PhD DEFENCE Thursday, March 12th, 2020
Student: Emily Button
Title: VASOPROTECTIVE FUNCTIONS OF HIGH-DENSITY LIPOPROTEINS ON THE CEREBROVASCULATURE AND THEIR RELEVANCE FOR ALZHEIMER'S DISEASE
Time and location: 9:00 AM; Room 200, Graduate Student Centre (6371 Crescent Road), UBC Point Grey Campus, Vancouver, BC
Supervisor: Dr. Cheryl Wellington

ABSTRACT

One in eleven Canadians over the age of 65 suffers from dementia, the most common form being Alzheimer's disease (AD). AD has traditionally been characterized by the presence of amyloid beta (Aβ) plaques and neurofibrillary tangles and in more recent years also by neuroinflammation and cerebrovascular dysfunction. We hypothesize that circulating high-density lipoproteins (HDL) may protect against such cerebrovascular dysfunction and inflammation to reduce AD risk. HDL in healthy people is already known to have several vasoprotective functions on cells in peripheral arteries and higher levels of HDL cholesterol (HDL-C) or apolipoprotein A-I (apoA-I), its primary protein component, in blood are associated with reduced AD risk. Furthermore, studies in AD transgenic mouse models suggest that HDL protects against vascular Aβ deposition, memory deficits, and neuroinflammation. This thesis used mouse models and *in vitro* human cellular models to extend the current knowledge on the protective effects of HDL against AD.

First, transgenic AD mice were employed to further investigate the role of HDL on cerebrovascular-specific pathologies in AD using a genetic approach and a pharmacological approach. Genetic loss of apoA-I in AD transgenic mice exacerbated vascular Aβ deposition, activation of cerebrovascular endothelial cell and vessel-associated astrocytes, global amyloid burden, neuroinflammation, and cognitive deficits. Pharmacological modulation of cholesterol metabolism exclusively outside of the brain resulted in reduced neuroinflammation, activation of cerebrovascular endothelial cells, and cognitive deficits. Next, 2-dimensional (2D) *in vitro* cell cultures of human brain-derived endothelial cells (EC) and 3D bioengineered human arteries were used to show that several of the known vasoprotective functions of HDL extend to brain cells and that HDL has novel protective functions against Aβ vascular deposition and Aβ-induced vascular inflammation in bioengineered tissues. Finally, efforts were made to develop high-throughput assays of these novel HDL functions in order to evaluate whether these functions are lost in people with AD or AD risk factors.

In summary, this thesis suggests novel pathways by which circulating HDL can promote cerebrovascular health using *in vivo* and *in vitro* models and suggests that improving the levels of functional HDL may be a valuable therapeutic or preventative strategy for AD.