignant brain tumor noted for its extensive vascularity, aggressiveness, and highly invasive nature, suggesting that cell migration plays an important role in tumor progression. The poor prognosis in GBM is associated with a high rate of tumor recurrence, and resistance to the standard of care chemotherapy, temozolomide (TMZ). The novel compound NEO212, a conjugate of TMZ and perillyl alcohol (POH), has proven to be 10-fold more cytotoxic to glioma stem cells (GSC) than TMZ, and is active against TMZ-resistant tumor cells. In this study, we show that NEO212 decreases migration and invasion of primary cultures of patient-derived GSCs, in both mesenchymal USCo2 and proneural USCo4 populations. Furthermore, in an in vivo orthotopic glioma model, NEO212 decreases tumor progression by reducing invasion of GSCs, thereby increasing survival time of mice. These studies indicate that NEO212, in addition to cytotoxicity, can effectively reduce migration and invasion in GSCs, thus exhibiting significant clinical value in the reduction of invasion and malignant glioma progression.



Phase I trial of intranasal NEO100, highly purified perillyl alcohol, in adult patients with recurrent glioblastoma.

Schönthal AH, Peereboom

DM, Wagle N, Lai R, Mathew AJ, Hurth KM, Simmon VF, Howard SP, Taylor LP, Chow F, da Fonseca CO, Chen TC.

Neurooncol Adv. 2021 Feb 12;3(1):vdaboo05. doi: 10.1093/noonjnl/vdaboo05.

■ Better treatments for glioblastoma (GBM) patients, in particular in the recurrent setting, are urgently needed. Clinical trials performed in Brazil indicated that intranasal delivery of perillyl alcohol (POH) might be effective in this patient group. Intranasal NEO100 was well tolerated at all dose levels and no severe adverse events were reported. PFS-6 was 33%, OS-12 was 55%, and median OS was 15 months. Four patients (33%), all of them with isocitrate dehydrogenase 1 (IDH1)-mutant tumors, survived >24 months. Intranasal glioma therapy with NEO100 was well tolerated. It correlated with improved survival when compared to historical controls, pointing to the possibility that this novel intranasal approach could become useful for the treatment of recurrent GBM.



Detection of perillyl alcohol and its metabolite perillic acid in postsurgical glioblastoma tissue after intranasal administration of NEO100: illustrative case.

Schönthal AH, Swenson S, Bonney PA, Wagle N, Simmon VF, Mathew AJ, Hurth KM, Chen TC.

J Neurosurg Case Lessons. 2022 Aug 22;4(8):CASE22215. doi: 10.3171/CASE22215.

■ Intranasal delivery of NEO100, a pharmaceutical-grade version of the natural monoterpene perillyl alcohol (POH), is undergoing clinical phase IIa testing as a treatment for glioblastoma (GBM). However, so far there is no evidence that intranasal delivery of NEO100 indeed results in POH reaching intracranial malignancies in a patient. After surgical removal of her recurrent GBM tumor, a patient received daily intranasal NEO100 therapy for more than 3 years before a second recurrence emerged. This is the first demonstration of POH and PA in brain tumor tissue from any patient. In view of the noninvasive and safe nature of this method, along with tentative indications of activity, our findings add confidence to the notion that intranasal administration of NEO100 holds potential as a new treatment option for brain-localized malignancies.

**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.



Newly Open: USC partners with TVax Biomedical to open the TVI-Brain-1 cancer vaccine

The USC Brain Tumor Center is now recruiting patients to a phase 2b personalized vaccine-based immunotherapy trial for newly diagnosed glioblastoma. TVI-Brain-1 (TVax Biomedical) is a treatment that uses each patient's own cancer cells collected during surgery to create a cancer-targeting vaccine. When the body is exposed to the vaccine, it stimulates T cells, which are harvested from the blood and are subsequently stimulated, expanded, and infused back to the patient. ClinicalTrials.gov identifier NCT05685004.

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	An Open-Label, Phase 1/2A Dose Escalation Study of Safety and Efficacy of NEO100 in Recurrent Grade IV Glioma	<ul style="list-style-type: none"> • Perillyl alcohol (inhaled) 	Phase 1/2A
3	A Phase 1/2 Study of Selinexor and Temozolomide in Recurrent Glioblastoma	<ul style="list-style-type: none"> • Selinexor + Temozolomide • Temozolomide 	Phase 1/2
4	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
5	Multi-Center Randomized Controlled Phase 2b Clinical Trial to Evaluate the Safety and Efficacy of TVI-Brain-1 Combined with Conformal Radiotherapy and Temozolomide Compared to Standard Therapy as a Treatment for Newly Diagnosed O6-Methylguanine Methyltransferase Negative (MGMT Unmethylated) Grade 4 Astrocytoma (GBM)	<ul style="list-style-type: none"> • TVI-Brain-1 + Radiation + Temozolomide • Standard therapy 	Phase 2b
6	GammaTile and Stupp in Newly Diagnosed GBM (GESTALT)	<ul style="list-style-type: none"> • GammaTile + Standard therapy • Standard therapy 	Phase 4
Meningioma			
7	An Open-Label, Phase 2 Study of NEO100 in Participants with Residual, Progressive or Recurrent High-grade Meningioma	<ul style="list-style-type: none"> • Perillyl alcohol (inhaled) 	Phase 2
8	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

1441 Eastlake Avenue
Los Angeles, CA 90033

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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Keck Medicine of USC

USC Brain Tumor Center



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To refer a patient, please call **(844) 33-BRAIN (844-332-7246)**

Make a Gift. Because of your support, we can provide Exceptional Medicine. Please contact **Brian Loew**, Senior Director of Development, Neurosciences, at Brian.Loew@med.usc.edu or visit www.keckmedicine.org/btc-donations

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