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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effective radiomitigator in vivo when administered after exposure to lethal doses of total body irradiation. METHODS/STUDY POPULATION: Tocoflexol was designed using computational techniques to improve binding to ATTP, the key transporter that reduces the rate of elimination of tocols. In vitro studies compared the antioxidant and cell uptake properties to conventional tocotrienols. Next, we used a mouse model of lethal total body irradiation to evaluate its radioprotection efficacy (treating before radiation). To determine the optimal administration route for radiomitigation (treating after radiation), we will test oral and subcutaneous dosing. Mouse survival will be monitored for 30 days after irradiation. Sample tissues will be taken to evaluate the ability of tocoflexol to protect key organs from acute radiation syndrome. The bioavailability of tocoflexol will be evaluated in a rodent model. RESULTS/ANTICIPATED RESULTS: Known Results: Results show that tocoflexol has potent antioxidant properties and high cell uptake. When tocoflexol was administered 24 hours before exposure to lethal doses of radiation, tocoflexol-treated mice showed 100% survival. Anticipated Results: Because of its improved bioavailability and pharmacokinetic properties, we expect that tocoflexol will show radiomitigation efficacy when administered 24 hours after radiation, improving survival and protecting key organ systems from acute radiation syndrome. DISCUSSION/SIGNIFICANCE: There is an unmet need for safe and effective radiomitigators that can offer multi-organ protection and be rapidly administered in the event of nuclear emergencies. Demonstration of radiomitigation efficacy will position tocoflexol as a prime candidate to be developed into a nuclear medical countermeasure and stockpiled for emergencies.

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## Electroencephalographic Correlate of Sensory Over-Responsivity in Adults with Chronic Tic Disorders

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OBJECTIVES/GOALS: To identify an electroencephalographic (EEG) signature of SOR in adults with TS METHODS/STUDY POPULATION: We will recruit 60 adults with CTD and 60 sex- and age-matched healthy controls to complete scales assessing severity of SOR (Sensory Gating Inventory, SGI), tics, and psychiatric symptoms. Subjects will then be monitored on dense-array scalp EEG during sequential auditory and tactile sensory gating paradigms, as such paradigms have been shown to correlate with self-report measures of SOR in other populations. Single-trial EEG data will be segmented into 100-ms epochs and spectrally deconvoluted into standard frequency bands (delta, theta, alpha, beta, gamma) for pre-defined regions of interest. We will conduct between-group contrasts (Wilcoxon rank-sum) of band-specific sensory gating indices and within-group correlations (Spearman rank correlations) between sensory gating indices and SGI scores. RESULTS/ANTICIPATED RESULTS: We hypothesize that, relative to controls, adults with CTD exhibit impaired sensory gating and that extent of impairment correlates with severity of SOR. 14 adults with CTD (9 men, 5 women) and 16 controls (10 men, 6 women) have completed the protocol to date. Within this sample, adults with CTD showed significantly reduced sensory gating compared to controls in frontal (CTD median 0.12 dB (interquartile range -0.15–0.70 dB); control -0.37 dB (-0.80–-0.13 dB); p = 0.01) and parietal (CTD 0.17 dB (-0.08–0.50 dB); control -0.20 dB (-0.43–0.10 dB); p = 0.01) gamma band during the 100-200 ms epoch in the tactile paradigm. No significant between-group differences were evident for the auditory paradigm. Among adults with CTD, multiple sensory gating indices significantly correlated with SGI scores. Enrollment continues. DISCUSSION/SIGNIFICANCE: Results aim to clarify the extent of sensory gating impairment in TS and identify a clinical correlate of neurophysiologic dysfunction in the disorder. Such knowledge has direct implications for identification of candidate neurophysiologic biomarkers, an express goal of the National Institutes of Health.

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## Exploring gastrointestinal bacterial colonization in rosacea as a biomarker for systemic abnormalities in innate immunity

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OBJECTIVES/GOALS: To investigate the relationship between abnormal bacterial colonization of the gastrointestinal (GI) tract and systemic abnormalities in innate immunity as it contributes to the pathogenesis of rosacea. METHODS/STUDY POPULATION: This is a prospective observational study of patients with erythematotelangiectatic or papulopustular rosacea. The study participants will undergo urea breath testing for Helicobacter pylori (Hp) and hydrogen-methane breath testing for small intestinal bacterial overgrowth (SIBO). Colonic microbiome analysis will be performed using 16S rRNA sequencing of fecal samples. Further, key pro-inflammatory cytokines will be quantified from serum samples. Markers for rosacea subjects and subgroups will be compared by standard analysis of variance methods where appropriate, and Tukey studentized range tests will be done for specific comparisons. Chi-square tests will be used to assess group differences in categorical data. At least 42 subjects will be studied to provide 80% power atÎ±-0.05. RESULTS/ANTICIPATED RESULTS: We hypothesize that the results of this study will support an observed relationship between abnormal GI bacterial colonization and systemic innate immunity abnormalities in rosacea as determined by three primary endpoints: a significantly greater prevalence of Hp and SIBO in rosacea participants, presence of pro-inflammatory cytokines linked to rosacea pathogenesis including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-Î±, and Granulocyte-macrophage colony-stimulating factor (GM-CSF), and observation of distinct, metabolically active colonic bacterial communities specific to rosacea participants. DISCUSSION/SIGNIFICANCE: By identifying rosacea as a cutaneous manifestation of a more systemic inflammatory disease, the results of this study will have implications for the development of important pharmacological interventions targeting key inflammatory pathways in rosacea pathogenesis.

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## Exploring the Genetic Contribution to Oxidative Stress in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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OBJECTIVES/GOALS: Strong evidence has implicated oxidative stress (OS) as a disease mechanism in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The study aim was to assess whether a C>T single nucleotide polymorphism (SNP) (rs1800668), which


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