Name: Amanda Vanderplow

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Major Professor: Michael Cahill PhD

Degree Objective: Endocrinology and Reproductive Physiology

Background:

Ph.D. University of Wisconsin-Madison, Madison, WI. Graduate Program in Endocrinology and Reproductive Physiology. Advisor: Michael Cahill PhD. *August 2017-Current*

M.S. Northern Michigan University, Marquette, MI. Department of Biology. Advisor: Dr. Valerie Hedges PhD. *August 2015-May 2017*

B.S. Aquinas College, Grand Rapids, MI. Major: Psychology. Concentrations: Biology. Advisor: Ben Chihak PhD. *August 2010-December 2014.*

B.A. Aquinas College, Grand Rapids, MI. Major: French. Concentrations: French Language and Culture. Advisor: Michel Pichot PhD. *August 2010-May 2014*

Certificat de la Langue Française. Université Catholique de l'Ouest, Angers, France. *January 2013-March 2013*

Current Research Project:

My first project focuses on maternal breathing dysfunction during pregnancy and its potential to increase risk for neuropsychiatric disorders in offspring. Sleep disordered breathing (SDB) is prevalent among pregnant women as a consequence of pregnancy-related changes and increasing rates of maternal obesity. SBD refers to recurring episodes of complete or partial obstruction of the airway during sleep that lead to intermittent hypoxia. In animal studies, intermittent hypoxia induces increased oxidative stress and inflammation. SBD is a potent inflammatory stimulus, inducing chronic inflammation that contributes to many of the morbidities associated with SBD. Furthermore, epidemiological studies suggest that maternal inflammation is associated with the development of neuropsychiatric disorders in her offspring. While there is growing evidence demonstrating that SBD is associated with adverse maternal-fetal pregnancy outcomes, the impact of SBD on neurodevelopmental outcomes in offspring remains sparse. The purpose of this study is to investigate the effect of gestational intermittent hypoxia on the cognitive function of juvenile offspring rats. Pregnant rat dams were exposed to chronic intermittent hypoxia (8 hrs/day, 2 min 10.5% O2 separated by 2 min of 21% O2) or normoxia from gestation days 10-21 (GIH and GNX, respectively). Juvenile (4-6 week) offspring were tested in a Y-maze spontaneous alternation task, an open field task, a novel object recognition test, and a social interaction test. Juvenile GIH male offspring showed patterns of cognitive impairment relative to GNX males. In contrast, female GIH offspring did not exhibit behavioral impairments compared to GNX females. To investigate the relationship between

neuron structural changes in the medial prefrontal cortex (mPFC) and our observed behavioral phenotypes, ex-vivo brain tissue was sectioned and biolistically transformed using tungsten particles coated with red fluorescent DiI dye to visualize dendrites and dendritic spines. GIH male offspring showed an increase in dendritic spine density in pyramidal neurons of the mPFC when compared to GNX males. Together, these data suggest that GIH sex-dependently alters cognitive phenotypes in GIH offspring. The presence of cognitive impairments selectively in GIH males has potentially interesting implications in understanding the contributions of prenatal insults to the emergence neuropsychiatric phenotypes.

My second project focuses on the role of mTOR pathway alterations in contributing to bipolar disorder neuronal and behavioral phenotypes. Bipolar disorder (BP) is a chronic, disabling and life-threatening illness. BP is characterized by affective processing and recurrent episodes of mania, hypomania, depression, or mixed states and, in about half of the cases, a history of psychosis. Further, cognitive and executive function impairments are core features of BP that exist even in the absence of ongoing mania or depression. BP affects approximately 1-2% of the general population and is among the top 10 most disabling illnesses worldwide. However, this high prevalence is frequently unrecognized due to the clinical features of BP, which leads to inadequate treatment, high medical cost, high rates of comorbidity, and increased mortality, particularly from suicide and cardiovascular disease. Evidence from several studies suggest dysfunctions in corticolimbic circuitries, particularly impairments in structural plasticity and activity of the dorsal lateral prefrontal cortex (DLPFC). Notably, the loss of dendritic spine density in the pyramidal neurons of the DLPFC is theorized to give rise to the cognitive/executive function impairments of bipolar disorder. While many candidate risk genes for BP have been identified, little is known regarding protein alterations that contribute to this disorder. This is important because it is becoming increasingly clear that biological markers of BP would help clinicians to establish an early diagnosis and potentially lead to the development of improved therapeutic treatments to alleviate dysfunctions within BP. mTOR signaling is a critical integrator of neuronal activity that affects many cell biological processes such as cell growth, metabolism, protein translation and stability, and autophagy, among others. Emerging evidence indicates that even subtle alterations in mTOR signaling are often associated with neurodevelopmental and neuropsychiatric disorders. The P13K-PDK1-Akt-mTOR pathway is enriched in many neuronal compartments, including dendrites and dendritic spines, where it plays a role in the regulation of neuronal function and structure. Preliminary data from the Cahill lab identified a loss of Akt and mTOR activity in the DLPFC of a well-characterized cohort of male BP subjects without psychosis (BP-NP), with no associated changes in male BP with psychosis (BP-P) subjects, or in female bipolar disorder subjects. Further, we identified an increase in the activity of the serine/threonine kinase ULK1, a key downstream target that is normally inhibited by mTOR, in male BP-NP subjects compared to male BP-P subjects. Importantly, the activity of other mTOR targets such as S6K and 4EBP1 were not altered in BP-NP subjects, suggestive of the specific involvement of ULK1. As active ULK1 facilitates autophagy, these data suggest that one consequence of the reduction in Akt-mTOR activity in the DLPFC of male BP-NP is increased ULK1-mediated autophagy. These data are in keeping with a recent study that identified a reduction in DLPFC spine density in individuals with BP relative to controls. Despite its established role in autophagy, little is known regarding the direct effects of ULK1 activity on the stability of dendritic spines and its consequent

effects on key cognitive behavioral phenotypes. Elucidating these roles of ULK1 could potentially lead to the identification of key therapeutic targets for the treatment of bipolar disorder.

Honors:

- Endocrinology and Reproductive Physiology Annual Research Symposium Best of Session Oral Presentation Award: 2019
- Team Science Fellowship: 2017-2019

Grants Received:

Publications:

Bailey A. Kermath, **Amanda M Vanderplow**, and Micheal E Cahill. Dysregulated Prefrontal Cortical RhoA Signal Transduction in Bipolar Disorder with Psychosis: New Implications for Disease Pathophysiology. *Cerebral Cortex (April 2019).*

Elizabeth Kiernan, Tao Wang, **Amanda M Vanderplow**, Sneha Cherukuri, Michael Cahill and Jyoti Watters. Neonatal intermittent Hypoxia Induces Lasting Sex-specific Augmentation of Rat Microglial Cytokine Expression. *Frontiers in Immunology* (July 2019*).*

Submitted Paper:

BA Kermath, **AM Vanderplow**, EN Seablom, AM Novak, CR Bernhardt, and ME Cahill. Stress-mediated prefrontal cortical Rap1 induction produces synaptic dysgenesis, aberrant neuronal engagement, and associated cognitive decline (Submitted to Molecular Psychiatry)

National Presentations:

“Maternal sleep disordered breathing during pregnancy induces behavioral and synaptic aberrations in the offspring: potential implications for autism spectrum disorders” **Amanda M. Vanderplow**, Bailey A. Kermath, Andrea C. Ewald, Steve M. Johnson, Tracy L. Baker, Jyoti J. Watters, Michael E. Cahill. Oral Presentation, Society for Neuroscience, Chicago, IL, October 2019

“Maternal sleep disordered breathing during pregnancy induces behavioral and synaptic aberrations in the offspring: potential implications for autism spectrum disorders” **Amanda M. Vanderplow**, Bailey A. Kermath, Andrea C. Ewald, Steve M. Johnson, Tracy L. Baker, Jyoti J. Watters, Michael E. Cahill. Poster Presentation, Society for Neuroscience, Chicago, IL, October 2019

“Maternal Breathing Dysfunction During Pregnancy Alters Microglial Activates and Increases Risk for Psychiatric Disorders in Her Offspring”. Cahill ME, **Vanderplow AM**, Kiernan EE, Johnson SM, Baker TL, and Watters JJ. Poster Presentation, Experimental Biology, San Diego, CA, April 2018.

Other Presentations:

"Maternal Breathing Dysfunction During Pregnancy Increases Risk for Neuropsychiatric Disorders in Her Offspring". **Vanderplow AM**, Kermath BA, Ewald A, Johnson SM, Baker TL, Watters JJ, and Cahill ME. Oral Presentation, ERP Research Symposium, Madison, WI, April 2019.

"Maternal Breathing Dysfunction During Pregnancy Increases Risk for Neuropsychiatric Disorders in Her Offspring". **Vanderplow AM**, Kermath BA, Watters JJ, and Cahill ME. Poster Presentation, ERP Research Symposium, Madison, WI, May 2018.

Teaching and Mentorship:

Community Outreach Volunteer, **Edgewood Middle School, Madison, WI.** Lead groups of 7th graders in a project designed to teach them how to use a microscope to learn about bacteria and microorganisms. *April 2018.*

ERP Service:

ERP Committee, University of Wisconsin, Madison, WI. *August 2018 - Current*

ERP Recruitment Committee, University of Wisconsin, Madison, WI. *January 2018 – Current*