Augusta Brain Aging & Neurodegeneration Symposium

March 18, 2022

Georgia Cyber Center
Plug-n-Play Auditorium, Hull McKnight Building
100 Grace Hopper Lane, Augusta, GA 30901

8:15-8:45 am	**Check-in & Breakfast**	
8:45-9:00 am	**Welcome and Introduction**	
SESSION I – Inflammatory and Epigenetic Basis of Brain Aging and Alzheimer's Disease		
9:00-9:35 am	**Riqiang Yan, PhD** *Professor and Chair, Neuroscience University of Connecticut School of Medicine, Farmington, CT*	***"Enhancing neurogenesis to reverse neuronal loss in AD mouse models by CX3CL1 back signals"***
9:35-10:10 am	**Marcelo Wood, PhD** *Professor and Chair, Neurobiology & Behavior, University of California Irvine, CA*	***"Investigating the interface of epigenetics and metabolism underlying memory formation in the adult, aging, and AD brain"***
10:10-10:35 am	**Xin-Yun Lu, MD, PhD** *Professor and Chair, Neuroscience & Regenerative Medicine, Medical College of Georgia at Augusta University, GA*	***"Epigenetic mechanisms linking aging and stress to cognitive impairment in AD"***
10:35-10:55 am	Coffee Break	
SESSION II – Vesicular, Hormonal and Neural Dysfunction in Alzheimer's Disease		
10:55-11:30 am	**John Cirrito, PhD** *Associate Professor, Neurology, Washington University, School of Medicine, St. Louis, MO*	***"Sex-dependent effects of stress on Aβ metabolism"***
11:30-12:05 am	**Sandro Da Mesquita, PhD** *Assistant Professor, Neuroscience, Mayo Clinic, Jacksonville, FL*	***"Lymphatic drainage at the meningeal-brain interface in aging and Alzheimer's disease"***
12:05-12:30 pm	**Frank Deak, MD, PhD** *Associate Professor, Neuroscience & Regenerative Medicine, Medical College of Georgia at Augusta University, GA*	***"Function of synaptobrevin-1 in neurotransmission and as a risk factor of late-onset Alzheimer's disease"***
12:30-1:30 pm	**Lunch**	

SESSION III – Advancing Neurodegeneration Research in the Cyber Age		
1:30-2:05 pm	**Subhojit Roy, MD, PhD** *Professor, Pathology and Neurosciences, University of California, San Diego, CA*	***"Gene editing strategies for Alzheimer's disease"***
2:05-2:30 pm	**Danielle Mor, PhD** *Assistant Professor, Neuroscience & Regenerative Medicine, Medical College of Georgia at Augusta University, GA*	***"Investigating α-synuclein neurotoxicity in Parkinson's and Alzheimer's diseases using C. elegans"***
2:30-3:00 pm	**Eric Vitriol, PhD** *Associate Professor, Neuroscience & Regenerative Medicine, Medical College of Georgia at Augusta University, GA*	***"ALS-linked PFN1 mutants cause mitochondria defects through loss and gain of function"***
3:00-3:25 pm	**Jason Orlosky, PhD** *Associate Professor, Computer and Cyber Science, Augusta University, GA*	***"Genetic crossover in the evolution of time-dependent neural networks"***
3:25-3:45 pm	Break	
SESSION IV – Neurological Comorbidities and Therapeutics of Alzheimer's Disease		
3:45-4:20 pm	**Jeannie Chin, PhD** *Associate Professor, Neuroscience, Baylor College of Medicine, Houston, TX*	***"Role of the thalamic reticular nucleus in Alzheimer's-related sleep disruptions and disease progression"***
4:20-4:55 pm	**Qin Wang, MD, PhD** *Professor, Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, AL* *(will join AU faculty on April 1)*	***"Neural-specific targeting of adenosine A1 receptor to control seizures and inhibit epileptic activities in an Alzheimer's model"***
4:55-5:20 pm	**David Blake, PhD** *Professor, Neuroscience & Regenerative Medicine, Medical College of Georgia at Augusta University, GA*	***"Stimulation of the cholinergic basal forebrain boosts brain neurotrophins and improves behavior in young and old monkeys, and Alzheimer's model mice"***
5:20-5:30 pm	**Closing Remarks**	

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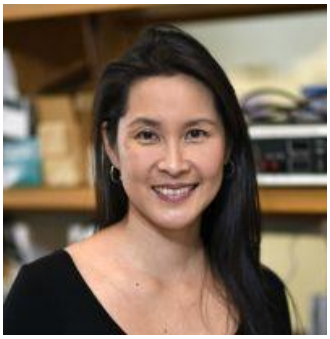
Invited Speakers

Jeannie Chin, PhD



Associate Professor, Department of Neuroscience
Baylor College of Medicine, Houston, TX

"Role of the thalamic reticular nucleus in Alzheimer's-related sleep disruptions and disease progression"

Sleep disruptions promote increases of amyloid β (Aβ) and tau in the brain and increase Alzheimer's disease (AD) risk, but the precise mechanisms that give rise to sleep disturbances have yet to be defined. Our recent studies indicate that the thalamic reticular nucleus (TRN) may be a master regulator of behavioral and cognitive deficits in AD due to its roles in sleep maintenance, regulation of slow wave sleep (SWS), attention, and cognitive processing. When we examined the TRN in transgenic mice that express mutant human amyloid precursor protein (APP), we found reduced neuronal activity, increased sleep fragmentation, and decreased SWS time as compared to nontransgenic littermates. Selective activation of the TRN using excitatory DREADDs restored sleep maintenance, increased time in SWS, and reduced amyloid plaque load in both hippocampus and cortex. Our findings suggest that the TRN may play a major role in symptoms associated with AD. Current efforts are focused on determining whether intrinsic, synaptic, and/or circuit mechanisms underlie the reduced TRN activity that we observe in both APP mice and patients with AD. Enhancing TRN activity might be a promising therapeutic strategy for AD to improve symptoms and slow or prevent disease progression.

John Cirrito, PhD

Associate Professor, Department of Neurology
Washington University, School of Medicine
St. Louis, MO

"Sex-dependent effects of stress on Aβ metabolism"

Individuals with chronically elevated stress are at higher risk of developing Alzheimer's disease (AD). Similarly, studies in mouse models of AD demonstrate that acute stress increases Aβ and tau levels and chronic stress increases the pathology of these proteins. Additionally, almost 70% of people living with AD are female. Interestingly, stress-induced corticotrophin releasing factor receptors (CRF-Rs) signal differently in females and males. In females, CRF-Rs normally activate PKA/ERK, whereas in males CRF-Rs are withdrawn from the plasma membrane by β-arrestin, resulting in significantly less CRF signaling. We hypothesized that the involvement of β-arrestin in the stress signaling pathway in males underlies the differences in Aβ levels in response to stress. We used in vivo microdialysis to measure brain interstitial fluid (ISF) Aβ levels every hour for several hours before, during, and after acute restraint stress in living APP transgenic mice with and without inhibitors of CRF signaling pathways. To study the influence of beta-arrestin1 on stress-induced

changes in Aβ, we measured the effects of acute stress on Aβ levels in male and female beta-arrestin1 knock-out mice. In females, acute restraint stress causes a rapid increase in brain interstitial fluid (ISF) Aβ levels in the hippocampus, whereas Aβ in males does not change. The increase in females is blocked by inhibiting the CRF receptor (CRF-R), PKA and ERK pathways. In male beta-arrestin1 knockout mice, stress increases ISF Aβ levels nearly identically to females. Our data suggest that stress causes sex-dependent increases on Aβ and that are mediated by CRF-R/β-arrestin signaling. Determining the cellular pathways that differ between the sexes could identify risks of developing AD and lead to therapeutics to specifically modulate the stress response in AD, potentially that vary by sex.

Sandro Da Mesquita, PhD

Assistant Professor, Department of Neuroscience
Mayo Clinic, Jacksonville, FL

" Lymphatic drainage at the meningeal-brain interface in aging and Alzheimer's disease"

Alzheimer's disease (AD) is the most prevalent form of dementia. We have recently shown that proper meningeal lymphatic drainage is important for brain fluid flow, learning and memory in aging and for brain amyloid beta (Aβ) clearance in mouse models of AD. Ablation of meningeal lymphatic vasculature in young-adult AD transgenic mice exacerbated Aβ pathology not only in the brain parenchyma but also in the meningeal dural vasculature, both pathological features that closely resemble what is observed in AD patients. In our new studies we show that a progressive deposition of meningeal Aβ with aging leads to gene expression changes in meningeal lymphatic endothelial cells and an accelerated reduction in meningeal lymphatic vessel coverage in the 5xFAD mouse model. Interestingly, modulating meningeal lymphatic function in AD transgenic mice affects the clearance of Aβ by monoclonal antibodies, a feature that is closely associated with transcriptomic changes in brain blood endothelial cells and microglia. Furthermore, genes that are highly expressed in lymphatic vasculature are associated with increased risk for AD and comprise markers of genetic variance in microglia isolated from the AD brain. We are now turning our attention to the interaction between genetic factors that increase the risk for AD by modulating meningeal lymphatic drainage and immunity. Collectively, our data emphasizes the notion that a dysfunctional meningeal lymphatic vasculature impacts on Aβ accumulation, brain blood vascular responses, microglial activation, and immunotherapy in AD. Targeting brain drainage by meningeal lymphatics could represent an efficient therapeutic strategy to improve brain cell function, clearance of toxic amyloid and cognition in AD.

Subhojit Roy, MD, PhD

Professor, Departments of Pathology and Neurosciences
University of California, San Diego, CA

"Gene editing strategies for Alzheimer's disease"

Gene therapy is making a comeback. With its twin promise of targeting disease etiology and 'long-term correction', gene-based therapies are particularly appealing for neurodegenerative diseases, for which conventional pharmacologic approaches have been disappointing. The recent success of a viral-vector-based gene therapy in spinal muscular

atrophy—promoting survival and motor function with a single intravenous injection—offers a paradigm for such therapeutic intervention and a platform to build on. Advances in genome manipulation such as gene editing offers unprecedented therapeutic opportunities, and it is difficult to imagine a future where gene-based therapies will not have a role in more common neurodegenerative diseases like Alzheimer's and Parkinson's. In this talk, I will outline current efforts in applying therapeutic gene editing to Alzheimer's disease and highlight an APP gene-targeting strategy developed by our laboratory.

Qin Wang, MD, PhD

Professor, Department of Cell, Developmental and Integrative Biology
University of Alabama at Birmingham, AL
Professor, Department of Neuroscience and Regenerative Medicine
Medical College of Georgia, Augusta University, GA (new affiliation from April 1)

"Neural-specific targeting of adenosine A1 receptor to control seizures and inhibit epileptic activities in an Alzheimer's model"

Epileptic seizures are common sequelae of stroke, acute brain injury and chronic neurodegenerative diseases, including Alzheimer's disease (AD), and cannot be effectively controlled in approximately 40% of patients, thereby necessitating the development of novel therapeutic agents. Activation of the A1 receptor (A1R) by endogenous adenosine is an intrinsic mechanism to self-terminate seizures and protect neurons from excitotoxicity. However, targeting A1R for neurological disorders has been hindered by side effects associated with its broad expression outside the nervous system. Here we aim to target the neural-specific A1R/neurabin/RGS4 complex that dictates A1R signaling strength and response outcome in the brain. We developed a molecule that blocks the A1R-neurabin interaction to enhance A1R activity. This agent shows marked protection against kainate-induced seizures and neuronal death, and reduces epileptic spike frequency in an AD mouse model with spontaneous seizures. Significantly, the anticonvulsant and neuroprotective effects of this agent are achieved through enhanced A1R function in response to endogenous adenosine in the brain, thus avoiding side effects associated with A1R activation in peripheral tissues and organs. Our study informs new anti-seizure therapy applicable to epilepsy and other neurological illness with comorbid seizures.

Marcelo Wood, PhD

Professor and Chair, Department of Neurobiology & Behavior
University of California, Irvine, CA

"Investigating the interface of epigenetics and metabolism underlying memory formation in the adult, aging, and AD brain"

The ability to learn, consolidate and retrieve information begins to decline with normal aging, a major risk factor for Alzheimer's Disease (AD) and dementia. In addition to aging, sedentary behavior ranks first in the US and third in the world as a risk factor for causing cognitive decline and exacerbating AD. As observed by

our lab and others, hippocampus-dependent learning is facilitated by exercise in situations that are usually subthreshold for memory consolidation and requires the induction of brain-derived neurotrophic factor (BDNF). Our data suggest that specific exercise patterns can engage a 'molecular memory' for that experience that persists through periods of sedentary behavior and enables a short exercise session, to again, induce hippocampal BDNF and facilitate memory. We have proposed that epigenetic mechanisms mediate this "molecular memory" of exercise, as the epigenome represents a signal transduction platform that is capable of encoding past experience, current metabolic states (because nearly every epigenetic modification is a metabolite) and establishing stable changes in cell function that lead to long-term changes in behavior. Preliminary data have lead us to propose the novel hypothesis that specific patterns of exercise establish a molecular feedback loop that integrates rate-limiting aspects of acetyl-CoA metabolism and histone acetylation/methylation mechanisms to modulate gene expression required for long-term memory formation and synaptic plasticity. Overall, we hope to improve our understanding of how the epigenome integrates information from metabolism (acetyl-CoA dynamics) and experience (exercise), how this interplay becomes impaired with aging and in the context of AD, and how pharmacological modulation of acetyl-CoA dynamics may improve age- and AD-related cognitive dysfunction.

Riqiang Yan, PhD

Professor and Chair, Department of Neuroscience
University of Connecticut School of Medicine, Farmington, CT.

"Enhancing neurogenesis to reverse neuronal loss in AD mouse models by CX3CL1 back signals"

Previous studies have revealed the cellular functions of CX3CL1 via interaction with its receptor CX3CR1. In this study, we report a unique role of CX3CL1 that is independent from this mechanism. We show that the intracellular CX3CL1 fragment, which is released after γ-secretase cleavage, translocates into the cell nucleus and induces transcriptional regulation of genes important for cell growth and proliferation. Mice overexpressing either full-length CX3CL1 (Tg-CX3CL1) or its C-terminal fragment (Tg-CX3CL1ct) exhibit enhanced adult neurogenesis via activation of TGFβ2/3 and Smad2. Enhanced adult neurogenesis was suppressed when Smad2 expression was deleted in neurons, supporting a role for the CX3CL1ct-TGFβ-Smad pathway in adult neurogenesis. When Tg-CX3CL1 mice were crossed with an Alzheimer's mouse model, which overexpresses mutant tauP301S and develops neurodegeneration with a shorter lifespan, we noted reversal of neurodegeneration, significantly increased survival time, and enhanced learning and memory. Hence, CX3CL1ct has a back-signaling function by reversing neuronal loss.