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Quantification of the HIV reservoir in the gut-associated lymphoid tissue

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OBJECTIVES/GOALS: The major obstacle to an effective cure or remission for HIV infection is the integration of HIV into the genome of long-lived resting cells which constitute the so-called viral reservoir. With this study we want to elucidate the changes of the gut-associated HIV reservoir at different stages of viral suppression METHODS/STUDY POPULATION: Recent studies have shown that after long-term (>7 years) clinical suppression of peripheral HIV RNA, the circulating viral reservoir does not seem to decline further and, in fact may expand. The gastrointestinal associated lymphoid tissue (GALT) harbors by far the largest fraction of the latently infected cells, however not much is known about its changes over time.We thus quantified the HIV viral reservoir in the GALT by identifying HIV viral transcripts via 10X single-cell RNA sequencing at two GALT-sites in five PWH and compared the amount of HIV RNA found in the group of PWH with early (< 7years) vs late (> 7years) peripheral virological suppression (plasma HIV RNA <20copies/mL). RESULTS/ANTICIPATED RESULTS: Study participants had been diagnosed with HIV infection for a median (IQR) of 31 (32-34) years and had consistently undetectable peripheral blood HIV RNA for the previous 8 (4-15) years. In PWH with consistent viral suppression < 7yrs, 4 (2-6) HIV transcripts were identified in the ileum and 25 (13 – 38) in the colon. In PWH with consistent viral suppression > 7yrs, 0 (0-4) HIV transcripts were identified in the ileum and 7 (14-11) in the colon. Based on these preliminary results we plan to expand our cohort and confirm these results using Proviral DNA quantification. We anticipate that the viral decay in the GALT will follow a slower dynamic than what has been reported for the peripheral blood achieving a steady state after more than 7 years of peripheral viral suppression. DISCUSSION/SIGNIFICANCE: Despite the remarkable progress the survival and quality of life of PWH, after forty years from its first discovery, HIV infection remains uncurable. Considering its critical role, efforts are needed to better understand the dynamics of the GALT-associated HIV reservoir.

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Maternal PTSD and Child Brain Function During Implicit Emotion Regulation

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OBJECTIVES/GOALS: Maternal mental health, such as post-traumatic stress disorder (PTSD), is closely linked to child mental health. PTSD in mothers is associated with their children's emotional responses. We examined associations between maternal PTSD and child brain function during emotion regulation. METHODS/STUDY POPULATION: Eight children ages 10-12 years, whose mothers had trauma histories, performed the Emotional N-Back task during functional MRI scanning. Mothers and children each reported on their trauma exposure and PTSD symptom severity. BOLD response to fearful faces during the Emotional N-Back was extracted from two specific brain regions of interest, amygdala and anterior cingulate cortex. These regions are involved in emotional response and attentional control, which are processes intrinsic to emotion regulation. An independent samples t-test was conducted on children's BOLD response to fearful faces, with maternal PTSD symptom severity (high, low) as the independent variable. A parallel analysis was conducted with child PTSD symptom severity (high, low) as the independent variable. RESULTS/ANTICIPATED RESULTS: We found a main effect of maternal PTSD within brain regions of relevance to implicit emotion regulation. Compared to children whose mothers reported low PTSD symptom severity (n=4), children whose mothers reported high PTSD symptom severity (n=4) showed greater responsiveness to fearful faces in anterior cingulate cortex (t=2.04, p=.09,d=1.44) and amygdala (t=2.44, p=.05, d=1.72) at trending significance. A parallel analysis with child PTSD symptom severity showed no differences in brain function by this factor (ps=.55-.61). DISCUSSION/SIGNIFICANCE: Our pilot study is the first, to our knowledge, to examine associations between maternal PTSD and brain function during emotion regulation in their children. This study lays a foundation for future work; our goal is to explore dysfunction in emotion regulation neurocircuitry as one mechanism linking maternal PTSD to their children's mental health.

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Investigating the Role of FOXA2 During the Transition to Neuroendocrine Prostate Cancer

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OBJECTIVES/GOALS: The goal of this project is to characterize the efficacy of FOXA2 as a potential biomarker for patients with metastatic castrate-resistant prostate adenocarcinoma (CRPC) before transitioning to neuroendocrine prostate cancer (NEPC). NEPC currently has no therapeutic options and poor mechanistic understand of its origins. METHODS/STUDY POPULATION: In our study, we have utilized a multi-omics approach to characterize the potential efficacy of FOXA2 as a prognostic biomarker in numerous patient-derived castrate-resistant prostate cancer (CRPC) models. We have performed ATAC-, ChIP-, RNA-seq and proteomics to fully characterize where FOXA2 is binding genome-wide, how FOXA2 alters chromatin accessibility dynamics, identify regulatory gene targets of FOXA2, and identify FOXA2 protein-protein interactors. We have supported these findings using publicly available data from independent CRPC and NEPC patient cohorts and prostate cancer cell models. RESULTS/ANTICIPATED RESULTS: Our findings show that FOXA2 overexpression suppressed androgen signaling and promoted progression to a NEPC phenotype under short- and long-term androgen deprivation conditions, respectively. Further, FOXA2 redirected the chromatin accessibility landscape to be consistent with an NEPC gene expression program, including increased chromatin accessibility for key NEPC transcription factors. FOXA2 ChIP-seq showed FOXA2 to be bound at known NEPC driver genes and epigenetic modifiers across multiple stages of prostate cancer progression. Lastly, we discovered that FOXA2 physically interacts with key NEPC TFs and epigenetic regulators, suggesting that these FOXA2 physical interactions are required for NEPC

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progression. DISCUSSION/SIGNIFICANCE: This project will determine the efficacy of FOXA2 as a biomarker in advanced prostatecancer samples, which will translate as a potentially useful tool for clinicians to use for treatment of advanced prostate cancer patients.

Regulatory Science

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Examination of Labeling for Geriatric Sub-Populations in Recently Approved Type 2 Diabetes Drugs

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OBJECTIVES/GOALS: To assess labels of drugs approved for Type 2 Diabetes (T2D) for the inclusion of geriatric sub-population data (ages 65-74, 75-84, ≥85) since January 1, 2013, in accordance with international guidance and US regulations in recognition of an aging populations and global demographics. METHODS/STUDY POPULATION: Utilizing FDA Guidance for Industry: Labeling for Human Prescription and Biological Products - Implementing the Physician's Labeling Rule (PLR) Content and Format Requirements and the International Council for Harmonization of Technical Requirements (ICH) E7 guidance "Studies in Support of Special Populations: Geriatrics" as reference for assessing labels. The Center for Drug Evaluation and Research (CDER) new drugs/biologic approvals database was filtered for drugs approved between Jan. 1, 2013 and Dec. 31, 2022 with approved T2D indications. Examined original drug labels and supplements from Drugs@FDA for geriatric use efficacy and safety wording in Section 8.5 (Use in Specific Populations, Geriatric Use), for labels. Subpopulation data in labeling for ages 65-74, 75-84, and ≥85 was analyzed. RESULTS/ANTICIPATED RESULTS: Seven T2D drugs (Trulicity, Tresiba, Adlyxin, Ozempic, Steglatro, Kerendia, Mounjaro) approved within the specified time period were analyzed. In the current examination, all labels contain information regarding efficacy differences between ages 65+ and 75+, however, none contain information on efficacy for ≥85 populations. Four of the seven drugs have been updated with increased data from further efficacy trials for older adults conducted after initial approval. The remaining three drugs have only been reworded, or not changed at all, with no further efficacy trials conducted. DISCUSSION/SIGNIFICANCE: This research shows the gap in representation of older adults in clinical trial data and T2D drugs' labeling. Despite having a higher usage of T2D drugs compared to the general population, older adults and especially the oldest-old (≥85) are underrepresented. Additional demographic requirements ensuring diversity in clinical trials is needed.

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Dihydroxyacetone, a combustion of electronic cigarettes, promotes cardiac-specific injury through metabolic and mitochondrial imbalances*

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OBJECTIVES/GOALS: Electronic cigarettes have become increasingly popular, with various combustion products generated in the process. Dihydroxyacetone (DHA), a carbohydrate made during the heating process. Exposures may reach high micromolar to low millimolar doses of DHA per day and no studies have been done to understand the effects of DHA in the heart. METHODS/STUDY POPULATION: Here, we examine if DHA contributes to these using rat cardiomyocytes, H9c2 cells, and rat cardiac tissues to DHA evaluating metabolic and mitochondrial effects. Using the cells, we will investigate metabolic and mitochondrial pathways using Seahorse, protein expression changes in nutrient sensing pathways, and understand dose-dependent effects of DHA in the heart. Metabolite pools will also be evaluated to understand the changes promoted by DHA. Oxidative stress as previously observed in other cell models will also be measured. Key findings in the cardiac cells will be investigated in the cardiac tissues exposed to DHA. RESULTS/ANTICIPATED RESULTS: We have previously shown DHA induces oxidative stress, metabolic changes, and mitochondrial dysfunction in various cell line models. Interestingly, these effects are highly cell-type dependent. E-cigarettes are known to have toxic cardiac effects, including arterial stiffness, endothelial dysfunction, vascular injury, and oxidative stress. Changes in glycolytic, fatty acid synthesis, and the citric acid cycle enzymes and metabolites were found in the H9c2 cells. We also observed increased mitochondrial ROS and fuel changes due to DHA exposure. In DHA exposed cardiac tissues, we observed oxidative stress and mitochondrial fission and fusion dynamics altered. DISCUSSION/SIGNIFICANCE: These data suggest further study at physiologically relevant doses is warranted to understand how DHA inhaled impacts the long-term health of vapers. As well as the regulation of DHA in e-cigarettes as it has been deemed as safe for topical applications and warned against inhalation.

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Use of Expanded Access at Michigan Medicine and Associations with Neighborhood Factors

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OBJECTIVES/GOALS: Socioeconomic status (SES) affects risk of disease and access to therapies. The expanded access (EA) pathway allows for the clinical use of investigational products for patients who have serious illness but no Food and Drug Administration (FDA)-approved therapeutic options. The SES of patients who receive EA is unknown. METHODS/STUDY POPULATION: We reviewed the patients who were approved for treatment through a single-patient EA pathway between 2018 and 2023. Using Michigan Medicine (MM) DataDirect software linked to the MM electronic medical record system, we linked the EA pathway patients to neighborhood data from the National Neighborhood Data Archive (NaNDA) to compare neighborhood related markers of affluence among EA patients and others treated at MM. We used descriptive statistics to compare variables between EA pathway patients and

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