IIMS INSTITUTE FOR INTEGRATION OF MEDICINE AND SCIENCE

14TH ANNUAL FRONTIERS OF TRANSLATIONAL SCIENCE RESEARCH DAY

Posterboard #: 1

Presenter: Sevan Alwan, PhD

Institution: UT Health San Antonio

Category: Faculty (any rank)

Predicted Clinical Impact of New Compound in Schistosoma Therapy

Sevan N. Alwan, Alexander B. Taylor, Michael Tidwell, Stanton F. McHardy, Michael D Cameron, Philip T. LoVerde

Human schistosomiasis is a disease caused by parasitic species of the genus Schistosoma. Schistosoma affects over 251 million people worldwide, accompanied by severe clinical symptoms, socioeconomic problems, and more than 200,000 deaths per year. About 90% of the schistosomiasis disease burden occurs in sub-Saharan Africa, where the major forms of schistosomiasis are caused by Schistosoma haematobium (urogenital disease) and Schistosoma mansoni (intestinal-hepatic disease). S. haematobium causes female genital schistosomiasis that leads to formation of lesions within the vaginal tract of women with a risk of progression to infertility and a risk of HIV coinfection if left untreated. S. mansoni is endemic in sub-Saharan Africa. This parasite causes chronic hepatic or intestinal illnesses and malnutrition in both Africa and Brazil and suspected to be directly involved in hepato-carcinogenesis. Due to the large overlap of Schistosoma haematobium - and Schistosoma mansoni -endemic regions in Africa, many people are at risk of co-infection, these mixed foci have a potential adverse effect on their association with bladder and liver pathology. Treatment has relied on the anthelmintic drug Praziquantel (PZQ) for more than 20 years. Mass drug administration in sub-Saharan Africa, where most of the cases occur, has led to the appearance of reduced efficacy of PZQ, which portends the selection of fully drug resistant pathogens. Moreover, PZQ does not prevent reinfection and it is not active against juvenile stages resulting in rapid re-activation after 2 to 3 weeks from PZQ treatment. These limitations strongly warrant the need for new therapeutics with better cure rate. Our focus is on Oxamniquine (OXA), a previous treatment of S. mansoni that fails to treat S. haematobium infections. We have successfully reengineered OXA using structure-function-guided approaches to produce CIDD-0149830 with major advancements over current Schistosoma therapies. CIDD-0149830 reduced the worm burden of S. haematobium and S. mansoni adult worms up to 80% in animal models, an advantage over OXA. Similarly, CIDD-0149830 overcame one of the major limitations of PZQ treatment. CIDD-0149830 kills 100% of juvenile stage of S. haematobium and S. mansoni in vitro. Importantly, CIDD-0149830 kills 100% of PZQ-resistant parasite in in vitro studies. Our goal is to demonstrate the efficacy of CIDD-0149830 to advance to clinical studies. We expect CIDD-0149830 to be effective in animal models as well since CIDD-0149830 and PZQ have a different mode of action.

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Posterboard #: 2

Presenter: Anton Avanceña, PhD

Institution: The University of Texas at Austin

Category: Faculty (any rank)

Patterns and timing of alcohol use disorder treatments among cancer survivors in the US: findings from a real-world study

Anton L.V. Avanceña, Jyun-Heng Lai, Minh Nguyen

Introduction: Alcohol use disorder (AUD) among cancer survivors is associated with poor health outcomes such as increased risks for rehospitalization, new malignancies, and mortality. Despite the availability of AUD treatments, their use and effects are not well understood in this population. This retrospective cohort study aims to assess the patterns and timing of AUD treatments among cancer survivors with AUD. Methods: We analyzed Merative MarketScan® commercial claims and supplementary Medicare data (2011-2021). We included individuals who were diagnosed with a malignant neoplasm and AUD with 1 year of continuous enrollment before and after their AUD diagnosis. We identified use of Food and Drug Administration (FDA)-approved and non-FDA approved pharmacotherapies and psychosocial therapies for AUD. We assessed AUD treatments annually in all cancer survivors and in subgroups like survivors of alcohol-related cancers. Descriptive statistics were used to measure the proportions and mean and median time to initiating AUD treatments. Results: Preliminary results show that among 74,609 cancer survivors with AUD (2011-2021), the proportion that received FDA approved pharmacotherapies naltrexone, acamprosate, and disulfiram was 4.2%, 1.4%, and 0.8%, respectively. Among six non-FDA-approved pharmacotherapies for AUD we considered, ondansetron (14.6%) and gabapentin (9.4%) were the most common. About 26.6% of cancer survivors received psychotherapy and/or alcohol counseling, and 1.1% underwent inpatient alcohol rehabilitation. In time trend analyses, we found an increased use of FDA-approved pharmacotherapies, including a 6% increase for naltrexone from 2012 to 2020. Psychotherapies were the first AUD treatment received by most cancer survivors, with a median time of 14 (interquartile range [IQR] 78) days. Time to first FDA-approved pharmacotherapy was 47 days (IQR 180). Conclusion: We found that a small proportion of cancer survivors with AUD received recommended pharmacotherapies with a delay in treatment initiation. Interventions may be needed to increase use of AUD treatments among cancer survivors to reduce the risk of alcohol-related harms.

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Posterboard #: 3

Presenter: Colin Court, MD, PHD

Institution: UT Health San Antonio

Category: Faculty (any rank)

Decreased Primary Tumor Th2 Cell Tumor Infiltration is Associated with Liver Metastases Across Cancer Types

Colin M. Court MD PhD, Madeline Silva MD, Shirley Nah, MD, Ankur Tiwari MD, Brett L. Ecker MD, Sukeshi P. Arora MD, Neil B. Newman MD, Caitlin A. Mcintyre MD, Mio Kitano MD MPH, Alexander A. Parikh MD MPH

Introduction: Advances in systemic therapy, and particularly immunotherapy, have improved outcomes in metastatic cancer and have led to recognition of an oligometastatic phenotype for certain sites of metastases. As the indications for surgery in oligometastatic disease evolve, it is important to understand the organotropism of different cancers as well as the immune context in which metastases occur. Recent evidence from early phase trials has shown that liver metastases are associated with resistance to immunotherapy, raising the possibility of a unique immune association with this site of spread. We therefore investigated the association of liver metastases with the primary tumor immune microenvironment across cancer types. Methods: The Cancer Genome Atlas(TCGA) primary clinical databases (gdacv.2016_01_28) were used to develop a comprehensive recurrence dataset that was correlated with the immune infiltrate signatures (Thorrson, 2018). Immune fractions within the leukocyte population were estimated using CIBERSORT. Genomic and immunologic subtypes were compared to patient outcomes using Welch's t test and Cox models. Results: Of the cohort of 10,211 patients from 32 cancer types, 1529 patients had a recurrence recorded. Of these 1529 recurrences, 843 were distant metastases while 686 were local recurrences. The location of distant metastasis was available for 725 patients(86%) with most(94%) patients having a single site listed. Metastases were present in patients with 22 cancer types with the most common primary sites being skin/soft tissue(n=284), GI(n=211), or GU(n=97) cancers. Patients with liver metastases(mean=-112.2) were found to have lower Th2 cell immune infiltration scores than other sites of recurrence(mean=282; $t=8.8$, $p<0.001$, $q=1.12e-16$). A sensitivity analysis of cancer subsets revealed the strongest association of Th2 cell infiltration with GI cancers ($p < 0.001$) when compared to GU and skin/soft tissue. No association with Th2 cell infiltration was noted for metastasis to lung, peritoneum, or brain. Th2 cell infiltration was not associated with survival in the cohort of all patients or all GI patients. Conclusions: This exploratory study highlights the immune characteristics of primary tumors associated with eventual liver metastases, characterized by significantly lower Th2 cell immune signatures compared to other sites of recurrence. These findings have implications for the surgical management and immunotherapeutic approaches to metastatic cancer patients, particularly in those with liver metastases.

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Posterboard #: 4

Presenter: Falguni Das, PhD

Institution: UT Health San Antonio

Category: Faculty (any rank)

High glucose increases tyrosine phosphorylation of PKM2 to initiate a feedback loop involving PDGFRβ to activate mTORC1 for mesangial cell (MC) injury in diabetic nephropathy (DN)

Falguni Das, Ph.D., Nandini Ghosh-Choudhury, Ph.D., Balakuntalam S. Kasinath, MD., Kumar Sharma, MD. & Goutam Ghosh Choudhury, Ph.D.

Pathologic features of diabetic nephropathy (DN) include renal hypertrophy and matrix expansion. Recently, increased activity of the glycolytic enzyme pyruvate kinase M2 (PKM2) has emerged as a key player in cancer cells. In the present study, we examined the role of tyrosine phosphorylation of PKM2 in mesangial cell injury and in mice models of type 1 and type 2 diabetes. Incubation of MCs with 25 mM glucose (HG) increased the expression of PKM2 in a time dependent manner. HG induced translocation of PKM2 into the nucleus. Furthermore, HG increased the phosphorylation of PKM2 at tyrosine-105 residue in both cytosol and nucleus. We have recently shown a role of PDGFRβ in DN. We hypothesized that PDGFRβ may regulate PKM2. JNJ, a PDGFRβ inhibitor, abrogated HG-stimulated PKM2 expression and tyrosine phosphorylation. Interestingly, expression of kinase dead PKM2 K367M mutant inhibited HG-induced MC hypertrophy. Intriguingly, a tyrosine phosphorylation deficient mutant PKM2 Y105F also had the same effect. In contrast, overexpression of wild type PKM2 induced MC hypertrophy similar to HG treatment. Mesangial matrix expansion is an aspect of DN. Both PKM2 K367KM and PKM2 Y105F mutants mitigated HG-stimulated expression of fibronectin, collagen I (α2) and PAI-1 whereas, overexpression of PKM2 had the opposite effects similar to HG. Previously, we reported that Akt/mTORC1 signaling regulates MC pathologies. We found that kinase dead and phosphorylation deficient mutants of PKM2 suppressed HG-stimulated Akt and mTORC1 activity while overexpression of PKM2 increased their activities. Interestingly, Akt and mTORC1 inhibitors MK2206 and rapamycin, respectively abrogated expression and tyrosine phosphorylation of PKM2. While addressing the in vivo relevance, we found increased expression and tyrosine phosphorylation of PKM2 concomitant with fibronectin, PAI-1 and collagen I (α2) expression in the renal cortex of OVE26 and db/db mice, models of type 1 and type 2 diabetes, respectively. Our results discover a previously unrecognized HG-stimulated novel positive feedback mechanism involving PDGFRβ, tyrosine phosphorylated PKM2 and activated mTORC1 in diabetic nephropathy.

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Posterboard #: 5

Presenter: Maria Gaczynska, PhD

Institution: UT Health San Antonio

Category: Faculty (any rank)

Calming the cytokine storm with proteasome-targeting immunomodulators.

Maria E. Gaczynska, Abul Azad, Eusondia Arnett, Viraj Kulkarni, Jonathan Bohmann, Larry Schlesinger, Doug Frantz, Pawel Osmulski

Cytokine storm is a part of aberrant immune response during coronavirus infection, sepsis and other life-threatening systemic inflammatory syndromes. Activated pro-inflammatory macrophages secrete excess of cytokines (inflammatory signals) that trigger positive feedback loops driven hyperinflammation and rapid damage of lungs, heart, kidneys and brain. Activation of NFκB transcription factor (nuclear factor kappa B) is central to the storm. Interleukin 6 (IL-6) is a major NFκB dependent cytokine of the storm. NFκB is activated by the major and essential intracellular protease, the proteasome, which is involved in many aspects of immune response. The proteasome is a modular enzyme with many forms and functions, and only some of its forms are required for NFκB activation. Our goal was to suppress NFκB activation and mitigate the cytokine storm by shifting the balance of proteasome forms toward those not efficient in NFκB activation but still effective in supporting intracellular proteostasis and normal, not hyperactive, immune response. We developed two classes of small molecules that shift the equilibrium between proteasome forms toward those with lower capacity to activate NFκB. The small molecules act as specific regulators of dimerization between proteasome modules. The compounds are based on pipecolic ester scaffolds and 7-chloroquinoline scaffolds. The pipecolic ester compounds were rationally designed to fit in specific allosteric pockets on the proteasome surface to affect the dimerization of modules. The specific chloroquinoline compounds were selected from a small library by in vitro screen with the purified human proteasome. Their binding to allosteric pockets on the proteasome was confirmed by molecular docking and biochemical tests. Cell culture and in vitro studies enabled selection of three leads: two chloroquinolines and one pipecolic ester derivative. These three small molecules have good drug-like properties, are non-toxic to human cultured immune cells and non-toxic to mice. Importantly, the three leads significantly suppressed production of IL-6 in a model of cytokine storm: human primary macrophages activated by lipopolysaccharide (LPS). This ongoing collaborative project is now nearing the start of in vivo tests in a mouse model of coronavirus infection and cytokine storm.

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Posterboard #: 6

Presenter: Nanshu Lu, PhD

Institution: UT Austin

Category: Faculty (any rank)

Ultrathin wireless chest e-tattoo for mobile and continuous tracking of stroke volume

Nanshu Lu, Sarnab Bhattacharya, Francesca Santucci

Cardiovascular diseases are the leading cause of death globally. Noninvasive, accurate, and continuous cardiovascular monitoring can enable the early detection of heart diseases and preemptive intervention to prevent serious cardiac complications. However, unobtrusive, ambulatory, and comprehensive cardiac monitoring is still a challenge as conventional electronics are rigid, heavy, or consume too much power for long-term measurement. This poster presents a thin (200 μm), stretchable (20%), lightweight (2.5 g), wireless, and low-power (<3 mW) wearable cardiac monitoring device that conforms to the human chest like a temporary tattoo sticker, correspondingly known as an e-tattoo. This chest e-tattoo features trimodal electro-mechano-optical sensing including electrocardiography (ECG), seismocardiography (SCG) and photoplethysmography (PPG). We develop a filter, averaging, empirical mode decomposition (FAD) signal processing framework to perform motion compensation for SCG under mild human motions. We have also developed a machine learning framework to infer Stroke Volume out of the e-tattoo measurables and derivatives. The LVET and Stroke Volume obtained by the e-tattoo were validated against FDA-cleared patient monitor on fourteen healthy human subjects under various postures and activities. The mechanical imperceptibility and low power consumption of this e-tattoo permit 24-h continuous ambulatory monitoring. This e-tattoo is currently being tested on ICU patients at Texas Children's Hospital and pediatric patients in Cleveland Clinic.

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Posterboard #: 7

Presenter: Neelam Mukherjee, PhD

Institution: UT Health San Antonio

Category: Faculty (any rank)

A Novel Anti-Tumor Axis in Bladder Cancer: CCL2 Induces Tumor Suppression via Recruitment and Activation of CCR2+ T Cells

Neelam Mukherjee, Niannian Ji, Zhen-Ju Shu, and Robert S. Svatek

Background: The tumor microenvironment is where tumors and immune cells interact, with chemokines and their receptors governing immune cell recruitment. While chemokines impact cancer growth in various tumors, their role in bladder cancer (BCa) remains unclear. CCL2 (C-C motif ligand 2), a prominent chemokine, facilitates immune cell trafficking by binding to CCR2. CCL2 has been linked to immunosuppressive monocyte recruitment in other cancers, leading to clinical trials testing anti-CCL2 therapies. Significance: BCa often begins as non-muscle-invasive tumors, offering potential for immunotherapy due to a high mutational load. However, frequent recurrence leads to costly and invasive examinations. Existing therapies, while promising, suffer from low response rates and a lack of response markers due to inadequate recruitment of anti-tumor immune cells. This study uncovers a novel chemokine-mediated immune cell recruitment pathway in BCa, with implications for new immunotherapies, either standalone or in combination with standard treatments. Methods: To explore CCL2 signaling, we used WT and CCL2-deficient mice (CCL2KO) exposed to the carcinogen BBN and challenged WT, CCL2KO, and CCR2KO mice (lacking the CCL2 receptor) with MB49 BCa cells. T cell adoptive transfer and depletion were employed to clarify T cells' role in CCL2's impact on BCa. The effects of intravesical recombinant CCL2 (rCCL2), alone or with gemcitabine, in BCa models were examined. We also assessed the influence of anti-CCL2 on BCa growth and studied the nitration of CCL2 in BCa. Results: Surprisingly, CCL2KO and CCR2KO mice exhibited higher tumor incidence and growth in various BCa mouse models, contradicting expectations. T cell depletion nullified the protective effect, but it was restored with adoptive transfer of CCR2+ T cells into CCR2KO mice, showing enhanced T cell activation and tumor specificity. Anti-CCL2 treatment promoted BCa growth. Intravesical rCCL2, alone or with gemcitabine, reduced bladder tumor growth and enhanced survival in BCa-bearing mice. Bladder tumors were found to induce post-translational nitration of CCL2, inhibiting T cell recruitment, a phenomenon reversed by exogenous rCCL2. Chemical nitration of rCCL2 compromised its therapeutic efficacy, reducing bladder T-cell infiltration and increasing monocyte infiltration in BCa. Conclusions: The protective role of CCL2/CCR2 in BCa contradicts the existing paradigm, while post-translational nitration suppresses the T cell-mediated anti-tumor BCa axis.

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Posterboard #: 8

Presenter: Pawel Osmulski, PhD

Institution: UT Health San Antonio

Category: Faculty (any rank)

Charting cellular adhesion with Multivalent Adhesive Probe AFM (MAPA)

Pawel Osmulski and Maria Gaczynska

Adhesion of cells defined by chemical composition of the interacting cell surfaces is the key factor determining organism development, tissue integrity, immune response, and cancer metastasis. Enormous progress in this field achieved in recent years has been hampered by limited biophysical tools capable to simultaneously measure adhesive properties of live cells, to qualitatively determine chemistry governing cell bonding and to analyze distinct types of adhesion. Atomic force microscopy (AFM) based force spectrometry provides data on viscoelastic properties and limited receptor-targeted surface composition. Here we explored a new technology that delivers adhesion maps and chemical surface composition maps of live cells. Our AFM based technology uniquely detects dispersive adhesion based on van der Waals interactions. Dispersive adhesion is especially relevant for invasive cells devoid of tumor microenvironment and searching for interactions, such as circulating tumor cells (CTCs). We determined that properties of frequency spectra of an AFM probe momentarily engaged in oscillation mode - based van der Waals interactions with an object strongly depend on chemistry of the tested material. We used the frequency spectra to distinguish between distinct synthetic surfaces, cultured cells and also between patient-isolated non-cancerous cells, tumor cells and CTCs. We named the corresponding technology Multivalent Adhesive Probe AFM (MAPA). It enables to extract specific qualitative and quantitative data on dispersive cell adhesion (no cell indentation, no elastic component) from broad-range frequency spectra of chemically modified AFM probes vibrating within the van der Waals distance above the cell surface. First, we determined technical benchmarks to measure adhesiveness using synthetic model surfaces. After optimization of AFM probes, we established procedures for analysis of spectral response of the probes to interactions with substrates and derived spectral signatures specific for single biomaterials. Next, we extended the technology to access adhesion of human cultured cancer cells, control and challenged with circulation-simulating fluid shear stress or induction of epithelial to mesenchymal transition; both conditions known to strongly affect viscoelastic properties but with unexplored effects on dispersive adhesion. Finally, we tested the power of MAPA on CTCs isolated from the blood of lung cancer patients, aiming to classify CTCs with better and distinct sensitivity than our established AFM classifications based on viscoelastic properties. The successful qualitative and quantitative interrogation of cell attractiveness holds the promise not only to better understand fundamental biological processes but also adds the capability to follow disease progression and response to therapies for improved diagnosis and prognosis.

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Posterboard #: 9

Presenter: Dan Smelter, PharmD, PhD

Institution: UT Health San Antonio

Category: Faculty (any rank)

Combination Antimicrobials to Overcome Immunosenescence and S. aureus Infective Endocarditis

Dan F. Smelter, Grace G. Lee, Sunil K. Ahuja, Warren E. Rose,

Infective endocarditis (IE) is a life-threatening systemic disease with significant morbidity and 30-day mortality near 25%. The current age of peak incidence of IE is 70 years of age, and the most common causative organism, which is now Staphylococcus aureus, has known mechanisms for immune evasion. Furthermore, as patients age, immunosenescence impacts their ability to clear infectious pathogens while comorbidities often reduce their capacity to safely undergo surgical intervention as treatment for IE, highlighting the need for improved antibiotic therapy. Following a retrospective analysis of IE and endovascular infections caused by methicillin susceptible S. aureus (MSSA) at a single healthcare center over 10 years (n=90), our data show an age-associated increase in the infection duration (5.2±1.3 days <50 years of age vs. 12.9±4.0 days ≥50 years), as well as a significant age-associated increase in 30d mortality (6.7% mortality for patients <50 years of age vs. 35% mortality for those ≥50 years P=0.0041). Our lab studies combination antibiotics as a method for improving antimicrobial activity and clearance of the infection. Cefazolin plus ertapenem is a unique combination that has recently shown exceptional success in the rapid clearance of persistent MSSA infections. While in vitro synergy of the combination is modest, our data suggests that it may improve clearance in vivo through activation of the immune system, stimulating release of interleukin-1β (IL-1β) from isolated peripheral mononuclear cells. This combination antibiotic strategy warrants further investigation as we seek improved therapeutic approaches and outcomes in the most vulnerable populations.

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Posterboard #: 10

Presenter: Casey Straud, PsyD

Institution: UT Health San Antonio

Category: Faculty (any rank)

Enhancing massed prolonged exposure with cannabidiol to improve posttraumatic stress disorder: A pilot RCT

Straud, C. L., Roache, J. D., Ginsburg, B. C., Baig. M. R., King, V. L., Barron, S., Blount, T. H., Young-McCaughan, S., & Peterson, A. L.

VA/DoD PTSD clinical practice guidelines consistently recommend trauma-focused psychotherapy as a first-line intervention for posttraumatic stress disorder (PTSD) treatment. However, there is still significant room for improving outcomes given that almost 50% of Veterans do not achieve PTSD remission following treatment. Novel medications that can be combined with trauma-focused psychotherapies and target the same mechanisms are of particular interest. Cannabinoids have attracted considerable attention in recent years based on their purported ability to treat a myriad of physical and psychiatric conditions. Among available cannabinoids, cannabidiol (CBD) has demonstrated the greatest promise. There is strong rationale that CBD may offer some of the benefits of cannabis without the negative and intoxicating effects of marijuana. Specifically, CBD has been reported to decrease anxiety and facilitate extinction learning which are two primary components thought to be important in trauma-focused psychotherapies. This poster will present findings from the first ever randomized controlled trial combining CBD with a trauma-focused psychotherapy, prolonged exposure (PE). The primary aims of the study were to explore the feasibility, safety, and potential benefits of this integrated intervention. Participants (N=23) were randomized to 250mg B.I.D. CBD or placebo and all received 10 daily sessions of PE over 2 weeks. Assessments were completed at baseline, weekly during treatment, and at 1-month posttreatment. Results demonstrated there was a 5.8 point mean change score difference in PTSD severity between conditions on the PTSD Checklist (PCL-5) in favor of CBD. As is common in pilot studies, this effect was not statistically significant ($p>.05$), but reflected a small effect size difference ($d=0.17$). Both conditions had large within group reductions on the PCL-5 following treatment well beyond the 10 point change commonly reflective of clinically significant improvement on this measure. CBD reductions (30.5 points, $p=.002$, $d=0.90$) were somewhat larger than those seen in the placebo group (24.7 points, $p=.009$, $d=0.69$). Most participants (87.5%). regardless of randomization, no longer met criteria for PTSD on the CAPS-5 at the 1-month follow-up assessment. Overall, findings show a signal of support for the hypothesis that the CBD benefits of CBD would be to augment extinction learning that occurs during and after trauma-focused psychotherapy. Full results will be presented during the poster session. Findings from this study suggest a larger RCT is warranted to formally test the efficacy of CBD combined with trauma-focused psychotherapy for PTSD.

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Posterboard #: 11

Presenter: Neelanjan Vishnu, PhD

Institution: UT Health San Antonio

Category: Faculty (any rank)

Mitochondrial Magnesium Channel Mrs2: Mechanisms to Therapeutics in Sepsis

Neelanjan Vishnu, Manigandan Venkatesan, Madesh Muniswamy

Sepsis instigates a complex cascade of cellular disruptions, profoundly affecting mitochondrial function through the dysregulation of intracellular magnesium (Mg2+), an essential cofactor in energy metabolism and cellular viability. The imbalance of mitochondrial Mg2+, orchestrated by the Mrs2 channel, plays a critical role in this phenomenon, facilitating the Mg2+ influx necessary for maintaining mitochondrial integrity and supporting bioenergetic processes. Our investigation explores the intricate Mg2+ dynamics within mitochondria amid sepsis, with a particular focus on the impact of elevated lactate levels, a signature of sepsis-induced metabolic distress. Our findings reveal that lactate prompts a significant depletion of Mg2+ in the endoplasmic reticulum (ER), necessitating an increased mitochondrial Mg2+ uptake via the Mrs2 channel. This sequence of events leads to a significant bioenergetic impairment, characterized by diminished ATP production and escalated oxidative stress, undermining cellular and mitochondrial function. We closely examine how specific glycolytic byproducts, namely Glycerol-3-phosphate (G3P), Phosphoenolpyruvate (PEP), and Dihydroxyacetone phosphate (DHAP), which also deplete ER Mg2+ levels affect Mrs2 channel activity, revealing a complex regulatory mechanism of mitochondrial Mg2+ management during sepsis. Employing both pharmacological and genetic methodologies, our study delineates how the Mrs2 channel governs Mg2+ flow and its consequential effects on mitochondrial energy metabolism under septic conditions. This involves thorough analyses of cellular metabolites and advanced live-cell imaging techniques to capture the subtle Mg2+ dynamics and their implications on cellular energetics during sepsis. Our research indicates that a long-term Western diet alters liver metabolism in mice, leading to an increase in glycolysis and a corresponding decline in TCA cycle intermediates, mirroring the metabolic reprogramming observed in macrophages after (Lipopolysaccharide) LPS exposure. This metabolic alteration towards a glycolysis-dominant profile under septic conditions is further exacerbated by a Western diet, emphasizing the interplay between nutrition, metabolic stress, and mitochondrial functionality in sepsis. The dietary impact on sepsis outcomes highlights the potential of nutritional strategies as adjunctive interventions in sepsis management, suggesting that dietary modifications could ameliorate mitochondrial Mg2+ dysregulation and improve mitochondrial resilience. In summary, our study underscores the crucial function of the Mrs2 channel in regulating mitochondrial Mg2+ homeostasis during sepsis, offering insights into the molecular and cellular mechanisms of Mg2+ dysregulation. These insights identify potential therapeutic interventions targeting the Mrs2 channel to alleviate mitochondrial dysfunction in sepsis, contributing to the development of innovative treatments. This research advances our understanding of the complex interrelations between mitochondrial Mg2+ dynamics, energy metabolism, and the pathophysiology of sepsis, laying the groundwork for novel therapeutic approaches to this formidable condition.

Posterboard #: 12

Presenter: Enya Vroom, PhD, MS

Institution: UT Health San Antonio

Category: Faculty (any rank)

Patient and Provider Demand for and Readiness to Adopt Medications for Stimulant Use Disorders in Real-World Settings: Pre-Planning toward Accelerated Implementation

Enya B. Vroom, Erin P. Finley, Tara E. Karns-Wright, Carma Deem Bolton, & Jennifer Sharpe Potter

Aims: Although stimulant use disorders are on the rise in the US, fewer than one-third of adults with methamphetamine use disorder receive treatment and no medications are FDA-approved for treatment. Recent research has shown efficacy of a medication-assisted treatment (MAT) for stimulant use disorder, but little is known regarding patient and provider demand for or readiness to adopt such treatments. This study examined patient and provider perspectives on injectable naltrexone and oral bupropion as treatment for stimulant use disorders in real-world practice settings. Methods: Virtual, semi-structured interviews were conducted with patients with a history of substance use disorder (SUD) treatment (n=20) and prescribing providers and other care team professionals (e.g., social workers) delivering care for patients with SUD (n=20). Participants were recruited from NIDA Clinical Trials Network sites. Interviews elicited perceptions of treatment demand, barriers and facilitators to adopting MAT for stimulant use disorders, and recommendations to support future implementation. Interviews were transcribed and rapid qualitative analysis was used to distill and compare findings within and across patient and provider samples. Results: Preliminary results suggest patient barriers such as access to transportation, insurance coverage, and stigma from family and community related to MAT may pose significant challenges to successful adoption and implementation. Additionally, participants discussed that naltrexone injections may be triggering for patients who inject drugs, and noted education and outreach to families and communities will be important to increase understanding of MAT and stimulant use disorders. Conclusions: Examining patient and provider perceptions of MAT for stimulant use disorders provides a better understanding of the level of demand and readiness for adoption of such treatments. This information, rooted in the lived experiences of patients and providers, provides a foundation for the selection of tailored implementation strategies that will assist in accelerating adoption of medications to treat stimulant use disorders in future scale-up and spread.

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Posterboard #: 13

Presenter: Cynthia Estrada Zuniga, MD, PhD

Institution: UT Health San Antonio

Category: Other Research Scientist

Validation of an organoid model to effect precision medicine in pheochromocytoma and paraganglioma

Cynthia M Estrada-Zuniga1, Hector Gonzalez-Cantu1, Maite Calucho2,3, Bethany Landry1, ZiMing Cheng1, Huyen Thi-Lam Nguyen2, Ahmad Al Shihabi2, Qianjin Guo1, Paul Boutros4, Nicole Bechmann5, Graeme Eisenhofer5, Yanli Ding6, Patricia L.M. Dahia1,7, and Al*

Background Pheochromocytomas and paragangliomas are uncommon, slow-growing neural crest-derived tumors that secrete catecholamines and display considerable genetic, clinical, biochemical, and morphological diversity, with frequent disruption of hypoxia pathways. Approximately 60% of PPGLs have an identifiable genetic driver, many of which can be part of clinically complex hereditary syndromes. The surgical removal of tumors is the most effective treatment for PPGLs. However, in some instances, such as metastatic, recurrent, or inoperable PPGLs, other forms of treatment must be employed, and few options are currently available. It becomes essential to have a study model available that is amenable to drug screening. Here we describe a patient-derived PPGLs organoid model. By studying the histologic, biochemical, functional, and molecular characterization, we show that this model resembles the primary tumors and lends itself to high-throughput drug screening. Methods Twenty-two samples of PPGLs were successfully included in the protocol, generating organoids from fresh and/or frozen tissue that uses few cells with no need for expansion. The samples were derived from patients aged 15-83 years carrying SDHB, CSDE1, NF1, VHL, EPAS1, RET, MAML3 mutations or unknown driver event. Organoids were characterized using the following strategies: 1) histology/immunohistochemistry, 2) catecholamine secretion (by LC-MS/MS), 3) sequencing (bulk or single cell RNAseq, 4) drug screening, and 5) growth rate estimation quantified using a machine learning-based pipeline. Results PPGL organoids were cultured both short-term (6 days) and long-term (4 weeks), both under normoxia and 1% hypoxia. Several viable cell types were identified by H&E staining. ChGA and TH neural crest markers staining confirmed the neural crest origin of the organoids both at early and late cultures, S100 and CD34 indicated the presence of sustentacular and endothelial (vascular) cells, respectively. In addition, nuclear positivity of the stem cell marker OCT4 suggested that precursor cells might be detectable. We confirmed that the catecholamines secreted by the organoids matched the pattern of the primary tumor both in short and long cultures (3/3). Sensitivity profiles of 35 drugs (alone or in combination) pinpoint tumor-specific responses. Growth rate and sequencing data analyses are ongoing. Conclusions We successfully established PPGL organoids that closely mimic the heterogeneity of the original tumor. These models will provide the ability to investigate tumor initiation and progression and may reveal novel patterns of drug sensitivity and resistance, which could pave the way for the establishment of precision medicine in inoperable/advanced PPGLs. Significance PPGLs organoid model could pave the way for the establishment of precision medicine in inoperable/advanced PPGLs.

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Posterboard #: 14

Presenter: Ariel Gomez, MPH

Institution: UT Health San Antonio

Category: Other Staff/Adjunct Faculty (Associate Professor)

Using Mixed Methods and Community Based Participatory Research to Understand and Address Prediabetes in South Texas: A CHW TAB Project

Ariel Gomez, MPH; Ludivina Hernández, CHW-I; Belinda Flores, RN, BS, CHW-I; Raquel Romero, MD, MPH, CDCES, CHW-I; Juana Escareño, BS, CHWI; Paula Winkler, M.Ed., CHW-C; Elisabeth de la Rosa, MS, CHW; Virginia Lopez, CHW; Olivia Morris, MPH; Kathryn Kanzl

Methods: This is a Community Based Participatory Research (CBPR) project using an explanatory sequential mixed-methods design. CHW TAB members collected data and participated in all aspects of the project (e.g., study design, survey development, focus group facilitation, etc.). Phase 1 (Quantitative study) procedures included gathering data via a 9-item survey in English and Spanish administered by each participating CHW in 2022 at community events (n=106). Phase 2 (Qualitative study) involved gathering in-depth data about pre-diabetes management, including challenges and opportunities, which will inform CHW-led intervention development. Three English and one Spanish focus groups were conducted with participants from 6 counties (n=65). Results/Anticipated Results: Most survey participants identified as Hispanic, and half were diagnosed with pre-diabetes. 87.8% reported that prediabetes is a problem in their community. Preliminary focus group findings indicate that knowledge and support for managing prediabetes is missing in South Texas. Many participants report feeling "doomed" to develop type 2 diabetes but were eager to share their experiences. Additionally, participants report that family and culture play a large part in their ability to eat healthier foods. Rapid analysis of qualitative data, conducted by TAB members, is underway, which will be followed by data synthesis. Discussion: This CBPR study will illuminate knowledge gaps, strengths, and areas for promoting and empowering better health behaviors among South Texans with pre-diabetes. Data will inform the next study phase, development of a CHW-led educational intervention through our TAB.

IIMS INSTITUTE FOR INTEGRATION OF MEDICINE AND SCIENCE

14TH ANNUAL FRONTIERS OF TRANSLATIONAL SCIENCE RESEARCH DAY

Posterboard #: 15

Presenter: Syeda Munawar

Institution: UT Health San Antonio

Category: Other Staff

Exploring the Role of TMEM127, a regulator in tumor evasion , in macrophages

Syeda Y. Munawar, Viviane Nascimento da Conceicao, Jonathan D. Lefkowitz, Patricia L.M. Dahia

The tumor suppressor TMEM127 has emerged as a pivotal regulator of insulin dynamics, exhibiting tissue-specific effects. Previous investigations have demonstrated that mice lacking TMEM127 display a lean phenotype, are shielded against fatty liver disease, and maintain insulin sensitivity, implicating TMEM127 in metabolic pathways intertwined with immune response modulation. Leveraging single nuclei RNA sequencing (RNAseq) data, we observed elevated TMEM127 expression in macrophages and T cells compared to other cells, underscoring its potential significance in immune cell function. To unravel the intricate interplay between TMEM127 and macrophage polarization pathways-namely M1 and M2-we embarked on a comprehensive exploration. By subjecting raw mouse macrophage cells to lipopolysaccharide (LPS) induction, we aimed to induce MHC Class 1 pathway polarization and delve deeper into the nuances of the MHC Class 2 pathway, particularly in monocytes, with a focus on macrophages. Our preliminary findings unveiled a robust upregulation of TMEM127 expression at both the protein and RNA levels following LPS induction across all experimental setups. Remarkably, LPS treatment precipitated the activation of inflammatory markers within the MHC Class 1 pathway in both wild-type and knockout cells, with knockouts exhibiting heightened expression of PSTAT3 at the protein level. Conversely, other markers displayed comparable increases in expression across the groups. At the RNA level, our data showcased a notable elevation in iNOS expression in wild-type cells relative to knockouts. Collectively, our results point towards a proinflammatory response induced by LPS in M1 phenotype macrophages, shedding light on the intricate regulatory role of TMEM127 in orchestrating immune cell dynamics. This multifaceted exploration holds promise for delineating novel therapeutic targets and advancing our understanding of immune-metabolic exchange.

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Posterboard #: 16

Presenter: Shreya Prasanna, MSc

Institution: UT Health San Antonio

Category: Other Staff

Factors impacting readiness for implementation of an electronic shared decision-making tool for knee osteoarthritis: A tale of two orthopedic surgery clinics

Shreya Prasanna, BPTh, MSc, Joel Tsevat, MD, MPH, Raquel Romero, MD, MPH, CDE, Dr. Prakash Jayakumar, M.D., Ph.D., Lauren Uhler, MPH, Sarah Lill, MA, Julian Brunner, PhD and Erin Finley, PhD, MPH

Background: Shared decision-making (SDM) is central to patient-centered care in preference-sensitive conditions such as knee osteoarthritis. Joint Insights (JI) is an artificial intelligence (AI)-based tool for SDM that uses patient-reported outcomes and clinical data to predict likelihood of clinical improvement following total knee arthroplasty. This in-depth case study examined factors impacting implementation of JI in two academic orthopedic surgery clinical settings featuring different patient populations, electronic health records (EHR), and models of care (traditional care vs. 360-degree holistic value-based care). Methods: We conducted six periodic reflections (lightly guided qualitative discussions) at multiple timepoints with implementation teams at each site. Discussions centered on implementation activities, challenges encountered, and solutions identified by the two teams. Reflections were recorded and transcribed; qualitative data were examined using matrix analysis informed by the sociotechnical model for health information technology. We identified key challenges and solutions for JI integration across each domain of the sociotechnical model (e.g., human-computer interface). Institutional ethics approval was obtained. Findings: JI integration was impacted by common challenges encountered at both sites: the proprietary nature of JI and the two EHRs; difficulty in automating data extraction from the EHRs; competing information technology (IT) demands, including the COVID-19 pandemic; policy regulations around data transfer and storage; difficulty aligning with clinic workflow; and staff turnover in EHR and IT departments. At the traditional care site, additional barriers included slow buy-in from the clinical staff and infrastructure challenges (e.g., wi-fi connectivity). The value-based care site lacked clarity on costs and funding sources for the technical integration. Potential solutions included hiring a centralized system navigator at each site for IT implementation and, tailoring the JI interface to improve workflow compatibility. Implications: Complex challenges are likely to emerge when integrating AI and EHR-based tools into busy clinical practices. In this case study, challenges involved institutional IT department constraints, workflow revamping, data use agreements, and other barriers. Already important individually, dynamic interaction among these challenges can significantly impact readiness for technology adoption and implementation. Studying integration of AI tools can inform assessment of system capacity, identify potential pitfalls, and improve planning for locally tailored solutions in IT implementation.

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Posterboard #: 17

Presenter: Derek Rodriguez, PhD

Institution: University of Texas at San Antonio

Category: Other Research Scientist

Therapeutic delivery of soluble fractalkine ameliorates vascular dysfunction in the diabetic retina

Derek Rodriguez, Kaira A. Church, Chelsea T. Smith, Difernando Vanegas, Sandra M. Cardona, Isabel A. Muzzio, Kevin R. Nash, Astrid E. Cardona

Diabetic retinopathy (DR), a serious complication of chronic hyperglycemia leading to vision loss, is characterized by neurodegeneration, vascular damage, and glial activation. Inflammation caused by activated resident macrophages (microglia) exacerbates retinal damage by releasing pro-inflammatory cytokines that increase vascular permeability. The microglial receptor, CX3CR1, binds to fractalkine (FKN), a protein expressed on neuronal membranes (mFKN), that undergoes constitutive cleavage to release a soluble domain (sFKN)that inhibits microglia neurotoxic potential. Murine CX3CR1-or FKN-deficiency enhanced microglial activation, vascular and neuronal damage in experimental DR. This project will test the hypothesis that overexpression of sFKN via recombinant adeno-associated viral vectors (rAAV-sFKN) will prevent vascular damage, reduce astrogliosis, and maintain the integrity of the blood-retinal barrier(BRB). rAAVs expressing mFKN or sFKN will be delivered to intact retinas during diabetes. Endothelial cells (CD31), astrocytes (GFAP), tight junction (ZO-1), and gap junction(Cx43) proteins will be analyzed. Vascular integrity will be monitored by assessing the extravasation of the blood protein fibrinogen into retinal tissues. This project aims to characterize vascular health by focusing on vascular integrity mediated by mFKN and sFKN.Using immunofluorescence, high-resolution confocal imaging,behavioral assay, and flow cytometry our results show that sFKN minimizes microglia activation, fibrinogen extravasation, astrogliosis, and abnormal blood vessel morphology.sFKN, but not mFKN significantly reduces diabetes-associated vision loss using a two-choice discrimination take to assess visual acuity. rAAV treatment does not alter peripheral immune responses in blood but shift microglia to their homeostatic profile in the central nervous system.These results highlight sFKN as a potential therapeutic intervention to ameliorate vascular dysfunction and BRB integrity in DR,providing insight for developing novel treatment strategies and preventing vision loss.

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Posterboard #: 18

Presenter: Ariana Samaniego

Institution: UT Health San Antonio

Category: Other Staff/Post baccalaureate

Impact of maternal high-fat diet on female offspring lifespan and susceptibility to breast cancer in murine model

Ariana Samaniego BSA, David Schmerber BA, Sureshkumar Mulampura Achuthan Pullai PhD, Meera Rath, PhD, Egle Bytautiene Prewit, MD, PhD

Introduction: Obesity has been linked to adverse long-term health consequences and could shorten an individual's lifespan. Research studies have shown that women with obesity have higher estrogen levels, increasing their risk of breast cancer. This study seeks to determine if offspring born to obese mice have an increased risk of developing breast cancer and experiencing shorter lifespans than those born to non-obese mice. Methods: Pups born to dams fed a standard fat (SF) or high fat (HF) diet for three months before pregnancy, during pregnancy, and lactation were weaned at 21 days old and placed on an SF diet. The female pups were kept. At five weeks of age, blood samples from all pups were collected via tail snip. At six weeks, all, except one, females per dam received 10 mg 7,12-dimethylbenz[a]anthracene (DMBA) in peanut oil by oral gavage. One female per litter received peanut oil only and served as the control. DMBA or peanut oil was administered weekly for four weeks until the mice were nine weeks old. From 12 weeks of age, every week, mice were weighed, mammary glands were palpated for abnormal growth, and blood samples were collected. Blood samples are continued to be collected every two months until natural death or tumors become 10% of body weight. Currently, we have longitudinal data for every mouse up to 36 weeks of age. Klotho concentrations were measured using blood serum samples collected at 25 weeks of age. Analysis was performed using appropriate statistical methods. P of less than 0.05 was considered statistically significant. Results: The average body weights were not significantly different between SF and HF female pups administered DMBA (P=0.53) or peanut oil (P=0.41). Repeated Measures analysis revealed statistically significant differences by treatment (P=0.008) and by age (P<0.0001) among the four groups. Klotho concentrations were not significantly different between SF and HF mice given DMBA (P=0.56) at 25 weeks of age. Three SF+DMBA, four HF+DMBA, and two SF+peanut oil mice died by week 32 of age. By the age of 27 weeks, no tumors were found in the SF mice, while five of the HF+DMBA mice had a combined total of 9 tumors in mammary glands, uterus, and ovaries. Conclusion: Maternal obesity and DMBA administration negatively affected female offspring weight. Aging marker - Klotho - concentration levels were similar at 25 weeks between SF and HF mice receiving DMBA or peanut oil. Analysis at older age is needed to assess potential impacts on offspring lifespan. The presence of tumors only in HF mice during tissue collection suggests that maternal obesity increases female offspring's susceptibility to breast and gynecological cancers.

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Posterboard #: 19

Presenter: David Schmerber, BA

Institution: UT Health San Antonio

Category: Other Staff/Research Associate

Does Lactation Reduce the Risk of Maternal Cardiovascular Disease in the Presence of Pre-pregnancy Obesity - Investigations in Mouse Model

David Schmerber, Ariana Samaniego, Meera Rath, Kaitlin D. Kersh, Ashlie-Chellsie Aminkeng, Egle Bytautiene Prewit

Introduction: The prevalence of obesity-a major cardiovascular risk factor-in pregnancy continues to rise in the US and other Western countries. Epidemiological data indicates that lactation is associated with lowering the risk of maternal cardiovascular disease (CVD). Thus, we sought to determine the effect of pregnancy followed by lactation on maternal weight and blood pressure (BP) in the early postnatal period in the model of pre-pregnancy obesity. Method: Blood pressure was measured via tail cuff in 5-6-week-old CD-1 female mice. And mice were weighed. Then, mice were randomly allocated to either a high-fat (HF) diet (60% kcal fat) or a standard-fat (SF) diet (5% kcal fat). After three months of allocated diets, BP and weight were determined again, and then mice were bred. After delivery, within 24 hours, pups were removed from a group of HF mice, so they did not lactate (HFNL). The pups from the rest of the HF (HFL) and SF (SFL) dams were weaned at 21 days of age, so these mice breastfed their litters. BP was measured at one month post-delivery. Weight and BP results were analyzed using appropriate statistical methods (statistical significance $P<.05$). Results: After three months on a diet, HF mice weighed significantly more than SF animals ($P=0.0005$). At one month post-delivery, the weight in SFL was significantly lower than in HFL ($P=0.0196$) and HFNL ($P=0.0004$). And the HFL mice weight was significantly less than in HFNL animals ($P=0.014$). There were no statistically significant differences in systolic BP between SF and HF groups after three months on the diets. One month after delivery, systolic BP was lowest in the SFL group and highest in HFNL mice, while systolic in HFL was comparable to SFL animals. Results were not statistically different because of the small number of animals per group. DBP results followed the systolic BP pattern but with no statistically significant differences. Conclusion: In a murine model of pregnancy obesity, results point to the beneficial effect of pregnancy with lactation on maternal weight in the early postnatal period. Further investigations are needed to dissect the effects of pregnancy and lactation on maternal cardiovascular health in the presence of pre-pregnancy obesity.

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Posterboard #: 20

Presenter: Josephine Schultz

Institution: UT Health San Antonio

Category: Other High School Visiting Student

Can Light Pollution Color Impact Melatonin in Mallows or Metamorphosis?

Josephine Schultz

Artificial light at night (ALAN) can disrupt wildlife seasonal phenology. Many animals produce melatonin, a hormone regulating circadian rhythms, in the dark. ALAN, especially from cool white lights rich in blue wavelengths (400-500 nm) can inhibit melatonin synthesis. In Lepidoptera melatonin modulates diapause, molting, and adult emergence, so deficiency may cause these important events to be mistimed. In plants it is unclear if melatonin production requires darkness or gives circadian feedback. In this study ALAN color effects on melatonin levels were examined in painted lady butterflies and their host plant mallow. The hypothesis was: ALAN from white or blue lights will reduce melatonin in chrysalises and mallows more than no ALAN, or reddish-orange (750 - 600 nm) lights. Mallows (16 each) or caterpillars (40 each) were exposed to ALAN from either white, blue or reddish-orange lights or no ALAN for four nights or until chrysalises formed. Leaves and hemolymph were collected 4 hours after dark onset and were shielded from light and frozen until melatonin measurement. Melatonin in leaf (500 mg) extracts was variable, averaging 0.76 ng/ml, with no group differences. In hemolymph there was more melatonin ($p < 0.01$) in orange (mean ± S.E.M. = 0.64 ± 0.12 ng/ml) versus blue (0.15 ± 0.04 ng/ml) or white (0.23 ± 0.08 ng/ml) groups. Melatonin in chrysalises was therefore reduced by white and blue ALAN. This may be why butterflies exposed to white ALAN emerged earlier than unexposed ones.

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Posterboard #: 21

Presenter: Morgan Smith, M.S.

Institution: UT Health San Antonio

Category: Other Research Assistant-Senior

Python-Based Machine Learning for Three-Dimensional Human Brain Model Segmentation and Analysis

Morgan Smith, MS, Elizabeth Ochoa, PhD, Mallory Keating, HT (ASCP), Margaret E. Flanagan, MD, and Kevin F. Bieniek, PhD

Background: Pathology and cell loss in neurodegenerative diseases results in brain atrophy of specific neuroanatomical structures, and is often characterized by subjective, qualitative severity measures. Three-dimensional (3D) imaging and modeling technologies now permit visualization and quantitative analysis approaches, including model mesh segmentation. One such platform for this approach is Python, a coding software containing libraries that facilitates the manipulation, visualization, and analysis of various data forms. We aim to apply these techniques to assess patterns of neurodegeneration in 3D brain surface models. Methods: 3D scanned brain .obj files were imported into Python. These file types function as 3D meshes and can be visualized using Python coding segments (various modules), Blender, and several other software applications. The .obj files of 3D brain models were simplified using Python software mesh decimation. This decimation reduced the number of faces, edges, and vertices and allowed for the manual segmentation of 3D models in Blender. We used the volume, area, number of vertices, edges, and faces to segment the 3D models based on readily identifiable cortical gyri and sulci. Next, we focused on automating segmentation of large, well-defined structures, namely the cerebellum and cerebrum. Segmentation was performed using vertices and texture mapping for comparative analysis. Using the manual mesh segmentation data from these 3D models, Python software machine learning techniques were applied to automate the mesh segmentation of various brain regions based on a healthy brain structure. Such techniques were preprocessing mechanisms to balance the exported data set and several verification methods to ensure testing accuracy. Results: Using these techniques, we assessed tissue structural and tinctorial properties of the human postmortem autopsied brain to segment 3D models based on neuroanatomical location. We have developed and piloted machine learning techniques within the Blender application, which can be utilized to accurately identify anatomically correct structures of the brain. We have also adapted and applied several machine learning mechanisms to process, train, and test our data in automated segmentation. Conclusions: Our findings provide support for the utilization of machine learning techniques to identify specific areas of the brain using 3D brain models. Additional research, validating against other imaging modalities including magnetic resonance imaging, is necessary to confirm the consistency surface mesh segmentation (both manual and automated) to other brain atrophy metrics. We believe these tools have broad applicability in practice (including guided tissue sectioning), research and education. Funding Disclosure: This work is supported by funding from the National Institute on Aging (P30-AG066546; R01-AG070214), Texas Alzheimer's Research & Care Consortium, Zachry Endowment for Alzheimer Research, Reed Precision Medicine Center, and the J.M.R. Barker Foundation.

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Posterboard #: 22

Presenter: Benjamin Turbow, N/A

Institution: Trinity University

Category: Other Research Assistant

Immune dynamics of SIV infection in CD8+ cell depleted baboons

Benjamin Turbow, Veronica Obregon-Perko, Amanda Mannino, Vida Hodara, Laura Parodi, Emma Mask, Jessica Callery, and Luis D. Giavedoni

When infected with simian immunodeficiency virus (SIV), baboons share many characteristics with human elite controllers of HIV, including therapy-free control of virus levels, the maintenance of CD4 counts, lack of AIDS progression, regulation of immune activation, and the elicitation of an immune response. The mechanisms by which baboons are capable of elite control of SIV are still unclear, however, our group has shown baboon CD8+ cells dampen infection in baboon CD4 T-cells ex vivo through aspects of innate immunity. To investigate the in vivo role of CD8+ cells, we used specific depleting antibodies to remove circulating CD8□+ cells from a group of baboons (Cohort 1, C1), while treating a control group (Cohort 2, C2) with an irrelevant antibody. Both cohorts were then infected with SIVmac and observed that C1 baboons had viral loads similar to rhesus macaques infected with the same virus. Algorithmic analysis was performed on PBMCs and lymph node (LN) from the two cohorts to identify the dynamics in immune cell population across the course of infection. While CD8 T-cells did recover in C1, they were primarily CD8 memory cells as opposed to CD8 naïve T cells in both the periphery and LN. NK cells, also targeted by CD8 depletion, recovered to their baseline levels. To examine differences in gene expression between C1 and C2, scRNAseq was performed on cells taken from C1 and C2 at peak infection. Reference mapping was used to identify populations of cells based on their expression profiles. SIV transcripts were enriched in C1's CD4 T-cells, especially the T regulatory cells . Transcripts for cytokine receptors and ligands like RANTES, IL2RA, and CXCR3 were enriched in C1's CD4 T-cells compared to C2's, corresponding to a state of immune activation that is not present in C2. Considered alongside previous evidence of CD8 T-cell dependent viral control with no prior exposure to SIV, our findings reveal a model where control of SIV in baboons is regulated not by naïve CD8 T-cells but rather by CD8 T-cells with a memory phenotype that are capable of responding to stimuli from antigenically unrelated pathogens, preventing the expansion of activated cell types in the periphery that would augment viral infection. As such, baboons hold great promise as a model for investigating innate mechanisms of HIV control.

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Posterboard #: 23

Presenter: Omar Villanueva, MS

Institution: UT Health San Antonio

Category: Other Staff/Research Assistant

Demarcated, hypomineralized enamel opacities depend on overexpressed ameloblastin

Omar Villanueva, Yong-Hee Patricia Chun, Chunyan Tan , Madeline E Colley , Stephan BH Bach , Roberto J Fajardo , Cong-Dat Pham

Demarcated enamel opacities are developmental defects linked to molar-incisor hypomineralization (MIH) with a robust prevalence in children. Etiologic factors include environmental and epigenetic factors, however, the pathophysiology is not clear. Understanding of the pathways is complicated as ameloblasts undergo apoptosis and are lost during tooth eruption. The retention of enamel proteins has been implicated in MIH. The goal of the study was to analyze enamel in the presence of the overexpression of the enamel protein ameloblastin (Ambn) in mice.: Transgenic Ambn was overexpressed in mice from the amelogenin promoter encoding full-length Ambn. Ambn was overexpressed in separate mouse lines at four increasing concentrations and analyzed by Western Blot, mCT, histology and immunostaining. Mice overexpressing Ambn displayed opaque enamel at low concentration and demarcated lesions at high concentrations of reduced mineral content. At low Ambn concentration, enamel opacities started close to the dentino-enamel junction (DEJ) in the inner enamel and contained 17-kDa Ambn cleavage products. At high Ambn concentration, opacities were demarcated and Ambn species of 17 kDa and higher were found. Ameloblasts demonstrated prolonged secretory and transition stages, thin basement membrane and shortened maturation stages. When opacities expanded to the enamel surface adjacent ameloblasts were detached and formed cysts within the enamel organ. Conclusions: The overexpression of Ambn in murine secretory ameloblasts results in enamel hypomineralization with opaque or sharply demarcated boundaries, phenotypically similar to MIH.

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Posterboard #: 24

Presenter: Paulina Ramirez, MD

Institution: UT Health San Antonio

Category: Clinical Fellow/Resident

Targeting LIPA as a Therapeutic Strategy in Type I and II Endometrial Cancer via induction of Endoplasmic Reticulum Stress

Paulina Ramirez, Suryavathi Viswanadhapalli, Xue Yang, JungMo Ahn, Ganesh Raj, Philip Valente, Edward Kost, Ratna K. Vadlamudi

Among women, endometrial cancer (EC) is the fourth most prevalent type of cancer. Endometrioid EC (type I) accounts for about 80% of EC, whereas the remaining 20% is made up of serous EC (types S and II), clear cell EC (type I), mixed EC, and uterine carcinosarcoma (type I) (type I). A specialized organelle known as the endoplasmic reticulum (ER) plays a key role in protein folding and maturation as well as other cellular processes. Due to their rapid development, EC cells demonstrate severe ER stress (ERS) and have a persistent, increased need for de novo protein synthesis. We reasoned that the enhanced basal level of ERS in EC represents a critical vulnerability and drugs that further aggravate this already engaged system can exhaust its protective features and cause apoptosis. Since enhanced basal ERS is frequently detected in all molecular subtypes of EC, such an approach will have broad therapeutic efficacy and overcome tumor heterogeneity. My mentor lab recently identified a compound, ERX-315, that potently (IC50~50nM) induces ERS and apoptosis in EC cells. Molecular studies identified lysosomal acid lipase A (LIPA) protein as the critical target of ERX-315. The objective of this proposal is to test the efficacy of ERX-315 in treating EC. Our overarching hypothesis is that the binding of ERX-315 to LIPA enhances ERS and induces apoptosis and targets a critical vulnerability (the high basal ERS) in EC. In Aim 1, we will Establish the therapeutic significance of the LIF/LIFR axis in vitro using ERX-315 and multiple EC cells. In Aim2, we will define the mechanism of ERX-315 in treating EC using biochemical and genomic approaches. In Aim 3, we establish the translatability of ERX-315 in treating EC using patient derived organoids and xenograft models. The proposed studies are clinically significant as they will establish the therapeutic utility of targeting ERS in EC using ERX-315 and thus pave way for developing new therapeutic strategies for EC treatment.

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Posterboard #: 25

Presenter: Iriscilla ayala, PhD

Institution: UT Health San Antonio

Category: Postdoctoral Fellow

The Transcriptional Function of TCF7L2 is Spatially Restricted in Liver and Regulates Zonated Metabolic Pathways Which Contribute to Liver Disease

Iriscilla Ayala, Skanda Hebbale, Chris Shannon, Ivan Valdez, Marcel Fourcaudot, Terry Bakewell, Sami Heikkinen, Luke Norton

Single nucleotide polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with Type 2 Diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD). The metabolic function of TCF7L2 in the liver remains to be fully elucidated, but we hypothesized that TCF7L2 contributes to NAFLD through the regulation of zonal metabolic pathways. Using single nuclei RNA sequencing, we examined Tcf7l2 expression in periportal (PP) hepatocytes around the portal triad and pericentral (PC) hepatocytes surrounding the central vein of the liver. To visualize TCF7L2 transcriptional activity we used a TCF reporter mice, which expresses an H2B-eGFP fusion protein downstream of the conserved TCF DNA binding site. We disrupted Tcf7l2 transcriptional activity in mouse liver by breeding mice with a floxed Tcf7l2 exon 11, which encodes part of the DNA binding domain (DBD), to albumin-Cre mice (Hep-TCF7L2ΔDBD). Eight-week-old mice were fed a choline-deficient amino acid-defined high fat (CDAHFD) diet for 8 weeks. In liver samples harvested from these mice, we examined disruption to several key zonated metabolic pathways, and quantified the development of fibrosis. Single nuclei analysis revealed that Tcf7l2 mRNA was expressed primarily in parenchymal cells of the liver but was ubiquitous across the liver lobule. However, in immunofluorescence analysis of TCF reporter mice, the transcriptional activity of TCF7L2 was highly restricted to PC hepatocytes. Classic PC hepatocyte markers, including glutamine synthetase (Glul), were absent in Hep-TCF7L2ΔDBD mice. Following the CDAHFD, Hep-TCF7L2ΔDBD mice developed more severe fibrosis in histological analysis, and expressed elevated levels of genes involved in fibrogenesis, collagen synthesis and TGFβ signaling. Hep-TCF7L2ΔDBD mice also displayed hepatic cholesterol accumulation following the CDAHFD, which was likely the result of impaired pericentral bile acid synthesis. Our results suggest that TCF7L2 plays an important role in the regulation of zonated metabolic pathways, which may contribute to the development of fibrosis. Ongoing analyses are exploring the mechanisms regulating the zonal transcriptional activity of TCF7L2.

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Posterboard #: 26

Presenter: Cody Black, PharmD, PhD

Institution: UT Health San Antonio

Category: Postdoctoral Fellow

Diverse Role of Porins and blaCTX-M in Mediating Ertapenem Resistance Among Carbapenem Resistant Enterobacterales

Cody A. Black, Raymond Benavides, Sarah M. Bandy, Steven S. Dallas, Gerard Gawrys, Wonhee So, Alvaro G. Moreira, Samantha Aguilar, Kevin Quidilla, Dan F. Smelter, Kelly R. Reveles, Christopher R. Frei, Jim M. Koeller, Grace C. Lee

Among carbapenem-resistant Enterobacterales (CRE) are diverse mechanisms, including those that are resistant to meropenem but susceptible to ertapenem, adding further complexity to the clinical landscape. This study investigates the emergence of ertapenem-resistant, meropenem-susceptible (ErMs) Escherichia coli and Klebsiella pneumoniae CRE across five hospitals in San Antonio, Texas, USA, from 2012 to 2018. The majority of the CRE isolates were non-carbapenemase producers (NCP; 54%; 41/76); 56% of all NCP isolates had an ErMs phenotype. Among ErMs strains, E. coli comprised the majority (72%). ErMs strains carrying blaCTX-M had, on average, 9-fold higher copies of blaCTX-M than CP-ErMs strains as well as approximately 4-fold more copies than blaCTX-M-positive but ertapenem- and meropenem-susceptible (EsMs) strains (3.7 vs. 0.9, $p < 0.001$). ErMs also carried more mobile genetic elements, particularly IS26 composite transposons, than EsMs (37 vs. 0.2, $p < 0.0001$). MGE- ISVsa5 was uniquely more abundant in ErMs than either EsMs or ErMr strains, with over 30 more average ISVsa5 counts than both phenotype groups ($p < 0.0001$). Immunoblot analysis demonstrated the absence of OmpC expression in NCP-ErMs E. coli, with 92% of strains lacking full contig coverage of ompC. Overall, our findings characterize both collaborative and independent efforts between blaCTX-M and OmpC in ErMs strains, indicating the need to reappraise the term "non-carbapenemase (NCP)", particularly for strains highly expressing blaCTX-M. To improve outcomes for CRE-infected patients, future efforts should focus on mechanisms underlying the emerging ErMs subphenotype of CRE strains to develop technologies for its rapid detection and provide targeted therapeutic strategies.

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Posterboard #: 27

Presenter: Sean Kilroe, PhD

Institution: UT Health San Antonio

Category: Postdoctoral Fellow

Lipidomic and metabolomic response of skeletal muscle to short term disuse atrophy in middle-aged adults.

Sean P. Kilroe1,5, Zachary Von Ruff1,2, Emily J. Arentson-Lantz3, Hanna Kalenta, Jennifer J. Linares, Trevor B. Romsdahl, William K. Russell, Douglas Paddon-Jones, Blake B. Rasmussen

Authors: Sean P. Kilroe1,3, Zachary Von Ruff1,3, Hanna, Kalenta1,3, Jennifer J. Linares1, Emily J. Arentson-Lantz2,3, Trevor Romsdahl1, William Russell1, Blake B. Rasmussen1,3. 1 Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, Texas 77555 2 Department of Nutrition, Metabolism and Rehabilitation Science, University of Texas Medical Branch, Galveston, TX 77555 3 Center for Metabolic Health, University of Texas Medical Branch, Galveston, TX 77555 Title: Lipidomic and metabolomic response of skeletal muscle to short term disuse atrophy in middle-aged adults. Introduction Research on muscle disuse has primarily focused on the mechanisms underlying the regulation of muscle cell atrophy. The utilization of a modern 'omics' approach allows for a more extensive assessment of how skeletal muscle metabolism may contribute to disuse atrophy and reduced function. Methods Healthy, middle-aged adults (n=11; 57.1±1.5y; BMI 28.9±1.5kg·m-2; 6m, 5f) underwent 7 days of unilateral leg immobilization via unilateral lower limb suspension (ULLS). Muscle biopsies from the m vastus lateralis of the immobilized (IMM) were collected prior to and following immobilization. We used a targeted lipidomic and metabolomic approach to determine the effects of disuse atrophy on polar metabolites and lipid species in skeletal muscle. Results A total of 960 individual lipids and 205 polar metabolites were identified. A paired samples t-test showed that after 7 days of unilateral leg immobilization 39 lipid species and 3 polar metabolites were significantly increased, in contrast 9 lipid species and 24 polar metabolites were significantly reduced (fold change > 2, $P<0.05$) in the IMM leg. Of these 39 lipid species that were elevated, 27 were phosphatidylglycerols and phosphatidylinositols. Pathway analysis found significant differences after immobilization. Amino acid metabolism, particularly phenylalanine, tyrosine and arginine metabolism pathways were significantly reduced after disuse ($P<0.05$). Conclusions Short-term muscle disuse atrophy in middle-aged humans increases specific lipid species (e.g., phosphatidylinositols and phosphatidylglycerols) while reducing pathways linked to specific amino acid metabolism (e.g., phenylalanine, tyrosine, and arginine).

IIMS INSTITUTE FOR INTEGRATION OF MEDICINE AND SCIENCE

14TH ANNUAL FRONTIERS OF TRANSLATIONAL SCIENCE RESEARCH DAY

Posterboard #: 28

Presenter: Alison Luckey, PhD

Institution: UT Health San Antonio

Category: Postdoctoral Fellow

Genome-wide association study of visual memory and spatial organization in a community setting: The CHARGE Consortium

Alison M. Luckey, Qiong Yang, Mohsen Sharifi Tabar, Muralidharan Sargurupremraj, Joshua C. Bis, Christiane Reitz, Habil Zare, Richard P. Mayeux, Karen A. Mather, Perminder S. Sachdev, Michele K. Evans, Stéphanie Debette, Sudha Seshadri, Annette L. Fitzpat

Background: Poor visual memory task performance is predictive of cognitive decline and dementia. Additionally, deficits in perceptual organization tasks are sensitive to dementia severity. However, no Genome-Wide Association Study (GWAS) has assessed the genomic basis of cognitive visual-spatial phenotypes in a large sample to date. To inform future epidemiological studies where visuospatial memory may be compromised in normal aging, this study aimed to identify common genetic variants associated with visual memory and spatial organization in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. Methods: We included dementia- and stroke-free participants aged 45 years or older from up to eight cohorts that performed cognitive tasks assessing delayed visual memory (e.g., Benton Visual Retention Test (BVRT, n=10,932) and Visual Reproductions, n=5,565) or spatial organization (i.e., Hooper Visual Organization Test (HVOT, n=5,055)). Each cohort used linear regression models to relate common genetic variants imputed to the 1000 Genomes panel to each cognitive phenotype. Models adjusted for age, sex, population stratification, education, and study-specific covariates (if applicable). Summary statistic results for the BVRT were meta-analyzed using METAL. Combined-GWAS was used for a joint analysis of all traits. Results: We identified a genome-wide significant variant related to BVRT performance located near the TSHZ3 gene (rs10425277, p=6.76×10-9). TSHZ3 is important for the development and functioning of cortical projecting neurons and may be implicated in the progression of Alzheimer's disease through the repression of CASP4 transcription. Multi-trait analyses including BVRT, visual reproductions, and HVOT identified two additional variants of interest near CNTNAP5 (rs72842999, p=3.1×10-7) and ZFPM2 (rs2957459, p=6.5×10-7), both of which are overexpressed in the brain and have important implications for neurodevelopment. Conclusion: Our findings suggest variants related to visual memory and spatial orientation are implicated in neurodevelopmental and degenerative pathways. Additional analyses are underway to replicate these findings and extend functional annotations.

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Posterboard #: 29

Presenter: Meera Rath, PhD

Institution: UT Health San Antonio

Category: Postdoctoral Fellow

Maternal treatment with statins lowers pro-inflammatory response to lipopolysaccharide in the fetal intestine and lungs

Meera Rath, Kate Neuhoff, Sureshkumar Mulampurath Achuthan Pillai, Tia Conway, Kaitlin D. Kersh, Egle Bytautiene Prewit

Introduction: Premature birth has been associated with neonatal complications. Several studies have implicated inflammation to be responsible for fetal injury and preterm birth. Our lab showed that statin administration reduced the inflammatory markers in maternal serum and fetal brain when administered before exposure to lipopolysaccharide (LPS). We wanted to extend our findings to other fetal organ systems to evaluate whether inflammation is leading to other vital fetal organ injuries that might further increase the risk of neonatal morbidity. Hence, we hypothesized that prenatal statin administration in pregnant mice would reduce the inflammatory responses in the fetal tissue in an LPS-induced systemic inflammation model. Methods: On day 15, pregnant CD-1 mice received an intraperitoneal injection of LPS (250 µg in saline) 2 hours before administration of saline, simvastatin, or pravastatin (both at 10 µg/g of body weight in saline). Dams who received saline injections at both time points served as negative controls. Six hours after the last injection, dams were euthanized, and fetal tissues were collected. After determining fetal gender, protein extraction was performed from the intestines and lungs from 2-3 male and 2-3 female pups per dam. Maternal circulating total cholesterol and C-reactive protein (CRP) were measured with appropriate assays. Concentrations for IL-6, IL-1b, TNFa, IL-4, and IL-10 were measured using MULTIPLEX Luminex® multiplex immunoassays and analyzed by gender using One-Way or Kruskal-Wallis ANOVA followed by Dunn's multiple comparisons test (statistical significance: $P<0.05$). Result: Maternal cholesterol levels were not affected by the administration of either statin. CRP levels were significantly elevated in the LPS-treated ($P=0.002$); neither statin lowered those levels. LPS significantly elevated IL-6, IL-1□, and TNF-□ in fetal intestines and lungs of both sexes. Simvastatin treatment significantly reduced the IL-1β concentration in the male ($P=0.04$) and female ($P=0.02$) intestines compared to the LPS-treated group($P=0.04$). No other cytokine levels were significantly affected by the statin treatment. Conclusion: The findings suggest that statin administration reduces the ongoing inflammatory response in the fetal intestine and lung and does not have an effect on maternal cholesterol. Further investigation is ongoing to determine the causal mechanism.

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Posterboard #: 30

Presenter: Leen Abazid, MD, PhD student

Institution: UT Health San Antonio

Category: Student

Brain Alterations Associated with Obesity: A Coordinate-Based Meta-Analysis of Case-Control Studies

Leen Abazid; Eithan Kotkowski; Crystal Franklin; Amy Garrett; Peter Fox

Objective: The primary objective of this study was to identify brain alterations associated with obesity. A secondary objective was to determine whether obesity-related alteration distributions were dependent upon the presence of metabolic syndrome. Methods: Alteration likelihood estimation (ALE) meta-analysis was performed on peer-reviewed, case-control contrast (obese vs non-obese), voxel-based morphometric and physiologic studies. Three meta-analyses were performed: All obesity (AO), metabolically healthy obesity (MHO), and metabolically unhealthy obesity (MUO). Results: Thirty-two studies reporting a total of 50 non-duplicative contrasts (MHO, 23; MUO, 27) met inclusion criteria, collectively representing 3,368 participants (obese, 1,781; non-obese, 1587). The AO ALE yielded eight cerebral foci (three nuclear, five cortical) in regions behaviorally implicated in reward seeking. The MHO ALE yielded seven cerebral foci (four nuclear, three cortical), similar to AO in location and behavioral loading. The MUO ALE yielded three cerebellar and one occipital foci in a distribution distinct from AO/MHO but resembling a distribution reported in metabolic syndrome. Conclusions: The distribution of gray-matter alteration in both AO and MHO ALE images predominantly involved the cerebral reward circuitry, suggesting a mechanism linked to food addiction. Obesity with metabolic syndrome exhibited a cerebellar alteration, indicating metabolic stress that is implicated in cognitive impairment. This finding partially replicated a large-cohort VBM study on metabolic syndrome.

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Posterboard #: 31

Presenter: Emily Aller

Institution: UT Health San Antonio

Category: Student

Exploring the Potential of EC359 in Inducing Ferroptosis for Targeting Type I and II Endometrial Cancers

Emily Aller, Xue Yang, Paulina Ramirez, Megharani Mahajan, Hareesh B. Nair, Edward R. Kost, Ratna K. Vadlamudi, Suryavathi Viswanadhapalli

Background: Endometrial cancer is the most common cancer of the female reproductive tract with the rates of diagnosis and death slowly rising over the past ten years. As such, finding ways to improve or enhance current therapy options is currently needed. Recently, a set of studies have identified a new drug that targets the cellular receptor LIFR as being promising in treating Endometrial Cancers (ECa). This drug, EC359, is capable of reducing the viability and invasiveness of both Type I and the more aggressive Type II ECa. However, the mechanism by which EC359 induces ECa cell death remains unclear. There is some evidence that EC359 is capable of inducing apoptosis in ECa, but it has also been characterized as a ferroptosis-inducer in breast and ovarian cancers. Thus, we are investigating the ability of ECa to kill cells via Ferroptosis in type I and Type II ECa. Methods: The effects of EC359 on ECa cells were evaluated using colony formation, and MTT based cell viability assays. Mechanistic investigations were performed with Western blot, RT-qPCR, and transmission electron microscopy (TEM). The efficacy of the combination therapy with LIFR inhibitor EC359 was investigated using patient derived xenograft (PDX) models. Results: Using cell viability and colony formation assays, we have demonstrated that inhibiting ferroptosis markedly reduces EC359's ability to reduce cell growth and viability. Additionally, treatment with EC359 results in a reduction of critical anti-ferroptosis proteins. TEM studies revealed the induction of mitochondrial death through ferroptosis. With the current evidence that EC359 is a ferroptosis inducer in ECa, we have also investigated its ability to eradicate ECa as part of a combination therapy with the current first-line ECa chemotherapeutic, Carboplatin both in vitro and in vivo, which had promising results. Conclusion: Overall, these data suggest that EC359 is a potent inducer of ferroptosis in ECa with the potential to serve as an additional tool in ECa treatment regimes.

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Posterboard #: 32

Presenter: William Arnold, BS

Institution: UT Health San Antonio

Category: Student

LIFR targeted therapy for treating low grade serous ovarian cancer

2. Arnold C, Lyons YA, Ebrahimi B, Santhamma B, Kost ER, Nair HB, Viswanadhapalli S, and Vadlamudi RK

Background: Ovarian cancer (OCa) is the deadliest of all gynecologic cancers in the United States. About 10% of all cases of serous ovarian cancer have the unusual histology named low-grade serous carcinomas (LGSOC), that has a distinct clinical behavior with a unique molecular landscape. LGSOC is characterized by a younger age at diagnosis, indolent progression, and chemotherapy resistance. BRAF and KRAS mutations occur in 33% and 35% of LGSOC cases, respectively. LGSOC is frequently detected when the malignancy is in advanced stage and LGSOC relapses in about 70% of patients with advanced disease. Therefore, new targeted therapies are required. Since LGSOC uniquely expresses mutations of either BRAF or KRAS, and because Leukemia Inhibitor Factor (LIF) expression is induced by oncogenes such as KRAS, we reason that the LIF/LIFR axis represents a unique target for treating LGSOC. The objective of this study is to test the utility of blocking LIF/LIFR axis using LIFR inhibitor EC359 in treating LGSOC. Methods: The expression of LIF and its receptor LIFR was profiled using multiple established LGSOC cells and primary LGSOC model cells. The effects of EC359 on LGSOC cells were evaluated using cell viability, colony formation, and apoptosis assays. Mechanistic investigations were conducted with Western blotting, reporter assays and RT-qPCR analysis. The in vivo efficacy of LIFR inhibitor EC359 as a targeted therapy was investigated using LGSOC cell-based xenografts. Results: Western blot analysis confirmed expression of LIFR and LIF in established LGSOC and primary LGSOC cells and functional autocrine loop of LIF/LIFR signaling. The treatment with the LIFR inhibitor EC359 significantly reduced LGSOC cell viability, cell survival, and increased apoptosis. The activation of downstream LIFR signaling including STAT3, mTOR, AKT, and p42/44 MAPKs markedly decreased by EC359 treatment. EC359 enhanced the efficacy of trametinib, a currently used medication of LGSOC. EC359+trametinib as a combination therapy showed more efficacy over monotherapy of EC359 or trametinib in reducing cell viability and colony formation. Using cell-based xenograft and PDX models, we demonstrated that the EC359 at 5mg/kg dose significantly reduced the LGSOC xenograft growth compared to the vehicle control. Conclusions: Together, our findings support the existence of LIF/LIFR autocrine loops, and EC359 is a viable treatment option for LGSOC.

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Posterboard #: 33

Presenter: Adriana Baker, MD/PhD Student

Institution: UT Health San Antonio

Category: Student

ERX-315: A Potential Treatment Option for Hepatocellular Carcinoma (HCC)

Adriana Baker, Xue Yang, Uday P. Pratap, Suryavathi Viswanadhapalli, Ratna K. Vadlamudi, PhD.

Background: Hepatocellular carcinoma (HCC) accounts for more than 90% of instances of liver cancer, which ranks as the fifth most frequent cancer in the United States. Furthermore, Texas leads the nation in the age-adjusted incidence of HCC. Less than 15% of people with HCC survive to see their fifth year of life, and the disease's incidence is increasing more quickly than that of any other malignancy. There is an immediate need for new HCC treatment approaches. The unfolded protein response (UPR) and endoplasmic reticulum (ER) stress have been recognized as targetable vulnerabilities in recent genomic investigations. After testing more than two thousand synthetic oligo-benzamides, our lab found ERX-315, the lead molecule that causes ER stress and cancer cell death without affecting normal cells. The lysosomal acid lipase (LAL)-encoding protein LIPA was identified as ERX-315's target. This study aims to evaluate ERX-315's potential for therapeutic targeting of HCC. Methods: Hepatic tissue micro arrays and Immunohistochemistry (IHC) were used to confirm expression of LIPA. LIPA expression in HCC tumors was also confirmed using TNM data base. ERX-315's impact was evaluated using six well-established HCC cell lines using the MTT and colony formation assays. ERX-315's specificity was confirmed by CRISPR-KO of LIPA in three different cell lines. For mechanistic investigations, Western blotting, RT-qPCR, and the splicing assay were employed. HUH7 organoids generated from xenografts were utilized to evaluate the effects of ERX315 ex vivo. HUH7 cell-based xenografts were used to validate the efficacy of ERX-315. Results: TNM plot analysis revealed that HCC tumors exhibited elevated levels of LIPA expression in comparison to normal tissue. Analysis of hepatic tissue micro array (TMA) samples showed that compared to normal tissue, HCC samples exhibit increased levels of LIPA expression. ERX-315 treatment significantly decreased both colony formation and cell viability (IC50 between 30-150nM). Compared to WT, KO of LIPA dramatically reduced the number of colonies and cell viability in HCC cell lines. Mechanistic studies using splicing assay, RT-qPCR, and Western blotting demonstrated elevated levels of ER stress indicators upon treatment with ERX-315 in a dose dependent manner. Xenograft-derived HUH7 organoids' cell viability was considerably reduced by ERX-315. ERX-315 therapy dramatically decreased the tumor volume in HUH7 xenograft models. Conclusion: Collectively, our results suggest that ERX-315 promotes ER stress and apoptosis in HCC in vitro, ex vivo, and in vivo. ERX-315 represents a promising novel therapeutic option for HCC.

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Posterboard #: 34

Presenter: Ramya Smithaveni Barre, MS

Institution: UT Health San Antonio

Category: Student

Nluc-expressing Influenza A Viruses for effective evaluation of Viral Infections

Ramya Smithaveni Barre, Kevin Chiem, Aitor Nogales, Rebecca L. Pearl, Randy A. Albrecht, Luis Martinez-Sobrido

Influenza A viruses (IAV) are single-stranded, negative-sense RNA viruses that infect multiple mammalian and bird species and are responsible for seasonal infections and occasional pandemics in humans associated with significant health and economic consequences. Studies with IAV require secondary methodologies to detect the presence of virus in infected cells or in validated animal models. To overcome this limitation, we have modified the non-structural (NS) viral segment to develop IAV-expressing fluorescent proteins, which enables easy tracing of the virus in infected cells. However, the expression of fluorescent proteins does not allow tracking viral infection in entire animal using in vivo imaging systems (IVIS). We have generated recombinant IAV expressing nanoluciferase (Nluc) from the viral NS segment to overcome this limitation. In vitro, Nluc-expressing recombinant IAV exhibited growth kinetics and plaque phenotype comparable to wild-type (WT) IAV. Notably, recombinant Nluc-expressing IAV were neutralized with monoclonal antibodies and inhibited by antivirals to levels comparable to those observed in cells infected with WT IAV. Importantly, IAV expressing Nluc allows effective tracking of viral infection in vivo, with morbidity, mortality, and viral titers comparable to those observed with WT IAV. These recombinant Nluc-expressing IAVs represent an excellent tool for monitoring viral infections, studying virus-host interactions, and identifying novel prophylactics and therapeutics for treating IAV infections in vitro and in vivo.

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Posterboard #: 35

Presenter: Kaitlyn Bejar, MS

Institution: UT Health San Antonio

Category: Student

The Analysis of N-glycans and Collagen to Predict Prostate Adenocarcinoma Outcome

Kaitlyn Bejar MS, Jordan Hartig, Richard Drake PhD, Peggi Angel PhD, Teresa Johnson-Pais PhD, Robin Leach PhD

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer related death in American men. However, the majority of men with prostate cancer die with their cancer and not from their cancer. Distinguishing indolent from aggressive disease and early identification of men at risk of developing aggressive, metastatic disease is of great clinical importance. Tumor extracellular matrixes are comprised of fibrillary and non-fibrillary collagens, fibronectin, and proteoglycans. Observed with the reactive stroma changes in collagen peptides and extracellular matrix are alterations in N-linked glycans attached to glycoproteins in the stroma and tumor regions. Recent technological advances allow for the analysis of N-glycans and collagens on the same tissue specimen, leading to the potential of glycan- and collagen-based biomarkers for prostate cancer. Matrix assisted laser desorption/ionization mass spectrometry can be utilized to characterize N-glycan profiles in formalin fixed paraffin embedded tissues. Collagen may also be characterized using ECM-targeted collagenase MALDI imaging. These approaches were used to analyze prostatectomy samples with different clinical outcomes. Tissue microarrays containing tissues from 75 non-progressors (no evidence of disease; NED) and 50 metastatic cases (MET) were examined. From a combined list of 90 N-glycans and 500 collagenase peptides, the average AUC intensity value for each glycan and collagen peptide was extracted and assessed as a predictor of metastatic progression. Three N-glycans and three collagen peptides were found to discriminate between NED and MET cases with statistical significance. Both a collagen peptide and N-glycan were discovered as promising biomarkers to predict metastasis. Future validation studies are needed utilizing an independent cohort to confirm biomarker potential. There is also a need to determine if the addition of these biomarkers can strengthen current genomic classifier's ability to predict metastatic prostate cancer.

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Posterboard #: 36

Presenter: Marissa Brown

Institution: UT Health San Antonio

Category: Student

Magnetic Resonance Biomarkers of Metabolic Dysfunction-Associated Steatotic Liver Disease

Marissa Brown, BS, Juan A. Vasquez, PhD, Alexander J. Moody, PhD, Venkata Katabathina, MD, John Blangero, PhD, Geoffrey D. Clarke, PhD

Objective/Goals: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major public health concern due to its increasing prevalence and association with type 2 diabetes mellitus (T2DM). Non-invasive magnetic resonance-based biomarkers can aid in the monitoring of disease progression and identification of patients at high risk for chronic liver disease. Methods/Study Population: Over 600 subjects will be recruited from the San Antonio Mexican American Family Study and from a second study, which consists of (i) T2DM patients diagnosed with either MASLD or metabolic dysfunction-associated steatohepatitis (MASH) or (ii) metabolically healthy controls. Hydrogen-1 MRS and diffusion-weighted MRI (DW-MRI) will be used to measure liver fat fraction and liver stiffness biomarkers, respectively. Several potential biomarkers of liver stiffness will be evaluated in vivo using the intravoxel incoherent motion (IVIM) model for DW-MRI. To further improve the diagnostic accuracy of patients with liver fibrosis, we will integrate MRI/MRS data with relevant clinical indicators of hepatic metabolism. Results will be compared to biopsy samples to evaluate the model's diagnostic accuracy. Results/Anticipated Results: Based on preliminary data, we predict that IVIM will be able to accurately diagnose hepatic fibrosis in patients with MASLD, allowing it to easily be implemented into clinics with high-field MRI units. Previous studies have already shown correlations between IVIM estimates and fibrosis stages, however none of them included additional clinical indicators of liver disease in their models. We have already found significant differences in metabolic measurements such as fasting plasma glucose and HbA1c levels. Additionally, the use of machine learning in the development of these models has shown improvements in the ability to extract features from the data. The aim is to achieve high accuracy and robustness in the staging of liver fibrosis. Discussion/Significance of Impact: Over 100 million people in the US are affected by MASLD, and without treatment or intervention, it progresses from hepatic steatosis to MASH, fibrosis (liver stiffening), and ultimately to hepatic cirrhosis and hepatocellular carcinoma (HCC). Continued research efforts and clinical implementation of MRI and MRS are vital in combating the growing burden of MASLD.

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Posterboard #: 37

Presenter: Karina Cantu, PhD student

Institution: UT Health San Antonio

Category: Student

Identifying Berberine's Mechanism of Action to Enhance Social Behavior

Karina Cantu, Bridgette Stewart, Anja C. Shakocius, Juliet Garcia Rogers, Sophia Torres, Riley McDaniel, Ruben Vasquez, Ian Pak, Brett C. Ginsburg, Georgianna G.

Social withdrawal is a debilitating and treatment-resistant symptom of psychiatric disorders such as autism and schizophrenia. In preclinical studies in mice, we found acute intraperitoneal (i.p.) injection of the isoquinoline alkaloid berberine at 5 mg/kg enhances social sniffing during social interaction preference tests in female mice, and social dominance in male mice relative to vehicle control treatment. Prior publications indicate that berberine has antidepressant-like properties that may be due to changes it induces in the kynurenine-serotonin pathway. Kynurenine is a product of tryptophan metabolism and may direct tryptophan away from serotonin (5-HT) production. Berberine was reported to disrupt several enzymes along this pathway to favor 5-HT synthesis in brain, ultimately enhancing brain derived neurotrophic factor (BDNF) expression to produce antidepressant-like effects. Given this we hypothesized that both acute and chronic berberine administration would enhance social behaviors by increasing brain 5-HT and BDNF levels. To test this, mice were treated with either berberine or vehicle control for 50 min (acute, via i.p. injection) or 3-4 weeks (chronic, via 0.5 - 4 g/L dissolved in drinking water), tested for social behaviors in social preference and social dominance tasks and were then humanely euthanized to measure blood glucose and collect serum and brain. Non-fasting blood glucose levels averaged 100 - 126 mg/dl and did not differ among treatments. Brains were immediately frozen on a bed of powdered dry ice and stored at -80°C until use. Homogenates from 3 mm hippocampal and frontal cortex punches were made to measure 5-HT using enzyme-linked immunosorbent assay kits and each protein level was measured by Bradford assay. We found brain 5-HT levels of around 3 ng/mg protein and BDNF levels of around 100 fg/mg protein did not significantly differ after either type of berberine treatment. To investigate further, we measured whole brain 5-HT, 5-hydroxyindole acetic acid (5-HIAA), and kynuric acid levels by gas-chromatography-mass spectroscopy and observed they were unaffected by the berberine treatment, in agreement with our brain punch ELISA findings. Frozen serum was used to measure serum concentrations of the stress hormone corticosterone, and we found that berberine treatment significantly reduced ($p < 0.05$) the corticosterone levels relative to vehicle controls ($N = 8$). Taken together our findings indicate that the mechanism of action for berberine to reduce social behavior is unlikely to involve 5-HT metabolism or BDNF levels in brain but instead may correspond with attenuation of the stress response. A future direction will be to examine the effect of the chronic treatment on brain 5-HT2 receptor expression, as this receptor is targeted by atypical antipsychotics that are used in the treatment of autism and schizophrenia.

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Posterboard #: 38

Presenter: Navom Gupta

Institution: Health Careers High School

Category: Student

Repurposing a Cholesterol-Lowering Drug for COVID-19 Therapy

Navom Gupta

COVID-19 is a devastating disease which has caused millions of deaths worldwide. It is caused by infection with the SARS-CoV-2 virus. mRNA-based vaccines help generate short-term protective immunity. A small molecule-based drug (Paxlovid) helps block a key viral enzyme (MPro) 's activity and viral replication. However, additional medications are needed to block viral replication in high-risk factor patients suffering from long COVID and underlying comorbidities (higher inflammation, cardiovascular diseases, diabetes, cancer, etc.). Statins are cholesterol-lowering drugs used to treat antiinflammation and high cholesterol-associated conditions for decades. Statins were also reported to act as antiviral agents against SARS-CoV-2, but the mechanism was unclear. In this research project, I evaluated the potential of a major statin drug (Lovastatin) for its direct binding to the SARS-CoV-2 MPro enzyme. I used computational modeling and molecular docking software. My results suggest that Lovastatin can directly bind to the catalytic pocket of the SARS-CoV-2 MPro enzyme in two different orientations. These results highlight the potential of statins for repurposing into COVID-19 therapy.

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Posterboard #: 39

Presenter: Lavanya Gupta

Institution: Basis San Antonio Shavano-Campus

Category: Student

A pen to better human health

Lavanya Gupta

Bacterial contamination in drinking water and food significantly threatens public health, particularly in developing countries. In particular, the presence of pathogenic strains of Escherichia coli (or E. coli) in water can lead to outbreaks of infectious diseases and cause diarrheal and other gastrointestinal diseases such as abdominal cramps, nausea, and fever. In developing countries, where healthcare resources are limited, these diseases can have severe societal and economic consequences, especially among vulnerable populations such as children and the elderly. Although E. coli contamination in water in the United States is not common yet, an outbreak among children in California in 2016 was mainly caused by a Shiga-toxin-producing E. Coli O157 strain. I propose to develop an efficient and handy device (a pen) for quickly detecting bacteria in water samples. My successful research could provide people with an innovative and multipurpose pen that can be carried anywhere and used for detecting bacterial contamination in water samples.

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Posterboard #: 40

Presenter: Jonathan Lefkowitz

Institution: UT Health San Antonio

Category: Student

Investigation of the Impact of TMEM127 in Tissue-Specific Cell Signaling

Jonathan Lefkowitz, Qianjin Guo, Subramanya Srikantan, Patricia L. M. Dahia

TMEM127 is a poorly known transmembrane protein recognized as a susceptibility gene in hereditary adrenal tumors, pheochromocytomas, with a similar molecular profile to those found in the Multiple Endocrine Neoplasia Type 2 (MEN2) syndrome. However, TMEM127 mutations are not associated medullary thyroid carcinoma, a hallmark of MEN2. We previously found that TMEM127 alters insulin sensitivity in a tissue-specific manner. We generated transcriptome data from the livers of 31 adult mice from these 3 strains and their controls to gain insights into the mechanisms of Tmem127 regulation of metabolism. Gene Set Enrichment Analysis (GSEA) of CMV-KO and AKO DEGs revealed upregulation of immune-related, stress response and growth factor pathways. Multi-Subject Single Cell (MuSiC) deconvolution of the bulk liver RNAseq supported that immune-related cells may be involved in this response. Alix et al. separately found that Salmonella effector SteD requires TMEM127 to decrease surface MHCII levels, suggesting that TMEM127 may downregulate surface proteins in a cell-specific context4. To begin to explore this hypothesis, we compared receptor protein expression in Tmem127 WT and CMV-KO mice. Our Western Blot analysis of bulk liver and adrenal gland showed accumulation of EGFR, FGFR and PDGF-α in KO samples. We further analyzed cell lysates from adrenal gland, spleen, and thyroid samples of WT and Tmem127 KO mice and found that RET levels were elevated in KO tissue. These data support of our hypothesis of a potential role for TMEM127 on surface protein regulation. Additional analysis is warranted to confirm whether TMEM127 regulates metabolism, immunology, and tumor development through broad regulation of several surface proteins.

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Posterboard #: 41

Presenter: Abitha Madesh

Institution: UT Health San Antonio

Category: Student

ERMA (TMEM94) is an essential component of endoplasmic reticulum P-type Mg2+ ATPase

Abitha Madesh

In eukaryotes, Mg2+ is the most abundant divalent cation essential for cellular functions and is associated with several clinical conditions, including migraines, cardiovascular diseases, diabetes, obesity, chronic neurologic/kidney diseases, cancer, and preeclampsia. Intracellular Mg2+ (iMg2+) is muffled by phosphometabolites, nucleic acids, and proteins in eukaryotes. However, ligand-induced mobilization of the remaining unbound free iMg2+ can control several cellular functions. Intracellular ion mobilization is tightly regulated through organelle-specific ion channels and transporters. Since 1906, several findings alluded that iMg2+ has a second messenger role. The proposition of iMg2+ as a second messenger raises important fundamental question: How do Mg2+ transporters facilitate rapid Mg2+ influx when the intra- and extracellular [Mg2+] are nearly comparable? Recently, it was revealed that the glycolytic end-product lactate induces rapid depletion of endoplasmic reticulum (ER) Mg2+ stores, followed by robust refilling phenomenon. However, the molecular entity of ER Mg2+ uptake machinery is unknown. Here I found that ER is the major iMg2+ compartment refilled by a previously undescribed ER-localized protein, TMEM94. Conventional and AlphaFold2 predictions suggest ER Mg2+ ATPase (ERMA) is a multi-pass transmembrane protein with N- and C-termini, analogous to P-type ATPases. However, ERMA uniquely combines an ATPase domain and a GMN motif for ERMg2+ uptake. Experiments reveal that a tyrosine residue is crucial for Mg2+ binding and activity that is conserved in both prokaryotes and eukaryotes. Cardiac dysfunction by haplo-insufficiency, abnormal Ca2+ cycling in Erma+/- cardiomyocytes and ERMA mRNA silencing in human iPSC-cardiomyocytes collectively define ERMA as a key determinant of ERMg2+ uptake in eukaryotes.

IIMS INSTITUTE FOR INTEGRATION OF MEDICINE AND SCIENCE

14TH ANNUAL FRONTIERS OF TRANSLATIONAL SCIENCE RESEARCH DAY

Posterboard #: 42

Presenter: Erik Marchant, MS (PhD Student)

Institution: UT Health San Antonio

Category: Student

Short-term muscle disuse in humans increases gene expression associated with muscle atrophy while downregulating genes linked to mitochondrial and amino acid metabolism

Erik Marchant, Zachary Von Ruff, Sean Kilroe, Emily Arentson-Lantz, Steven Widen, Jill Thompson, Alejandro Villasante-Tezanos, Blake B. Rasmussen, and Doug Paddon-Jones

Background: Reductions in size, strength, and protein synthesis occur during skeletal muscle disuse (ex. bed rest, immobilization, casting, etc) and worsen with aging. The molecular mechanisms that drive these adaptations are still being explored. Our goal is to characterize phenotypic and molecular skeletal muscle changes in middle-aged men and women following short-term inactivity. Methods: Eleven healthy middle-aged (50-65) men and women completed 7 days of unilateral leg disuse . Subjects were fitted with a sling on their left leg and were provided with crutches and/or walker to remain non-weight bearing on the left leg. Skeletal muscle samples were obtained from the vastus lateralis at baseline and day 7. Approximately 900 million 75bp single-end reads were obtained from extracted RNA using an Illumina NextSeq550. Libraries were prepared using the Smart-3SEQ method. Differential gene expression (DGE) analysis was performed using the DESeq2 library in R. A Benjamini-Hochberg adjusted p-value <0.05 was used to determine if a gene was differentially expressed. Significantly enriched pathways (FDR<0.05) were identified using the ToppGenne suite of software. Results: Our preliminary data found that 388 were differentially expressed in the disused leg following 7 days of unilateral leg suspension (262 upregulated, 126 downregulated). Genes associated with reductions in muscle protein synthesis (IGFN1), sarcopenia (CHRNA1), and muscle disuse atrophy (GADD45A) were upregulated. Genes associated with mitochondrial function (PERM1, COQ10A) and mTORC1 activation (SLC38A3/SNAT3) were downregulated. Pathway analysis found that the TP53 network was significantly enriched among the upregulated genes, whereas pathways related to the TCA cycle, electron transport chain, and amino acid metabolism were enriched in downregulated genes. Conclusions: Short-term muscle disuse in middle-aged humans increases gene expression associated with muscle atrophy while downregulating genes linked to mitochondrial function and amino acid metabolism.

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Posterboard #: 43

Presenter: Zoe Millspaugh

Institution: UT Health San Antonio

Category: Student

Practitioner's Reported Experiences in Treating and Addressing the Oral Health in Patients of Refugee and Immigrant Populations

Zoe Millspaugh, Dr. Rahma Mungia, Melanie Tavera, Caitlin Sangdahl

Purpose: This study explored the dental practitioner's reported confidence levels and challenges in addressing and treating patients from the refugee and immigrant populations in Texas as well as practitioner inclination to participate in future research concerning this demographic. Methods: A 5-question survey ("Quick-Poll") was conducted through the South Texas Oral Health Network (STOHN) Practice-Based Research Network (PBRN). A total of N=43 dental practitioners that are members of STOHN responded. Results: 65% (n=28) reported that 0-10% of their patient population identified as refugees, immigrants, asylum-seekers, or resettled individual's populations, 20% (n=9) reported having 11-20% of this population in their practice, 4% (n=2) reported 21-30%, 2% (n=1) reported 31-40%, and 7% (n=3) reported above 50% of their patients belonged to these populations. The most common oral health challenges in this population were unrestored teeth and the need for urgent dental care (92%; n=39), advanced levels of periodontal disease (81%; n=34), and partial or full edentulism (59%; n=25). More than half (57%; n=24) of practitioners indicated they were very confident in their abilities to effectively address the oral health needs of these patients. Practitioners address cultural considerations regarding this patient population by offering culturally sensitive treatment options (57%; n=24), providing interpreter services for cultural nuances (57%; n=24), and tailoring educational materials to their cultural norms (52%; n=22). Furthermore, 45% (n=19) of the practitioners showed interest in participating in a future refugee and immigrant oral health study. Conclusions: This quick poll showed that, regardless of the level of exposure to the refugee, immigrant, asylum-seeker or resettled patient most of the practitioners were confident in their abilities to successfully address their oral health needs with cultural sensitivity. Just under half of the practitioners expressed a need to enhance their confidence in effectively providing treatment to these groups. Even though most practitioners were confident, they were still enthusiastic about further comprehensive research addressing cultural competency in the care of this population.

Posterboard #: 44

Presenter: Khaled Nassar, MS

Institution: UT Health San Antonio

Category: Student

PELP1 inhibitor SMIP-34 increases therapeutic efficacy of topoisomerase inhibitors in treating TNBC

Khaled Mohamed Nassar, John R Sanchez, Durga Meenakshi Panneerdoss, Behnam Ebrahimi, Yang Xue, Uday P Pratap, Salvador Cardenas Alejo, Gangadhara Reddy Sareddy, Suryavathi Viswanadhapalli, and Ratna K Vadlamudi

BACKGROUND: Triple negative breast cancers (TNBCs) account for a sizable portion of breast cancer deaths (15-24%) and are characterized by a more aggressive clinical course, a worse prognosis, and a higher propensity to metastasize. Proline-, glutamic acid-, and leucine-rich protein 1 (PELP1) is an oncogene that plays a critical role in TNBC progression. PELP1 expression is deregulated in TNBC, and its status is a prognostic indicator of poor TNBC survival. There is a major knowledge gap regarding the mechanisms by which PELP1 contribute to TNBC progression. Recently, a small molecule inhibitor of PELP1 (SMIP34) which binds to and degrades PELP1 was developed. The Objective of this proposal is to define the molecular mechanism of action of PELP1 inhibitor SMIP34 in TNBC progression and to pave the path for a novel combination therapy. METHODS: We used multiple TNBC cell lines, PELP1 inhibitor SMIP34 and 140 FDA-approved medications in combination with SMIP34 in this study. Effect SMIP34 combination therapy on cell survival was measured using MTT and colony formation, and Annexin V based apoptosis Assays. Mechanistic studies were done using RT-qPCR, western blotting, immunoprecipitation, proximity ligation and mass spec assays, reporter genes assays, immunofluorescence, and comet assays. The utility of SMIP34+TI combination therapy was evaluated using MDA-MB-231 xenografts, patient-derived organoids (PDOs) and explants (PDEs). RESULTS: We performed an in vitro screening of 140 FDA-approved drugs in combination with SMIP34. Results showed that SMIP34 sensitized TNBC cells to five FDA approved drugs. Of the five drugs, 3 drugs Gemcitabine, Valrubicin, and Mitoxantrone, induce DNA damage by inhibiting topoisomerase (TI), a protein that cleaves and reconnects DNA during replication. We validated the ability of SMIP34 to enhance the efficacy of topoisomerase inhibitors using two additional TNBC cells and confirmed synergistic activity using several in vitro assays including cell viability, colony formation, and apoptosis. In agreement with PELP1 role in DNA damage response, Western analyses showed higher levels of γ-H2AX in SMIP34+TI combination therapy to monotherapy. The Comest assay results further supported the increased DNA damage caused by the combination therapy of SMIP34+TIs. Mechanistic studies using Proximity TurboID labelling followed by immunoprecipitation identified topo isomerase 2A and 2B as a potential interactor of PELP1. Immuno precipitation experiments confirmed that PELP1 interacts with topo isomerase 2A and 2B. Further, gene correlation analysis of PELP1 and TO2A in TCGA data bases revealed that PELP1 expression is highly correlated with TOP2A, and TOP2B in TNBC. SMIP34+ Mitoxantrone (TI) combination treatment significantly reduced the growth of TNBC PDEXs, PDOs in vitro and reduced MDA-MB-231 xenograft tumor progression compared to vehicle or monotherapy treatment. Conclusion: Together, these results suggest a novel targeted therapy for the treatment of TNBC, involving the combination of a topoisomerase inhibitor and the PELP1 inhibitor SMIP34.

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Posterboard #: 45

Presenter: Durga Meenakshi Panneerdoss (First-year Undergraduate Student at UTSA)

Institution: UT Health San Antonio

Category: Student

LIPA inhibitor ERX-208 improves the effectiveness of DNA damaging drugs in the treatment of ovarian cancer

Durga Meenakshi Panneerdoss, Khaled Mohamed Nassar, William Cole Arnold, Suryavathi Viswanadhapalli, Edward Kost, Jung-Mo Ahn, Ganesh V. Raj, and Ratna K. Vadlamudi

Background: Ovarian cancer (OCa) is a prevalent gynecologic malignancy with the greatest fatality rate. After initially responding to chemotherapy treatment, many OCa patients eventually develop resistance, which ultimately results in death. Efficient treatments are essential for enhancing survival of patients with advanced OCa. Our laboratory recently developed ERX-208, a small molecular inhibitor with an IC50 of 100-200 nM in OCa cells. ERX-208 acts on lysosomal acid lipase A (LIPA), inducing heightened endoplasmic reticulum stress and cell death via apoptosis. This study seeks to establish whether ERX-208 improves the effectiveness of existing FDA-approved drugs in addressing chemotherapy resistance. Methods: In our study, we conducted in vitro screening of 147 FDA-approved chemotherapy drugs combined with ERX-208, to test the effect on the cell viability of ovarian cancer (OCa) model cells. The analysis utilized the Synergy Finder Plus software tool to examine drug combination dose-response data and determine the best synergy and combination sensitivity scores. Additionally, we verified the synergistic activity through various in vitro assays, including proliferation, colony formation, cell cycle, DNA damage, apoptosis, and invasion assays. Results: Utilizing in vitro screening with cell viability assays, we observed that ERX-208 sensitizes OCa cells to six FDA-approved compounds which induce DNA damage and inhibit cell cycle progression. Mitomycin, Oxaliplatin, Trifluridine, Capecitabine, Epirubicin hydrochloride, and Bleomycin sulfate were selected based on having the highest synergy scores among the 147 compounds tested. We then validated the ability of ERX-208 to enhance the therapeutic efficacy of these chemotherapeutic compounds using multiple OCa model cell lines. Notably, ERX-208 treatment sensitized OCa cells to these agents by reducing cell viability, colony formation, cell cycle progression, invasion, and enhancing DNA damage and promoted apoptosis. Ongoing studies are exploring mechanistic insights into the observed synergy and validating these findings using preclinical xenograft models. Conclusions: In summary, our findings indicate that combining ERX-208 with DNA damaging agents enhances their activity, highlighting the potential efficacy of ERX-208 combination therapy in the treatment of OCa.

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Posterboard #: 46

Presenter: George Parra, MS

Institution: UT Health San Antonio

Category: Student

Proteomic and structural analysis of the oncogenic EWS::FLI1 spliceosomal interactome

George L. Parra, Susan T. Weintraub, Bernard Fongang, David S. Libich

The EWS::FLI1 gene fusion is implicated as a source of oncogenic activity in the majority of Ewing sarcoma (EwS) cases (>70%). EWS::FLI1 is composed of RNA-binding protein EWS (EWS) and ETS transcription factor Friend leukemia integration 1 (FLI1). It is thought that EWS::FLI1 and EWS participate in mRNA processing and spliceosomal activities, however, the structural interaction mechanisms are unknown. Proteomic experiments show spliceosomal proteins are present in both EWS and EWS::FLI1 interactomes, including proline-rich-region-binding spliceosomal peptidyl-prolyl isomerases (PPIs). EWS::FLI1 contains a low complexity domain (LCD), enriched in proline residues, imparts intrinsic structural disorder and acts as a multivalent binding region. Here we used modern proximity labelling techniques that exploit a biotin ligase fused to EWS and EWS::FLI1 to identify their interactomes. This approach is particularly well suited for intrinsically disordered proteins since it does not rely on binding affinities but rather the physical distance between interacting proteins. From these experiments we identified specific and unique interactions between EWS and EWS::FLI1 and PPI proteins that we hypothesized were mediated by the LCD (EWSLCD) common to both proteins. We employed NMR to provide insight into the interaction between PPIL1 and the EWSLCD and identified the binding sites on both proteins. Specifically, our studies will yield actionable insights regarding the protein-protein interfaces in EWS::FLI1 that can be targeted to attenuate its oncogenic activity. Defining the interaction interfaces of EWS::FLI1 is central to understanding its pathophysiology and importantly, identification of potential therapeutic targets. Combining novel discovery proteomics with cutting-edge NMR approaches will provide unparalleled insight into the transformative mechanics of EWS::FLI1.

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Posterboard #: 47

Presenter: Gilbert Pratt III, MS

Institution: UT Health San Antonio

Category: Student

Radiation Injury and its Temporal Effects on Microbiome Diversity

Gilbert Pratt III, MS; Vincent Pham, BS; James Bynum, PhD; Susannah Nicholson, MD, MS, FACS

Since the mid-twentieth century, susceptibility to radiation injury has increased, with more than 285 recorded incidents in nuclear reactors between 1945 to 1987. This increase is attributable to factors such as occupational exposure in nuclear medicine, low-carbon alternative energy production, research and development industries, and most concerning is the threat of deliberate releases by terrorist organizations. Proliferatively active cells (hematopoietic and intestinal) are highly susceptible to radiation insults. Our group has reported the richness and diversity of the gut microbiome in severely injured trauma patients significantly correlated with required blood transfusion volumes and mortality. There remains a paucity of literature examining gut microbiota beyond seven days post-acute radiation exposure. As a supplementary study to a current model development addressing radiation injury with hemorrhage, we investigated the temporal flux in gut microbial diversity after acute radiation exposure. Male Sprague Dawley rats (8-10 weeks) were exposed to whole-body radiation injury (1Gy/min), We evaluated rectal and cecal microbiota up to fourteen days post-exposure in groups exposed to 5.5Gy (n=4) or 7Gy (n=6). Rectal feces were collected daily initiating before radiation exposure to fourteen days post-injury, and cecum feces were collected prior to euthanasia. Healthy naïve rats (n=4) were used as cecum baseline controls. The V3-V4 variable region of the 16S rRNA gene was amplified from fecal genomic DNA for sequencing. 5.5Gy exposure resulted in sublethal dose for our study with 100 % survival while a 66.67% probability of survival for 7Gy. Non-survivors presented dysbiosis in the firmicutes/bacteroidetes ratio and an elevated proteobacteria at baseline. Further, a profound 23-fold increase in verrucomicrobiota, along with increased desulfobacterota and actinobacteriota were observed on day 14. Cecal patescibacteria were present in naïve controls and eliminated in both groups. Non-survivors presented increased cecal proteobacteria and actinobacteriota phylum. Additionally, 7Gy survivors showed increased proteobacteria, verrucomicrobiota, cyanobacteria, desulfobacterota and deferribacterota. Our results suggest that radiation injury alters gut microbial diversity, which remained unresolved throughout the observed time course. We are currently working on statistical analysis and assessing the microbial class, genus and species diversity of our results and how these population shifts may impact blood metabolomic and lipidomic outcomes.

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Posterboard #: 48

Presenter: Yusheng Qian, MS

Institution: UT Health San Antonio

Category: Student

How cancer spreads: strategies of biophysical adaptations of tumor cells to mechanical stress in blood.

Yusheng Qian, Pawel Osmulski, , Tim H. Huang, April Risinger, Meizhen Chen, Jacob Essif, Maria E. Gaczynska

Metastasis: the spread of primary cancer to distant locations is the major cause of cancer death. In epithelial-origin cancers (carcinomas) metastasis is seeded by circulating tumor cells (CTCs) shed to the blood by primary tumor. Majority of CTCs die very quickly as the blood is a hostile environment for them. These cells are not professional blood cells like leukocytes or erythrocytes. CTCs are devoid of their protective tumor environment and are subjected to fluid shear stress that can easily mechanically damage them. Despite that, a sufficient number of CTCs survive to reach distant tissues and not only settle in them but also start metastatic growth. How this may happen? To reveal the mystery of CTCs resilience we set to recreate the fluid shear stress in a cell culture model of prostate cancer spread. The static culture with cells growing on a surface of dish may represent a tumor, but not a circulation. We subjected human cultured prostate cancer cells to circulation-imitating fluid shear stress in a microfluidic system to create "model CTCs". We used cells of distinct origin, genetic background and aggressiveness: 22Rv1, DU145 and C4-2, as well as human benign prostatic hyperplasia cells BPH-1. We challenged the cells for up to 1 hour of fluid shear stress conditions corresponding to high-end veins or low-end capillaries (7 dyne/cm2). Some cells were able to survive even the longest stress, albeit with significant differences between cell lines. With atomic force microscopy (AFM) - based profiling we tested mechanical properties of surviving cells and compared them with non-stressed cells. We found that surviving cancer cells, in contrast to benign cells, become "mechanically fit" to withstand the circulation challenge. Gain of adhesiveness and ability to cluster with other cells was the most striking feature for cancerous cells but not benign cells. Clustering bestows protection in a recreated microenvironment: cell cluster is less prone to mechanical damage than a single cell. Moreover, our "model CTCs", but not stresses benign cells, gained migratory ability, tested by the TransWell assay. Migratory skills are important for CTCs to extravasate and settle in metastatic site. Finally, to pinpoint the mechanism behind the mechanical fitness we tested profiles of expression of marker proteins of epithelial-mesenchymal transition (EMT), stress-related proteins and elements of cytoskeleton. We found that gaining mechanical fitness does not follow the strait-line EMT and instead relies on epithelial-mesenchymal plasticity. Moreover, we observed a dramatic rebuilt of cytoskeleton in model CTCs after a short stress, apparently to adapt to mechanical conditions in the circulation. The study points at novel strategies behind metastasis and points at potential vulnerabilities of aggressive cancer cells on their way to spread.

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Posterboard #: 49

Presenter: Iman Salafian, PhD Candidate

Institution: The University of Texas at Austin

Category: Student

Development and testing of a multifunction gastric feeding tube capable of vital sign monitoring

1-Iman Salafian, MS, PMP, 2-Alan Groves, MD, 3-Chris Rylander, PhD, 4-Angie Englert, BSN, CCRN

Premature births pose significant healthcare challenges, requiring specialized care in Neonatal Intensive Care Units (NICUs). Traditional methods for feeding and monitoring vital signs in preterm infants often involve multiple invasive devices, which can be cumbersome and pose risks to the delicate health of these infants. This poster outlines the development and evaluation of the Trinity Tube, a novel multifunctional catheter designed to simultaneously provide gastric feeding, vent excess abdominal gas, and monitor vital signs such as airway respiratory pressure, electrocardiogram (ECG), core body temperature, and heart rate in preterm infants. The project aims to improve clinical outcomes by integrating these critical functions into a single, less invasive device. The research encompasses several phases, including in vitro benchtop tests to optimize the tube's design based on factors such as length, diameter, material, and air humidity; IRB-approved clinical studies to evaluate the tube's efficacy in measuring esophageal airway pressure and obtaining EMG and ECG signals in preterm infants; and the final design and specification phase, incorporating outcomes from human studies, market research, and technical viability assessments. The project anticipates demonstrating the Trinity Tube's ability to accurately and reliably monitor vital signs and support respiratory therapy in preterm infants, potentially leading to better-informed clinical decisions and improved patient outcomes. The final design phase aims to finalize the specifications for a production-grade Trinity Tube, setting the stage for subsequent performance and safety testing as part of the FDA 510(k) clearance process.

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Posterboard #: 50

Presenter: Lacey Sell, MS

Institution: UT Health San Antonio

Category: Student

Mouse Models of Human CNTNAP1-associated Congenital Hypomyelinating Neuropathy and Genetic Restoration of Murine Neurological Deficits.

Lacey B. Sell, Cheng Chang, Qian Shi, Manzoor Bhat

CNTNAP1 encodes the transmembrane Contactin associated protein 1 also known as Caspr. Caspr is located in the paranodal region of all myelinated axons, flanking either side of the node of Ranvier. It is required for axonal domain organization and participates in the propagation of action potentials. This unique organization allows for saltatory action potentials to occur, increasing the speed and effectiveness at which neurons can communicate. Around 30 human CNTNAP1 mutations have been identified, which are associated with dysregulation and disorganization of these domains causing various forms of congenital hypomyelinating neuropathies. Symptoms include slowed nerve conduction, intellectual disability, muscle atrophy, respiratory issues and a high rate of infant mortality. Currently, there are no treatments for the neuropathies caused by CNTNAP1 mutations. This highlights the importance of fully characterizing these mutations to develop future therapeutics. Using CRISPR/Cas9 methodology, our lab created two mouse models containing a single nucleotide substitution in Cntnap1. Either Arginine to Cysteine at 765 (Cntnap1-R765C), or Cystine to Arginine at 324 (Cntnap1-C324R). A genetic combination of mutation over a null allele (R765C/-, C324R/-) mimics human CNTNAP1-mutation-associated hypomyelination neuropathies. The mutation/null mice have reduced Caspr protein levels, disrupted axonal domain organization and slowed nerved conduction, with loss of balance and motor coordination. To explore potential therapeutic options, a tissue-specific overexpression of Cntnap1 mouse model was used, where a wild-type copy of Cntnap1 was induced to express in neurons, in the mutation/null backgrounds. After initiation of wild-type Caspr protein, the mutation/null mice start to display improvements, including increased nerve conduction, increased levels of Caspr protein, restoration of the organization of axonal domains in the spinal cord and sciatic nerve and improvement of motor coordination and balance. All the phenotypic manifestations show progressive restoration in a time-dependent manner. Together, our studies are the first to uncover the mechanistic impact of human CNTNAP1 mutations in a mouse model and provide a proof of concept for developing future treatments for human clinical trials for hypomyelinating neuropathies caused by CNTNAP1 mutations. Currently, our lab is testing an AAV vector containing CNTNAP1 in mice as a possible therapeutic for future human clinical trials.

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Posterboard #: 51

Presenter: Chris Serrano

Institution: University of Texas at San Antonio

Category: Student

DNA Methylation Association with Obesity in a Hispanic Childhood Obesity Cohort

Chris Serrano,

Obesity is an ongoing issue characterized by an imbalance of energy intake and expenditure, disproportionately affecting population groups such as Hispanics. Genetic and epigenetic risk factors for childhood obesity may differ from those identified in adult cohorts. We are examining blood-based DNA methylation signatures in Hispanic children (age 4-19 years; average 11.0 +/- 0.2) who participated in the Viva la Familia study (VIVA), a family-based study designed to identify genetic risk factors for childhood obesity. It included 24-hour room calorimetry, providing extensive phenotypic data on energy utilization and metabolism for our analyses. Using MethylSeq and a hybrid candidate gene/genome-wide probe library, we profiled 2.6 million CpG sites in 916 Hispanic children. Body mass index (BMI; h2=0.39, p=5.3x10-9) and percent fat (%fat; h2=0.44, p=5.7x10-13) were heritable. We tested for associations between DNA methylation levels and these phenotypes using inverse-normalization and adjusting for covariates (sex, age, age2, and their interactions). Based on ~350 samples, we did not find significantly associated CpG loci, however we do see several CpG loci that show nominally significant associations with each phenotype after adjusting p-values for multiple comparisons using Benjamini and Hochberg's FDR method. Among the genes with the most significantly associated CpGs were KLB (BMI; p=2.3x10-7) and ZHX2 (%fat; p=5.1x10-7), which have previously been implicated in obesity and plasma lipid metabolism, respectively. We are currently analyzing the full data set (n=916), and anticipate that analysis of all samples plus consideration of the correlation structure of the CpG sites will allow us to identify differentially methylated loci significantly associated with childhood obesity in an at-risk population.

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Posterboard #: 52

Presenter: Vidya Sharma, MA, RD, LD, CDCES

Institution: UT Health San Antonio/UTSA

Category: Student

Assessment of Dietary Intake and Comparison to MyPlate in Community-Dwelling Older Adults in Bexar County

Vidya Sharma, Salma Abdelrahman, Michelle Aguilar, Marilu Martinez, Erica T. Sosa, Meizi He, Zenong Yin, Tianou Zhang, Sarah L. Ullevig

Background: Congregate Meal Programs (CMP) serve over 2000 older adults in the City of San Antonio, Texas. Importantly, 33% of these older adults live below the poverty level, and 18% are at high nutritional risk. Objectives: The purpose of this study is to assess food group consumption in older adults participating in CMPs in San Antonio in comparison with the MyPlate equivalents. Design: This study consists of a cross-sectional sample of the older adult population attending congregate meal centers. Methods: Two nonconsecutive 24-hour dietary recalls were collected using the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24, National Cancer Institute). Older adults (n=411) from 13 congregate meal sites took part in the study. Recalls less than 800 or above 3000 kcal were excluded. A total of 667 recalls were included in the present analysis. Results: Average age of the participants was 71 years (SD±6.56) of whom 78% (n=320) were females and 60% (n=247) were of Hispanic ethnicity. Importantly, 66% (n=272) had an average annual household income of <$40,000. Protein consumption was within the recommended range. Most of the participants reported consuming one (SD±1.12) fruit cup equivalent serving and 1.6 (SD±1.34) vegetable cup equivalent servings. This is lower than the recommended average intake of 1 ½ to 2 cups and 2 to 3 ½ cups of MyPlate equivalent servings for fruits and vegetables respectively. In comparison to whole grain, refined grain consumption was significantly higher at 4.28-ounce equivalent (SD±2.76) compared to 0.75-ounce equivalent (SD±1.10) for whole grain. Additionally, dairy consumption averaged 1.1 cup (SD±1.04) and was lower than the recommended intake of 3 cup equivalent servings. Conclusions: The findings suggest that most participants did not incorporate an adequate consumption of fruits, vegetables, whole grains, and dairy in their daily diet. Nutrition education and intervention studies are needed to address nutritional inadequacies in this population.

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Posterboard #: 53

Presenter: Annie Smelter, BS

Institution: UT Health San Antonio

Category: Student

Persistent Inflammatory Lipotoxicity Impedes Pancreatic β-cell Function in Diet-Induced Obese Mice Despite Correction of Glucotoxicity

Annie A. Smelter, Ivan A. Valdez, Juan Pablo Palavicini, Terry M. Bakewell, Marcel Fourcadot, Iriscilla Ayala, Luke Norton

Insulin resistance is a hallmark feature of Type 2 Diabetes (T2D), but the progression of the disease is closely linked to a deterioration in β-cell mass and function. While the precise mechanisms of β-cell failure are unclear, chronic hyperglycemia (glucotoxicity) and dyslipidemia (lipotoxicity) are considered contributing factors; however, the relative importance of these insults on β-cell function remains controversial. To examine this, we dissociated glucotoxicity from lipotoxicity using a high-fat diet (HFD)-fed mouse model of T2D and the glucose-lowering SGLT2 inhibitor, canagliflozin (CANA). As expected, HFD-feeding impaired glucose tolerance and isolated islet function. However, despite improvements in glucose tolerance and indices of β-cell insulin secretory function in vivo, CANA failed to restore isolated β-cell function. Shotgun lipidomics analysis of isolated islets revealed that HFD-feeding induced glycerophospholipid remodeling with a persistent increase in arachidonic acid (20:4)-enriched molecular species. Further analysis revealed that lysophosphatidylcholine (LPC) was the predominant lipid class elevated in HFD islets following correction of glucotoxicity with CANA. In follow-up experiments, LPC stimulations acutely and dose-dependently impaired glucose-stimulated insulin secretion (GSIS) in isolated wild-type islets, mechanistically linking this lipid class to β-cell dysfunction. Our findings indicate that persistent inflammatory lipotoxicity impedes β-cell function in diet-induced obese (DIO) rodents even after normalization of hyperglycemia. If replicated in humans, these data suggest that interventions targeting lipotoxicity may be beneficial for the long-term protection of pancreatic β-cell function in T2D.

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Posterboard #: 54

Presenter: Kate Tuite

Institution: UT Health San Antonio

Category: Student

Role of paraventricular thalamus to orbitofrontal cortex pathway in the effects of stress on reversal learning

Tuite, Kathleen; Girotti, Milena; Morilak, David A.

Stress-related psychiatric disorders, such as major depressive disorder and anxiety disorders, have cognitive flexibility deficits that persist even after other symptoms of these disorders go into remission. Reversal learning, a form of cognitive flexibility necessary to adapt to a changing environment, is disrupted in stress-related psychiatric disorders. The orbitofrontal cortex (OFC) mediates reversal learning, and hyperactivity in the OFC is associated with depression and obsessive-compulsive disorder in humans. Using a reward-based discrimination digging task to assess reversal learning in rodents, preliminary data using Fos immunohistochemistry showed a significant decrease in Fos in the lateral OFC following reversal learning. Further, we have previously reported that chronic stress impairs reversal learning and potentiates responses to excitatory input in the OFC, and that inducing long-term depression in the mediodorsal thalamus to OFC pathway reverses these deficits, indicating that increased activity in projections to the OFC is detrimental to reversal learning. However, the circuit-level mechanisms underlying stress-induced reversal learning deficits are not well established. The paraventricular thalamic nucleus (PVT) is highly stress responsive and is known to provide excitatory input to the OFC. Utilizing retrograde tracing from the OFC combined with ΔFosB immunohistochemistry we found that the PVT projects strongly to the OFC and this projection is repeatedly activated by chronic stress. Therefore, we next tested the hypothesis that input to the OFC from the PVT, when activated chemogenetically or by chronic stress, will disrupt reversal learning. We used an adeno-associated virus to deliver an excitatory (Gq) DREADD, an inhibitory (Gi) DREADD, or GFP control into the PVT under the control of the CaMKII promoter, and implanted guide cannulae into the lateral OFC for pathway specific in/activation. Animals received microinjections of the DREADD agonist clozapine-N-oxide (300 μM, i.c. 0.75 μL) directly preceding the reversal learning task. Activating the PVT-OFC pathway with the Gq DREADD significantly impaired reversal learning in non-stressed animals, while inhibiting the PVT-OFC pathway with the Gi DREADD in chronically stressed animals reversed the stress-induced deficits in reversal learning. These results suggest that increased activation in the PVT to OFC pathway is detrimental to reversal learning, and this potentially contributes to the detrimental effects of chronic stress. This implicates a circuit not yet investigated in the role of chronic stress in disruptions in cognitive flexibility. Future experiments will determine how dysfunction in the PVT-OFC pathway may disrupt other OFC-related circuits.

IIMS INSTITUTE FOR INTEGRATION OF MEDICINE AND SCIENCE

14TH ANNUAL FRONTIERS OF TRANSLATIONAL SCIENCE RESEARCH DAY

Posterboard #: 55

Presenter: Eden Valenzuela

Institution: South Texas Oral Health Network

Category: Student

Knowledge About Food Insecurity Among Dental Practitioners: Preliminary Findings from the National Dental Practice-Based Research Network

Eden Valenzuela, Mungia R, Testa A, Hernandez DC, Cunha-Cruz J, Garcia KM, Gilbert GH, National Dental PBRN Collaborative Group

Objective: Food insecurity is a household-level economic and social condition characterized by limited access to nutritious food. While prior literature establishes a relationship between food insecurity and poor oral health outcomes, there is a lack of knowledge of how dental practitioners view food insecurity in professional practice. This study explored dental practitioners' views on food insecurity screening and its impact on oral health. Methods: A 5-question survey ("Quick Poll") was conducted through the National Dental Practice-Based Research Network (PBRN) in the United States. A total of 332 dental practitioners who are members of the National Dental PBRN responded. Results: Preferences for food insecurity screening in dental settings showed substantial variability: 30% in favor, 39% neutral, and 29% against. When identifying the primary oral health issue influenced by food insecurity, 68% pinpointed dental caries. Over half (53%) expressed comfort in directing food-insecure patients to relevant resources. Notably, 61% of respondents expressed interest in being involved in future food insecurity clinical studies. Conclusions: This preliminary study underscores the relevance of food insecurity in the professional dental setting and suggests that the clinical setting may be well suited for educational programs designed to improve the oral health of food-insecure patients. Future research may achieve this goal, including a PBRN clinical study of interventions to improve oral health among food-insecure patients.

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14TH ANNUAL FRONTIERS OF TRANSLATIONAL SCIENCE RESEARCH DAY

Posterboard #: 56

Presenter: Aishwarya Vemula, BS

Institution: UT Health San Antonio

Category: Student

Investigating Nasal and Parotid Activity in Neuropsychiatric Disorders

Aishwarya Vemula, Jacob M. Chmielecki, Joyce G. Schwartz, and William T. Phillips

Introduction: Our study introduces a novel pathophysiological concept for neuropsychiatric disorders (NPD), implicating nasal lymphatic drainage impairment as a potential causative factor and therapeutic target. Through an analysis of bone scan records, a pattern of increased nasal blood pooling was observed in patients with various NPD diagnoses, suggesting a shared underlying mechanism that hinders the clearance of brain waste proteins, potentially contributing to the pathology of mood disorders, sleep disturbances, chronic headaches, and migraines. Methods: We conducted a retrospective examination of the medical records of 200 patients who underwent technetium-99m methylene diphosphonate bone scans with early whole-body blood pool scans (WBBPS) and delayed 3-hour scans. Focusing on the nose-to-heart max ratio (NHMR) from WBBPS, we evaluated the association of this ratio with NPD diagnosis and the use of neuropsychiatric medications (NPM). The study utilized Mann-Whitney U tests and Pearson correlations to investigate the relationships between NHMR and NPD variables, followed by multivariate regression to determine the independent contribution of NHMR to the burden of disease. Results: We found that NHMR significantly and positively correlated to the number of NPD diagnoses (P=0.0013) and the number of NPM classes prescribed to a patient (P=0.004). Specifically, it correlated to the diagnosis of depression (P=0.029), correlating even stronger with depression that was severe enough to require medication (P=0.004). Regression analysis further identified NHMR as a significant predictor of a patient's number of NPD diagnoses (β=1.29, P=0.013), number of classes of NPM prescriptions (β=1.71, P=0.011), and likelihood of having depression requiring medication (β=0.323, P=0.040). Conclusion: The study reveals a notable increase in nasal blood pooling in patients with NPD, supporting the hypothesis that nasal lymphatic and glymphatic dysfunction may play a role in the etiology of these disorders. The observed pattern aligns with the hypothesis of reduced clearance of neural waste products, potentially exacerbating NPD symptoms. These insights offer compelling evidence for modulation of parasympathetic nervous system activity as a novel treatment strategy, specifically targeting nasal turbinate regulation to mitigate the effects of NPDs. This paradigm shift in understanding the pathogenesis of psychiatric conditions could pave the way for innovative treatment modalities.

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Posterboard #: 57

Presenter: Sheryl Vu, BS

Institution: UT Health San Antonio

Category: Student

Development of a SUper Fusion Activator Boosting Natural Killer Cells Anti-tumor immunity in the Tumor Immune Microenvironment

Sheryl Vu, B.S., Gang Huang, Ph.D

Annually, there are two million new cancer cases and 609,360 cancer-related deaths in the United States. While conventional treatments like surgery, chemotherapy and radiation therapy have been pivotal, they often accompany debilitating side effects. Immunotherapy emerges as a promising alternative, harnessing the body's immune system to combat cancer with much fewer adverse effects. Natural Killer (NK) cells are front-line immune cells with potent cytotoxicity. Despite the encouragement of NK-based therapies, clinical outcomes, and patient responses, NK-based immunotherapies have more room to improve due to the complicated immune-suppressive tumor immune microenvironment (TIME). Our project introduces a novel immunotherapeutic protein, the super-fusion activator (SFA). This protein is created by combining two key proteins, R-Spondin 3 (Rspo3) and MHC class I chain-related protein A (MICA), to enhance the functionality of NK cells within the TIME. Rspo3 is crucial in promoting the terminal differentiation of NK cells, while MICA activates NK cells. By fusing Rspo3 and MICA (Rspo3-MICA), we aim to induce terminal differentiation and activation of NK cells, enhance their cytolytic activity within the TIME, and therefore suppress tumor growth. The exciting data shows that the SFA exhibits significant promise as an immunotherapeutic strategy. We utilize the B16F10 melanoma environment to study the SFA. The single-cell flow cytometry analysis revealed that SFA increases terminal differentiation and activation in tumor-infiltrating NK cells, enhancing their functional capacity. Additionally, flow-based NK cytotoxicity assays indicated the increased killing capacity of SFA-induced NK cells against a target cell line ex vivo. To validate the NK cells' cytotoxicity efficacy, we performed in vivo tumor challenge assays. The data showed reduced tumor growth in B16F10-SFA tumor-bearing mice compared to control groups, suggesting that the SFA significantly increased NK cells' anti-tumor immunity in the TIME. This project represents a novel translational approach that could bridge the gap between translational research and clinical application. By optimizing NK cell functionality within the TIME and addressing immunosuppression in cancer treatment, we strive to develop more effective and personalized immunotherapeutic strategies for cancer patients who have not yet benefited from immunotherapy.

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14TH ANNUAL FRONTIERS OF TRANSLATIONAL SCIENCE RESEARCH DAY

Posterboard #: 58

Presenter: Anne Wells, MS

Institution: UT Health San Antonio

Category: Student

Identifying a Downstream Target of TBX1, a Gene Encoded in the 22q11.2 locus, for Oligodendrogenesis and Cognitive Function

Anne Maire Wells, Takeshi Hiramoto, Takahira Yamauchi, Shuken Boku, Gina Kang, Noboru Hiroi

Cognitive deficits are debilitating impairments seen across neuropsychiatric disorders, some of which are thought to arise from aberrant structural development. Copy number variations (CNVs) are relatively large genetic deletions or duplications that result in a wide spectrum of neuropsychiatric symptoms in humans. Carriers of 22q11.2 hemizygous deletions exhibit various cognitive deficits. Heterozygous deletion of Tbx1, a transcription factor gene encoded within the 22q11.2 locus, results in cognitive speed deficits and myelin deficits in the fimbria of adult mice (Hiramoto et al., 2022; Mol Psych). Moreover, when Tbx1+/- was initiated in post-embryonic stem cells by tamoxifen in neonatal mice (P1-5) in nestinCreERTM;Tbx1flox/+ mice, mice exhibited slow speed to complete spontaneous alternation in a T-maze without slow motor movement; when Tbx1+/- was initiated in adolescent mice (P21-25), there was no cognitive deficit. As Tbx1 is enriched in post-embryonic stem cells and in zones of postnatal neurogenesis (e.g., subventricular zone [SVZ]), we hypothesize that Tbx1 may play critical role in the proliferation and maintenance of stem cells in the SVZ via an oligodendrocyte-specific downstream target, which may be critical to the myelination of the fimbria (Hiramoto et al., 2011; Human Mol Genet.). Our ChIP-seq analysis showed that TBX1 binds to a locus near FoxG1, a gene implicated in adult neurogenesis, cerebral dysmyelination, and neurodevelopmental disorders. In neonatal mice, we demonstrate differential colocalization of FOXG1 and TBX1, as well as markers for subpopulations of stem cells, immature neurons, and oligodendrocyte precursor cells (OPCs) in the SVZ proper and the fimbria. We also demonstrate that FOXG1 also colocalizes with TBX1 in proliferating stem cells harvested from the SVZ in vitro. Experiments are in progress to demonstrate successful siRNA silencing of Tbx1 and its effect on functional FOXG1 expression.

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Posterboard #: 59

Presenter: Vanessa Young, MS

Institution: UT Health San Antonio

Category: Student

Sleep Duration and Cognition Performance in Middle-Aged and Other Adults: What is the Role of Depression?"

Vanessa M. Young, Rebecca Bernal, Andree-Ann Baril, Joy Zeynoun, Crystal Wiedner, Alexa Beiser, Matthew P. Pase, Jayandra J. Himali, Sudha Seshadri

Background: Sleep is a fundamental physiological mechanism that is increasingly recognized for its impact on cognitive health in aging populations. Age-related changes in sleep patterns are a common occurrence among older adults and often manifest as difficulties in both falling and staying asleep. In recent studies, short (≤6h) and long (≥9h) sleep duration have been associated with increased risk for cognitive decline and Alzheimer's disease compared to sleeping 7-8 hours per night. Sleep, depression, and cognitive problems may present co-concurrently; however, their complex interrelationships and impact on cognition remain poorly understood. We examined the association between self-reported sleep duration and global cognition in adults aged 45 and above, and whether depression status modifies this association in the community-based Framingham Heart Study Third-Generation, Omni 2, and Offspring cohorts. Methods: Participants were dementia-and-stroke-free adults (n=1,853, mean age 49.8[SD 9.2] years; 57% female). A composite measure of global cognition was calculated from neuropsychological tests assessing four cognitive domains. Sleep duration was categorized as short (≤6h; n=451), average (>6-<9h[reference]; n=1277), and long (≥9h; n=125). Depression was defined as CES-D scores ≥16 or undergoing pharmacological treatment (n=448; 32%). Multivariable linear regression models assessed the association between self-reported sleep duration categories and global cognition, adjusting for age, sex, education, and time between sleep and cognitive assessments. Results: Relative to average sleep duration, long sleep was associated with worse global cognition (β±SE: -0.24±0.07; p<0.001), while short sleep was not (-0.03±0.04; p=0.393). Depression modified the association (p=0.015), where long sleep duration was associated with poorer global cognition only among those with depression (-0.33±0.11; p<0.001), but not among those without (-0.17±0.09; p=0.057); whereas short sleep duration was not associated with cognition in those with (-0.05±0.09; p=0.051) and without depression (-0.03±0.04; p=0.496). Conclusions: Long but not short sleep duration was associated with lower global cognition. This association was observed only amongst those with depression, suggesting that excessive sleep may worsen cognitive deficits in those with mood depression. Further analysis on domain-specific tasks will elucidate complex sleep-cognition-depression relationships to inform sleep and depression treatment strategies for maintaining cognition in older age.