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

of

BRIGETTE CHURCH

BSc Hons. (University of Victoria, 2013)

“Interactions of *Treponema pallidum* with human platelets”

Department of Biochemistry and Microbiology

Tuesday, December 15, 2020
9:00 A.M.
Conducted Remotely

Supervisory Committee:
Dr. Caroline Cameron, Department of Biochemistry and Microbiology, University of Victoria
(Supervisor)
Dr. Martin Boulanger, Department of Biochemistry and Microbiology, UVic (Member)
Dr. John Webb, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Brian Christie, Division of Medical Sciences, UVic (Outside Member)

External Examiner:
Dr. Catherine Brissette, Department of Biomedical Sciences, University of North Dakota

Chair of Oral Examination:
Dr. Kristin Semmens, Department of History, UVic

Dr. Stephen Evans, Acting Dean, Faculty of Graduate Studies
Abstract

Treponema pallidum ssp. pallidum is the causative agent of syphilis, a multi-stage bacterial infection, transmitted sexually or from mother-to-child, with an unparalleled range of symptoms arising from the ability of treponemes to penetrate any tissue and cross immune privileged endothelial barriers to access the brain, the eye, and the fetus. Further, without treatment T. pallidum evades immune clearance and persists within the host to establish a chronic infection. These characteristics suggest that T. pallidum may have evolved unique mechanisms for immune escape and to mediate host-cell interactions.

The findings presented in this dissertation contribute to our knowledge of T. pallidum pathogenesis by investigating a previously unexplored host-cell interaction, between T. pallidum and human platelets. These results validate the hypothesis that, as a pathogen which successfully utilizes vascular dissemination, T. pallidum would not only encounter, but interact with human platelets, complex cells now viewed as vascular sentinels that participate in many host-pathogen interactions.

This is the first study to demonstrate that T. pallidum interacts with human platelets and to characterize and quantify these interactions using high resolution microscope imaging techniques (video and frame analysis). These interactions were shown to be complex, reversible and mediated by motile treponemes localizing to stationary, (slide-adhered) activated platelets, versus to free-floating, inactive platelets. In addition, it was found that T. pallidum discriminates between the level of platelet activation and preferentially localized to the most activated platelet. Treponema pallidum was also able to induce platelet activation following an extended lag period.

Modified chemotaxis assays quantified by flow cytometry, were used to investigate the migration of T. pallidum in response to the plasma of platelets differentially activated with infection-relevant host components (thrombin, collagen). The results herein reveal that T. pallidum discriminates between different mechanisms of platelet activation, with a significant preference towards the secretions of collagen-activated platelets (under these experimental conditions), compared with that of inactive or thrombin-activated platelets.

Previously, T. pallidum chemotaxis had been investigated through genomic characterization and molecular interaction studies with recombinant proteins. This investigation is the first time
live *T. pallidum* was utilized for *in vitro* chemotaxis assays and is also the first study of pathogen chemotaxis in response to the secretions of differentially activated platelets.

The body of work in this dissertation provides a foundation to further investigate the role of *T. pallidum*-platelet interactions during infection, adding a new host-cell interaction to our understanding of *T. pallidum* pathogenesis. The evidence that the molecular gradients of host components can affect *T. pallidum* migration suggests an important role for chemotaxis during *T. pallidum* infection. Together, the characterization of platelet-interactions and treponeme chemotaxis in response to host components, adds to our knowledge of *T. pallidum*-host interactions, and eludes to additional pathogenic strategies that may facilitate *T. pallidum* dissemination and immune evasion.