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*

SYDNEY PASCETTA

On Wednesday, December 14, 2022 at 10:00 a.m. (online)

Thesis Title: **Hypoxia-induced NPY1R and NPY5R are linked to breast cancer progression and can be antagonized with commercially available inhibitors**

Examination Committee:

Dr. Michael Emes, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Jim Uniacke, Dept. of Molecular and Cellular Biology
Dr. Melissa Perreault, Dept. of Biomedical Sciences
Dr. Ray Lu, Dept. of Molecular and Cellular Biology
Dr. Karla Williams, Faculty of Pharmaceutical Sciences, University of British Columbia (External Examiner)

Advisory Committee:
Dr. Jim Uniacke (Advisor)
Dr. Terry Van Raay
Dr. Melissa Perreault
Dr. Roger Moorehead

Abstract: Neuropeptide Y (NPY) is the most abundant neuropeptide in the mammalian central and peripheral nervous system. It acts on the cardiovascular, digestive, immune, endocrine, nervous, and immune systems. Various NPY receptors (NPYRs) display elevated expression in different types of cancers, but NPY1R and NPY5R are the most highly expressed in breast tumours. Here, we investigate how hypoxia, a feature that drives malignancy in the tumour microenvironment, influences the activity of NPYRs. We show that NPY1R and NPY5R expression and activity are directly influenced by hypoxia inducible factors (HIFs) in both ER+ (MCF7) and ER- (MDAMB-231) cell lines. We found that cells are more responsive to NPY5R stimulation in hypoxia compared to normoxia, leading to enhanced migration and proliferation. We demonstrate that we can impede these augmented responses through pharmacological inhibition of NPY1R in MDAMB-231 and NPY5R in MCF7. We establish that these cellular responses occur in both cell monolayers and spheroids, which recapitulate the tumour microenvironment more closely. In line with this, we find that expression of NPY1R and NPY5R correlate with negative prognostic variables in breast tissue samples from the Ontario Tumour Bank. This study reveals for the first time that hypoxia-induced NPYRs render cells more sensitive to NPY stimulation, and that this response can be impeded by blocking the receptors. Since breast tissue is highly innervated by the nervous system, and the expression of NPYRs correlate with negative patient prognosis, further research into antagonizing these receptors may aid in the development of novel therapeutics and personalized treatment plans.

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Curriculum Vitae: Sydney completed her BIPS-P-BSH and BA in French literature and language at Queen's University in 2017. She then began her PhD in Molecular and Cellular Biology under the supervision of Jim Uniacke in all 2017.

Publications: Pascetta S.A., Kirsh, S.M., Cameron, M., Uniacke, J., (2022). Pharmacological inhibition of neuropeptide Y receptors Y1 and Y5 influences hypoxic breast cancer migration, proliferation, and signaling. Manuscript in progress.

Kirsh, S. M.*, Pascetta, S. A.*, & Uniacke, J. (2022). Spheroids as a 3D model of the hypoxic tumor microenvironment. Manuscript submitted for publication. In The Tumor Microenvironment: Methods and Protocols (Manuscript). Springer Nature.

Medeiros, P. J., Pascetta, S. A., Kirsh, S. M., Al-Khazraji, B. K., & Uniacke, J. (2022). Expression of hypoxia inducible factor-dependent neuropeptide Y receptors Y1 and Y5 sensitizes hypoxic cells to NPY stimulation. The Journal of Biological Chemistry, 298(3), 101645. https://doi.org/10.1016/J.JBC.2022.101645

Holmes, D. R., Bredow, M., Thor, K., Pascetta, S. A., Sementchoukova, I., Siegel, K. R., … Monaghan, J. (2021). A novel allele of the Arabidopsis thaliana MACPF protein CAD1 results in deregulated immune signaling. *Genetics*, *217*(4). https://doi.org/10.1093/GENETICS/IYAB022