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*

VICTORIA REA

on Thursday, July 7, 2022 at 1:30 p.m. (online)

Thesis Title: **Impacts of microbially derived metabolites on neural development and neural gene expression in the context of neurological disorder**

Examination Committee:

Dr. Ray Lu, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Terry Van Raay, Dept. of Molecular and Cellular Biology
Dr. Emma Allen-Vercoe, Dept. of Molecular and Cellular Biology
Dr. Andrew Bendall, Dept. of Molecular and Cellular Biology
Dr. Eric Samarut, Faculty of Medicine, University of Montreal (External Examiner)

Advisory Committee:
Dr. Terry Van Raay (Advisor)
Dr. Emma Allen-Vercoe
Dr. Andreas Heyland

Abstract: Colonization of the human gut microbiota begins before birth and continues through adulthood where it collectively consists of trillions of microorganisms. Studies have shown that the gut microbiota is required for proper organ development as an absence of microorganisms causes significant developmental deficits to their host. Given that an absence of microbiota has a negative impact on other developmental systems and that rapid nervous system development coincides with bacterial colonization, it was hypothesized that microbial absence also negatively impacts neural development. This was made with the assumption that this is at least in part due to the products of bacterial metabolism as certain metabolites such as short chain fatty acids are known to act as neurotransmitters and modulate neural cell functioning. The overall objective of this thesis was to use zebrafish neurodevelopment as a proxy for evaluating the contribution of gut-derived microbe metabolites to early neural development and gene expression. To this end, we first evaluated the contributions of metabolites isolated from the adult zebrafish gut to embryonic germ-free zebrafish and found that zebrafish gut derived metabolites are sufficient to rescue the expression of neurodevelopment genes. We then assessed the impact of metabolites in the context of neurological disorder by investigating differences in neural gene expression and nervous system development of germ-free embryos treated with metabolites derived from neurotypical (NT) individuals or individuals with autism (ASD). Here we found differences in gene expression and alternative splicing between the NT and ASD group, as well as between two ASD subgroups, pointing to

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the use of this research for further investigation into different ASD subtypes. Finally, we explore how prebiotics and antibiotics can impact human fecal samples of neurological disorder via two independent case studies. In the first we found that prebiotic treatment increased abundance of Firmicutes and downregulated several ASD risk genes in an ASD sample. In the second we found that antibiotic treatment correlated with downregulation of ASD risk genes in a patient with PANDAS.

Curriculum Vitae: Victoria completed her B.Sc. (Hons.) in Biological Science at the University of Guelph in 2017. She began her graduate studies in the lab of Dr. Terry Van Raay in the Winter of 2018 in the MSc program. Victoria later transferred to the PhD program in the Summer of 2019.

Publications: Rea, V., Bell, I., Ball, T. and Van Raay T. (In Press). Gut-derived metabolites influence neurodevelopmental gene expression and wnt signalling events in a germ-free zebrafish model. Microbiome.

Rea, V. and Van Raay T. (2020). Using zebrafish to model autism spectrum disorder: A comparison of ASD risk genes between zebrafish and their mammalian counterparts. Front. Mol. Neurosci. 207:13. doi:10.3389/fnmol.2020.575575

Bingham, B.E., Rea, V., Robertson, L., Smith, A. and Jacobson, L. (2021). Frequency, topic, and preferences: Tracking student engagement with several modalities of student–instructor contact in a first-year course. FEBS. doi:10.1002/2211-5463.13315