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*

CARYS JONES

on Tuesday, April 21, 2020 at 1:30 p.m.

Thesis Title: **Structure, function, and inhibition of peptidoglycan *O*-acetyltransferase A from *Staphylococcus aureus***

Examination Committee:

Dr. A. Bendall, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. C. Khursigara, Dept. of Molecular and Cellular Biology
Dr. J. Weadge, Dept. of Biology, Wilfred Laurier University
Dr. C. Whitfield, Dept. of Molecular and Cellular Biology
Dr. N. Strynadka, Dept. of Biochemistry and Molecular Biology, University of British Columbia (External Examiner)

Advisory Committee:

Dr. A. Clarke (Co-Adv.)
Dr. C. Khursigara (Co-Adv.)
Dr. J. Weadge

Abstract: Peptidoglycan (PG) is an essential cell wall component of most bacteria and serves to resist turgor pressure and protect the cell. O-Acetylation of PG is an important modification utilized by both Gram-positive and Gram-negative bacteria to regulate autolysins and provide resistance to host-immune attack by lysozyme. This modification commonly occurs in pathogens, including *Staphylococcus aureus*. In Gram-positive bacteria, PG O-acetylation is accomplished by a single bimodal enzyme, *O*-acetyltransferase A (OatA). As a recognized virulence factor, OatA is of interest in the development of novel strategies to overcome antimicrobial resistance. In this study, *S. aureus* OatA was subjected to a large high-throughput screen to identify and characterize inhibitors of the enzyme. To improve our understanding of the PG O-acetylation system as a whole, the structure and function of both domains of *S. aureus* OatA were also investigated. The topology of the N-terminal transmembrane domain was determined, and putative functional residues were investigated with *in vivo* and *in vitro* mutagenesis studies. A model for its mechanism and interaction with the C-terminal domain is proposed. Furthermore, the crystal structure of the C-terminal domain of *S. aureus* OatA is presented alongside an analysis of its catalytic mechanism.

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Curriculum Vitae: Carys began her Ph.D. graduate program in the lab of Dr. Anthony Clarke, in May 2016, immediately following her completion of Bachelor of Science (Honours) degree at the University of Guelph in April 2016.

Awards:

NSERC Alexander Graham Bell Canada Graduate Scholarship - CGS-D (May 2019)
OGS (2017/18 school year and 2018/19 school year)
Dr. and Mrs. Kenneth F. Gregory Graduate Scholarship (Jan 2019)
Arthur Richmond Memorial Scholarship (May 2018)
NSERC - CGS-M (May 2016-April 2017)

Publications: **Jones, C.S.**, Sychantha, D., Howell, P.L., Clarke, A.J. (2020) Structural basis for the function of the extracytoplasmic domain of OatA from *Staphylococcus aureus* as an *O*-acetyltransferase. In revision with the Journal of Biological Chemistry.

Brott, A.S., **Jones, C.S.**, Clarke, A.J. (2019) Development of a high throughput screen for the identification of inhibitors of peptidoglycan *O*-acetyltransferases, new potential antibacterial targets. Antibiotics 8(2): 65.

Carlucci, C., **Jones, C.S.**, Oliphant, K., Yen, S., Daigneault, M., Carriero, C., Robinson, A., Petrof, E.O., Weese, J.S., Allen-Vercoe, E. (2018) Effects of defined gut microbial ecosystem components on virulence determinants of *Clostridioides difficile*. Scientific Reports 9: Article 885.

Sychantha, D., Brott, A.S., **Jones, C.S.**, Clarke, A.J. (2018) Mechanistic pathways for peptidoglycan O-acetylation and de-O-acetylation. Frontiers in Microbiology 9: Article 2332.

Sychantha, D., **Jones, C.S.**, Little, D.J., Moynihan, P.J., Robinson, H., Galley, N.F., Roper, D.I., Dowson, C.G., Howell, P.L., Clarke, A.J. (2017) *In vitro* characterization of the antivirulence target of Gram-positive pathogens, peptidoglycan *O*-acetyltransferase A (OatA). PLOS Pathogens 13(10): e1006667.