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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tests. Identifying specific proteins with the potential to become a preventive test should eventually lead to a reduction in morbidity and mortality of PC. The results of this work should lay the foundation that can guide future research.

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Identifying Gaps in Elderly Fecal Incontinence Management

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OBJECTIVES/GOALS: Fecal incontinence is associated with increased caregiver strain, reduced patient dignity and diminished quality of life. A spectrum of incontinence exists, along with a paucity of available solutions for patients and their caregivers. This research aims to stratify this space and identify gaps within the existing solution landscape. METHODS/STUDY POPULATION: To understand this problem, a literature review was performed with key search terms specific to fecal incontinence. These included, anal incontinence epidemiology, fecal incontinence in nursing homes, and incontinence management. To determine gaps within the existing solution landscape, key search terms related to existing solutions for fecal incontinence were also included. These included, fecal management systems, rectal incontinence therapies, and anorectal incontinence procedures.' To perform a population segmentation, white papers, review articles, and cross-sectional studies were reviewed to break down the burden of incontinence in older adults living in nursing facilities and in the community. RESULTS/ANTICIPATED RESULTS: Two unaddressed populations were identified, the first being independent adults over the age of forty, particularly women, who suffer from frequent, bothersome incontinence. These 1.2 million patients are active, living at home, and they restrict their daily activities due to incontinence. However, there are several durable and effective solutions for patients who have sufficient sphincter tone or who are surgical candidates. The second population identified are caregiver dependent older adults residing in nursing facilities who suffer from severe incontinence. This population of 160,000 is affected more severely by consequences of fecal and are poorly served by solutions that are largely absorptive such as diapers and pads. DISCUSSION/SIGNIFICANCE: Although two populations were identified, caregiver dependent older adults residing in nursing homes were identified to have a significant unmet need within incontinence care. Current solutions are onerous and transient, preventing ease and duration for use by caregivers and nurses.

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Identifying Opportunities and Challenges for Translational Informatics Approaches to Real-World Data: A Diabetes Case Study

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OBJECTIVES/GOALS: Diabetes is a group of chronic metabolic diseases and significant gaps remain in our understanding of disease etiology, treatment regimens, and diabetes-related complications. The objective of study is to demonstrate how informatics techniques can leverage real-world data for diabetes research and identify barriers for implementation. METHODS/STUDY POPULATION: We evaluated informatics applications of real-world data in diabetes research conducted by the Facelli Research Group. The types of real-world data were categorized into clinical records, diabetes-related repositories, wearable sensors, and other data sources. Translational informatics applications were characterized into thematic groups of 1.) use of electronic health records, registries, and claims and other data sources to generate real-world evidence, 2.) evolution of novel methods to accelerate generation and use of real-world data, and 3.) infrastructure to support the generation and use of real-world data in translational science. A literature review is being conducted to identify additional articles meeting these themes focused on diabetes research. RESULTS/ANTICIPATED RESULTS: 6 research projects were included for analysis. The diabetes-focus spanned type 1 diabetes, type 2 diabetes, and general diabetes mellitus. Informatics methods included machine learning and data mining while real-world data sources included electronic medical records, the Environmental Determinants of Diabetes in the Young (TEDDY) study, continuous glucose monitors, and the U.S. Environmental Protection Agency (EPA) air pollution monitors. Overall, computability of real-world data, linkage of medical concepts to standardized terminologies, volume of data, and adoption of novel artificial intelligence methods were major determinants of successful implementation. Future work will systematically evaluate informatics applications of real-world data in diabetes from the academic community at large. DISCUSSION/SIGNIFICANCE: Translational informatics approaches are poised to leverage real-world data and better understand diabetes etiology, treatment regimens, and diabetes-related complications. By understanding barriers and opportunities for informatics methods, we can expedite translational applications in diabetes research.

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Identifying vaginal microbiome profiles that influence tenofovir distribution in the female genital tract*

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OBJECTIVES/GOALS: An ex-vivo tissue model has been developed to predict target concentrations of tenofovir diphosphate (TFVdp; active metabolite of tenofovir) but has not been utilized to see how vaginal dysbiosis affects TFVdp/dATP exposure in female genital tract (FGT). My central hypothesis is that presence of specific anaerobic bacteria will increase dATP in FGT. METHODS/STUDY POPULATION: De-identified HIV-negative cervical tissues from women undergoing gynecological surgeries will be procured and a punch biopsy will be used to create explants. TFVdp/dATP concentrations were both tested in both aerobic and anaerobic conditions after a 24-hour incubation in tenofovir (TFV) to determine any changes between conditions. TFVdp/dATP in cervical tissue was be measured using LC-MS. Next, media and explants were collected at baseline to characterize donor microbiome for 6 donors. 16S microbiome sequencing was performed on extracted DNA to obtain the relative abundances of each bacteria species present. To test changes in dATP/TFVdp due to the microbiome, explants will be incubated in TFV for 24 hours with Prevotella and Dialister to specifically see how microbiomes dominated by these taxa affect dATP. RESULTS/ANTICIPATED RESULTS: There was no significant difference in TFVdp formation between aerobic and anaerobic conditions after a 24-hour tenofovir incubation ($p = 0.2$) for 8 donors. dATP was not quantifiable at 24 hours in explants, so explants are being collected before 24hrs during a TFV incubation to determine how quickly dATP depletes after collection. We were able to characterize the donor microbiome in media and tissue at baseline and 24hrs which had inter variability. We did not see any presence of Prevotella or Dialister in any donors. We are working on characterizing

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