
International Symposium on NeuroVirology
held jointly with the
Society on NeuroImmune Pharmacology
INTERNATIONAL SOCIETY FOR NEUROVIROLOGY
FOUNDED 1998
SOCIETY ON NEUROIMMUNE PHARMACOLOGY
SNIP
April 10-14, 2018
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Chicago, Illinois, USA
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Speaker Abstracts (without poster, in alphabetical order of first authors as of 3/29/2018):

S1

Role of astrocytes in HAND

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HIV infection of the brain leads to a spectrum of neurologic diseases collectively termed HIV-Associated Neurocognitive Disorders (HAND). HAND persists despite maximal HIV suppression. The cellular and molecular mechanisms driving HAND are not entirely clear. We study the role of astrocytes in HAND. Astrocytes perform vital functions to maintain blood-brain barrier integrity, neuronal homeostasis, and immune regulation. Today, there is a greater appreciation for the role of astrocytes in health and neurodegenerative diseases. We show that HIV and inflammatory signals down regulate Wnt/β-catenin (a pro-survival) pathway in astrocytes leading to neuronal injury. Further, we show that HIV leads to astrocyte senescence by down regulating □-catenin using in vitro studies and two small animal models (a humanized mouse model of HIV/NSG-huPBMCs & HIV-transgenic rats). Consequences of down regulation of β-catenin results in robust inhibition of two key proteins in the glutamate/glutamine cycle, glutamate transporter excitatory amino acid transporter 2 (EAAT2 or GLT-1 in rodents) and glutamine synthetase (GS), induces the proinflammatory cytokines IL-6 and the chemoattractant IL-8, and removes the transcriptional block to HIV replication in astrocytes. Gain of β-catenin function in astrocytes ameliorate and/or reduce these negative effects. Lastly, plasma expression of an antagonist of the Wnt pathway (Dickkopf-related Protein 1/DKK1) is associated with HIV-associated neurocognitive impairment. Collectively, these studies indicate that disruption of β-catenin signaling in astrocytes leads to both virologic (heightened HIV replication) and biologic (senescence & a neuroinflammatory profile) consequences, which would have profound impact on neuronal health. As such, β-catenin induction in astrocytes is a candidate therapeutic target for HAND and other neurodegenerative diseases where this pathway is disrupted.

S2

Adolescent stress sex-specifically alters neuroimmune reactivity in the hippocampus and periphery

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Adversity early in life predicts psychiatric disorders such as depression and anxiety and an immune component may be involved. We have previously shown that chronic adolescent stress (CAS) in rats primes the hippocampal inflammatory response in adulthood. However, the mechanism of CAS-induced priming, and associated sex differences, are currently undefined. We tested the hypothesis that CAS exaggerates induction of pro-inflammatory NF-kappa-B pathway in adult hippocampus without compromising peripheral immune response, and assessed potential sex differences. Male and female adolescent rats underwent the CAS paradigm or received no stress. Five weeks following the last stressor, all rats received a single, systemic injection of either low dose of lipopolysaccharide (LPS) or vehicle to unmask possible priming effects of CAS. Hippocampal total RNA was used to perform RNA-Seq and enriched transcriptional pathways were identified using gene set enrichment analysis (GSEA). To assess the impact of CAS on peripheral NF-kappa-B function, we measured DNA binding activity of NF-kappa-B in spleen and plasma concentrations of IL-1beta, IL-6 and TNF-alpha. GSEA identified NF-kappa-B as

the most enriched pathway in CAS rats compared to non-stressed, same-sex controls following LPS. Targeted qPCR confirmed that CAS exaggerated the induction of I-kappa-B, p65, and p52 in males and females. CAS also led to an enhanced enrichment of the glucocorticoid receptor (GR) signaling pathway in females, suggesting altered balance between GR and NF-kappa-B signaling. In contrast to the hippocampal findings, indices of peripheral inflammation were not impacted by CAS in females. Male CAS rats mounted a blunted serum corticosterone and exaggerated serum IL-1β response to LPS, suggesting possible glucocorticoid resistance. Our results indicate that chronic stress experienced during adolescence leads to long-lasting changes to the hippocampal transcriptome. We conclude that while CAS enhances innate immune reactivity in both males and females, the mechanism and manifestation of such alterations may be sex-specific.

S3

Modeling microglia to explore the immune component of neurodegenerative disease

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Genetic studies have implicated microglia, the resident innate immune cells of the central nervous system (CNS), as playing a role in susceptibility to neurodegenerative diseases, however translating these genetic findings into targetable molecular outcomes is challenging as human microglia are not readily accessible. Therefore, previous studies utilized the more easily accessible innate immune cell type, monocytes. But do these monocyte eQTLs really reflect genetic driven gene expression changes in the context of the CNS environment? In the present study, we developed an *in vitro* cell model system composed of human monocyte-derived microglia-like (MDMi) cells that recapitulated key aspects of microglia phenotype and function. We used this model system to perform an eQTL study examining 94 genes from loci associated with MS, AD, and PD. We identified six loci in which the risk haplotype drives the association with both disease susceptibility and altered expression of a nearby gene (cis-eQTL). For two of these, differential gene expression dictated by the disease associated loci was only present in the MDMi, not the monocytes. This demonstrates that the genotype-driven gene expression can be context-specific and highlights the importance of examining genotype-induced gene expression in CNS-relevant cell types.

S4

Role of Intergins in Modulating SIV/HIV Pathogenesis on Gut-Brain Axis

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The gut-brain axis (GBA) that acts as a conduit between the gut and brain plays a pivotal role in relaying neural and immunological signals between the two organs. During acute infection, HIV/SIV targets gut CD4+ T cells and macrophages that express high numbers of CCR5-expressing activated CD4+ T cells. The integrin α4β7 is found at high levels on the surface of some CD4+ T cells and is involved in gut- cell trafficking. Increased frequency of α4β7hi-expressing CD4+ T cells within the gastrointestinal associated lymphoid tissues (GALT) during infection appears to correlate with increased viral loads and enhanced disease progression. Our recent studies demonstrated that administration of anti-α4β7mAb to ART-treated SIV-infected RMs resulted in significant suppression of plasma/GALT viral loads even after ART treatment interruption. Since the gut and brain are connected via the GBA, we hypothesize controlling viral loads in the GALT will lead to diminished viral reservoirs in the two compartments. Recent findings on the role of α4β7 in attenuating viral progression in the gut and brain during HIV/SIV infection will be presented at the meeting.

S5

Endolysosome de-acidification affects the structure and function of endolysosomes as well as their ability to interact with and signal between other intracellular organelles

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Endolysosomes are highly dynamic acidic organelles critical for a wide spectrum of biological functions including their classical roles in degrading various macromolecules, damaged organelles, and protein aggregates, and their new roles in signaling and plasma membrane repair. Endolysosomes are especially important for neural cells, because neurons are post-mitotic cells that require constant protein quality control and membrane turnover. The acidic environment ion the lumen of endolysosomes is maintained primarily by vacuolar H^+ ATPase. Besides high concentrations of protons, endolysosomes contain a spectrum of highly active protease enzymes as well as high concentrations of a variety of cations including calcium and iron. Loss of the proton gradient in endolysosomes leads to de-acidification, impaired degradation capabilities, abnormal accumulation of various macromolecules, and a profound redistribution of endolysosomes inside of cells. Endolysosome de-acidification also leads to efflux of readily releasable stores of calcium and iron, and these released cations can affect endolysosome trafficking and the cross-talk between endolysosomes and other organelles. Here, we will present data from others and us showing that neuronal endolysosomes contain readily releasable stores of calcium, that calcium released from endolysosomes upon deacidification can induce the release of calcium from other organelles and increase influx through the plasma membrane, that deacidification-induced calcium release from lysosomes leads to lysosome exocytosis, and that deacidification-induced iron release can affect mitochondria function. Increased awareness of the complexities involved in inter-organellar signaling might help lead to a renewed interest in cell biology, classically defined. (This work was supported by P30GM103329, R01MH100972, R01MH105329, R21DA040519.)

S6

Heterogeneity of primary human microglia at the single cell level

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In this presentation, we will discuss a novel evaluation of human microglia using modern single cell sequencing technologies. Leveraging both fresh autopsy and surgical samples, primary human microglia were isolated from frontal or temporal cortical tissue. We obtained individual transcriptomes from over 16,000 microglia purified from cortical tissue of 12 subjects. These data yield an intriguing first look at the extent of inter- and intra-individual heterogeneity in human microglial populations. We identify a dozen different subtypes. In most individuals, there is a large cluster of homeostatic microglia and smaller numbers of microglia have differentiated to different cell states. Some of these are enriched for genes linked to diseases such as multiple sclerosis or Alzheimer's disease. However, there is not a single "disease associated microglia". There are also several microglial cell states that are only seen in a subset of subjects, hinting at an extensive heterogeneity in the cell states that these highly plastic cell can adopt. Thus, we have an interesting first appreciation of the complexity of microglial subpopulations in the human brain that will help to guide a new generation of studies of human neuroimmunology.

S7

Decoding Astrocyte Diversity in the Adult and Malignant Brain

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Astrocytes are the most abundant cell type in the brain and perform a wide array of functions, yet the nature of their cellular heterogeneity and how it oversees these diverse roles remains shrouded in mystery. Using an intersectional FACS-based strategy, we identified 5 distinct astrocyte subpopulations present across 3 brain regions that exhibit extensive molecular diversity. Application of this molecular insight towards function revealed that these populations differentially support synaptogenesis between neurons. We identified correlative populations in mouse and human glioma, finding that the emergence of specific subpopulations during tumor progression corresponds with the onset of seizures and tumor invasion. In sum, we have identified subpopulations of astrocytes in the adult brain and their correlates in glioma that are endowed with diverse cellular, molecular, and functional properties. These populations selectively contribute to synaptogenesis and tumor pathophysiology, providing a blueprint for understanding diverse astrocyte contributions to neurological disease.

S8

Neuropathologic correlates and genetic architecture of microglial activation in the aging brain

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Microglia, the resident immune cells of the brain, are increasingly studied for their roles in brain health. However, little is known about the molecular-genetic causes or consequences of microglial activation in the aging human brain. We assessed the effect of microglial activation in the aging human brain by calculating the proportion of activated microglia (PAM), based on morphologically defined stages of activation (I, II, or III) in four cortical and subcortical regions sampled postmortem from up to 225 elderly subjects. We found that cortical and not subcortical PAM measures were strongly associated with β-amyloid and tau-related neuropathology, as well as rates of longitudinal cognitive decline, independent of APOE ε4. The effect size of PAM measure is substantial, being comparable to that of APOE ε4, the strongest genetic risk factor for Alzheimer's disease (AD). Causal mediation modeling suggests that PAM accelerates cognitive decline indirectly via an increase in tau pathology, supporting an upstream role for activated microglia in AD. Genome-wide analyses identified two independent loci (rs2997325 and rs183093970) that influence cortical PAM ($p < 2.5x10-8$), one of which (rs2997325) also affected in vivo microglial activation measures from positron emission tomography scans in an independent cohort. Polygenic scoring found a genetic overlap of PAM burden with several immune and aging-related traits, primarily AD and educational attainment. We implicated activated microglia as having a causal role in worsening cognitive decline via tau pathology. We also identified and validated a novel locus that influences microglial activation, providing a strong biological foundation for further investigation. Finally, genetic predisposition to higher microglial activation correlates with genetic risk for several traits including educational attainment, raising the intriguing possibility that genetic determinants of microglial activation may affect early life cognitive processes important for scholarly performance.

S9

LASER ART THERANOSTICS: Pathways for HIV Eradication

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Long-acting slow effective release (LASER) antiretroviral therapy affects antiretroviral therapy (ART) by improving antiretroviral drug (ARV) half-life and delivery to anatomic HIV sanctuaries. Chemical modification of ARVs and their encasement into nanoparticles improves macrophage particle uptake and release. LASER ART particles are 200-400 nanometers in size and able to house hydrophobic drug within excipients. Particle size, surfactant coating, surface charge and shape facilitates antiretroviral delivery. An advantage of LASER ART over conventional ART lies in the ability to form stable nanocrystals containing significant drug concentrations for drug release at sites of persistent viral growth. This yields > 50-fold improvements in drug pharmacokinetic and tissue reservoir biodistribution profiles. Hydrophilic drugs can also be converted to hydrophobic prodrugs that prolong host carboxyesterase cleavage. Nanoparticles of myristoylated nucleoside and nonnucleoside reverse transcriptase and integrase inhibitors showed improved efficacy and half-life based on macrophage depot formation. Multimodal imaging for theranostic nanoprobes were created to facilitate studies of ARV biodistribution. Intracellular drug trafficking, transport, retention and delivery schemes are the current platforms used to facilitate viral eradication strategies.

S10

Mouse models for HIV-1 elimination

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A variety of humanized mouse models have been developed for use as model systems to test strategies that effect HIV-1 elimination. Mice reconstituted with human CD34+ hematopoietic stem cells (HSC) can reflect natural HIV-1 infection including viral persistence in the nervous system. The characterization of such models that employ NOD/*scid*-IL2Rγc-/- (NSG or NOG) mice show persistent viral infection in CD4+ T cells and monocyte-macrophages in lymphoid and genitourinary tissues and the brain (in meninges and perivascular areas). Transplantation of human glial to NSG mouse creates an astrocyte network in subventricular subregions of the mouse brain. HIV-1 infection results in defense signaling patterns. To generate human myeloid cells in brain we prepared transgenic NOG mice expressing the human interleukin 34 (IL-34) gene with links to colony stimulating factor 1 receptor (CSF1R) establishing tissue human resident microglial cells in mouse brain tissue. Human IL-34 transgenic NOG mice transplanted with CD34+ HSC were employed to test the consequences of HIV-1 infection to human microglia. Infection was demonstrated with up to 70% infected human microglial cells distributed in the frontal cortex, striatum, hippocampus, thalamus, cerebellum and brain stem. Systemic infection of humanized mice resulted in viral ingress across the blood brain barrier. The newly generated blood brain mice is being used to study viral invasion, persistence and strategies for HIV-1 eradication.

S11

Increases in CCR5-medited inflammation underlie the neuronal injury, behavioral deficits, and altered rewarding properties of opiates in an HIV-1 Tat transgenic model.

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Opiate exposure can exacerbate the pathophysiology of HIV in the nervous system by increasing inflammation, glial reactivity, and neuronal injury/dysfunction. However, unlike the exaggerated inflammation and neuropathology seen with combined opiates and HIV-1, HIV-1 Tat-induction in

transgenic mice decreases the antinociceptive properties and physical dependence, and reduces the physical dependence and locomotor activity to opiates, which is accompanied by reductions in μ-opioid receptor (MOR) activation as assessed by [^{35}S]GTPγS binding. Tat-induced increases in inflammation coincide with decreases in the potency and efficacy of opiates. Prior and ongoing studies imply that CCR5 has a significant role in opiate and Tat-induced interactive inflammation, gliosis, and neuronal injury *in vitro* and *in vivo*. To test whether CCR5-mediated inflammation altered opiate responsiveness, pharmacologic (maraviroc) and genetic [inducible Tat(±); constitutive CCR5−/− transgenic mice] strategies were used. Acute (4 day) maraviroc pretreatment blocked the effects of Tat, reinstating morphine potency in non-tolerant mice and restoring withdrawal symptomology in morphine-tolerant mice. During acute withdrawal, HIV-1 Tat significantly exacerbated morphine-conditioned place preference; maraviroc potentiated these effects, while maraviroc alone exerted no behavioral effects. Alternatively, following prolonged (≥2 weeks) maraviroc exposure or in CCR5(−/−) transgenic mice, the effects of morphine and Tat were markedly altered—suggesting adaptive changes are operative. Our data suggest that Tat-dependent alterations in MOR-CCR5 interactive signaling increase neuroinflammation, gliosis, and neuronal injury, which results in the diminished therapeutic efficacy and an apparent increased abuse liability of opiates in HIV-infected individuals. Support: NIH R01 DA034231 and K02 DA027374

S12

Nrf2 activation in astrocytes modulates disease progression in mouse models of Parkinson's and Alzheimer's disease

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The brain is very sensitive to changes in redox status, thus maintenance redox homeostasis in the brain is critical for the prevention of accumulating oxidative damage. Aging is the primary risk factor for developing neurodegenerative diseases. In addition to age, genetic and environmental risk factors have also been associated with disease development. Markers of increased oxidative stress, protein and DNA modification, inflammation, and dysfunctional proteostasis have all been implicated in contributing to the progression of neurodegeneration. The ability of the cell to combat oxidative damage and maintain clearance mechanism for misfolded aggregating proteins determines the cells fate. A critical pathway in this regard is the Nrf2-ARE pathway. Nrf2 activation has been shown to mitigate many pathologic mechanisms associated with Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and multiple sclerosis. In contrast, genetically knocking-out Nrf2 exacerbates neuronal death in models of PD, HD, Alexander's disease, and aggravates experimental autoimmune encephalomyelitis, a model of multiple sclerosis. *In vitro* studies have indicated that the Nrf2 pathway is relatively unresponsive in neurons; whereas, Nrf2 is highly inducible in astrocytes. Indeed, astrocytic-specific Nrf2 activation confers protection to co-cultured neurons *in vitro*. To determine if this observation could translate to the *in vivo* situation, transgenic mice with astrocyte-specific overexpression of Nrf2 (GFAP-Nrf2 mice) were generated. The GFAP-Nrf2 mice have significantly increased resistance to chemical models of Parkinson's disease (MPTP) and HD (complex II inhibitor-malonate). In addition, we have demonstrated that the GFAP-Nrf2 mice extend the life span, delay disease onset, and protect against neurodegeneration in mouse model of ALS, Alexander's disease, and PD. In the PD model overexpressing mutant alpha-synuclein, astrocytic Nrf2 overexpression prevents the autophagy dysfunction associated with disease progression. This talk will discuss some of these experiments in greater detail, as well as ongoing viral and transgenic approaches using Nrf2 in PD and AD.

S13

What do reactive astrocytes do?

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Although reactive astrocytes are rapidly generated following brain injuries, infection and neurodegenerative and neuroinflammatory diseases, their role in trauma and disease states is not well understood. Previously we distinguished two reactive astrocyte subclasses based on the kind of inducing injury. We named these classes "A1" and "A2". Based on their gene profiles we hypothesized that they were harmful and helpful respectively. We have shown that the harmful A1 reactive astrocytes are induced by classically-activated neuroinflammatory microglia. Specifically, we found that activated microglia induce A1s by secreting Il-1α, TNFα, and C1q, and that these factors together are necessary and sufficient to induce A1s both in vitro and in vivo. A1s have little ability to promote neuronal survival, outgrowth, synaptogenesis or phagocytosis and instead are powerfully toxic to neurons and oligodendrocytes. We further showed that A1s are present in human Alzheimer's disease, Huntington Disease, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis, and that death of axotomized CNS neurons is prevented when A1 formation is blocked with neutralizing antibodies to Il-1α, TNFα, and C1q. We now show the role of A1 neurotoxic reactive astrocytes in the context of neurodegeneration in both acute (ischemia) and chronic (glaucoma) mouse models. Taken together our findings strongly suggest that A1s drive death of neurons in neuroinflammatory insult and in neurodegenerative disorders, and point the way forward for developing new treatments for these diseases.

S14

Diet-induced inflammation in female monkeys is related to disinhibited eating and alterations in corticostriatal circuits

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Consumption of highly palatable, calorically dense diets (CDD) is rewarding, as CDD intake leads to dopamine (DA) release that activates corticostriatal rewards pathways. CDD-induced changes in appetite and the concomitant accumulation of body fat accumulation over-time in obese individuals are associated with decreased DA 2 receptor (D2R) levels and functional connectivity (FC) in corticostriatal regions. One mechanism that may contribute to these diet-induced disruptions in reward circuitry is inflammation. While increased peripheral cytokines concentrations are associated with decreased central DA concentrations, decreased D2R levels in the striatum, and decreased FC between the prefrontal cortex (PFC) and nucleus accumbens (NAcc), it remains unclear whether consumption of an obesogenic diet increases neuroinflammation to disrupt corticostriatal reward pathways. Using a non-human primate animal model, tested the hypothesis that diet-induced peripheral inflammation and neuroinflammation will predict increased calorie intake, altered DA concentrations, and decreased corticostriatal FC. Socially housed adult female rhesus monkeys that were maintained in one of two dietary conditions for one year. One cohort of females (n=18) was fed a typical low calorie primate laboratory diet (LCD), and a second cohort (n=16) had access to both the LCD and a CDD. All animals were fed *ad lib* using a previously validated automated feeding system. Female monkeys with access to a CDD for one year in a dietary choice condition consumed more total calories and gained more weight than females with access to only a LCD. Females with access to the diet choice showed greater peripheral CRP levels, lower CSF DA levels and greater HVA:DA ratios. CRP levels in females with access to a diet choice predicted decreased FC between the NAcc and the ventromedial PFC. However, increased HVA:DA ratios mediated the effect of CRP on NAcc-vmPFC connectivity, suggesting that diet-induced inflammation decreases presynaptic DA to alter corticostriatial functional connectivity. Additionally, microglia

activation within the dorsolateral and orbitofrontal prefrontal cortices was greater for females in the obesogenic diet condition compared to females with access to only a LCD. Heightened microglia activation in females in the diet choice condition predicted increased calorie intake, greater peripheral and central inflammation. Taken together, our results indicate that increased inflammation may contribute to alterations in reward pathways to facilitate increased caloric intake in an obesogenic dietary environment.

S15

Cannabinoid modulation of the gut brain axis in chronic HIV/SIV infection

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Although, long-term combination anti-retroviral therapy (cART) has dramatically improved the life expectancy of human immunodeficiency virus (HIV) infected patients, chronic gastrointestinal disease/dysfunction and deficits in CNS immune activation persist. Emerging evidence points to pro-inflammatory perturbations of the gut-brain axis as potentially contributing to CNS immune activation and reservoir persistence in HIV infected patients on ART. This study examined the effect of cannabinoid [(delta-9-tetrahydrocannabinol (THC)] administration to cART naïve chronically SIV-infected rhesus macaques (RMs) on plasma and tissue viral loads, intestinal T-cell dynamics, gut and oral dysbiosis, plasma markers of microbial translocation (lipopolysaccharide binding protein) and epigenetic changes in intestinal epithelium and basal ganglia. Although, plasma viral loads did not differ between the Vehicle (VEH-SIV) and cannabinoid (THC-SIV) treated groups, cannabinoid treatment significantly attenuated activation induced T-cell proliferation and exhaustion as early as 14 days until 120 days post SIV infection. Interestingly, cannabinoids prevented *Lactobacillus* depletion in colon and saliva and reduced plasma levels of lipopolysaccharide binding protein (LBP) during chronic SIV infection. In basal ganglia, although SIV RNA levels did not differ between the two groups, miR-155 and miR-142-3p, two important miRNAs that regulate proinflammatory signaling were significantly upregulated in VEH-SIV but not THC-SIV RMS. These data are amply supported by our previously published findings on reduced levels of TNFα, IL1β, IL6 and MCP1 in striatum of cannabinoid treated SIV-infected RMs. Overall, our findings suggest that cannabinoids exert protective effects in the GI tract and brain in chronic HIV/SIV infection. These potentially involve direct effects on the brain and indirect effects by blocking inflammation stemming from microbial translocation. Future studies are needed to determine the impact of cannabinoids on the gut brain axis in the setting of cART.

S16

Self-administration of methamphetamine in rats induces Parkinson's disease-like pathology

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Parkinson's disease (PD) is a neurodegenerative disorder that is diagnosed once motor deficits are present, i.e., "clinical" PD. The "subclinical" progression of PD involves initial reduction of dopaminergic neurons in the nigrostriatal pathway, inflammation, and accumulation and aggregation of α-synuclein (α-syn) in brain and gut neurons. Recent retrospective studies reveal that individuals with a history of methamphetamine (meth) dependence are up to three-fold more likely to develop PD (Callaghan *et al. Drug Alcohol Depend*, 2012; Curtin *et al. Drug Alcohol Depend*, 2015), suggesting that meth may initiate subclinical features of PD that eventually manifests as clinical PD. Supporting this hypothesis, we revealed that laboratory rats self-administering small doses of meth exhibit moderate, *abstinence-time dependent* reductions in tyrosine hydroxylase (TH); wherein, like PD, gut (Flack *et al. Eur J Neurosci*, 2017 and striatal lesions precede nigral lesions (Kousik *et al. Eur J Neurosci*, 2014). To

extend this work to include other biomarkers of PD, we further studied male Sprague Dawley rats self-administering meth for 14 days and saline-yoked controls. PD-like motor behavior was assessed every week. Brain and colon tissues were harvested one or 56 days after the last meth session and prepared for immunoblotting or immunohistochemistry of α-syn and GFAP. We determined that PD-like motor deficits were not observed during meth self-administration or one day after the last meth session, but did emerge during the 56 day forced abstinence period. One day after meth treatment, we observed (i) no changes in striatal GFAP or α-syn, a time at which there is no change in striatal TH (Kousik *et al.*, 2014), (ii) an increase in the number of α-syn+ cells in the nigra ($p<0.05$), and (iii) an increase in the amount of in GFAP ($p<0.001$) and α-syn ($p<0.001$) in myenteric neurons of the colon, a time at which there is a decrease in myentric TH (Flack *et al*., 2017). Following 56 days of meth abstinence, we observed (i) decreased α-syn in the striatum ($p<0.05$), (ii) the increase in the number of α-syn+ cells was maintained in the nigra ($p<0.01$), and (iii) colon GFAP and α-syn returned to control levels. These data support the concept that meth initiates subclinical nigrostriatal and colon PD-like pathology, which, upon protracted abstinence, progresses to nigrostrial dysfunction that is sufficient to result in clinically-relevant PD-like motor pathology, even though the colon recovered. These studies offer insights into the enhanced vulnerability of meth abusers to develop PD.

S17

Probing dynamic neuroimmune interactions involving brain mu-opioid receptors and plasma IL-1 family cytokines in negative affective states

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Existence of mind-body interactions have been reported for centuries both anecdotally and (more recently) via rigorous scientific studies. However, in order to fully understand the impact of the mind on human physiology, we must be able to characterize underlying mechanisms. Availability of molecular brain imaging tools and their application to behavioral research facilitates probing of potential mechanisms underlying significant mind body relationships. Of particular relevance these mind-body phenomena are interactions between stress activated opioid neurotransmission in the brain and potent stress-activated plasma immune factors, IL-1 family cytokines. Bi-directional communications have been various reported (in animal models) between peripheral immune factors and brain mu-opioid receptor activation. However, these neuro-immune phenomena are substantially under-investigated in-vivo in humans. In 3 separate whole brain (voxel-by-voxel) analyses in our lab, we identified significant interactions between in-vivo measures of stress-activated brain mu-opioid receptors and simultaneous stress-activated plasma IL-1 family cytokines during standardized, experimental induction of 3 separate affective states. As a follow-up, in preliminary TSPO PET brain imaging study, we find that brain microglial activity (quantified by ^{11}C-PBR28 PET) is highly associated with measures of mood, fatigue, and behavioral coping style. Brain regions where these effects localized overlapped across analyses and are believed component to circuits critically involved in 1) processing emotionally salient and stressful events and 2) modulating expectation/reward behavior. Taken together, these findings provide novel, in-vivo evidence of specific neuro-immune mechanisms underlying common mind body interactions frequently identified across a range of illnesses including co-morbid depression, substance use disorders, and additional medical illnesses impacted by psychosocial stress (coronary artery disease, infectious diseases, etc.). We believe these novel and innovative research paradigms will pave the way for future research studies aimed at enhancing secondary prevention strategies in depression, substance use disorder, and their commonly co-morbid medical illnesses (HIV, coronary artery disease, etc.).

S18

Cognitive and neurostructural consequences of cancer treatments

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Impaired cognitive function in cancer survivors is a common problem and typically attributed to the negative effects of cancer treatments on the brain. Beyond diminishing quality-of-life, these cognitive impairments increase healthcare costs, morbidities, and ultimately, mortality. The underlying mechanisms by which cancer treatments cause "chemobrain" remain unspecified, however deteriorations in brain microstructure (gray and white matter), correlated with poor cognitive performance, have been identified as a possibility. The hypothesis for this project is that systemic taxol chemotherapy treatment impairs cognitive functions and induces long-term white matter damage using a novel tumor-resected mouse breast cancer survivor model. To model typical breast cancer survivors, all female Balb/c mice were ovariectomized and a single mammary tumor was induced using murine 67NR cancer cells. Because the tumors are non-metastatic, after 2.5 weeks of growth (tumors ~1 cm^3), all tumors were surgically resected. Half of the mice received paclitaxel chemotherapy (30 mg/kg i.p.; every other day for 6 cycles); the other half received vehicle. All mice underwent brain diffusion tensor imaging (DTI) either immediately after the last chemotherapy treatment or 2.5 months later. After imaging, neuroinflammation was quantified in brain tissues using qPCR. An additional cohort of mice underwent cognitive behavioral testing at the same time points. Immediately after the final dose, chemotherapy significantly altered multiple aspects of DTI anisotropy in widespread brain regions (hippocampus, hypothalamus, thalamus, brainstem, and cerebellum) and inversely decreased the apparent diffusion coefficients relative to vehicle controls. Chemotherapy simultaneous induced neuroinflammation and fatigue behavior. Moderate taxol chemotherapy treatment acutely induces overt brain gray matter imaging and transcriptional changes. Using models to relate imaging biomarkers to underlying pathology and cognitive changes can be translated clinically to identify patients at risk for developing cognitive deficits and to monitor progress or treatment efficacy of chemotherapy-induced brain changes.

S19

Patterns and predictors of cognitive impairment among HIV-infected women

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Background: HIV-associated cognitive impairment (CI) remains a major clinical issue in HIV care and a high priority for HIV research. Although the incidence of dementia has markedly decreased in the era of combination antiretroviral therapy, 30-60% of individuals will exhibit CI at some point during their lifetime. Understanding the patterns, predictors, and mechanisms of CI among HIV-infected (HIV+) individuals is critical for developing adjunctive therapies to improve cognition. We have been focusing on these issues in women, in some cases compared to men, as they are a relatively understudied group and, for a multitude of reasons (e.g. high prevalence of psychological risk factors (PRF)), may be at greater risk for CI compared to HIV+ men. **Methods**: We first examined sex differences in neuropsychological (NP) performance using women from the Women's Interagency HIV Study (WIHS; 419 HIV+, 291 HIV-) and a matched group of men from the Multicenter AIDS Cohort Study (MACS). Next, we examined patterns and predictors (PRFs) of HIV-associated CI over a 4 year study duration within WIHS (631 HIV+, 301 HIV-). Moving from epidemiological to mechanistic studies, we examined the role of inflammation and the hypothalamic-pituitary-adrenal (HPA) axis as potential mechanisms underlying CI. The first study examined cross-sectional associations between monocyte-driven inflammatory markers and NP performance in the WIHS. The second study used low dose hydrocortisone (LDH) as an experimental test of whether inflammation and the HPA axis underlie CI. The LDH study was a double-

blind, placebo-controlled, cross-over study in HIV+ women (n=36) randomized to either hydrocortisone (10mg oral) or placebo. We investigated the acute (30 minutes) and delayed effects of LDH (~4 hours) on cognition. Cortisol and immune levels were measured in saliva and anxiety and mood were measured in questionnaires. **Results**: A direct comparison of WIHS and MACS participants revealed that HIV+ women performed more poorly on select cognitive domains compared to HIV+ men. In a replication of our previous cross-sectional studies, we found CI in learning, memory, and attention and a decrease in motor skills over time in HIV+ compared to HIV- women. Although HIV+ and HIV- women had similar rates of PRFs, stress in particular was found to negatively influence verbal abilities in HIV+ compared to HIV- women. Mechanistically, in our cross-sectional study, higher levels of monocyte-driven inflammatory markers were associated with lower NP performance in HIV+ women. In our pharmacological challenge study, LDH enhanced learning and memory both 30-45 min after LDH administration and after 4 hours. Decreases in inflammatory markers with LDH were associated with better cognition in women. **Conclusions**: HIV+ women are more cognitively vulnerable than HIV+ men in several cognitive domains. Prominent cognitive deficits in HIV+ women are evident in the domains of learning, memory, and attention. Mechanistic work implicates inflammation and alterations in the HPA axis as potential mechanisms underlying the stronger association between stress and cognitive impairment in HIV+ compared to HIV- women.

S20

Saving the Synapse: Pruning and Plasticity in Development and Disease

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Neural activity is needed to fine tune brain circuits. MHC Class I molecules and PirB receptor, thought previously to function only in immunity, act at neuronal synapses to regulate synapse pruning and plasticity. Changes in expression could contribute to Autism and Schizophrenia, and possibly to synapse loss in Alzheimer's disease

S21

The CD33 locus dictates a differential TREM1 response in reaction to amyloid beta

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Alzheimer's Disease GWAS identified genes implicated in inflammation, including CD33. Our group reported an association of the CD33 risk allele with increased myeloid cell surface CD33 expression and decreased $A\beta_{1\text{-}42}$ internalization. We explored whether genotype differences in CD33 respond differently to stress. Monocytes were treated with $A\beta_{1\text{-}42}$ stress and we showed that treatment induced higher apoptosis and lower uptake capacity in monocytes with the risk allele. Whereas, cells of the protective allele had lower apoptosis and an increase of TREM1 expression. TREM1 function was evaluated in stress responsiveness and monocytes with risk allele were treated with a TREM1 agonist, resulting in a decrease of apoptosis and an increase of uptake. Furthermore, a specific association between CD33 and neuritic plaques was observed in human brain tissue. Evidence suggests that CD33 expression is related to neuritic plaques, and CD33 may regulate the myeloid cell response to $A\beta_{1\text{-}42}$ in a TREM1 dependent manner.

S22

Neuroinflammatory mechanisms of morphine-induced hyperalgesia

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Morphine is commonly used to manage pathological pain such as HIV-associated pain. However, recent clinical evidence indicates that chronical use of morphine in fact exacerbates pain state. The mechanism by which morphine exacerbates pain pathogenesis is unclear. We have used the morphine-induced hyperalgesia (MIH) mouse models to investigate the molecular and cellular processes contributing to MIH development. Our data suggest that critical role of glial reaction and the expression of pro-inflammatory cytokines in the spinal dorsal horn. We further determined the contribution of Wnt signaling pathways in the control of the morphine-induced neuroinflammation. Our findings may provide insights into the pathogenesis of MIH.