COLLEGE OF BIOLOGICAL SCIENCE
Department of Molecular and Cellular Biology

ANNOUNCEMENT: Interested members of the University Community are invited to attend the Final Oral Examination for the Degree of **Doctor of Philosophy** of

Christian Carlucci

of the Department of Molecular and Cellular Biology
on Thursday, March 2, 2017 at 1:00 p.m. in SSC 3317

Thesis Title: **Examining the effects of defined microbial ecosystems on *Clostridioides difficile* growth and virulence**

Examination Committee:
Dr. M. Brauer, Dept. of Molecular and Cellular Biology (Chair)
Dr. E. Allen-Vercoe, Dept. of Molecular and Cellular Biology
Dr. C. Khursigara, Dept. of Molecular and Cellular Biology
Dr. J. MacInnes, Dept. of Pathobiology
Dr. Gayatri Vedantam, University of Arizona

ABSTRACT

Christian Carlucci B.Sc. (Hons.) **Advisor: Dr. Emma Allen-Vercoe**

Many cases of *Clostridioides* (formerly, *Clostridium*) *difficile* infection (CDI) are unresponsive to current antibiotic treatment strategies, and often patients suffer from recurrent infections characterized by severe diarrhea and colonic inflammation. We have developed a defined and standardized stool-derived microbial ecosystem therapeutic (MET-1), which has been used to cure two patients of rCDI in a proof-of-principle trial. To investigate the mechanisms behind the ability of the healthy human gut microbiota to protect against *C. difficile in vitro*, we used MET-1 and other defined microbial ecosystems to model health and disease states. Using a single-stage chemostat distal gut model to support the growth of bacterial communities, we characterized the compositional and metabonomic profiles of two defined microbial ecosystems derived from the microbiota of a healthy donor (MET-1 and DEC58), and two ecosystems representative of a dysbiotic state. Dysbiotic ecosystems were individually created through both the omission of Lachnospiraceae from DEC58, and treatment of chemostat-cultured DEC58 with ciprofloxacin, a broad-spectrum antibiotic. Both perturbed ecosystems were shown to have altered, but distinct taxonomic and metabonomic compositions compared to DEC58. We then examined the effects of defined microbial ecosystem-associated metabolites on the vegetative cell growth, sporulation, germination, spore outgrowth, toxin gene expression and secretion of two clinically important *C. difficile* ribotype strains, 027 and 078. Additionally, the cytotoxicity and metabonomic profiles of *C. difficile* were

assessed in response to treatment with each defined microbial ecosystem. Although there was large heterogeneity in the growth and virulence characteristics between *C. difficile* strains in response to defined microbial ecosystems, the results from this study suggest that defined microbial ecosystem-associated metabolites may influence *C. difficile* virulence by decreasing secreted toxin A and B levels *in vitro* and protecting against TcdB-mediated cytotoxicity. The identification of these antagonistic properties complements our existing knowledge of gut microbiota-specific anti-virulence mechanisms against *C. difficile*, and will guide the development and optimization of novel defined microbial ecosystem formulations for the effective treatment of rCDI.

CURRICULUM VITAE

Christian obtained his B.Sc. in Biomedical Science (Honours with distinction) at the University of Guelph in 2012, and began his PhD in the laboratory of Dr. Emma Allen-Vercoe in the summer of the same year. Christian has served as the President of the Molecular and Cellular Biology Graduate Student Council (2014-2015), was on the Board of Directors for the Graduate Student's Association (2013-2014), and was a member of the CBS Careers in Biology Organizing Committee (2013-2015).

AWARDS

College of Biological Sciences PhD Award (2012-2016)
Ontario Graduate Scholarship (2014-2015)
Travel grant and oral presentation, the 5th International *Clostridium difficile* Symposium in Bled, Slovenia (2015)

PUBLICATIONS:

Fecal microbiota-based therapeutics for recurrent *Clostridium difficile* infection, ulcerative colitis and obesity. 2016. Carlucci C, Petrof EO, Allen-Vercoe E. EBioMedicine 13:37-45.
(Note: Image selected as cover art for this issue)

Interaction between a broad-spectrum antibiotic and silver nanoparticles in a human gut ecosystem. Das P, Saulnier E, Carlucci C, Allen-Vercoe E, Shah V and Walker VK. 2016. Journal of Nanomedicine and Nanotechnology. 7(5) doi: 10.4172/2157-7439.1000408

A human gut ecosystem protects against *C. difficile* disease by targeting TcdA. 2016. Martz SL, Guzman-Rodriguez M, He SM, Noordhof C, Hurlbut DJ, Gloor GB, Carlucci C, Weese S, Allen-Vercoe E, Sun J, Claud EC, Petrof EO. Journal of Gastroenterology. doi: 10.1007/s00535-016-1232-y (in press)

Antivirulence activity of the human gut metabolome. 2014. Antunes LC, McDonald JA, Schroeter K, Carlucci C, Ferreira RB, Wang M, Yurist-Doutsch S, Hira G, Jacobson K, Davies J, Allen-Vercoe E, Finlay BB. mBio. 5(4): e01183-14