

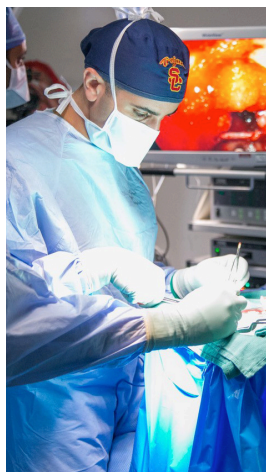
USC BRAIN TUMOR CENTER

Report

Volume 1 • Issue 2

SPRING 2021

From the Director



The USC Brain Tumor Center (BTC) has made incredible strides over the past year on behalf of our brain tumor patients, and with regard to advancing clinical care and research. Our multidisciplinary team of clinicians, scientists, engineers and dedicated administrators have been focused on key goals for growth and sustainability of the BTC over the next 5-10 years. Led by Dr. Frances Chow and Aida Lozada, our clinical trials portfolio has more than quadrupled over the past year, providing patients whom have

a variety of brain tumors with advanced investigational options for their conditions. Numerous advances in research are also being realized across our campuses and partnering institutions, and include several high impact publications, some of which are featured in this issue of the quarterly BTC newsletter.

Dr. Josh Neman was named Scientific Director of the USC BTC and will help the center by guiding research efforts as we strive for a cure. We additionally welcome Nancy Hart, RN, who will serve as the dedicated Nurse Navigator for the USC BTC. Finally, as COVID-19 hopefully continues to subside, we are pleased to announce resumption of several key symposia USC is proud to host, such as the **22nd Annual Brain Tumor Update** and the **11th Annual Symposium on Brain Metastases and Spine Tumors**, which will be virtual events co-hosted with the Cleveland Clinic in October 2021.

Finally, and perhaps most exciting, we hope to announce the recruitment of a senior Neuro-Oncologist who will serve as the Co-Director of the USC BTC in the upcoming 2021-22 academic year. Stay tuned for exciting developments from the USC BTC team. As the largest provider of care for brain tumor patients of any academic center in Southern California, please let us know how we can be of service to you and your patients.

Gabriel Zada, MD, MS, FAANS, FACS

Professor of Neurological Surgery, Otolaryngology, and Internal Medicine
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USC Brain Tumor Center Announces Inaugural Scientific Director

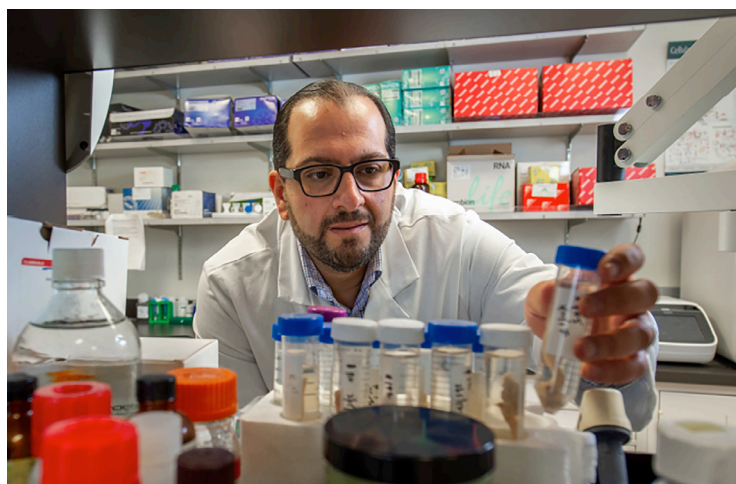
Winston Churchill once said, “We make a living by what we get, but we make a life by what we give.” As a cancer researcher, Dr. Josh Neman’s commitment to pursuit treatment and help others has become more than a career, but a way of life for him. Dr. Neman’s goal is to always bring others together in partnership, inspire them to learn through critical thinking and creativity – strategies he will use as the inaugural **Scientific Director of the USC Brain Tumor Center (BTC)**.

Dr. Neman specializes in the convergent fields of Neuroscience and Cancer. As the Director of the Laboratory of Cancer Neuroscience (www.cancerneuroscience.org) at Keck School of Medicine of USC, Dr. Neman’s translational research investigates the biology of brain metastases (cancers that spread

to the brain—i.e. breast, lung, melanoma, prostate) and pediatric brain tumors. His expertise and strengths in stem cell biology and neuroscience have allowed him to develop novel molecular, cellular, and therapeutic approaches to study the interaction between the brain and cancer cells (termed the tumor microenvironment). Dr. Neman’s goal is to uncover novel mechanisms used by the nervous system to promote tumor growth and spread. This will ultimately result in development of improved strategies for cancer prevention and treatment of patients with these devastating diseases.

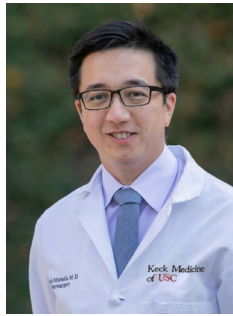
Dr. Neman received his doctoral degree at the UCLA David Geffen School of Medicine in Neurobiology. He then went on to complete his Cancer Biology Fellowship at the City of Hope’s Beckman Research Institute where he was a California Institute

Continues on page 3



Josh Neman, PhD

Two Million Dollar Pledge Creates Endowed Professorship and Supports Lab Studies Evaluating Long Noncoding RNAs Modulating Migration After Cellular Injury



Frank Attenello, MD, MS

The Harry and Florence Sloan Foundation recently pledged \$2 million to create the Sloan Family Endowed Professorship in Neurological Surgery. This gift was made in honor of Dr. Frank Attenello and in recognition of his pioneering clinical, research, and educational efforts

that so deeply impacted their family. Endowed professorships provide a secure source of funding that enables trailblazers, like Dr. Attenello, to pursue avenues of scientific inquiry that might seem risky, or to strike out on what may be a long and difficult study, with the knowledge that their work will be supported.

The Foundation first began supporting Dr. Attenello's quest in understanding the role of stem cells in neural recovery in 2017. With gifts like this, grateful patients and their families can provide hope to countless people in the community and improve the quality of life.

Long noncoding RNAs (lncRNAs) are a novel class of RNAs representing up to 80% of the genome, though only a handful of lncRNAs have been demonstrated with function in neural stem cells. To identify novel lncRNAs that modulate neural stem cell behavior, Dr. Frank Attenello's lab employs a technique known as CRISPR, the subject of the 2020 Nobel Prize in Chemistry.

The lab's CRISPR-interference screens are capable of simultaneously evaluating thousands of novel candidate genes as they modulate neural stem cell behavior. To date, Dr. Attenello's lab has identified over 50 new lncRNAs modulating cell growth and migration.

Dr. Attenello's research has identified two novel lncRNAs that are increased with cellular injury and modulate migration of these cells. This lncRNA is a particularly exciting candidate as it is highly correlated with patient outcomes, and also controls well-characterized master regulators of cell migration.

Dr. Attenello's lab is now characterizing the manner by which cell stress increases this lncRNA, and the manner by which this lncRNA affects stem cell migration. Targeting of these genes may ultimately significantly improve patient outcomes.

SELECTED PUBLICATIONS



Cortisol promotes breast-to-brain metastasis through the blood-cerebrospinal fluid barrier

Robert A. Herrera, Krutika Deshpande, Vahan Martirosian, Behnaz Saatian, Alex Julian, Rachel Eisenbarth, Diganta Das, Mukund Iyer, Josh Neman

Cancer Reports. 2021;e1351. <https://doi.org/10.1002/cnr2.1351>

■ Elevated basal cortisol levels are present in women with primary and metastatic breast cancer. Although cortisol's potential role in breast-to-brain metastasis has yet to be sufficiently studied, prior evidence indicates that it functions as a double-edged sword—cortisol induces breast cancer metastasis *in vivo*, but strengthens the blood-brain barrier (BBB) to protect the brain from microbes and peripheral immune cells.



Preclinical assessment of the efficacy and specificity of GD2-B7H3 SynNotch CAR-T in metastatic neuroblastoma

Babak Moghimi, Sakunthala Muthugounder, Samy Jambon, Rachele Tibbetts, Long Hung, Hamid Bassiri, Michael D. Hogarty, David M. Barrett, Hiroyuki Shimada, Shahab Asgharzadeh

NATURE COMMUNICATIONS | (2021) 12:511 | <https://doi.org/10.1038/s41467-020-20785-x>

■ The ability to utilize preclinical models to predict the clinical toxicity of chimeric antigen receptor (CAR) T cells in solid tumors is tenuous, thereby necessitating the development and evaluation of gated systems. Here we found that murine GD2 CAR-T cells, specific for the tumor-associated antigen GD2, induce fatal neurotoxicity in a costimulatory domain-independent manner. Meanwhile, human B7H3 CAR-T cells exhibit efficacy in preclinical models of neuroblastoma. Seeking a better CAR, we generated a SynNotch gated CAR-T, GD2-B7H3, recognizing GD2 as the gate and B7H3 as the target. GD2-B7H3 CAR-T cells control the growth of neuroblastoma *in vitro* and in metastatic xenograft mouse models, with high specificity and efficacy. These improvements come partly from the better metabolic fitness of GD2-B7H3 CAR-T cells, as evidenced by their naïve T-like post-cytotoxicity oxidative metabolism and lower exhaustion profile.



Clocking cancer: the circadian clock as a target in cancer therapy

Francesca Battaglin, Priscilla Chan, Yuanzhong Pan, Shivani Soni, Meng Qu, Erin R Spiller, Sofi Castanon, Evanthis T Roussos Torres, Shannon M Mumenthaler, Steve A Kay, Heinz-Josef Lenz

Oncogene. 2021 May;40(18):3187-3200. doi: 10.1038/s41388-021-01778-6. Epub 2021 Apr 12.

■ Disruption of the cellular pathway modulating endogenous 24-h rhythms, referred to as “the circadian clock”, has been recently proven to be associated with cancer risk, development, and progression. This pathway operates through a complex network of transcription-translation feedback loops generated by a set of interplaying proteins. The expression of core circadian clock genes is frequently dysregulated in human tumors; however, the specific effects and underlying mechanisms seem to vary depending on the cancer types and are not fully understood. In addition, specific oncogenes may differentially induce the dysregulation of the circadian clock in tumors. Pharmacological modulation of clock components has been shown to result in specific lethality in certain types of cancer cells, and thus holds great promise as a novel anti-cancer therapeutic approach. Here we present an overview of the rationale and current evidence for targeting the clock in cancer treatment.

“Inaugural Scientific Director” continued

for Regenerative Medicine (CIRM) Fellow focusing on brain tumors. He joined the Department of Neurological Surgery, Physiology and Neuroscience here at the Keck School of Medicine in 2014. Since then, Dr. Neman has been the recipient of multiple research awards from from National Institutes of Health/National Cancer Institute, American Cancer Society, American Brain Tumor Association, STOP Cancer, METAvivor, Susan G Komen Breast Cancer Foundation, and the U.S. Department of Defense.

Since joining USC, Dr. Neman continues to employ his leadership and mentorship abilities -- including being the current Director of Cancer Biology & Genomics Doctoral Program where he is involved in mentoring 31 future PhD graduate students. Dr. Neman is also a strong supporter of involving the community in basic and transla-



when I can see my team members’ drive, passion, and focus in achieving their goals. For these reasons, as a leader, my philosophy has always been: when my team members succeed...I succeed.”

tional research — this involves engaging with patients, patient advocates, and their families by bringing them into the laboratory setting. Along with the American Brain Tumor Association, he currently organizes the Annual Brain Tumor 5K walk and Education Day at the University of Southern California’s Park campus.

As the Scientific Director of the USC BTC, Dr. Neman’s goals are to advance and promote the center’s research program. According to Dr. Neman, “It gives me a tremendous satisfaction

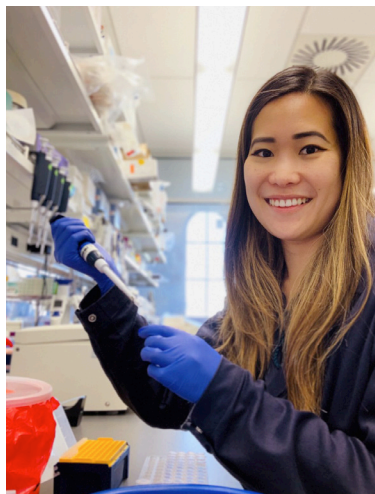
NIH Funded Fellowship Supports Research Studying Relationship Between Glioblastoma Stem Cells and 24 Hour Sleep-Wake Cycle in Mammals

By Priscilla Chan, PhD Candidate, Cancer Biology & Genomics, Kay Lab, Michelson Center for Convergent Biosciences, Keck School of Medicine of USC

Glioblastoma multiforme (GBM) is the most prevalent and malignant primary brain tumor type, with patients succumbing to the disease at an average of 5 years following diagnosis. Although current treatment methods are highly aggressive, which include surgical resection followed by simultaneous temozolomide (TMZ) chemotherapy and radiation treatment, they have not been able to provide a cure. Glioblastoma stem cells (GSCs) pose a major challenge to GBM treatment given that they are resistant to current GBM treatment modalities, invade the normal brain, promote new blood vessel formation, and can reform tumors. Furthermore, GSCs remain difficult to treat due to the unique characteristics of the brain which limit the use of treatment methods proven effective for other types of cancer.

The **Steve Kay Laboratory** at Keck School of Medicine of USC, in collaboration with Dr. Jeremy Rich’s lab at the University of Pittsburgh Medical Center, discovered that GSCs have a unique dependence on core circadian clock components, **Brain and Muscle ARNT-Like 1 (BMAL1)** and **Circadian Locomotor Output Cycles Kaput (CLOCK)**.

Circadian rhythms in mammals are produced by collective gene expression cycling generated by BMAL1, CLOCK, and their negative regulators, Cryptochrome1/2 (CRY1/2), Period1/2 (PER1/2) and REV-ERB α/β , in individual cells. BMAL1 and CLOCK interact and form a two protein complex (BMAL1::CLOCK) that induces expression of clock controlled genes and their negative regulators. This pattern of gene expression creates roughly a 24-hour cycling of physiological processes such as hormone secretion, inflammatory responses, and metabolism, to name a few. Decrease in the expression levels of either the BMAL1 or CLOCK gene in GSCs leads to specific



reduction in the level of stem cell and metabolism genes while increasing occurrence of cell death of GSCs that was not observed in normal, non-cancerous neurons or neuronal stem cells (NSCs). Furthermore, treatment of GSCs with two classes of small pharmacological clock compounds: REV-ERB agonists (inhibits expression of the BMAL1 gene) or CRY stabilizers (impedes the activity of BMAL1::CLOCK) recapitulates the effects seen in the genetic reduction experiments. Additionally, chromatin immunoprecipitation sequencing (ChIP-seq) experiments revealed that, in comparison to NSCs, the GSC chromatin (a DNA, RNA, and protein structure that serves to condense DNA) structure is more open and accessible. With a more accessible chromatin structure, BMAL1::CLOCK can increase the levels of its downstream gene targets in GSCs resulting in the increase of many different cellular processes that can support cancer cell function and survival relative to non-cancerous cells.

Consequently, in my F31 fellowship I proposed to interrogate two independent aims: 1) determine what proteins are modulating the chromatin landscape of GSCs to allow for increased BMAL1::CLOCK-driven increase in gene expression; and 2) interrogate the efficacy and applicability of the two different classes of small pharmacological clock compounds as a novel paradigm for GBM treatment, either in combination with each other or with current GBM treatment methods. Collectively, this project will further illuminate the role of circadian clock components in tumorigenesis and how to leverage such dependency on the clock for innovative treatment options in GBM and potentially other difficult to treat cancers in which the clock is driving cancer survival and progression.

CLINICAL TRIALS: Now Enrolling at the USC Brain Tumor Center

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

An Open-Label, Phase 1/2A Dose Escalation Study of Safety and Efficacy of NEO100 in Recurrent Grade IV Glioma

NEO100-01 is a Phase 1/2A open-label study of perillyl alcohol (NEO100) in patients with recurrent glioma. NEO100 is delivered four times a day by intranasal administration using a nebulizer and nasal mask for up to 6 months. There is no placebo arm. This is the first nasal administration in the US. ClinicalTrials.gov Identifier: NCT02704858

Stereotactic Radiosurgery (SRS) Compared with Collagen Tile Brachytherapy

This trial will be a randomized controlled study comparing the efficacy and safety of intraoperative radiation therapy using GammaTile versus SRS 3-4 weeks following metastatic tumor resection. GammaTile is a biocompatible permanently implanted system. Each GammaTile unit is composed of a collagen "tile" that contains 4 Cesium-131 (Cs-131) titanium-encased sources. ClinicalTrials.gov Identifier: NCT04365374

Single Fraction Stereotactic Radiosurgery Compared with Fractionated Stereotactic Radiosurgery in Treating Patients with Resected Metastatic Brain Disease (CTSU- A071801)

This phase 3 trial studies how well single fraction stereotactic radiosurgery works compared with fractionated stereotactic radiosurgery in treating patients with cancer that has spread to the brain from other parts of the body and has been removed by surgery. Single fraction stereotactic radiosurgery is a specialized radiation therapy that delivers a single, high dose of radiation directly to the tumor and may cause less damage to normal tissue. Fractionated stereotactic radiosurgery delivers multiple, smaller doses of radiation therapy over time. ClinicalTrials.gov Identifier: NCT04114981

Olaparib in Treating Patients with Advanced Glioma, Cholangiocarcinoma, or Solid Tumors with IDH1 or IDH2 Mutations

This phase 2 trial studies how well Olaparib works in treating patients with recurrent glioma, cholangiocarcinoma, or solid tumors with IDH1 or IDH2 mutations. Olaparib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. ClinicalTrials.gov Identifier: NCT03212274

Standard Chemotherapy vs Chemotherapy Guided by Cancer Stem Cell Test in Recurrent Glioblastoma (CSCRGBM)

This study will confirm the utility of chemosensitivity tumor testing on cancer stem cells (ChemOLD) as a predictor of clinical response in malignant brain tumors such as recurrent glioblastoma and anaplastic astrocytoma. Patients with an unlimited number of recurrences and multifocal disease are candidates for this study. ClinicalTrials.gov Identifier: NCT03632135

A Study of Selinexor in Combination with Standard of Care Therapy for Newly Diagnosed or Recurrent Glioblastoma

This is a global multicenter, open-label, randomized study to evaluate a combination regimen with or without Selinexor. The study will independently evaluate 3 different combination regimens in 3 treatment arms in participants with new glioblastoma, MGMT promotor unmethylated disease in Arm A, MGMT methylated in Arm B, and participants with recurrent glioblastoma regardless of MGMT status in Arm C. ClinicalTrials.gov Identifier: NCT04421378

Pivotal, Randomized, Open-label Study of Optune® Concomitant with RT & TMZ for the Treatment of Newly Diagnosed GBM (EF-32)

This study will test the effectiveness and safety of Optune® given concomitantly with radiation therapy (RT) and temozolomide (TMZ) in newly diagnosed GBM patients, compared to radiation therapy and temozolomide alone. In both arms, Optune® and maintenance temozolomide are continued following radiation therapy. Optune® is a medical device that has been approved for the treatment of recurrent and newly diagnosed glioblastoma (GBM) by the Food and Drug Administration (FDA) in the United States, and Optune® has obtained a CE mark in Europe for recurrent and newly diagnosed GBM. ClinicalTrials.gov Identifier: NCT04471844

Study to Evaluate Eflornithine + Lomustine vs Lomustine in Recurrent Anaplastic Astrocytoma (AA) Patients (STELLAR)

The purpose of this study is to compare the efficacy and safety of eflornithine in combination with Lomustine, compared to Lomustine taken alone, in treating patients whose Anaplastic Astrocytoma has recurred/ progressed after radiation and temozolomide chemotherapy. ClinicalTrials.gov Identifier: NCT02796261

Observation or Radiation Therapy in Treating Patients with Newly Diagnosed Grade II Meningioma That Has Been Completely Removed by Surgery (NRG-BN003)

This randomized trial studies how well radiation therapy works compared with observation in treatment patients with newly diagnosed grade II meningioma that has been completely removed by surgery. Radiation therapy uses high energy x-rays to kill the tumor cells and shrink tumors. ClinicalTrials.gov Identifier: NCT03180268

Trial of Enzastaurin Plus Temozolomide During and Following Radiation Therapy in Patients with Newly Diagnosed Glioblastoma with or Without the Novel Genomic Biomarker, DGM1

This study will be conducted as a randomized, double-blind, placebo-controlled, multi-center trial. Enzastaurin will be added to the standard treatment of radiation and chemotherapy in patients with glioblastoma. Patients will be evaluated for the biomarker DGM1, which in other cancer types was shown to correlate with improved survival upon treatment with Enzastaurin. ClinicalTrials.gov Identifier: NCT03776071

A Phase I/II Study of Nivolumab plus or minus Ipilimumab in Combination with Multi-Fraction Stereotactic Radiosurgery for Recurrent High-Grade Radiation-Relapsed Meningioma

This trial studies the side effects and best dose of nivolumab when given together with multi-fraction stereotactic radiosurgery with or without ipilimumab in patients with recurrent grade II-III meningioma. Immunotherapy with the checkpoint inhibitors nivolumab and ipilimumab - may help the immune system attack cancer, and interfere with tumor growth and spread. Stereotactic radiosurgery is a specialized radiation therapy that delivers a single, high dose of radiation directly to the tumor and may cause less damage to normal tissue. ClinicalTrials.gov Identifier: NCT3604978

USC Brain Tumor Center

1441 Eastlake Avenue
Los Angeles, CA 90033

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

USC has the highest volume of neurosurgical brain tumor cases of any academic center in SoCal.

- California's Office of Statewide Health Planning and Development (OSHPD),
Calendar Year 2019, most recent data available.

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**