University of Victoria | Graduate Studies

Notice of the Final Oral Examination
for the Degree of Doctor of Philosophy

of

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BSc (University of Alberta, 2013)

"Interactions of the *Treponema pallidum* adhesin Tp0751 with the human vascular endothelium"

Department of Biochemistry and Microbiology

Tuesday, June 18, 2019
9:00 A.M
Clearihue Building
Room B017

Supervisory Committee:
Dr. Caroline Cameron, Department of Biochemistry and Microbiology, University of Victoria (Supervisor)
Dr. Perry Howard, Department of Biochemistry and Microbiology, UVic (Member)
Dr. John Burke, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Fraser Hof, Department of Chemistry, UVic (Outside Member)

External Examiner:
Dr. Rebekah DeVinney, Microbiology, Immunology & Infectious Disease, University of Calgary

Chair of Oral Examination:
Dr. Wanda Boyer, Department of Education Psychology & Leadership Studies, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

Treponema pallidum ssp. *pallidum* is the causative agent of syphilis, a sexually transmitted infection characterized by multi-stage disease and diverse clinical manifestations. *Treponema pallidum* undergoes rapid vascular dissemination to penetrate tissue, placental, and blood-brain barriers and gain access to distant tissue and organ sites. The rapidity and extent of *T. pallidum* dissemination is well documented, but the molecular mechanisms that underlie this process have yet to be fully elucidated. Tp0751 is a *T. pallidum* adhesin that interacts with vascular factors and mediates adherence to endothelial cells under shear flow. This dissertation explores the molecular interactions and functional outcomes of Tp0751-mediated vascular endothelium adhesion.

The findings presented herein demonstrate that recombinant Tp0751 adheres to human macrovascular and microvascular endothelial cells, including cerebral brain endothelial cells. This interaction is confirmed using live *T. pallidum*, where spirochete-endothelial cells interactions are disrupted with Tp0751-specific antiserum. Further, the 67 kDa laminin receptor (LamR) is identified as an endothelial receptor using affinity chromatography coupled with mass spectrometry to isolate and identify Tp0751interacting proteins from endothelial cells membrane extracts. Notably, LamR is a brain endothelial cell receptor for other neurotropic invasive pathogens. Evaluation of endothelial intercellular junctions reveals that recombinant Tp0751 and live *T. pallidum* disrupt junctional architecture. However, transwell solute flux assays reveal that Tp0751 and *T. pallidum* do not alter endothelial barrier integrity. The transendothelial migration of *T. pallidum* can be partially abrogated with an endocytosis inhibitor, implying a transcellular route for barrier traversal. However, a subpopulation of *T. pallidum* localizes to intercellular junctions, indicating paracellular traversal may also be employed. These findings enhance our understanding of the mechanics of *T. pallidum* attachment to endothelial cells and suggest that *T. pallidum* may use both paracellular and transcellular mechanisms to traverse the vascular endothelium without altering barrier permeability. A more complete understanding of this process will facilitate vaccine development for syphilis.