Welcome to the 8th Annual Midwest Brain, Behavior and Immunity Meeting! The aim of these meetings continues to allow for collaboration among research laboratories in the Midwest in the field of psychoneuroimmunology, while promoting the visibility of the field’s trainees. Scientists of all levels will be on-hand to share their expertise and research findings in this multidisciplinary field. We have talks ranging from CNS disorders, cancer, sleep, pain and integrative therapies, to specific components of immune-modulated pathways.

This year, special presentations will be given by:

Rodney Johnson, PhD University of Illinois, Urbana-Champaign – Cornerstone Lecture on Friday, December 1st.

Jonathan Kipnis, PhD University of Virginia – Keynote Lecture on Saturday, December 2nd.

We encourage senior investigators and trainees alike to reach out and network with others you may not know, all in an effort to increase one’s awareness of other research agendas and opportunities.

Thank you for your continued support and we hope that you enjoy this year’s meeting!

Jennifer Knight, Andrew Steelman, & Derek Wainwright
2017 Meeting Organizers
Acknowledgements

We gratefully acknowledge the following for their generous contributions:

Paul Eubig
Laura Gralton Philanthropic Fund, Medical College of Wisconsin
Linda Janusek
Kathryn J. Jones
Keith W. Kelley
Herbert Matthews
Patricia Rush
Andrew Steelman
Derek Wainwright
**Agenda – Friday, December 1st**

**Baldwin Auditorium, Robert H. Lurie Medical Center, Northwestern University**

1:00 – 1:40 Registration

1:45 – 1:50 Welcome – **Derek Wainwright, PhD** *Northwestern University*

1:50 – 2:00 BBI Introduction – **Jackie Newman** *University of Illinois Urbana-Champaign*

**Session 1: Substance P, CNS Disorders, and Brain Tumors**

Session Chairs:
- Lijie Zhai, PhD *Northwestern University*
- Ann Ragin, PhD *Northwestern University*

2:00 – 2:20 **Amanda Brandow, DO, MS** *Medical College of Wisconsin* – “Substance P is Increased in Patients with Sickle Cell Disease and Associated with Haemolysis and Hydroxurea Use”

2:20 – 2:40 **Michal Juda, BS** *University of Illinois Urbana-Champaign* – “Indoleamine 2,3-dioxygenase 1 (IDO1) Protects Against Picornavirus-Induced Seizures in Mice”

2:40 – 3:00 **William Drobyski, MD** *Medical College of Wisconsin* – “Host Interleukin 6 Production Regulates Inflammation but not Tryptophan Metabolism in the Brain During Murine GVHD”

3:00 – 3:20 **Lijie Zhai, PhD** *Northwestern University* – “Cell-Specific IDO1 Differentially Drives GBM Immunosuppression”

3:20 – 3:40 **Erik Ladomersky, PhD** *Northwestern University* – “Combination Immunotherapy with IDO1 Inhibition Enhances Treatment Efficacy in Multiple Models of Glioblastoma Model”

3:40 – 4:00 **Derek Wainwright, PhD** *Northwestern University* – The Failure of Immunotherapy for Treatment of Glioblastoma: We’re Not in Melanoma Anymore, Toto”

******** BREAK ********

4:00 – 4:15

4:15 – 5:00 **Cornerstone Lecture: Rodney Johnson, PhD** *University of Illinois Urbana-Champaign* - “Aging, microglial cell priming and discordant communication between the immune system and brain”

5:00 – 7:00 Poster session and social hour
Session 2: Childhood Adversity, Stress, and Sleep
Session Chairs:
Aimee Karstens, MA University of Illinois at Chicago
Annie Thomas, PhD, RN Loyola University Chicago
Yi Sun University of Illinois Urbana-Champaign

8:00 – 8:20  Dina Tell, PhD Loyola University Chicago – “During Stress, Heart Rate Variability Moderates the Impact of Childhood Adversity in Women with Breast Cancer”

8:20 – 8:40  Christopher Coe, PhD University of Wisconsin-Madison – “Persistent Immune Effects of Early Institutionalization in Adopted Adolescents”

8:40 - 9:00  Makeda Austin, BS Northwestern University – “Socioeconomic Disadvantage in Early Childhood, But Not Adulthood, Predicts Accelerated Epigenetic Aging of Monocytes”

9:00 – 9:20  Rose Meacham, PhD University of Illinois Urbana-Champaign – “Quantifying Affective Immersive Experiences in Virtual Reality”

9:20 – 9:40  Karen Kotz, PhD, APN, NNP-BC Loyola University Chicago – “Sleep Quality Across Pregnancy: Relationship with Psychological Well-Being and Inflammation”

9:40 – 10:00  Rekha Balachandran University of Illinois Urbana-Champaign – “Pharmacological Challenges Examining the Underlying Mechanism of Altered Response Inhibition and Attention Due to Circadian Disruption in Adult Long-Evans Rats”

* * * * * * * BREAK * * * * * * *

10:00 – 10:20

Session 3: IL-6, Neuroinflammation, and Immunoregulation
Session Chairs:
Suzanne Segerstrom, PhD, MPH University of Kentucky
Christopher Coe, PhD University of Wisconsin-Madison

10:20 – 10:40  Makoto Inoue, PhD University of Illinois Urbana-Champaign – “Immune Cell-Mediated Neuronal Damage in the Brain During Cryptococcus-Associated Immune Reconstitution Inflammatory Syndrome”
10:40 – 11:00  **Suzanne Segerstrom, PhD, MPH University of Kentucky** – “Latent Infection, Self-Regulation, and Executive Function in Older Adults”

11:00 – 11:20  **Rebecca G. Reed, PhD University of Kentucky** – “Synergistic Effect of CMV and Stress on Immunosenescence in a Longitudinal Study of Older Adults”


11:40 – 1:00  LUNCH (provided)

**Session 4: Peripheral Inflammation and Pain**

**Session Chairs:**
Jennifer Knight, MD, MS *Medical College of Wisconsin*
Gregory Freund, MD *University of Illinois Urbana-Champaign*
Adrienne Antonson, PhD candidate *University of Illinois Urbana-Champaign*

1:00 – 1:20  **Stephanie Matt, PhD candidate University of Illinois Urbana-Champaign** – “Inhibition of DNA Methylation with Zebularine Alters Lipopolysaccharide-Induced Neuroinflammation in Mice”

1:20 – 1:40  **Matthew Jefferson, PhD candidate Iowa State University** – “PKR as a Conserved, Early Neuroinflammatory Mediator Under Viral, Bacterial, and Metabolic Change: A Role in Parkinsonian Pathogenesis?”

1:40 – 2:00  **Sandi Tenfelde, PhD, APN, WHNP-BC Loyola University Chicago** – “A Gentle Yoga Program for Women with Urgency Urinary Incontinence”

2:00 – 2:20  **Adrienne Antonson, PhD candidate University of Illinois Urbana-Champaign** – “Porcine Fetal Microglial Cells Are Transiently Altered by Maternal Viral Infection”

2:20 – 2:40  **Jennifer Knight, MD, MS Medical College of Wisconsin** – “Pre-Transplant Tocilizumab is Associated with More Severe Depression, Anxiety, Pain, and Sleep Following Allogeneic Hematopoietic Cell Transplantation”

2:40 – 3:00  **Charles Raison, MD University of Wisconsin-Madison** – “What’s Hot: Immune System Contributions to the Antidepressant Effects of Whole Body Hyperthermia”

* * * * * **BREAK** * * * * *

3:00 – 3:15

3:15 – 4:00  **Keynote Speaker: Jonathan Kipnis, PhD University of Virginia** – “Meningeal Immunity and Lymphatics in Brain Disorders”

4:00  Closing Remarks – BBI Annual Meeting Organizers
Location of the Robert H. Lurie Medical Research Center
Oral Presentation Abstracts
(Those marked with * are also being presented in poster format)

**Substance P Is Increased in Patients with Sickle Cell Disease and Associated with Haemolysis and Hydroxurea Use**
Brandow AM, Wandersee NJ, Dasgupta M, Hoffmann RG, Hillery CA, Stucky CL, Panepinto JA
Sickle cell disease (SCD) pain transitions from acute to chronic for unknown reasons. Chronic elevation of the pain neurotransmitter substance P (SP) sensitizes pain nociceptors. We evaluated SP levels in controls and SCD patients during baseline and acute pain and investigated associations between SP and age, gender, pain history, haemolysis and hydroxyurea (also termed hydroxyurea) use. Plasma SP levels were measured using enzyme-linked immunosorbent assay. Independent samples t-test compared SP levels between: (i) SCD baseline and controls, and (ii) SCD baseline and acute pain. Multivariate linear regression determined associations between SP and age, gender, pain history and hydroxyurea use. Spearman correlation determined an association between SP and haemolysis. We enrolled 35 African American controls, 25 SCD baseline and 12 SCD pain patients. SCD patients were 7-19 years old. Mean ± standard deviation SP level (pg/ml) in SCD baseline was higher than controls (32.4 ± 11.6 vs. 22.9 ± 7.6, P = 0.0009). SP in SCD pain was higher than baseline (78.1 ± 43.4 vs. 32.4 ± 11.6, P = 0.004). Haemolysis correlated with increased SP: Hb (r = -0.7, P = 0.0002), reticulocyte count (r = 0.61, P = 0.0016), bilirubin (r = 0.68, P = 0.0216), lactate dehydrogenase (r = 0.62, P = 0.0332), aspartate aminotransferase (r = 0.68, P = 0.003). Patients taking hydroxyurea had increased SP (β = 29.2, P = 0.007). SP could be a mediator of or marker for pain sensitization in SCD and a biomarker and/or target for novel pain treatment.

**Indoleamine 2,3-Dioxygenase 1 (Ido1) Protects Against Picornavirus-Induced Seizures in Mice**
Viral infection accounts for the largest specified cause of encephalitis-associated hospitalizations. Survivors of viral encephalitis are at high risk for developing post-encephalitic epilepsy although the mechanisms underlying this effect are ill-defined. In the current study, we used the Theiler’s murine encephalomyelitis virus (TMEV) preclinical model to induce icterus and epileptogenesis and test the hypothesis that activation of the kynurenine pathway modulates the incidence and severity of seizures. We found that intracerebral injection of TMEV increased hippocampal cytokine (Tnf, Il6, Ifng) and Ido1 expression within two days of infection. Compared to wild-type C57BL/6 mice, infected Ido1/- mice had an increased seizure incidence, viral RNA load and proinflammatory cytokine expression by day 8 post-infection. Infected Ido1/- mice had reduced numbers of CA1 hippocampal neurons. Furthermore, infected Ido1/- mice demonstrated increased hyperexcitability and decreased anxiety-like behavior compared to C57BL/6 mice. Our findings suggest that Ido1 has protective action during picornavirus-induced icterogenesis and neuropathology.

**Host Interleukin 6 Production Regulates Inflammation but Not Tryptophan Metabolism in The Brain During Murine GVHD**
William R. Drobsky, Ludovic Belle, Vivian Zhou, Kara L. Stuhr, Margaret Beatka, Emily M. Siebers, Jennifer M. Knight, Michael W. Lawlor, Casey Weaver, Misato Hashizume, Cecilia J. Hillard
Graft versus host disease (GVHD) induces pathological damage in peripheral organs leading to clinical manifestations. Patients with GVHD can also have behavioral alterations affecting overall cognitive function; the extent to which GVHD alters inflammatory and biochemical pathways in the brain remains poorly understood. We employed murine GVHD models to demonstrate that donor T cells accumulate in the brain and affect a proinflammatory cytokine milieu associated with specific behavioral abnormalities. Host IL-6 was identified as a pivotal cytokine mediator. Host indoleamine 2,3 dioxygenase was up-regulated in GVHD in an IL-6 dependent manner in microglial cells and accompanied by dysregulated tryptophan metabolism in the raphe nucleus and prefrontal cortex. Blockade of the IL-6 pathway reduced donor T cell accumulation, inflammatory cytokine gene expression, and host microglial cell expansion, but did not reverse GVHD-induced tryptophan metabolite
dysregulation, indicating that inhibition of IL-6 signaling attenuates neuroinflammation, but does not reverse all brain metabolic abnormalities during GVHD.

* Cell Specific IDO1 Differentially Drives GBM Immunosuppression
Lijie Zhai, Ph.D.; Erik Ladomersky, Ph.D.; Carlos R Dostal, B.S.; Kristen L Lauing, Ph.D.; Kathleen Swoap, B.S.; Leah K Billingham, B.S.; Galina Gritsina, M.S.; Meijing Wu, Ph.D.; Robert H McCusker, Ph.D.; David C Binder, MD/PhD; Derek A Wainwright, PhD
Indoleamine 2, 3 dioxygenase 1 (IDO1), a tryptophan (Trp) catabolic enzyme, has been hypothesized to contribute toward the suppression of tumor immunity. We previously demonstrated that tumor cell-, but not non-tumor cell-IDO1, suppresses T cell-mediated glioblastoma (GBM) regression in mice. Paradoxically, the survival advantage mediated by immune checkpoint blockade is abrogated by non-tumor cell IDO1-deficiency. In current study, we demonstrate that, non-tumor cells, rather than mouse GBM cells, are the dominant contributor to IDO1-mediated enzyme activity. We also show the novel associations between maximally-effective immune-checkpoint blockade-mediated survival, non-tumor cell IDO1 and intra-GBM Trp catabolite levels. These data suggest for the first time that, GBM cell-mediated immunosuppression is IDO1 enzyme independent, while the survival benefits of immune checkpoint blockade require non-tumor cell IDO1 enzyme activity. This work indicates that choosing an appropriate IDO1 pharmacologic will maximize the effectiveness of future immune checkpoint blockade approaches.

Combination Immunotherapy with IDO1 Inhibition Enhances Treatment Efficacy in Multiple Models of Glioblastoma Model
Erik Ladomersky, Lijie Zhai, Kristen L. Lauing, Meijing Wu, C. David James, Roger Stupp, Derek A. Wainwright
Progress in improving outcomes for glioblastoma (GBM) patients has been modest at best. Despite maximum surgical resection, radiotherapy (RT), and chemotherapy, the combination of which is considered the best treatment for GBM, median overall survival (OS) is only approximately 15 months. In this preclinical study, the efficacy of the novel, IDO1 inhibitor, BGB-5777, was investigated when used in combination with PD-1 blockade and/or whole brain radiation (WBRT) in an immunocompetent mouse model of GBM. Mice engrafted with the GL261 tumors and treated with the combination therapy showed a significant increase in overall survival (53 days) compared to IgG treated mice (25 days). This therapy regimen also significantly increased durable survival (>120 days) (P<0.0001) in mice ic. IDO1 overexpressing GL261 or CT-2A cells. Ultimately, the data suggest that using radiation to induce potential immunogenicity and/or inflammation in GBM, while co-inhibiting immunosuppression, is a rational and potentially clinically-beneficial pursuit.

During Stress, Heart Rate Variability Moderates the Impact of Childhood Adversity in Women with Breast Cancer
Dina Tell, Herbert L. Mathews, Robert L. Burr, Linda Witek Janusek
Childhood adversity has long-lasting neuro-biological effects that can manifest as exaggerated stress responsivity to environmental challenge, including a dysregulated hypothalamic-pituitary-adrenocortical axis and increased levels of inflammatory mediators. In this investigation, vagal activity was assessed for its capacity to moderate the relationship between childhood adversity and stress responsivity during Trier Social Stress Test (TSST). Thirty women with breast cancer underwent TSST; their heart rate was recorded to assess vagal tone (high frequency component of heart rate variability) and saliva samples collected to measure cortisol and IL-6. Vagal tone during the TSST moderated the effect of childhood adversity. Women who had lower vagal modulation during TSST and greater childhood adversity showed a larger rise in cortisol and IL-6 compared to women with lower adversity. The findings demonstrate that childhood adversity and lower vagal tone are associated with an elevated stress response. Inflammatory and HPA dysregulation subsequent to stress may impair cancer control.
Persistent Immune Effects of Early Institutionalization in Adopted Adolescents
Christopher L. Coe, Bonny Donzella, and Megan Gunnar

Early rearing can affect many aspects of immunity, but most studies focus primarily on inflammatory processes. Our research extends a previous finding indicating that CD4+ and CD8+ lymphocytes were skewed in adolescents adopted after spending their infancy in institutions (Esposito et al., 2016). Blood samples were obtained from 100 teens (57 adopted, 43 control; mean 16.5 yr; mean age at adoption: 1.5 yr). Optimized 18-color immunophenotyping was employed to characterize subsets on a BD LSR Fortessa. Four stimulants were used to polarize cellular responses (PHA, LPS, PMA/IO, anti-CD3/CD28 MoAB). Eighteen cytokines were quantified in the stimulated supernatants. A number of persistent immune effects were found even after adoption into supportive families. More consistent and larger differences were observed in the adopted adolescent males than females. Our presentation will emphasize T cell immunity rather than the proinflammatory pathways more typically examined in studies of early adversity.

Socioeconomic Disadvantage in Early Childhood, But Not Adulthood, Predicts Accelerated Epigenetic Aging of Monocytes
Makeda Austin, Edith Chen, Kharah Ross, Michael S. Kobor, & Gregory E. Miller

Low socioeconomic status (SES) in both childhood and adulthood independently contribute to increased risk for aging-related chronic diseases. One mechanistic hypothesis for these associations involves faster cellular aging of immune cells, which could plausibly contribute to chronic disease pathogenesis by compromising host resistance and/or upregulating inflammation. However, little is known about the association between life course SES and cellular aging. Accordingly, the present study examines the association of childhood and adulthood SES with a novel biomarker of cellular aging termed the “epigenetic clock,” in monocytes. Additionally, we examine health behaviors and depressive symptoms as potential explanatory pathways. The study involved 335 participants between the ages of 15 and 55 from Vancouver, Canada and surrounding areas. Enrolled participants had to fit into four life-course SES trajectories, corresponding to low-low, low-high, high-low and high-high combinations of childhood (ages 0 to 5) and current SES respectively. Cellular aging of monocytes was measured using Horvath’s DNA-methylation derived measure of epigenetic age acceleration. Results indicated that socioeconomic disadvantage during early childhood, but not adulthood, was associated with accelerated epigenetic aging of monocytes. Subsequent path analyses were inconsistent with scenarios in which health behaviors or depression played an explanatory role in the main effect. These findings suggest socioeconomic disadvantage in early childhood is independently predictive of cellular aging of immune cells, and that this association is not modified by upward SES mobility later in life.

* Quantifying Affective Immersive Experiences in Virtual Reality
Subject to change: Rose Meacham, Dr. Steve DiVerdi, Dr. Bhautik Joshi

Though VR has been coined the “empathy machine” the technical reasons why this might be the case are not scientifically supported. During this research project we will identify which 3D cinematic techniques enhance user engagement and how these differ from user engagement with 2D videos. Research has demonstrated that significant behavioral changes result from VR based training and that individuals have heightened empathic responses for characters in VR films compared with 2D films. Our study will not only help set a new standard for this type of cinema, it will also enhance the development of new behavioral training techniques that are currently used by clinicians and professionals. It will provide clinicians with a new tool to treat conditions such as PTSD, anxiety, phobias, and trauma. Results from this study can help individuals with autism or Asperger’s improve their social skills by practicing in controlled VR environments. It can also help improve VR training used for athletes and actors, as well as fighting unconscious bias and discrimination. The deliverables from this research will provide a comprehensive qualitative and quantitative analysis of user engagement to specific 3D cinematic techniques and provide metrics to help clinicians, developers, researchers, and creatives design the most accurate immersive based behavioral modification techniques.
Sleep Quality Across Pregnancy: Relationship with Psychological Well-Being and Inflammation
Karen Kotz, Dina Tell, Herbert Mathews, Linda Janusek
Increasingly, poor sleep is linked to health risks. Pregnant women often experience poor sleep; however, the extent to which disturbed sleep during pregnancy contributes to psychological morbidity and dysregulation of proinflammatory cytokines critical for the timing of gestation remains unknown. The purpose of this study was to investigate the relationship among poor sleep, psychological well-being, and levels of the proinflammatory cytokine TNF-alpha across pregnancy. Pregnant women completed self-report measures of psychological well-being and sleep quality, and provided blood samples for measurement of plasma TNF-alpha. Findings revealed that lower sleep quality related to lower psychological well-being across pregnancy. Also, there was a trend for poor sleep to correlate with greater levels of TNF-alpha during the second trimester of pregnancy. These findings emphasize the need to assess sleep quality in pregnant women and to implement strategies to improve maternal sleep quality, which can benefit maternal health and optimize birth outcomes.

* Pharmacological Challenges Examining the Underlying Mechanism of Altered Response Inhibition and Attention due to Circadian Disruption in Adult Long-Evans Rats
Rekha Balachandran, Katherine Hatcher, Megan Sieg, Margaret Richards, Michael Leventhal, Megan Mahoney, Paul Eubig
Circadian disruption (CD) impacts endogenous rhythms governing behavior and physiology. Our study investigated the effect of 2 models of CD on response inhibition (RI) and attention. Adult Long-Evans rats tested under the 2 models of CD had reduced RI, which has not been previously reported, and were less attentive than controls. We postulated, based on our results, that an interaction between cholinergic and dopaminergic neurotransmitters was key in the relationship between circadian rhythmicity and RI, particularly in the prefrontal cortex, where DA release is modulated by nicotinic acetylcholine (nACH) receptors. We performed pharmacological challenges, combining an nACh agonist and DA receptor antagonist under 3 circadian conditions to identify differential effects of the drugs on RI. The results indicate an interaction between cholinergic and dopaminergic neurotransmitters that is differentially affected by 2 forms of CD.

* Immune Cell-Mediated Neuronal Damage in The Brain During Cryptococcus-Associated Immune Reconstitution Inflammatory Syndrome
Yee Ming Khaw, Mary Clutter, Makoto Inoue
Immune reconstitution inflammatory syndrome (IRIS) is an adverse syndrome induced when immune function is restored in immunocompromised patients with pre-infection of pathogens such as fungi, mycobacteria, and viruses. Among several pathogen-associated IRISs, Cryptococcus-associated IRIS (C-IRIS) is one of the most serious diseases implicated in the death of IRIS patients and is reported in HIV-infected patients undergoing antiretroviral therapy and immunocompromised patients who have received a solid-organ transplant. To identify mechanisms of C-IRIS development, we recently developed a mouse model for C-IRIS, wherein mice deficient in immune components, including CD4+ T cells, are infected with Cryptococcus pneumonia, and then receive transferred CD4+ T cells. Similar to phenotypes in patients with C-IRIS, C-IRIS mice display inflammation and mortality. C-IRIS mice also showed an accumulation of CD4+T cells in the brain and severe brain damage before mouse death. Thus, we hypothesize that CD4+ T cells induce brain neuronal damage via edema.

Latent Infection, Self-regulation, and Executive Function in Older Adults
Suzanne C. Segerstrom, Rebecca G. Reed
Recent attention to the effects of latent infection on human brain and behavior has focused on the parasite Toxoplasma, which directly infects the brain, and herpesviruses, which infect diverse cells and are also associated with proinflammatory immunosenescence, which in turn could affect the brain. The present investigation tested prospective effects of baseline Toxoplasma and cytomegalovirus (CMV) among 147 older adults (age 60-93 at baseline). Participants were administered a measure of self-regulation (BRIEF) and a battery of executive function tests semiannually up to 9 times. Multi-level models with administrations at Level 1 and people at Level 2 included baseline age, education, and administrations as covariates. CMV+ status (79%) and titers associated with poorer self-regulation (status: t(411)=2.15, p=.03; titers: t(637)=2.61, p=.009) but not
executive functions. The proinflammatory immunosenescence associated with CMV may have greater implications for control over behavior and cognition with aging compared with direct infection of the brain by Toxoplasma.

**Synergistic Effect of CMV and Stress on Immunosenescence in a Longitudinal Study of Older Adults**
Rebecca G. Reed, Steven R. Presnell, Charles T. Lutz, & Suzanne C. Segerstrom
Stress can reactivate cytomegalovirus (CMV), a herpesvirus implicated in immunosenescence. We investigated how CMV and stress synergistically predict immunosenescence both between- and within-people over time. Older adults (N=149, baseline age 60-93, 72% CMV+) reported perceived stress and provided blood (for CMV IgG and senescence markers on T and NK cells) biannually for 2.5 years. In multilevel models (covariates: sex, age), higher CMV titers associated with higher T and NK cell senescence between people (p’s<.003) but lower NK cell senescence within people (p=.01). Stress alone was not associated with immunosenescence, however, between people, older adults with low stress and CMV titers had the lowest T cell senescence whereas those with high CMV titers had higher senescence regardless of stress levels (interaction: p=.036). Older adults’ immune health may be resilient to within-person fluctuations in stress and CMV over time; stable levels may have greater implications on T compared with NK cell immunosenescence.

**The Role of Annexin A1 in Experimental Pancreatitis**
Rand T. Akasheh, Jason M. York, Robert Cabay, Giamila Fantuzzi
Annexin A1 (ANXA1) is a glucocorticoid-regulated protein, known for its anti-inflammatory effects. A Possible role of this protein in experimental pancreatitis was never investigated. We aimed to evaluate the effect of ANXA1 deficiency on markers of inflammation and pancreatic pathology in a mouse model of cerulein-induced acute and chronic pancreatitis. Acute pancreatitis was induced by treating female BALBc WT and ANXA1 KO mice with 8 and 5 ip injections of PBS or cerulein at a dose of 50 μg/Kg. The same dose of 5 cerulein injections was given twice a week for 5 weeks to induce chronic pancreatitis. Serum Interleukin (IL)-6 and IL-10 were measured through ELISA. Histological markers of pancreatic inflammation and fibrosis were evaluated by H&E and Sirius red staining. Our findings indicate that ANXA1 deficient mice express higher IL-6 in acute pancreatitis and develop higher pancreatic fibrosis in chronic pancreatitis. In conclusion, ANXA1 modulates systemic inflammation in acute pancreatitis and protects from fibrosis in chronic pancreatitis.

* Inhibition of DNA Methylation with Zebularine Alters Lipopolysaccharide-Induced Neuroinflammation in Mice
Stephanie M. Matt, Jalisa D. Zimmerman, Marcus A. Lawson, Angela C. Bustamante, Monica Uddin, and Rodney W. Johnson
Inhibitors of DNA methyltransferases (DNMTs), the enzymes that catalyze DNA methylation, alter DNA methylation globally in the brain and at individual neural plasticity-associated genes. However, the way DNMT inhibitors centrally influence lipopolysaccharide (LPS)-induced neuroinflammation is not known. Specifically, we sought to determine if the DNMT inhibitor zebularine would alter sickness behavior and DNA methylation of IL-1β as well as gene expression in the hippocampus and microglia. Novel findings indicate that adult mice pretreated with intracerebroventricular (ICV) zebularine recovered faster from LPS-induced sickness. Further, gene expression of inflammatory markers, epigenetic regulators, and the microglial sensory apparatus were altered by zebularine alone or in combination with LPS. Zebularine and/or LPS also led to decreased DNA methylation of the IL-1β proximal promoter at 4 and 48 hours after LPS. Taken together, these data suggest that modulation of DNA methylation with a DNMT inhibitor in the brain can affect molecular mechanisms of neuroinflammation. Supported by NIH AG016710
**PKR as a Conserved, Early Neuroinflammatory Mediator Under Viral, Bacterial, & Metabolic Challenge: A Role in Parkinsonian Pathogenesis?**
Matthew A. Jefferson, Rudy J. Valentine, Arthi Kanhasamy, Marian L. Kohut
Neuroinflammation resulting from various host and environmental factor detriments has emerged as a well-recognized component of Parkinsonian pathogenesis. Our lab has previously identified the expression of double-stranded RNA-dependent protein kinase (PKR) in murine brains fed a long-term high fat diet, whose canonical response is antiviral in peripheral tissues. In an effort to understand this intracellular stress response, we have characterized its CNS expression under: LPS, Influenza A/PR/8/34, and Diet-Induced Obesity (DIO) challenges in C57BL/6 mice. While LPS has been used as a pro-inflammatory control state, Influenza and DIO challenges have been followed by a secondary challenge with MPTP, a dopaminergic neurotoxin that recapitulates the nigrostriatal degeneration observed in Parkinson’s disease (PD). Overall, PKR gene and protein up-regulation appears selective to the hippocampus, and is met with microglial activation in dual challenges. Although ongoing, current PKR inhibitor studies are being performed to determine the preclinical therapeutic relevancy of this neuroinflammatory signature.

**A Gentle Yoga Program for Women with Urgency Urinary Incontinence**
Sandi Tenfelde, PhD, APN, Dina Tell, PhD, Lindsey Garfield, PhD, APN, Linda Janusek, PhD, RN
Purpose: Women with urgency urinary incontinence (UUI) struggle to manage this chronic health condition. Evidence suggests low-grade systemic inflammation and elevated proinflammatory cytokines contribute to bladder dysfunction. Yoga has been shown to reduce inflammation. The purpose of this study is to demonstrate the extent to which yoga improves UUI symptom burden.
Methodology: This pilot intervention was twice weekly, 8 week long gentle yoga program. Outcome measures include symptom burden (e.g. Pelvic Floor Distress Inventory) and biological markers (e.g. IL-6, CRP, TNFalpha).
Results: Twelve women (48-66 years) completed the pilot study. The majority reported symptoms as “much better” (n=4, 33.3%) and “a little better” (n=5, 41.7%). Symptom bother (t(11)=3.463, p=0.005) and TNF alpha were significantly reduced (t(9)=2.88, p=0.009).
Conclusions: Yoga for women with UUI symptoms reduces symptom burden and demonstrate reduced inflammation. The findings from this pilot study provide data to support yoga for women to self-manage their chronic health conditions.

**Porcine Fetal Microglial Cells Are Transiently Altered by Maternal Viral Infection**
Adrienne Antonson, Rodney W. Johnson
Prenatal exposure to maternal infection increases the risk of psychiatric disorders, though the mechanisms remain unknown. We hypothesized that maternal immune activation (MIA) elicits transient fetal microglia activation concomitant to maternal symptoms of infection. Pregnant gilts were inoculated with porcine reproductive and respiratory syndrome virus (PRRSV) on gestational day (GD) 76 and fetuses were collected 7 and 21 days post-inoculation (dpi). Maternal PRRSV treatment reduced fetal brain weight at 21 but not 7 dpi. At 7 dpi, primary fetal microglia from PRRSV-infected litters expressed more MHCII and CD68, and displayed reduced phagocytic and chemotactic activity compared to controls. At 21 dpi, only MHCII and chemotaxis differed. Fluidigm analysis revealed that microglia sensome genes were differentially regulated due to MIA. Overall, these data suggest that the activity of fetal microglia are transiently altered by maternal viral infection, revealing a potential mechanism through which MIA could negatively impact prenatal neurodevelopment.

**Pre-Transplant Tocilizumab Is Associated with More Severe Depression, Anxiety, Pain, and Sleep Following Allogeneic Hematopoietic Cell Transplantation**
Tocilizumab, an IL-6 receptor antagonist, has shown early promise in preventing acute graft-versus-host disease (aGVHD) in allogeneic hematopoietic cell transplant (HCT) recipients. IL-6 is also a key cytokine implicated in inflammation-associated mood dysregulation. We therefore hypothesized that tocilizumab would reduce
depression, anxiety, fatigue, sleep disturbance, and pain among allogeneic HCT recipients. This clinical trial compared pre- and post-HCT data from 25 patients receiving one dose of prophylactic tocilizumab prior to allogeneic HCT to a control group of 63 patients not receiving tocilizumab. Contrary to our initial predictions, allogeneic HCT patients administered tocilizumab to block the actions of IL-6 experienced significantly worse depression, anxiety, pain, and sleep as compared to allogeneic HCT patients who did not receive the receptor antagonist. The possibility that blockade of peripheral IL-6 receptors leads to the increased release of other cytokines, increased central nervous system IL-6 levels, or actions of other physiological systems warrants further investigation.

What’s Hot: Immune System Contributions to the Antidepressant Effects of Whole Body Hyperthermia
Charles L. Raison, Michael Caruso, Angelica Medrano, David Smith, Christopher A. Lowry
Mild-intensity whole body hyperthermia (WBH) has emerged as a novel treatment for major depressive disorder (MDD). In this context a single WBH treatment has been shown to produce a rapid and sustained antidepressant response. To evaluate the impact of WBH on circulating immune biomarkers, as well as potential associations between these biomarkers and behavioral responses to treatment, both ELISA and multiplex methods were used to evaluate a range of pro- and anti-inflammatory cytokines immediately prior to treatment, immediately following treatment and at 1 and 4 weeks post-treatment. Compared to sham treatment, WBH induced a large and time-limited increase in interleukin (IL)-6 while having no effect on other cytokines. Increased IL-6 associated with acute mood improvement and longer-term antidepressant response, as well as with core body temperature reached during treatment. The implications of these findings for the behavioral effects of IL-6 as an immune molecule and muscle-produced myokine will be discussed.
Poster Presentation Abstracts

Reduced Immunity to Measles in Adults with Major Depressive Disorder
Bart N. Ford, Robert H. Yolken, Faith B. Dickerson, T. Kent Teague, Michael R. Irwin, Martin P. Paulus, Jonathan Savitz

Depression can inhibit vaccine efficacy in adults. Nevertheless, it is unclear whether adult-onset depression impairs immunity from childhood vaccinations. Here, we tested for the presence of IgG antibodies against measles in volunteers with current major depressive disorder (dMDD, n=85), remitted MDD (rMDD, n=82) as well as healthy controls (HC, n=136), all born after the introduction of the measles vaccine in 1963. Logistic regression analyses controlling for age and sex showed that both the dMDD group (OR=2.07, p=0.026) and the rMDD group (OR=1.98, p=0.040) had increased rates of seronegativity to measles compared to HC. Conceivably, onset of depression subsequent to vaccination may reduce the ability of the immune system to maintain the long-term antibody protection normally conveyed by vaccination. Because lower IgG titres are associated with increased risk of measles infection, MDD may increase the risk and severity of infection.

Effects of Tumor Experience on Sickness Behavior After an Immune Challenge
Santos, J.S., Jordan, K., Bever, S.R., Pyter, L.M.

Tumors change inflammatory responses to challenges in cancer survivors, although the underlying mechanisms are unknown. We tested the extent to which tumor resection attenuates these alterations following an i.p. immune challenge (lipopolysaccharide [LPS]). Tumors were induced in mice using mammary cancer cells and resected after 2.5 weeks (some tumors were left intact). Some surgical controls received a vehicle injection (n=3), whereas other controls (n=4), tumor (n=5) and tumor-resected (n=3) mice received LPS. Tnfa and IL-6 mRNA decreased several brain regions of tumor-bearing mice; this effect was attenuated for tumor-resected mice. Tumors attenuated changes in body temperature and locomotion 24 h after LPS injection compared to controls (LPS), while tumor-resected mice exhibited intermediate responses. Reduced body mass and food intake were observed in all groups compared to control (no LPS) 24 h after LPS injection. Our results indicate differences in sickness behavior responses after cancer experience.

Effects of Time-of-Day on Cancer-Associated Brain and Behavior

Both time-of-day and cancer modulate inflammatory activity and behavior, which may relate to behavioral issues (e.g. fatigue) in cancer survivors. To test the extent to which tumors affect behavior and immunity in a time-of-day-dependent manner, mammary tumors were induced in mice: some tumors were resected (“tumor resect”), others remained intact (“tumor”), controls received sham surgery. Twenty days after treatments, cognitive performance and activity were assessed. Behavior testing followed by tissue collection were completed during the light phase in half of the mice (treatment balanced) and during the dark phase in the other half. Preliminary data suggest that tumor and tumor resection increased hippocampal Cd11b and IL-1b mRNA during the dark phase. Dark phase behavioral testing increased overall activity, but was less pronounced in the tumor resect group. Mixed time and treatment interactions were observed for cognitive performance. These results suggest that accurate reporting and strategic measurement of these variables is essential.

Prenatal Stress, Inflammation and Depressive Risk: An Epigenetic Link
Lindsey Garfield, PhD, Herbert L. Mathews, PhD, Linda Janusek, PhD, RN, FAAN

Minority women who experience increased life stress are at greater risk for depression during pregnancy. We previously reported stress exposure to associate with epigenetic modifications (DNA methylation) and a proinflammatory phenotype. Excess inflammation may increase risk for prenatal depression. In this study oxytocin, a hormone with anti-inflammatory activity, and proinflammatory cytokines (IL-6 and TNF-alpha) were assessed with respect to maternal psychological well-being. Pregnant minority women (N=32) provided blood samples for circulating oxytocin, IL-6 and TNF-alpha, and completed instruments measuring depressive symptoms (CESD), perceived stress (PSS), chronic stress (CSQ), sleep quality (PSQI), and fatigue (MSFI). Thirty-nine
percent of women reported elevated depressive symptoms, which was associated with greater perceived stress (p=.08) and fatigue (p=.09). DNA hypomethylation was related to perceived stress (p=.009), poor sleep (p=.043), and TNF alpha levels (p=.038). The results suggest an epigenetic link for greater inflammation, stress, fatigue, and poor sleep during pregnancy; all of which may increase depressive risk in minority women.

**Bollywood Dance Intervention to Promote Physical Activity and Mental Well-Being in Asian Indian Girls**

Annie Thomas, Linda Janusek, Shweta Singh, Jorgia Connor

Asian Indians are at high risk for obesity-related cardio-metabolic disease. Such risk emerges during adolescence. Culturally appropriate interventions promote physical activity and reduce such risk. Dance in any form is a stress buster and has many health benefits. The purpose of this study was to evaluate the effect of Bollywood Dance on cardio-metabolic risk (BMI, percent body fat, waist circumference, blood pressure and heart rate) and perceived physical and mental well-being in Asian Indian girls. Thirty subjects (14-21 years) were enrolled into a 60-minute trainer-led dance session, along with a DVD based dance session at home for 6 weeks. A quantitative survey and a semi-structured interview evaluated subjects’ satisfaction with, and barriers and facilitators to engaging in the dance sessions. Data analysis is ongoing. The study findings will inform the feasibility of planning a culturally appropriate and sustainable physical activity intervention among Asian Indian girls, thus preventing cardio-metabolic risk.

**Mother-Reared and Nursery-Reared Infant Rhesus Macaques Develop Distinct Gut Microbiomes**

Danielle Rendina, Gabriele R. Lubach, Mark Lyte, Gregory J. Phillips, and Christopher L. Coe

Bacterial colonization of the intestine has a major role in the postnatal development and maturation of the immune and endocrine systems, and the composition of the infant gut microbiome is dynamic. We assessed how the disruption of these developmental patterns through alterations of diet and early life exposure to the maternal microbiome influenced microbiome maturation in infant rhesus macaques. Rectal swabs were obtained from forty-five infants that were either born via c-section and nursery reared (NR) or born vaginally and mother reared (MR) to determine microbial diversity by rRNA gene amplicon sequencing at 2, 4 and 8 weeks postnatal. While there were no differences in alpha diversity, principal coordinates analysis (PCoA) showed that community structure was significantly different between NR and MR infants (p<0.05). At the genus level, the relative abundance of Bifidobacterium and Prevotella, commensal microorganisms, were lower in NR infants. These observed differences suggest formula-fed or cesarean-delivered infants have different trajectories of gut bacterial colonization in later infancy, which could have implications for future health.

**CNS Neuronal Damage in A Mouse Model of Multiple Sclerosis**

Yee Ming Khaw, Makoto Inoue

Multiple sclerosis (MS) is a clinically significant T-cell mediated autoimmune disease characterized by demyelinating and neurodegeneration in the central nervous system (CNS). Therapies targeting neuronal damage in the CNS are thought to reduce or prevent MS disease symptoms. Thus, understanding of immune-related mechanism of neuronal damage is necessary to identify a novel and effective therapeutic protocol for MS treatment. We recently reported an experimental MS model using C57BL6 mice characterized by chronic paralysis and motor dysfunction as well as neuronal damage in the CNS. We found that Th17 cells, a CD4+ T cell subtype, but not Th1 cells, have acquired a neurotoxic phenotype in this model. In addition, neurodegenerative type of MS model mice showed strong activation of microglia in the CNS, which may drive progressive neurodegeneration. The findings introduce neurodegeneration and related immune cells in this phenotype.
Autoimmune Encephalopathy (AE) Correlation Between Cunningham Panel and Functional Brain Imaging with Brain SPECT: A Pilot Study
S. Best M.D.; D. Pavel M.D.; A. Cross MS; C. Shimasaki Ph.D.; B. Cochran ND.
The correlation between the Cunningham panel’s 5 different parameters and brain SPECT imaging was evaluated in 47 patients grouped as much as possible into 3 clinical types of: chronic, semi-chronic and acutely ill. Three cases best fitting these clinical stages are presented here. Representative SPECT images for each case will be displayed, together with the graphic display of the Cunningham panel result.
Results: Brain SPECT: in chronic dysfunction, there was extensive underperfusion. In acutely ill, there was diffusely marked and extreme hyperperfusion. In semi-chronic, there was a mixture of both.
Cunningham panel: the most common abnormality was in the values of anti-dopamine receptor D1 and of anti-Tubulin.
Conclusions: All cases of abnormal SPECT had also abnormal Cunningham results. We suggest that a clearly abnormal brain SPECT adds to the indications for a Cunningham panel. The exact correlation between image pattern, Cunningham results and treatment response awaits additional study.

CYP Epoxigenases Metabolize of -3 Fatty Acid Endocannabinoids to Form a Novel Class of Anti-inflammatory Lipid Mediators
Josephine E. Watson and Aditi Das
Endocannabinoids (eCBs) are endogenous cannabinoids that activate cannabinoid receptors in humans. Omega-6 eCB derivatives of arachidonic acid (AA), anandamide (AEA) and 2-arachidonoylglycerol (2-AG) were the first shown endogenously produced. Synthesis, degradation and metabolism of these metabolites have been investigated, however the metabolism of omega-3 derived eCBs remains to be elucidated through the epoxygenase (EPOX) pathway. Previously our lab has shown that cytochrome P450 2J2 (CYP2J2) and 2D6 (CYP2D6) produces epoxide derivatives from AEA and 2-AG. This data supports that CYP2J2 and CYP2D6 may metabolize other bioactive fatty acid amides, such as DHA and EPA derived eCBs, docosahexaenoic ethanolamide (DHEA) and eicosapentaenoic ethanolamide (EPEA), respectively, for physiologically purposes. Omega-3 eCBs, DHEA and EPEA have been implicated in brain development and reduction of cancer cell migration. Herein, we report the metabolism of DHEA and EPEA by CYP2J2 and CYP2D6 to form epoxide derivatives that are exhibit pharmacological and anti-inflammatory properties.

Microglia-GBM Crosstalk is Affected by EGFRvIII
Jan Lumibao, Andrew J. Steelman, H. Rex Gaskins
Glioblastoma (GBM) is the most common and malignant form of brain cancer in adults. Genetic aberrations of EGFR are prevalent in GBM, and the EGFRvIII mutant shows the poorest clinical outcomes. We are investigating how tumor-associated microglia (TAMs), along with EGFRvIII, may potentiate tumor malignancy. We examined the effect of GBM cell-conditioned media (CM) on microglial secreted factors. U87 and U87vIII CM induced secretion of chemokines and proteins involved in cell invasion. U87vIII CM induced greater microglial secretion of most soluble factors detected compared to U87 CM. We also assessed the impact of microglial CM on GBM system xc- expression. HMC3 microglia CM decreased SLC7A11 and xCT expression in U87 cells, but increased expression in U87vIII cells. These data demonstrate that induction of system xc- by microglia-secreted factors is enhanced by EGFRvIII in GBM. Collectively, the data show differential microglia-GBM crosstalk that is affected by the EGFRvIII mutant.

The Effects of Postnatal Exposure of Methamphetamine in Male Sprague-Dawley Rats on Attention, Compulsivity, and Impulsivity in the 5-Choice Serial Reaction Time Task
Sieg ML, Balachandran RC, Clancy BM, Jablonski SA, Williams MT, Vorhees CV, Eubig PA
Methamphetamine use negatively affects attention and memory, and the neurotoxic mechanisms have been reasonably established. Developmental exposure to methamphetamine has previously been associated with learning and attentional deficits; however, the mechanisms of these effects are less clear. We aimed to replicate the effects of prenatal exposure to methamphetamine on impulsivity, compulsivity, and motivation in the 5-
choice serial reaction time task (5CSRTT) shown by Lloyd et al (2013) in C7B1/J6 mice in male Sprague-Dawley rats. Rats were dosed with methamphetamine (10 mg/kg) or saline twice per day on postnatal day 6-16. Rats were tested in the 5CSRTT as adults (4-4.5 months of age) in both sustained attention and select attention. Rats continued to test in the 5CSRRT during drug challenges to examine the effects of a dopamine agonist and two specific dopamine receptor antagonists. Rats were also tested in the delay discounting task to further examine impulsivity and compulsivity.

**Circadian Disruption Alters Clock and Biotransformation Gene Expression in the Livers of Adult Long-Evans Rats**
Emma Sullivan, Rekha Balachandran, Paul Eubic
Shift work and light at night have been shown to disrupt circadian rhythms (controlled by the suprachiasmatic nucleus) which can lead to a multitude of health problems including increased risk of cardiovascular problems, cancer, and metabolic problems. Disruptions in circadian rhythms can change the daily cyclic expression of proteins not only in the brain, but also in peripheral organs such as the liver. We examined the expression of specific clock and biotransformation genes shown to be under circadian control in the livers of three groups of rats. Two groups had disrupted circadian rhythms modeling shift work and light at night. Preliminary results showed altered expression of clock genes bmal1, clock, and cry1 in the circadian-disrupted rats compared to the control rats. Altered expression of these genes in the liver suggests overall desynchronization of circadian-controlled genes throughout the body.

**Cardiometabolic Risk as A Mediator Between Socio-Environmental Stressors and Posttraumatic Stress Disorder Symptom Severity**
Terri deRoon-Cassini, Meredith Halling
While individuals living in disadvantaged neighborhoods have higher reported stress, it is unknown if this is associated with increased PTSD symptoms. Additionally, it is not well understood if cardiometabolic risk, a component of allostatic load, is a mediator between exposure the socio-environmental stress and increased PTSD symptom severity. We investigated whether exposure to socio-environmental stressors were associated with PTSD symptom severity, and if cardiometabolic risk mediates this relationship in a representative sample of Wisconsin residents. Three socio-environmental factors were examined: 1) Census block group-level Economic Hardship Index (EHI), a composite measure of neighborhood-level socioeconomic statistics, 2) neighborhood environment score, based on perceived presence of crime, traffic, litter/garbage, and healthy food, and 3) experiences of daily discrimination.