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 ***Master of Science*** *of*

MORGAN MIZZONI

On Thursday, September 5th, 2024 at 1:00 p.m. (SSC 2315)

Thesis Title: **The hypoxia-induced alternative splicing of ribosomal protein S24 promotes cancer cell viability and increases translational activity under hypoxic conditions**

Examination Committee:

Dr. Shaun Sanders, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Jim Uniacke, Dept. of Molecular and Cellular Biology
Dr. Ray Lu, Dept. of Molecular and Cellular Biology
Dr. Marc Coppolino, Dept. of Molecular and Cellular Biology

Advisory Committee:
Dr. Jim Uniacke (Advisor)
Dr. Ray Lu
Dr. John Vessey

Abstract: The ribosome has recently shifted from being viewed as a uniform, indiscriminate machine to a dynamic protein complex with specific roles in gene regulation, demonstrating variability in protein composition across different environments. The ribosomal protein S24 (RPS24) is alternatively spliced to produce distinct long and short RPS24 protein isoforms that incorporate into ribosomes. Our group has found that the RPS24L variant is consistently increased in hypoxia and spheroids (*in vitro* tumour models) in several cancer cell lines. Hypoxia (low oxygen) is a common characteristic of solid tumours and has been associated with malignant progression, reduced therapeutic response, and poor patient prognosis. An increasing degree of evidence indicates that the negative effects of hypoxia on cancer progression are mediated by hypoxia-induced genomic and proteomic alterations, enabling cancer cells to survive in low oxygen environments. Here we show that RPS24L produces a more stable protein isoform which aids in hypoxic cell survival and proliferation. Altering the natural RPS24L/S variant ratio in hypoxia through RPS24S overexpression significantly reduces translational activity, underscoring the crucial role of RPS24L in protein synthesis under hypoxic conditions. This alternative splicing event may facilitate hypoxic adaptation in the tumour microenvironment and promote malignant progression. This research contributes to the growing body of evidence highlighting the significant link between ribosome heterogeneity and cancer progression and may inform strategies for treating cancers where tumour hypoxia contributes to therapeutic resistance.

Curriculum Vitae: Morgan completed her B.Sc. (Hons.) in Biological Science with a minor in Molecular Biology and Genetics at the University of Guelph in Spring 2022. She then began her M.Sc in Molecular and Cellular Biology in Fall 2022 under the supervision of Dr. Jim Uniacke.

(continued)

Awards: Ontario Graduate Scholarship (Winter 2023), Graduate Tuition Scholarship (Fall 2022), Dr. Anne Innis Dagg Summer Research Assistantship (Summer 2022)

Publication: Kerry, J., Specker, E.J*., **Mizzoni, M***., Brumwell, A., Fell, L., Goodbrand, J., Rosen, M.N., and Uniacke, J. (2024). Autophagy-dependent alternative splicing of ribosomal protein S24 produces a more stable isoform that aids in hypoxic cell survival. FEBS Lett 598, 503–520. https://doi.org/10.1002/1873-3468.14804.