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Heart Rate Variability in Opioid Use Disordered Participants Undergoing Buprenorphine-Assisted Detoxification

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OBJECTIVES/GOALS: This study explored whether gabapentin (GBN) differentially impacted heart rate variability (HRV) and whether HRV was associated with opioid withdrawal ratings among participants with opioid use disorder (OUD) undergoing a randomized, double blind placebo-controlled, trial (RCT) of GBN during a buprenorphine (BUP)-assisted taper. METHODS/STUDY POPULATION: Participants (ages 18-64) with OUD, no recent use of benzodiazepines/barbiturates, and no major psychiatric disorders or unstable medical conditions were enrolled in the RCT, inducted onto BUP starting week 1 day 1 and randomly assigned to receive adjunct GBN or placebo starting week 1 day 3. All participants began a 10-day BUP-taper beginning week 2 day 3. HRV measures were assessed on week 1 day 2 (before GBN/placebo induction), week 2 day 2, and week 3 day 5 (end of BUP taper). HRV metrics were analyzed using Two Sample T-Test to determine differences between GBN vs. Placebo. Correlations between HRV metrics and opioid withdrawal ratings administered at the above timepoints will be analyzed using Spearman correlation. RESULTS/ANTICIPATED RESULTS: 28 participants underwent at least 1 HRV session that resulted in usable data. Preliminary statistical analyses revealed that HRV trended lower for GBN subjects during PB exercises than Placebo subjects, demonstrated by a higher mean heart rate for GBN subjects compared to Placebo subjects (p=0.0506) at the end of the BUP-taper (week 3 day 5). We expect future analyses to demonstrate a negative correlation between certain HRV metrics indicative of parasympathetic tone and opioid withdrawal rating assessment scores indicative of withdrawal severity. Such findings would demonstrate an association between opioid withdrawal severity and lower parasympathetic tone and HRV. DISCUSSION/SIGNIFICANCE: Individuals with OUD have previously been shown to have a lower parasympathetic tone than individuals without OUD. Additionally, opioid withdrawal has been shown to be associated with reduced parasympathetic tone. Our initial findings suggest that adjunct GBN administration was not associated with lower parasympathetic tone during PB exercises.

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Hepatomegaly and fatty liver infiltration among unhealthy weight pediatric population in Puerto Rico

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OBJECTIVES/GOALS: A quarter of Puerto Rican pediatric population are overweight or obese. Pediatric obesity is established as a global public health concern that will develop liver complication as a Non-alcoholic fatty liver disease (NAFLD). This study aims to determine the association between body weight, liver size and texture in Puerto Rican pediatric population. METHODS/STUDY POPULATION: Twenty-nine (n=29) pediatric participants (20 unhealthy weight and 9 healthy weight) between 7 to 19 years underwent panoramic ultrasound imaging of the RLL. Craniocaudal RLL measurement and liver texture were evaluated. Body mass index and waist circumference were also compared. Shapiro-Wilk test and students t-tests were attained with significance at $p < 0.05$. RESULTS/ANTICIPATED RESULTS: Statistical differences were detected between healthy weight and unhealthy weight pediatric patients: (1) RLL craniocaudal diameter (p=0.006); (2) waist circumference ($p < 0.001$); (3) BMI ($p < 0.001$). Unhealthy weight (overweight and obese) pediatric patients presented a greater number of livers with fat infiltration (13) and hepatomegaly (15). DISCUSSION/SIGNIFICANCE: This preliminary results showed that liver size was larger and fatty infiltration are relatively frequent among overweight and obese pediatric patients. Prevention of unhealthy weight and the diagnosis of changes in liver texture and size among pediatric patients is important to prevent progressing of liver disease and avoid irreversible damage.

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High Potency STING Agonists Induce Adaptive Immunity-Dependent Curative Responses in an Immune Checkpoint Blockade-Refractory Glioblastoma Model

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OBJECTIVES/GOALS: Glioblastoma (GBM) is the most common and aggressive adult primary brain malignancy. Clinically, GBM is refractory to T cell immune checkpoint blockade (ICB), in part due to its dense immune suppressive myeloid stroma. Here we show that myeloid-targeting STING agonists can repolarize the GBM microenvironment to cure ICB-refractory GBM models. METHODS/STUDY POPULATION: Using the synthetic cyclic di-nucleotide STING agonist IACS-8803 (8803) we treated orthotopic ICB-refractory QPP8 orthotopic murine GBM tumors intratumorally. We then analyzed survival and performed high parameter flow cytometry profiling of the tumor immune microenvironment following STING agonist treatment. To assess the contribution of adaptive immunity to STING agonist therapeutic efficacy, we treated orthotopic QPP8 tumors implanted in RAG1 KO mice and monitored survival. RESULTS/ANTICIPATED RESULTS: We found that STING agonist therapy cured murine orthotopic QPP8 tumors, in contrast to ICB that showed no survival benefit. In RAG1-/- mice bearing QPP8 tumors STING agonist therapy extended survival, however, the curative effect observed in wild-type mice was lost in the absence of adaptive immunity. STING agonist-treated QPP8 tumors displayed increased counts of CD8 T cells and NK cells, and decreased CD8 T cell PD1 expression. Infiltration of STING-treated gliomas by Ly6C+ F4/80+ Mono-MDSC substantially increased; however, these cells expressed reduced CD206 and CD163, suggestive of reduced immuno-suppression. Finally, in the cervical LN of QPP8-treated mice the frequency and CD80/CD86 expression of cDC1 cells increased.â€‹ DISCUSSION/SIGNIFICANCE: ICB has failed in GBM, and the suppressive myeloid stroma remains a major barrier to generating anti-GBM

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T cell responses. Our work shows that STING activation, which primarily targets innate immunity myeloid cells 'upstream' of T cells in the antitumor immunity cycle, can cure ICB-refractory GBM tumors in an adaptive immunity-dependent manner.

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Hyperorality in Frontotemporal Dementia: Psychiatric and Neural Correlates Across the Disease Course

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OBJECTIVES/GOALS: To describe cognitive and psychiatric symptom profiles of individuals with bvFTD and hyperorality. We test two hypotheses: (1) individuals with hyperorality show more severe psychiatric profiles and (2) neuroanatomic correlates of hyperorality in advanced bvFTD differ from those with early bvFTD. METHODS/STUDY POPULATION: Participants were enrolled in ALLFTD–a multi-site longitudinal study in FTD. We selected the 354 participants who had a primary clinical diagnosis of bvFTD, 344 of whom had data on hyperorality. Each participant underwent extensive clinical interviews and examinations, structural neuroimaging, and blood sampling. Five anatomic regions of interest were identified and analyzed based on previously identified neuroanatomic correlates of hyperorality. Differences in participant characteristics and clinical outcomes were compared using t-tests for continuous variables and PearsonÏ‡2 tests for categorical variables. Linear multivariate regression controlling for age and total intracranial volume (TIV) was used to examine associations between atrophy in regions of interest and hyperorality status. RESULTS/ANTICIPATED RESULTS: Early-stage participants with hyperorality had poorer self-monitoring, empathic concern, and perspective taking as well as higher CDR behavioral subscale scores compared to those without hyperorality. Advanced stage participants with hyperorality had higher scores on the Social Behavior Observer Checklist compared to those without hyperorality. Early-stage participants with hyperorality displayed higher rates of ritualistic/compulsive behavior and motor disturbance. Advanced stage participants had higher rates of apathy, ritualistic/compulsive behavior, anxiety, and elation. In the advanced stage participants, hyperorality was associated with atrophy in the right dorsal striatum, the right ventral striatum, and the right insula cortex. DISCUSSION/SIGNIFICANCE: Hyperorality emerges early and is accompanied by neuropsychiatric symptoms prior to significant neurodegeneration. Overtime, participants with hyperorality develop more psychiatric symptoms as well as atrophy in striatal and insular brain regions. Our findings suggest a role for novel interventions like non-invasive brain stimulation.

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Identification of MCAK Inhibitors that Induce Aneuploidy in Triple Negative Breast Cancer Models

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OBJECTIVES/GOALS: Microtubule poisons, like Taxol, are used to treat triple negative breast cancer (TNBC) and may induce lethal aneuploidy in cancer cells. Patients initially respond, but often develop drug resistance. New targeted drugs that cause aneuploidy may be a valuable approach to therapy. One potential target is the Kinesin 13 MCAK, which limits aneuploidy. METHODS/STUDY POPULATION: TCGA and GSE47561 databases were probed for MCAK expression, and data was stratified by subtype and survival statistics. Knockdown studies were performed to test whether MCAK knockdown sensitizes cells to taxanes for cell proliferation and for induction of aneuploidy. FRET and image-based screens were used to identify MCAK inhibitors from small molecule inhibitor libraries. Inhibitors were then tested for functional effects in multiple cell-based assays and for clonal growth in colony formation assays. RESULTS/ANTICIPATED RESULTS: MCAK expression is upregulated in TNBC and associated with reduced overall survival. Knockdown of MCAK caused a two-to-five-fold reduction of the IC50 for Taxol in cancer cell lines, with no change in normal cell lines. Taxol treatment or MCAK knockdown increased aneuploidy induction, with no additive effect between the two. Our small molecule screen identified three putative MCAK inhibitors, which induced aneuploidy in both taxane-sensitive and taxane-resistant cells. These inhibitors also reduced clonogenic growth, and the most potent inhibitor, C4, caused an approximate five-fold reduction in the IC50 for Taxol in cell proliferation assays. DISCUSSION/SIGNIFICANCE: MCAK can serve as a biomarker of breast cancer prognosis. MCAK knockdown or inhibition sensitizes cancer cells to Taxol without affecting normal cells, making it a potential target in combination therapy. MCAK inhibitors also reduce growth as single agents in taxane resistant lines, giving them potential use as therapies in resistant disease.

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Identification of Proteomic Biomarkers in Puerto Ricans with Pancreatic Cancer

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OBJECTIVES/GOALS: Our objective is to establish a proteomic protein labeling method from tumor tissue and blood samples obtained from patients undergoing surgery for pancreatic cancer in Puerto Rico. Our goal is to discover potential biomarkers in the patient tumor/blood samples that are not expressed in normal control samples obtained from potential organ donors. METHODS/STUDY POPULATION: A pilot study with ten patients undergoing surgery for pancreatic cancer will obtain tumor tissue and blood samples. Protein extracts isolated from tissue/cells will be reduced, alkylated, and digested overnight. Samples will be labeled with TMT reagents and mixed before fractionation and cleanup. Labeled samples will be analyzed with a high-resolution Orbitrap LC-MS/MS before data analysis to identify peptides and quantify the reporter ions. The altered proteins will be analyzed by ELISA to confirm their presence. The protein arrangements will be compared with results from proteomic profile banks to assess their prevalence. As controls, parallel protein analyses will be performed on normal tissue/blood samples from organ donors, facilitated by our local organ procurement organization. RESULTS/ANTICIPATED RESULTS: We anticipate finding proteogenomic material defining PC and new proteomic subtypes not previously described in this population. In addition, studying protein overexpression and underexpression can identify relevant genes and potential biomarkers. We hypothesize that PC in the Hispanic population will show slight variations in tumor protein expression than in other populations, which could lead to the discovery of a new Hispanic-specific biomarker. DISCUSSION/SIGNIFICANCE: We expect to provide essential information that will influence the next steps in developing future screening

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