abnormalities will be exacerbated as the disease state progresses, but at least partially ameliorated with the restoration of dystrophin function. DISCUSSION/SIGNIFICANCE: DMD is a fatal disease with no known cure. Patients develop heart failure in their teens and die in their 20s, so any new insight that may prolong life and improve quality of life for patients is drastically needed. This would be the most accurate preclinical model of DMD cardiomyopathy to date and would investigate yet-untapped aspects of the disease state.

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Analysis of Clinical, Histologic, and Molecular Characteristics of Proliferative Verrucous Leukoplakia

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OBJECTIVES/GOALS: This study aims to develop objectively scored histological characteristics of early oral leukoplakia, which may be correlated with molecular pathways predictive of progression into proliferative verrucous leukoplakia (PVL). The secondary aim is to develop a biomarker profile to be used in diagnosis, staging, and management of PVL. METHODS/STUDY POPULATION: Clinical and pathology records of 120 patients with oral leukoplakia and/or PVL were reviewed. Eight patients were selectedâ€"all had serial biopsies over time leading to PVL suspicion. Specimens were deidentified and subjected to blinded examination by a board certified oral pathologist, then scored relative to the extent of each of the commonly accepted histologic characteristics of PVL: hyperkeratosis, acanthosis, blunt rete ridges, hyperchromatic nuclei, increased nuclear-cytoplasmic ratio, dyskeratosis, and surface corrugation. Given these results, a larger subset of patient samples will be labeled and assayed for expression of epidermal growth factor receptor tyrosine kinases and downstream pro-oncogenic signaling mediators. Expression of these factors will be tested against progression to PVL. RESULTS/ANTICIPATED RESULTS: Histologically, in scoring the specimens from eight subjects, the characteristics of acanthosis, dyskeratosis, and blunted rete ridges had the strongest correlation with eventual progression to PVL. These criteria will therefore be recommended as an objective histopathologic method of identification of patients with high risk of development of PVL, and therefore malignant potential. We expect the results of the biomarker assay to provide a molecular basis for predicting PVL pathogenesis. Particularly, we anticipate pro-oncogenic targets such as EGFR, PI3K, Akt, and mTOR pathways will show increased expression as leukoplakic lesions progress. These results would then provide the basis for testing patient samples for expression of these markers in a longitudinal study of PVL emergence and progression. DISCUSSION/SIGNIFICANCE: The aggressive nature of PVL, with a rate of malignant transformation of 61% and mortality rate of 40%, requires close clinical monitoring in order to improve patient outcomes. Therefore, well defined objective clinical, histologic, and molecular criteria are critical for early detection of sites likely to progress to PVL and subsequent malignancy.

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Assessment of Mental Health Needs of Transgender Adults Seen at a Midwest Transgender Center

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OBJECTIVES/GOALS: Prior studies suggest that transgender individuals are at greater risk of mental health problems. This study aims to determine the mental health care needs of the adult transgender population seen at a tertiary referral hospital in the Midwest region of the United States and assess necessary resources to provide optimal care. METHODS/STUDY POPULATION: This descriptive, retrospective, cross-sectional study included all new transgender patients > 18 years old, seen at the Washington University Transgender Center since December 2019 through May 2022. Electronic medical record data obtained from their initial and subsequent follow-up visits include 1) Demographics: date of birth, age, race, ethnicity, sex assigned at birth, gender identity, zip code of residency 2) Mental health diagnosis: Previous mental health diagnosis, mental health history 3) Mental health care access: mental health providers, mental health treatment, previous mental health admission, resources provided in clinic. RESULTS/ANTICIPATED RESULTS: 487 patient records were reviewed. Median age at initial visit was 24 years (18 - 75 yr), with 46% identify as woman, 37% as man. Predominantly white (84%), 11% were black. 93% had primary health insurance At the first visit, 81% reported having some mental health diagnosis: depression (88%), anxiety (71%), attention deficit disorder (21%). Prior suicide attempt reported on 12% and 5% with self-harm behavior. Only 48% had a therapist and 22% had an established psychiatrist First follow up occurred with a median of 4 months (1-22 months). 4 patients reported new suicide attempt, 3 reported new self-harm behavior. 9 patients required a hospital admission due to a psychiatric condition. 4% reported a new mental health diagnosis (most common: depression and anxiety). No changes noted on access to therapist or psychiatrist DISCUSSION/SIGNIFICANCE: Our study shows that adult transgender individuals have high rates of depression, anxiety, and overall psychological distress which is exacerbated by poor access to mental healthcare. This indicates a critical need to include mental healthcare professionals during the evaluation of adult transgender individuals

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Caspase-1 mediated inflammatory response - a critical player in concussive mild traumatic brain injury (mTBI) associated long term pain

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OBJECTIVES/GOALS: Patients who have experienced conjunctive mild traumatic brain injuries (mTBIs) suffer from a number of comorbidities, including chronic pain. Despite extensive studies investigating the underlying mechanisms of mTBI-associated chronic pain, the role of inflammation after mTBI and its contribution to long-

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term pain are still poorly understood. METHODS/STUDY POPULATION: Given the shifting dynamics of inflammation, it is important to understand the spatial-longitudinal changes and their effects on TBI-related pain. Utilizing a recently developed transgenic caspase-1 luciferase reporter mouse, we characterized the bioluminescence signal evident in both in vivo and ex vivo tissues following repetitive closed head mTBIs. This allowed us to reveal the spatiotemporal dynamics of caspase-1 activation in individual animals over time. Furthermore, we utilize various proteomic and behavioral assays to evaluate the role of caspase-1 mediated inflammation in the development and progression of injury-associated chronic pain. Lastly, by blocking inflammasome caspase-1 activation with a specific inhibitor, we assess its clinical potential as the next therapeutic approach to pain. RESULTS/ANTICIPATED RESULTS: We established that there were significant increases in bioluminescent signals upon protease cleavage in the brain, thorax, abdomen, and paws in vivo, which lasted for at least one week after each injury. Enhanced inflammation was also observed in ex vivo brain slice preparations following injury events that lasted for at least 3 days. Concurrent with the in vivo detection of the bioluminescent signal were persistent decreases in mouse hind paw withdrawal thresholds that lasted for more than two months postinjury. Using MCC950, a potent small molecule inhibitor of NLRP3 inflammasome-caspase 1 activity, we observed reductions in both caspase-1 bioluminescent signals in vivo and caspase-1 p45 expression by immunoblotting and an increase in hind paw withdrawal thresholds. DISCUSSION/SIGNIFICANCE: Overall, these findings suggest that neuroinflammation in the brain following repeated mTBIs is coincidental with a chronic nociplastic pain state, and repeated mTBI-associated events can be ameliorated by a highly specific small molecule inhibitor of NLRP3 inflammasome activation.

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Childhood Emotional Neglect on Nucleus Accumbens Connectivity in Adult Survivors of Trauma

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OBJECTIVES/GOALS: Neuroimaging research has found that childhood maltreatment is related to reduced activation of the nucleus accumbens. The long-lasting impact of this relationship is not as well understood. This study aims to explore the association between childhood emotional neglect and reward-related functional connectivity in an adult trauma sample. METHODS/STUDY POPULATION: Participants (N=169, M age=, 32.2; SD=10.3; women=94) experienced a traumatic injury and were recruited from a Level I Trauma Center. Two-weeks post injury, participants completed the Childhood Trauma Questionnaire (emotional neglect M=10.6; SD=5.2), a self-reported, retrospective account of childhood maltreatment, and underwent a resting-state functional magnetic resonance imaging (fMRI) scan. Whole-brain resting-state left and right nucleus accumbens connectivity analyses were completed using the CONN Toolbox. RESULTS/ANTICIPATED RESULTS: Whole-brain left nucleus accumbens connectivity analyses revealed one significant region (angular gyrus (AG); p DISCUSSION/SIGNIFICANCE: Results suggest that childhood emotional neglect is related to nucleus accumbens connectivity and a brain region associated with memory, attention, and theory of mind in adult survivors of trauma. Early life emotional neglect may be contributing to heightened baseline reward sensitivity–particularly for social rewards (implicated by the AG).

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Chronic HIV infection influences the immune response during acute COVID-19 and long COVID

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OBJECTIVES/GOALS: Despite highly effective antiretroviral therapy, people living with HIV (PLWH) experience chronic immune activation and inflammation which may influence the progression of infections such as SARS-CoV-2. Here, we explore the immune response and clinical outcomes in HIV(+) and HIV(-) individuals experiencing acute COVID-19 and long COVID (LC). METHODS/STUDY POPULATION: We performed flow cytometric analyses on peripheral blood mononuclear cells from the following: 1) HIV(-) individuals experiencing acute COVID-19, 2) PLWH experiencing acute COVID-19, and 3) pre-COVID-19 pandemic PLWH. Additionally, we will perform similar analyses for the following: 1) PLWH experiencing LC, 2) PLWH previously infected with SARS-CoV-2 who recovered, 3) pre-COVID-19 pandemic PLWH, and 4) HIV(-) individuals experiencing LC. Flow cytometry panels include surface markers for immune cell populations, activation and exhaustion surface markers (with and without SARS-CoV-2-specific antigen stimulation), and intracellular cytokine staining. We will also analyze how chronic HIV infection and other clinical and demographic factors (e.g., age, CD4 %) impact persistent symptomatic burden. RESULTS/ANTICIPATED RESULTS: Acute COVID-19 results–Overall, PLWH had higher baseline expression of activation markers OX40 and CD137 on CD4+ and CD8+ T cells, along with increased levels of TNFa producing CD8+ T cells. Interestingly, PLWH had increased expression of exhaustion markers PD1 and TIGIT but decreased expression of TIM3 on CD4+ and CD8+ T cells. Additionally, PLWH had decreased levels of IL-2 and IFNg producing CD4+ T cells which suggests functional exhaustion. Long COVID-19 expected results–we hypothesize that the activation and inflammation seen in chronic HIV infection will lead to more immune dysregulation and subsequently worsened symptomatic burden. Additionally, we hypothesize that PLWH may have different frequencies of certain LC manifestations, such as increased rates of neurocognitive impairment. DISCUSSION/SIGNIFICANCE: Our findings suggest that chronic HIV infection influences acute immune response during SARS-CoV-2 infection, and that PLWH have variable expression of exhaustion markers which warrants further study. Additionally, our findings in the LC cohort will aid in characterizing clinical manifestations and immunologic mechanisms of LC in PLWH.

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Development of a novel tocotrienol analogue, tocoflexol, as a radiomitigator

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OBJECTIVES/GOALS: We have designed an analogue of the Vitamin E tocotrienols called tocoflexol, which improves their pharmacokinetic limitations to make it an effective radiation medical countermeasure. Our goal is to demonstrate that tocoflexol is an

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