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CENTER FOR INFECTIOUS DISEASE & IMMUNITY (CIDI) &
BRAIN & BEHAVIORAL HEALTH INSTITUTE (BBHI)

Science Seminar

November 7, 2022 from 10 – 11 am
Fitz Hall Room 303 – In-person!

Speaker:
T. Dianne Langford, PhD
Associate Dean, Research &
Professor, Neural Sciences, Professor,
Center for Substance Abuse Research,
Temple University, Philadelphia

"HIV-mediated dysregulation of Aquaporin 4 may contribute to the accumulation of aberrant proteins in the brain"

About the Talk: The glymphatic fluid clearance system promotes the exchange of interstitial fluid (ISF) and cerebrospinal fluid through the arterial perivascular spaces into the brain. This process is facilitated in part by aquaporin-4 (AQP4) water channels located primarily on astrocyte end feet abutting endothelial cells of the blood brain barrier. Changes in expression levels or mislocalization of AQP4 from astrocytic end feet to the soma can lead to decreased ISF flow leading to buildup of extracellular waste products like hyperphosphorylated Tau (pTau). pTau accumulation is a neuropathological hallmark in Alzheimer's disease (AD) and in some people with human immunodeficiency virus (HIV). Approximately 50% of people with HIV (PWH) suffer from HIV-associated neurocognitive disorders (HAND), which is a spectrum disorder linked to cognitive and motor decline in PWH.

Limited studies have shown that in HIV CNS infection expression levels of AQP4 in brain homogenates from the mid-frontal gyrus of PWH with symptomatic HAND were significantly increased compared to those with asymptomatic HAND, which raises the question if AQP4 function and subcellular localization may contribute to cognitive status. In addition, common single nucleotide polymorphisms (SNPs) in the aqp4 gene have been associated with more rapid cognitive decline in some neurodegenerative diseases. Therefore, it is possible that common mutations in aqp4, subcellular mislocalization, dysfunction, expression levels or post-translational modifications contribute to HAND. Studies in other neuroinflammatory diseases have shown dysregulation of AQP4 through the adenosine A2aR (A2aR) signaling. A2aR activation leads to PKC-mediated inhibitory phosphorylation of AQP4 (Ser180, Ser276) that is proposed to contribute to channel internalization, mislocalization and decreased expression.

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Our overall hypothesis is that in PWH, changes in AQP4 may contribute, in part, to HAND by decreasing clearance of toxic aberrant proteins and HIV mechanistically alters AQP4 in part via dysregulation of A2aR. Data from these studies may lead to the discovery of new mechanisms by which HIV and anti-retroviral therapy contribute to impaired AQP4 functioning in aging PWH. HIV-associated neurocognitive disorder (HAND) occurs in 50% of people with HIV causing decreased quality of life. The impact of this proposal may uncover mechanisms through which HIV induces AQP4 mislocalization through A2aR thereby contributing to glymphatic dysfunction and HAND. Elucidating these mechanisms will allow for potential new targets for improved clearance of toxic products from the brain.

About the Speaker: Dr. Langford graduated from the University of Alabama in 1996 with a PhD in Cellular/Molecular Biology. She completed post-doctoral training at the University of California San Diego and was promoted to Assistant Professor in the Departments of Medicine and Neuroscience in 2004 focusing on neuropathology of neurodegenerative diseases. Dianne studied HIV-associated cognitive impairments and other age-related disorders. She joined Temple University School of Medicine in 2007 as an Assistant Professor in Neuroscience where she continued to study HIV. She was promoted to Associate Processor in 2011 and Professor in 2016. Dr. Langford expanded her research to include the study of repeated subconcussive head impacts in athletes where she assesses genetic risk as well as other factors contributing to long-term outcome. She now serves as the Associate Dean for Research at the Temple University School of Medicine, where she enjoys building team science by facilitating translational collaborations among basic scientists and clinicians. Interacting with students at all levels to help them realize options and opportunities is one of her favorite aspects of her job.

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