2026 International Cancer Neuroscience Symposium

ABSTRACT BOOK

POSTER SESSION FOR

FRIDAY, FEBRUARY 20, 2026

TMC^3 Collaborative Building

Houston, TX

Theme: Neuroimmunology

Poster # 1

Abstract Title: Leveraging Neuroimmune Interactions to Enhance Anti-Tumor Immunity

Authors: Susanna Manenti (Scripps Research), J. Sebastian Jara, Pratikiran Bajgain, Stanislav Dikiy, Alejandra Mendoza

The peripheral nervous system detects environmental cues such as heat, touch, and noxious stimuli through specialized sensory neurons that project into most body tissues. Emerging evidence indicates that these neurons can also infiltrate tumors, where they influence cancer initiation, progression, and therapeutic response. Elevated tumor innervation correlates with adverse clinical outcomes, yet global inhibition of nerve growth remains clinically impractical due to the essential physiological roles of peripheral nerves.

Our research investigates how sensory neurons regulate the tumor microenvironment (TME), with a particular focus on their interactions with immune cells. Using mouse models of melanoma, here we show that tumors undergo rapid innervation by sensory fibers and concurrent infiltration by diverse immune cell populations. Through high-resolution imaging, neuronal tracing and scRNA sequencing we visualize intratumoral nerve networks and identify the neuronal subtypes involved. Tumors reprogram neuronal activity within specific populations, which in turn modulates immune cell recruitment and function in the TME.

To dissect these mechanisms, we are developing integrated experimental platforms to map the immune and tumor cell subsets that directly engage with neurons. We are also testing how controlled modulation of neuronal activity shifts the balance between tumor-promoting and tumor-suppressive immune responses. These approaches combine advanced imaging, genetic perturbation, and functional assays to link neuronal signaling with immune dynamics in situ.

By defining how neurons shape the TME, our work aims to uncover therapeutic strategies that selectively target pro-tumor neuronal pathways without compromising normal nerve function. Modulating neuronal influence within tumors has the potential to restrain tumor progression and enhance the efficacy of existing immunotherapies.

This study positions the peripheral nervous system as an active regulator of the TME rather than a passive bystander. A deeper understanding of neuron–immune cell communication in cancer may reveal novel intervention points and inform the development of precision neuromodulatory strategies to improve patient outcomes.

†*Professional Development Award*

† Poster # 2

Abstract Title: TIM-3 Blockade Preserves Motor and Cognitive Function After Tumor Clearance in DMG Preclinical Models

Authors: Sandra Morales-Sánchez (University of Navarra), Iker Ausejo-Mauleon, Andrea Lacalle, Sara Nuin, Iñaki Beasain, Daniel Palacios-Alonso, Reyes Hernandez-Osuna, Javier Marco-Sanz, Jaime Gállego Pérez-Larraya, Marta M. Alonso

Background: Diffuse midline gliomas (DMGs) are aggressive pediatric brain tumors with poor prognoses and limited treatment options. While radiotherapy remains the standard of care, it is not curative and often causes cognitive impairment due to therapy-induced neuroinflammation. In this context, TIM-3 (T-cell immunoglobulin mucin-3) has emerged as a promising immunotherapy target. We previously showed that TIM-3 inhibition improved survival in preclinical immunocompetent DMG models resulting in 50% of cured-mice with immune memory. However, its long-term effects on cognitive and motor functions remain unexplored. This study evaluates the motor and cognitive consequences of TIM-3 blockade therapy in the long-term survivor (anti-TIM-3-LTS) mice, investigating its impact on neuroinflammation and brain resident populations.

Methods: Motor coordination, memory, and learning were assessed in anti-TIM-3-LTS mice using rotarod, pole, and bar tests for motor function, and NORT, FCT, and MWM tests for cognition at one- and two-months post-tumor clearance. Neuroinflammation was evaluated via immunofluorescence, assessing astrocyte/microglia activation and chronic T-cell infiltration. Additionally, pro-inflammatory cytokine (TNF-α, IL-1β, IFN-γ) and neuronal marker (Dcx, Syn1) expression levels were measured.

Results: Motor and cognitive functions in anti-TIM-3-LTS mice were preserved compared to non-tumor controls, with no sex-based differences. Moreover, immunofluorescence analyses two months after tumor elimination showed no persistent activation of reactive astrocytes/microglia, with no chronic T-cell infiltration detected in the cortex, cerebellum, hippocampus, and pons of the anti-TIM-3-LTS mice. Expression levels of pro-inflammatory cytokines were comparable across groups, and neuronal markers linked to synaptic function and neurogenesis also remained unaffected in the above-mentioned locations of the brain.

Conclusions: Overall, we demonstrated that TIM-3 inhibition controls DMG growth, and does not lead to long-term neuroinflammation that in turn could result in cognitive and/or motor dysfunction. These findings highlight TIM-3 as a promising immunotherapeutic target for DMG, with the potential to enhance survival while maintaining the quality of life of patients.

Significance to the cancer neuroscience field: This study establishes the neuroimmune safety profile of TIM-3 blockade in DMG, showing that effective immune therapy can preserve neural and glial homeostasis in the long term. These results provide essential evidence supporting the safe incorporation of TIM-3–targeted strategies into pediatric neuro-oncology.

Poster # 3

Abstract Title: Tumor ICOSLG acts as a key immune checkpoint supporting Treg maintenance in Glioblastoma

Authors: Marie Naturel (Sorbonne University), Julien Novarino, Marie Fornier, Thomas Da Costa Pereira, Kawtar Daddi, Maite Verreault, Gilles Marodon

Introduction: Despite the remarkable success of immune checkpoint inhibitors in several cancer types, their efficacy in glioblastoma (GBM) remains extremely limited. This lack of response is partially due to an immunosuppressive microenvironment. Regulatory T cells (Tregs) defined as FOXP3+, CD25+ and ICOS+ CD4+ T cells, are key contributors to the immunosuppression in many cancers. However, their specific role in human GBM is not well understood. The inducible T-cell costimulator ligand (ICOSLG), sole ligand of ICOS can be expressed by various human tumors but its effect on human Treg homeostasis in

GBM remains unknown. We therefore hypothesize that ICOSLG expression by GBM cells is essential for maintaining Treg and promoting immune suppression within the tumor microenvironment.

Methods: To explore the role of ICOS–ICOSLG signaling in a relevant in vivo model, we developed an orthotopic GBM Patient-Derived Xenograft (PDX) model in humanized mice reconstituted with hematopoietic progenitors. An ICOSLG-negative PDX was transduced with a lentivector expressing ICOSLG to assess its impact on Tregs. To assess the therapeutic relevance of our findings, PDX-bearing mice were treated with a clinically approved human antibody blocking ICOSLG (Prezalumab) combined with anti–PD-1 therapy (Nivolumab). Tumor growth was monitored using bioluminescence imaging and immune infiltration was assessed by spectral flow cytometry.

Results: Analysis of The Cancer Genome Atlas (TCGA) reveals that ICOSLG is overexpressed in GBM tissue, correlating with higher Treg abundance, both being associated with poorer overall survival, supporting our hypothesis. The humanized PDX model showed successful engraftment and immune infiltration, including activated human $CD4^+CD25^+FOXP3^+$ Tregs expressing CTLA-4, TNFRSF9, and ICOS, as in GBM patients. Gain of function experiments show that ICOSLG overexpression in tumor cells increases Treg frequency and activation in the brain only. In contrast, blocking ICOSLG and PD-1 decreases Treg frequencies and CTLA-4 expression.

Conclusion: This study establishes a functional humanized orthotopic GBM model to evaluate immune–tumor interactions and immunotherapies. It identifies tumor-expressed ICOSLG as a key regulator of Treg function within the GBM microenvironment.

Significance to the Cancer Neuroscience Field: This work advances our understanding of the immune mechanisms driving GBM progression and resistance to immunotherapy. It positions ICOSLG as a central immune checkpoint essential for Treg maintenance in GBM, offering a novel therapeutic avenue to overcome GBM immune evasion and improve response to checkpoint blockade.

Poster # 4

Abstract Title: Neuroimmune Signaling Influences Immune-Cell Phenotypes in Immunocompetent versus Immunosuppressed Tumor Microenvironments

Authors: Lilach Pasvolsky (MD Anderson Cancer Center), Hinduja Sathishkumar, Yen Vu, Caitlyn Stewart, Jordan Chatwin, Shamima Akhter, Xiayu Roa, Veena Kochat, Tongxin Xie, Frederico Omar Gleber Netto, Moran Amit

Background: Neuroimmune interactions affect the tumor microenvironment through signaling that drives tumor growth and immunity. Neurotransmitter receptors mediate neural–immune communication and regulate immunity, yet their expression within tumor-infiltrating immune cells remains poorly defined. Given that neurotransmitters can both activate and suppress immune responses, and that immunosuppressed patients exhibit increased tumor susceptibility, we hypothesized that altered expression of neurotransmitter receptors shapes immune phenotypes and distinguishes immunocompetent from immunosuppressed tumors.

Methods: Biopsies from non-melanoma skin tumors, including both groups, were analyzed to characterize neuroimmune signaling. Single-cell RNA sequencing (IC = 13, IS = 23) after $CD45^+$ immune-cell enrichment profiled neurotransmitter and neuromodulator receptors across immune-cell subsets using CellTypist. In

parallel, spatial transcriptomic data (IC = 26, IS = 67) mapped receptor distribution within the tumor microenvironment.

Results: Whole-transcriptome profiling identified 149 neuroreceptor genes, with 117 detected and 15 showing measurable expression in immune cells. Immune-cell subset proportions were similar between groups, and receptor transcripts were uniformly low with no difference in mean expression between IC and IS tumors. However, distinct patterns were seen among receptor-positive cells. IC tumors showed more receptor-expressing dendritic cells, B cells, and T cells with purinergic (P2RX1), cholinergic (CHRM3), neuropeptide (VIPR2), and glutamatergic (GRIK1, GABRB2) signaling, suggesting a preserved neuroimmune profile. In contrast, IS tumors had higher PTGER4 and CHRNA5/6 expression in NK cells, indicating prostaglandin- and nicotinic-linked inhibitory signaling. Spatial analysis showed low but selective receptor expression, confirming limited receptor-positive immune cells. Purinergic (P2RX1, P2RY11, ADORA2A) and prostaglandin/neuropeptide (PTGER4, VIPR2) receptors appeared mainly in dendritic cells, $CD4^+$ T cells, and Tregs, while cholinergic (CHRM3, CHRNA7) and glutamatergic (GRIK1, GRM3) were seen in smaller T and dendritic subsets, indicating selective neuroimmune signaling in adaptive and antigen-presenting cells.

Conclusion: Spatial and scRNA data showed low receptor expression, suggesting neuroimmune signaling is primarily ligand-driven rather than dependent on receptor abundance. In immunocompetent tumors, purinergic and neuropeptide receptors were most prominent in dendritic and T cells, reflecting a coordinated immune-tumor environment. IS tumors showed stronger adenosine and prostaglandin signaling and higher nicotinic expression in NK cells, consistent with an inhibitory neuroimmune profile. These findings suggest that targeting these pathways may help restore immune responsiveness in immunosuppressed tumors.

Significance: This work links systemic immune status to neuroimmune signaling in the tumor microenvironment, showing that communication is preserved in immunocompetent conditions but disrupted by immunosuppression. These insights provide a basis for therapies that restore neuroimmune balance and strengthen antitumor immunity.

Poster # 5

Abstract Title: Neuromedin U activates Neutrophils to create and immunosuppressive environment in Prostate Cancer

Authors: Michela Perego (The Wistar Institute), Dario Altieri

Background: Advanced prostate cancer (PCa) has a 35% 5-year survival rate, with immunotherapy using checkpoint inhibitors (ICI) ineffective due to low T-cell infiltration, classifying PCa as an immunologically “cold” tumor. The mechanisms leading to the cold tumor microenvironment (TME) remain unknown. We have been studying PCa evolution in transgenic mouse model and immunotyping the infiltrates over time to identify mechanisms responsible for the cold phenotype, and thus new immunotherapeutic targets.

Results: We found that at the earliest point in tumor development when full malignant transformation of the prostate has not yet happened large numbers of polymorphonuclear neutrophils (PMN) infiltrate into the prostate. This early infiltrating PMN have suppressive features and correlate with a decrease in T cells infiltration. Genetic profiling showed elevated levels of Neuromedin U (NmU) in mouse prostate cells during PMN infiltration, which was confirmed by higher NmU levels in mouse plasma during this time. We found that NmU directly induced human and mouse PMN migration and promoted their T cell suppressive function

TME. By Immunohistochemistry, we showed that NmU expression is increased in PCa compared to benign and pre-neoplastic lesions. NmU ablation in a subcutaneous PCa model with different genetic background mirrored those results, lead to reduced tumor growth, lack of PMN infiltration and strong anti-tumor CD8 in the prostate. Because pharmacological inhibitors of NmU are not yet available, we implemented a sequential therapeutic strategy in transgenic mice. First, we blocked PMN suppressive activity during the early phase of prostate cancer (PCa) development, coinciding with massive PMN infiltration, to enable T-cell entry into the prostate. This treatment slowed tumor growth but did not fully eliminate PCa. We then administered immune checkpoint inhibition (anti–PD-1 therapy) to target the residual tumor. The sequential combination led to complete tumor regression, accompanied by robust cytotoxic, antigen-specific T-cell infiltration and reversal of the immunosuppressive tumor microenvironment.

Discussion and Conclusions: NmU, upregulated in several cancers, promotes immune cell recruitment via NmUR1. In PCa, we find that early NmU production activates NmUR1 on PMNs, driving their prostate infiltration and T-cell suppression, establishing a “cold” TME early in tumorigenesis.

Significance: Our work uncovered a new possibility for new targeted therapies in PCa, directly targeting NmU, it’s receptor or its downstream signaling. Additionally, the impairment of PMN suppressive ability, enables T cell accumulation in the that reverted the “Cold” tumor TME, making PCa sensitive to ICI therapy.

Poster # 6

Abstract Title: Glioma genetic drivers dictate function of TREM2-expressing tumor-associated myeloid cells

Authors: Mekenzie Peshoff (UT Health Houston), Dimitrios Kleidonas, Jiaying Zheng, Mengdi Fei, Praveen N. Pallegar, Long-Jun Wu

Triggering receptor expressed on myeloid cells 2 (TREM2) is a critical modulator of phagocytosis, inflammation, and survival for microglia and other macrophages. In neurodegenerative disorders, microglia expressing TREM2 play a protective role at distinct phases of disease progression, enabling uptake of toxic protein aggregates and dead neurons. TREM2 is also highly expressed on tumor-associated macrophages in a variety of cancers, promoting an immunosuppressive microenvironment. We and others have previously investigated the role of TREM2 in gliomas with confounding results, with publications suggesting TREM2 could be pro-tumorigenic or anti-tumorigenic depending on experimental context (Peshoff, et al. Neuro Oncol.) In this study, we aim to resolve these findings by investigating the role of TREM2 across progression of gliomas with unique genetic drivers using immunocompetent mouse models. We employ syngeneic glioma stem cell lines generated via retroviral vectors expressing a dominant negative p53 along with amplification of human PDGFB or oncogenic HRAS G12V to model proneural and mesenchymal glioblastomas, respectfully. Additionally, we developed a novel conditional TREM2 knockout mouse (CX3CR1-CreER/+:TREM2-flox/flox) to selectively delete TREM2 during tumor initiation versus progression. In contrast to our previous results demonstrating enhanced GL261 and CT2A growth in TREM2 null mice, we demonstrate that TREM2 deficiency results in decreased tumor volume and improved survival when mice are challenged with Ras-driven gliomas. Furthermore, TREM2 deficient mice display a more immunostimulatory microenvironment with increased T cell infiltration. We employ an in vitro co-culture system of primary mouse microglia with these glioma stem cells to understand how microglial sense and respond to different genetic subtypes. Using ex vivo brain slice imaging, we find that TREM2-mediated processes such as

microglial chemotaxis and proliferation are impacted by secreted factors from glioma cells in a mutation-dependent manner. Together, these results indicate discrepancies in the literature regarding the function of TREM2 in gliomas may be explained by the tumor genetics behind the cell lines used, which can provide a framework for understanding subtypes of gliomas that may respond to TREM2-modulating therapy. This work also raises fundamental questions for the cancer neuroscience field about how microglia sense and regulate activity of different glioma subsets.

Poster # 7

Abstract Title: Oral microbiota dysbiosis promotes melanoma tumor growth and contributes to pre-metastatic niche preparation in the brain

Authors: Rene Rico (MD Anderson Cancer Center), Sarah B. Johnson, Vivian R. Orellana, Ashish V. Damania, Matthew C. Wong, Nadim J. Ajami, Jennifer A. Wargo, Golnaz Morad

Background: Evidence suggests a link between oral microbiota and the brain in the context of brain development and neurological diseases; however, its contribution to brain tumors is underexplored. In this study, we investigated the role of oral microbiota dysbiosis (OMD) in brain metastasis (BrM) development. We hypothesized that OMD could influence the early stages of BrM development, particularly pre-metastatic niche (PMN) preparation.

Methods: Mice with subcutaneous BP melanoma tumors, with no intracranial tumors, were used to model the PMN preparation stage during BrM development. To induce OMD, 5 days after primary tumor injection, mice were treated with chlorhexidine gluconate mouthwashes every 12 hours for 10 days. Saliva and stool samples were collected longitudinally and analyzed via 16S rRNA amplicon sequencing. Primary melanoma tumors were measured using a caliper. Brain samples were collected and analyzed by mass spectrometry and immunohistochemistry.

Results: Chlorhexidine treatment led to OMD, as verified by a reduction in alpha diversity and alterations in bacterial composition of the oral microbiota. The gut microbiota remained unchanged. Mice with OMD demonstrated a significant increase in primary tumor growth compared to controls ($p=0.039$). In the brain, OMD resulted in upregulation of proteins associated with acute inflammation and a reduction in peri-vascular extracellular matrix and adhesion proteins.

Conclusion: Our investigation suggests oral microbial imbalance is associated with alterations of the peri-vascular niche and may contribute to PMN preparation. Ongoing studies in our group investigate the impact of these OMD-induced alterations on BrM development, providing insights for microbiota-targeted translational applications.

†*Professional Development Award*

† Poster # 8

Abstract Title: Platelets drive immune suppression and glioblastoma growth in a sex-dependent manner via PAR4 and ERβ binding and signaling

Authors: Anthony Sloan (Cleveland Clinic Research), George Bukenya, Anu Aggarwal, Juyeun Lee, Daniel Rosaff, Tyler J. Alban, Ivan Juric, Daniel J. Silver, Vargab Baruah, Liza Tack, Tanvi Navadgi, Natalie

Reitz, Gavin P. Tannish, Samrutha Kamatala, Xueer Yuan, Jesse Coker, Alliefair Scalise, Bhairavi Rajasekar, Alex Vincenti, Erin Mulkearns-Hubert, Craig M. Horbsinki, Andrew E. Sloan, Christopher G. Hubert, Jacquin Luo, Joshua B. Rubin, Evi X. Stavrou, Falk W. Lohoff, Matthew Grabowski, Christine O'Connor, Marvin T. Nieman, Naseer Sangwan, Timothy A. Chan, Alok A. Khorana, Andrew Dhawan, Scott J. Cameron, Justin D. Lathia

Introduction: Cancer-related thrombosis is the second leading cause of death for cancer patients, including those with glioblastoma (GBM), the most common primary malignant brain tumor. Patients with GBM have a 30% risk of venous thromboembolism. Sex differences in cancer outcomes, including GBM, are shaped by biological, hormonal, and immune factors, influencing disease progression, treatment responses, survival, and the tumor microenvironment (TME). Platelets, as key regulators of immune responses and tumor progression, may contribute to these sex-based differences by influencing the dynamics of the TME, however, the precise molecular mechanisms remain unclear.

Methods: To address this knowledge gap, we leveraged human samples and syngeneic GBM mouse models with a series of platelet-specific functional assays, high-resolution follow cytometry-based immune profiling, platelet proteomics, and functional GBM assays.

Results: Here we show that glioblastoma (GBM) patients exhibit heightened platelet reactivity driven specifically by PAR4 signaling. In murine GBM models, both pharmacological inhibition of PAR4 using BMS986120 and genetic deletion of PAR4 significantly prolong survival in females but not males. This survival advantage is estrogen-dependent: it is preserved in chromosomal male–hormonal female mice within the four-core genotype (FCG) model and is rescued in ovariectomized mice treated with estrogen. The survival benefit is TME-specific and is mediated by platelet-driven enhancement of $CD8^+$ T cell infiltration into the tumor. Inhibition of platelet PAR4 signaling increases calcium signaling through an estrogen-dependent interaction between PAR4 and estrogen receptor β (ERβ)—a receptor interaction not previously described. PAR4-activated platelets within the TME suppress $CD8^+$ T cell function, and depletion of $CD8^+$ T cells abolishes both the tumor-induced platelet reactivity and the survival benefit conferred by PAR4 inhibition.

Conclusions: These findings demonstrate how activated platelets interact and regulate immune cell populations in GBM. These results suggest that the hyper-thrombotic state seen in many GBM patients simultaneously contributes to the immunosuppressive TME. In addition, these results identify therapeutic strategies to leverage the platelet hyperactivity seen in GBM by hyperactive thrombin-PAR4 for sex-dependent therapeutic purposes.

Significance to the cancer neuroscience field: These findings highlight an important role for platelets in the neuroimmunology of GBM, as a sex-specific modulator of the immune response. These observations set the stage for how these platelet-mediated interactions impact other neural population in the TME and how these mechanisms can be targeted as GBM therapies.

Poster # 9

Abstract Title: Rewiring Cancer: Mechanistic Insights into Lung-Brain Crosstalk and Interoceptive Control

Authors: Yujuan Su (University of California San Diego), Xin Sun

Body–brain communication, or interoception, is essential for maintaining physiological homeostasis, yet its contribution to cancer remains largely unexplored. The lung, as a primary interface between the body and the environment, is richly innervated by sensory (afferent) and motor (efferent) neurons that continuously convey information between the lung and the brain. Recent findings have revealed fundamental roles of these neural pathways in regulating physiology. However, how interoceptive circuits that sense, integrate, and modulate organ function contribute to disease, especially cancer, remains poorly understood. My recent study mapped the cell-type diversity and projection architecture of lung–innervating neurons and identified a multi–nodal neural circuit that is necessary and sufficient to sense and respond to allergen–induced airway constriction, a hallmark of asthma (Su et al., 2024). This discovery represents the first complete lung–brain–lung circuit known to control pulmonary function, providing a foundation for investigating neural contributions to cancer.

Small cell lung cancer (SCLC) is among the most lethal forms of lung cancer, characterized by rapid proliferation, widespread metastasis, and poor treatment outcomes. SCLC cells exhibit both neuroendocrine and neuronal properties and are extensively innervated by afferent and efferent nerves. Recent studies demonstrate that ablating sensory or sympathetic nerves suppresses tumor growth and extends survival, implicating neural modulation in SCLC pathophysiology. However, whether and how lung–brain interactions regulate SCLC initiation and progression remains unknown.

To address this gap, I will combine retrograde viral tracing, single–nucleus RNA sequencing, and tissue clearing–based whole–organ imaging to define the anatomical and molecular features of lung–innervating neurons in SCLC–bearing mice. Brain activity mapping through Fos expression and projection–specific activity reporters will be used to determine how peripheral tumor signals are represented in central circuits. Chemogenetic and optogenetic manipulations of identified neuronal subtypes will then test their causal roles in tumor initiation and progression. Transcriptomic profiling of tumor–associated neurons will reveal whether and how these neurons upregulate neuroimmune or stress–response genes to influence tumor growth. Together, these studies will uncover a previously unrecognized neural dimension of lung cancer biology. By elucidating how lung–brain circuits modulate tumor progression, my work aims to bridge neurobiology, immunology, and oncology, offering a novel conceptual and mechanistic framework for cancer neuroscience. Identifying neuromodulatory targets within this axis could ultimately inspire new therapeutic strategies for neuroendocrine lung cancers.

Poster # 10

Abstract Title: Cancer-derived microRNAs reprogram neurons through exosomes to regulate tumor immune microenvironment

Authors: Tongxin Xie (MD Anderson Cancer Center), Shamima Akhter, Simone Anfossi, Adewale Adebayo, Frederico O. Gleber-Netto, Kinga Nemeth, Lan Pang, Masayoshi Shimitzu, Megan L. Uhelski, Yan Li, George A. Calin, Moran Amit

Introduction: Solid tumors sculpt their microenvironments to maximize their growth and metastatic potential. Previously, we showed that head and neck squamous cell carcinoma (HNSCC) cells reprograms tumor-associated sensory neurons (TANs) towards an adrenergic phenotype and promotes tumor progression. The impact of this neuronal reprogramming on the tumor immune microenvironment remains undefined.

Aims and hypothesis: To understand how neuronal transdifferentiation regulates the antitumor immune response, we tested our hypothesis that shuttling cancer-derived microRNAs to TANs via exosomes induces an immunosuppressive neuronal phenotype in the tumor microenvironment (TME) that undermines the anti-tumor immune response.

Methods: We first checked the stability of HNSCC-derived exosomes and their cargo (i.e., microRNA [miR]) in the TME. Then, we assessed the miR transfer to TANs both in vitro and in vivo using HNSCC syngeneic models, and we measured miR enrichment in the trigeminal ganglia neurons after exosome injection. We used RNA sequencing to assess the trigeminal ganglia's transcriptome and a single-cell multiplex enzyme-linked immunosorbent assay to evaluate the functional status of CD8+ T cells cocultured with cancer cells with or without TANs. We also conducted co-culture of neuronal cells with exosomes of miR-knock-out cancer cells to assess the effect of the miRs on the regulation of cytokines and injection of miR antagomirs to the trigeminal ganglia of 4NQO-treated mice to determine the neuron reprograming the tumor immune microenvironment.

Results: Cancer cell–derived exosomes and their cargo were stable for up to 14 days in the TME and were taken up by TANs both in vitro and in vivo. The injection of exosomes into the peripheral nerves led to miR324a and miR21 upregulation in the associated trigeminal ganglionic soma, indicating that cancer-derived exosomes mediated crosstalk between cancer and neuronal cells. The RNA sequencing of human and mouse neuronal cells transfected with miR21 and miR324a revealed down regulation of multiple immune pathways, including the neuroinflammation, T-cell receptor signaling, toll-like receptor, macrophage differentiation and growth inhibition, antigen-processing, interleukin (IL)-6, programmed cell death protein 1/programmed death-ligand 1, acute-phase response signaling, IL-8, wound-healing, IL-9, IL-17A, IL-23, IL-2, IL-10, IL-7, IL-4, IL-33, IL-36, CD28, CD40, Stat-3, and NFkB, leading to downregulation of cytokines in the models of co-culture of neuronal cells with cancer cells. Furthermore, the single-cell proteomic assay (IsoPlexis) indicated that the co-culture of CD8+ T cells with cancer cells and neuronal cells significantly downregulated the effector phenotype markers (e.g., granzyme B, interferon gamma, tumor necrosis factor alpha) in activated T cells compared with that of the co-culture of CD8+ T cells with neuronal cells only, indicating that the interaction of cancer cells with

sensory neurons regulate the immunosuppressive TME. Meanwhile, the data of co-culture of neuronal cells with exosomes of miR-knock-out cancer cells and injection of miR antagomirs to the trigeminal ganglia of 4NQO-treated mice are being analyzed.

Conclusions: Our study illuminates that cancer cell–derived miRNAs are transported to neural cells via exosomes, to orchestrate a profound modulation of gene expression within the neuronal cells, resulting in reduced secretion of cytokines, dampening T-cell activity, leading to an immunosuppressive microenvironment. Future studies are needed to investigate tumor associated neurons as a potential target in immune oncology.

Poster # 11

Abstract Title: Structural ontogeny of protein-protein interactions

Authors: Aerin Yang (Swiss Federal Technology Institute of Lausanne), Hanlun Jiang, Kevin M. Jude, Deniz Akpinaroglu, Stephan Allenspach, Alex Jie Li, James Bowden, Carla Patricia Perez, Liu Liu, Po-Ssu Huang, Tanja Kortemme, Jennifer Listgarten, K. Christopher Garcia

Introduction: Understanding how protein binding sites evolve interactions with other proteins could hold clues to targeting “undruggable” surfaces. Natural protein–protein interfaces often display exquisite specificity and high affinity, yet the evolutionary routes by which initially naïve or “silent”
surfaces acquire such properties remain largely unknown. To address this fundamental question, we sought to reconstruct the evolutionary trajectories of new protein interfaces in a controlled experimental setting using synthetic coevolution. This approach allows simulation of the de novo formation of protein complexes and the mapping of energetic and structural pathways that underlie binding-site emergence.

Methods: We applied synthetic coevolution to engineer new interactions between initially noninteracting protein Z-domains. Iterative rounds of selection and diversification were used to evolve binding under controlled selective pressures. Structural families of evolved complexes were solved by X-ray crystallography, and their interaction landscapes were analyzed computationally. A machine learning–guided fitness landscape was constructed to infer epistatic couplings and identify key residue pairs involved in early stages of interface formation.

Results: We isolated seven distinct structural families of Z-domain complexes. Synthetic complexes explored multiple shallow energy wells through ratchet-like docking trajectories, whereas naturally evolved complexes converged in a deep, narrow energy minimum with fixed geometry. Analysis of the reconstructed fitness landscape revealed early “seed” contacts between binding partners that anchored encounter complex formation, guiding subsequent refinement of the interface.

Conclusion: Our findings indicate that naïve protein surfaces possess shallow energy landscapes that disfavor tight binding, likely reflecting evolutionary counter-selection against nonspecific adhesion. This explains how selective binding can arise through progressive stabilization of key anchoring contacts.

Significance to the cancer neuroscience field: Although developed in a generic protein-evolution framework, these results illuminate fundamental principles relevant to neuronal and tumor adhesion systems, where dynamic yet specific protein interactions underlie signaling and growth control. Understanding how new interfaces evolve offers conceptual routes to design synthetic molecules capable of modulating protein–protein contacts central to neuron–cancer communication and other complex signaling environments.

Reference: Aerin Yang et al., Science, in press (2025)

Poster # 12

Abstract Title: Macrophage-mediated brain-bone marrow crosstalk triggers emotional stress-induced glioma growth

Authors: Linjie Zhao (West China Hospital, Sichuan University), Zhengnan Yang, Jingtian Zhou

Stress increases cancer morbidity and mortality. Here, we found that situational or hormonal stress accelerated tumor growth and decreased survival of glioma-bearing mice. Integrated analysis of syngeneic glioma samples revealed that stress induced CD45+CD11b+C5aR1+ macrophages, which we designated as stress-associated macrophages (SAMs), and decreased NK cells in the tumor microenvironment. Parabiosis using Ms4a3creRosa26-LSL-tdTomato/+ with wildtype tumor-bearing mice challenged by chronic stress demonstrated that SAMs originated from bone marrow monocytes. Stress-mediated sympathetic nerve activation induced ADRB2+ monocytes in the bone marrow to become SAMs. SAM abundance correlated with patient stress

levels and portended prognosis. SAMs demonstrate higher CD36 expression that triggered overburden and peroxidization of intracellular lipids, dampening phagocytotic capacity of SAMs. Either genetic depletion of SAMs or pharmacologic C5aR inhibition selectively dampened glioma growth in stress-challenged mice. Collectively, stress reprograms tumor immune landscape with induction of molecularly-distinguished monocyte-derived macrophages and loss of NK cells, revealing paradigms for immune-based cancer therapies.

Poster # 13

Abstract Title: Hv1 Proton Channel Controls Macrophage Antigen Presentation and Anti-Tumor Immunity in Glioma

Authors: Jiaying Zheng (UT Health Houston), Lingxiao Wang, Shunyi Zhao, Katayoun Ayasoufi, Meijie Wang, Praveen N. Pallegar, Peter R. Strege, Langni Liu, Yushan Wan, Wenjing Zhang, Emma N. Goddery, Manling Xie, Arthur Beyder, Aaron J. Johnson, Long-Jun Wu

In the tumor microenvironment of glioblastoma, myeloid cells act as a double-edged sword—they are a major cellular component suppressing the immune response while serving as a promising therapeutic target. Our study sheds light on the voltage-gated proton channel Hv1, predominantly expressed in myeloid cells, as a pivotal regulator of their physiological functions. Elevated Hv1 expression correlates strongly with poor prognosis in glioblastoma patients, underscoring its clinical significance. Using a glioma mouse model, we demonstrated that Hv1 depletion markedly extended survival. To overcome the limitations of existing tools, we engineered novel transgenic mouse lines optimized for Hv1 research. Our findings revealed tumor-induced Hv1 upregulation, with glioma-associated macrophages identified as the principal contributors. Crucially, we identified that Hv1 in infiltrating macrophages as the major driver of survival phenotype differences. Through a multi-faceted approach combining in vivo two-photon imaging, spectral flow cytometry, and spatial transcriptomic sequencing, we discovered that Hv1 depletion limits macrophage infiltration and enhances antigen presentation, ultimately fostering a stronger adaptive immune response. These findings establish the Hv1 channel as a crucial new immunoregulator within the brain tumor milieu, offering a promising target for reprogramming macrophage function to combat glioblastoma.

Poster # 14

Abstract Title: Auditory Sensation Regulates Immune-Checkpoint Blockade Responses

Authors: Shengtao Zhou (Sichuan University), Yanjia Hu, Jian Liang

Introduction: Central nervous system (CNS) has been shown to participate in the regulation of survival and progression of peripheral tumors, including through the construction of neural circuit and secretion of hormones or neurotransmitter. However, it remains unclear whether CNS plays a role in the resistance of peripheral tumors to immune-checkpoint blockade (ICB) treatment.

Methods and Results: Compared to ICB-sensitive tumors, neurons in the inferior colliculus (IC) region were activated in ICB-resistant tumors. Chemogenetic inhibition of IC neurons eliminates the resistance of tumors to ICB treatment while inhibition of IC neurons led to development of resistance of sensitive tumors to ICB therapy. Earplug treatment or destruction of auditory nerves enhance responses of resistant tumors to ICB

therapy. Single-cell RNA sequencing of immune cells within local tumor microenvironment shows that inhibition of IC neurons limits the exhaustion of T cells and enhances the infiltration of cytotoxic CD8+ T cells.

Conclusion: Activation of IC neurons leads to resistance of cancer to ICB therapy by inducing T cell exhaustion and lowered cytotoxic CD8+ T cell infiltration in local tumor microenvironment. Targeting auditory sensation might reverse ICB therapy resistance in cancer.

Significance to the cancer neuroscience field: We have established the functional connection between auditory sensation and the treatment response of tumors to ICB therapy, providing a potentially novel therapeutic strategy for ICB-resistant tumors.

Theme: Neural Neoplasms

Poster # 15

Abstract Title: Circadian targeting improves glioma cell response to Temozolomide

Authors: Paula Bender (UT Health Houston), Kristin Eckel-Mahan

Gliomas are common and lethal brain tumors, with high-grade variants exhibiting aggressive growth and therapeutic resistance. Standard treatment with surgery, radiation, and temozolomide (TMZ) chemotherapy offers limited survival benefits, highlighting a need for improved treatment strategies. Chronotherapy aims to enhance treatment efficacy by aligning drug administration with the body's natural 24-hour cycles (i.e., circadian rhythms). The circadian clock, regulated by the transcription factors BMAL1 and CLOCK, regulates DNA repair, cell cycle progression, and apoptosis. Nobiletin (NOB), a flavonoid found in citrus peels, enhances circadian rhythms by increasing BMAL1 expression and has been demonstrated by our lab to exhibit anti-cancer effects in hepatocellular carcinoma and acute myeloid leukemia.

To investigate circadian regulation in glioma, we synchronized several murine and patient-derived glioma cell lines using serum shock. Glioma cells displayed disrupted clock gene rhythmicity, which persisted even after overexpression of BMAL1 and CLOCK. Overexpression, however, did alter the expression of additional circadian and tumor-related genes. In treatment studies, combination treatment with NOB and TMZ reduced glioma cell viability more effectively than either treatment alone, and the reduction in viability showed a circadian pattern. Single and combination treatments also differentially modulated circadian and tumor-related gene expression and rhythmicity.

Together, these findings suggest that circadian disruption may contribute to glioma progression and aggressiveness, and that targeting circadian pathways could enhance the efficacy of chemotherapy. Ongoing studies are expanding this work to additional glioma cell lines, in vivo syngeneic models, and patient-derived xenografts to further examine how NOB and timed TMZ influence circadian gene activity and tumor growth. Ultimately, this research may help establish circadian-based strategies to improve outcomes for glioma patients.

Poster # 16

Abstract Title: Unraveling the Role of Astrocyte-Mediated 'Neurophagy' in Brain Tumors

Authors: Laura Civiero, Coletto Erika, Giusti Veronica, Letizia Mazzarella, Giusto Elena, Kaur Gurkirat, Balbo Benedetta, Alessando Mormino, Stefano Garofalo

Introduction: Astrocytes, together with microglia, are capable of internalizing and degrading neuronal corpses and synaptic terminals. While the contribution of tumor-associated microglia is relatively well characterized, little is known about astrocyte behavior within the tumor microenvironment (TME). Preliminary evidence suggests that astrocyte-mediated elimination of synaptic terminals occurs via the atypical chemokine receptor 3 (ACKR3), a protein markedly overexpressed in glioblastoma multiforme (GBM). Here, we aim to elucidate novel mechanisms of astrocyte-mediated neuronal elimination in GBM. We hypothesize that astrocytes acquire a pro-tumor phenotype, promoting tumor expansion by clearing neuronal processes and creating space for tumor growth.

Methods: Using a combination of in vitro and in vivo GBM models together with proteomic profiling, we examined the phagocytic behavior of astrocytes within the tumor context.

Results: Astrocytes located at the peritumoral regions of GBM mouse models exhibited overexpression of ACKR3 and other phagocytosis-related markers. Conditional astrocyte-specific deletion of Ackr3 significantly reduced tumor volume in vivo. Moreover, in cultured human astrocytes, pharmacological inhibition of ACKR3 impaired their ability to internalize synaptic material, an activity that was markedly enhanced upon exposure to GBM-conditioned media. The molecular mechanisms underlying astrocyte–GBM communication during neuronal debris clearance are currently being investigated through secretome analysis.

Conclusion: The TME plays a pivotal role in GBM progression and therapeutic resistance. Our findings highlight an aberrant astrocytic behavior within the TME, characterized by enhanced neuronal phagocytosis mediated by ACKR3. These results identify ACKR3 as a promising therapeutic target to modulate astrocyte activity in brain tumors.

Significance to the Cancer Neuroscience Field: This study uncovers a novel mechanism through which astrocytes contribute to brain tumor progression, providing new insights and potential avenues for therapeutic intervention in cancer neuroscience.

Poster # 17

Abstract Title: Patterns and Predictors of Treatment-Associated Effects Following Gamma Knife Radiosurgery for Brainstem Metastases

Authors: Darien Colson-Fearon (MD Anderson Cancer Center), Srivatsa Vedala, Subha Perni, Mary Frances McAleer, Debra N. Yeboa, Thomas H. Beckham, Martin C. Tom, Todd Swanson, Chenyang Wang, Caroline Chung, Amol J. Ghia, Jing Li, Diana Kaya, Rami Eldaya, Betty Kim, Sujit Prabhu, Jeffrey S. Weinberg, Barbara J. O'Brien, Prashant Dogra, Tina Briere, Dennis S. Mackin Jr, Brian De

Introduction: Stereotactic radiosurgery (SRS) is a cornerstone in the management of brain metastases. However, treatment of lesions within the brainstem remains challenging due to high risk of treatment-associated effects (TAEs) that can cause severe or irreversible neurologic deficits. Data guiding parameters that optimize tumor control while minimizing toxicity remain limited. This study characterized the incidence, timing, and outcomes of TAEs following SRS for brainstem metastases.

Methods: Patients treated with Gamma Knife SRS for metastatic brainstem lesions at MD Anderson Cancer Center between January 2010 and July 2025 were retrospectively analyzed. Demographic, treatment, and outcome data were collected. TAE was defined as persistent lesion enlargement with new perilesional edema and low concern for progression after multidisciplinary review. Supporting features included lack of elevated perfusion on MRI, new steroid requirement, and/or new neurologic symptoms. Symptomatic TAEs were graded using CTCAE criteria. Univariable and multivariable logistic regressions were performed to identify predictors of TAE.

Results: A total of 274 patients with 326 brainstem metastases were identified. 323 (99%) of the lesions were treated in a single fraction, while 3 lesions were treated using fractionated SRS. Median follow-up was 48.6 months (IQR, 16.3–90.0), and median overall survival was 10.2 months (IQR, 4.4–29.9). Radiographic TAEs occurred in 30 lesions (9.2%), affecting 25 patients (9.1%). 18 patients (6.6%) were symptomatic, with 5 grade

1, 4 grade 2, 9 grade 3, and 5 grade 4 toxicities. Median time to onset of TAE was 3.7 months (IQR, 1.6–7.7). Median prescription dose was 17 Gy (IQR, 16–18) prescribed to the 53% isodose line (IQR, 50–70%). Median target volume was 0.06 cc (IQR, 0.02–0.22) in those without TAE versus 1.1 cc (IQR, 0.13–3.57) with TAE. Overall, the rates of local control at 1 and 2 years were 97.0% (CI, 92.6 -98.7%) and 95.7% (CI, 90.0%-98.1%), respectively. On multivariable analysis, larger target volume (OR 2.62 [CI, 1.84–3.74]) and lower prescription dose (OR 0.78 [CI, 0.63–0.95]) were associated with TAE.

Conclusions: Among patients treated with SRS for brainstem metastases, lower dose and larger volume were associated with increased risk of TAE. These results emphasize the need for refined dose–volume constraints and potential use of fractionation to improve the therapeutic ratio.

Significance to cancer neuroscience: This work contributes to the emerging field of cancer neuroscience by characterizing the unique effects of targeted radiotherapy on the brainstem, informing precision medicine practices in patients with intracranial disease.

Poster # 18

Abstract Title: Single Cell Spatial Profiling of the Matrisome Identifies Region-Specific Adhesion and Signaling Networks in Glioblastoma

Authors: Arpan De (MD Anderson Cancer Center), Santiago A. Forero, Ali Pirani, John E. Morales, Marisol De La Fuente-Granada, Sumod Sebastian, Jason T. Huse, Leomar Y. Ballester, Jeffrey S. Weinberg, Frederick F. Lang, Kadir C. Akdemir, and Joseph H. McCarty

Introduction: The matrisome is the repertoire of extracellular matrix (ECM) genes, proteins and ECM-associated factors which includes core matrisome components such as collagens, proteoglycans, and glycoproteins that provide structural support, as well as ECM-affiliated proteins like growth factors, cytokines, and enzymes that interact with or modify the ECM. In addition to providing structural integrity to tissues, the matrisome critically regulates key cellular behaviors, including adhesion, migration, proliferation, differentiation, and signal transduction. In the human brain, ECM components promote normal development and physiology. ECM adhesion and signaling pathways are often dysregulated in brain pathologies including the malignant cancer glioblastoma (GBM). In the highly heterogeneous GBM microenvironment, where malignant cells exhibit transcriptional diversity and interact with stromal components, the matrisome likely mediates pro-tumorigenic communication networks. Our understanding of which specific matrisome genes drive GBM's invasiveness and therapeutic resistance remains surprisingly limited.

Methods: We have used Xenium-based spatial transcriptomics (10x Genomics) to detect and quantify RNA transcripts at single-cell resolution within their native tissue context, capturing the in situ expression patterns of nearly 400 matrisome genes, cell-type-specific and related markers across human brain tumor and normal brain specimens.

Results: Transcriptionally diverse GBM cell populations display unique ECM expression profiles and spatial enrichment patterns in distinct intratumor regions harboring tumor and stromal cell populations (astrocytes, neurons, oligodendrocytes, microglia/macrophages and endothelial cells). Comparisons of GBM versus lower-grade II and III astrocytoma samples identifies differential expression of key ECM components, including elevated levels of ECM glycoproteins (IGFBP2 and MGP) and ECM-affiliated proteins (ANXA1 and ANXA2). In addition, we detected spatially enriched expression of COL8A1 (collagen), LUM (proteoglycan), and POSTN

(glycoprotein) in perivascular stromal cells. Computational analysis reveals ECM ligand-receptor networks between GBM and stromal cells, particularly in regions of microvascular proliferation and pseudopalisading necrosis.

Conclusion: This work shows heterogeneous patterns of ECM gene expression and differential enrichment of many matrisome genes in cancer cells and stromal cell types in select spatial regions in GBM. This spatial atlas provides emerging insights into ECM control of brain tumor initiation and progression and identifies potential therapeutic interventions to improve survival of patients with GBM.

Significance to the cancer neuroscience field: Spatial mapping demonstrates largely non-overlapping expression of ECM signatures in GBM stromal cell types, particularly in vascular endothelial cells and microglia/macrophages. We have identified several ECM ligand-receptor pairings that mediate adhesion and communication between cancer cells and stromal cells in the GBM microenvironment.

Poster # 19

Abstract Title: Understanding Glia-Associated Neurological Issues Associated with Neurofibromatosis Type 1 (NF1) Tumor Predisposition Syndrome

Authors: Alesandra Echeandia (The University of Texas MD Anderson Cancer Center), Anand Singh, Momo Harris, Cheng-En Shen, Chhay Hok, Kechen Ban, Renae E. Bertrand, Sama A. Alnassiry, Benjamin Deneen, Yuan Pan

Neurofibromatosis Type 1 (NF1) is a common tumor predisposition syndrome that affects approximately 1 in 3,000 individuals and is associated with neurological deficits in up to 75% of patients. While previous studies have intensively investigated the effects of Nf1 mutation in neurons, the specific contribution of Nf1-mutant glial cells to NF1-related neurological dysfunction remains largely unexplored. In this study, we focus on investigating how Nf1-mutant astrocytoma and astrocytes impact central nervous system function at behavioral, cellular, and molecular levels. Towards this point, we developed astrocyte-specific Nf1 mutant mouse models to assess in vivo behavioral changes, as well as in vitro astrocyte morphological and functional alterations. Preliminary data suggest a trend in mutant mice toward longer durations to complete the Puzzle Box Test, reduced time spent in the center during the Open Field Test, a negative discrimination index in the Novel Object Place Recognition Test, and increased latency to complete the Beam Walk Test. Moreover, we are developing a model to investigate the influence of Nf1 mutations in the interaction between NF1-associated glioma and astrocytes. The RAS/MAPK signaling pathway plays a central role in the development of NF1-associated gliomas and has also been implicated in the regulation of neurological function. Given that Nf1 functions as a negative regulator of this pathway, future studies aim to investigate how astrocyte-specific Nf1 loss alters RAS/MAPK signaling, with a focus on its contribution to NF1-associated neurological deficits

Poster # 20

Abstract Title: Disrupted Inhibitory Networks Underlie Long-Range Circuit Remodeling in Glioma

Authors: Hannah Farnsworth (Harvard Medical School/Brigham & Women's Hospital), Meghan Pinter, Garret Scarpa, Joshua Park, Alexis Franklin, Rachel Davis, Kaylee Gentry, Humsa S. Venkatesh

Bidirectional electrochemical signaling between neurons and cancer cells within the tumor microenvironment (TME) plays a critical role in the progression of pediatric high-grade glioma (pHGG). Recent studies, however, have demonstrated that these cancers form long-range, neuron-tumor networks across the brain, establishing gliomas as a systemic disease. Yet, how the activity changes induced by glioma–neural interactions extend to distal circuits remains an unknown. To begin answering this question, we used a prefrontal cortical, patient-derived xenograft model of pHGG and performed whole-brain cFos mapping to identify regions beyond the TME with increased neuronal activation. We found that cFos expression was most elevated in areas connected to the TME and enriched in parvalbumin (PV) interneurons, such as the retrosplenial (RSP) and primary visual (VISp) cortices. Patch-clamp electrophysiology revealed impaired inhibitory but preserved excitatory transmission in the RSP, highlighting the selective vulnerability of inhibitory neurons to glioma-induced circuit dysfunction. To determine whether these cellular changes translate to alterations in circuit function we examined behavioral readouts associated with cFos-high regions. We observed enhanced neuronal responses in VISp to light stimuli and deficits in spatial navigation tasks mediated by the RSP, demonstrating that gliomas induce long-range, circuit-specific remodeling.

Building upon our observation that PV interneurons are selectively vulnerable within glioma-affected distal circuits, we sought to investigate the mechanisms driving this susceptibility. The function of PV interneurons is tightly regulated by specialized extracellular matrix structures known as perineuronal nets (PNNs), leading us to hypothesize that PNN degradation may underlie PV cell dysfunction within cFos-high regions. Consistent with this hypothesis, we observed reduced PNN fluorescence intensity and decreased numbers of PNN^+ PV cells in the RSP and VISp. Notably, these regions also exhibited increased densities of microglia in direct contact with PNNs. Given the established role of microglia in mediating PNN remodeling and degradation, we next investigated whether microglial depletion could restore PNN integrity and circuit function. Treatment with a CSF1R inhibitor led to the recovery of PNN^+ PV cell counts and reduced cFos expression in the RSP, implicating microglia–PV interneuron interactions in glioma-mediated activity dysregulation at distant brain sites.

Collectively, these findings demonstrate that pHGG extends its influence well beyond the local tumor site, actively reshaping distal microenvironments to create a pro-tumorigenic brain-wide environment. By uncovering microglia-mediated PNN degradation as a driver of long-range circuit dysfunction, our work broadens the understanding of how tumor-neural interactions orchestrate systemic remodeling in glioma.

Poster # 21

Abstract Title: Integrative Single Cell RNA and Spatial Profiling Identify Mechanisms of Neonatal Brain Hemorrhage Pathophysiology and Repair

Authors: Santiago Forero (The University of Texas MD Anderson Cancer Center), Zhihua Chen, Ali Pirani, Arpan De, Zachary Wise, Xiaofeng Zheng, John E. Morales, Joseph H. McCarty

Precise regulation of cell-cell communication within brain neurovascular units (NVUs) is essential for maintaining normal tissue physiology. Integrins, which play critical roles in cell migration and adhesion, regulate many of these signaling pathways. Dysregulation of integrin function can lead to pathologies such as uncontrolled angiogenesis, endothelial barrier disruption, and intracerebral hemorrhage (ICH). Within the tumor microenvironment of the brain, abnormal integrin function also contributes to tumor initiation and progression. However, the cellular and molecular mechanisms linked to integrin dysfunction are not well understood. In this

study, we employed fixed single cell RNA profiling coupled with spatial in situ gene expression profiling to characterize NVU signaling pathways associated with ICH in Itgb8/b8 integrin mutant mice. In this model, early neonatal stages of ICH were characterized by downregulation of extracellular matrix (ECM)-associated signaling factors (Adamtsl2, Htra3, and Lama4) linked to canonical TGFb activation and signaling in endothelial cells. Conversely, the progressive resolution of ICH involved upregulation of neuroinflammatory signaling networks (Gas6 and Axl) alongside activation of iron metabolism pathway components (Hmox1, Cp, and Slc40a1) in microglia/macrophages. Integrated computational modeling identified ligand-receptor signaling networks between perivascular glial cells and angiogenic endothelial cells. Collectively, these findings illuminate molecular pathways that govern NVU maturation and provide novel mechanistic insights into ICH pathogenesis and repair in Itgb8 mutant mice. Understanding NVU responses to integrin dysregulation may ultimately help elucidate novel therapeutic strategies to restore neurovascular physiology in cancer patients.

Poster # 22

Abstract Title: CycloSal Prodrugs for the Treatment of ENO1-deleted and ENO1-heterozygous Glioblastoma Tumors

Authors: Brian Grindel (MD Anderson Cancer Center), Nasir Uddin, Lauren E. Fuller, Ben Finkenbein, Nirurita Mahadev, David Piwnica-Worms, Noah Hornstein, Florian Muller, Steven W. Millward

Concomitant deletion of Enolase 1 (ENO1) during tumor suppressor loss in glioblastoma (GBM) and other cancers reveals a therapeutic vulnerability known as collateral lethality. Targeting the paralogue enolase 2 (ENO2) can inhibit the growth of tumor cells lacking ENO1 by shutting off glycolysis while sparing normal cells retaining ENO1. The phosphonate drug HEX was developed to target ENO2 and shows promising tumoristatic activity in orthotopic models of ENO1-/- GBM. However, this requires high dosing (>150 mpk daily), owed to its dianionic character and poor membrane permeability. We synthesized a series of cycloSal-modified HEX derivatives to mask the negatively charged phosphate groups. The cycloSal group is thought to go through a two-step decomposition mechanism to function as a “molecular clock” allowing distribution and cell penetration prior to release of the active HEX pharmacophore. One derivative, MNU-3-7, showed enhanced serum stability over other compounds and was highly effective at killing ENO1 deficient cell lines. When testing top compounds in GBM (ENO1-/-) subcutaneous xenograft tumors, MNU-3-7 had less systemic toxicity but maintained tumor inhibition at a much lower doses compared to HEX (30 mpk daily). On-target inhibition of glycolysis was observed by FDG-PET and subsequent confirmed by ex-vivo metabolomic analyses. MNU-3-7 resulted in robust inhibition of glycolysis and nucleotide biosynthesis suggesting drug combinations to enhance efficacy.

Poster # 23

Abstract Title: Targeting miR-10b-Driven Oncogenic Pathways in Glioblastoma Using Small-Molecule Inhibitors

Authors: Maria-Ancuta Jurj (The University of Texas MD Anderson Cancer Center), Michael A. Attathikhun, Sanjay Kumar Singh, Meng Chen, Venkata Narayana Vidadala, Frederick Lang, Gabriele Varani, George A. Calin

Introduction: Glioblastoma (GBM) is driven by extensive molecular heterogeneity that confers aggressive growth, therapeutic resistance, and poor clinical outcomes. Standard therapies remain largely palliative, reinforcing the need for new approaches targeting the molecular pathways sustaining gliomagenesis. Among microRNAs (miRs) dysregulated in GBM, miR-10b functions as a potent oncogenic regulator that enhances proliferation, invasion, and apoptosis resistance. Targeting miR-10b with Small Molecule Inhibitors of miRNAs (SMIRs) represents an emerging approach to restore tumor suppressor networks and inhibit gliomagenesis.

Methods: miRNA expression profiling was initiated through analysis of TCGA glioblastoma dataset, which identified miR-10b as one of the most significantly upregulated microRNAs in tumor tissues compared to normal brain. These findings were validated by RT-qPCR in an independent cohort of glioblastoma patient samples, confirming robust miR-10b overexpression. Subsequently, functional studies were conducted using patient-derived xenografts (PDXs) and 3D brain organoids. The small-molecule inhibitor SMIR-10b, rationally designed to selectively bind the precursor form of miR-10b and block its maturation, was applied to PDX-derived glioblastoma cells and organoid models. RT-qPCR, western blotting, and immunofluorescence were used to evaluate the molecular consequences of SMIR-10b treatment on the expression of downstream tumor suppressors PTEN and HOXD10. Furthermore, scRNA-seq was employed to characterize the transcriptomic remodeling induced by SMIR-10b and to elucidate its impact on tumor–neuron interactions within the organoid microenvironment.

Results: SMIR-10b treatment selectively reduced mature miR-10b levels by binding to nuclear pre-miR-10b, blocking its maturation and leading to nuclear accumulation of precursor transcripts. This inhibition restored PTEN and HOXD10 expression, resulting in decreased proliferation and invasiveness of GBM cells. In brain organoid co-cultures, SMIR-10b markedly reduced tumor expansion without affecting neuronal viability or synaptic marker expression. scRNA-seq revealed transcriptional reprogramming consistent with reduced oncogenic signaling and restored tumor suppressor pathways.

Discussion: These results highlight the central role of miR-10b in sustaining glioblastoma aggressiveness and demonstrate the feasibility of pharmacologically targeting miRNA maturation. SMIR-10b exerts selective antitumor activity while preserving neuronal integrity, addressing one of the main challenges in developing brain-penetrant therapeutics.

Conclusions: SMIR-10b represents a promising therapeutic avenue in glioblastoma by inhibiting miR-10b maturation, reactivating tumor suppressor genes, and reducing tumor proliferation in preclinical models.

Significance to Neuroscience: This study provides the first evidence that selective inhibition of a brain-enriched oncomiR using a small molecule can suppress glioblastoma growth without perturbing neuronal function. These findings bridge molecular oncology and neurobiology, opening new avenues for miRNA-based therapeutics in malignant brain tumors.

Poster # 24

Abstract Title: Sensory neuron activity promotes tumor progression in malignant peripheral nerve sheath tumor (MPNST) via TRPV1^{+} nociceptor signaling

Authors: Khalill Ali Ahmad Kasm (MD Anderson Cancer Center), Kechen Ban, Madeline Nicole Ansley, Anand Singh, Khushboo Irshad, Sara Maupin-Garcia, Cheng-En Shen, Seynabou Diagne, Maria Monserrath Olivera

Acevedo, Tahara T Trimble, Momo K Harris, Aishani S Gargapati, Sami Mohd Rasheed, Kendal Willcox, Peter M Grace, Angela Hirbe, Andrew J Shepherd, and Yuan Pan

Introduction: Neural infiltration is a hallmark of malignancy and correlates with poor clinical outcomes in several cancers. Neuronal activity is emerging as a driver of cancer progression and pain, raising interests in nociceptors as potential therapeutic targets. Several cancers cause intractable pain and are innervated by sensory neurons, suggesting that nociceptor activity may both mediate pain and promote tumor progression. We used MPNST as a model to investigate how sensory neuron activity contributes to tumor growth.

Methods: In vivo models were generated by engrafting mouse MPNST cells into the sciatic nerve of mice, followed by pain behavioral assays and tumor growth measurements. We selectively stimulated Aβ, Aδ, and C fibers to assess sensory neuron subtype-dependent effects on tumor progression. The transient receptor potential vanilloid 1 channel (TRPV1) antagonist, AMG9810, was used in vitro and in vivo to test the role of $TRPV1^+$ nociceptors in tumor growth. Primary dorsal root ganglion (DRG) sensory neuron cultures were prepared for multielectrode array recordings, calcium imaging and co-culture with MPNST cells.

Results: MPNST-bearing mice exhibited hypersensitivity to mechanical and thermal pain stimuli and exhibited ongoing pain. MPNST-conditioned media increased sensory neuron activity, intracellular calcium concentration, and ATF3 expression in DRG neurons. Selective stimulation of C fibers, but not Aβ or Aδ fibers, enhanced tumor growth, which was blocked by AMG9810. Conditioned media from activated $TRPV1^+$ DRG neurons increased MPNST cell growth in vitro, suggesting a role of neuronal activity-dependent paracrine factors in driving tumor cell growth.

Conclusion: MPNST is a painful and aggressive cancer originating in the peripheral nerves. Our findings reveal a feedforward loop that MPNST cells increase $TRPV1^+$ nociceptor activity, which further promotes tumor progression. Targeting nociceptors may offer a dual therapeutic benefit by alleviating cancer pain and limiting MPNST growth.

Significance to the cancer neuroscience field: This study uncovers a direct link between sensory neuron activity and peripheral nerve tumor progression. By identifying $TRPV1^+$ nociceptors as active participants in the malignant microenvironment, our work expands current understanding beyond neuron-tumor proximity to functional crosstalk driving disease outcomes. These findings establish MPNST as a tractable model for investigating neural regulation of tumor biology and highlight sensory neuron signaling as a promising therapeutic axis to simultaneously modulate cancer pain and tumor.

Poster # 25

Abstract Title: Investigating the role of lipid metabolism alterations on genomic instability and extrachromosomal DNA formation during glioblastoma tumorigenesis

Authors: Ece Kilinc (MD Anderson, GSBS), Yinglu Guan, Takashi Shingu, Kaylene J. Lu, Jian Hu)

Glioblastoma (GBM) is the most common central nervous system malignancy in adults, with a median survival of ~15 months. Standard-of-care has improved minimally over two decades, underscoring need for new therapeutic strategies. Over 60% of GBM tumors harbor oncogene amplifications on extrachromosomal DNA (ecDNA), a key driver of rapid genome evolution and therapy resistance. Although ecDNA is a promising

therapeutic target, the mechanisms governing ecDNA generation and retention remain poorly understood, limiting development of effective strategies to eliminate it in tumor cells. We previously showed that Quaking (QKI) gene is frequently mutated or deleted in GBM, and QKI protein is a co-activator of PPARβ in regulating lipid metabolism. QKI deletion in neural stem cells (NSCs) lowers the unsaturated-to-saturated fatty acid ratio, alters membrane composition, and increases DNA damage. Collectively, these findings prompted our hypothesis that defective lipid homeostasis compromises nuclear envelope (NE) integrity, increasing genomic instability and ecDNA formation.

We analyzed genomic/transcriptomic data from three human GBM cohorts to correlate lipid pathway alterations with tumor ecDNA status. For in vivo studies, we used the Nestin-CreERT2; QkL/L; PtenL/L; Trp53L/L (QPP) genetically engineered mouse model which spontaneously develops GBM. To determine ecDNA status, QPP genomes were analyzed with the AmpliconSuite-pipeline and results were validated using immunofluorescence (IF) and fluorescence in situ hybridization (FISH) assays. NE morphology was assed by IF for nuclear lamins (Lamin A/C and B1). Acute QKI deletion experiments, testing immediate effects on NE morphology, were performed in primary and pre-malignant NSCs.

Across human GBM cohorts, defective lipid homeostasis, especially downregulated sphingolipid metabolism, significantly correlated with ecDNA presence. In QPP, 24% of tumors were ecDNA-positive; amplified oncogenes shared with human ecDNAs included PDGFRA, KIT, KDR, CHIC2, and FIP1L1. PDGFRA expression was significantly increased in QPP versus pre-malignant PP (Nestin-CreERT2; PtenL/L; Trp5 QKI 3L/L) controls, and FISH identified extrachromosomal PDGFRA foci only in QPP. In QPP tumors, we observed altered NE morphology marked by; blebbing, elongation, rupture, and micronuclei formation minimal changes in PP samples. Acute QKI deletion reproduced these phenotypes.

Our data supports a novel model in which dysregulation of lipid metabolism compromises NE integrity, thereby promoting genomic instability and ecDNA biogenesis.

Collectively, these findings indicate that restoring NE integrity, potentially through lipid supplementation, could suppress ecDNA formation and increase GBM responsiveness to therapy. Moreover, QPP is the first mouse model that generates spontaneous ecDNA. Leveraging QPP as a preclinical model could accelerate therapeutic discoveries and significantly improve survival outcomes.

Poster # 26

Abstract Title: Neuroligin-3 Interaction with CSPG4 Regulates Normal and Malignant Glial Precursors Through Mechanotransduction

Authors: Yoon Seok Kim (Swiss Federal Technology Institute of Lausanne), Shawn M. Gillespie, Anna C. Geraghty, Belgin Yalçın, Alexis English Ivec, Aerin Yang, Rebecca Mancusi, Jared Hysinger, James Reed, Richard Drexler, Michael Quezada, Karen Malacon, Pamelyn Woo, Youkyeong Gloria Byun, Christopher Mount, Mable Lam, Yuan Pan, J. Bradley Zuchero, Jacqueline Trotter, Michelle Monje

Introduction: Neuronal activity promotes the growth of high-grade gliomas through the secretion of neuroligin-3 (NLGN3), a synaptic adhesion protein that acts as a potent mitogen for glioma cells. However, the mechanisms by which NLGN3 signals at the glioma cell surface remain poorly understood. Here, we identify the cell-surface proteoglycan CSPG4 (also known as NG2) as a key binding partner of NLGN3 and reveal a previously unrecognized mechanotransduction pathway that links neuronal cues to glioma proliferation.

Methods: We combined biochemical interaction assays, live-cell imaging, electrophysiology, and genetic models to dissect NLGN3-induced signaling in glioma cells and oligodendrocyte precursor cells (OPCs). Recombinant NLGN3 ectodomain and CSPG4-expressing glioma cultures were used to map binding interfaces and analyze downstream signaling events. Mechanical responses were measured by membrane tension imaging and patch-clamp electrophysiology, while genetic disruption of PIEZO1, ADAM10, or CSPG4 assessed the requirement of each component. In vivo studies employed patient-derived xenograft and conditional knockout models to evaluate tumor growth and pathway dependency.

Results: NLGN3 directly interacts to the extracellular domain of CSPG4, triggering ADAM10-dependent ectodomain shedding of both CSPG4 and NLGN3. This proteolytic processing increases plasma membrane tension and activates the mechanosensitive ion channel PIEZO1, leading to Ca^{2+} influx, membrane depolarization, and AKT phosphorylation. Genetic deletion or pharmacological inhibition of PIEZO1 abrogated NLGN3-induced signaling and tumor growth. Likewise, CSPG4-deficient glioma cells failed to respond to NLGN3 stimulation, establishing that NLGN3-CSPG4 interaction is required for mechanotransduction. In vivo, PIEZO1 knockout significantly attenuated the NLGN3/CSPG4-dependent glioma phenotype, supporting a functional role for this axis in tumor progression.

Conclusion: Our findings define a mechanistic framework in which neuronal NLGN3 engages CSPG4 on glioma cells to trigger ADAM10-mediated shedding, mechanical activation of PIEZO1, and pro-tumorigenic signaling. This cascade represents a direct molecular link between synaptic activity, extracellular matrix remodeling, and mechanosensitive growth control in the tumor microenvironment.

Significance: This study uncovers mechanotransduction as a fundamental mechanism in activity-dependent glioma progression. By connecting neuronal signals to tumor mechanosensing, the NLGN3–CSPG4–PIEZO1 axis broadens the conceptual foundation of cancer neuroscience and identifies novel therapeutic targets at the interface of neuronal adhesion, extracellular proteolysis, and ion channel signaling.

†*Professional Development Award*

† Poster # 27

Abstract Title: Brain Neurodevelopment-Derived Polygenic Biomarker for Prognostic Stratification of Pediatric and Adult Brain Tumors: The Fetal-to-Adult Index (FTAI)

Authors: Hyunyong Koh (Baylor College of Medicine/Texas Children's Hospital)

Introduction: Despite major advances in brain tumor molecular classification, early transcriptome-based prognostic tools remain limited—particularly in low-resource or pediatric settings where comprehensive molecular testing is often unavailable. Polygenic, transcriptome-derived indices may better capture biological heterogeneity than single-gene markers. To address this gap, we developed a fetal-to-adult index (FTAI), a transcriptomic metric reflecting developmental maturation, to enable biologically informed risk stratification across pediatric and adult brain tumors.

Methods: Spatiotemporal human brain transcriptomic data from the Allen Brain Atlas were used to curate fetal- and adult-enriched gene sets. Gene set variation analysis (GSVA) and principal component analysis (PCA) were applied to assess developmental separation, using genes such as SOX2, PAX6, OLIG2 (fetal) and GFAP, S100B, SYN1 (adult). FTAI was then computed for 1,001 tumors, including pediatric brain tumors

(PBTs, n=404), lower-grade gliomas (LGGs, n=522), and glioblastomas (GBMs, n=75). Associations with survival were evaluated using Kaplan–Meier, Cox proportional hazards, and logistic regression models adjusted for age, sex, and race.

Results: Developmental gene expression clearly separated fetal from adult brains, with the first principal component explaining ~40% of variance. FTAI showed strong correlation with chronological age, peaking in infancy and declining with maturation. Across tumor cohorts, FTAI significantly differed among groups ($p=6.9\times10^{-11}$). Higher FTAI was associated with worse overall survival in both PBTs (HR 2.2, $p=1.5\times10^{-3}$; aOR 2.8, $p=1.1\times10^{-3}$) and LGGs (HR 1.86, $p=3.6\times10^{-4}$; aOR 2.6, $p=1.4\times10^{-3}$), but not in GBMs ($p>0.05$). Machine learning models incorporating FTAI (random forest, XGBoost) achieved survival prediction AUCs up to 0.72. Sensitivity analyses within individual pediatric subtypes were non-significant, likely reflecting small sample sizes.

Conclusion: FTAI represents a polygenic, developmentally reflective transcriptomic score that stratifies prognosis across heterogeneous brain tumors. Its static, biologically interpretable nature allows integration into both large-scale and targeted sequencing workflows, providing a scalable framework for biologically guided prognostication.

Significance to the Cancer Neuroscience Field: By linking neurodevelopmental transcriptomic signatures to tumor prognosis, this work bridges developmental neurobiology and neuro-oncology. FTAI introduces a conceptually novel, evolutionarily grounded framework for assessing tumor aggressiveness and maturation state—supporting precision prognostication, especially in pediatric and resource-limited settings.

Poster # 28

Abstract Title: A Novel Radiotracer Targeting the Cystine/Glutamate Antiporter xCT for Glioblastoma Imaging

Authors: Zhiwen Liu (The University of Texas MD Anderson Cancer Center), Seok-Yong Lee, Xiaoxia Wen, Robert T. Ta, Tomoyuki Mashimo, Jianbo Wang, F. William Schuler, Ryan Patrick Coll, Dimitra K. Georgiou, Deborah Healey, Harshan Ravi, C. Chad Quarles, H. Charles Manning

Introduction: Glioblastoma is the most aggressive malignant primary brain tumor in adults, with a median survival average of only about 14 months after diagnosis. The system xc– antiporter, consists of transport xCT (SLC7A11) and 4F2hc (SLC3A2), imports intracellular L-cystine and exports intracellular L-glutamate at a 1:1 ratio. Expression of xCT is highly upregulated in glioblastoma and has been shown to regulate redox balance to scavenge or neutralize reactive oxygen species (ROS), thereby promoting tumor growth, invasion, and resistance. Despite the potential of xCT as a promising target for glioblastoma diagnosis and therapy, there is currently a lack of approved xCT-targeted radiotracers.

Methods: To develop new xCT-targeted radiotracers, a series of novel small molecules were synthesized and screened for xCT activity in cell-based assays. Several small molecule hits were identified, including those with increased xCT activity, such as ZLF16. This small molecule was radiolabeled with fluorine-18 (18F) to generate radiotracer [^{18}F]ZLF16. Stability of the radiotracer in PBS and serum were measured by radio-HPLC. Cellular uptake and xCT specificity were evaluated in U251MG and U87MG human glioblastoma cell lines. An orthotopic U87MG human glioblastoma rat model was established by using U87MG-luc cells, and tumor growth was monitored by bioluminescence imaging and magnetic resonance imaging, Dynamic positron

emission tomography/computed tomography scans (90 min) were performed to assess in vivo tumor uptake of [^{18}F]ZLF16.

Results: We synthesized a novel small molecule-based radiotracer [18F]ZLF16, which demonstrated high stability in serum, strong cellular uptake and high xCT specificity in human glioblastoma cell lines. In vivo multimodal imaging revealed significant accumulation of [^{18}F]ZLF16 in U87MG tumor but low background uptake in healthy brain, achieving a significant tumor-to-brain ratio. Radiotracer accumulation in regions of edema was also negligible.

Conclusion: We developed a novel radiotracer of xCT activity, [18F]ZLF16, which was capable of visualizing human U87MG tumors in rats, highlighting its potential for noninvasive imaging and potentially theranostic applications in glioblastoma. Further evaluation of this and other agents are under way.

Significance to the cancer neuroscience field: Our study introduces a new xCT-targeted imaging approach for human glioblastoma, highlighting its potential as a PET tracer for identifying glioblastoma and guiding future targeted therapeutic interventions.

Poster # 29

Abstract Title: Dysregulation of Fatty Acid Metabolism Induces Nuclear Envelope Defects and Genomic Instability in Glioblastoma

Authors: Kaylene Lu (The University of Texas MD Anderson Cancer Center UT Health Houston Graduate School of Biomedical Sciences), Yinglu Guan, Takashi Shingu, Ece Kilinc, Bhumi Maniyar, Jian Hu

Introduction: Glioblastoma (GBM) is an aggressive primary brain tumor that remains highly refractory to treatment. It harbors a unique genomic landscape defined by chromosomal alterations; however, unlike in other organs, mutator mechanisms in the brain are poorly understood. The brain is the fattiest organ in the body and undergoes rapid lipid turnover, necessary for neurodevelopment and brain function. On a cellular level, fatty acids (FAs) dictate lipid molecule complexity to facilitate membrane dynamics. Our group established Quaking (Qki) as a transcriptional coactivator for FA metabolism genes. Notably, Qki deletion on a pre-malignant background induces GBM tumors in vivo. Here, we investigate the cellular and molecular mechanisms connecting FA dysmetabolism to genomic instability during gliomagenesis.

Methods: We employed several models of FA dysmetabolism using primary neural stem cells (NSCs) and glioma stem cells (GSCs), including 1) Qki knockout, 2) GPAT3/4 overexpression, 3) Seipin knockdown, and 4) FA supplementation. We applied electron and IF microscopy to visualize membrane structures and performed reactive oxygen species (ROS) and lipid peroxidation assays for cellular stress readouts. Furthermore, we leveraged 1) Qki-deficient genetic mouse models and 2) mice orthotopically implanted with pre-malignant NSCs and fed varying FA diets. Resulting tumors were used for histological evaluation, IF staining, and whole genome sequencing.

Results: In Qki-deficient tumors, we observe elevated chromosomal alterations and widespread membrane defects including those associated with the nuclear envelope (NE). ROS-associated DNA damage patterns were absent despite elevated total ROS, indicating an alternative mutator mechanism. The NE depends on proper membrane dynamics for its functions, including the maintenance of genomic integrity. In Qki-deficient cells, we observe abnormal nuclear shape, nuclear blebbing and micronuclei formation. Such NE abnormalities

are also observed with GPAT3/4 overexpression, Seipin knockdown, and FA supplementation. Lastly, we demonstrate that mice on FA diet develop tumors that display atypical mitotic figures, multinucleated giant cells, and nuclear lamin defects.

Conclusion: Overall, we propose that defective FA metabolism serves as a mutator mechanism in gliomagenesis, inducing genomic instability through the disruption of the NE. Future work seeks to examine NE lipid composition and dynamics, as well as in vivo genomic instability, in the context of FA dysmetabolism.

Significance: We aim to provide a fundamental understanding of lipid metabolism in the maintenance of nuclear function and genomic organization in the brain. Ultimately, these findings can be translated to develop new GBM paradigms utilizing lipid-related markers or NE features for patient prognosis and treatment stratification.

Poster # 30

Abstract Title: Oligomer-Aβ42 suppress glioma progression via potentiating phagocytosis of microglia

Authors: Jie Lu (Sun Yat-Sen University Cancer Center), Zhenqiang He, Hao Duan, Depei Li, Yonggao Mou

Aims: Glioma is characterized by an immunosuppressed environment and a poor prognosis. The accumulation of Amyloid β (Aβ) leads to an active environment during the early stages of Alzheimer's disease (AD). Aβ is also present in glioma tissues; however, the biological and translational implications of Aβ in glioma are elusive.

Methods: Immunohistochemical (IHC) staining, Kaplan-Meier (KM) survival analysis and Cox regression analysis on a cohort of 79 patients from our institution were performed to investigate the association between Aβ and the malignancy of glioma. Subsequently, the potential of oligomer-Aβ42 (OAβ42) to inhibit glioma growth was investigated in vivo and in vitro. Immunofluorescence staining and phagocytosis assays were performed to evaluate the activation of microglia. Finally, RNA-seq was utilized to identify the predominant signaling involved in this process and in vitro studies were performed to validate them.

Results: A positive correlation between Aβ and a favorable prognosis was observed in glioma. Furthermore, OAβ42 suppressed glioma growth by enhancing the phagocytic activity of microglia. Insulin-like growth factor 1 (IGF-1) secreted by OAβ42-activated microglia was essential in the engulfment process.

Conclusion: Our study proved an anti-glioma effect of Aβ, and microglia could serve as a cellular target for treating glioma with OAβ42.

Poster # 31

Abstract Title: Crosstalk Between Stroke and Glioma: Ischemia-Enhanced Glioma Infiltration

Authors: Christine Madamba (Baylor College of Medicine), Qi Ye, Hyun Kyoung Lee

Glioblastoma (GBM) is an aggressive primary brain tumor with dismal survival rates. GBM is difficult to treat due to its ability to invade neighboring brain regions, rendering complete surgical resection nearly impossible. During tumor progression, several pathological changes occur in the tumor microenvironment (TME) including increased neuronal hyperactivity and network dysfunction. Interestingly, similar neurophysiological and

pathological changes also occur following stroke, a leading cause of death and disability worldwide. Clinical evidence from large cohort studies reveals a significant co-occurrence of ischemic stroke with primary brain tumors, including GBM, suggesting a possible mechanistic link between these two diseases. Consistent with this, comparative transcriptomic analysis of human high-grade gliomas and various neurological disorders identified stroke as having the greatest overlap of differentially expressed genes. These findings prompted us to investigate how stroke might influence glioma progression and infiltration. Using innovative stroke-glioma mouse models, we combined a validated photothrombotic stroke model with both human GBM patient-derived glioma cells in immunodeficient mice and de novo GBM models in immunocompetent mice to study this relationship. Interestingly, we found that stroke injury significantly accelerates tumor progression. Across both experimental systems, we found that when stroke is induced in the brain hemisphere opposite to the tumor, we observe enhanced directional infiltration towards the infarcted hemisphere. Single-cell RNA sequencing analysis further revealed that stroke-associated tumors exhibit transcriptional signatures enriched for infiltrative signatures corresponding to the leading edge of human GBM (IVY-GAP database), suggesting that stroke injury may create a pro-infiltrative TME. Ongoing studies aim to understand both microenvironmental and tumor-intrinsic mechanisms mediating this interaction, with a particular focus on how stroke-induced neuronal hyperactivity may potentiate glioma infiltration. This work provides novel insights into a previously underappreciated intersection between cerebrovascular injury, stroke, and glioma biology. By revealing how stroke can accelerate glioma progression through neural and microenvironmental remodeling, our study bridges two major fields – brain injury and cancer neuroscience. These findings not only advance our understanding of how brain injury can influence tumor behavior but also opens new avenues for risk assessment and development of anti-infiltrative therapies for stroke-cancer patients.

Poster # 32

Abstract Title: Intracranial Electrical Fields for the Treatment of Glioblastoma

Authors: Hanna Minns (Oregon Health and Science University), Nemanja Useinovic, Daniel Cleary

Introduction: Glioblastoma (GBM) is the most common and deadliest malignant primary brain tumor, with median survival under two years. Despite decades of research, outcomes remain poor, underscoring the need for novel therapeutic approaches. A promising new direction in GBM treatment involves the use of electrical fields to inhibit tumor growth. Tumor Treating Fields (TTF), which deliver intermediate-frequency fields via scalp electrodes, extend survival by approximately five months. However, this extracranial approach is limited by poor field precision, energy attenuation, and the requirement for >18 hours of daily wear. These barriers may be overcome through intracranial stimulation, in which implanted electrodes deliver localized, high-intensity fields directly adjacent to the tumor.

Methods: Optimal stimulation parameters were first evaluated in vitro using two murine glioma cell lines (C6, F98). Low-impedance platinum electrodes connected to a function generator delivered 48 hours of continuous stimulation (200 kHz; 1–3.5 V; sine, square, or triangle waves). For in vivo studies, orthotopic gliomas were generated by injecting luciferase/mCherry-expressing F98 cells into rat cortex, followed by implantation of paired platinum electrodes adjacent to the tumor site and extracranial fixation of the housing assembly.

Results: Electrical stimulation induced a dose-dependent suppression of tumor cell growth in vitro, with higher voltages producing greater growth inhibition across both sine and square waveforms. In vivo, tumor-bearing rats tolerated chronic electrode implantation and preliminary stimulation without emerging neurological deficits

or infections. Longitudinal bioluminescent imaging reliably tracked tumor burden, with increased photon flux correlating with disease progression.

Conclusion: We demonstrate that intracranial electrical field delivery is feasible in tumor-bearing rodents and that optimized stimulation parameters suppress glioma growth in vitro. Ongoing work will determine whether these parameters improve survival and reduce tumor burden in vivo, advancing towards a novel, implantable electrical field therapy for GBM.

Significance to the cancer neuroscience field: Electrical stimulation is commonly used to modulate the behavior of brain cells such as glia and neurons. The work described here understands how electrical stimulation can also act on malignant glial populations within the central nervous system, paving the way for a new application of electrical stimulation and a novel therapeutic avenue for brain tumors.

Poster # 33

Abstract Title: A Human Neuronal Co-Culture System Reveals Early Glioblastoma-Neuron Communication

Authors: Ouada Nebie (Ohio State University), Niyi Adelakun, Liwen Zhang, Luke Kollin, Brian Fries, Akhil Medikonda, Monica Venere, Pierre Giglio, Nam Chu and Nhat Le1

Glioblastoma (GB, IDH wild type) is the most aggressive primary brain tumor in adults, with recurrence driven by residual tumor cells that re-establish interaction with surrounding neurons. While neuronal activity is recognized as a driver of GB progression, the earliest neuronal responses to tumor contact remain poorly understood. Existing models rarely capture these acute events or the heterogeneity of responses generated by tumors of different origins, limiting insight into the earliest neuron-tumor interactions.

We developed a dual-interface human iPSC-derived neuronal culture system to investigate acute neuronal responses to glioblastoma exposure. Neurons were challenged with either established GB cell lines or patient-derived glioblastoma cells (PDGCs). Using quantitative proteomics, high-resolution imaging, and immunological assays, we characterized compartment-specific neuronal changes and mapped activated signaling pathways. We also screened selective inhibitors for their effects on both tumor proliferation and neuronal integrity.

Within 24 hours of exposure, neurons displayed synaptic remodeling and activation of GB-related signaling cascades. Proteomic analysis of GB exposed neurons revealed enrichment of pathways associated with GB and abnormalities in neuronal circuits. Notably, the U-87MG cell line, but not PDGCs, induced pronounced synaptic disruption, neurite retraction, and MAPK pathway activation, with distinct molecular signatures across neuronal compartments. ERK1/2 and p38 MAPK signaling were differentially activated depending on the GB cells source, correlating with specific structural and functional synaptic alterations. Targeted inhibition of MAPK components significantly suppressed U-87MG proliferation and preserved neuronal architecture.

We present a human neuronal culture model that detects and discriminates the earliest neuron-derived responses to glioblastoma from diverse tumor sources. By linking neuronal remodeling to tumor-specific signaling pathways, the platform uncovers both the heterogeneity of neuron-tumor interactions and early, targetable vulnerabilities. This system offers a translational tool to advance understanding of GB recurrence and to guide development of therapies with dual neuroprotective and anti-tumor efficacy.

Poster # 34

Abstract Title: Immune microenvironment remodeling in primary IDHmt gliomas reveals microglia reprogramming and T cell divergence

Authors: Patrick Nylund (MD Anderson Cancer Center), Benjamin Whitfield, Pravesh Gupta, Yang Liu, Krishna Bhat and Jason Huse

Introduction: Gliomas account for approximately 25% of all central nervous system (CNS) tumors in adults and are disproportionately lethal, despite representing only ~1.6% of all cancer cases. Large-scale genome sequencing efforts have revealed that IDH-wildtype (IDHwt) and IDH-mutant (IDHmt) adult gliomas are biologically distinct entities, where the IDH mutational status distinguishes glioblastomas (IDHwt) from astrocytomas (AS) (IDHmut) or oligodendrogliomas (OD) (IDHmut). One of the defining features that separates IDHmt AS from OD is the presence of recurrent mutations in the chromatin-related gene ATRX, which are typically found in AS alongside an intact 1p/19q chromosomal arm. These molecular profiles now form a key part of the 2021 WHO classification of CNS tumors. Recent studies have highlighted differential interactions between tumor cells and microglia/macrophages in AS compared to OD, suggesting that microglia could directly influence tumor cell phenotype. However, the impact of microglia on distinct immune cell populations in AS versus OD remains poorly understood.

Methods: To address this, we performed single-cell RNA sequencing on microglial and tumor infiltrating immune cells from surgically resected primary IDHmt ASs and ODs.

Results: Our analysis revealed extensive reprogramming of tumor-associated microglia states in AS versus OD. In ATRXmt AS, we observed an enrichment of MHC-IIlow pro-inflammatory and activated microglia. Conversely, ATRXwt ODs exhibited increased proportions of antigen presentation-competent microglia, including an MHC-I/MHC-IIhi interferon-γ-responsive population and an MHC-IIhi anti-inflammatory cluster. In line with this, we found that naïve CD4 T cells were enriched in AS, while mature populations such as cytotoxic CD4 T cells, exhausted CD4 T cells and T regs were overrepresented in OD.

Conclusion: These data suggest an association between enriched MHC-IIhi microglia and enhanced differentiation of CD4 T cells in ODs compared to ASs, hinting at a role for microglial cells in driving the contexture of the T cell compartment in these two glioma subtypes. Further analysis is ongoing to dissect the phenotype of CD8 T-, NK- and myeloid cells in AD versus OD. Additionally, ligand-receptor interaction analysis is being performed to identify microglia-driven ligand/receptor axes that may differentiate AD from OD.

Significance to the cancer neuroscience field: This work provides insights into new potential glia-driven immune mechanisms that may underly subtype-specific tumor behaviors and therapeutic vulnerabilities.

Poster # 35

Abstract Title: Salidroside Impairs Glioma Progression via CYP2E1-Neuroglobin Cytochrome C Redox Signaling Axis

Authors: Lakshmi Priya Panda (All India Institute of Medical Sciences), Dev Kumar Tripathy, Suryanarayan Biswal, Gaurav Chhabra, Kalpana Barhwal

Introduction: Glioblastoma (GB) represents the most aggressive and fatal form of primary brain tumor, accounting for approximately 50–60% of adult astrocytic tumors and 12–15% of all intracranial neoplasms. Despite substantial progress in surgical resection, radiotherapy, and chemotherapy, prognosis remains poor, with a median survival of only 12–18 months and a 5-year survival rate below 5%. Therefore, identifying effective therapeutic agents that can target multiple tumor pathways is of great clinical importance. The present study investigated the anti-proliferative and anti-cancer potential of salidroside, a bioactive glucoside derived from Rhodiola rosea, on human glioblastoma cells.

Methods: The study analyzed glioma specimens from the Department of Neurosurgery, AIIMS Bhubaneswar and was extended in vitro using U87MG and LN229 cells supplemented with or without salidroside. We assessed cell viability, mitochondrial membrane potential, oxidative stress and cell death; migration and invasion assays evaluated anti-proliferative effects. mRNA expression of Neuroglobin (NGB) and protein levels of NGB, Cytochrome c and Caspase-3 were quantified by qRT-PCR and Western blotting.

Results: Salidroside treatment significantly reduced U87MG and LN229 cell viability, migration, and invasion in a dose-dependent manner. Mechanistic analysis revealed that salidroside enhanced CYP2E1 activity, resulting in increased reactive oxygen species (ROS) generation and depletion of NADPH, thereby disturbing the intracellular redox balance. The ensuing oxidative stress triggered neuroglobin degradation, mitochondrial iron accumulation and lipid peroxidation, culminating in ferroptosis. These events were accompanied by a loss of mitochondrial membrane potential, release of cytochrome c, and activation of caspase-3, indicating the involvement of mitochondrial-mediated ferroptotic cell death.

Conclusion: The present study demonstrates that salidroside reduces the viability, migration, and invasion of U87MG and LN229 glioma cells through apoptosis- and ferroptosis-mediated mechanisms, likely driven by enhanced CYP2E1 activity involved in its oxidative metabolism. Salidroside treatment elevated oxidative stress and depleted NADPH in U87MG and LN229 glioma cells, disrupting cellular redox balance. The resulting oxidative modification and degradation of neuroglobin led to mitochondrial iron accumulation and impaired cytochrome c redox cycling. Excess ferrous iron–induced oxidative stress caused mitochondrial membrane potential loss, lipid peroxidation, and cytochrome c release, collectively triggering apoptotic and ferroptotic cell death pathways.

Significance to the cancer neuroscience field: Our findings impart novel mechanistic insight into the redox–ferroptosis axis in glioblastoma. These results not only expand current understanding of redox regulation in glioma biology but also highlight salidroside as a promising candidate for tumor-suppressive intervention in the emerging field of cancer neuroscience.

Poster # 36

Abstract Title: Targeting P300/CBP boosts anti-tumor immune response driven by Delta-24-RGD in pediatric Diffuse Midline Gliomas

Authors: Akhila Parthasarathy (MD Anderson Cancer Center), Maria Frost, Andrew Gillard, Dong Ho Shin, Andres Lopez Rivas, Hong Jiang, Xuejun Fan, Angelis Morales Rivera, Claudia Solbes Riera, Candelaria Gomez-Manzano, Juan Fueyo

Introduction: Pediatric diffuse midline glioma (DMG), H3K27-altered, is a lethal brain tumor with a median survival of less than 12 months. Approximately 80% of cases carry the H3K27M oncohistone mutation, which

disrupts epigenetic regulation by inducing global H3K27 hypomethylation and hyperacetylation. These changes contribute to tumor progression and resistance to conventional therapies, including chemotherapy and radiotherapy, which offer a primarily palliative benefit. Therefore, the current therapeutic landscape underscores an urgent need for innovative treatment strategies capable of altering the disease trajectory.

Methods: Building on our prior clinical testing of the oncolytic adenovirus Delta-24-RGD in adult glioblastoma and pediatric DIPG (Phase I trials: NCT00805376 and NCT03178032), we investigated the therapeutic potential of combining Delta-24-RGD with pharmacological inhibition of the acetyltransferase P300/CBP. Immunoblotting was used to assess histone acetylation changes post-treatment. Combinatorial efficacy of Delta-24-RGD+P300i was evaluated with cell viability assays and ZIP synergy scoring. Secretome profiling and immune cell infiltration analyses using luminex and flow cytometry, respectively, were performed to assess immunomodulatory effects. In vivo studies in immunocompetent murine DMG models were performed to measure tumor burden following combination therapy.

Results: Delta-24-RGD treatment led to a time-dependent reduction in H3K27ac and H3K18ac in both human and murine DMG cell lines. Co-treatment with P300/CBP inhibitors (C646 and CPI-1612) synergistically decreased cell viability, with ZIP scores reaching upto 16.82. Luminex and proteome array analyses revealed an upregulation of chemokines associated with lymphocyte migration and inflammation in mice treated with a combination of Delta-24-RGD and C646/CPI-1612 at 7-days post-treatment. This effect persisted with combination therapy on day-14, highlighting the influence of P300 inhibition in maintaining an inflammatory milieu post virotherapy. Notably, mice treated with Delta-24-RGD and C646 exhibited a 7-fold increase in $CD38^{+}iNOS^{+}$ inflammatory macrophages and a 3-fold increase in $CD8^{+}$ T cells compared to Delta-24-RGD monotherapy on day-7. In vivo, the combination therapy resulted in a marked reduction in tumor burden compared to monotherapies or controls.

Conclusion: Combining P300/CBP inhibition with Delta-24-RGD oncolytic virotherapy enhances anti-tumor efficacy in DMG/DIPG models by reducing tumor cell viability and amplifying inflammatory immune response. These findings support further clinical investigation of this combinatorial strategy.

Significance to the Cancer Neuroscience Field: This study highlights a novel therapeutic approach that integrates epigenetic modulation with immunogenic virotherapy to target pediatric DMG/DIPG. By disrupting tumor-promoting acetylation and enhancing immune infiltration, this strategy addresses key challenges in treating these aggressive brain tumors and opens new avenues for translational research in cancer neuroscience.

Poster # 37

Abstract Title: Whole-brain postmortem single-nucleus profiling reveals spatially dependent glioblastoma effects on disease-associated oligodendrocytes

Authors: Jacqueline J. Peng (University of Pennsylvania), Sydney N. Oliver, Nelson F. Freeburg, Gayathri Konanur Gopikrishna, Daniel Chafamo, Neriman Tokcan, Donald M. O'Rourke, Zev A. Binder, MacLean P. Nasrallah, Dana Silverbush

Introduction: Glioblastoma (GBM) is a highly aggressive brain cancer with poor prognosis. Most molecular studies rely on surgical samples, limiting access to infiltrative margins and non-neoplastic regions. Postmortem

tissue offers a unique opportunity to capture GBM's full spatial impact across the brain and reveal how tumor presence reshapes surrounding and distant neural environments.

Methods: We established a postmortem GBM donation and analysis framework addressing clinical, experimental, and computational challenges. From four GBM patients, we collected over 84 brain sections encompassing tumor core, margin, non-lesional, and brainstem regions. Guided by histopathology of flash-frozen and FFPE tissues, we selected 14 samples for single-nucleus RNA sequencing (snRNA-seq). To ensure robust detection of subtle transcriptional signals in postmortem tissue, we applied a denoising pipeline optimized for single-nucleus data, enabling the creation of a comprehensive whole-brain spatial atlas of GBM progression and infiltration.

Results: Our dataset revealed distinct oligodendrocyte states that varied with proximity to the tumor. Tumor-adjacent oligodendrocytes displayed upregulation of inflammatory and immune-related pathways compared to those in distant regions, defining a reactive, disease-associated phenotype. This transcriptional profile was also enriched in external datasets from GBM, multiple sclerosis, and traumatic brain injury, suggesting convergence on shared injury-like oligodendrocyte responses. Spatial transcriptomics indicated co-localization of mesenchymal GBM cells and macrophages with these disease-associated oligodendrocytes, with their combined presence amplifying inflammatory signaling. Ligand-receptor analysis further implicated FGF pathway interactions as potential mediators of these state transitions near the tumor.

Conclusion: Through denoised postmortem single-nucleus profiling across the entire brain, we reveal how glioblastoma alters oligodendrocyte states in a spatially dependent manner. These findings suggest that tumor proximity drives an injury-like, disease-associated oligodendrocyte response that may contribute to GBM-related neural dysfunction.

Significance: Our whole-brain postmortem approach expands the spatial and cellular scope of GBM investigation, uncovering tumor-proximal changes in oligodendrocyte biology that illuminate new facets of glioblastoma's impact on the surrounding brain.

Poster # 38

Abstract Title: Early and Late Gamma Electrocorticography Signatures Enhance Localization of Language Cortex During Awake Craniotomy Procedures

Authors: Sujit Prabhu (The University of Texas MD Anderson Cancer Center), Israt Tasnim, Priscella Asman, Kyle Noll, Giuseppe Pellizzer, Nuri Ince

Introduction: Preserving language during tumor resection is critical but challenged by the time-intensive, complex nature of direct electrical stimulation (DES). High-gamma electrocorticography (ECoG) captures real-time, task-induced cortical responses, yet concordance with DES remains underexplored.

Objective: Evaluate how early and late high-gamma ECoG responses align with DES across auditory, object, action, and descriptive naming tasks and relationships with postoperative language outcome.

Methods: Seventeen patients (14 gliomas, 3 metastases) underwent awake craniotomy. ECoG was recorded, and bipolar DES was applied on the same subdural grid across the four tasks. Early (100–200 ms) and late (>200 ms) high-gamma activity (30–150 Hz) and DES-positive sites were co-registered in standard MNI-152 space. Spatial overlap was quantified using Dice-Sørensen (D-S) coefficients, with accuracy assessed by

ECoG–DES contact proximity (exact/adjacent, <1 cm) across tumor, peritumoral (<2 cm), and whole-grid ROIs. Language outcomes were determined from neurologic exams, and a subset (N=11) also underwent longitudinal neuropsychological testing of expressive language.

Results: DES-positive sites were identified in 15/17 (88%) patients, primarily during auditory and action naming. Auditory naming elicited gamma activity in all patients, with early and late responses, reflecting sensory and extended semantic processes, observed in 10/17(59%) cases, showing strong concordance with DES (early: D-S= 0.63, 95% CI: 0.51–0.74; early + late: D-S = 0.66, 95% CI: 0.54–0.77). Non-auditory tasks showed predominantly late gamma responses, with modest DES overlap (object: D-S= 0.34; action: D-S= 0.42; descriptive: D-S= 0.37), suggesting broadly distributed cortical networks. Accuracy in all tasks ranged from 76–95% within the whole grid; auditory naming achieved 83% sensitivity and 82% specificity in the peritumoral ROI. No DES-positive sites were resected. Four patients showed postoperative decline on at least 1 language test, with decline in semantic fluency associated with resection of Object Naming gamma sites (Z=-1.83, p=.044) and presence of Action Naming ECoG features near the surgical cavity (Z=-2.25, p=.014). At 6 months, 14/17 (82%) patients had no speech deficits; 8/9 with preoperative deficits improved, while 2 had a new deficit potentially related to tumor progression and/or adjuvant treatment effect.

Conclusion: Gamma activity during auditory naming reliably predicts DES-defined language eloquence for safe maximal resection of brain tumors. Importantly, gamma activity may indicate eloquence even when localizations are unconfirmed via DES, as resection effect near task-based ECoG features appears related to risk of surgically-acquired cognitive-linguistic decline in the relatively early postoperative period.

Poster # 39

Abstract Title: Feasibility and Safety of Ipsilesional High-Frequency rTMS for Early Motor Recovery after Resection of Motor-Eloquent Brain Tumours

Authors: Sujit Prabhu (The University of Texas MD Anderson Cancer Center), Priscella Asman, Esteban Ramirez-Ferrer, Ahmad Ali, Kyle Noll, Antony Liu

Background: Post-operative motor deficits following resection of intrinsic brain tumours significantly impair quality of life and survival. Repetitive transcranial magnetic stimulation (rTMS) has shown promise for motor rehabilitation, yet only contralesional low-frequency stimulation (CL-LFS) has been tested in this setting. Ipsilesional high-frequency stimulation (IL-HFS), effective in stroke recovery, has not previously been explored in patients with brain tumours due to several safety concerns such as seizure risk, wound healing, and cranial implant heating.

Methods: A retrospective review was conducted of four patients who received IL-HFS and six who received standard CL-LFS following resection of intrinsic motor-eloquent tumours. Patients were eligible for IL-HFS if they had preserved ipsilateral motor evoked potentials. Pre- and post-rTMS myotomal strength (MRC scale) and functional status (AM-PAC 6-Click Daily Activity and Mobility scales) were compared using the Wilcoxon signed-rank test. Adverse events were recorded.

Results: All patients demonstrated significant improvements in MRC grade across assessed myotomes ($p < 0.05$). Strength gains were greater in lower- than upper-limb myotomes, and CL-LFS yielded slightly larger improvements overall. AM-PAC scores improved in both groups. No seizures or heating effects occurred. One IL-HFS patient required wound revision, likely due to it being a third operation through the same wound. The

same patient had a 30-second syncopal episode during the last of 13 rTMS sessions that did not clinically fit with a seizure. Another patient reported transient paraesthesia in the unaffected foot, resolving within 24 hours. Finally, another patient who had two programmable ventriculoperitoneal shunts in situ did not demonstrate any shunt setting changes.

Conclusions: IL-HFS rTMS can be safely administered in the early post-operative period following tumour resection. These preliminary findings support further prospective trials evaluating ipsilesional excitatory paradigms—alone or combined with contralesional inhibitory stimulation—to optimise motor recovery in patients with brain tumours.

†*Professional Development Award*

† Poster # 40

Abstract Title: Elucidating Neurodevelopmental Trajectories in Cancer with Topic Modeling: Revealing Persistent External Granule Layer Lineages in Medulloblastoma

Authors: Nick Low (Seattle Children's Research Institute), Ashmitha Rajendran, John H. Gennari, Siobhan S. Pattwell

Introduction: The rhombic lip and external granular layer (EGL) orchestrate cerebellar neurogenesis, producing over half of all adult human brain neurons. Dysregulation of these developmental processes drives medulloblastoma pathogenesis, particularly Sonic Hedgehog (SHH) subgroup tumors arising from granule neuron precursors. Standard cell clustering approaches often miss transient EGL progenitor populations, leaving unanswered which developmental programs persist in pediatric brain tumors. Our research uses topic modeling to systematically identify and transfer developmental transcriptional signatures across technologies and disease states.

Methods: We applied topic modeling to sequencing of 15,556 nuclei from post-conception week (PCW) 17 human fetal cerebella. Topics were validated by transfer to an independent dataset (119,954 nuclei, PCW 12.5) using gene set variation analysis (GSVA), then applied to medulloblastoma bulk RNA-sequencing (876 tumors). Spatial validation used in situ hybridization from the Allen Developing Mouse Brain Atlas.

Results: Using topic modeling, we identified seven distinct groups within EGL development, from proliferative outer EGL through differentiating inner EGL to migrating granule neurons. These revealed previously unrecognized cellular heterogeneity, including distinct rhombic lip-to-glial versus rhombic lip-to-neuronal lineage trajectories. Topics successfully transferred across independent datasets with different sequencing technologies. Spatial validation confirmed EGL-specific localization patterns, including outer-to-inner gradients matching computational predictions. When applied to medulloblastoma, EGL-derived topics confirmed GNP origins and revealed age-specific associations: SHHα retained proliferative outer EGL programs, SHHδ showed intermediate progenitor signatures, while SHHβ and SHHγ exhibited transitional and differentiating EGL states.

Conclusion: We show that topic modeling can be applied to systematically identify conserved transcriptional programs across datasets without data integration, successfully bridging normal development and cancer biology. Age-specific developmental programs persist in SHH medulloblastoma subtypes with distinct molecular signatures corresponding to differing prognoses and levels of treatment responses.

Significance to Cancer Neuroscience: This work establishes types of pediatric brain cancer as arrested neurodevelopment, where tumor heterogeneity reflects developmental stage at transformation. By mapping precise EGL developmental windows onto tumor subtypes, we can better understand stage-specific therapeutic vulnerabilities. Our framework is generalizable and can be applied to the developmental origins across all pediatric and adult brain tumors. In addition, this transferable methodology solves the fundamental challenge of connecting exponentially growing developmental atlases to clinical datasets, providing a scalable path for precision medicine that can match patients to treatments based on developmental identity rather than histology alone. This positions neurodevelopmental biology as the essential reference frame for understanding, stratifying, and treating pediatric brain cancer.

Poster # 41

Abstract Title: Modeling BRAF-driven glioma in human cerebral organoids reveals HOXB9 as a mediator of post-therapy tumor regrowth

Authors: Md Imtiaz Khalil (The University of Texas MD Anderson Cancer Center), Iolanda Scognamiglio, Alessia Savarese, S.P. Marisetty, N. Bhattacharya, L. Zhang, G. Cappuccio, M. Maletic-Savatic, Giannicola Genovese, Giulio F. Draetta, Luigi Perelli

Despite strong initial responses to combined BRAF and MEK inhibition in BRAF-altered gliomas, relapse and refractory disease remain frequent. Understanding the molecular mechanisms underlying resistance is essential for improving long-term therapeutic outcomes.

We established a pre-clinical glioma model leveraging human induced pluripotent stem cell–derived cerebral organoids engineered to express BRAFV600E and a GFP reporter for lineage tracing. These somatic mosaic genetically engineered cerebral organoids (SM-geCOs) were analyzed for tumorigenicity, phenotypic heterogeneity, and treatment response. Bulk RNA sequencing, immunohistochemistry, and functional assays were performed to identify and validate molecular mediators of resistance.

SM-geCOs developed glioma-like lesions expressing astrocytic, neuronal, and proliferative markers, and transplantation confirmed their tumorigenic potential. Upon exposure to dabrafenib, SM-geCOs displayed heterogeneous responses, including stable disease, acquired resistance, and intrinsic resistance—mirroring patient outcomes. Transcriptomic profiling of GFP^+ cells revealed a significant upregulation of HOX genes on chromosome 17, with HOXB9 as the most prominent candidate. Validation by immunohistochemistry and Western blot confirmed HOXB9 overexpression in both SM-geCOs and recurrent patient tumors. Loss-of-function experiments demonstrated that HOXB9 promotes glioma cell proliferation in vitro and in vivo. ChIP-seq identified EGFR as a direct transcriptional target of HOXB9, suggesting a feedback loop through the BRAF–HOXB9–EGFR axis that may drive MAPK pathway reactivation following targeted therapy.

Our findings identify HOXB9 as a key oncogenic mediator of adaptive resistance and post-therapy regrowth in BRAF-driven glioma.

This study introduces a robust human organoid platform that integrates neurodevelopmental context into glioma modeling, enabling mechanistic dissection of therapy resistance at the neural–cancer interface. By uncovering the role of HOXB9 in MAPK pathway reactivation, this work provides new insights into glioma plasticity and highlights potential targets for preventing recurrence in BRAF-mutant brain tumors.

Poster # 42

Abstract Title: Assessing the Value of CBV in Identifying Early Recurrence Risk in Glioblastoma

Authors: Mahsa Servati (MD Anderson Cancer Center), Ziyu Fu, Aliya Anil, Nazanin K Majd, Vinaykumar K Puduvalli, C. Chad Quarles

Introduction: Glioblastoma (GBM) is highly aggressive, with recurrence common despite maximal standard therapy. Cerebral blood volume (CBV) from DSC-MRI quantifies tumor vascularity and helps distinguish true progression from pseudoprogression. Standardized relative CBV (sRCBV) thresholds validated by Anil et al., 2024, against image-localized histopathology differentiate recurrence (sRCBV >1) and indicate viable tumor presence (sRCBV >1.37, ~88% probability). This study evaluates whether the fraction of high-sRCBV voxels serves as an early indicator of recurrence, identifying thresholds linked to recurrence onset.

Methods: Fifteen post-therapy MRI time points from six IDH1-wild-type GBM patients (five female, one male; age 49–81 years) were retrospectively analyzed under IRB approval (2012-0441, PI Dr. Puduvalli). All received Stupp-protocol chemoradiotherapy (VMAT 6000cGy/30 fractions) and temozolomide, followed by surveillance until recurrence. Only DSC-MRI scans acquired after chemoradiation were included. All studies used the consensus single-dose, low-flip-angle (30°) protocol without preload. Standardized RCBV maps were generated using IB Neuro with BSW leakage correction and registered to contrast-enhanced T1-weighted (T1CE) images. Tumor masks were defined semi-automatically on T1CE. The fraction of high-sRCBV voxels (fH) was calculated as voxels with sRCBV >1.37 divided by total tumor voxels. The interval between each scan and radiologic recurrence (Δt) was recorded. Associations between fH and Δt were tested using quadratic regression, ROC analysis for early (≤120 days) vs late recurrence, Youden-index thresholding, and Cox proportional-hazards modeling.

Results: Across 15 time points, fH showed a borderline-significant inverse relationship with time to recurrence (R^2 =0.35, p = 0.073). ROC analysis yielded AUC = 0.74 (95% CI 0.44–0.96) with an optimal threshold of fH ≈ 0.03. Higher fH correlated with increased recurrence hazard (β = 4.26, HR = 70.47 per +1.0 fH). Tumors with ~27% high-sRCBV voxels corresponded to a 120-day median recurrence-free survival.

Conclusion: Preliminary findings indicate that the fraction of high-sRCBV voxels within the enhancing tumor may serve as a quantitative indicator of glioblastoma recurrence risk. Although limited by small sample size and retrospective design, consistent trends suggest that higher vascular fractions correspond to shorter recurrence intervals and increased risk of regrowth. Ongoing work is expanding this analysis to a larger, multi-timepoint cohort to improve statistical power and define clinical thresholds for integration into CBV visualization tools.

Significance to the Cancer Neuroscience Field: Quantifying vascular heterogeneity through high-sRCBV fractions provides a noninvasive biomarker connecting tumor perfusion and recurrence dynamics. This aligns with the neural neoplasm framework by integrating vascular–neural interactions within the tumor microenvironment to refine prognosis and guide mechanism-based therapeutic strategies in GBM.

Poster # 43

Abstract Title: Understanding the Therapeutic Response to Vorasidenib in IDH-Mutant Glioma Models

Authors: Harsha Sugur (MD Anderson Cancer Center), Pratibha Sharma, Vinay K. Puduvalli

Introduction: Vorasidenib, a dual IDH1/2 inhibitor, has recently received FDA approval for the treatment of Grade 2 IDH-mutant (IDH-mt) gliomas. By targeting and reducing IDH-mutant protein activity, Vorasidenib modulates tumor metabolism and epigenetic regulation, leading to fundamental changes in the biology and microenvironment of these gliomas. However, it remains unclear how these molecular alterations influence the tumor's sensitivity to standard-of-care treatments such as radiation and chemotherapy, which remain essential therapeutic options for patients with recurrent or progressive high-grade IDH-mt gliomas. Our study aimed to evaluate the biological and therapeutic interactions between Vorasidenib and radiation in IDH-mt glioma models, providing insights into how IDH inhibition may affect subsequent treatment response.

Methods: We utilized a panel of IDH-mutant glioma cell lines—BT-142, GSC-522, and GSC-818—to assess cellular responses to combined Vorasidenib and radiation treatment. Synergy scores for cell viability were determined using Vorasidenib (10–50 μM) in combination with radiation (4–10 Gy). To further explore the biological impact, cell-cycle and protein expression analyses were performed to elucidate molecular mechanisms underlying treatment response. In parallel, organotypic human glioma slice cultures representing various IDH-mt tumor grades are being used to validate and extend these findings in a more physiologically relevant ex vivo system.

Results: BT-142, an oligodendroglioma-derived cell line harboring a homozygous IDH mutation, demonstrated pronounced sensitivity to both Vorasidenib and radiation. Vorasidenib treatment alone did not significantly alter cell-cycle progression when compared to controls, however, radiation induced, change in phases of cell-cycle in response to DNA damage, which increased with vorasidenib treatment. In contrast, the IDH-mt astrocytoma-derived lines GSC-522 and GSC-818, both derived from recurrent Grade 4 tumors, displayed inherent radiation sensitivity that was not significantly enhanced by Vorasidenib treatment.

Conclusion: Our findings suggest that IDH-mt oligodendroglioma cells are more responsive to Vorasidenib, which may enhance radiation-induced cytotoxicity through mechanisms independent of cell-cycle regulation, potentially by metabolic reprogramming. Conversely, IDH-mt astrocytomas display limited responsiveness to Vorasidenib, highlighting fundamental biological differences in treatment response between IDH-mt glioma subtypes. Ongoing in vitro and in vivo studies are further assessing the functional and translational relevance of these findings.

Significance to the Cancer Neuroscience Field: This study helps explain how IDH inhibition changes glioma biology and treatment sensitivity. It highlights that metabolic targeting with Vorasidenib may improve radiation response in some gliomas and supports precision strategies for personalized therapy approaches in IDH-mutant glioma patients.

Poster # 44

Abstract Title: Murine Glioma Models That Recapitulate the Human Glioma–Neuron Connectome

Authors: Han Nhat Tran (Weil Cornell Graduate School, Houston Methodist), Jose Maldonado, Jia-Shiun Leu, Caiyi Wang, Thomas Wong, Nourhan Abdelfattah, Jihye Paik, Massimo Squatritto, Joshy George, Kyuson Yun

Introduction: Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adult with a 15-month median survival. Previous neuroscience-focused research reported reciprocal interactions between

glioma cells and neurons, suggesting that GBM cells integrate into neural circuits and exploit synaptic signaling to drive tumor progression. However, the extent to which currently used mouse models of glioma, such as GL261, can be used to gain mechanistic insights in this intriguing biology is unclear. To address this gap, we leveraged five genetically distinct glioma models we deeply characterized in the Yun lab to make cross-species comparison about neurotransmitter expression and potential neural connections.

Methods: We analyzed single-cell RNA sequencing (scRNA-Seq) from gliomas established by transplanting five distinct glioma tumorsphere lines (and GL261 as a reference) into the striatum of C57BL6/J mice. From this dataset, we assess the expression different neurotransmitter receptors, synthesizing enzymes, and synaptic signaling machinery. We also performed multiplexed immunofluorescence analysis of candidate neurotransmitters to confirm their protein expression in the gliomas and in-vitro neuron-glioma coculture assays to assess functional connectivity.

Results: scRNA-Seq revealed that glioma cells from the five GBM models differentially express multiple neurotransmitter receptor families, including glutamatergic, GABAergic, and cholinergic receptors, with remarkable faithfulness to human GBM data. In contrast, GL261 gliomas did not express most of these molecules. Immunofluorescence analysis further confirmed abundant AMPA receptor expression within the TME of these models, whereas GL261 showed minimal expression. In neuron-glioma coculture, tumorsphere from five models forming structural connections with neurons, indicating the capacity for activity-dependent neuron-glioma interactions.

Conclusion: Our findings demonstrate that the five tumorsphere-derived models reproduce neuron-glioma connectome features observed in human GBM, including neurotransmitter receptors expression and the capacity to form neuron-tumor connectivity. We report heterogeneous levels and patterns of neurotransmitter expression in our cohort of mouse gliomas and make specific predictions about their sensitivity to pharmacological agents that inhibit specific neurotransmitter pathways. In constrast, GL261 is a poor model of human GBM and should not be used in cancer neuroscience studies.

Significance to cancer neuroscience field: This work highlights the critical importance of selecting a biologically relevant model when studying GBM. The new cohort of murine GBM models that faithfully recapitulate the neuron-glioma connection observed in human tumors enables more accurate intervention studies and mechanistic investigation.

Poster # 45

Abstract Title: The Role of Astrocyte Calcium Signaling in Glioblastoma Growth

Authors: Kate Wheeler (Texas Children's Hospital, Baylor College of Medicine), Christine Madamba, Qi Ye, Hyun Kyoung Lee

Glioblastoma (GBM) is a highly aggressive brain tumor with a poor prognosis despite current treatments. Its rapid progression is driven by both intrinsic tumor properties and dynamic interactions within the tumor microenvironment (TME) that contribute to treatment resistance and influence glioma growth. Recent studies have shown that bidirectional neuron-glioma interactions can drive both tumor growth and neuronal hyperactivity. Although astrocytes are key regulators of neuronal function, their role in GBM growth remains unclear. To investigate astrocyte-glioma interactions during tumor progression, we used an in utero electroporation based mouse model to generate de novo GBM tumors followed by single-cell RNA sequencing

at early and late stage GBM. This analysis revealed distinct tumor-associated astrocyte (TAA) clusters with reduced expression of calcium signaling related genes in late-stage tumors, suggesting that astrocyte calcium dysfunction may contribute to GBM progression. Because calcium activity is a proxy for astrocyte physiological function, we next investigated whether modulating calcium signaling in astrocytes influences tumor growth. To test whether increasing astrocyte calcium activity affects GBM progression, we delivered astrocyte-targeting AAVs expressing GqDREADD (As-GqDREADD) into tumor-bearing mice to chemogenetically stimulate intracellular calcium activity. Activation of As-GqDREADD in these mice led to a significant reduction in tumor size and proliferation, along with an increase in median survival. To determine whether reducing astrocyte calcium activity can drive tumor growth, we used As-CalEx, which induces astrocyte-specific expression of a plasma membrane calcium pump that extrudes intracellular calcium. Attenuating astrocyte calcium activity with As-CalEx led to a significant increase in tumor size and proliferation, suggesting that reduced astrocyte calcium signaling promotes GBM growth. To evaluate whether secreted astrocyte-derived factors contribute to these effects, we conducted an in vitro pilot experiment using conditioned media from As-GqDREADD stimulated primary astrocytes. Glioma cells treated with this conditioned media exhibited reduced proliferation and migration, suggesting that astrocyte-secreted signaling molecules may influence tumor behavior. Mass spectrometry analysis of conditioned media from As-GqDREADD stimulated astrocytes is underway to identify candidate molecules responsible for these effects. Together, these findings demonstrate that astrocyte calcium activity plays a central role in regulating GBM growth and highlight the importance of astrocytes in shaping tumor progression. By showing that astrocytes can impact glioma progression, this work strengthens the emerging framework of cancer neuroscience and identifies glial cells as important modulators of tumor progression and promising therapeutic targets.

Poster # 46

Abstract Title: TGF-β Signaling as a Checkpoint for Microglial Regulation of Myelin

Authors: Keying Zhu (Karolinska Institutet), Yun Liu, Vijay Joshua, Jianing Lin, Stephen Fancy, Heela Sarlus, Robert Harris, Harald Lund

Microglia regulate central nervous system myelination during embryonic development and adult homeostasis, yet whether microglia–myelin interactions are subject to spatiotemporal control remains unclear. By examining spinal cord white matter tracts, we found that myelin degeneration was particularly pronounced in the dorsal column (DC) during normal aging. This was accompanied by molecular and functional alterations in DC microglia, including upregulation of TGF-β signaling. Disruption of microglial TGF-β signaling triggered uncontrolled microglial activation and myelin loss in the DC, leading to neurological deficits that worsened with age. snRNA-seq analyses revealed the emergence of a TGF-β–responsive microglial subset and a disease-associated oligodendrocyte subset, both spatially confined to the DC. Moreover, we discovered that microglia depend on an autocrine TGF-β mechanism to protect myelin in this region. Together, these findings establish TGF-β signaling as an essential checkpoint that preserves microglial resilience to age-related myelin degeneration, underscoring a previously unrecognized mechanism with regional specificity and spatially restricted microglia–oligodendrocyte crosstalk.

Theme: Neurotoxicity

Poster # 47

Abstract Title: ImmunoPET in Cranial Radiotherapy-Induced Neuroinflammation

Authors: Taylor Brinson (UT Health Graduate School of Biomedical Sciences), Evanta Kabir, Onder Otlu, Ronnie The Phong Trinh, Wei Xiong, Yaima L. Lightfoot, Wiliam J. Ray, Zhiqiang An, Ningyan Zhang, Federica Pisaneschi

Introduction: In the central nervous system, neuroinflammation is driven by complex inflammatory networks that initially protect the brain's parenchyma but can become damaging when chronically activated. One indicator of neuroinflammation is the activity of antigen-presenting and immune-associated cells, like microglia. Among their regulatory pathways, TREM2 (triggering receptor expressed on myeloid cells-2) is a compelling biomarker for its association with microglial activation, phagocytosis, neuroinflammatory signaling, and even tumor microenvironment remodeling. Cranial radiotherapy (CRT), an essential treatment for brain tumors, can create adverse effects on healthy brain tissue, including oxidative stress, blood-brain barrier disruption, chronic glial activation, and potential cognitive impairment. Despite the clinical significance of these effects, there is a lack of reliable in vivo imaging tools that can monitor neuroinflammation. Using ImmunoPET (Positron Emission Tomography), we aim to address this knowledge gap by visualizing neuroinflammation with a novel radiotracer, 89Zr-TREM2-Tfr_BsAb, that reports uptake by myeloid cells, especially microglia, in a TREM2-mediated manner.

Methods: To model neuroinflammation, C57BL/6 mice received intraperitoneal injections of lipopolysaccharide (LPS) before administration of 89Zr-TREM2-Tfr_BsAb. PET/CT imaging was conducted to assess tracer uptake in the brain, followed by ex vivo immunohistochemistry to quantify microglial activation. A separate cohort was subjected to a single 20 Gy dose of whole-brain CRT to induce radiation-associated neuroinflammation. These animals were imaged using the same ImmunoPET protocol to evaluate tracer accumulation in irradiated versus control brains.

Results: PET/CT imaging revealed significantly higher uptake of 89Zr-TREM2-Tfr_BsAb in the brains of LPS-treated mice compared to controls. Ex vivo immunohistochemistry confirmed an increased density of IBA1-activated microglia in the LPS group, correlating with elevated tracer uptake. Similarly, CRT-exposed mice exhibited increased 89Zr-TREM2-Tfr_BsAb uptake in the brains of irradiated mice relative to non-irradiated controls.

Conclusions: We demonstrate that 89Zr-TREM2-Tfr_BsAb serves as a sensitive and specific imaging agent for detecting microglial activation in both LPS-induced and CRT-induced models of neuroinflammation. The tracer's uptake pattern reflects localized immune activity, validating its potential for longitudinal monitoring of neuroinflammatory processes in the CNS.

Significance to the Cancer Neuroscience Field: This work introduces a molecular imaging approach to visualize neuroinflammation following CRT. The development of 89Zr-TREM2-Tfr_BsAb as a TREM2-specific ImmunoPET agent provides a translational tool for assessing treatment-related neurotoxicity, identifying early biomarkers of cognitive impairment, and potentially informing therapeutic strategies for neuroprotection in cancer survivors.

† Poster # 48

Abstract Title: Chemotherapy-Induced Disruption of TrkB–AKT–PAK5–SNPH Pathway in Sensory Neurons

Authors: Jordan Chatwin (MD Anderson Cancer Center), Hinduja Sathishkumar, Shamima Akhter, William McCarthy, Yen Vu, Tongxin Xie, Andrew Lara, Moran Amit

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of platinum-based chemotherapy. It is often associated with impaired mitochondrial motility and axonal damage in neurons. Debilitating side effects can prevent patients from finishing treatment, yet the molecular mechanisms underlying these disruptions remain poorly understood.

Aims & Hypothesis: This study investigates how chemotherapy affects mitochondrial dynamics, focusing on key regulators of axonal transport and mitochondrial anchoring. We hypothesize that axonal stress caused by platinum-based chemotherapy specifically affects the TrkB–AKT–PAK5–SNPH pathway, with additional interactions between MAP2 and KIF5b, leading to impaired mitochondrial motility and anchoring imbalances that contribute to neuronal damage.

Methods: Fixed-cell imaging and ImageJ analysis were used to assess colocalization between the axonal marker β3-tubulin and the mitochondrial marker TOMM20, as well as between β3-tubulin and syntaphilin (SNPH), to examine mitochondrial colocalization and anchoring under chemotherapeutic stress. Live-cell imaging of sensory neurons was used to measure mitochondrial motility following chemotherapy. Western blotting was performed to examine phosphorylation and expression of the TrkB–AKT–PAK5–SNPH pathway, as well as transport-related proteins including KIF5b, SNPH, and MAP2, to evaluate how chemotherapy affects the molecular machinery regulating mitochondrial trafficking. Human iPSC-derived sensory neurons were exposed to cisplatin. ATP staining on iPSC-derived sensory neurons measured cellular ATP production levels under chemotherapy exposure.

Results: Fixed-cell imaging and ImageJ analysis showed a significant decrease in colocalization between β3-tubulin and TOMM20 and a significant increase in colocalization between β3-tubulin and SNPH under cisplatin exposure. Live-cell imaging revealed a significant reduction in mitochondrial velocity and an increase in dendritic mitochondrial accumulation and neuronal ATP activity. Western blot analysis showed significantly decreased TrkB phosphorylation and reduced downstream AKT and PAK5 signaling in the presence of cisplatin. SNPH expression was significantly increased, while KIF5b levels were reduced, and MAP2 expression and its association with KIF5b were altered under chemotherapeutic stress. ATP staining showed significantly decreased cellular ATP levels in cisplatin-treated neurons compared to control.

Conclusions: The findings support our hypothesis that cisplatin disrupts the TrkB–AKT–PAK5–SNPH signaling axis and destabilizes MAP2–KIF5b interactions in human sensory neurons. These disruptions correspond with reduced mitochondrial transport, increased mitochondrial anchoring, and decreased ATP levels, indicating impaired energy production and axonal integrity in cisplatin-treated neurons. This suggests that CIPN involves signaling-dependent regulation of mitochondrial transport mechanisms. Targeting components of this pathway could inform neuroprotective strategies and guide future studies aimed at reducing chemotherapy-induced neurotoxicity in cancer patients.

Significance for Cancer Neuroscience: This work identifies a signaling network linking neurotrophic receptor activity to mitochondrial trafficking, cytoskeletal organization, and neuronal health during chemotherapy

exposure. Chemotherapy-induced neurotoxicity currently lacks effective therapeutic solutions. By defining molecular targets within this pathway, our findings could support the development of clinical interventions that mitigate neurotoxicity and enable the use of more permissive cytotoxic protocols, improving delivery of anticancer therapeutics while preserving neuronal function.

Poster # 49

Abstract Title: Apparent Diffusion Coefficient as an Early Imaging Biomarker of Radiation-Induced Cognitive Decline in High-Grade Glioma

Authors: Ory Haisraely (MD Anderson Cancer Center), Jeffrey Scott Wefel, Bikash Panthi, Kyle Richard Noll, Andrew Elliott, Sara Thrower, Eleni Konstantinopoulou, Holly Langshaw, Wasif Talpur, Catherine Sullaway, Todd Swanson, Chenyang Wang, Martin Tom, Thomas Beckham, Wen Jiang, Debra Yeboa, Mary Frances McAleer, Susan Lynne McGovern, Jing Li, Caroline Chung

Background: Radiation therapy (RT) for high-grade glioma prolongs survival but may injure adjacent normal brain, particularly the hippocampus. Diffusion-weighted MRI–derived apparent diffusion coefficient (ADC) is a sensitive marker of microstructural injury, yet its dynamics during RT and relationship to cognition remain unclear.

Methods: In a prospective trial, 24 adults with glioblastoma (KPS ≥60) receiving partial-brain RT (60 Gy/30 fractions) underwent weekly MRI and concurrent cognitive testing with the Cogstate battery. Hippocampal ADC change from week 1 to week 6 was the primary imaging metric. Associations with hippocampal dose, tumor location, and cognitive outcomes were analyzed using correlations, effect sizes, and regression models.

Results: Median combined hippocampal dose was 14.5 Gy (range 9.9–21.6). Hippocampal ADC increased steadily during RT, with a median relative rise of 16% (range 3–28%), most pronounced between weeks 4–6. Patients with cognitive decline showed larger ADC increases than those without: composite decline 13% vs. 7% (Cohen's d = 1.0), FSBT decline 12% vs. 6% (d = 0.8), and FNLT decline 11% vs. 7% (d = 0.5). Other domains showed smaller differences. Stratification confirmed a dose–response: >20% ADC increase corresponded to ≥75% decline rates across several domains, while ≤5% change was associated with <30% decline. In multivariable analysis, ADC increase >10% (OR 1.55, 95% CI 1.08–2.22, p=0.025) and frontal tumor location (OR 1.21, 95% CI 1.17–1.56, p=0.041) independently predicted composite decline, whereas hippocampal dose alone was not significant.

Conclusions: Hippocampal ADC increases occur early during RT and are strongly associated with cognitive decline. Larger ADC changes discriminated between decline and stable groups and showed a clear dose–response pattern, outperforming dose metrics. These findings support ADC as a promising early biomarker of neurocognitive risk and a potential tool for adaptive or neuroprotective strategies.

Poster # 50

Abstract Title: Non-Invasive Biomarkers of Neuroinflammation: Breath VOCs Predict Severe ICANS in CAR T Recipients

Authors: Teny John (MD Anderson Cancer Center), Hamid Rudsari, Amalia Z Berna, Ehsan Irajizad, Johannes F. Fahrmann, Yang Liu, Joe Logan, Sairah Ahmed, Sattva S Neelapu, Neeraj Y. Saini, Audrey Odom John

Background: Immune effector cell–associated neurotoxicity syndrome (ICANS) remains a major complication of CAR T-cell therapy, yet early prediction is challenging. Non-invasive biomarkers such as exhaled breath volatile organic compounds (VOCs) offer a promising avenue for risk stratification and mechanistic insights.

Methods: We conducted a longitudinal prospective study of adult (≥18 years) diffuse large B cell lymphoma patients who received axicabtagene ciloleucel CAR T-cell therapy from March 2023 to June 2024. From each subject, 1 L of exhaled breath and room air samples were collected at 4 time points: before CAR T-cell (baseline) and 3 occasions after CAR T-cell, starting day +1. Air and breath samples were analyzed with a two-dimensional gas chromatography–time-of-flight mass spectrometry with a Bench TOF system. ICANS was graded according to ASTCT guidelines, and grade ≥2 was considered severe. Prediction models were developed based on baseline data. Random forest analysis was applied to principal component analysis scores and a five-fold cross-validation was employed to assess the model's performance.

Results: We enrolled 29 patients, and 26 patients' breath samples were analyzed. Median age was 60 years (IQR 49-67), and 22 (76%) were male. 12/26 (46%) developed severe ICANS. Twelve baseline breath VOCs predicted severe ICANS with an AUC of 0.82. The model showed an overall accuracy of 66%, with a specificity of 90% and a sensitivity of 77%. Notably, several alkanes (e.g., undodecane, tetradecane) and oxygenated monoterpenes (e.g., α-terpineol) emerged as top predictors and exhibited moderate stability. Aromatic hydrocarbons such as p-xylene and cumene, also enriched in predictive models, may signal blood–brain barrier disruption and altered membrane integrity. These compounds plausibly reflect oxidative stress, lipid peroxidation, neuroinflammatory cascades, and microbiome changes implicated in ICANS pathophysiology.

Conclusions: Pre-CAR T therapy, breath VOC signatures demonstrate potential for early ICANS risk stratification. Biological plausibility of key VOCs supports their role as non-invasive markers of neuroinflammation and systemic oxidative stress. Future work should validate these findings in larger cohorts and explore multi-omic integration to refine predictive accuracy and mechanistic understanding.

Significance to the cancer neuroscience field: We identified a panel of exhaled breath VOCs that can non-invasively predict severe ICANS before CAR T-cell therapy, with high specificity and biologically plausible links to neuroinflammation and oxidative stress. These findings offer a novel, scalable approach to early neurotoxicity risk stratification in cancer immunotherapy. This work bridges cancer neuroscience and systems biology, with the potential to transform the monitoring of neuroimmune complications in immunocompromised patients.

Poster # 51

Abstract Title: When Mitochondria Stop Moving: Impaired Organelle Dynamics and Morphological Collapse in Chemotherapy-Treated Trigeminal Ganglion Neurons, Implications for Trigeminal Neuralgia

Authors: William McCarthy (UT Health Science Center at Houston), Hinduja Naidu Sathishkumar, Mario Heles, Shorook Naara, Shamima Akhter, Tongxin Xie, Yen Vu, Jordan Chatwin, Brown Andrew Lara, Lilach Pasvolsky, Moran Amit

Background: Trigeminal neuralgia in cancer patients can result from chemotherapy-induced nerve injury, particularly from platinum compounds and taxanes that cause direct axonal injury and ganglion cell damage. Chemotherapy-induced peripheral neuropathy can manifest as trigeminal neuralgia-like symptoms through direct injury to trigeminal ganglion neurons, with mechanisms including axonal degeneration, reduced neuronal arbor complexity, and mitochondrial dysfunction. The trigeminal ganglion is particularly vulnerable to chemotherapy-induced neurotoxicity, with resulting orofacial pain and sensory disturbances significantly impacting quality of life in head and neck cancer patients. While chemotherapy-induced trigeminal neuropathy affects up to 68% of patients receiving neurotoxic agents, the specific morphological and functional changes in trigeminal ganglion cells remain incompletely characterized. This study investigated the morphological damage and mitochondrial dysfunction in trigeminal ganglion neurons following chemotherapy exposure.

Methods: Trigeminal ganglia were harvested from adult mice and dissociated trigeminal ganglion neurons were cultured. Cells were exposed to clinically relevant concentrations of cisplatin and docetaxel. Neuronal architecture of trigeminal ganglion cells was quantified using Gen5 Cytation 7 neurite outgrowth module with neurofilament immunofluorescent signal thresholding, measuring dendrite branch count, neurite length, and area. Mitochondrial dynamics within trigeminal neurons were assessed via 5-minute time-lapse microscopy sequences using MitoBright dye with Laplacian of Gaussian detection and Single Linear Assignment Problem linking, analyzed in ImageJ's TrackMate plugin. Spatial particle tracking analyzed mitochondrial velocity and distribution patterns within trigeminal ganglion neurons.

Results: Cisplatin and docetaxel induced significant morphological damage in cultured trigeminal ganglion neurons. Both chemotherapy agents substantially reduced dendrite branch count, total neurite length, and neuronal area compared to vehicle-treated controls. Quantitative morphometric analysis via Sholl analysis revealed marked reductions in arbor complexity in trigeminal ganglion cells exposed to chemotherapy. Additionally, both cisplatin and docetaxel severely impaired mitochondrial dynamics within trigeminal neurons, with significant reductions in mean mitochondrial velocity and disrupted directional movement patterns. Spatial tracking analysis demonstrated altered mitochondrial distribution, with impaired trafficking to distal neuronal processes where metabolic demand is highest.

Conclusions: This study provides detailed characterization of chemotherapy-induced damage to trigeminal ganglion neurons, demonstrating severe morphological alterations and mitochondrial dysfunction that likely underlie trigeminal neuropathy in cancer patients. The profound structural damage and impaired cellular energetics observed in trigeminal ganglion cells exposed to cisplatin and docetaxel explain the persistent orofacial sensory deficits experienced by head and neck cancer patients. These findings highlight the urgent need for neuroprotective strategies to preserve trigeminal ganglion cell integrity during cancer treatment.

Poster # 52

Abstract Title: Radiation-induced neurogenic inflammation and hyperinnervation impedes therapeutic response in head and neck cancer

Authors: Neha Mokhasi (University of Pittsburgh), Joseph O. Veliz, Ashlyn G. Rickard, Megan A. Atherton, Yvonne M. Mowery, Nicole N. Scheff

Introduction: Pain during and after radiation therapy (RT) for head and neck cancer (HNC) is a major clinical challenge due to its multifactorial etiology and variable management. Radiation-induced pain typically co-

develops with oral mucositis (OM), an inflammatory condition defined as tissue damage to the oral mucosa resulting in highly symptomatic lesions. Sensory innervation of the oral cavity is dense and TRPV1-expressing peptidergic afferents have been strongly implicated in both oral cancer immunosurveillance and RT-induced OM. We predict that blockade of sensory signaling will improve radiation therapeutic response and reduce OM severity in head and neck cancer.

Methods: We developed a novel, oral mucositis-pain mouse model, induced by focal, image-guided RT that delivers a single focal RT (15Gy) regimen localized to the anterior oral cavity. Naïve C57Bl/6 mice and a syngeneic orthotopic HNC mouse models were used to characterize RT-induced tongue ulceration, changes in body condition, nociceptive behavior and trigeminal ganglia neuron (TGN) plasticity, injury and regeneration. Prophylactic local sensory denervation using resiniferatoxin (RTX) prior to RT was used to test the impact of sensory nerves on RT-induced pain and OM.

Results: Single focal RT resulted in peak weight loss (-26±5%) and tongue ulcerations by post-RT day (PRD) 12 but were able to full recovery by PRD 21. Nociceptive behaviors associated with OM were detectable at PRD10-14 as measured by the dolognawmeter, mouse grimace scale, and open field assay. We found a 2-fold increase in Calca/CGRP expression in mandibular TGNs on PRD 12 (peak) compared to sham RT which persistented in TGNs at PRD 21 (recovery). Local RTX into tongue on PRD0, PRD4 and PRD8 was used to test the impact of sensory nerves on OM development/recovery. RTX treatment mice had a 93% reduction in ulcer formation and 50% less weight loss compared to vehicle treatment. Additionally, using 3 different syngeneic tumor models, we found a significant increase in S100-immunoreactive nerve density in tumor tissue 2 weeks after mice received a single focal RT compared to sham suggesting that RT by itself can induce neuronal sprouting in the oral cavity.The interplay between RT-induced sprouting and OM severity is currently under investigation.

Conclusion: These findings demonstrate that prophylactic sensory denervation significantly reduced ulcer formation and weight loss, suggesting that targeting sensory signaling may mitigate RT-induced toxicity in HNC. Further investigation into mechanisms linking RT-induced neuronal sprouting to OM pathogenesis may reveal additional targets for improving outcomes during treatment.

Poster # 53

Abstract Title: FDG PET cerebral metabolic phenotypes in breast and prostate cancer survivors with cognitive impairment

Authors: Bryan Neth (Mayo Clinic Rochester), Sampath Gogineni, Leland Barnard, Nick Corriveau-Lecavalier, Mary Ellen Koran, Kathryn J Ruddy, Dan Childs, Ugur Sener, Val Lowe, Clifford Jack, Ronald Petersen, David Knopman, Jeffrey Wefel, Jonathan Graff-Radford, David Jones

Introduction: Cognitive impairment is a common and distressing concern amongst cancer survivors. The underlying pathologic etiology of cognitive impairment is poorly understood in this setting. FDG PET can be utilized to understand cerebral metabolic patterns associated with established degenerative causes of cognitive impairment, although there are few studies assessing FDG PET in cancer-related cognitive impairment (CRCI).

Methods: Our cohort included well-characterized patients from the Mayo Clinic Study of Aging (MCSA) with pathology confirmed diagnosis of breast or prostate cancer. All patients completed FDG PET imaging for

research. StateViewer analysis was performed on each FDG PET scan (svFDG) and provided log odds for 14 clinical phenotypes based on an established reference library including the ability to match to cognitively unimpaired groups. We conducted a descriptive analysis.

Results: 99 patients with history of either breast (n=33) or prostate (n=66) cancer (55% were diagnosed with cancer ≥5 years from MCSA entry) and svFDG were included. All patients had objective cognitive impairment (mild cognitive impairment – n=40, dementia – n=59). Median age at imaging was 88 years (range: 83-90), and 71 years (range: 65-77) at cancer diagnosis. Prior cancer treatment exposures included surgery (55%), radiotherapy (34%), hormone therapy (25%), chemotherapy (13%), and immunotherapy (1%). 35% were APOE4 positive. A svFDG phenotype match (if log odds >1 and $p<0.05$) was found in 85% (n=84) of patients, with 23% (n=23) having 2 significant matches. The most common phenotypes were limbic-predominant amnestic neurodegenerative syndrome (LANS; n=18), normal pressure hydrocephalus (n=17), Alzheimer's disease (n=14), and cognitively unimpaired (n=24).

Conclusion: Our results demonstrate that there are heterogenous cerebral metabolic phenotypes underlying cognitive impairment in breast and prostate cancer survivors, including a high proportion of patients without a neurodegenerative metabolic pattern. Analyses are limited by our sample, which includes mostly older patients who had cancer in the distant past. Further work in this cohort will relate FDG patterns with clinical phenotypes and the impact of specific cancer treatment exposures.

Significance to the cancer neuroscience field: This study provides important insight into how cerebral metabolism differs among cognitively impaired cancer survivors. Future prospective studies incorporating longitudinal FDG PET may improve understanding of etiologic contributors to CRCI at different times throughout cancer survivorship.

†*Professional Development Award*

† Poster # 54

Abstract Title: Mitochondrial motility and axonal degeneration in CIPN: Mouse and human sensory neuron models.

Authors: Hinduja Sathishkumar (MD Anderson Cancer Center), Lilach Pasvolsky, Yen Vu, Jordan Chatwin, William McCarthy, Caitlyn Stewart, Shamima Akhter, Tong Xin Xie, Frederico Omar Gleber Netto, Moran Amit

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of cisplatin treatment, leading to long term sensory damage. Mitochondrial dysfunction contributes to axonal degeneration, and its role in sensory neurons remains unclear. We hypothesize that cisplatin impairs mitochondrial transport and structure by disrupting microtubule integrity, leading to axonal energy deficits and degeneration.

Methods: Effects of cisplatin were studied on mitochondrial behavior in three models: mouse trigeminal ganglia (TGs), human induced pluripotent stem cells (iPSCs) derived sensory neurons- dorsal root ganglia(rDRGs), and human nerve samples. TGs were treated with chemotherapy in vitro and the nerve samples from two different cohorts where one group received chemotherapy (n=8) and the other group is treatment naive (n=5) were labeled with MitoBright Light Green and imaged using Andor XD Revolution Spinning Disc microscope to quantify the mitochondrial motility. Mitochondrial mean velocity was quantified using trackmate spatial particle tracking algorithm, and motile mitochondria were determined by kymography. TEM was performed on iPSCs to

assess the mitochondrial morphology, including cristae integrity, calculating the cristae-to-mitochondrial area ratio using FIJI.

Results: Live cell imaging of the TG's revealed that under control conditions, mitochondria showed robust bidirectional transport reflected by diagonal traces on kymographs. Cisplatin exposure noticeably disrupted this movement, resulting in fewer motile mitochondria (control: 41.29 ± 6.784; cisplatin: 25 ± 11.18; $p < 0.001$) and increased stationary populations, with vertical traces indicative of disrupted axonal transport. Spatial particle tracking analysis of nerve samples from patients treated with platinum-based chemotherapy (n=8) and treatment naive (n=5) using trackmate revealed the reduction in velocity (control: 5.758 ± 0.798 μm/s; cisplatin: 1.804 ± 0.467 μm/s; $p < 0.001$) of mitochondrial movement in cisplatin treated group than controls confirming impaired trafficking. TEM analysis on iPSCs supported these findings: control neurons displayed intact double membranes and densely packed cristae, while cisplatin treated samples exhibited mitochondrial swelling, disrupted membranes, and fragmented cristae. Quantitative morphometry revealed a significant reduction in the cristate-to-mitochondrial area ratio (control: 0.075 ± 0.01; cisplatin: 0.043 ± 0.005; ANOVA $p < 0.001$).

Conclusions: Cisplatin disrupts mitochondrial dynamics and ultrastructure, impairing axonal energy homeostasis and contributing to sensory neuron degradation in CIPN. These findings provide mechanistic evidence that targeting mitochondrial dynamics may offer therapeutic benefits to prevent or reverse neuropathy.

Significance to the cancer neuroscience field: Preserving mitochondrial motility represents a promising therapeutic avenue against CIPN and offers mechanistic insight relevant to broader neuropathic and neurodegenerative conditions where mitochondrial transport is disrupted.

Poster # 55

Abstract Title: Application of Nanoscale Metal-Organic Frameworks Against Chemotherapy-Induced Cognitive Impairments in Zebrafish Model

Authors: Charan Singh (Hemvati Nandan Bahuguna Garhwal University, A Central University), Sabiya, Sonima Prasad, Arti Singh

Introduction: This present study investigates the enhanced therapeutic potential of thymoquinone (TQ)-loaded nanosized Zeolitic Imidazolate-based metal-organic frameworks (TQ@ZIF-8) against a doxorubicin (DOX)-induced zebrafish chemobrain model.

Methods: NanoMOFs were developed using an industrially scalable and reproducible spray drying method. After synthesis, these were subjected to solid-state investigations, including FTIR, DSC, PXRD, TEM, and EDS-SEM, as well as in vitro release studies and radical scavenging activity assays using the DPPH method. After establishing the in vitro potential of TQ@ZIF-8, we conducted in vivo studies, including neurobehavioral (T-Maze, Novel Tank Test), biochemical (LPO, AChE, SOD, and GSH), inflammatory markers (TNF α and IL 1β) estimation and histopathological analyses.

Results: Drug loading into ZIF-8 was confirmed by FTIR, UV-Vis spectrophotometric and DSC techniques. The structural integrity and crystallinity of ZIF-8 remained unchanged after drug loading, as demonstrated by the PXRD data. TEM analysis revealed the rhomboidal morphology with a nanosized range. In vitro drug release kinetics showed 74±5.5% and 50±1.5% TQ released from TQ@ZIF-8 and free TQ, respectively, in PBS (7.4).

The greatest rate of antioxidant scavenging was achieved with Vitamin C (72.77 ± 5.7%) at a concentration of 200 µg/ml, and was 68.09 ± 2.5% and 56.39 ± 3.1% for TQ@ZIF-8 and TQ, respectively, at identical intensity. Furthermore, in vivo studies on zebrafish model exhibited that DOX dosage relatively impaired cognitive activity in T-Maze, and downregulated spatial memory and locomotor activity in the novel tank diving test and downregulation in GSH and SOD rates and upregulation in LPO, AChE, IL 1β and TNF-α levels in comparison to the vehicle group, along with changes in brain histopathology. Upon treatment, TQ@ZIF-8 (18.75 mg/kg; equivalent to TQ) vis-à-vis unformulated TQ (12.5 mg/kg) restored cognitive function and biochemical levels and downregulation of inflammatory markers. There was a remarkable difference. Additionally, histopathological analysis revealed that the TQ@ZIF-8 treatment had enhanced neuroprotective effects compared to the DOX- and TQ-treated zebrafish groups, possibly due to the antioxidant and anti-inflammatory properties of TQ.

Conclusion: Our study demonstrated the potential of spray-dried TQ@ZIF-8 as a promising approach for treating chemotherapy-induced cognitive impairments.

Significance to the cancer neuroscience field: The current research work enables researchers to investigate the mechanisms of DOX-induced neurotoxicity, including oxidative stress and inflammation, which can lead to cognitive decline. Additionally, our work suggests the application of phytoactive-loaded nanoMOFs in the treatment of chemobrain caused by chemotherapeutic agents, thereby bridging the fields of nanomedicine and cancer neuroscience.

Poster # 56

Abstract Title: Understanding long-term cognitive side effects of pediatric brain tumor chemotherapy and therapeutic mitigation via enhanced mitophagy

Authors: Anand Singh (MD Anderson Cancer Center), Kechen Ban, Momo Harris, Shungu Zimbwa, Meishan Zhou, Alesandra Echeandia Marrero, Renae Bertrand, A. Khalil Ali Ahmad Kasm, Tamra E. Ogilvie, Rajasekaran Mahalingam, Yuan Pan

Introduction: Advances in cancer treatment have raised the survival rate of children with brain tumors to 75.5%. However, treatments can lead to long-term side effects, including chemotherapy-induced cognitive impairments (CICI). The mechanisms behind pediatric brain tumor-associated CICI are poorly understood, and no FDA-approved treatments exist to prevent or reverse them.

Methods: We developed a preclinical model by administering carboplatin to 3-week-old juvenile wild-type mice. Cognitive function was assessed using the puzzle box test (PBT, executive function) and novel object place recognition test (NOPRT, working memory/attention). For cellular and molecular studies, we conducted single-nucleus RNA sequencing, immunohistochemistry, and Seahorse assay.

Results: Two months after cessation of juvenile carboplatin exposure, mice exhibited deficits in PBT and NOPRT, indicating enduring cognitive impairments. We noted a reduction in astrocyte density and morphological complexity in the hippocampus of these mice, while the densities of microglia and oligodendroglia remained unchanged. Further transcriptomic analyses revealed that juvenile exposure to carboplatin disrupts mitochondrial pathways in hippocampal astrocytes but not in neurons. Supporting the in vivo findings, carboplatin decreased the number of human hippocampal astrocytes and lowered their mitochondrial oxygen consumption rate in vitro. Given that astrocytes can exchange mitochondria with neurons

to support synaptic communication, we isolated synaptosomes to evaluate mitochondrial function. The results indicate that juvenile carboplatin exposure also compromises synaptic mitochondrial function. To counteract the mitochondrial deficits in both astrocytes and neurons, we administered urolithin A, a mitophagy-inducing compound, to juvenile carboplatin-exposed mice in adulthood. Urolithin A alleviated the cognitive and mitochondrial deficits caused by carboplatin. Additionally, urolithin A exhibited an inhibitory effect on the growth of medulloblastoma cells in vitro, suggesting a potential strategy for alleviating CICI in medulloblastoma survivors.

Conclusions: Our findings reveal that juvenile carboplatin exposure impairs hippocampal astrocyte mitochondria and cognitive function, which can be alleviated by administering a mitophagy enhancer.

Significance to the cancer neuroscience field: This study highlights the role of astrocytes in CICI and identifies mitochondrial dysfunction as a central mechanism linking cancer therapy to neural circuit dysregulation. By demonstrating that pharmacological enhancement of mitophagy can restore cognitive and mitochondrial function, these findings introduce a novel therapeutic avenue for mitigating neurocognitive side effects in pediatric brain tumor survivors, an emerging frontier in cancer neuroscience.

Poster # 57

Abstract Title: Tracking Chemotherapy-Induced Endosomal and Axonal Trafficking Deficits Using the Fluorescent Peptide Probe dTAT488

Authors: Caitlyn Stewart (MD Anderson Cancer Center), Xudong Qiu, Hinduja Sathishkumar, Lilach Pasvolsky, Yen Vu, Moran Amit

Introduction: Chemotherapy-induced neurotoxicity is a major complication of cancer treatment contributing to sensory neuropathy and cognitive impairment. A key but understudied mechanism is disrupted endosomal and axonal transport, essential for neuronal dynamics. Cisplatin disrupts axonal transport and mitochondrial dynamics, causing synaptic and structural degeneration. To examine these mechanisms, we leveraged dTAT488—a fluorescent tagged derivative of the HIV-1 trans-activator of transcription (TAT) peptide, a highly charged cell-penetrating domain that follows endosomal routing and enables visualization of intracellular trafficking. We hypothesized that cisplatin disrupts transport of systemically administered dTAT488 along peripheral and central neuronal pathways, impairing trafficking essential for neuronal communication.

Methods: Adult mice were treated with cisplatin or PBS control, followed by tail vein injections of dTAT488. In vivo imaging system (IVIS) analysis assessed peptide trafficking and accumulation in brain and peripheral tissues. Brains, sciatic nerves, and retinas were harvested for cryo-sectioning. Coronal brain sections encompassing the prefrontal cortex (PFC) and hippocampus—regions implicated in chemotherapy-induced cognitive dysfunction—were prepared for immunohistochemistry (IHC). Planned markers include GFAP and Iba1 (astrocytic/microglial activation), β3-tubulin and SOX10 (neuronal/Schwann cell identity), NFL (axonal integrity), and Tomm20 (mitochondrial distribution). Signal intensity and co-localization with dTAT488 will be quantified using ImageJ and Visiopharm to assess trafficking across neural and glial populations. Quantitative IHC outcomes will be correlated with behavioral measures from von Frey, hot plate, novel object recognition (NOR), and puzzle box assays to evaluate whether trafficking disruption predicts sensory and cognitive dysfunction.

Results: Baseline pre-treatment behavioral assessments confirmed consistent sensory and cognitive performance across groups. Post-treatment assays will determine whether cisplatin-induced trafficking deficits correlate with behavioral outcomes. IVIS imaging showed markedly reduced brain dTAT488 fluorescence in cisplatin-treated mice compared to controls, consistent with disrupted neuronal trafficking. Retinal imaging showed a similar trend of prolonged fluorescence retention in retinal blood vessels, suggesting degradation impairments. Analyses of sciatic tissues are ongoing to evaluate peripheral deficits. Quantitative correlations between IVIS, IHC, and behavioral outcomes will assess the predictive value of dTAT488 as a biomarker for chemotherapy-induced neurotoxicity.

Conclusion: These preliminary findings demonstrate that cisplatin disrupts endosomal and axonal trafficking and highlight dTAT488 as a novel in vivo tool to visualize and quantify these transport deficits.

Significance to the Cancer Neuroscience Field: Disrupted neuronal trafficking provides mechanistic insight into chemotherapy induced neurotoxicity. dTAT488 serves as a novel biomarker to study CNS and PNS effects and may inform strategies to preserve neuronal integrity and cognitive function in cancer patients.

Poster # 58

Abstract Title: Neuronal Regulation of Melanoma Progression and Metastasis

Authors: Xiyue (Shirley) Wang (UT Southwestern Medical Center), Sean Morrison

The tumor microenvironment (TME) is a critical player in tumor progression, as cancer cells actively remodel their surroundings to support their growth and dissemination. Among TME components, peripheral nerves are emerging as key regulators of cancer progression. While the importance of this interaction is established, the precise mechanisms by which specific nerves regulate cancer progression are largely unknown. Using melanoma as the main model, our study aims to explore extracranial neuron-cancer crosstalk and its impact on tumor proliferation and metastasis.

To investigate these interactions, we developed an ex-vivo coculture system with melanoma cells and sensory neurons from dorsal root ganglia (DRG) or sympathetic neurons differentiated from neural crest stem cells (NCSCs). This co-culture system allowed us to thoroughly examine the cancer-neuron dialogue, including changes in cancer cell proliferation, migration, and invasion, as well as alterations in neuronal neurite sprouting patterns and signal conduction. We also observed that neurons and melanoma cells form direct physical contacts which express synaptic marker synaptophysin, suggesting the formation of functional, synapse-like structures, which implies the direct interaction between the two.

To validate these findings in vivo, we used confocal and light-sheet microscopy to examine the tumor innervation landscape. Deep tissue imaging confirmed that both primary melanoma tumors and distant metastases in the lung and liver are innervated. We observed nerves growing from the peripheral stroma into the primary tumor mass, and often alongside blood vessels before extending into metastatic nodules. Using light-sheet microscopy for whole-organ imaging, we discovered that the presence of lung metastases may also alter the global innervation pattern compared to healthy tissue, suggesting the reciprocal crosstalk between cancer and nerves.

Together, this study establishes a framework for understanding the pro-metastatic dialogue between peripheral nerves and melanoma. Our next steps would incorporate techniques like chemo-genetics and calcium imaging

to further observe and model these interactions. These insights may uncover novel therapeutic targets to disrupt nerve-cancer crosstalk and inhibit cancer metastasis.

Theme: Neural Neoplasms

Poster # 59

Abstract Title: Defective Lipid Homeostasis Induced by QKI Loss is a Mutator on Gliomagenesis

Authors: Yinglu Guan (The University of Texas MD Anderson Cancer Center), Takashi Shingu, Kaylene J. Lu, Ece Kilinc, Traver G. Hart, Jianhua Zhang, Yiwen Chen, Yon Son Betty Kim, Jian Hu

Introduction Cancer development is a multistep process requiring the accumulation of mutations to transform normal cells into cancer cells. Mutators, which can be intrinsic or environmental factors, accelerate the rate of mutations, thereby promoting tumorigenesis. While certain cancer types, such as melanoma, lung cancer, and breast cancer, can be clearly linked to these mutators, many other cancers-particularly those arising from non-epithelial tissues like brain tumors-lack obvious mutators. Interestingly, glioblastoma (GBM), despite the absence of clear mutators, exhibit the highest frequency of chromosomal structural alterations, including chromothripsis and extrachromosomal DNA (ecDNA).

Methods To investigate potential mutators in GBM, we analyzed a large cohort with high-resolution sequencing to capture chromosomal structural variants. To test the hypothesis that defective lipid metabolism functions as a mutator in promoting GBM formation, we deleted a series of transcription factors/co-activators in the Nestin-CreERT2;PtenL/L;Trp53L/L GBM-prone background.

Results Among all metabolic pathways, we found that the downregulation of lipid metabolism was significantly correlated with the formation of chromosomal structural variants, particularly ecDNA. Deletion of key regulators of fatty acid and sphingolipid metabolism, such as Pparβ and Quaking (Qki), significantly accelerated GBM formation. Mechanistically, an imbalance in saturated and unsaturated fatty acid composition that was induced by Qki deletion or dietary modulation led to impaired membrane fluidity and integrity in mitochondria and the nuclear envelope. Damaged mitochondria increased reactive oxygen species (ROS) production, and, critically, the compromised nuclear envelope allowed ROS to penetrate the nucleus. Conversely, restoring proper lipid composition by an UFA-rich diet or a Pparβ-Qki agonist could constrain tumor growth.

Conclusion In conclusion, defective lipid homeostasis acts as a mutator by driving genomic structural alterations and ecDNA formation, thereby promoting gliomagenesis. However, the vulnerabilities associated with impaired lipid metabolism offer potential therapeutic opportunities, particularly through targeting lipid-related pathways.

Significance to the cancer neuroscience field Our study provides a deeper insight into lipid metabolic dysregulation of GBM and a candidate for diagnosis and therapy. It will also contribute to the development of therapeutic strategies that specifically target QKI-depleted GBM.

Theme: Neurobiology

Poster # 60

Abstract Title: Tumour-Brain Crosstalk Restrains Cancer Immunity Via a Sensory-Sympathetic Axis

Authors: Haohan K Wei (University of Pennsylvania Perelman School of Medicine), Chuyue D Yu, Bo Hu, Xing Zeng, Hiroshi Ichise, Liang Li, Yu Wang, Ruiqi L Wang, Ronald N Germain, Rui B Chang, Chengcheng Jin

Body-brain communication has emerged as a key regulator of tissue homeostasis. Solid tumours are innervated by different branches of the peripheral nervous system, and increased tumour innervation is associated with poor cancer outcomes. However, it remains unclear how the brain responds to tumours in peripheral organs, and how tumour-brain communication influences cancer immunity. Here, we identify a tumour-brain axis that promotes oncogenesis by establishing an immune-suppressive tumour microenvironment (TME). Combining genetically engineered mouse models with neural tracing, tissue imaging, and single-cell transcriptomics, we demonstrate that lung adenocarcinoma induces innervation and functional engagement of vagal sensory neurons, a major interoceptive system connecting visceral organs to the brain. Mechanistically, Npy2r+ vagal sensory nerves transmit signals from lung tumours to brainstem nuclei, driving elevated sympathetic efferent activity in the TME. This, in turn, suppresses anti-tumour immunity via β2-adrenergic signaling in alveolar macrophages. Disruption of this sensory to-sympathetic pathway through genetic, pharmacological or chemogenetic approaches significantly inhibited lung tumour growth by enhancing immune responses against cancer. Collectively, these results reveal a bidirectional tumour-brain communication involving vagal sensory input and sympathetic output that cooperatively regulate anti-cancer immunity; targeting this tumour-brain circuit may provide new treatments for visceral organ cancers.