UNIVERSITY of GUELPH

COLLEGE of BIOLOGICAL SCIENCE

DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY

Announcement:

All interested members of the university community are invited to attend the Final Oral Examination for the degree of ***Doctor of Philosophy*** *of*

ABDALLA ALBEELY

on Tuesday, May 17, 2022 at 1:30 p.m. (online)

Thesis Title: **Elucidating a role for glycogen synthase kinase-3 in the regulation of neuronal oscillatory function: Relevance to learning and memory**

Examination Committee:

Dr. John Vessey, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Melissa Perreault, Dept. of Biomedical Sciences
Dr. Craig Bailey, Dept. of Biomedical Sciences
Dr. Terry Van Raay, Dept. of Molecular and Cellular Biology
Dr. Wilder Doucette, Department of Psychiatry, Dartmouth College (External Examiner)

Advisory Committee:
Dr. Melissa Perreault (Adv)
Dr. Ray Lu
Dr. Craig Bailey

Abstract: Aberrant activity of the protein glycogen synthase kinase-3β (GSK-3β) has been implicated in disorders of cognitive dysfunction, such as Alzheimer's Disease and schizophrenia, disorders that also exhibit a dysregulation in neuronal oscillatory activity. However, a direct functional relationship between region-specific changes in GSK-3β activity, neuronal oscillations, and learning and memory has not been elucidated. Here, we demonstrated that an adeno-associated viral vector (AAV)-mediated increase in GSK-3β activity in the prefrontal cortex (PFC) or ventral hippocampus (vHIP) of rats induced learning and memory impairments during the object recognition, object location and/or object in place tasks, neuronal oscillatory deficits in theta and/or gamma spectral power, and elevated levels of pathogenic tau phosphorylation, a GSK-3β substrate, in those same brain regions. Next, considering the widespread expression of GSK-3, and its diverse role in multiple cellular mechanisms, we investigated other approaches to regulate GSK-3β activity in a more neuroanatomically restricted way, specifically via the dopamine 5 receptor (D5R). AAV-mediated knockdown of D5R in the PFC region, where the D5R is highly expressed, induced learning and memory impairments in recognition memory, associative memory, as well as spatial memory. These changes were accompanied by increased theta spectral power in multiple brain regions, and increased PFC GSK-3β activity. Finally, considering the prominent role that GSK-3β plays in cognitive dysfunction, we used the methylazoxymethanol acetate (MAM) model of schizophrenia to assess whether alterations in learning and memory, and neuronal oscillatory activity, were associated with changes in GSK-3 activity and/or expression and to assess sex differences in these measures. The study revealed sex-specific differences in learning and memory function, with male MAM animals

Continued…

exhibiting deficits during the learning trials in the T-maze task, and the female MAM animals showing deficits in reversal learning. These deficits were accompanied by sex-specific differences in oscillatory activity in the theta and high gamma frequencies, and region-specific changes in the levels and/or activity of GSK-3 and phosphorylated tau protein. Collectively, these findings suggest that aberrant GSK-3 signalling may have a central involvement in disorders of cognitive dysfunction through the regulation of neurophysiological network function.

Curriculum Vitae: Abdalla completed his B.Sc. (Hons.), Zoology at the University of Khartoum in 2010. He then completed his M.Sc. in Molecular and Cellular Biology in Winter 2016 under the supervision of Dr. Nazar and Dr. Bendall. In Summer 2017, he began his Ph.D. program in Molecular and Cellular Biology with a specialization in Neuroscience under the supervision of Dr. Perreault.

Publications: **Albeely AM**, Ryan SD, Perreault ML. Pathogenic Feed-forward Mechanisms in Alzheimer's and Parkinson's Disease Converge on GSK-3. Brain Plast. 2018; 4(2):151-167

Albeely AM, Williams OOF, Perreault ML. GSK-3β Disrupts Neuronal Oscillatory Function to Inhibit Learning and Memory in Male Rats. Cell Mol Neurobiol. 2021 Jan 3. doi: 10.1007/s10571-020-01020-z. Epub ahead of print. PMID: 33392916

Albeely AM, Rasmussen D, Perreault ML. A Role for Cortical Dopamine D5 Receptors in The Regulation of Neuronal Circuit Function and Memory (Submitted)