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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