University of Victoria | Graduate Studies

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

of

MATTHEW PARKER

BSc (Dalhousie University, 2009)

"Protein Recognition of Clinically-Relevant Carbohydrates"

Department of Biochemistry and Microbiology

Friday, June 5, 2015
10:00 A.M.
David Turpin Building
Room A144

Supervisory Committee:
Dr. Stephen Evans, Department of Biochemistry and Microbiology, University of Victoria (Supervisor)
Dr. Alisdair Boraston, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Chris Upton, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Cornelia Bohne, Department of Chemistry, UVic, (Outside Member)

External Examiner:
Dr. Pawel Grochulski, Canadian Light Source, University of Saskatchewan

Chair of Oral Examination:
Dr. Andrew Marton, Department of Pacific and Asian Studies, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

A diverse array of proteins has evolved to detect and affect carbohydrate structures, thereby performing critical roles in important biological events. Carbohydrate recognition usually employs a high degree of precision, as discriminating between two carbohydrate structures can depend on a single hydrogen bond or the configuration of a hydroxyl group. My work has focused on the molecular recognition of carbohydrate antigens by two biologically important classes of carbohydrate-binding proteins: antibodies and lectins. Single crystal x-ray diffraction has been employed to study the IgG2a antibody LPT3-1 and the lectins *Griffonia simplicifolia* 1-A4 (GSI-A4) and *Lathyrus odoratus* lectin (*LOd*L). LPT3-1 targets the conserved inner core structure of lipooligosaccharide from *Neisseria meningitidis,* the leading cause of meningitis and septicaemia. Structural characterization of LPT3-1 with an inner core fragment demonstrates how this antibody achieves selective cross-reactivity to variants of the inner core and provides insight that could support the development of a broadly protective *N. meningitidis* vaccine. Legume lectin GSI-A4 displays specificity towards the terminal galactose and *N*-acetyl-D-galactosamine of carbohydrates, yet the closely related lectin GSI-B4 will only recognize a terminal galactose. The structures of GSI-A4 co-crystallized with two different carbohydrates reveals the mechanism by which GSI-A4 displays this cross-reactivity, which allows for specific recognition of two important tumour-associated carbohydrate antigens. *LOd*L is a member of the Mannose/Glucose legume lectin family that can recognize an array of clinically significant antigens including abnormal glycosylation patterns on gp120 of HIV. Characterization of *LOd*L in complex with glucose at high resolution provides a putative primary sequence and molecular level insight into the molecular recognition displayed by this lectin. Structural data indicates *LOd*L is cross-reactive with the related glucose epimer mannose, and would display a similar if not identical affinity for glucose and mannose, enabling cross-reactivity with oligosaccharides displaying a terminal mannose. The similarity in sequence and primary recognition between *LOd*L and *Pisum sativum* lectin (PSL) suggests that *LOdL* also shares oligosaccharide specificity with PSL and similarly could demonstrate anti-HIV activity. Overall, the structural characterization of these three carbohydrate-binding proteins reveals mechanisms by which antibodies and lectins can employ selective cross-reactivity to discriminate among clinically-relevant carbohydrate structures.