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*

# BRIANA LOCKE

**on Monday, May 13th, 2024 at 1:00 p.m.** (SSC 2315)

**Thesis Title**: **CREB3/LUMAN as a novel regulator of lipid metabolism: an *in vitro* analysis**

## Examination Committee:

Dr. Matthew Kimber, Dept of Molecular and Cellular Biology (Exam Chair)
Dr. Nina Jones, Dept. of Molecular and Cellular Biology
Dr. Ray Lu, Dept. of Molecular and Cellular Biology
Dr. Terry Van Raay, Dept. of Molecular and Cellular Biology
Dr. Leslie Buck, Dept. of Cells and Systems Biology, University of Toronto (External Examiner)

**Advisory Committee:**
Dr. Ray Lu (Adv)
Dr. Nina Jones
Dr. David Mutch

**Abstract:** CREB3/Luman is a transcription factor that is associated with the cellular stress response. Stress and the regulatory factors that respond to it have been implicated in lipid metabolism and the mechanisms used to maintain homeostasis of such. When unmitigated, cellular stress can cause dysregulation of lipid metabolism and lead to various metabolic-associated health issues including metabolic syndrome and type II diabetes mellitus. Recently, CREB3 has been implicated as a regulatory factor of lipid metabolism. Through various cellular models of metabolism, this research aims to find new downstream targets of CREB3 that can elucidate the mechanisms that lead to physiological effects connected to lipid metabolism. A liver cell model was used to provide an analysis of the effect of CREB3 in lipid metabolism through understanding its relationship with the master metabolic regulator, PGC-1α. It was found that CREB3 positively regulates *PPARGC1A* promoter activation. Calcium stores were differentially regulated in this model, suggesting the impact of CREB3 may be calcium-linked. Furthermore, altered CREB3 expression was associated with downstream targets of PGC-1α involved in fatty acid oxidation. Then, an adipocyte cell model was established as a model of adipogenesis to understand the direct role CREB3 has in regulating lipogenesis in adipose tissue. This cell model was characterized as a novel, robust model of adipogenesis that can be used for further studies on the regulatory factors involved in adipogenic pathways. With this model it was found that under endoplasmic reticulum (ER) stress, adipogenesis is impaired and there is a corresponding increase in ER stress response markers, including CREB3. Overall, the work presented here provides valuable information regarding the role of CREB3 in lipid metabolism, but also establishes a foundation for future work that will impact the study of human health.

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**Curriculum Vitae:** Briana obtained her Bachelor of Science (Honors) with distinction in Molecular Biology and Genetics, with a minor in Statistics at the University of Guelph in 2019. In the winter of 2020, she entered into the MCB M.Sc. program at the University of Guelph under the supervision of Dr. Ray Lu, and in the spring of 2021 transferred into the Ph.D. program.

**Publications:** Locke, B., Campbell, E., and Lu, R. (2024). LUMAN/CREB3 mediates the transcriptional regulation of PGC-1α, a master regulator of energy homeostasis and mitochondrial biogenesis. [Accepted] FEBS Lett.

Locke, B., and Lu, R. (2024). Establishment of immortalized porcine intramuscular preadipocytes for the study of lipid metabolism. [Submitted].