2026 International Cancer Neuroscience Symposium

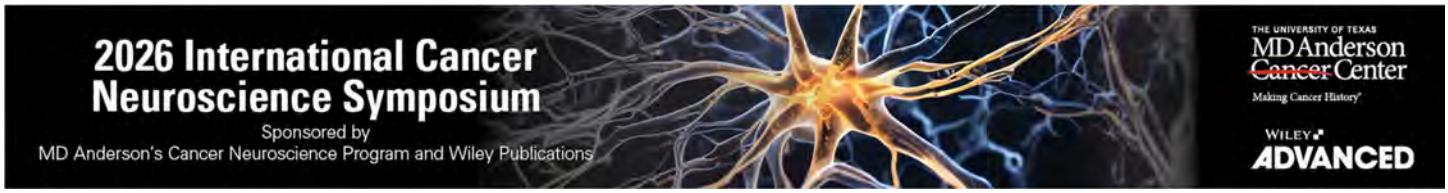
ABSTRACT BOOK

POSTER SESSION FOR

THURSDAY, FEBRUARY 19, 2026

TMC^3 Collaborative Building

Houston, TX



Theme: Neurobiology

Poster # 1

Abstract Title: Neural modulation and tumor–neuron crosstalk in a microfluidic co-culture model of pancreatic cancer

Authors: Jinchul Ahn (Korea Institute of Science and Technology), Seok-Hyeon Kang, Dongwoo Oh, Sieun Choi, Hwanseok Jang, and Seok Chung

Introduction: Perineural invasion (PNI), a histopathological hallmark of many cancers, underscores the role of nerve cells and their microenvironment as regulators of tumor progression. Pancreatic ductal adenocarcinoma (PDAC) exhibits the highest incidence of PNI and serves as a key model of tumor–nerve interaction. However, limited access to human PDAC tissue and the anatomical complexity of the pancreas have made most mechanistic studies dependent on animal or ex vivo models, hindering translation to human biology. To address this gap, we developed a human cell–based microfluidic platform that enables direct co-culture of PANC1 tumor spheroids and peripheral neuron (PN) spheroids within a three-dimensional collagen matrix.

Methods: PN spheroids were generated from human small-molecule neural precursor cells and co-cultured with PANC1 spheroids in a collagen hydrogel confined in a microfluidic chip. Neuronal activity was monitored by Fluo-4 calcium imaging, while axonal distribution and PANC1 migration were quantified by confocal microscopy. Total RNA from PANC1 and PN spheroids was subjected to bulk RNA sequencing, differential expression analysis, and gene set enrichment analysis (GSEA) to identify pathways altered by co-culture.

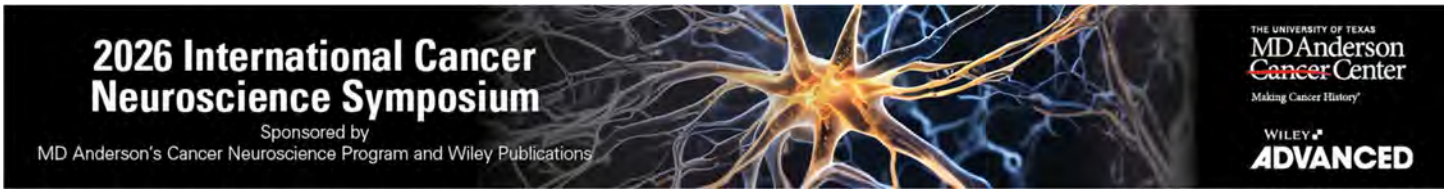
Results: Co-culture with PN spheroids markedly enhanced PANC1 cell migration within the collagen matrix and promoted directional axon growth toward the tumor spheroids, suggesting reciprocal chemotropic signaling. PN spheroids displayed more frequent calcium transients with reduced overall fluorescence, indicating altered excitability. Transcriptomic analysis revealed increased expression of immediate early and neuropeptide-related genes (FOS, JUN, CREB1, TAC1) in PN spheroids, consistent with a reactive neuronal state. In PANC1 spheroids, co-culture induced stress- and metabolism-related transcripts (BTG2, GADD45B, mitochondrial tRNAs) while suppressing ATP metabolic genes. GSEA indicated enrichment of TNFα/NFκB, interferon response, hypoxia, and epithelial–mesenchymal transition pathways, consistent with enhanced motility and adaptive stress signaling.

Conclusion: Peripheral neurons actively modulate pancreatic cancer cell behavior through bidirectional signaling that promotes neuronal activation and tumor migration. This human-based microfluidic co-culture model offers a physiologically relevant platform to study neuron–tumor communication and identify neural drivers of cancer invasion.

Significance to the cancer neuroscience field: This work bridges cancer biology and neuroscience by isolating neuron–tumor interactions from immune or stromal influences. It reveals that peripheral neurons can autonomously drive cancer aggressiveness, highlighting neural signaling as a therapeutic target in pancreatic cancer.

Poster # 2

Abstract Title: Microglial and astroglial activation in a mouse orofacial cancer model and the impact of various treatments.



Authors: Jeffrey Barr (Sanford Research), Austin Walz, and Paola D Vermeer

Sensory information from oral and facial regions is initially processed in the spinal trigeminal nucleus, specifically in the caudalis (Vc) subregion. Using a mouse model of head and neck cancer, we've previously demonstrated that tumor-infiltrating nerves connect to distinct brain areas via the ipsilateral trigeminal ganglion, and that this neuronal circuit is more active in the presence of cancer. The aim of this study was to investigate whether astroglia and microglia in the Vc and associated brain regions may be involved in the alterations observed in the presence of orofacial cancer. The effects were tested on Vc astroglia hyperactivity, as revealed by glial fibrillary acid protein (GFAP) labeling or microglial hyperactivity, as revealed by Ionized calcium binding adaptor molecule 1 (Iba1) labeling. Compared with contralateral regions and tumor-naïve mice, a significant increase of Iba1-positive cells was found in ipsilateral Vc, principal sensory nucleus of trigeminal nerve (PrV), Facial motor nucleus (VII), and a significant increase of GFAP-positive cells in the facial motor nucleus of male and female mice. These increases in both Iba1 and GFAP were significantly inhibited by administration of carprofen, by selective ablation of TRPV1-expressing sensory neurons by Resiniferatoxin (RTX), or by treatment with cisplatin-based chemoradiation. The increases in glial activation did not correspond completely with previous measures of neuronal activity via Fos labeling. These findings suggest that glial activation may be involved differentially in the enhanced responses of tumor associated neurons and Inflammatory hyperalgesia associated with orofacial cancer.

Poster # 3

Abstract Title: Role of acetylcholine in Perineural Invasion of Head and Neck Cancers: Insights from Patient-Derived Organoids

Authors: Poulomi Biswas (University of Missouri Columbia), Santosh Anand, Patrick Tassone, Syamantak Khan

Introduction: Perineural invasion (PNI) is a major pathological feature in several aggressive cancers, particularly in head and neck squamous carcinomas (HNSCCs). Nevertheless, the molecular mechanisms of (PNI) and the underlying neuronal-tumour crosstalk remain poorly understood. A major bottleneck to overcoming this challenge is the lack of an accurate and clinically relevant model to study PNI. To this end, we used patient-derived HNSCCs organoids to model how neurotrophic factors and neurotransmitters influence cancer growth, invasion, and molecular reprogramming.

Methods: A biobank comprising seven patient-derived organoids was established from HNSCCs and matching adjacent noncancerous tissues. Organoids were treated with acetylcholine (ACh, 10-100 ng/µL), its analogue carbachol (10-100 µM), and glial cell line-derived neurotrophic factor (GDNF, 50- 500 ng/µl). Transwell invasion assays were performed using three cancer organoids (derived from retromolar trigone, buccal mucosa, and mandibular gingiva) and a normal organoid (buccal mucosa). Finally, RNA sequencing was performed on an organoid line derived from floor-of-mouth cancer to identify key changes in gene expression induced by Ach and to determine whether they correlate with previously known alterations associated with PNI in HNSCCs.

Results: ACh and carbachol markedly enhanced organoid proliferation, while GDNF produced minimal effects. ACh and carbachol induced significant cellular migration within 48 hours in Transwell assays. In contrast to normal-tissue control, migrated cells from tumour organoids showed a unique ability to form new organoids in the lower chamber. RNA sequencing indicated upregulation (>1.5-fold change) of most of the matrix

metalloproteinases, including MMP9, MMP1, MMP3, MMP19, MMP2, MMP7, and several other epithelial–mesenchymal transition (EMT)-associated genes. These signatures are concordant with previous gene expression studies performed in PNI of HNSCCs (Tassone, 2022; Zhang 2019). Several novel gene expression signatures induced by ACh are currently being studied.

Conclusion: These results reveal that ACh alone can trigger tumour proliferation, EMT, and MMP upregulation in tumour-organoids, implicating its potential role in perineural invasion of HNSCCs.

Significance in Cancer Research: As ACh is the primary neurotransmitter in the peripheral nervous system, this preliminary study lays the foundation of our hypothesis that ACh is a key regulator of PNI in HNSCCs. Understanding this pathway may provide new therapeutic opportunities to disrupt tumour–nerve crosstalk and improve outcomes in patients with PNI-positive cancers.

Poster # 4

Abstract Title: Triple-Negative Breast Cancer Cells Activate Sensory Neurons via TRPV1 to Drive Neurite Outgrowth and Tumor Progression

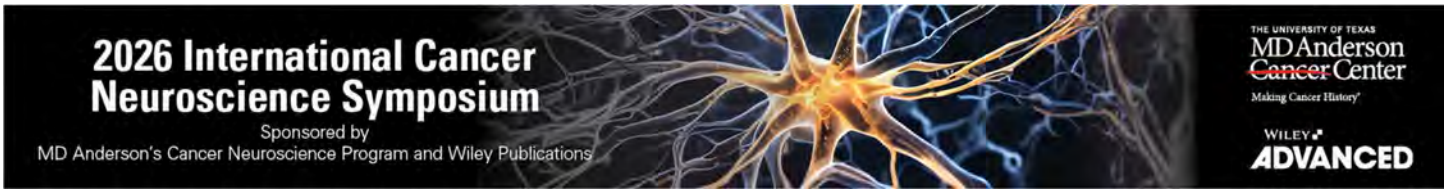
Authors: Hanan Bloomer (Tufts University), Savannah R. Parker, Audrey L. Pierce, Wesley Clawson, Mallory M. Caron, Thomas Gerton, Ankit Pandey, Thanh T. Le, Tolulope Adewumi, Charlotte Kuperwasser, Michael Levin, Madeleine J. Oudin

Introduction: The tumor microenvironment in triple-negative breast cancer (TNBC) is characterized by increased sensory nerve density, which contributes to cancer progression by promoting migration and metastasis. However, the origin of tumor-innervating nerves and the mechanisms driving sensory innervation into tumors remain poorly understood. We reasoned that increased tumor innervation requires neurite outgrowth from preexisting dorsal root ganglia (DRG) neurons in adjacent healthy tissue. TRPV1, a calcium-permeable cation channel, drives action potential generation and neurite outgrowth, and is upregulated in human breast tumors. We hypothesized that TNBC-derived cues activate TRPV1 on sensory neurons, triggering regenerative programs that promote tumor innervation and TNBC progression.

Methods: Retrograde labeling with DiI determined the source of tumor-innervating nerves. Primary DRG neurons were co-cultured with TNBC or non-tumorigenic cells for immunofluorescence of activation markers (ATF3, cFos, CGRP, TRPV1, cJun, IL6), neurite morphology, and microelectrode array (MEA) recordings. DRG explants were embedded in a 3D hydrogel to assess directional neurite outgrowth. RNA-seq and knockout mouse models (Tprv1-/-, IL6-/-) were used to dissect downstream mechanisms. Finally, syngeneic TNBC cells were injected into wild-type and Trpv1-/- mice to evaluate tumor growth and metastasis.

Results: We first demonstrated that mammary tumors progressively recruit sensory nerves originating from the DRG. Additionally, we found that TNBC cells induce neuronal firing and activation in a TRPV1-dependent manner. In both 2D and 3D models, TNBC cells promoted neurite outgrowth, which is abrogated with Trpv1 knockout. Transcriptomic and functional analysis identified cJun and IL6 as downstream mediators of TRPV1-driven neurite outgrowth. Finally, in Trpv1 knockout mice, TNBC tumors exhibit delayed growth and reduced lung metastasis.

Conclusion: In summary, we find that tumor cells drive sensory neuron activation and outgrowth via TRPV1-c-Jun-IL6 signaling, and inhibiting TRPV1 can reduce metastasis in TNBC.



Significance: This work uncovers a novel role for TRPV1 in mediating crosstalk between TNBC cells and sensory nerves. Targeting TRPV1 or downstream mediators may provide a new therapeutic strategy to disrupt neural remodeling within the tumor microenvironment and reduce tumor growth and metastasis.

Poster # 5

Abstract Title: Early Brain Responses to Peripheral Melanoma and the Role of TRPV1+ Sensory Neurons

Authors: Destiny Brockhaus (University of South Dakota-Sanford Research), Jeffery Barr, Craig Welbon, Sebastien Talbot, Paola Vermeer

Introduction: Brain metastasis remains a major cause of mortality for melanoma patients, yet little is known about how the brain responds to peripheral tumors prior to secondary colonization of the central nervous system. Despite the infiltration of TRPV1-expressing nerves into primary melanomas, the impact of these nerves on brain metastasis remains unknown. In peripheral head and neck cancer, tumors engage with TRPV1+ neurons to form a circuit that projects into the brain. This tumor-brain circuit suggests that tumor-neuron interactions at the primary site may influence metastatic spread to the brain. This project will define time course of the tumor-brain circuit establishment in melanoma and determine when central neural and glial changes occur. In addition, we will determine the contribution of TRPV1+ tumor-infiltrating neurons to these processes.

Methods: Juvenile C57BL/6 mice were chemically ablated of TRPV1-expressing neurons with resiniferatoxin (RTX), and then intradermally injected with YUMMER1.7 melanoma cells. On days 7, 12 and 17, n=5 mice/time point received intra-tumoral injection with Wheat Germ Agglutinin (neural tracer). Three days later, animals were euthanized and their brains and tumors harvested. Confocal microscopy will assess WGA-positive neural circuitry while immunofluorescent staining of brain sections for neural (cFos, δFos) and glial (IBA-1, CD68, GFAP) activation markers will establish the time course of central activation.

Results: Preliminary studies suggest that peripheral melanoma induces central neuronal and glial activation prior to CNS metastasis. Early tracing experiments indicate that TRPV1+ tumor-infiltrating neurons form functional connections with central circuits, potentially serving as conduits for tumor-to-brain communications. $TRPV1^{+}$ neuron ablation alters these responses, significantly slowing tumor growth and progression. Notably, female mice exhibit slower tumor growth compared to males, and ongoing work will determine whether sex influences the intensity, timing, or location of brain activation.

Conclusion: These studies provide the first evidence that the brain may respond to peripheral melanoma before metastatic colonization. By combining immunohistochemistry and neuronal tracing, this project establishes a framework for dissecting the cellular and molecular pathways that mediate tumor–brain communications.

Significance to cancer neuroscience: Our findings suggests that central neurons and glia may detect, and possibly respond to, peripheral malignancies at their earliest stages. The inclusion of sex as a biological variable further strengthens the relevance of this work, as differences in tumor growth may reveal new insights into susceptibility and treatment response. Identifying these pathways could uncover novel targets for therapeutic intervention at the intersection of cancer biology and neuroscience.

Poster # 6

Abstract Title: Targeting sympathetic neural signaling to control multi-organ metastasis in metastatic triple negative breast cancer

Authors: Aeson Chang (Monash University), Annabel Manoleras, Savannah Young, Shenhong Zhu, Xingying Zhu, Erica Sloan

Metastatic triple negative breast cancer (TNBC) is highly aggressive with low overall survival, particularly in patients with multi-organ metastasis. Chemotherapy remains the first line treatment for metastatic TNBC and is routinely combined with emerging therapies, including immunotherapy and PARP inhibitors. However, despite these novel therapeutic options there has been little improvement in overall survival, highlighting the urgent need for novel approaches to treat metastatic TNBC.

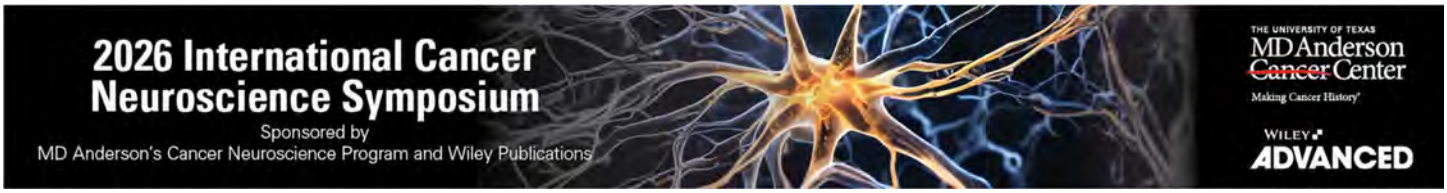
We have previously shown that sympathetic neural signaling regulates progression of early stage TNBC, including response to chemotherapy treatment. However, the effect of sympathetic neural signaling in metastatic TNBC is unknown. To investigate this, we used 4T1.2 orthotopic mouse model of TNBC and resected the primary tumor to model advanced disease. Once cancer recurrence at distant sites was detected by bioluminescence imaging, mice were administered norepinephrine (mini-osmotic pump, or vehicle) to mimic sympathetic neural signaling and progression of recurrent disease was tracked using bioluminescence imaging. Norepinephrine increased the rate of local and regional recurrence (vs. vehicle, $p=0.01$, log-rank (Mantel-Cox) test, n=14/group). While norepinephrine did not affect total metastatic burden, it increased the frequency of multi-organ metastasis (vs. vehicle, $p<0.01$, Fisher's exact test), primarily by increasing the incidence of liver metastasis in these mice (50% vs. 7% in vehicle, $p<0.05$). We recently discovered that doxorubicin increases sympathetic innervation in metastatic sites, suggesting amplified sympathetic neural signaling in metastatic TNBC. To examine if inhibition of sympathetic neural signaling can improve doxorubicin control of multi-organ metastasis in advanced disease, mice with recurrent disease were treated with the anthracycline chemotherapy doxorubicin, and 6-hydroxydopamine was administered intraperitoneally concurrently to ablate sympathetic innervation. In nerve-ablated mice, doxorubicin reduced the incidence of multi-organ metastasis (27% vs. 75% in non-ablated mice, n=8-11/group), specifically by reducing the incidence of liver metastasis (27% vs. 63% in non-ablated mice).

These findings reveal a potential role for sympathetic neural signaling in regulating multi-organ metastasis and suggest that blocking sympathetic neural signaling is a novel therapeutic approach to improve chemotherapy control of multi-organ metastasis. However, future mechanistic works to understand how sympathetic neural signaling regulates multi-organ metastasis is warranted.

Poster # 7

Abstract Title: Chronic Opioid-Induced Mitochondrial Damage Rewires $CD8^+$ T-Cell Metabolism and Promotes Immune Dysfunction in Cancer

Authors: Kala Chand Debnath (MD Anderson Cancer Center), Paloma L Aventi-Strafile, Megan Uhelski, Yuesong Wu, Chengcan Yang, Zaiye Li, Wang Gong, Yumin He, Xin Hu, Charisse Ursin, Kohei Okuyama, Sydnye Shuttleworth, Wanqing Cheng, Andrew Gregory Sikora, Jian Hu, Brian Koss, Christopher R Donnelly, Yuying Xie, Juan Cata, Yu Leo Lei



Background: Opioids are essential for managing cancer-related pain, especially in head and neck squamous cell carcinoma (HNC), where pain is intensified by chewing and swallowing. While side effects like addiction and respiratory depression are manageable, chronic opioid use causes systemic immune suppression, increasing infection risk and reducing immune checkpoint blockade (ICB) efficacy. Over half of HNC patients remain on opioids a year post-treatment, highlighting the urgent need to understand opioid-driven immune modulation.

Methods: Morphine-tolerant mice were generated with 14 days of morphine administration. $CD8^+$ T cells were analyzed for mitochondrial structure, ROS, and metabolism. Seahorse and proteomics identified metabolic disruptions. The role of OPRM1 was tested using methylnaltrexone and Oprm1-/- mice. Tumor growth and immune responses were assessed in subcutaneous, orthotopic, and bone marrow transfer (BMT) models.

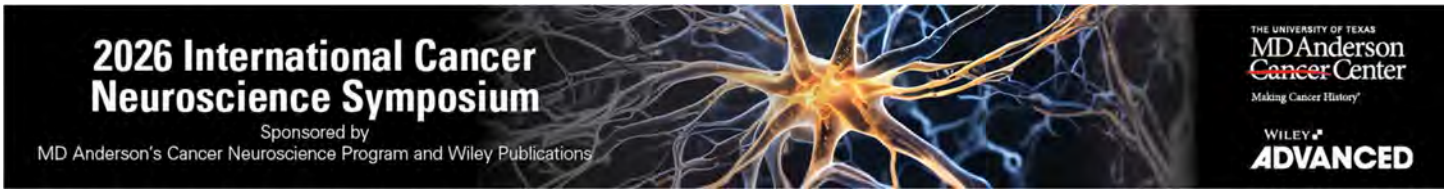
Results: To determine whether chronic opioid exposure affects immune function, mice were rendered morphine-tolerant after 14 days of treatment, with tolerance confirmed by ED_{50} determination using probit analysis. Morphine-tolerant mice exhibited a marked collapse in mitochondrial respiration in $CD8^+$ T cells, reflected by significantly reduced maximal and spare respiratory capacity. Unbiased proteomic profiling revealed upregulation of interferon-stimulated genes (ISGs) and downregulation of key mitochondrial regulators, including MTRF1 and GLS2, indicating impaired mitochondrial translation and bioenergetic stress. Consistent with these findings, chronic morphine elevated mitochondrial and cellular reactive oxygen species (ROS) and reduced mitochondrial volume. Transmission electron microscopy demonstrated extensive mitochondrial damage, including cristae loss and decreased mitochondrial area. These alterations were mitigated in $Oprm1^{-/-}$ mice and by co-treatment with the peripheral μ-opioid receptor antagonist methylnaltrexone. In tumor implantation studies using NOOC2 and MOC2-E6/E7 models, Oprm1 deletion significantly slowed tumor growth and enhanced infiltration of $CD45^+$ immune cells, TCR-β^+ and $CD8^+$ T cells, as well as CD127^high^KLRG1^low^ memory $CD8^+$ T cells. Conversely, morphine exposure reduced survival in orthotopic HNC models and directly promoted tumor cell growth. Bone marrow transfer experiments showed that recipients of morphine-conditioned marrow had reduced hematopoietic stem and progenitor cells ($Lin^-Sca1^+c\text{-}Kit^+$), diminished lymphoid and NK cell populations, and increased PD-$L1^+$ and $Siglec15^+$ myeloid cells, leading to impaired anti-tumor immunity. Clinically, in a cohort of 285 HNC patients receiving immune checkpoint blockade, opioid use correlated with reduced lymphocyte counts, increased NLR, PLR, and MLR, and poorer progression-free survival, underscoring the immunosuppressive impact of chronic opioid exposure.

Conclusion: Chronic morphine exposure impairs mitochondrial structure and metabolism in $CD8^+$ T cells, leading to oxidative stress and a collapse of mitochondrial metabolism. This mitochondrial impairment compromises anti-tumor immunity and promotes tumor growth in opioid-tolerant conditions. Opioid-driven immune dysfunction is a previously underappreciated side effect that significantly restricts the expansion of effectors.

Poster # 8

Abstract Title: The Systemic Effects of the Local SCLC Microenvironment on Neural Circuitry

Authors: Alexis Franklin (Brigham and Women's Hospital/Harvard Medical School), Rojina Karimirad, Emily Anderegg, Rachel Davis, Hannah Farnsworth, Kaylee Gentry, Eleena Sherman, Garrett Scarpa, Humsa Venkatesh



Small cell lung cancer (SCLC) is a lethal, highly metastatic cancer with limited treatment options available. The majority of SCLC patients present with extensive disease, including frequent metastasis to the brain, underscoring the need to better understand how tumor progression interacts with the nervous system. Recent findings from our lab demonstrated how peripheral innervation via the vagus nerve contributes to tumor progression in the lungs; however, it remains unknown how the local tumor microenvironment (TME) in the lungs affects neural activity of connected regions. Through a combination of multisynaptic tracing and brain-wide activity mapping, we characterized lung-brain connectivity and established neural activity changes in multiple connected regions. With calcium imaging techniques, we confirmed tumor development in the lungs induces hyperactivity of one of these connected regions, the ventral tegmental area (VTA). We found reducing peripheral innervation of the local TME by directly transecting the vagus nerve reversed the tumor-induced activity changes in the VTA. Furthermore, we tested the tumor bearing mice in a behavioral task dependent on the VTA, and we found the tumor bearing mice exhibit a significant behavioral change. Future work will include cytokine panels to assess how the local changes of the TME induce these systemic neural activity changes and whether ablation of the VTA affects tumor burden in the lungs. Together, these findings support a bidirectional interaction between the TME of peripheral tumors and connected brain regions, redefining SCLC as a systemic neurologic disease. This paradigm may open new therapeutic avenues targeting the neural integration of cancer.

Poster # 9

Abstract Title: Inflammatory Neuropathy in Mouse Models of Colorectal Cancer: Implications for Chemotherapy-Induced Peripheral Neuropathy

Authors: Caitlyn Gaffney (MD Anderson Cancer Center), Angela M. Casaril, Iqbal Mahmud, Bo Wei, Karen M. Valadez, Elizabeth A. Kolb, Fisher R. Cherry, Theresa A. Guise, Philip L. Lorenzi, Lei Shi, Carolyn L. Hodo, Andrew J. Shepherd

Introduction: Colorectal cancer (CRC) is the third most common cancer in the United States; each year about 150,000 individuals are diagnosed. Advances in screening and treatment regimens, including oxaliplatin-based regimens, such as 5-fluorouracil, leucovorin & oxaliplatin (‘FOLFOX’) have led to an increase of long-term CRC survivorship. However, FOLFOX and similar regimens cause prolonged neurological symptoms in up to 80% of patients. Current studies of chemotherapy-induced peripheral neuropathy (CIPN) are done in young-adult, cancer-free, male rodents that are naïve to surgery. However, this does not model adjuvant chemotherapy seen clinically. Here, we developed a combined model of orthotopic colorectal cancer and adjuvant oxaliplatin, to more accurately replicate clinical CIPN.

Methods: Cecal injections using the MC38 colon adenocarcinoma cell line were induced in 8-week and 52-week-old C57BL/6 mice. Three weeks following injection, mice underwent cecum removal surgery (cecectomy). The mice were then allowed to recover for 10 days before FOLFOX treatment began. Tumor growth was monitored for 8 weeks by bioluminescent imaging before, during, and after cecectomy and FOLFOX treatment. Behavioral tests were conducted throughout this process to characterize stimulus-evoked pain sensitivity (von Frey and coldgreaves), ongoing/spontaneous pain sensitivity (CPP and burrowing), motor coordination (beam walk), and gait (Catwalk).

Results: We have previously shown neuronal dysfunction directly induced by tumor growth alone. Mice with CRC develop peripheral neuropathy associated with subtle locomotor deficits, without overt hypersensitivity.

Our findings suggest CRC can be causally linked to a subacute form of chronic inflammatory demyelinating polyneuropathy across species, which may represent an under-reported, yet important risk factor for neurological dysfunction in CRC survivors. Indeed, matched dosing of oxaliplatin or a FOLFOX-like regimen caused more persistent hypersensitivity in CRC mice.

Conclusions: Collectively our data suggest that subclinical neuropathy secondary to CRC may represent an under-reported, yet important risk factor for persistent neurological dysfunction in CRC survivors. Further studies are needed to elucidate the mechanisms involved in CIPN induced by FOLFOX treatment in aged mice.

Poster # 10

Abstract Title: Schwann Cell derived Chromosome 4 Chemokines modulate Cancer Cell Viability

Authors: Mara Goetz (Technical University Munich, TUM Klinikum Rechts der Isar), Clara Mueller, Eyuep Yoendem, Helmut Friess, Carmen Mota-Reyes, Rouzanna Istvanffy, Ihsan Ekin Demir

Introduction: Pancreatic ductal adenocarcicnoma (PDAC) exhibits an exceptionally high incidence of neural invasion (NI) and extensive neuroplastic remodeling. The severity of NI serves as an independent prognostic factor for overall survival, as well as for local recurrence. Schwann cells (SCs) - the principal neuroprotective glial cells of the peripheral nervous system - constitute the primary cellular counterparts of cancer cells during neural invasion, facilitating PNI through the formation of SC tracks. Previous work of our group has demonstrated the first functional interaction of SCs and PDAC cells, namely PDAC progression, stromal remodeling, and diminished tumor-associated survival. Co-culture experiments of human PDAC cells and human SCs (hSCs) revealed that hSCs exhibited robust upregulation of the chemokines CXCL2, CXCL3, and CXCL8, while PDAC cells showed enhanced expression of IL-6 and IL-17A. In this study, we investigate the underlying mechanisms of this interaction and identify a bidirectional glia–cancer crosstalk.

Methods: Human SCs (hSCs) were stimulated with recombinant Interleukin-6 (IL-6; Fc=40ng/ml, based on prior dose-response tests) and Interleukin 17a (IL-17a; Fc=40ng/ml) for 24 hours, followed by gene transcription analysis as well as protein expression analysis using qRT-PCR and ELISA. Human PDAC cell lines (T3M4) as well as murine PDAC cell lines (KPC) were exposed to chemokines for 24 hours (CXCL2, CXCL3, CXCL8; Fc=40ng/ml) and subjected to qRT-PCR and ELISA. Cell viability of these PDAC cell lines after treatment with CXCL2, CXCL3 or CXCL8 after 24, 48 and 72 hours was assessed using MTT assays. For in situ validation, a human PDAC tissue microarray was examined by immunofluorescence, staining for Glial Fibrillary Acidic Protein (GFAP), IL-6, Cytokeratin Pan, and DAPI.

Results: Stimulation of hSCs with IL-6 and IL-17A confirmed induction of CXCL2, CXCL3 and CXCL8 at both the mRNA and protein levels (compared to control (PBS); $p<0.0001$). Conversely, exposure of human and murine PDAC cells to CXCL2, CXCL3, or CXCL8 led to elevated expression of IL-6 and IL-17A (compared to control (PBS); $p<0.001$). Treatment of murine PDAC cells (KPC) with the respective chemokines significantly increased cell viability after 24 and 48 hours (CXCL2/CXCL3/CXCL8 $p<0.0001$). Increased cell viability after chemokine treatment was also confirmed in human PDAC cells (T3M4), however after 48 hours (CXCL2 and CXCL3 $p>0.001$; CXCL8 $p<0.01$) and 72 hours ($p<0.0001$) compared to control treatments. Preliminary analysis of human PDAC tissues demonstrated co-localization of IL-6 and GFAP, indicating the presence of SCs and crosstalk of SC with PDAC cells within the tumor microenvironment.

Conclusion and Significance to the Cancer Neuroscience Field: SCs promote PDAC progression through a reciprocal chemokine–interleukin signaling crosstalk, particularly involving CXCL2, CXCL3 derived by SCs, and IL-6 and IL-17a, derived by PDAC cells. The concurrent induction of these chromosome 4 encoded chemokines suggests a coordinated activation of the CXCL gene cluster, potentially mediated by epigenetic regulatory mechanisms. Targeting this pro-tumorigenic feedback loop may therefore offer a promising therapeutic strategy to disrupt PNI and, consequently, PDAC progression.

Poster # 11

Abstract Title: IL-6R Blockade by Small Protein Ligands Attenuates Cancer Cell Migration and Nociceptor Sensitization

Authors: Mario Heles (The University of Texas MD Anderson Cancer Center), Megan L. Uhelski, Yan Li, Nicolas Cortes-Mejia, Hajira Elahi, Claudio Esteves Tatsui, Laurence D. Rhines, Robert Y. North, Yaroslava Groza, Petr Maly, Patrick M. Dougherty

Cancer pain in head and neck (HN) malignancies arises from tumor-driven neuroinflammation that resists conventional therapies, making it one of the most debilitating and under-treated symptoms in oncology. Despite aggressive use of opioids and radiation therapy for palliative care, many HN cancer patients continue to experience uncontrolled pain, reflecting a critical unmet need for new mechanism-based interventions that target the neuroinflammation in tumor-driven pain. Interleukin-6 (IL-6) signaling via IL-6Rα has emerged as a central driver of neuronal sensitization within the tumor microenvironment. Here, we introduce novel small protein IL-6Rα blockers (NEFs) with dual analgesic and migrastatic potential.

NEFs were generated via ribosome display from an albumin-binding domain library targeting human IL-6Rα. Their effects were evaluated in cancer cell migration and proliferation assays and in human dorsal root ganglion (DRG) neurons derived from organ donors without chronic pain history or from cancer patients with neuropathic pain undergoing surgical DRG resection. Neuronal excitability in primary human DRG cultures was quantified using whole-cell patch-clamp recordings following exposure to IL-6 or IL-6 + NEFs.

We successfully recapitulated the sensory neuron phenotype characteristic of neuropathic pain patients in vitro by inducing IL-6–mediated sensitization in organ donor–derived DRG neurons. NEFs effectively prevented IL-6–induced depolarization, reduced spontaneous firing frequency, and restored rheobase to baseline levels. Their potency matched that of monoclonal IL-6R antibodies while offering high molecular stability and reduced immunogenic risk. In tumor assays, NEFs suppressed migration and proliferation of PaTu pancreatic cancer cells and IL-6–driven migration of GAMG glioma cells, confirming selective disruption of IL-6–dependent signaling across diverse tumor types.

Together, these findings highlight NEFs as multifunctional inhibitors capable of targeting IL-6 signaling across neuronal and tumor systems. We are the first to establish a robust and scalable human DRG-based in vitro model of cancer-associated neuropathic pain, laying essential groundwork for translational studies. IL-6R blockade with NEFs prevented cytokine-induced nociceptor sensitization, while the parallel suppression of cancer cell migration underscored the therapeutic synergy of NEFs as small, stable, and highly specific protein inhibitors.

By integrating neurophysiology, molecular pharmacology, and tumor biology, these findings provide mechanistic evidence that disrupting IL-6 signaling can simultaneously limit cancer invasiveness and alleviate

neuroinflammation-driven pain, advancing the development of next-generation therapeutics for IL-6–rich malignancies such as HNSCC.

Poster # 12

Abstract Title: Adhesion of Cancer Cells to Schwann Cells Leads to Metabolic Adaptations with Increased Glutamine Synthetase Activity

Authors: Rouzanna Istvánffy (Technical University of Munich School of Medicine), Haoyu Quan, Kaan Çifcibaşı, Linhan Ye, Lei Ren, Ihsan Ekin Demir

Introduction: Neural invasion is a hallmark of pancreatic ductal adenocarcinoma (PDAC) and is associated with poor prognosis. During neural invasion, cancer cells establish direct contact with Schwann cells. This study aimed to elucidate the molecular mechanisms governing Schwann–cancer cell adhesion and its metabolic consequences that promote neuroinvasion.

Methods: Adhesion assays were performed to assess Schwann–cancer cell interaction in vitro. Immunohistochemistry on human PDAC tissues evaluated adhesion molecule expression in situ. Transcriptomic alterations were analyzed by quantitative PCR and RNA sequencing, while quantitative metabolomics, Western blotting, and phospho-kinase arrays characterized metabolic and signaling changes. To assess the in vivo relevance, sciatic nerve invasion assays were conducted using peripheral hypomyelination (Pmp22^Tr-J^) mice and mice with conditional deletion of Cdh2 in GFAP-positive Schwann cells.

Results: Adhesion assays and tissue analyses revealed that Schwann and cancer cells in contact express higher levels of β1-integrin and L1CAM. Inhibition of these molecules in cancer cells, but not in Schwann cells, significantly reduced adhesion. Metabolomic profiling demonstrated elevated L-glutamine levels in cancer cells co-cultured with Schwann cells, accompanied by increased glutamine synthetase (GS) activity in Schwann cells. Phospho-kinase analysis identified p38 as a regulator of GS upregulation, and pharmacological inhibition of p38 reduced GS expression. Co-cultured cancer cells exhibited enhanced phosphorylation of EMT- and invasion-related kinases Akt and Erk. In vivo, cancer cells injected into Pmp22Tr-J mice or Cdh2-deficient Schwann cell mice showed significantly reduced neural invasion compared with wild-type controls.

Conclusion: Adhesion of pancreatic cancer cells to Schwann cells occurs in a β1-integrin– and L1CAM-dependent manner, leading to reciprocal metabolic adaptations that promote neural invasion. Schwann cell–derived glutamine production, regulated via p38 and GS, represents a metabolic support mechanism for invading cancer cells.

Significance to the Cancer Neuroscience Field: This study identifies a novel metabolic interaction between Schwann and cancer cells that links adhesion signaling to glutamine metabolism. By uncovering Schwann cell–specific adaptations that facilitate neuroinvasion, it advances understanding of cancer–nerve crosstalk and provides new therapeutic targets at the intersection of tumor metabolism and neural biology.

Poster # 13

Abstract Title: Exosome-Mediated Crosstalk Between Pancreatic Cancer Cells and Schwann Cells Promotes Tumor-Nerve Interaction and Cancer Aggressiveness

Authors: Didem Karakas (Acibadem Mehmet Ali Aydinlar University), Sila Sigirli, Taner Kasapoglu, Basak Kavaklioglu, Nazlihan Aztopal, Merve Erkisa, Bulent Ozpolat, Engin Ulukaya, Ihsan Ekin Demir, Guralp Onur Ceyhan

Introduction: Pancreatic cancer (PCa) exhibits pronounced neurotropism, characterized by neural invasion (NI) and remodeling that lead to severe pain, drive local aggressiveness, and predict poor prognosis. While NI has traditionally been attributed to direct cancer–neuron interaction, emerging evidence underscores a pivotal role for Schwann cells (SCs) in this process. However, the mechanisms by which SCs mediate tumor–nerve communication remain largely undefined. Here, we explored how exosome-mediated signaling governs reciprocal interactions between PCa cells and SCs and contributes to tumor progression.

Methods: Patient-derived PCa tissues were analyzed by immunohistochemistry to detect proteins indicative of exosomes, nerves, and activated SCs, assessing exosomal localization within NI regions. In vitro, SCs were treated with exosomes derived from PCa cell lines (PANC-1, BxPC-3) to assess their effects on proliferation, migration, invasion, and dedifferentiation. Reciprocal experiments investigated how SC-derived exosomes influence PCa cell invasion and epithelial–mesenchymal transition (EMT). The exosome inhibitor, GW-4869, was used to confirm the exosome dependence, while the reciprocal orientation and directed migration between PCa cells and SCs or dorsal root ganglia neurons (DRGs) were evaluated using a 3D migration assay. Exosomal miRNA profiling and bioinformatics analyses identified candidate miRNAs and their target pathways.

Results: PCa-derived exosomes significantly increased SC migration and invasion, accompanied by elevated GFAP expression and morphological changes indicative of dedifferentiation toward a tumor-supportive phenotype. Conversely, tumor-educated SC-derived exosomes enhanced PCa invasiveness and promoted EMT. Inhibition of exosome secretion by GW-4869 reversed these effects and impaired reciprocal migration in 3D migration models, confirming the central role of exosomal signaling in PCa–SC/neuron communication. miRNA profiling revealed enrichment of miR-125b-5p, miR-29a-3p, miR-10a-5p, and miR-200c, implicating exosomal cargo in regulating pathways linked to tumor aggressiveness.

Conclusion: Our findings reveal that PCa and SCs engage in an active, exosome-mediated dialogue that reprograms both partners toward a pro-invasive state, providing a mechanistic link between exosomal communication and cancer neurobiology. Ongoing transcriptomic analyses of exosomal cargo aim to uncover additional molecular players and identify new therapeutic targets to disrupt the tumor–nerve interface.

Significance to the Cancer Neuroscience Field: This work establishes exosomes as pivotal mediators of the PCa–nerve axis, demonstrating that SC–derived vesicles actively shape tumor behavior and neural niche. Characterization of exosomal cargo, particularly from SCs, reveals molecular pathways connecting neural remodeling to tumor progression. These findings advance our understanding of cancer neurobiology and guide future research toward identifying novel exosome-based therapeutic targets to halt disease progression.

Poster # 14

Abstract Title: Integrative Spatial Multiomics and Cross-Platform Analysis to Decipher Neural Invasion in Pancreatic Cancer

Authors: Raphael Kfuri-Rubens (Helmholtz Munich), Carmen Mota Reyes, Lennard Halle, Julian Elias Friedrich, Kaan Cifcibasi, Pilar Acedo, Lola Alonso, Gülsum Yurteri, Mara Göetz, Lidia Estudillo, Raquel Benitez, Kyra Fraser, Nicole Pfarr, Sebastian Lange, Katja Steiger, Fabian Mairinger, Alex Muckenhuber, Lola Luna Reyes, Bastian Meyer, Carsten Jäger, Bo Kong, Christoph Michalski, Dieter Saur, Didem Karakas, Güralp O. Ceyhan, Rouzanna Istvannffy, Pan Gen EU investigators, Helmut Friess, Nuria Malats, Fabian Theis, Ekin Ihsan Demir

Perineural invasion (PNI) is a major route of local spread in pancreatic ductal adenocarcinoma (PDAC), yet its molecular and cellular underpinnings remain opaque. We systematically mapped the neural–tumor interface by performing spatially resolved multi-omics on primary human PDAC, integrating genomics, single-nucleus transcriptomics, spatial transcriptomics, and spatial proteomics. An iterative deep-learning integration pipeline, benchmarked against alternative fusion and feature-selection strategies, resolved >70 cellular states. Multiple-instance learning on single-cell embeddings prioritized Schwann cells as top attention-weighted predictors of the PNI phenotype, underscoring their pivotal role in neural remodeling and tumor invasion. Across >200 spatial regions of interest, we identified a multimodular ligand–receptor interactome linking neural and Schwann signaling to invasive, stem-like, and EMT-like tumor programs. Recurrent axes included SPP1→CD44/PTGER4, MMP7→ERBB4, ECM–integrin hubs (COL/FN/TNC→α/β integrins), and a neuropeptidergic NPY→NPY2R pathway predicted to suppress cAMP and engage ERK/AKT/Rho signaling in adjacent glia and cancer cells. Spatial proteomics validated deployment of these pathways within PNI niches and associated them with focal-adhesion formation and myelin-downregulation signatures. Cross-species comparisons with pancreas-innervating dorsal root ganglia from a neuroinvasive TPAC mouse model revealed a significant overlap of neuropeptidergic and matrix modules. Functionally, targeted perturbation of the tumor–nerve NPY axis using genetic and antibody-based interventions in orthotopic and TPAC models reduced innervation, curtailed neural invasion, and extended survival, establishing causality for this circuit. Our multiomic interactome mapping connects Schwann-derived signals to aggressive tumor phenotypes, highlights actionable nodes of nerve–cancer communication, and provides a platform for mechanistic and therapeutic interrogation of PDAC neural invasion, including opportunities to repurpose neuroactive drugs.

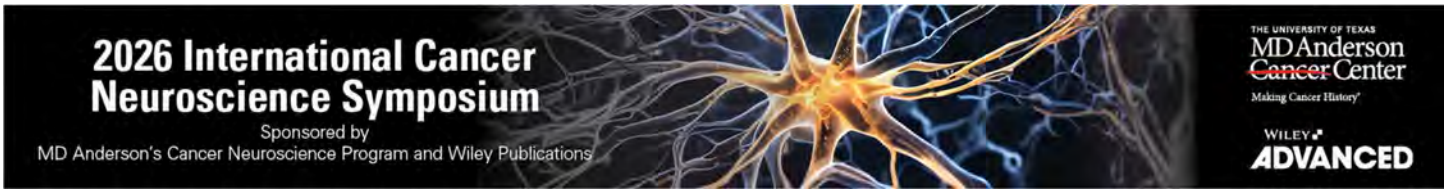
Poster # 15

Abstract Title: Neuronal neuropeptide Y (NPY) involvement in nerve-cancer crosstalk and perineural invasion in epithelial and non-epithelial cancer models.

Authors: Joanna Kitlinska (Georgetown University), Dawid Sigorski, Susana Galli, Sung-Hyeok Hong, Sara Misiukiewicz, Yiwen Li, Isabella Yockey, Ewa Izycka-Swieszewska

Introduction: The role of perineural invasion (PNI) in locoregional dissemination is important but dependent on the primary tumor type and localization. Neuropeptide Y (NPY) is a pleiotropic neuropeptide secreted from peripheral nerves and involved in cancer biology.

Methods: To determine the role of NPY in PNI we used orthotopic xenograft models of two malignancies expressing NPY and its receptors - Ewing sarcoma (ES) and prostate cancer (PC)



Results: Our work revealed that the regional bone lesions developing in the lumbar vertebral column in ES and PC models are initiated by cells migrating from primary tumors toward spine along nerves. However, the pattern of ES and PC invasion varied significantly. ES tumors invaded deep into the spinal cord, causing limb paralysis in mice. In contrast, PC tumors migrated along the vertebral column, forming paravertebral tumors. We have shown that in ES this process is dependent on the endogenous NPY levels, as the tumor cells that do not secrete their own NPY are attracted to the peptide released from neighboring nerves. Consequently, knock-down of endogenous NPY in ES xenografts significantly exacerbated PNI, while NPY overexpression in NPY-low xenografts inhibited this process. Using an in vitro migration assay, we have confirmed that PNI observed in vivo associates with the increased chemotaxis toward neuronal conditioned medium (N-CM) from sympathetic and sensory ganglia, as well as recombinant NPY in both ES and PC cells. However, in ES the chemotactic effect of NPY and N-CM was completely blocked by Y1R inhibition in tumor cells, while in PC cells the combination of Y1R, Y2R and Y5R antagonists only partially decreased N-CM-induced chemotaxis.

Conclusion: Neuronal NPY acts as chemoattractant for cancer cells expressing its receptors, and thereby stimulates PNI. However, the differential patterns of invasion and NPY-dependence indicate interactions with different nerve types, and warrant further investigations.

Significance: Targeting NPY receptors may become a novel strategy to block locoregional cancer invasion. Given the previously established role of the NPY system in stimulating cancer cell proliferation, chemoresistance and distant metastases, such treatment may become an effective therapy preventing the disease progression.

Poster # 16

Abstract Title: TRPV1+ sensory neurons promote metastasis via nociceptin-OPRL1 signaling

Authors: Matthew Knarr (University of Pennsylvania), Sarah Kimmel, Katherine Cummins, Dusan Racordon, Gabriel Mingo, Hunter Reavis, Timothy Lippert, Taku Harada, Ryan Hausler, Jamie Moon, Austin Nguyen, Jinho Lee, Ann E. Walts, Ryan Coopergard, Boris Winterhoff, Analisa DiFeo, Roger A. Greenberg, Paola Vermeer, Sandra Orsulic, Joanna Pucilowska, Dave SB Hoon, Gordon B. Mills, and Ronny Drapkin

Introduction: Metastasis remains the primary cause of cancer-related mortality, yet the influence of nerve signaling within the tumor microenvironment (TME) on metastasis is poorly understood. Here, we uncover a critical role for TRPV1-expressing sensory nerves in driving metastatic progression of the most common and deadly gynecological malignancy, high-grade serous ovarian cancer (HGSOC).

Methods & Results: We demonstrate that HGSOC tumors actively recruit TRPV1+ sensory nerves in part by secreting the neurotrophic factor secretory leukocyte protease inhibitor (SLPI), which is amplified and overexpressed in approximately 70% of HGSOCs. We go on to show that TRPV1+ sensory nerves release the endogenous opioid-related neuropeptide nociceptin into the local and regional HGSOC TME. Nociceptin binds its cognate receptor OPRL1 on HGSOC cells to promote tumor growth, survival, and dissemination. Genetic or pharmacologic disruption of TRPV1, nociceptin, or OPRL1 profoundly impairs metastasis and improves survival in multiple in vivo models. Patient datasets reveal that this signaling axis is associated with poor prognosis across several cancer types.

Conclusions: TRPV1–nociceptin–OPRL1 signaling is a robust indicator of poor prognosis in multiple cancers, including ovarian cancer, and is critical for successful metastatic dissemination of HGSOC.

Significance to cancer neuroscience field: These findings define a previously unrecognized neural signaling axis in cancer and identify the TRPV1–nociceptin–OPRL1 pathway as a potential therapeutic target for limiting metastasis.

Poster # 17

Abstract Title: Assessing cancer-related pain by behavioral tests in mice with oral tumors

Authors: Attila Kovacs (Sanford Research and University of South Dakota), Paola D. Vermeer

Introduction: Quantifying oro-facial pain is complicated as this richly innervated area contains multiple overlapping fields associated with different sensory modalities. Here, we tested the utility of marble bury, burrowing, and our newly developed facial von Frey test to assess oral cancer-related pain.

Methods: C57BL/6J mice were separated into four experimental groups (10 mice/group) as follows: 1) oral MOC2-7 tumor implantation; 2) oral tumor implantation + carprofen (non-steroidal anti-inflammatory commonly used for pain); 3) No tumor; 4) No tumor + carprofen. All groups underwent behavioral testing twice a week before and after tumor implantation. While the marble bury test classically assesses obsessive/compulsive and anxiety-like behaviors, it can also serve as a measure of pain. The burrowing test measures a mouse's innate behavior to remove food from a tube. While it is a test of general well-being, it also serves as a measure of pain. Facial von Frey tests the mechanical sensitivity of the right (tumor-bearing) and left (no tumor) cheek. For this, the mouse’s movements are gently restricted by holding its tail while von Frey filaments were used to touch each cheek using the simplified up-down method.

Results: On days 28 and 30 post-tumor implantation, male mice buried significantly less marbles than no tumor control animals; treatment with carprofen prevented this decline. On day 30 post-tumor implantation, tumor-bearing mice showed a significant decrease in the amount of food pellets removed from the tube; carprofen had no effect on this behavior. Starting on day 10 post-tumor implantation, the mechanical sensitivity of the tumor-bearing right cheek markedly increased as compared to no tumor control animals. Carprofen treatment prevented this increased sensitivity. Surprisingly, carprofen treatment caused a pronounced reduction in tumor growth in female but not male mice.

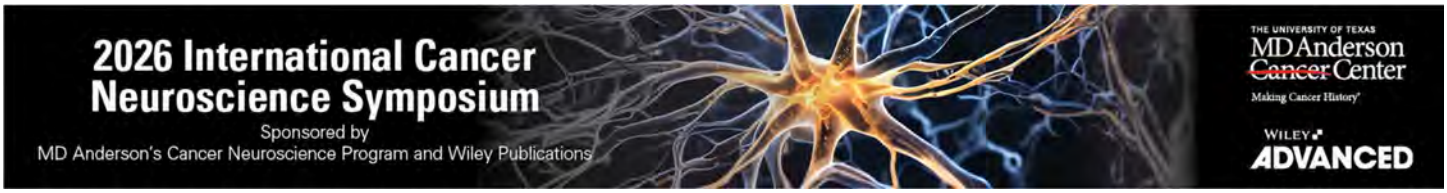
Conclusion: Our newly developed facial von Frey test does not require repeated conditioning or training and can detect increased mechanical sensitivity at the tumor site as early as 10 days after tumor implantation.

Significance to the cancer neuroscience field: We describe a new, simple facial von Frey test that can be used to measure pain caused by head and neck cancer in mice.

Poster # 18

Abstract Title: SEAK193 is a potent and highly BBB-penetrable anti-mitotic agent and shows promising efficacy in treating breast cancer brain metastases

Authors: Wei Li (University of Tennessee Health Science Center), Kelli Adeleye, Raisa Krutilina, Duane D Miller, Tiffany Seagroves



Introduction: The major sites where breast cancer commonly metastasizes are the bones, liver, lungs, and brain. Approximately 15% to 30% of metastatic breast cancer patients develop breast cancer brain metastasis (BCBM). Despite the recent significant advances in the treatment of primary tumors, the incidence of BCBMs has increased. This increase is most likely due to improved patient survival and thus time for cancer cell dissemination, the limited efficacy of primary tumor therapies in treating BCBMs, the selection of chemoresistant metastatic clones upon treatments, and more importantly, the lack of drugs that penetrate the blood-brain barrier (BBB). Compared with other major metastasis sites (bones, liver, and lungs) where the quality of life (QofL) is still manageable to some extent, patients with BCBMs have much more severe impairments in QofL and significantly lower survival. Therefore, there is a significant unmet medical need to develop an effective treatment for patients with BCBMs.

Methods: Using comprehensive medicinal chemistry and cancer biology approaches, we have discovered and developed a new anti-mitotic molecule, SEAK193, as a potentially effective treatment for BCBMs.

Results: Our data shows that SEAK193: (1) has a clear mechanism of action confirmed by its co-crystal structure with tubulin, surface plasmon resonance spectroscopy, and EBI competitive binding assays; (2) has excellent metabolic stability and pharmacokinetic profiles; (3) is highly potent against drug-resistant breast tumor models in vivo; (4) has high brain penetration and shows substantial preclinical efficacy in a highly aggressive, clinically relevant taxane-refractory (TxR) BCBM TNBC PDX (HCI-10); and (5) shows promising ability to potentiate anti-PD-L1 immunotherapy, which could enhance inhibition of extracranial metastases.

Conclusions and Significance to the cancer neuroscience field: Further characterization and development of SEAK193 as a potential clinical candidate could significantly benefit not only patients with BCBMs, but also patients with brain metastasis from other cancer types or patients with primary brain tumors.

Acknowledgement: The work is supported by NIH/NCI grants R01CA14876 (WL and DDM) and R01CA276152 (WL and TNS), with additional support from a DoD grant HT9425-23-1-0216 (WL) and the University of Tennessee College of Pharmacy Drug Discovery Center (WL).

†*Professional Development Award*

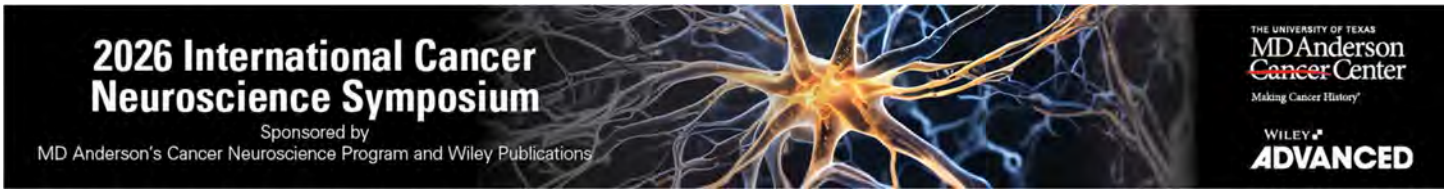
† Poster # 19

Abstract Title: Remodelling of the sympathetic nervous system impairs chemotherapy control of metastatic breast cancer

Authors: Annabel Manoleras (Monash University), Erica K. Sloan, Aeson Chang

Triple-negative breast cancer (TNBC) is an aggressive malignancy for which chemotherapy remains first-line standard of care. We previously demonstrated that TNBC exploits sympathetic nervous system (SNS) signaling to reduce chemotherapy efficacy by increasing sympathetic innervation in primary tumors. Organs that are commonly colonised by metastasis are highly innervated by the SNS. However, the effect of chemotherapy on sympathetic innervation at metastatic sites and their impact on disease progression remain unclear.

To investigate this, we used 4T1.2 and MDA-MB-231HM orthotopic xenograft mouse models of advanced TNBC, using bioluminescent imaging to detect metastatic relapse following primary tumor resection. To evaluate the functional impact of SNS activity of doxorubicin chemotherapy, 6-hydroxydopamine (6-OHDA; i.p.)



was used to induce chemical sympathectomy and metastatic burden was quantified using bioluminescence imaging. Chemical denervation with 6-OHDA significantly enhanced doxorubicin control of 4T1.2 metastasis ($p = 0.04$), suggesting the SNS may impair doxorubicin efficacy. Given that TNBC metastases are often innervated with sympathetic nerves, we used tyrosine hydroxylase (TH) immunostaining to investigate sympathetic neural architecture in doxorubicin-treated metastatic organs. Doxorubicin significantly increased TH+ nerve density in metastatic lung (4T1.2: $p = 0.009$; MDA-MB-231HM: $p = 0.04$) and liver (4T1.2: $p < 0.001$; MDA-MB-231HM: $p = 0.02$) tissue but had no effect in tumor-naïve organs. qRT-PCR on RNA isolated from 4T1.2 metastatic lung ($p = 0.02$) and liver ($p = 0.04$) tissue revealed that doxorubicin induced a significant increase in Ngf expression. To determine if tumor cell-derived NGF was involved in doxorubicin-induced remodelling of the SNS in metastatic tissues, we used 4T1.2 tumor cells with a CRISPR-mediated NGF knockout (KO). Doxorubicin had no effect on TH+ nerve density in 4T1.2-NGFKO lung ($p = 0.83$) and liver ($p = 0.33$) metastasis, indicating that tumor-derived NGF mediates doxorubicin-induced sympathetic nerve remodelling. We asked if doxorubicin efficacy was improved in the absence of sympathetic nerve remodelling, where bioluminescence imaging revealed that doxorubicin had a ~10-fold improvement in metastasis control in 4T1.2-NGFKO mice, relative to 4T1.2-wildtype mice ($p = 0.01$; 2way ANOVA on log10 transformed data, followed by Dunnett's test). Statistical analysis performed using unpaired Student's t test, unless otherwise stated.

These findings reveal a bidirectional interaction between the SNS and doxorubicin response, whereby doxorubicin promotes sympathetic innervation in metastatic organs through tumor cell-derived NGF, which subsequently impairs its therapeutic efficacy. This suggests that targeting neural signaling during chemotherapy treatment may be a novel strategy to improve clinical outcomes for patients with metastatic TNBC.

†*Professional Development Award*

† Poster # 20

Abstract Title: Sensory-Sympathetic Nerve Circuit Modulates the Tumor Microenvironment in Head and Neck Cancer

Authors: Andre Martel Matos (University of Pittsburgh), Lisa A. McIlvried, Marci L. Nilsen, Megan A. Atherton, Nicole N. Scheff

Head and neck squamous cell carcinoma (HNSCC) causes severe pain, stress and sympathetic dysregulation, which exceeds most other cancers. We hypothesize that sensory input from the tumor microenvironment (TME) drives increased sympathetic tone and plasticity, creating a feedback loop resulting in immunosuppression and tumor growth.

We prospectively accrued 119 OSCC patients (69.4±10, 65% male) for the assessment of patient-reported outcomes and circulating NE. A syngeneic orthotopic tongue cancer mouse model (MOC2) was used with nociceptive behavior assays, calcium imaging, PCR, immunohistochemistry, mass spectrometry to understand the mechanism for sympathetic-sensory nerve circuit and neuronal plasticity.

OSCC patients had 4-fold increase in platelet NE which positively correlated with patient-reported spontaneous/ongoing pain ($r=0.634$). NE concentration was also identified as an independent predictor of perineural invasion pathology. In preclinical oral cancer mouse models, we used RNA sequencing and PCR to characterize tumor-induced plasticity in sensory and sympathetic neurons. In tongue-innervating trigeminal neurons, we found upregulated genes related to neurotransmission (Notch1, Snap47, Adam17, Cacna2d1)

and axonogenesis (Ntrk1, Ntrk2, Plxnb2, Stmn2) from MOC2 tumor-bearing mice compared to sham. Sensory neurons also acquire adrenergic sensitivity due to a significant upregulation of excitatory Adra1d and a downregulation of inhibitory Adra2c; we functionally confirmed NE-induced activation of sensory nerve only in tumor mice. In SCG from tumor bearing mice, we found differentially expressed genes related to neurotransmission (Npy, Npy1r, Npy2r, Adra2a), neuronal firing (Ntrk, p75) and sprouting (Gap43, Stmn2, Sprr1a). Functional testing using Ca2+ imaging in dissociated SCG neurons revealed significant shift in the percent responsive SCG neurons to 3-30μM acetylcholine and a significant increase in the KCl-evoked depolarization, suggesting changes in voltage gated Ca2+ channel expression. Local chemical denervation of TRPV1-expressing TG neurons using resiniferatoxin (RTX) ameliorated tumor-induced pain behavior, increased infiltration of CD8 T cells 3-fold and significantly reduced tumoral NE concentration by 75.4±16%. Sensory denervation also prevented the gene expression changes in Adra2a and Ntrk in the SCG, but not those associated with sprouting as well as attenuated the shift in acetylcholine dose response and reduced depolarization-evoked transients in SCG neurons. Sympathetic denervation by surgical sympathectomy significantly reduced tumor size, spontaneous pain-like behaviors and immunosuppressive immune infiltrate.

These data suggest that diminished sensory neuron activity influences tumor-mediated sympathetic postganglionic neuronal plasticity and sensitization. While the cancer neuroscience field has traditionally studied sensory and sympathetic neurons separately, these data suggest a pivot to considering the impacts each fiber type on each other and the TME.

Poster # 21

Abstract Title: Role of sensory neurons in ER+ and TNBC breast cancers

Authors: Lisa McIlvried (University of Pittsburgh), Tyler R Fleming, Tian LeGrande, Andre A Martel Matos, Megan A Atherton, Nicole N Scheff

Introduction: Breast cancer (BC) progression involves complex interactions between tumor cells and the surrounding microenvironment, including the peripheral nervous system. Emerging evidence suggests that sensory neurons may play a critical role in cancer development through bidirectional signaling with tumor cells. However, the extent to which different BC subtypes engage with sensory innervation remains unclear.

Methods: We sought to evaluate the reciprocal relationship between sensory neurons and BC using two different syngeneic orthotopic mouse models, a 4T1.2 model of triple negative BC (TNBC, Balb/c) and SSM3 model of estrogen receptor positive (ER+, 129SvEv) BC. To evaluate the impact of tumor cells on sensory neurons we compared the phenotype of sensory afferent neurons innervating the tumor as well as sprouting and activation of sensory neurons in response to cancer cell conditioned media. To evaluate the impact of sensory neurons on tumors, we used in vitro assays to measure proliferation, migration and changes in gene expression. Ongoing experiments are evaluating the role of sensory signaling on anti-tumor immunity.

Results: We found that the majority (40-60%) of retrograde-labeled mammary fat pad (mFP) afferents are peptidergic across genotypes; there was a 2-fold increase in the percentage of CGRP-expressing mFP afferents in SSM3 but not 4T1.2 tumor-bearing mice. Luminex multiplex analysis of tumor cell media revealed that both BC cell lines released algogenic mediators and growth factors that can directly influence sensory neurons. Of note, the SSM3 cell line released significantly more nerve growth factor (NGF) protein, a neurotrophic factor required for the growth and survival of peripheral nerves, compared to 4T1.2 or control non-tumorigenic line. After 24 hour DRG culture with tumor cell conditioned media, we found that SSM3 induced a

significant, NGF-dependent increase in neurite outgrowth; however, there was no change in neurite outgrowth in response to 4T1.2 or control. Similarly, using calcium imaging, we found that SSM3 media evoked Ca2+ responses in significantly more mFP afferents compared to 4T1.2 or control. While both tumor cell lines express receptors for neuropeptides (Ramp1, Tacr1), CGRP exposure only evoked modest but significant increases in SSM3 proliferation. We found no impact of CGRP on cell line expression of Ngf or genes related to exhaustion (Pdl1, Tgfb).

Conclusion: Together, these data suggest that sensory nerves may play a bigger role in tumorigenesis of ER+ BC compared to TNBC. Understanding these neuron-tumor interactions within BC subtypes could reveal novel therapeutic targets, particularly as neuromodulatory therapies gain traction in oncology.

†*Professional Development Award*

† Poster # 22

Abstract Title: The Fas receptor promotes neural invasion by inducing a shift from apoptotic to migratory signaling in pancreatic cancer cells

Authors: Clara Muller (Technical University of Munich), Mara R. Goetz, Hossam Taher, Rüdiger Göß, Helmut Friess, Ihsan Ekin Demir

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with poor prognosis, frequently characterized by perineural invasion (PNI), an independent prognostic factor for disease-free and overall survival. Studies have shown increased expression of the FAS receptor (CD95) in PDAC. Beyond its role in apoptosis, FAS may influence cell migration, possibly contributing to PNI.

Methods: Transcriptomic analyses were performed on genetically engineered mouse models (GEMMs) with human-like PNI or non-PNI phenotypes. FAS RNA and protein levels were quantified in human and murine neuroinvasive PDAC cell lines using qRT-PCR and western blot. Tissue microarrays from PDAC patients with and without PNI were stained for FAS to assess clinical relevance. The non-apoptotic function of FAS was examined in 3D migration assays exposing murine dorsal root ganglia neurons to invasive PDAC cells. FAS signaling was modulated by neutralizing antibody, or Fas ligand (FasL) stimulation. CDC42 activation was analyzed by western blot to identify downstream signaling events.

Results: Transcriptomic data revealed higher FAS expression in PNI-positive GEMMs, consistent with elevated RNA and protein levels in neuroinvasive PDAC cell lines. In murine PDAC cells, FAS mRNA was significantly higher in the neuroinvasive TPC line than in the non-invasive KPC line ($n = 5$, $p = 0.0076$). Similarly, human PDAC cell lines T3M4 and SU.86.86 showed high FAS expression linked to their neuroinvasive phenotype. In 3D migration assays, PDAC cells migrated toward neurons, which decreased upon FAS inhibition and increased after FasL stimulation. Histological analysis revealed stronger FAS expression in nerve-invading PDAC tumors ($n = 27$; $p < 0.0001$). TCGA data ($n = 176$) confirmed that high FAS expression correlated with reduced survival ($p = 0.00014$; 5-year OS: 8% vs. 43%). Caspase-3 mRNA levels were only slightly increased, indicating limited apoptotic involvement. FasL treatment increased CDC42 activation and upregulated MMP2 and MMP9, defining a FAS–CDC42 axis in PDAC motility.

Conclusion: FAS is highly expressed in neuroinvasive PDAC, where it promotes tumor migration toward neurons via CDC42-mediated cytoskeletal remodeling. This pathway represents a potential therapeutic target to limit PNI and PDAC progression.

Significance to the cancer neuroscience field:

• Molecular driver of PNI: FAS/CD95 promotes tumor–nerve interactions and directed migration.

• Functional shift: High FAS induces a transition from apoptotic to migratory signaling.

• Clinical impact: Elevated FAS correlates with PNI-positive tumors and poor survival.

• Neurotropic behavior: FAS–CDC42 signaling enhances cytoskeletal remodeling and neuronal tropism.

• Therapeutic potential: Targeting this pathway may disrupt PNI-driven tumor spread and improve outcomes.

Poster # 23

Abstract Title: Sensory neurons promote tumor cell invasion via ECM remodeling

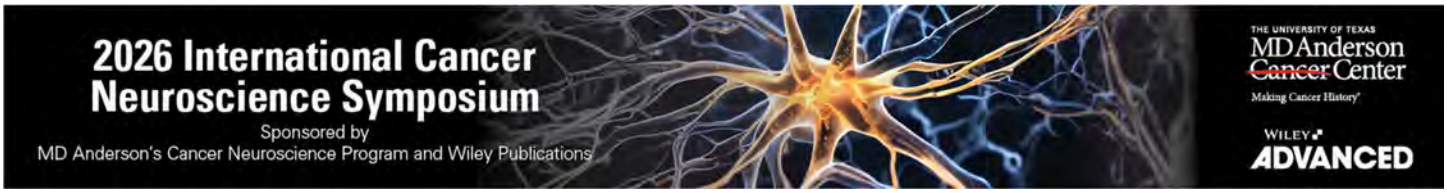
Authors: Ankit Pandey (Tufts University), Hanan Bloomer, Audrey Pierce, Hannah Shadmany, Madeleine Oudin

Introduction: Triple negative breast cancer (TNBC), which represents 10-20% of breast cancers globally has the worst prognosis among breast cancers and is hard to treat due to lack of targetable driver mutations. We have previously shown that there is increased sensory innervation in TNBC tumors compared to healthy breast, and we and others found that sensory nerves can drive breast cancer progression via direct contact and secreted factors. The extracellular matrix (ECM) is a major component of tumor microenvironment (TME) and has been shown to regulate many of the hallmarks of cancer. However, whether the ECM is involved in sensory nerve-tumor crosstalk remains unknown.

Methods: TNBC cells and DRG sensory neurons were cultured in 2D and 3D hydrogels. Second harmonic generation (SHG) to assess collagen I density. We isolated decellularized ECM produced by TNBC cells, DRG neurons or their co-culture, reseeded TNBC cells on it, and analyze the effect of nerve-derived ECM on invasion.

Results: We found that regions enriched with sensory nerves showed increased Collagen I abundance in human TNBC and mouse tumors. In 3D hydrogels, tumor cell and DRG neuron co-culture led to significantly smaller gels compared to each cell alone. Human tumor cells seeded on ECM generated by nerves invaded significantly more than when seeded on ECM secreted by reduction mammary fibroblasts. Addition of tumor cells to DRG neurons further increases pro-invasive effects on tumor cells. Sensory neurons secrete elevated levels of Collagen IV, V and VI and Fibronectin proteins in the presence of tumor cells. We also found increased levels of Collagen IV in presence of nerves in human TNBC samples.

Conclusion: Our data demonstrate that sensory nerves secrete pro-invasive ECM including proteins which have previously been shown to drive cancer cell invasion, an effect amplified in the presence of cancer cells. We also show that culturing DRG and cancer cells together increases their ECM remodeling capacity. In vivo we see increased collagen density in proximity of sensory neurons. Together these data suggests that sensory nerves could be contributing to cancer progression via the ECM.



Significance to the cancer neuroscience field: These results for the first time show that sensory nerves secrete pro-invasive ECM and identify a novel mechanism of tumor cell-nerve crosstalk. Understanding how nerves contribute to the TME will help us improve our ability to track metastatic disease and factors affecting local invasion and metastasis.

Poster # 24

Abstract Title: Mechanisms of resistance to anti-HER2 therapies in brain metastatic derivatives of inflammatory HER2-positive breast cancer models

Authors: Caroline Sabotta (Baylor College of Medicine), Fu-Tien Liao, Martin J. Shea, Sarmistha Nanda, Lanfang Qin, Mothaffar F. Rimawi, Carolina Gutierrez, C. Kent Osborne, Susan G. Hilsenbeck, Jamunarani Veeraraghavan, Rachel Schiff

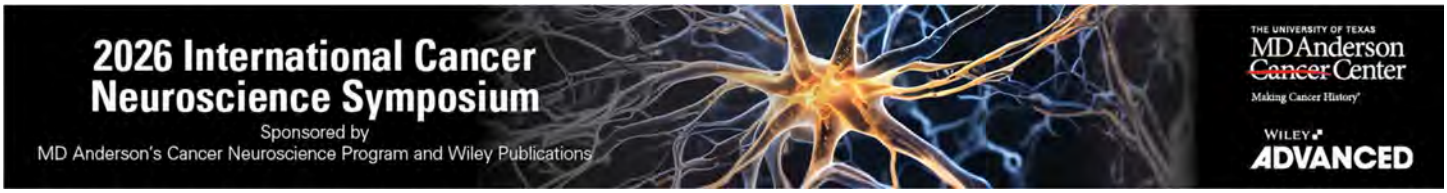
Introduction: HER2-positive (HER2+) breast cancer (BC) is an aggressive subtype with 30-50% incidence of brain metastases in metastatic patients. The HER2-selective tyrosine kinase inhibitor (TKI) tucatinib (Tuca), the pan-HER TKI neratinib (Nrb), and the novel HER2 antibody drug conjugate T-DXd are highly effective, including in treating brain metastases.

Methods: GFP/Luc tagged SUM190-BR3 (SUM190Br), a brain-tropic derivative of the HER2+/ER- inflammatory SUM190 model (harboring PIK3CA H1047R mutation), was used (Lyle, 2016). A Tuca resistant (TucaR) derivative was developed through long-term exposure to increasing doses of Tuca up to 1uM. Drug efficacy studies involved methylene blue-based cell growth and IC50 assays and included the Akt inhibitor (i) capivasertib (Capi, 1uM), T-DXd (5ug/mL), and the EGFR-specific TKI gefitinib (Gef, 1uM) or monoclonal antibody cetuximab (Cetux, 10ug/mL). The in vivo metastatic capacity of our resistant model was evaluated by intracardiac injection and bioluminescence imaging in immunocompromised mice.

Results: The naïve SUM190Br cells are intrinsically resistant to Tuca (IC50>600nM), but not Nrb (IC50<60nM). Western blot analysis of the TucaR model showed elevated levels of phosphorylated and total EGFR, suggesting pathway reactivation at time of resistance. Further, DNA and RNA-seq analysis showed high EGFR mRNA but with no copy number changes. As we previously showed in the BT474 TucaR model, the SUM190Br TucaR cells remain sensitive to Nrb. Further, Capi is effective as a single agent in the TucaR model ($p<.0001$). High EGFR has been shown to reduce the efficacy of T-DXd (Gupta, 2024). Indeed, Cetux improved the efficacy of T-DXd in our high EGFR TucaR model. Further, our highly aggressive TucaR model keeps brain tropism via intracardiac injection.

Conclusion: Our findings suggest the role of high EGFR and PIK3CA mutations in Tuca resistance, which warrants additional preclinical and clinical investigation. The recent DESTINY-Breast09 trial highlighted the promise of T-DXd together with the HER2 monoclonal antibody pertuzumab as the potential new first line for metastatic BC. Ongoing work seeks to elucidate if T-DXd plus pertuzumab is effective compared to T-DXd plus EGFRi in HER2+ BC with high EGFR.

Significance to the cancer neuroscience field: The proven efficacy of brain permeable HER targeted agents, including in the brain metastatic setting, positions them as a key therapy in neuro-oncology, and warrants better understanding of the associated resistance mechanisms. Our unique brain tropic TucaR models are crucial for developing novel treatment strategies to overcome resistance in the brain metastatic setting.



Poster # 25

Abstract Title: β-Adrenergic Signaling Promotes CXCL10-Dependent Anti-tumor Immunity in p53-Mutant Head and Neck Cancer

Authors: Robert Saddawi-Konefka (MD Anderson Cancer Center), Frederico Omar Gleber Netto, Deborah Silverman, Tongxin Xie, Shamima Akhter, Nicole R. Vaughn, Adewale Adebayo, Kala Chand Debnath, Shorook Naara, Shajedul Islam, Erik Knutsen, Emily Lorin Ashkin, Simone Anfossi, Sara Leahey, Patrick Hwu, Sebastien Talbot, Nicole N Sheff, Erica K Sloan, Jeffrey N. Myers, George A. Calin, Moran Amit

Introduction: Head and neck squamous cell carcinoma (HNSCC) shows limited immunotherapy responsiveness, particularly in TP53-mutant disease. While β-adrenergic signaling and p53 loss individually influence immune responses, their interaction in modulating anti-tumor immunity remains unexplored. We hypothesized that β-adrenergic signaling modulates anti-tumor immune responses in p53-deficient head and neck squamous cell carcinoma through indirect activation of cytotoxic T cells.

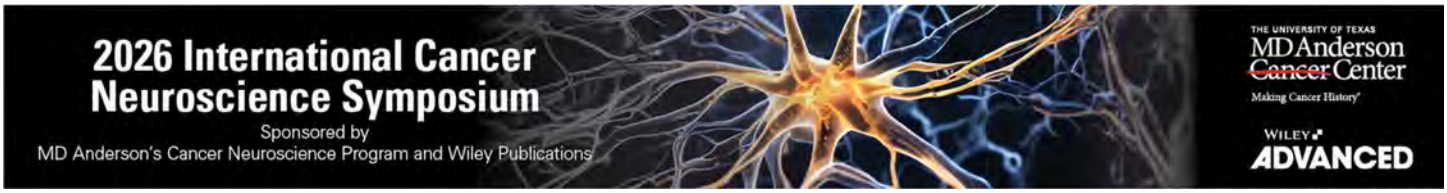
Methods: We used in vitro co-culture systems with CD8+ T cells and p53-deficient OSCC cell lines (PCI13) transduced with WT TP53 or control vectors, treating them with the β2-adrenergic agonist isoprenaline. To evaluate for cytotoxic activity and immune cell phenotypes, we performed T-cell cytotoxicity assays, Luminex cytokine profiling, RNAseq, and CyTOF analysis. We validated findings using spatial transcriptomics of 4NQO-induced oral lesions from p53-deficient mice and orthotopic MOC2 tumor models in Th-flox mice with ablated adrenergic innervation (AAV-CAG-iCre).

Results: Isoprenaline enhanced CD8+ T cell cytotoxicity specifically against p53-deficient OSCC cells but no effect on p53 WT cells. This was accompanied by selective upregulation of CXCL10 in p53-deficient cells. TCGA analysis revealed distinct ADRB2 correlations in TP53-mutant compared to TP53-WT OSCC, while spatial transcriptomic analysis of 4NQO-induced oral lesions confirmed widespread Adrb2 expression that correlated with immune response and neuronal signaling genes. RNAseq revealed activation of T cell effector pathways, while CyTOF showed increased CD8+ T cell activation markers including CD69+ and IFNγ+. In vivo, adrenergic ablation reduced tumor CXCL10 expression, decreased CXCR3+ T cell infiltration, shifted T cells toward exhausted phenotypes with increased PD-1 and TIM-3 expression, and accelerated tumor growth. CXCL10 neutralization abolished isoprenaline-induced anti-tumor effects. Concordantly, CyTOF analysis of Th-flox mice with genetic ablation of adrenergic nerves revealed markedly reduced activated CD8+ T cells.

Conclusions: This study reveals a novel neuro-immune interaction specific to p53-deficient cancer cells under adrenergic stimulation with significant impact on the promotion of anti-tumor immunity. Overall, β-adrenergic signaling promotes anti-tumor immunity in p53-deficient HNSCC through CXCL10-mediated T cell activation. These results highlight that β-adrenergic signaling acts as a context-dependent regulator of tumor immunity, reversing immune evasion specifically in p53-deficient tumors. This discovery establishes a mechanistic link between neural signaling, CXCL10-driven immune activation, and p53 loss, suggesting therapeutic potential for targeted β-adrenergic modulation in cancer.

Poster # 26

Abstract Title: Axon Guidance protein Neuropilin-2 Promotes Perineural Invasion and metastasis in Pancreatic Ductal Adenocarcinoma (PDAC)



Authors: Ashu Shah (University of Nebraska Medical Center), Esther Johnson, Imran Khan, Claire Sorrell, Zahraa Wajih Alsafwani, Jesse L Cox, Shailendra K Gautam, Moorthy P Ponnusamy, Surinder K Batra

Background and aims: Perineural invasion (PNI) occurs when tumor cells infiltrate surrounding nerves, contributing to metastasis and pain in cancer patients. PNI occurs in approximately 80% of PDAC patients and is linked to generally poorer survival outcomes. Despite the well-established clinical significance of PNI, its molecular mechanisms remain poorly understood. Axonal guidance molecules are frequently altered in PDAC and have been recently shown to play a role in PNI. Here, we report that neuropilin-2 (NRP2), an axonal guidance molecule, is associated with PNI and the poor survival of PDAC patients. Methodology: We investigated NRP2 expression and its association with PNI in PDAC by analyzing patient datasets and performing multiplex immunofluorescence (IF) and immunohistochemistry (IHC) experiments. We investigated the role of NRP2 in PNI and disease progression through in vitro cancer-neuron co-culture experiments and in vivo orthotopic syngeneic mouse models. Subsequently, the findings were validated through a mechanistic RNA-seq analysis of NRP2-proficient and silenced mouse tumors.

Results and conclusions: We observed high NRP2 expression in PNI regions of human tumors and a strong association with worse overall survival in PDAC patients. IHC studies for NRP2 and neuronal markers (TUBIII) showed a stronger correlation between NRP2 and neuronal density (innervation) in PNI areas than in non-PNI regions. PDAC cells (SU86.86, CD18) exhibited enhanced migration (65%, p=0.0027) and invasion towards neuronal cells derived from dorsal root ganglia (DRG) (56%, p=0.034) compared to low NRP2-expressing PDAC cells (COLO357). These results were substantiated in the standard DRG/Matrigel coculture models. Furthermore, culture supernatants from NRP2-proficient cells induced neuronal remodeling, as indicated by increased neurite length (400 μm) compared to NRP2 KD cells (137 μm) and enhanced branching, a notable feature linked to PNI. Reducing Nrp2 in the mouse model of PDAC led to lower nerve density and a significant decrease in tumor weight (75%, p = 4.5 × 10^ (-5)) and metastasis (60%, p= 0.023), indicating its possible role in preventing PNI and metastasis. Our initial mechanistic studies point to a possible interaction between NRP2 and the neuronal protein Nptx1. RNAseq analysis of differentially expressed genes and pathway enrichment in Nrp2-silenced mouse PDAC tumors is ongoing to identify the factors influencing PNI PDAC. Conclusions and future direction: Tumor-derived NRP2 mediates PNI, thereby affecting disease progression and metastasis in PDAC. The studies are underway to elucidate the role of NRP2-mediated PNI in cancer-associated pain. Significance: Strategies to disrupt NRP2-mediated PNI could be developed to prevent disease progression and alleviate pain in PDAC patients.

Poster # 27

Abstract Title: Aspirin Reprograms Pancreatic Stellate Cells to Suppress Tumor–Schwann Cell Interaction in Pancreatic Cancer

Authors: Sila Sığırlı (Acibadem Mehmet Ali Aydinlar University), Didem Karakas, Engin Ulukaya, Ihsan Ekin Demir, Güralp Onur Ceyhan

Introduction: Neural invasion (NI) is a major contributor to poor prognosis in pancreatic ductal adenocarcinoma (PDAC). Pancreatic stellate cells (PSCs), the dominant stromal population, enhance tumor aggressiveness and active even in pre-neoplastic pancreatic intraepithelial neoplasia (PanIN) lesions. Schwann cells guide cancer cell migration along nerves and are also found near PanINs, indicating that tumor–nerve-fibroblast crosstalk arises early in carcinogenesis. Yet, how PSCs regulate the communication between PDAC cells and

SCs remains poorly understood. Aspirin (ASA), an anti-inflammatory agent, may modulate the tumor stroma beyond its pharmacologic actions. We investigated whether ASA reprograms PSCs to limit their ability to promote PDAC–Schwann interactions to mitigate neural invasion.

Methods: PSCs were treated with non-cytotoxic doses of ASA (2.5 mM and 1.25 mM). Conditioned media (CM) were collected from untreated and ASA-treated PSCs. PANC-1 cells and SCs were exposed to these CMs, and their functional behaviors were compared. qPCR and Western blot were used to assess epithelial–mesenchymal transition (EMT) markers in PDAC cells and dedifferentiation markers (GFAP, S100) in Schwann cells exposed to NT or ASA-treated PSC media. Additionally, 3D migration model used to quantify the reciprocal migration between cancer and Schwann cell under NT or ASA pre-treated PSC CM. Mice bearing orthotopic PDAC tumors received oral ASA treatment to examine the in vivo impact of stromal modulation on microenvironmental modelling.

Results: Conditioned media from untreated PSCs strongly enhanced PDAC and Schwann cell migration and invasion, reflecting a robust PSC-driven pro-invasive phenotype. In contrast, ASA-treated PSC-CM significantly diminished these effects, suggesting a functional reprogramming of PSCs toward a tumor-restraining state. In 3D co-cultures, the untreated PSC secretome promoted dynamic, bidirectional PDAC–Schwann migration, which was almost completely reversed by ASA exposure. Furthermore, oral ASA treatment not only reduced orthotopic tumor burden but also reshaped PSC distribution and stroma density within the pancreas, indicating extensive stromal remodeling consistent with ASA-induced reprogramming of the tumor microenvironment.

Conclusion: The results demonstrate that aspirin attenuates PSC-mediated signaling involved in tumor–nerve crosstalk in PDAC. By reprogramming PSCs, ASA diminishes Schwann activation and PDAC neurotropism, highlighting stromal modulation as a feasible strategy to limit neural invasion.

Significance to the Cancer Neuroscience field: This study bridges stromal biology and cancer neuroscience by revealing that PSCs actively regulate Schwann cell behavior in PDAC. Our findings show that aspirin, a widely used and clinically accessible drug, can reprogram PSCs to disrupt this neuroinvasive axis, linking anti-inflammatory signaling to tumor-associated neuroplasticity.

Poster # 28

Abstract Title: Chemo-Immunomodulation as a Mechanistic Rationale for Combined Immuno-Oncology Therapy in Skull Base Squamous Cell Carcinoma

Authors: Yen Vu (MD Anderson Cancer Center), Hinduja Sathishkumar, Caitlyn Stewart, Lilach Pasvolsky, Jindal Sonali, Sharma Padmanee, Ehab Hanna, Robert Saddawi-Konefka, Moran Amit

Introduction: Skull base squamous cell carcinoma (SBSCC) is a rare, aggressive malignancy with a 5-year overall survival rate below 35% despite multimodal therapy. Chemo-immunomodulation, where chemotherapy exerts immunomodulatory effects beyond direct cytotoxicity, alters the tumor microenvironment by enhancing immune cell infiltration and reducing immunosuppression. Preclinical studies show that chemotherapy, sequenced prior to checkpoint blockade, enhances anti-tumor responses by reversing myeloid-derived suppressor cell-mediated immunosuppression. However, the extent to which chemo-immunomodulation occurs in human SBSCC, particularly the formation of tertiary lymphoid structures (TLS) as hubs of anti-tumor immunity, remains uncharacterized. We hypothesize that chemotherapy induces immunogenic tumor

microenvironment remodeling in SBSCC via TLS development, creating conditions that favor enhanced immunotherapy efficacy and improved clinical outcomes.

Methods: SBSCC tissue specimens from MD Anderson patients (N=5, with surgical controls, chemotherapy-only, and combination chemo-immunotherapy cohorts) were analyzed using multiplex COMET imaging (Lunaphore Technologies) to visualize immune cell phenotypes and spatial architecture. COMET imaging analysis quantified TLS density, B-cell follicle organization, and immune cell spatial clustering using customized image analysis algorithms. Immune cell abundance, distribution, TLS composition, and B-cell follicle organization were correlated with clinical response, disease-free survival, and overall survival.

Results: Multiplex imaging revealed significantly elevated immune infiltrates in the peritumoral regions of chemotherapy-treated SBSCC compared to untreated controls, with increased frequencies of $CD4^+$ and $CD8^+$ T cells, B cells, and various inflammatory populations. Chemotherapy-treated specimens showed organized TLS with distinct B-cell follicles and T-cell zones, indicating the generation of structured microenvironments for anti-tumor immune activation. Clinical outcomes differed by treatment regimen: surgery-only patients experienced rapid recurrence, chemotherapy-alone patients had stable disease or partial response with sustained disease control, and the patient receiving combination chemo-immunotherapy achieved partial response with durable tumor reduction at last follow-up. Disease-free survival was longest in chemotherapy-based groups, with the combination therapy patient showing the most durable response. Notably, the degree of immune infiltration and TLS maturity correlated directly with clinical outcomes, making treatment-induced TLS formation a potential predictive biomarker for immunotherapy response.

Conclusions: These findings provide direct evidence of chemo-immunomodulation in SBSCC, driven by chemotherapy-associated TLS formation and immune cell infiltration remodeling. The observed correlation between immune microenvironment remodeling and clinical outcomes supports chemotherapy-sequenced immunotherapy approaches in SBSCC.

Significance to the cancer neuroscience field: TLS maturity and density may serve as predictive biomarkers for immunotherapy response, supporting the rational sequencing of chemotherapy prior to checkpoint inhibition in SBSCC, with TLS-based imaging biomarkers potentially aiding patient stratification in future clinical trials.

†*Professional Development Award*

† Poster # 29

Abstract Title: Metabolic and Neuronal Signatures of Chemotherapy-Induced Cognitive Impairment Revealed by Hyperpolarized MR and Optical Imaging

Authors: Muxin Wang (MD Anderson Cancer Center), Xudong Qiu, Bill T Sun, José S Enriquez, Julia R Zickus, Jorge De La Cerda, Aldo T Morales, Khloe L Kelley, Lilach Pasvolsky, Moran Amit, Seth Gammon, David Piwnica-Worms, Chengyue Wu, Peter Grace, Komal Shah, Pratip K Bhattacharya

Chemotherapy-induced cognitive impairment (CICI) is reported in around 75% of chemotherapy patients and has long-lasting quality-of-life impacts. CICI is characterized by impairment of memory, learning, attention, and other executive functions. Mechanisms by which CICI occur include inflammation of neurons, stress due to free radical generation, and acceleration of age-related tauopathy development that leads to loss of synaptic

integrity. To date, no direct diagnostic test for CICI has been approved by the US Food and Drug Administration, creating an emergent need to identify metabolic markers that can detect CICI pathogenesis.

Our approach leverages two imaging modalities, hyperpolarized magnetic resonance imaging (HP-MR) with [1-13C]pyruvate and optical imaging with dTat488, to help disentangle the underlying biology of CICI by correlating with established behavioral measurements of cognitive decline. HP-MR, which increases conventional MRI signal by over 10,000-fold, is employed to measure the real-time metabolic conversion of dynamic nuclear polarization (DNP) hyperpolarized [1-13C]pyruvate to [1-13C]lactate in the brain in vivo. On the other hand, dTat488 is a fluorescent probe that is used to detect retinal ganglion cell injury in vivo by non-invasive fluorescence imaging, where the fluorescence signal is retained by anterograde axonal transport deficiency. We employed two groups of wildtype C57BL/6 mice, one treated with cisplatin to establish CICI, and one control group treated with PBS. Both groups are imaged before and after treatment. Behavioral assessments (puzzle box and novel target recognition tests), nuclear magnetic resonance (NMR) metabolomics, and histology results are correlated with imaging findings.

In HP-MR experiments, we found increased pyruvate to lactate conversion in CICI mice compared to controls (0.165 ± 0.013 vs. 0.128 ± 0.007; $t(10.77)=2.49$, $p=0.0303$; n=9 PBS, n=8 cisplatin), indicating metabolic shifts favoring glycolysis. This is consistent with known metabolic alterations caused by cisplatin-induced neuroinflammation. In addition, optical imaging, ex vivo metabolomics, and histology results all show better protection from cisplatin-induced toxicity in the retina compared to the brain. Although axonal transport is similar in both groups, there was more probe retention within blood vessels (219.9 ± 33.2 vs. 157.2 ± 15.7 A.U.; n=12 PBS, n=14 cisplatin), indicating systemic effects of cisplatin. These findings correlated well with declines in performance in behavioral tests.

Together, these results demonstrate that HP-MR and optical imaging provide a powerful multimodal framework that detects metabolic and neuronal transport alterations. These markers could improve clinical diagnosis and monitoring of CICI and have potential relevance in other neurodegenerative diseases as well.

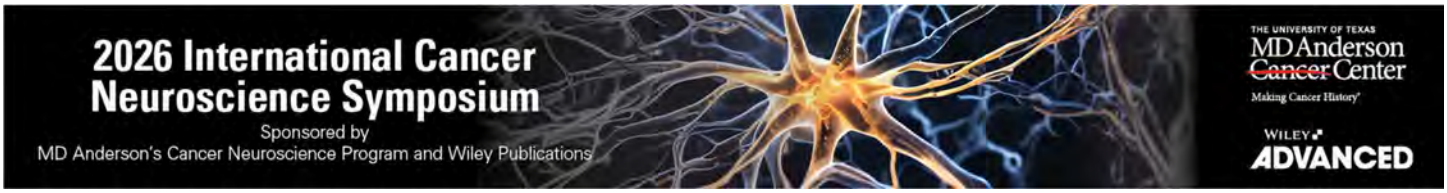
†*Professional Development Award*

† Poster # 30

Abstract Title: The Pdgfd-Pdgfrb axis orchestrates invasion, neurite outgrowth, and glial interactions in pancreatic cancer

Authors: Peter Wang (Massachusetts General Hospital), Nicole A. Lester, Ella N. Perrault, Jennifer Su, Dennis Gong, Carina Shiau, Jingyi Cao, Deniz Olgun, Phuong T. T. Nguyen, Jung Woo Bae, Jason W. Reeves, ShanShan He, Michael Patrick, Hongyoon Choi, Carlos Fernandez-del Castillo, Martin Hemberg, Mari Mino-Kenudson, William L. Hwang

Introduction: Nerves are an integral component of the tumor microenvironment, contributing to cancer progression, metastasis, morbidity, and mortality. Pancreatic ductal adenocarcinoma (PDAC), one of the most lethal malignancies with a five-year overall survival rate of only 13%, exhibits one of the highest rates of nerve involvement, with perineural invasion (PNI) observed in nearly all cases. While spatial transcriptomic profiling represents a promising new strategy to identify candidate tumor-nerve interactions, current platforms are limited in either cellular resolution or molecular coverage.



Methods: We employed whole-transcriptome Digital Spatial Profiling (WT-DSP) in a PDAC patient cohort (n = 29) and 6,200-plex Spatial Molecular Imaging (SMI) on a subset of tissue microarrays (TMAs) derived from the same patient samples to identify concordant genes that were upregulated in cancer cells proximal to (< 300 μm) nerves. To examine the role of these genes in tumor-nerve interactions, we utilized CRISPR-engineered mouse PDAC lines overexpressing individual genes identified from our screen. These malignant lines were used for co-cultures in vitro and to assess invasion in vivo. Nerve invasion, cancer-intrinsic cell invasion, and nerve outgrowth were assessed with live imaging (Incucyte) and confocal imaging.

Results: Using WT-DSP, we identified 1,328 genes enriched in PNI-associated malignant cells, including genes associated with extracellular matrix, nerve biology, cancer cell invasion, and PDGF signaling. Among these, PDGFD-PDGFRB emerged as a ligand-receptor pair showing strong overlap between WT-DSP and SMI. We found that upregulation of Pdgfd in cancer cell lines or addition of recombinant Pdgfd protein promotes nerve invasion in vitro and in vivo. Mechanistically, Pdgfd increases cell-intrinsic invasiveness, sensory nerve outgrowth, and direct physical engagement with glia by signaling through Pdgfrb on cancer cells, neurons, and glia. Pharmacological blockade of this axis reduced each of these processes in vitro as well as PNI in vivo.

Conclusion: We utilized a combined spatial transcriptomic screening approach to uncover candidate mediators of PNI. We found that Pdgfd-Pdgfrb signaling mediates PNI by coordinating multifaceted cancer-neuron-glia interactions and represents a potential therapeutic strategy aimed at disrupting harmful cancer-nerve crosstalk.

Poster # 31

Abstract Title: Targeting melanoma brain metastases through experimental chemotherapeutic induction of cellular deuteration stress

Authors: Georg Wondrak (The University of Arizona), Jana Jandova, Baldassarre Stea

Introduction: Despite recent progress aiming at therapeutic elimination of cancer cells through targeted molecular interventions, treatment options targeting brain cancers remain limited. Oncogenic reprogramming of cellular stress response pathways (an essential adaptation to tumor-intrinsic conditions of increased mutational burden, energy crisis, hypoxia, redox dysregulation, and proteotoxicity) represents a targetable molecular vulnerability of cancer cells. Recently, we have explored feasibility of chemotherapeutic induction of ‘deuteration stress” inducible by systemic exposure to ‘heavy water’ (deuterium oxide, 2H2O, D2O). Induction of deuteration stress through systemic administration of heavy water triggers the cellular ‘unfolded protein response’ (UPR) attributable to increased strength of deuterium (D)-based hydrogen bonds after D/H exchange impacting conformational stability of proteins. The occurrence of malignant melanoma brain metastases is a frequent event, attributed to the neural crest origin of cutaneous melanocytes. Here, using heavy water as an experimental chemotherapeutic we have explored the potential of systemic deuteration targeting melanoma brain metastases.

Methods: In an orthotopic bioluminescent SCID mouse model of BRAFV600E/NRASwt intracranial human A375 melanoma metastasis, chemotherapeutic efficacy of pharmacological deuteration (30% D2O in drinking water) was assessed. Peripheral systemic deuteration was confirmed by proton-MRI imaging and isotope-ratio mass spectrometry. Deuteration-induced modulation of melanoma cell stress response gene expression was profiled employing Nanostring-transcriptomic analysis. Expression of oncogenic aquaporin water channels (that might mediate increased sensitivity to D2O treatment through enhanced cellular uptake) was monitored.

Results: MRI-analysis indicated pronounced brain deuteration and ventricular D2O enrichment [reaching approximately 12 atom % (D/H)]. Bioluminescent tumor signal monitored as a function of treatment group (D2O versus H2O; 21 days treatment regimen) indicated pronounced chemotherapeutic efficacy of the D2O isotopologue regimen achieving tumor growth suppression by more than 80% as compared to H2O control. Moreover, D2O-induced cancer cell stress responses as analyzed at the transcriptomic level indicated pronounced induction of proteotoxicity (DDIT3 encoding CHOP) preferentially targeting malignant cells. In human metastatic melanoma tissue, AQP1, AQP3, and AQP9 overexpression represents a negative predictor of patient survival.

Conclusion: In an orthotopic murine xenograft model of human melanoma brain metastases, an oral deuterium oxide treatment regimen displayed chemotherapeutic efficacy accompanied by high levels plasma and CNS deuteration (> 10 %). Durability of response and interaction with standard of care interventions (including ionizing radiation and immune checkpoint inhibition are being explored.

Significance to the cancer neuroscience field: Systemic pharmacological induction of deuteration stress triggers a proteotoxic stress response of potential clinical utility targeting brain malignancies that are ‘hard-to-treat’ and ‘hard-to-reach’.

Poster # 32

Abstract Title: Hepatic innervation as a regulator of the pre-metastatic niche and liver metastasis in pancreatic cancer

Authors: Eyüp Yöndem (Technical University of Munich, School of Medicine), Rüdiger Göß, Alper Dogruoz, Achim Krüger, Rouzanna Istvanffy, Ihsan Ekin Demir

Introduction: Pancreatic ductal adenocarcinoma (PDAC) frequently metastasizes to the liver, but the influence of hepatic nerves on this process remains unclear. The liver is a densely innervated organ where sympathetic, parasympathetic, and sensory fibers regulate metabolism, inflammation, and regeneration, processes that also govern metastatic seeding (Bauer et al., 2024). Recent work demonstrated that sensory neurons form glutamatergic pseudo-synapses with pancreatic cancer cells, driving tumor progression through neuron–cancer communication (Ren et al., 2025). Building on this concept, we hypothesize that a liver–neuron–tumor axis remodels the hepatic pre-metastatic niche (PMN) and facilitates PDAC metastasis.

Methods: Human PDAC liver specimens, KPC mice, and intrasplenic metastasis models were analyzed using multiplex immunohistochemistry, 3D tissue clearing, viral tracing, and selective hepatic denervation. Neurotransmitter levels were quantified using LC–MS, and a spatial transcriptomics profile was generated to characterize nerve-dependent stromal remodeling. Functional assays using neuron- and tumor-conditioned hepatocytes assessed the pro-invasive effects of neural input on PDAC cells.

Results: Sympathetic (TH^+) fibers increased from 0.09 ± 0.05 % in normal liver to 0.42 ± 0.12 % in metastatic cores ($p < 0.01$), while total nerve density ($PGP9.5^+$) rose from 0.07 ± 0.03 % to 0.18 ± 0.06 % ($p < 0.05$). Early in PDAC progression, hepatic sympathetic remodeling was already evident, suggesting pre-metastatic neural activation. Selective hepatic denervation reduced the primary pancreatic tumor volume by approximately 45% and lowered hepatic serotonin, GABA, and acetylcholine levels by 30–50%, confirming the effective disruption of autonomic signaling. Spatial transcriptomics revealed a marked reduction in neuro-immune–stromal interactions after denervation, with decreased expression of α-SMA, PDGFRβ, and collagen I. Invasion assays

showed that hepatocytes exposed to neuron- and tumor-conditioned media promoted PDAC cell invasion by ~2.5-fold compared with serum-free controls, indicating that neuronal cues potentiate hepatocyte-derived pro-metastatic signaling.

Conclusion: Hepatic innervation acts as a functional driver of PDAC metastasis by establishing a neurochemical environment that primes the liver for tumor colonization. Disruption of this input through denervation suppresses both local tumor growth and systemic pro-metastatic signaling.

This work introduces the liver–neuron–tumor axis as a mechanistic bridge between peripheral neural activity and metastatic organotropism. By linking neural remodeling, neurotransmitter signaling, and microenvironmental reprogramming, it expands the emerging field of cancer neuroscience to include hepatic innervation as a therapeutic target for limiting PDAC metastasis.

Poster # 33

Abstract Title: Extracellular vesicle-mediated OGA transfer drives gallbladder cancer perineural invasion via RIPK1 deglycosylation-induced neuronal necroptosis and HMGB1-RAGE activation

Authors: Jingwei Zhao (Shanghai Jiao Tong University), Jiayun Zhu, Ziheng Wang, Wei Gong

Peripheral nerve invasion (PNI) is an early and decisive step in gallbladder cancer (GBC) progression that strongly predicts poor post-surgical outcome, yet its molecular underpinnings remain elusive. Here, we demonstrate that GBC-derived extracellular vesicles (EVs) deliver O-linked N-acetylglucosamine (OGA) to neurons, provoking RIPK1-dependent necroptosis. Subsequent neuronal release of HMGB1 engages RAGE on GBC cells, establishing a self-reinforcing loop that accelerates PNI. Mechanistically, EV-derived OGA suppressed RIPK1 glycosylation while enhancing its phosphorylation, thereby activating the RIPK1/RIPK3/MLKL axis to trigger neuronal necroptosis. Moreover, the RAGE antagonist FPS-ZM1 synergizes with gemcitabine to suppress tumor progression. Collectively, these findings uncover an EV-mediated feed-forward circuit in which RIPK1-dependent necroptosis and its effector HMGB1 drive PNI, positioning the HMGB1–RAGE axis as a tractable therapeutic target.

Theme: Neurobehavioral Health

Poster # 34

Abstract Title: Glymphatic Function as a Dual Resilience Mechanism: Strengthening Survival and Mitigating Symptom Burden in Long-Term Head and Neck Cancer Survivors

Authors: Sahil Bajaj (MD Anderson Cancer Center), C. Chad Quarles, Katherin Gilmore, Ying Qiao, Chinmay Mokashi, Max Wintermark, Michael Roth

Introduction. Glymphatic function, quantified via the diffusion tensor imaging along perivascular spaces (ALPS) index, may act as a resilience mechanism preserving neural integrity in cancer survivorship. However, how glymphatic efficiency interacts with brain microstructure—indexed by radial diffusivity (RD) and fractional anisotropy (FA)—to influence survival and daily functioning remains unclear. We hypothesized that glymphatic efficiency would modulate the associations between preserved gray matter (GM) and white matter (WM) microstructure and favorable outcomes, including longer survival and reduced symptom interference.

Methods. We studied 135 long-term head and neck cancer survivors (mean age = 64.16 years; 107 males). Brain MRI data, survival status (deceased = 44; alive = 85; unavailable = 6) and symptom interference (via MD Anderson Symptom Inventory) were collected through follow-ups. Symptom interference reflects the extent to which cancer-related symptoms disrupt active (e.g., work, walking, general activity) and affective (e.g., mood, relationships, enjoyment of life) domains. RD and FA were computed across 62 cortical GM regions, 14 subcortical GM regions, and 32 major WM fiber bundles. Stepwise regression assessed associations of RD and FA with survival and symptom interference, followed by moderation analyses testing the moderating role of the ALPS index.

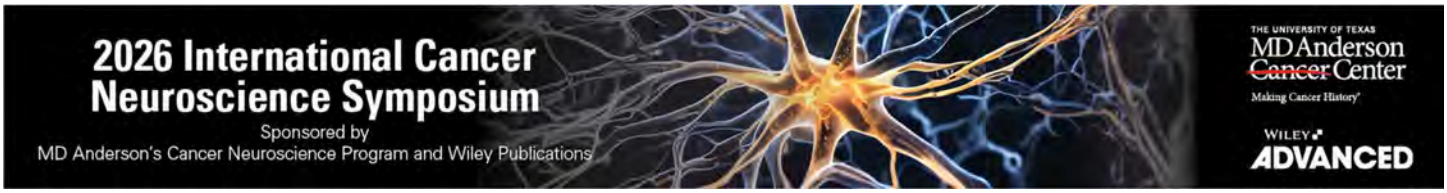
Results. Within GM, reduced RD in the left medial orbitofrontal cortex (MOFC) and elevated FA in the left entorhinal cortex predicted longer survival (βs = –1.79 and 9.45; ps < .001). Reduced RD in the left superior temporal cortex (STC) predicted lower active and affective symptom interference (βs = 6.33 and 5.59; ps < .001), while reduced FA in the right caudate–anterior cingulate cortex (CACC) predicted lower affective interference (β = 16.47; $p < .001$). In WM, reduced RD in the left uncinate fasciculus (UF) predicted lower affective interference (β = 3.96; $p < .001$). All associations survived multiple comparison correction. Higher glymphatic efficiency strengthened the survival benefits of preserved MOFC ($p < .01$), whereas the protective effects of preserved STC, altered CACC, and preserved UF on affective symptom interference were strongest at lower glymphatic efficiency (ps < .01).

Conclusion. Glymphatic efficiency shapes how brain microstructure influences survival and daily functioning in cancer survivors. It modulates the neurostructural underpinnings of both survival and emotional well-being, reflecting a region- and domain-specific mechanism of neural resilience.

Significance. The glymphatic system promotes brain resilience, enhancing GM-related survival and emotional well-being, and represents a potential therapeutic target to improve long-term outcomes in cancer survivorship.

Poster # 35

Abstract Title: Longitudinal nTMS-CST Mapping Reveals Topological Plasticity as a Biomarker for Motor Recovery in Peri-Rolandic Gliomas: A Pilot Study



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

Background: Preserving motor function in peri-Rolandic low-grade glioma (LGG) resection requires biomarkers of neuroplasticity to guide prognostication and rehabilitation. Navigated transcranial magnetic stimulation (nTMS) enables serial motor mapping, but lacks standardized integration with corticospinal tract (CST) tractography to quantify spatiotemporal reorganization.

Methods: In this prospective pilot, 17 adults (12 LGG, 5 non-glioma controls) underwent nTMS and diffusion MRI at baseline and 1, 6, 12 months post-resection. nTMS hotspots seeded CST tractography; metrics included resting motor threshold (RMT), centroid shift, convex-hull area, partial optimal transport (POT)/Gromov–Wasserstein (GW) distances for nTMS maps, and fractional anisotropy (FA), volume, overlap (Dice), and surface mismatch for CST. Linear mixed-effects models assessed group (deficit vs. non-deficit; n=3 vs. 14) and disease effects; Spearman correlations linked metrics to ΔKarnofsky Performance Status (ΔKPS).

Results: Feasibility was high (76% T_1 completion; ICC>0.80 for key metrics). Deficit patients showed elevated RMT ($F=7.59$, $p=0.0096$) resolving with recovery. nTMS centroids shifted ~15 mm anteroposteriorly early ($p<10^{-5}$), with transient hull expansion in deficits ($F=5.72$, $p=0.023$). POT/GW indicated topological stability, but glioma-specific inverse correlations with ΔKPS ($\rho=-0.54$, $q<0.05$). CST exhibited nominal degradation in deficits (ΔFA –5.2%; Dice $F=30.17$, $p<10^{-5}$ uncorrected), with boundary mismatch (ASSD $\rho=-0.67$, $q<0.05$) predicting poorer recovery in gliomas.

Interpretation: Longitudinal nTMS–CST mapping is feasible and reveals coordinated cortical expansion/contraction and subcortical boundary irregularity during recovery, with transport metrics capturing glioma-specific plasticity costs. This framework holds promise as a biomarker for motor outcomes, meriting validation in larger cohorts to inform personalized neurosurgical care.

Poster # 36

Abstract Title: A Comprehensive Clinical fMRI Software Solution to Enable Mapping of Critical Functional Networks and Cerebrovascular Reactivity in the Brain

Authors: Jian Ming Teo (MD Anderson Cancer Center), Kevin D. Tran; Mu-Lan Jen; Vinodh A. Kumar; Sujit S. Prabhu; Kyle R. Noll; Peng Wei; Sherise D. Ferguson; Chibawanye I. Ene; Frederick F. Lang; Max Wintermark; Cathy Elsinger; Ho-Ling Liu

Introduction: Considerable progress in systems neuroscience was facilitated by human neuroimaging, particularly group-level functional MRI (fMRI) studies for understanding of large-scale brain networks. While personalized functional mapping with task-based (tb) and resting-state (rs) fMRI is increasingly applied in clinical settings such as for presurgical evaluation, existing methods were intended for normative brain anatomy and often lack compatibility with lesioned-brains. This academic-industrial partnership project addresses this gap through the development of a comprehensive clinical fMRI software solution that enables personalized analysis of critical functional networks and cerebrovascular reactivity (CVR) in patients with brain tumors.

Methods: Using presurgical tb- and (rs-fMRI data from >600 MD Anderson patients, we developed probabilistic atlases of eloquent brain functional networks (language, motor and visual). Automated seed-based correlation

(SBC) analysis and independent component analysis (ICA) approaches for personalized rs-fMRI analysis were developed with probabilistic template matching to incorporate the above atlases. We developed data-driven approaches to CVR mapping using fMRI signal elevation, tested against model-based CVR mapping obtained from breath-hold recordings. Collaborating with NordicNeuroLab, these algorithms were integrated into the nordicMEDiVA clinical software platform via a versatile graphical user interface.

Results: Under the nordicMEDiVA platform, a rs-fMRI (nordicRSfMRI) module and a CVR mapping (nordicCVR) module were developed to support manual and automated SBC analysis, automated ICA, and flexible CVR regression options (breath-hold timing, whole brain average of CVR fMRI, whole brain average of rs-fMRI). The patient-based functional atlas and probabilistic template matching were successfully implemented in the automated SBC and ICA pipelines and robustly detect single-subject rs-fMRI networks of motor (hand, feet, tongue), visual and language. Data-driven CVR demonstrated comparable results to model-based CVR and recommendations for CVR mapping thresholds were systematically evaluated and determined. The GUI facilitates multi planar reconstruction and simultaneous multi-slice display for functional network identification and overlay of CVR maps to assess neurovascular uncoupling. The two modules developed in this project are expected to be submitted for FDA clearance in 2026.

Conclusion: We developed a comprehensive clinical software solution with methods intended to directly address the paucity of neuroimaging solutions compatible with lesioned brains. nordicRsfMRI and nordicCVR modules provide optimized workflows for mapping critical functional networks and CVR for fMRI confidence visualization.

Significance to the Cancer Neuroscience Field: This software addresses a critical need by facilitating single-subject brain function discoveries in lesioned brains, bridging a gap limiting potential systems neuroscience studies at the intersection of neural neoplasms, neurotoxicity and neurobehavioral health.

Poster # 37

Abstract Title: Chronic Stress-Driven Gz Platelet Activity Promotes Tumor Growth and Changes in Social Behavior in Ovarian Carcinoma

Authors: Maria Torres Carrizalez (MD Anderson Cancer Center Graduate School of Biomedical Sciences), Ashutosh Tripathi, Hani Lee, Jocelyn Mata, Tela Todd, Vahid Afshar-Kharghan, Anilkumar Pillai

Introduction: Ovarian cancer is the most aggressive gynecologic malignancy with 12,730 estimated deaths in 2025. Among the different risk factors, chronic stress has been recognized as a potential leading factor contributing to its development and progression. Notably, patients with ovarian cancer are frequently diagnosed with high levels of stress, having important psychological and physiological implications for these patients. Moreover, elevated platelet activity has been found to have a significant association with increased recurrence and worse survival in cancer patients. Our lab previously found that activation of the Gz protein in platelets has a pro-tumorigenic effect on ovarian tumor growth in mice. Interestingly, the Gz protein is activated by the stress hormone epinephrine by binding to the α2A platelet receptor. Therefore, we hypothesized that chronic stress exposure amplifies the Gz signaling activity in platelets, contributing to enhanced ovarian cancer tumor growth.

Methods: To test this hypothesis, control (Gzfl/fl) and Gz platelet-specific knockout (Gzfl/fl; PF4Cre) ovarian cancer tumor-bearing mice were exposed to the chronic unpredictable stress (CUS) paradigm for a three-week

period. Social behavior deficits were explored through the three-chamber social interaction test (SBSNT). Additionally, synaptic plasticity was assessed by immunoblotting of the synaptic marker PSD95 in the prefrontal cortex and hippocampus of tumor-bearing mice.

Results: Results showed that Gzfl/fl; PF4Cre mice exhibit a significant reduction in ovarian tumor growth compared to Gzfl/fl mice, with a significant and pronounced difference under chronic stress exposure ($p<0.01$). Furthermore, findings from the SBSNT revealed that tumor-bearing mice exhibit hypersociability under chronic stress in both control and Gz platelet-deficient mice, compared to non-stressed conditions ($p<0.0001$). Along with these results, stressed tumor-bearing mice exhibited elevated levels of the synaptic marker PSD95, particularly in the hippocampus ($p<0.001$).

Conclusion: Based on the above, we conclude that chronic stress has a pro-tumorigenic effect on ovarian cancer proliferation by modulating platelet function through the Gz signaling pathway. Additionally, it elucidates how the interplay between ovarian cancer and chronic stress promotes hippocampus-dependent hypersociability accompanied by elevated levels of PSD95 in this brain region.

Significance to the cancer neuroscience field: This project constitutes a novel approach to understanding the bidirectional interaction between ovarian cancer tumor cells and the brain that impacts tumor proliferation and social behavior. By elucidating the underlying mechanistic pathways, it aims to identify new therapeutic targets to improve the quality of life in patients experiencing high levels of chronic stress.

Theme: Neuroimmunology

Poster # 38

Abstract Title: Microglial NF-κB-Inducing Kinase (NIK) regulates Glioblastoma Multiforme (GBM) progression in a sex-dependent manner

Authors: Hasara Abeygunaratne (Texas A&M University), Justin N. Keeney, Kathryn M. Pflug, Caren Stuebe, L. Gerard Toussaint, Raquel Sitcheran

Introduction: Glioblastoma multiforme (GBM) is the most aggressive and lethal primary brain tumor, characterized by profound therapy resistance and striking sex disparities, where males experience higher incidence and poorer survival than females. The GBM tumor microenvironment (TME) is highly immunosuppressive and dominated by microglia and infiltrated myeloid cells that promote tumor growth, invasion, and immune evasion. Our previous studies have established NF-κB–Inducing Kinase (NIK) as a central regulator of cancer cell metabolic reprogramming and macrophage immune-metabolic activation. However, how NIK influences the metabolic and signaling landscape of the brain immune TME, and whether these effects differ between sexes, remains unclear.

Methods: We employed systemic and cell type-specific conditional knockout mouse models to identify the role of NIK in the GBM TME. Orthotopic implantation of syngeneic GL261 tumors was followed by survival, transcriptomic and immunohistochemical analyses to define how NIK loss impacts tumor growth, immune composition, and molecular signaling pathways.

Results: Both systemic and microglia-specific NIK deletion markedly reduced GBM tumor size and progression. Interestingly, microglial NIK ablation significantly improved survival in male but not female hosts, indicating sex-dependent differences in NIK tumor-promoting functions. In contrast, astrocyte- and myeloid-specific NIK deletion failed to reproduce these effects, confirming a unique microglial-intrinsic mechanism. Transcriptomic analyses demonstrated that loss of microglial NIK altered extracellular matrix remodeling, cell migration, angiogenesis, cytokine signaling, and circadian rhythm - key processes related to GBM progression.

Conclusion: Collectively, our findings highlight microglial NIK as a pivotal modulator of GBM progression that integrates immune-metabolic, tissue remodeling, and circadian programs in a sex-dependent manner. Targeting NIK within microglia may suppress tumor growth and improve survival outcomes, particularly in males, underscoring the necessity of integrating sex as a biological variable in GBM research.

Significance to the cancer neuroscience field: This study uncovers a previously unrecognized microglial NIK-dependent signaling axis that drives brain tumor progression. These new insights advance our understanding of neuroimmune-tumor crosstalk and positions NIK as a promising therapeutic target for precision, cell type- and sex-informed GBM therapy.

Poster # 39

Abstract Title: Spatial Transcriptomic Profiling of Neuroinflammatory and Neurodegenerative Sequalae Induced by Immune Checkpoint Inhibition

Authors: Munjal Acharya (University of California Irvine), Devyani Swami, Robert P. Krattli, Sanad M. El-Khatib, Shivashankar Othy

INTRODUCTION: Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways represent one of the most transformative advances in modern oncology. These therapies have revolutionized cancer treatment, markedly improving patient survival and quality of life. Our previous work demonstrated that ICI therapy induces glial dysfunction—characterized by microglial activation and astrogliosis—which amplifies neuroinflammation, disrupts synaptic and neuronal integrity, and contributes to cognitive impairment. These neuroimmune perturbations compromise hippocampal-dependent learning and memory, and memory consolidation processes. Despite these insights, the cell type–specific molecular mechanisms underlying ICI-induced neuroinflammation and neuronal dysfunction remain largely undefined. Addressing this critical gap, our current study provides a comprehensive spatial and transcriptomic framework to dissect the cellular interactions and gene networks that mediate neurotoxic responses to ICI therapy.

METHODS: We performed an integrated spatial transcriptomic analysis using a syngeneic melanoma mouse model, leveraging multiplexed error-robust fluorescence in situ hybridization (MERFISH) to profile spatial gene expression at the single-cell level. By combining single-cell and bulk RNA-seq analyses of the hippocampus, we examined the spatial distribution of microglia, astrocytes, and other neuroinflammatory markers, and investigated how ICI treatment alters gene expression patterns across cancer-bearing and non-cancerous mouse brain.

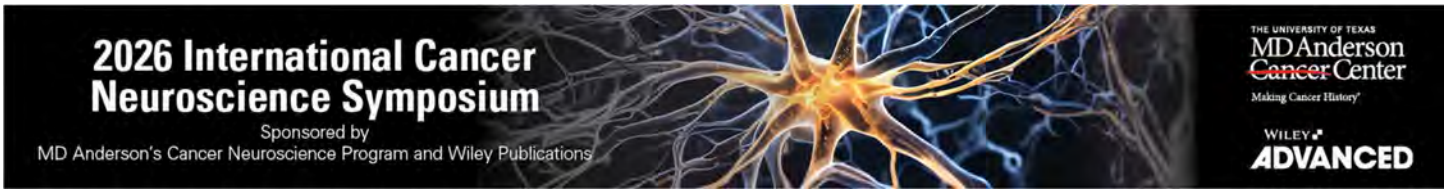
RESULTS: Spatial transcriptomics and RNA-seq analyses revealed upregulation of microglial, astrocytic, and T-cell markers, indicating disruptions in key pathways associated with neuroinflammation, synaptic function, and cellular signaling. Specifically, spatial transcriptomic profiling demonstrated dysregulation of cell type–specific markers including Gpr84 (microglia), Cdh20 (oligodendrocytes), and Nfkbiz (T cells), suggesting the dysfunctional immune microenvironment in melanoma and melanoma–ICI–treated groups.

CONCLUSION: We uncover cell type–specific gene signatures that reveal profound neuronal transcriptomic alterations post-ICI therapy. Consistent with our previous findings, these results confirm that ICI induces glial dysfunction—characterized by microglial activation and astrogliosis—which amplifies neuroinflammatory cascades, disrupts synaptic and neuronal integrity, and contributes to hippocampal-dependent cognitive impairments. By quantitatively mapping the spatial expression landscape of microglia, oligodendrocytes, astrocytes, and T cell–related genes alongside key markers of neuroinflammation and synaptic dysfunction, this work provides a high-resolution framework for understanding ICI-associated neurotoxicity. Collectively, these findings establish a strong link between ICI therapy and neuroinflammation-associated cognitive decline, while also revealing potential molecular targets for therapeutic intervention.

SIGNIFICANCE TO THE CANCER NEUROSCIENCE FIELD: This work not only solidifies the connection between ICI administration and neuroinflammation-associated cognitive deficits but also unveils prospective molecular targets to inform the development of neuroprotective strategies in Cancer Neuroscience.

Poster # 40

Abstract Title: Activated Satellite Glial Cells Drive Remodelling of Pancreatic Tumor Microenvironment Through Immune Cell Modulation



Authors: Mohammed Ashif (Cochin University of Science and Technology), Swathi Sasidharan, Sreeja Narayanan, Baby Chakrapani PS, Unnikrishnan Sivan

ABSTRACT: The neuronal niche has emerged as a dynamic and critical component of the pancreatic tumor microenvironment, playing a major role in the progression of pancreatic cancer (PC). PC mostly develops in the head region of the pancreas, an area rich in intrapancreatic ganglia, which are surrounded by satellite glial cells (SGCs). These SGCs are activated in response to injury or inflammatory conditions. The role of SGCs in the tumor microenvironment is not well explored. Our study aims to unravel the role of activated SGCs in the progression of pancreatic cancer and the modulation of the tumor microenvironment. Primary SGCs and primary pancreatic stellate cells (PSCs) were isolated from murine dorsal root ganglia and pancreas, respectively. The reactive state of the cells was validated by immunocytochemistry. The influence of activated SGCs on PC cells and PSCs was examined through gene expression profiling and flow cytometric analysis. The impact of glial secretory factors on macrophages, as well as the influence of glia-modulated macrophage secretory factors on pancreatic cancer cells, were studied using gene expression analysis, ELISA, western blot and alkaline phosphatase assay. Isolated SGCs showed positive expression of the reactive phenotype marker Glial Fibrillary Acidic Protein (GFAP). Our results reveal that SGC secretory factors increase the stemness of PC cells and activation of PSCs with extracellular matrix production. The macrophages elevated the TNF-α production upon exposure to glial secretory factors, which gradually reduced over time. This glia-modified macrophage-derived TNF-α subsequently increased the expression of Matrix Metalloproteinase-2 (MMP-2) and alkaline phosphatase (ALP) in pancreatic cancer cells. The expression of Tissue inhibitor of metalloproteinase 1 (TIMP-1) was downregulated. These findings suggest that activated SGCs may play a critical role in remodelling the pancreatic tumor microenvironment, thereby enabling the progression and invasion of pancreatic cancer cells. By identifying SGCs as active modulators of the tumor microenvironment, this work highlights the growing significance of the neuronal niche in PC. Activated SGCs affect cancer cell invasion, extracellular matrix remodelling, and inflammatory signalling through their interactions with macrophages and pancreatic stellate cells. Along with that, our findings bridge neuroscience and oncology, positioning SGCs as novel mediators of neuro-immune-tumor crosstalk rather than pain and open possibilities of potential therapeutic targets in cancer neuroscience.

Keywords: Cancer neuroscience, pancreatic cancer, satellite glial cell, pancreatic stellate cell, Macrophages

Poster # 41

Abstract Title: Breaking Barriers: Mannitol Enables MSC Trafficking and Immune Modulation in Glioblastoma

Authors: Siresha Bathina (MD Anderson Cancer Center), Joy Gumin, Daniel Ledbetter, Frederick F. Lang, Peter Kan, Christopher C. Young

Introduction: Previous studies explored mesenchymal stem cells (MSCs) as promising vehicles for therapeutic delivery in glioblastoma (GBM) due to their tumor-tropic properties. However, limited homing across the blood–brain barrier (BBB) remains a major challenge. Mannitol-induced osmotic BBB opening has been proposed to enhance cellular trafficking, yet its effects on MSCs recruitment and the tumor microenvironment remain poorly defined

Methods: We investigated the impact of mannitol on MSC homing in a U87 glioblastoma xenograft model in nude mice. Histological analyses included GFAP for astrocytic activation, CD31 for vascular density, IBA1 for

microglia/macrophage activation, and TMEM119/CD163 to differentiate resident microglia versus infiltrating macrophages. Tight junction integrity was assessed using Claudin-5, Occludin, and ZO-1 immunostaining.

Results: Mannitol significantly increased MSC homing to U87 tumors ($P<0.05$), accompanied by elevated GFAP expression and CD31+ vessel density ($P<0.01$). IBA1+ cells were enriched ipsilaterally compared with the contralateral hemisphere ($P<0.01$). Phenotypic characterization revealed reduced TMEM119+ resident microglia and increased CD163+ infiltrating macrophages within tumors ($P<0.05$). Furthermore, mannitol and MSC administration led to significant decreased expression of tight junction proteins Claudin-5, Occludin, and ZO-1, confirming BBB disruption and facilitating MSC trafficking into the tumor niche.

Conclusion: Mannitol converts MSC trafficking from a limiting step to an enabled step while actively reprogramming the GBM immune niche, revealing that BBB opening is not a passive conduit but an immune-active gateway event during cell-therapy delivery.

Significance to Cancer Neuroscience: This is the first study to evaluate the effect of mannitol on intracranial intra-arterial delivery of cell-based therapy for treatment of brain tumors. This study provides the first evidence that mannitol effectively enhances cellular therapeutic delivery to glioblastoma by transiently disrupting BBB integrity and modulating the tumor immune microenvironment. These data establish a novel mechanistic pathway which can modulate CNS immune privilege in cancer and other diseases.

Poster # 42

Abstract Title: Elucidating the impact of dendritic cell-derived extracellular vesicles on immunosurveillance of breast cancer cells in the brain

Authors: Drew Boagni (MD Anderson Cancer Center), Hao-nien Chen, Xianglian Yuan, Dihua Yu

Introduction: While targeted and immunotherapies have improved outcomes in HER2+ and triple negative breast cancer, long-term survival is limited by a high incidence of brain metastasis (BrM), for which treatment options are limited. Since dendritic cell-derived extracellular vesicles (DCEVs) can cross the blood-brain barrier and potentially enhance immune responses, we propose to utilize DCEVs to meet this clinical need.

Cancer cells can be detected and eliminated through immunosurveillance, which involves antigen uptake and presentation. Brain-resident microglia may be capable of this function, and we have found that these cells can take up intranasally delivered DCEVs in vivo. Further, microglia have been shown to have a role in modulating T cell infiltration and rejection of BC BrM tumors. Thus, activation of microglia through DCEVs may also enhance immune defenses against BC BrM.

Methods: To test the effects of DCEV on the antigen-presenting function of microglia, we stimulated CD11b+ brain-resident cells with OVA-loaded DCEV and cocultured with OVA-specific T cells stained with CFSE dye to track proliferation. To test the effects of DCEV on immunosurveillance in the brain, we treated with intravenous (i.v.) and intranasal (i.n.) DCEV to induce a systemic and local immune response, respectively. We modeled BC BrM by intracranial injection of EO771 mammary fat pad tumor cells. Tumor size was measured by MRI and immunophenotyping was conducted by flow cytometry analysis.

Results: T cells cocultured with CD11b+ cells from the brain (mostly microglia) proliferated with increased DCEV dose. Additional IFN-y enhanced proliferation of T cells cocultured with microglia, suggesting a potential feedback mechanism. We observed a near-significant trend of reduced BrM tumor size in mice treated with

temporally separated doses of i.v. and i.n. DCEV. This corresponded with an increased frequency of CD8+ T cells with a classical “T resident memory” phenotype.

Conclusion: These results suggest that DCEVs can enable brain-resident myeloid cells to activate antigen-specific T cells. Our in vivo data supports the potential for DCEVs to induce local immunosurveillance in the brain in which myeloid cells and T cells may function together to combat BC BrM.

Significance to the Cancer Neuroscience Field: The unique brain microenvironment has posed a challenge to developing effective immune-modulating strategies against brain tumors. Extracellular vesicles have recently emerged as promising therapeutic agents for a range of neurological diseases. This project sheds light on basic brain tumor immunology and the clinical potential of DCEVs as an immunotherapy.

Poster # 43

Abstract Title: CLEC9A-mediated activation of dendritic cells enhances antitumor immunity and immune remodelling in melanoma

Authors: Laura Brabenec (Karolinska Institutet), Sebastien Talbot

Introduction: With 10 million deaths in 2020, cancer remains one of the leading causes of mortality worldwide (WHO,2024). Despite intensive research, therapeutic options are limited, largely due to the high heterogeneity among cancer subtypes and affected patients. Cancer-cell-derived growth factors can induce hyperinnervation of tumors, often associated with pain, whereby sensory nerves contribute to tumor growth by establishing an inhibitory microenvironment that promotes treatment resistance (Santoni,2022; Restaino,2023). As the immune system plays a central role in recognizing and eliminating abnormal cells, current cancer research increasingly emphasizes immunological strategies (Dougan,2009). Evidence revealed that tumor-innervating nociceptor neurons release neuropetides that augment CD8+ T cell exhaustion in the context of melanoma (Balood,2022). Additionally, cDC1 cells play a pivotal role in melanoma by cross-presenting tumor antigens to $CD8^+$ T cells, driving effective cytotoxic responses and T cell recruitment. Their abundance correlates with improved antitumor immunity, and strategies enhancing cDC1 function, such as CLEC9A targeting, hold therapeutic promise.

Methods: 8 week old C57BL6/J mice were injected with B16F10-OVA cells intradermally in the flank. Tumor growth was assessed continuously. CLEC9A antibody was injected intraperitoneally (50µg/mouse), every other day for total of 4 doses, starting day 6. Immunomodulation was analysed by Flow cytometry of tumor tissue and tumor draining lymph nodes.

Results: In our study, Anti–CLEC9A treatment significantly inhibited tumor growth. Flow cytometric analysis revealed increased frequencies of central memory T cells and decreased naive and cytotoxic T cells in tumor-draining lymph nodes of anti–CLEC9A–treated mice. Within tumors, $CD8\alpha^+$ T cells, conventional type 1 dendritic cells (cDC1), and migratory dendritic cells were elevated compared with controls, indicating enhanced immune activation and antigen presentation within the tumor microenvironment.

Conclusion: Anti–CLEC9A treatment inhibited B16F10-OVA tumor growth and remodelled the immune landscape, enhancing dendritic cell-mediated antigen presentation and promoting a central memory T cell response in tumor-draining lymph nodes.

Significance to the cancer neuroscience field: These findings identify targeting CLEC9A as a promising strategy to enhance antitumor immunity and reshape the tumor microenvironment, revealing mechanistic links between dendritic cell activation, T cell memory formation, and neuroimmune regulation.

†*Professional Development Award*

† Poster # 44

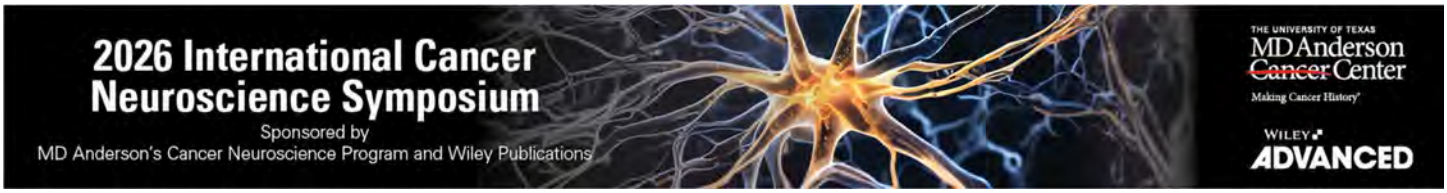
Abstract Title: Lymph Node Hyperinnervation in PDAC

Authors: Paulina Cabada Aguirre (University of Pittsburgh), Stephanie A. Fulton, Randall E. Brand, Aatur Singhi, Jami L. Saloman

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumor with an overall 5-year survival of 13% attributed to late diagnosis and resistance to chemotherapy, radiation and immune therapy. Moreover, PDAC tumors are highly heterogenous, with a diverse tumor microenvironment (TME) characterized by increased innervation assumed to be driven by neurotropic growth factors (GF). Cancer cells release GFs that can accumulate within primary tumors, metastatic sites, and adjacent lymphatic tissues. Previous studies have shown that sensory and sympathetic nerve fibers contribute to the immunosuppressive TME in PDAC. However, they have not addressed hyperinnervation in extra tumoral lymphoid tissues, which are the primary site for priming of tumor reactive T cells and tumor metastases. In this study, we demonstrate that hyperinnervation of pancreatic draining lymph node (dLN) is present in both human and animal models. For human samples, overall innervation was quantified using PGP9.5 pan-neuronal marker. Nerve bundles and fibers were further classified as sympathetic or sensory through staining with TH and CGRP. The positively stained area, normalized to LN size, was significantly increased in PDAC patients compared to healthy controls and correlated with disease progression. Using the CUBIC tissue clearing technique, we analyzed dLNs from control and tumor-bearing KP-/+C mice. Quantification revealed increased sympathetic and sensory innervation in tumor-bearing mice. qPCR analysis showed significantly increased mRNA for multiple growth factors BDNF, NGF, GDNF, TGFa, NTRN and ART in pancreatic dLN at 20 weeks. This suggests that the local production of GFs, not primary tumor derived, is a driver of hyperinnervation. qPCR analysis showed increased expression of GF receptors GFRa1, GFRa2, GFRa3, TGFB1R, TRKA and RET but not TRKB in tumor bearing mice. Significant upregulation of the GFRa family was also observed in the dorsal root ganglia neuronal cell bodies and fibers at the level of T13, a level containing LN innervating afferents. Tracing studies reveal two distinct neuronal populations innervating the pancreas and its dLN at thoracic DRG level. Based on previous studies highlighting the role of NGF in hyperinnervation of PDAC, we are in the process of testing lymph node-targeted NGF induced hyperinnervation as well as anti-NGF treatment to increase anti-tumor immune response and reduce hyperinnervation. Detail tracing of LN innervation as well as data exploring the mechanistic role of NGF in hyperinnervation induced immunosuppression will provide a possible localized therapeutic target for treatment of PDAC. Future research will further investigate neuro-immune modulation mechanisms, including the expression of immune checkpoint proteins on sympathetic nerves.

Poster # 45

Abstract Title: Investigating the Role of Opioid Signaling in Shaping the Tumor Microenvironment



Authors: Nicole Carter (Brigham and Women's Hospital, Harvard Medical School), Davide Mangani, Linglin Huang, Meromit Singer, Hanning Cheng, Lorin K. Johnson, David N. Taggart, Vijay K. Kuchroo, Aviv Regev, Ana C. Anderson

Introduction: The impact of neuroimmune interactions on disease outcomes is increasingly appreciated. Tumors are innervated by sensory neurons, and innervation is associated with worse outcomes; however, the intercellular communication between cancer cells, tumor-innervating neurons, and tumor-infiltrating immune cells remains poorly understood.

Methods: We conducted a longitudinal single cell RNA-seq analysis of the murine B16F10 melanoma immune infiltrate. From this, we uncovered that "exhausted" tumor-infiltrating CD8+ T cells which are ineffective at controlling tumor growth expressed Penk, encoding the endogenous opioid precursor pro-enkephalin (PENK), and Ogfr, encoding the non-canonical opioid growth factor receptor (OGFR). We employed an in vitro chronic stimulation assay to assess expression of Penk and Ogfr in response to chronic stimulation and to determine the impact of exogenous opioid treatment on exhaustion. We performed adoptive transfer experiments with tumor antigen-specific PENK-knockout or PENK-overexpression CD8+ T cells and assessed tumor growth control and cytotoxic capacity. Finally, we treated mice bearing immune checkpoint blockade (ICB)-resistant tumors with Penk KO tumor antigen-specific CD8+ T cells and anti-PD1 or with anti-PD1 and a peripherally acting opioid antagonist.

Results: Chronically stimulated CD8+ T cells increased Penk expression up to 1,920-fold as they developed exhausted phenotype and expressed Ogfr but not canonical opioid receptors. Treatment of chronically stimulated CD8+ T cells with exogenous met-enkephalin, the opioid peptide resulting from cleavage of PENK, or with morphine, increased expression of checkpoint receptors associated with exhausted phenotype. Penk overexpression in melanoma tumor antigen-specific CD8+ T cells worsened tumor growth control and cytotoxic capacity whereas Penk deletion improved tumor growth control and synergized with ICB. Pharmacologic blockade of opioid signaling in the tumor microenvironment likewise synergized with ICB.

Conclusion: CD8+ T cells produce opioids in response to chronic stimulation, and opioid signaling negatively impacts effector function and ability to control tumor growth. Ongoing experiments will investigate 1) the impact of opioids on tumor innervation and on sensory neuron excitability, 2) the effects of opioids in the tumor immune microenvironment, and 3) the role of the OGFR in mediating effects of opioids in immune cells.

Significance to the Cancer Neuroscience Field: Only ~20% of eligible cancer patients respond to ICB (Prasad et al., 2024), underscoring the need for novel strategies to improve efficacy. Our data suggest that blocking peripheral opioid signaling may improve ICB outcomes. Furthermore, cancer patients are routinely treated with opioids for pain management and thus understanding how opioid signaling impacts anti-tumor immunity has important clinical implications.

Poster # 46

Abstract Title: Impeding Breast Cancer Brain Metastases with Extracellular Vesicles from SHP1-Inhibited Dendritic Cells

Authors: Hao-Nien Chen (MD Anderson Cancer Center), Xiangliang Yuan, Drew Boagni, Yimin Duan, Jun Yao, Citu, Yi Xiao, Zhongming Zhao, Dihua Yu

Introduction: Breast cancer brain metastases (BCBrMs) pose a significant therapeutic hurdle. The blood-brain barrier (BBB) impedes antitumor immunotherapy responses, resulting in a paucity of antigen-specific T cells. Dendritic cells (DCs) play a crucial role in antigen-specific T cell priming and activation, presenting antigens both directly and via DCEVs. We have found that inhibiting SHP1, a DC-specific inhibitory checkpoint, enhances the antigen-presenting function of DCs and DCEVs. Recognizing the potential of EVs to traverse the BBB, we investigated the efficacy of DCEVs derived from SHP1-inhibited DCs (iSHP1-DCEVs) in stimulating antigen-specific T cells in the brain to combat BCBrMs.

Methods: Immunocompetent mice with EO771 cell-derived BCBrM were treated with DCEVs from tumor antigen-loaded Ctrl-DCs or SHP1-inhibited DCs.

Results: First, for proof-of-concept, we employed the OVA antigen as a tumor-specific antigen. Intracranial administration of OVA-loaded iSHP1-DCEVs promoted OVA-specific T cell activation in EO771-OVA cell induced brain lesions, leading to a marked reduction in tumor growth. Using non-invasive intranasal delivery, DCEVs accumulate in the brain, significantly curtailing BrM outgrowth. Next, iSHP1-DCEVs were loaded with genuine EO771 tumor lysate antigens, which effectively induced antigen-specific T cells and remarkedly hampered EO771-derived BrM growth. Mechanisic investigations revealed that myloid cells from BrM environment internalize iSHP1-DCEVs, harnessing and presenting their antigens to activate antitumor T cell immune response, highlighting the potential of this strategy in reshaping the brain's immune milieu.

Conclusion: Engineered iSHP1-DCEVs offer a promising avenue for amplifying antigen-specific T cell immune responses in the brain, holding potential for novel cancer immunotherapy to mitigate BCBrM.

Significance to the cancer neuroscience field: This study bridges cancer immunology and neuroscience by demonstrating that DCEVs can reprogram brain tumor myeloid cells to enhance antigen-specific T-cell activation within the brain, revealing a novel immune-neural interface for treating brain metastases.

Poster # 47

Abstract Title: Modulating glioblastoma tumor microenvironment with focused ultrasound and immunotherapy and prognostic value of preclinical PD-L1 occupancy imaging in glioblastoma.

Authors: Celine Chevaleyre (MD Anderson Cancer Center), Anthony Novell, Nicolas Tournier, Marie Valet, Camille Plédet, Caroline Denis, Laurène Jourdain, Erwan Selingue, Steven Dubois, Benoit Jego, Simone Krebs, Benoit Larrat, Hervé Nozach, Charles Truillet

Glioblastoma is highly aggressive due to an immunosuppressive tumor microenvironment (TME) and the restrictive nature of blood-brain barrier (BBB) which limits drug delivery. Focused ultrasound (FUS) enables reversible BBB permeabilization, enhancing therapeutic access and activating pro-inflammatory pathways that may boost immunotherapy. This study investigates the modulation of the glioblastoma TME resulting from the combination of anti-PD-L1 immunotherapy and FUS and evaluates the predictive value of PD-L1 occupancy immunoPET imaging during treatment.

Glioblastoma-bearing C57Bl/6 mice (GL261 or SB28 cells implanted in the right striatum) were treated with three injections of 400µg Avelumab, spaced 3 days apart. A transcranial FUS protocol was applied shortly before each injection to transiently open the BBB in both brain hemispheres (n=12 per group, 4 groups

including necessary controls). Tumors from these mice were analyzed by flow cytometry to assess treatment-dependent changes in TME composition. Another cohort of glioblastoma-bearing animals underwent the same treatment protocol (n=9 per group for each tumor model) and were additionally injected during the last treatment with [18F]F-C4Fc-MUT, an anti-PD-L1 antibody, and imaged 6h post injection. The survival of animals was then followed.

Macrophages and microglia were the immune populations most affected by the treatment. Irrespective of treatment, there was a significant decrease in the proportion of macrophages associated with the tumor. It was accompanied by an increase of the microglia proportion in animals treated with FUS. It increased from 25±8% of CD45+ cells to 45±12% in the FUS group and 43±11% in the FUS plus avelumab group. Treatment with avelumab alone or with FUS resulted in decreased accumulation of [18F]F-C4Fc-MUT compared with the double control and FUS-only groups. However, avelumab delivery by FUS did not result in significantly higher PD-L1 occupancy compared with treatment without FUS BBB opening (MeanSHAM+Ave = 4.2±3.1 %ID/cm3, MeanFUS+Ave = 2.8±2.6 %ID/cm3). Treatment with avelumab in combination with FUS prolonged the survival of animals in both tumor models. A correlation between maximum accumulation of [18F]F-C4Fc-MUT and animal survival was demonstrated.

Flow cytometry analysis of the TME mainly revealed effects on macrophages and microglia. Despite the opening of the BBB by FUS, which should have homogenized treatment delivery, significant variability in PD-L1 occupancy was observed. The correlation between [18F]F-C4Fc-MUT tumoral uptake and survival indicates that the higher the occupancy of PD-L1 by the treatment, the longer the animal's survival.

Significance: FUS-aided immunoPET of PD-L1 occupancy could provide a minimally-invasive theranostic approach to assess the likelihood of response of glioblastoma.

Poster # 48

Abstract Title: Impact of tumor innervation on the efficacy of photothermal therapy

Authors: Alissa Dory (Queen’s University), Ahad Mohammadi, Anaïs Roger, Tianhui Dong, Christos Boutopoulos, Sébastien Talbot

Cancer remains one of the leading causes of mortality worldwide, with metastatic melanoma, an aggressive skin cancer, causing over 62,000 deaths annually. This cancer is resistant to traditional treatments, including chemotherapy. Advances in immunotherapy, particularly immune checkpoint inhibitors (ICB), have marked a major turning point in melanoma treatment; however, 40 to 50% of patients develop resistance.

This has prompted us to explore strategies that can reduce this resistance and improve treatment outcomes. Among such approaches lies Photothermal therapy (PTT), a treatment that has shown great promise in triggering systemic anti-tumor immunity. Essentially, PTT is a clinically implemented treatment model that leverages near-infrared laser irradiation of solid tumors to induce localized heat, which in turn triggers immunogenic cell death, targeting both primary tumors and metastatic niches.

We previously showed that melanoma is hyper-innervated by TRPV1-expressing sensory neurons, which, upon activation, release neuromodulators that reshape local immunity. Therapeutic blockade of RAMP1, a key CGRP receptor component, reinstated T-cell effector function and restrained tumor progression. Beyond calcitonin gene–related peptide (CGRP), a potent driver of cytotoxic T-cell exhaustion, these neurons also

secrete Substance P (SP). In melanoma, SP is co-opted to establish a “chronic, non-resolving wound–like” state, fostering angiogenesis, stromal remodeling, and recruitment of immunosuppressive immune populations. Notably, both CGRP and SP are co-released by TRPV2-expressing sensory neurons.

While PTT generates localized heat capable of priming anti-tumor immunity, our modality employing temperature increase above 52°C can also activate thermosensitive ion channels. Therefore, we sought to investigate the role of TRPV2, a high-threshold heat-activated channel expressed in sensory neurons, and assess whether TRPV2-driven co-release of CGRP and Substance P further shapes the neuro-immune landscape during PTT. We hypothesized that disrupting sensory neurons in the tumor bed would synergize with PTT to overcome resistance to ICB.

In a murine melanoma model, this triple-combination strategy, including PTT, sensory neuron inactivation, and ICB, yielded striking therapeutic benefit. Treatment markedly delayed tumor growth ($p = 0.0003$), improved survival, and achieved complete regression in 42% of mice. Notably, 84% of mice resisted tumor re-challenge, demonstrating robust, durable immunological memory.

Looking ahead, our data position sensory neurons as temperature-responsive modulators of anti-tumor immunity. Understanding how TRPV2 integrates thermal cues with neuromodulatory output will be essential to optimize PTT-based immuno-oncologic interventions. Our combined therapeutic approach could represent a major advance in the treatment of metastatic melanoma by re-engaging the immune system for a durable and effective response.

Poster # 49

Abstract Title: Treg Cell-Specific Adaptations to The Brain Metastasis Microenvironment.

Authors: Hossein Ehsanbakhsh (Virginia Commonwealth University), He Shen, Amy L. Olex, Paula D. Bos

Introduction: Brain metastasis remains a major clinical challenge, driven by complex interactions within the brain tumor microenvironment. Regulatory T (Treg) cells, a subset of $CD4^+$ T cells with immunosuppressive functions, play pivotal roles in tumor progression. In addition to immune regulation, tissue-resident Treg cells can modulate local physiological processes. We hypothesized that Treg cells infiltrating the brain-metastatic niche acquire specialized adaptations that support metastatic outgrowth. Understanding these mechanisms may reveal novel therapeutic targets for brain metastasis.

Methods: To evaluate the role of Treg cells in brain metastasis, we employed brain metastatic mouse models combined with the genetic depletion of Treg cells. Fluorescence-activated cell sorting (FACS) was used to isolate Treg cells from brain metastases for single-cell RNA sequencing (scRNA-seq). Transcriptomic comparisons between brain-infiltrating and splenic Treg cells were performed to identify brain-specific molecular adaptations. Candidate genes were validated functionally using conditional knockout models, including Foxp3ERT2CreAregfl/fl mice, to determine the role of amphiregulin (Areg) in Treg-mediated modulation of the brain metastatic microenvironment.

Results: Depletion of Treg cells led to a marked reduction in brain metastatic burden, indicating a supportive role for these cells in tumor progression. scRNA-seq analysis revealed that brain-infiltrating Treg cells exhibited a unique transcriptional signature, characterized by increased expression of Areg and other tissue-adaptation markers. Functional studies using the Foxp3ERT2CreAregfl/fl model demonstrated that

selective deletion of Areg in Treg cells resulted in increased brain metastatic burden. These findings suggest that Treg-derived Areg exerts a protective, anti-tumor influence in the brain metastatic niche, potentially by modulating local non-immune stromal elements and maintaining tissue equilibrium within the metastatic microenvironment.

Conclusion: Treg cells exhibit specialized adaptations within the brain metastatic microenvironment that influence disease progression. Among these, Areg expression by Treg cells appears to regulate cellular dynamics within the metastatic niche, beyond their classical immunosuppressive functions. These findings broaden our understanding of how immune cells integrate into the brain metastatic milieu and identify the Areg–EGFR axis as a potential modulator of brain metastasis biology.

Significance to the Cancer Neuroscience Field: This study bridges cancer immunology and neuroscience by uncovering a neuroimmune regulatory mechanism through which Treg cells adapt to and shape the brain metastatic environment. The identification of Treg-derived Areg as a key modulator of the metastatic niche highlights a novel interface between immune regulation and neural tissue context. These insights provide a foundation for developing therapies that target immune–neural interactions to mitigate brain metastasis progression.

Poster # 50

Abstract Title: Opioid-Expressing B Cells Silence Tumor-Infiltrating Nociceptor Neurons

Authors: Tuany Eichwald (Queen's University), Maryam Ahmadi, Andre Martel Matos, Amin Reza Nikpoor, Karine Roversi, Mohammad Balood, Moutih Rafei, Fendi Obuekwe, Marci L. Nilsen, Ayana T. Ruffin, Gabryella Pinheiro, Laura Brabenec, Paola Vermeer, Tullia C. Bruno, Nicole N Scheff, Sebastien Talbot

Nociceptor neurons, which transmit pain signals, also regulate immunity by releasing immunomodulatory neuropeptides. In head and neck squamous cell carcinoma (HNSCC) and melanoma, our research has shown that tumor-innervating nociceptors modulate anti-tumor immunity through the release of calcitonin gene-related peptide (CGRP) and its interaction with receptor activity-modifying protein 1 (RAMP1). A retrospective analysis of clinical charts from HNSCC patients revealed that higher pain levels correlated with increased opioid use, perineural invasion, and decreased B-cell infiltration—factors associated with poorer survival outcomes. In silico single-cell RNA sequencing demonstrated that opioid use in HNSCC patients downregulates nociceptin/orphanin FQ (N/OFQ), an endogenous ligand for opioid receptor-like-1 (OPRL1). We identified B cells as the primary source of N/OFQ and observed that high expression of either Pnoc or Oprl1 correlates with better survival in both melanoma and HNSCC. In a mouse model of oral squamous cell carcinoma (oSCC), we found that nociceptor neurons in tongue tumors overexpress Oprl1 and exhibit severe mechanical pain hypersensitivity. Compared to healthy tissue, oSCC tumors have dense infiltration of nociceptor fibers and N/OFQ-expressing B cells. Pharmacological blockade of Oprl1 reduced HNSCC-induced mechanical pain. In a melanoma mouse model, tumor-innervating neurons also overexpressed Oprl1, and similar overexpression was observed when DRG neurons were co-cultured with B16F10 cells. Activating OPRL1 reduced tumor size, enhanced cytotoxic T-cell infiltration, and relieved cancer-induced thermal hypersensitivity. In contrast, depleting CD19+ B cells or blocking OPRL1 led to increased tumor growth, reduced CD8+ T-cell infiltration and cytotoxic potential, exacerbated pain, and elevated CGRP levels. Moreover, we discovered that Ramp1+ B cells express Pnoc, but this expression is suppressed by CGRP. Blocking RAMP1 reduced tumor growth and promoted B-cell Pnoc expression. Overall, these findings suggest

that targeting the N/OFQ and RAMP1 pathways could bolster anti-tumor immunity while simultaneously alleviating cancer-induced pain.

Poster # 51

Abstract Title: NONO or yes-yes in glioma viroimmunotherapy?

Authors: Andrew Gillard (MD Anderson Cancer Center), Dong Ho Shin, Akhila Parthasarathy, Andres Lopez-Rivas, Hong Jiang, Sanjay Singh, Maria Frost, Xuejun Fan, Christopher Alvarez-Breckenridge, Frederick Lang, Marta Alonso, Juan Fueyo, Candelaria Gomez-Manzano

Introduction: Glioblastoma (GBM) is a highly aggressive CNS malignancy with a median survival of only 15 months, underscoring the urgent need for new therapies. Oncolytic viroimmunotherapy, exemplified by Delta-24-RGD (DNX-2401)—a tumor-selective, replication-competent adenovirus—is under active clinical study for its capacity to destroy tumor cells and activate immune responses against “cold” GBM. However, immune-mediated clearance of the virus may compromise therapeutic efficacy.

Methods: We used bulk RNA sequencing of adenovirus-infected cells and tumors to identify activated pathways, with LC-MS/MS for protein interaction analysis. HDock-based in silico modeling, followed by co-immunoprecipitation, western blot, and immunofluorescence, defined NONO-cGAS-adenovirus complexes. Interferon induction and cGAMP were quantified by q-PCR and ELISA, respectively. In vivo models using Delta-24-RGD-luciferase were assessed for viral persistence, with proteome arrays and flow cytometry used to characterize changes in cytokine and immune populations after virotherapy.

Results: Adenoviral infection triggered a seven-fold increase in NONO expression in both murine and human glioma models. Mass spectrometry and immunoprecipitation confirmed the interaction of NONO with cGAS and the adenoviral DNA-binding protein E72K; these proteins colocalized in nuclear paraspeckles post-infection. Functional assays revealed that NONO promoted cGAMP induction via cGAS, enhancing innate immunity in tumor cells. Conditioned media from OV-infected cells activated macrophages in vitro. Importantly, NONO knockdown increased viral replication, prolonged viral persistence in vivo, and reduced proinflammatory cytokines and monocyte/macrophage recruitment to the tumor microenvironment. These findings suggest NONO-dependent immune sensing is a key determinant of oncolytic virus clearance and intratumoral immune activation.

Conclusion: NONO is a newly characterized sensor of adenovirus and a crucial regulator of innate immune responses during Delta-24-RGD virotherapy. By influencing immune activation, viral replication, and persistence, NONO emerges as a promising target for improving oncolytic viroimmunotherapy outcomes.

Significance to the cancer neuroscience field: Dissecting NONO’s role in innate immunity during oncolytic virus therapy provides critical insight for designing next-generation viroimmunotherapeutics for GBM. Integrating mechanistic immunology in vector design could ultimately provide more effective treatments for patients with this lethal disease, addressing an urgent unmet clinical need.

Poster # 52

Abstract Title: Glioma-associated neurons potentiate glioma radioresistance by facilitating the transfer of fresh mitochondria from peripheral macrophages to glioma cells via tumor microtubes

Authors: Xiaofan Guo (University of Pittsburgh Medical Center), Wei Qiu, Ruochuan Zhang, Hao Xue, Gang Li

The tumor microenvironment (TME), including mitochondrial dynamics, plays a pivotal role in the initiation and progression of glioblastoma. Beyond the traditional components of the TME, neurons have recently been identified as key regulators of glioma behavior. However, the role of glioma-associated neurons in mediating mitochondrial transfer and contributing to radiation resistance remains largely unexplored. Here, using neuronal ablation and chemogenetic techniques and in vivo mitochondrial tracking, we identified that radiation-exposed neurons in glioma secret unique exosomes that facilitate physical connections between glioma cells and tumor-infiltrating macrophages via tumor microtubes (TMs). These TMs enable the transfer of healthy mitochondria from newly recruited macrophages to irradiated glioma cells, thereby restoring glioma cell mitochondrial function. Mechanistically, neuronal exosomal FABP7 protein is transferred to glioma cells and facilitates the formation of tumor TMs by promoting the palmitoylation and subsequent plasma membrane localization of GAP43. Importantly, combined inhibition of neuronal activity and peripheral immune cell infiltration, followed by hypofractionated radiotherapy, significantly enhances the radiation efficacy in damaging glioma cells and improves the prognosis of glioma-bearing mice.

†*Professional Development Award*

† Poster # 53

Abstract Title: A CX3CL1–CX3CR1–Driven Neuro-Immune Circuit Amplifies Pain in Pancreatitis and Offers a Druggable Therapeutic Entry Point

Authors: Ibrahim Gurcinar (Technical University of Munich, School of Medicine), Okan Safak, Sergey Tokalov, Alper Dogruoz, Phillip Gärtner, David Jungwirth, Taylan Emir Gözeler, Helmut Friess, GO Ceyhan, R. Istvanffy, Ihsan Ekin Demir

Introduction: Many patients with pancreatitis struggle with pain, and current treatments often do not provide enough relief. This suggests that the mechanisms behind this pain involve more than local inflammation alone. Evidence indicates that immune cells and neurons communicate in a way that shapes pain development. The chemokine CX3CL1 (fractalkine) and its receptor CX3CR1 are present in both immune and sensory neuronal cells, placing them at a key point in this interaction. However, their role in pancreatitis-related pain has not been clearly defined.

Methods: Acute and chronic pancreatitis were induced in C57BL/6 mice using cerulein, and pain behavior was assessed with von Frey testing over time. Neuronal activation was evaluated by examining c-Fos expression in dorsal root ganglia (DRG) and spinal cord. To explore how CX3CL1 affects neuronal inflammatory responses, primary DRG neurons were stimulated with lipopolysaccharide and treated with an anti-CX3CL1 antibody before measuring IL-6 and CCL2 release. Pancreatic tissue was also examined histologically for inflammatory cell infiltration and tissue injury.

Results: Blocking CX3CL1 led to reduced mechanical sensitivity in both acute and chronic models. This improvement in pain behavior corresponded with fewer c-Fos-positive neurons in the spinal cord, suggesting less nociceptive signaling reaching the central nervous system. In cell culture, neutralizing CX3CL1 resulted in lower IL-6 and CCL2 release from DRG neurons after LPS stimulation, indicating a reduced neuro-inflammatory response. Treated mice also showed less inflammatory infiltration and tissue damage in the pancreas. These findings support the idea that CX3CL1–CX3CR1 signaling forms a neuro-immune loop that contributes to pain amplification. There are indications that this pathway interacts with macrophage-derived Cathepsin S and downstream PAR2-related signaling in neurons, which further supports the rationale for targeting CX3CL1 upstream.

Conclusion: Our data suggest that CX3CL1–CX3CR1 signaling plays an important role in linking immune activity with neuronal sensitization in pancreatitis. Targeting this axis may help reduce neuro-inflammation and offer a more specific way to manage pain in affected patients.

Significance to the Cancer Neuroscience Field: This work highlights how immune-derived signals can influence neuronal activity and pain perception. It also reflects a broader neuro-immune concept relevant to cancer-associated inflammation and nerve–tumor interactions. Understanding such pathways may support new strategies for pain management where cancer and the nervous system intersect.

†*Professional Development Award*

† Poster # 54

Abstract Title: Enteric Glial and Neuronal Remodeling Shapes the Tumor Microenvironment in Colorectal Cancer

Authors: Ebrahim Hamza (University Hospital Bonn), Reiner Schneider, Linda Schneider, Bianca Schneiker, Patrik Efferz, Elena Domenico, Marc Beyer, Sven Wehner

Introduction: Emerging evidence highlights the nervous system as a key regulator of tumor biology, yet the mechanisms by which the enteric nervous system (ENS) influences colorectal cancer (CRC) development remain largely unexplored. Enteric glial cells (EGCs) and enteric neurons are essential for intestinal homeostasis and immune modulation. This study investigates how neuro-glial interactions are transcriptionally reprogrammed in CRC and how these changes may shape the tumor microenvironment (TME).

Methods: Sox10-CreERT2 × Sun1-GFP and Baf53b-Cre × Sun1-GFP transgenic mice were used to isolate nuclei from enteric glia and neurons under naïve, DSS-induced colitis, and tumor conditions. Sorted GFP^+ nuclei were analyzed by bulk RNA sequencing to identify tumor-associated neuro-glial signatures. In parallel, immunohistochemical and confocal imaging were performed on colonic tissues to assess ENS remodeling, glial activation (GFAP, S100β), neuronal integrity (βIII-tubulin), and spatial interactions with infiltrating immune populations such as T cells ($CD3^+$), B cells ($B220^+$), and macrophages ($Iba1^+$), highlighting a neuro-immune interface within the tumor microenvironment.

Results: Bulk RNA sequencing revealed that the ENS undergoes profound transcriptional remodeling in the colorectal tumor microenvironment. Enteric glial cells (EGCs) displayed the most striking changes, adopting a gene signature characteristic of inflammation, remodeling, and migration. Tumor-associated glia upregulated Il1b, Mmp7, and Wnt10a, reflecting activation of cytokine-driven signaling, extracellular matrix remodeling,

and Wnt pathway induction. These transcriptional shifts suggest that EGCs transition into a reactive, pro-migratory, and immune-modulatory state capable of shaping local inflammation and tissue architecture.

Enteric neurons also exhibited distinct reprogramming under tumor conditions. Genes linked to sensory activity and immune communication, including Npas4 and Tnfsf10 (TRAIL), were prominently upregulated, indicating neuronal engagement in stress and apoptotic signaling networks. Spatial analyses reinforced these findings, revealing dense Sox10$^+$ glial processes and disrupted βIII-tubulin$^+$ neuronal fibers infiltrating tumor-adjacent regions in close contact with immune infiltrates. Areas with heightened glial activation coincided with increased immune cell density, supporting a functional link between ENS remodeling and immune recruitment.

Conclusion: Colorectal cancer induces distinct but coordinated transcriptional remodeling of enteric neurons and glia, establishing a neuro-immune dialogue that supports tumor-associated inflammation and microenvironmental remodeling.

Significance to the Cancer Neuroscience Field: This study identifies the enteric nervous system as an active participant in colorectal cancer pathogenesis. By linking neuronal and glial plasticity to immune modulation, these findings expand the boundaries of cancer neuroscience and highlight novel therapeutic opportunities targeting neuro-immune crosstalk in gastrointestinal malignancies.

Poster # 55

Abstract Title: Quaking regulates MHC II antigen presentation and macrophage immune activation in glioblastoma

Authors: Spring Hwang (MD Anderson Cancer Center), Ailiang Zeng
Introduction: Glioblastoma (GBM) is the most common and aggressive brain tumor that remains severely unresponsive to immunotherapy due to its profoundly immunosuppressive microenvironment. Tumor-associated macrophages (TAMs) comprise up to half of the GBM mass and are crucial mediators of this immune evasion. However, the molecular mechanisms that control macrophage antigen presentation and antitumor responses in the brain remain poorly understood. Quaking (QKI) is an RNA-binding protein with tumor-suppressive functions that we recently found to correlate positively with MHC II expression in GBM-associated macrophages. We hypothesized that QKI regulates macrophage antigen presentation and immune activation within the glioblastoma microenvironment.

Methods: Bone marrow–derived macrophages (BMDMs) were isolated from Cx3cr1-CreERT2; Qk^fl/fl^ mice and treated with 4-hydroxytamoxifen (4-OHT) to induce QKI deletion. Wild-type (WT) and QKI knockout (KO) BMDMs were stimulated with IFN-γ to induce MHC II antigen presentation. Quantitative PCR and immunoblotting were used to assess MHC-associated genes. Functional assays, including phagocytosis, DQ-OVA, and OT-II T cell co-culture, were used to evaluate antigen uptake, processing, and presentation. RNA sequencing was used to identify QKI-dependent pathways and networks associated with MHC II regulation.

Results: Although IFN-γ stimulation induced MHC II in QKI-KO macrophages, loss of QKI markedly reduced MHC II expression and impaired phagocytosis and antigen processing, indicating defective MHC II machinery. Additionally, QKI KO macrophages failed to activate CD4$^+$ T cells in co-culture assays. Transcriptomic analysis showed QKI loss downregulates pathways related to extracellular matrix interaction, focal adhesion, and phagocytosis, suggesting that QKI maintains macrophage structural and endocytic programs that enable

antigen processing. Importantly, pharmacologic activation of QKI with its co-activator agonist KD3010 upregulated MHC II expression, enhanced $CD4^+$ T cell activation, and prolonged survival in GBM-bearing mice, underscoring QKI's therapeutic relevance.

Conclusion: QKI is important for effective MHC II-mediated macrophage antigen presentation and antitumor response in glioblastoma. Its loss impairs MHC II machinery and programs important for phagocytosis and antigen processing, thereby promoting GBM immunosuppression.

Significance: This study identifies Quaking as a molecular link between post-transcriptional regulation and neuroimmune function in glioblastoma. By investigating how QKI governs macrophage antigen presentation within the CNS, our work reveals an RNA-dependent checkpoint of brain tumor immunity and highlights pharmacologic QKI activation as a potential strategy to restore antitumor immune function. Ongoing studies are investigating upstream regulators that suppress QKI, which may reveal new targets to overcome GBM immunosuppression.

Poster # 56

Abstract Title: Cancer cell secreted PTHLH/PTHrP drives neuroimmune axis in murine tongue tumor model

Authors: Ravi Kishan (University of Hong Kong), Weifa Yang, Richard Yu-xiong Su

Introduction: Intra-tumor nerve infiltration is strongly associated with poor prognosis in head and neck squamous cell carcinoma (HNSCC), yet the molecular mediators orchestrating neuroimmune crosstalk in this context remain incompletely understood.

Methods: This study utilized an integrated approach combining transcriptomic analysis, CRISPR-Cas9 gene editing, and preclinical models in both immunodeficient (BALB/c nude) and immunocompetent (C57BL/6J) mice to identify key regulators of this axis.

Results: Transcriptomic analysis of HNSCC patient samples revealed that PTHLH (parathyroid hormone-like hormone, or PTHrP) was significantly upregulated and correlated with neuroimmune gene signatures and poor immunotherapy outcomes. Functional validation using PTHLH knockout (KO) tumor cells demonstrated a substantial reduction in neurotrophic factors essential for nerve growth. In vivo, PTHLH deficiency did not impact tumor growth in immunodeficient hosts but markedly suppressed tumor burden in immunocompetent mice, indicating that its tumor-promoting effects are immune-dependent. Immune profiling revealed increased infiltration of CD8+ and CD4+ T cells, concomitant with decreased FOXP3+ regulatory T cells and PD-L1 expression in PTHLH-deficient tumors. Additionally, these tumors exhibited reduced Ki67 and B3-tubulin expression, suggesting suppression of both tumor growth and nerve density.

Conclusions: Collectively, these findings position PTHLH as a key secreted mediator that facilitates immunosuppression and nerve infiltration within the tumor microenvironment, particularly in tongue HNSCC. Targeting PTHLH signaling enhances anti-tumor immunity and impairs neural infiltration, thereby inhibiting tumor progression.

Significance to the cancer neuroscience field: This study advances the understanding of neuroimmune interactions in cancer and identifies PTHLH as a promising therapeutic target to disrupt tumor-nerve crosstalk and restore immune competence in nerve-rich malignancies such as HNSCC.

† Poster # 57

Abstract Title: Lymph Node Innervation by Sensory and Sympathetic Neurons Shapes the Anti-Tumor Immune Landscape

Authors: Laura Korycinska (University of Pittsburgh), Kunal Singh, Xiuzhen Liu, Gulnaz Sterling, Stephanie Fulton, Ion Mandoiu, Jami Saloman, Brian M Davis, Yuri Bunimovich

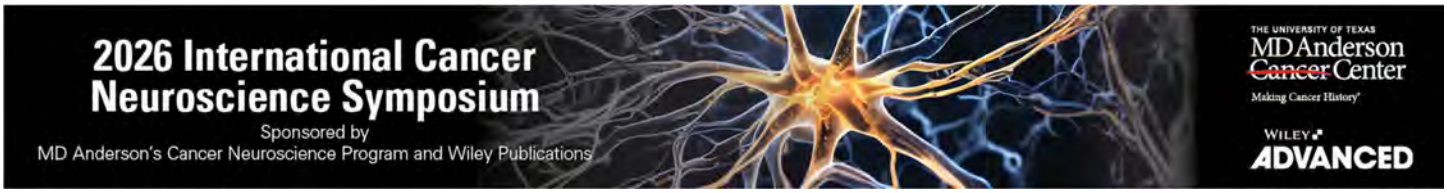
Introduction: Tumor-draining lymph node (TDLN) is an essential site where the adaptive immune response is initiated. LN are innervated by sympathetic and sensory neurons, but our understanding of neuro-immune interactions and their impact on cancer progression is limited. Previously, our group has shown that melanomas are innervated by sensory neurons which exert immunosuppressive effects in the tumor microenvironment (TME) (Vats, 2022).

Methods: To extend these findings to the TDLN, neurons innervating the LN and overlying skin were retrogradely labeled to trace their dorsal root ganglion (DRG) origin. Single-cell RNA sequencing (scRNA-seq) was performed on sensory neurons isolated from TDLN and tumor of B16F10 melanoma-bearing mice, and from the LN and skin of naïve mice, to identify neuronal populations at these sites. To examine how peripheral nerves in the TDLN impact tumor progression and immune response, genetic (NPYCre/iDTR and TRPV1Cre/iDTR mouse models) and chemical (6OHDA and RTX) approaches were used to ablate sympathetic and sensory neurons, respectively. Immune cells isolated from TDLN and tumor of denervated and control mice were used for scRNA-seq to evaluate the effect of denervation on immune populations.

Results: Retrograde labeling revealed that skin and LN are supplied by the same DRGs but are innervated by distinct sensory nerves with no overlap. UMAP analysis of scRNA-seq data identified transcriptionally distinct clusters between skin/tumor and LN/TDLN sensory neurons. Further analysis revealed that these clusters correspond to known sensory subtypes, with peptidergic neurons detected in the skin and tumor, and nonpeptidergic neurons within the LN and TDLN. Genetic and chemical ablation of sympathetic and sensory neurons resulted in reduced melanoma growth compared to the innervated controls. scRNA-seq analysis further revealed differences in abundance of immune subtypes and transcriptional signatures of immunosuppression in innervated controls that were not present in 6OHDA and RTX treated mice, suggesting that peripheral nerves in the TDLN inhibit immune activation and function.

Conclusion: These findings suggest that sympathetic and sensory nerves in the TDLN are a negative regulator of the anti-tumor response, preventing immune activation and promoting disease progression. Moreover, sensory nerves in the TDLN are distinct from those supplying the tumor, suggesting that neural regulation occurs through site-specific mechanisms.

Significance: These findings shift attention to the TDLN, a previously underappreciated site of neuroimmune crosstalk in cancer. Identifying the mechanisms of neural regulation of cancer beyond TME will provide insights into previously unrecognized mechanisms of immunosuppression, applicable for the development of novel therapeutic strategies.



Poster # 58

Abstract Title: Androgen loss weakens anti-tumor immunity via the hypothalamus-pituitary-adrenal axis to accelerate brain tumor growth

Authors: Juyeun Lee (Cleveland Clinic), Yoon-Mi Chung, Daniel J. Silver, Yue Hao, Dylan Scott Harwood, Lee Curtin, Julia R. Benedetti, Christine Ann Pittman Ballard, Michael Berens, Bjarne Winther Kristensen, Quinn T. Ostrom, Nima Sharifi, Justin D. Lathia

Introduction: Many cancers, including glioblastoma (GBM), show a male-biased difference in incidence and outcome. The cellular and molecular basis for this epidemiological difference remains unclear but likely involves sex hormone-regulated immune responses. While androgens are generally thought to suppress anti-tumor immunity, we discovered an unexpected tumor-suppressive role of androgens in brain tumors, revealing a brain-specific mechanism distinct from other cancers.

Methods: Male mice (5-6 weeks old) underwent castration or sham surgery followed by intracranial or subcutaneous implantation of syngeneic GBM or non-GBM (bladder cancer, melanoma) cells. Survival, immune cell profiles, and serum glucocorticoid and ACTH levels (mass spectrometry, ELISA) were analyzed. Transcriptomic changes in brain tissue were assessed using the NanoString Digital Spatial Profiler platform.

Results: We found that androgen depletion via castration accelerated tumor growth in the brain but slowed growth in the flank, suggesting a brain-specific suppressive role of androgens. Consistently, SEER database analysis showed that testosterone supplement in male GBM patients was associated with significantly extended overall survival and a reduced risk of death. Mechanistically, the accelerated brain tumor growth following androgen depletion was linked to impaired anti-tumor immunity, characterized by decreased anti-tumor cytokine production and increased T cell exhaustion. This was driven by elevated glucocorticoids due to hyperactivation of the hypothalamus-pituitary-adrenal (HPA) axis after castration. Blocking glucocorticoid receptors reversed anti-tumor immune responses and slowed tumor growth, confirming the central role of HPA axis dysregulation. Further analysis revealed that glucocorticoid signaling in myeloid cells contributed to an immunosuppressive tumor microenvironment. Importantly, this mechanism was brain-specific, as intracranial implantation of non-GBM tumors also triggered the HPA axis hyperactivation. Elevated neuroinflammation, marked by increased IL-1β and TNF, contributed to HPA axis hyperactivation, as blocking these cytokine pathways reversed the effect in castrated mice. Spatial transcriptomic analysis further showed that androgen signaling suppresses inflammasome activation in microglia and dampens neuroinflammatory responses, linking androgen loss to heightened neuroinflammation and downstream HPA axis-mediated immunosuppression.

Conclusion: These findings uncover a novel neuroendocrine mechanism by which brain tumors exploit androgen deprivation to enhance neuroinflammation and immune suppression.

Significance to the cancer neuroscience field: This work highlights the importance of organ-specific regulation of anti-tumor immunity that engages the HPA axis and identifies a previously unrecognized protective role of androgens in the brain. By bridging tumor immunology, neuroinflammation, and androgen biology, these findings open new avenues for translational studies aimed at improving outcomes for brain tumor patients.

Poster # 59

Abstract Title: Combining JAK inhibition with oncolytic virotherapy to reprogram immunosuppressive macrophages in glioblastoma

Authors: Andreas Lopez-Rivas (MD Anderson Cancer Center), Dong Ho Shin, Akhila Parthasarathy, Andrew G Gillard, Claudia Solbes, Alejandra Duran, Joy Gumin, Christopher Alvarez-Breckenridge, Frederick F Lang, Juan Fueyo, Candelaria Gomez-Manzano

Introduction: Treating glioblastoma remains a therapeutic challenge in oncology. Viroimmunotherapy is emerging as a promising new treatment approach. Our laboratory developed an oncolytic adenovirus, termed Delta-24-RGD, which has been tested in clinical trials for recurrent glioblastoma patients with encouraging results (NCT00805376, NCT02798406). Here, we aim to further improve the efficacy of Delta-24-RGD by targeting factors that maintain the immunosuppressive characteristics of gliomas.

Methods: We performed bulk RNA-sequencing of murine gliomas treated with Delta-24-RGD or control (PBS) and analyzed the upstream regulators using Ingenuity Pathway Analysis. A correlation plot of IFNγ and IDO1 transcript levels from 38 glioblastoma patient samples was obtained from the Delta-24-RGD plus Pembrolizumab clinical trial (NCT02798406) and analyzed in R Studio. Western blots and qPCR in glioma cells validated the IFNγ-induced IDO1 expression. To study macrophage polarization, bone marrow-derived macrophages (BMDMs) were stimulated with IFNγ or IL-4 in the presence or absence of a JAK inhibitor, and gene expression of immunosuppressive markers was assessed by qPCR.

Results: Bulk RNA-sequencing revealed IFNγ as the top upstream regulator in murine tumors treated with an oncolytic virus. In addition, we observed upregulation of the tryptophan metabolism and immunoregulator IDO1-AhR network in these treated tumors. We found a significant and positive correlation between IFNγ and IDO1 in glioblastoma tumor biopsies from the clinical trial. In vitro studies demonstrated that IFNγ treatment of glioma cells increased JAKs/STATs phosphorylation levels and IDO1 expression, which were abrogated entirely by concomitant treatment with a JAK inhibitor. Additionally, we observed that the JAK inhibitor reduced the expression of the anti-inflammatory genes (FIZZ1, ARG1, IDO1, and PD-L1) in polarized BMDMs.

Conclusion: IFNγ is the top upstream regulator activated in glioma-bearing mice treated with Delta-24-RGD, with concurrent activation of the IDO1-AhR immunosuppressive pathway. IFNγ and IDO1 are significantly and positively correlated in glioma tumor biopsies from the clinical trial, supporting this axis as clinically relevant. In vitro, IFNγ strongly induces the expression of IDO1 in glioma cells, whereas the JAK inhibitor reverses this effect. Ruxolitinib treatment also reduced the expression of anti-inflammatory genes in polarized BMDMs and increased the phagocytic activity of BMDMs, indicating a shift away from an immunosuppressive phenotype.

Significance to the cancer neuroscience field: This study demonstrates the feasibility of combining virotherapy with drugs targeting immunosuppressive pathways in gliomas, providing a strong rationale for translating this strategy into the clinical setting.

Poster # 60

Abstract Title: Cancer pain is controlled by enkephalins produced by regulatory T cells

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Introduction: Regulatory T cells (Treg) are an immunosuppressive subset of CD4+ T cells, essential for maintaining homeostasis and reducing inflammation. However, they also perform non-immune functions, such as regulating neuropathic pain. The mechanisms involved are poorly understood. We recently described that Treg expresses the proenkephalin (Penk) gene at high levels, this gene being the precursor of enkephalins opioid peptides with analgesic functions. Conditional deletion of Penk in Treg causes thermal hypersensitivity in mice without affecting their immunosuppressive functions. Cancer-related pain is a major issue for cancer patients, whether directly due to tumor growth itself or indirectly due to the treatments, particularly chemotherapies. Interestingly, the initial stages of cancer are rarely painful, which can delay diagnosis. We hypothesize that tumor-recruited Treg could mask tumor growth-related pain.

Method: To test our hypothesis, we use a Tamoxifen-dependent Treg-specific Penk depletion mouse model (Foxp3CreERT2 x Penklox/lox) in which MC-38 cancer cells are implanted into the hind paw of Treg-specific Penk-deleted mice (KO) or Cre-expressing littermate controls (WT). We evaluate mechanical sensitivity during tumor growth with the von Frey test. At the end of the experiment, we analyze the tumor and the draining lymph node by flow cytometry to determine the impact of depletion on the global immune response. We also evaluated the mechanical sensitivity of KO compared to WT mice in a model of oxaliplatin-induced pain.

Results: Using mRNA hybridization and flow cytometry, we first show that Treg expresses Penk in the tumor at higher levels than in the draining lymph nodes. Second, we observed comparable tumor growth between WT and KO mice, indicating that the lack of Penk in Tregs does not impact their suppressive function. Third, we show that Tregs are able to reduce TRPV1+ neurons depolarization in vitro. Finally, we show that KO mice are more sensitive to the initial pain provoked by tumor growth than WT mice. Remarkably, cancer pain in KO mice is fully reversible upon injection of WT Treg. The same hypersensitivity of KO mice to mechanical pressure is observed in the chemotherapy-induced pain model.

Conclusion: Together, these results highlight a novel and fundamental mechanism by which the immune system controls cancer-related pain. Inducing Penk expression in Treg may provide an effective solution for managing cancer-related pain, particularly chemotherapy-induced pain.

Significance to the cancer neuroscience field: Our results illustrate the intimate interplay between the tumor, the immune system and nociception. A better knowledge on those relations will provide novel avenues for therapy.