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*

ANDREA BRUMWELL

on Thursday, May 14, 2020 at 1:30 p.m.

Thesis Title: **Maiden exploration into hypoxic regulation of human ribosomal proteins.**

Examination Committee:

Dr. Andrew Bendall, Molecular and Cellular Biology (Exam Chair)
Dr. Jim Uniacke, Dept. of Molecular and Cellular Biology
Dr. Richard Mosser. Dept. of Molecular and Cellular Biology
Dr. Jasmin Lalonde Dept. of Molecular and Cellular Biology
Dr. Michael Charette, Dept. of Chemistry, Brandon University, Manitoba (External Examiner)

Advisory Committee:
Dr. J. Uniacke (Adv)
Dr. J. Vessey
Dr. R. Mosser
Dr. J. LaMarre

Abstract: Ribosomes were once considered static in composition because of their essential role in protein synthesis and kingdom-wide conservation. This view is changing however, as mutations in certain ribosomal proteins are tolerated by cells, albeit with disease phenotypes known as “ribosomopathies”. Heterogeneity in the protein composition of eukaryotic ribosomes is an emerging concept with evidence that different pools of ribosomes exist with transcript-specificity, although evidence in human cells is severely lacking. Furthermore, the influence of a physiological stressor on human ribosomal proteins has yet to be studied. We show that the polysome association of human RPS12 (eS12) is altered by low oxygen (hypoxia), a feature of the tumor microenvironment. Our data suggest that RPS12 (eS12) is enriched in hypoxic monosomes, which increases the heavy polysome association of structured transcripts APAF-1 and XIAP. We also show that alternative splicing of RPS24 (eS24) is substantially altered in cell culture models of tumor hypoxia (spheroids), which may be partly influenced by hypoxia and acidosis. Since APAF-1 and XIAP play opposing roles in apoptosis, these data may help to further understand cell death under stress. Additionally, alternative splicing of RPS24 changes the coding sequence, thus could provide heterogeneity to ribosomes as an adaptation to the spheroid/tumor microenvironment. Our data suggest that features of the tumor microenvironment, including hypoxia, may influence regulation of the human ribosome through changes in RP incorporation and the production of stress-specific RP isoforms.

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Curriculum Vitae: Andrea obtained her Bachelor of Science (Honours) at Bishop's University (QC) in April 2015. In the fall of the same year, she began her graduate program in the lab of Dr. Jim Uniacke.

Awards: Alexander Graham Bell Canada Graduate Scholarship - Doctoral (NSERC), 2018 – 2020.

Conference Travel Award (Canadian Cancer Society), 2018.

1st Place Poster Presentation (Toronto RNA Enthusiasts Day), 2017.

Alexander Graham Bell Canada Graduate Scholarship - Master's (NSERC), 2016 – 2017.

RiboClub Annual Meeting Travel Fellowship, 2016.

Ontario Graduate Scholarship, 2015 – 2016.

Publications: Jewer, M., Lee, L., Zhang, G., Liu, J., Findlay, S.D., Vincent, K.M., Tandoc, K., Dieters-Castator, D., Quail, D.F., Dutta, I., Coatham, M., Xu, Z., Guan, B.-J., Hatzoglou, M., **Brumwell, A.**, Uniacke, J., Patsis, C., Koromilas, A., Schueler, J., Siegers, G.M., Topisirovic, I., Postovit, L.-M. Translational control of breast cancer plasticity. Accepted by Nature Communications in March 2020 (MS ID: NCOMMS-19-08785-T). *(in press)*

Brumwell, A., Fell, L., Obress, L., Uniacke, J. (2020) Hypoxia influences polysome distribution of human ribosomal protein S12 and alternative splicing of ribosomal protein mRNAs. RNA. 26: 361–371

Rouleau, S., Glouzon, J.-P.S., **Brumwell, A.**, Bisaillon, M., Perreault, J.-P. (2017) 3′ UTR G-quadruplexes regulate miRNA binding. RNA. 23: 1172–1179

Besserer-Offroy, É., Brouillette, R.L., Lavenus, S., Froehlich, U., **Brumwell, A.**, Murza, A., Longpré, J.M., Marsault, É., Grandbois, M., Sarret, P., Leduc, R. (2017) The signaling signature of the neurotensin type 1 receptor with endogenous ligands. European Journal of Pharmacology. 805: 1–13