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*

BENJAMIN MUSELIUS

on Wednesday, June 19th, 2024 at 9:00a.m. (SSC 2315)

Thesis Title: The Organ Proteome Atlas of *Cryptococcus neoformans* Defines Novel Putative Biomarkers and Druggable Targets

Examination Committee:

Dr. Matthew Sorbara, Molecular and Cellular Biology (Exam Chair)
Dr. Jennifer Geddes-McAlister, Dept. of Molecular and Cellular Biology
Dr. Sarah Wootton, Dept. of Pathobiology, Ontario Veterinary College
Dr. Priyanka Pundir, Dept. of Molecular and Cellular Biology
Dr. Michael Moran, Dept. of Molecular Genetics, University of Toronto (External Examiner)

Advisory Committee:

Dr. Jennifer Geddes-McAlister (Adv)
Dr. Georgina Cox
Dr. Rebecca Shapiro
Dr. Sarah Wootton

Abstract: *Cryptococcus neoformans* is a fungal pathogen that most commonly infects immunocompromised individuals, killing over 120,000 people each year. Current diagnostic methods are ill-suited for utilization in less developed geographical regions where *C. neoformans* is most prevalent. Similarly, current treatment options, without undesirable side effects for the host, are limited due to the similarity of *C. neoformans* targets to the host, as a eukaryotic organism. Growing antifungal resistance in *C. neoformans* populations also contributes to the shrinking pool of effective therapeutics. In this Thesis, I developed and utilized a murine model of *C. neoformans* infection and, using state-of-the-art mass spectrometry-based proteomics, profiled both the host and pathogen proteome from temporal and spatial perspectives. From this analysis, I constructed the "CProteo Atlas" a publicly available resource containing in vivo infection data to enhance validation of *in vitro* findings. I demonstrated the dynamic nature of *C. neoformans* infection, showing proteome remodeling in a time and organ dependent manner. Next, I examined the ability of *C. neoformans* to infiltrate the central nervous system of the host by crossing the blood brain barrier. I identified a putative role for alpha-amylase in blood brain barrier crossing and as a novel biomarker for early infection. Finally, I examined the role of the spleen during *C. neoformans* infection, characterizing time-based biomarker signatures for both host and pathogen proteins, proposing multiple novel biomarkers of infection. Overall, this thesis contributes to our knowledge of *C. neoformans* pathogenesis, identifies novel biomarkers of infection, and proposes new durable targets with key roles during *in vivo* infection.

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Curriculum Vitae: Ben obtained his Bachelor of Science in Biomedical Science with a minor in Statistics at the University of Guelph in 2020. In the spring of 2020, he entered into the MSc. program in Molecular and Cellular Biology under the supervision of Dr. Geddes-McAlister. In the spring of 2021, he transferred into the PhD program.

Publications: **Muselius, B.,** Roux-Dalvai, F., Droit, A., Geddes-McAlister, J. (2023) Resolving the temporal splenic proteome during fungal infection for discovery of putative dual perspective biomarker signatures. *J American Society of Mass Spectrometry*. (Invited submission, Focus: Emerging scholars; front cover).

Muselius, B.[1], Sukumaran, A.[1], Yeung, J., Geddes-McAlister, J. (2020) Iron limitation in Klebsiella pneumoniae defines new roles for Lon protease in homeostasis and degradation by quantitative proteomics. *Front Microbiol*. [1]Authors contributed equally. 11:546.

Reitzel, C., Sukumaran, A., Zanetti, C., **Muselius, B.,** Geddes-McAlister, J. (2023) Phosphoproteome profiling of Klebsiella pneumoniae under zinc-limited and -replete conditions. *Microbiology Resource Announcement*. e00186-23

Reitzel, C., Sukumaran, A., O'Connor, S., **Muselius, B.,** Geddes-McAlister, J. (2023) Profiling of the phosphoproteome of Klebsiella pneumoniae under iron limited and replete conditions. *Microbiology Resource Announcement*. e00258-23

Ball, B., Woroszchuk, E., Sukumaran, A., West, H., Afaq, A., Carruthers-Lay, D., **Muselius, B.,** Gee, L., Langille, M., Pladwig, S., Kazi, S., Hendriks, A., Geddes-McAlister, J. (2021) Proteomic and secretome profiling of zinc availability in Cryptococcus neoformans identifies Wos2 as a subtle influencer of fungal virulence determinants. *BMC Microbiology*. 21: 341.

Muselius, B., Durand, S.L., Geddes-McAlister, J. (2021) Proteomics of Cryptococcus neoformans: From the lab to the clinic. *Int J Molecular Sciences*. 22: 12390

Sukumaran, A., Coish, J., Yeung, J., **Muselius, B.,** Gadjeva, M., MacNeil, A.J., Geddes-McAlister, J. (2019). Decoding communication patterns of the innate immune system by quantitative proteomics. *J Leukocyte Biol*. 1-12.

Awards: Charboneau post-doctoral fellowship – University of Calgary