I am quite pleased to share with you our latest quarterly USC Brain Tumor Center (BTC) Newsletter for Summer 2021. Despite the impact of COVID-19 and so many related hurdles in healthcare and science, our BTC team has managed to accomplish amazing things over the course of the past few months and 2021 in general. First and foremost, we are quite pleased to announce that Dr. Vahan Martirosian, Ph.D. in Neuroscience, has joined the BTC team as a research scientist and will be working with Dr. Josh Neman and myself to operationalize our BTC core live tumor collection and cell culture workflow program, which we are very excited about as a major step towards a true practice of personalized medicine for brain tumors.

Secondly, our expert team of care providers and social workers have started a monthly BTC patient support group, which we are confident will provide a more comprehensive experience to our BTC patients and their caregivers.

Over the past quarter, our team has been awarded grants for studying acoustic neuromas and other brain tumors using our 7T MRI and has published many high-quality scientific research articles in major journals, some of which are shared in this issue. Over the remainder of 2021, we are looking forward to some major educational conferences in partnership with the American Brain Tumor Association (ABTA), The Cleveland Clinic, and our very own USC Pituitary Center Symposium. We are also anticipating big news for the BTC which we hope to share in the next USC BTC newsletter!

Please stay tuned, and as always, thank you for your ongoing support of the USC BTC and its mission to provide unsurpassed clinical care to patients from all over the world and to cure brain tumors.

Gabriel Zada, MD, MS, FAANS, FACS
Professor of Neurological Surgery, Otolaryngology, and Internal Medicine Director, USC Brain Tumor Center gzada@usc.edu

Dr. Vahan Martirosian, Ph.D. is a new research scientist at the USC Brain Tumor Center. Dr. Martirosian received his B.S. degree in Biological Sciences from the University of California, Irvine. He was awarded the Excellence in Research distinction for his work studying the therapeutic benefits of stem cell transplantation in the brain for treatment of chemotherapy-induced chemobrain.

Dr. Martirosian later received his M.S. degree in Molecular Microbiology and Immunology and his Ph.D. in Medical Biology from the University of Southern California under the tutelage of Dr. Josh Neman. His doctoral studies focused on identifying metabolic mechanisms contributing to the metastasis of medulloblastoma, a pediatric brain tumor.

Dr. Martirosian’s work at the USC Brain Tumor Center aims to bridge the gap between the clinic and the laboratory to improve outcomes and prognoses of patients with brain tumors. His studies focus on performing translational research on a patient-by-patient basis through the analysis of genomics and drug screening assays to provide more personalized care for patients. Dr. Martirosian believes that strong collaborative effort between scientists and physicians will lead to better treatments for patients, thereby cementing the USC Brain Tumor Center as a leader in brain tumor therapies.

Vahan Martirosian, PhD joins the USC Brain Tumor Center

BRAIN TUMOR PATIENT CAREGIVER SUPPORT GROUP

The USC Brain Tumor Center now offers a monthly support group to caregivers of patients living with a brain tumor.

We are excited to announce the launch of our brain tumor caregiver support group. This group will provide the opportunity for family and friends of patients with brain tumors to come together and find common ground to help each other. We hope that each participant will come away feeling more supported in caring for their loved ones and have a safe space to discuss the challenges and victories in being a caregiver.

When: Second Thursday of each month 4-5:00p.m.
Location: Remote, via Zoom
Contact for Zoom link: Jinsy Rogers, LCSW, (323) 865-6057, Jinsy.Rogers@med.usc.edu
For more information, please contact Jinsy Rogers or Nancy Hart, Nurse Navigator, RN, (844) 332-7246, Nancy.Hart@med.usc.edu
Acoustic Neuroma Association Awards Research Grant to Study Facial Nerve Anatomy Using Novel 7T Magnetic Resonance Imaging

The Acoustic Neuroma Association Research Committee reviewed research proposals and awarded a research grant of $25,000 to Ben Strickland, MD. In an effort to more readily identify the course of the facial nerve in large vestibular schwannoma (VS) surgeries, Dr. Strickland’s research proposes applying the novel 7T magnetic resonance imaging (MRI). The program, “Ultra-high Field 7T Magnetic Resonance Imaging for Predictive Localization of the Facial Nerve in the Presence of Large Vestibular Schwannoma”, will compare facial nerve recognition in preoperative large vestibular schwannoma (Koos grade 3-4) patients on the 7T MRI compared to the traditional 3T.

Improved facial nerve visualization preceding attempted surgical resections can guide the surgeon’s expectations on where the facial nerve is located with respect to the tumor and thus prevent delayed recognition of the facial nerve and prevent facial nerve injury.

Vestibular schwannoma are benign tumors originating from Schwann cells of the vestibulocochlear nerve accounting for approximately 10% of intracranial neoplasms. While treatment strategies must be tailored to a case-by-case basis, the modalities most often utilized include a combination of surgical resection or radiosurgery.

Regardless of the employed treatment, the approach to the VS is always a risk / benefit analysis weighing the risk intervention poses to eloquent neurovascular structures against the benefit of obtaining tumor control and symptom relief. Paramount to this conversation is the preservation of facial nerve function. While early identification of the facial nerve is a surgical priority during tumor exposure, it is not always possible if the tumor is large and distorts normal anatomy. This leads to surgeons relying on distorted anatomic relationships and constant probing with a facial nerve stimulator in an attempt to identify the facial nerve prior to performing any radical tumor resection.

The American Brain Tumor Association Announces the 2020 Lucien Rubinstein Award Recipient, Edith Yuan, MS

The American Brain Tumor Association has chosen Edith Yuan, M.S. for the 2020 Lucien Rubinstein Award. As a member of Dr. Frank Attenello’s laboratory, Edith’s project, “Effects of Silencing Long Non-Coding RNA on the Malignancy of Glioblastomas", studied a type of molecule in cells called long non-coding RNA (lncRNA) and their impact on glioblastoma (GBM). Edith is a 2020 ABTA Jack & Fay Netchin Medical Student Summer Fellowship Recipient and a third-year medical student at the University of Southern California Keck School of Medicine. The Lucien Rubinstein Award is given to an ABTA Medical Student Summer Fellow who scored the highest marks from a panel of expert reviewers on the student’s final research report. The award is named in honor of the late Lucien J. Rubinstein, MD, who was a pioneer in neuropathology at the University of Virginia and a world-renowned brain tumor researcher.

Edith’s project helped identify how a novel lncRNA affects resistance to the chemotherapy drug temozolomide (TMZ), a standard therapy to treat GBM. She found that by decreasing the lncRNA level, the cancer cells respond better to TMZ. This cancer cell response indicated that the lncRNAs may be a promising target for overcoming resistance to TMZ in patients with GBM.

“It is a tremendous honor to receive the Rubinstein Award. Being recognized for my research in neuro-oncology is an unbelievably great achievement, and I am deeply grateful for the opportunity and support of the ABTA, my school, and my mentor,” said Edith. “The Rubinstein Award serves as an inspiration and encouragement to continue neuro-oncology research as a medical student and as a future physician-scientist.”

Although, the Covid-19 pandemic presented several challenges to Edith’s work, Dr. Attenello commended Edith’s motivation in completing the project. “When faced with obstacles, Edith is motivated to understand the challenge by referring to literature or trying alternative methods, constantly improving her problem-solving skills. The ABTA fellowship has provided her with unparalleled experiences in learning how to become a scientist. These experiences and skills will translate into better patient care as well.”

This year the USC Brain Tumor Center will sponsor the American Brain Tumor Association National Conference, September 11-12, 2021.
Learn more at: BTC.Keckmedicine.org

SELECTED PUBLICATIONS

**Advanced ADC Histogram, Perfusion, and Permeability Metrics Show an Association with Survival and Pseudoprogression in Newly Diagnosed Diffuse Intrinsic Pontine Glioma: A Report from the Pediatric Brain Tumor Consortium.**

*S Vajapeyam, D Brown, C Billups, Z Patay, G Vezina, MS Shiroishi, M Law, P Baxter, A Onar-Thomas, JR Fangusoro, IJ Dunkel, TV Pousaint


Diffuse intrinsic pontine glioma is a lethal childhood brain cancer with dismal prognosis and MR imaging is the primary methodology used for diagnosis and monitoring. Our aim was to determine whether advanced diffusion, perfusion, and permeability MR imaging metrics predict survival and pseudoprogression in children with newly diagnosed diffuse intrinsic pontine glioma. Baseline values, post-radiation therapy changes, and longitudinal trends for all metrics were evaluated for associations with survival and pseudoprogression.

**Improved Glioma Grading Using Deep Convolutional Neural Networks.**

*S Gutta, J Acharya, MS Shiroishi, D Hwang, KS Nayak


Accurate determination of glioma grade leads to improved treatment planning. The criterion standard for glioma grading is invasive tissue sampling. Recently, radiomic features have shown excellent potential in glioma-grade prediction. These features may not fully exploit the underlying information in MR images. The objective of this study was to investigate the performance of features learned by a convolutional neural network compared with standard radiomic features for grade prediction.

**Medulloblastoma Uses GABA Transaminase to Survive in the Cerebrospinal Fluid Microenvironment and Promote Leptomeningeal Dissemination.**


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. Our studies suggest ABAT expression fluctuates depending on metabolite changes in the tumor microenvironment, with nutrient-poor conditions upregulating ABAT expression.

**Comorbid Depression in Surgical Cancer Patients Associated with Non-routine Discharge and Readmission.**

*Casey Jarvis, Phillip A Bonney, Edith Yuan, Li Ding, Frances Chow, Anthony W Kim, William Mock, Gabriell Zada, Frank Attenello


To characterize the rates of depression across primary cancer sites, and determine the effects of comorbid depression among surgical cancer patients on established quality of care indicators, non-routine discharge and readmission. Patients undergoing surgical resection for cancer were selected from the Nationwide Readmissions Database (2010-2014). Multivariable analysis adjusted for patient and hospital level characteristics to ascertain the effect of depression on post-operative outcomes and 30-day readmission rates. Non-routine discharge encompasses discharge to skilled nursing, inpatient rehabilitation, and intermediate care facilities, as well as discharge home with home health services. Rates of depression vary amongst surgically treated cancer patients by primary tumor site. Comorbid depression in these patients is associated with increased likelihood of non-routine discharge and readmission.

**Radiation Therapy for Brain Metastases: A Systematic Review.**

*Adam Garsa, Julie Jang, Sangita Baxi, Christine Chen, Olamigoke Akinniran, Owen Hall, Jody Larkin, Aneesa Motala, Susanne Hempel


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

**In vivo CRISPR Screening for Novel Noncoding RNA Functional Targets in Glioblastoma Models.**

*Frank Attenello, Kathleen Tsung, Isaac Bishara, Yong-Hwee Eddie Loh, Thomas Chen


CRISPR screens have been utilized heavily in vivo to identify functional coding and noncoding genes in a large number of cell types, including glioblastoma (GB), though no prior study has described the evaluation of CRISPR screening in GB in vivo. Here, we describe a protocol for targeting and transcriptionally repressing GB-specific long non-coding RNAs (lncRNAs) by CRISPR interference (CRISPRi) system in vivo, with tumor growth in the mouse cerebral cortex. Given the target-specific parameters of each individual screen, we list general steps involved in transducing guide RNA libraries into GB tumor lines, maintaining sufficient coverage, as well as cortically injecting and subsequently isolating transduced screen tumor cell populations for analysis.
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

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

This will study the utility of chemosensitivity tumor testing on cancer stem cells (ChemoID) 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

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

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: NCT04385374

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 promoter 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

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 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

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

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

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

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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.

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

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