Notice of the Final Oral Examination
for the Degree of Master of Science

of

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BSc (University of Victoria, 2013)

“Ironing out the Pathophysiology of Neurodegeneration with Brain Iron Accumulation (NBIA)
Clinical Investigations and Disease Modelling Yield Novel Evidence of Systemic Dysfunction and Provide a Robust and Accurate Disease Model of NBIA”

Department of Biology

Thursday, April 19, 2018
9:00 A.M.
Hickman Building
Room 120

Supervisory Committee:
Dr. Patrick Walter, Department of Biology, University of Victoria (Co-Supervisor)
Dr. Raad Nashmi, Department of Biology, UVic (Co-Supervisor)
Dr. Patrick MacLeod, Medical Genetics, Vancouver Coastal Health (Outside Member)

External Examiner:
Dr. Patrick Nahirney, Division of Medical Sciences, UVic

Chair of Oral Examination:
Dr. Caetano Dorea, Department of Civil Engineering, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies
Neurodegeneration with Brain Iron Accumulation (NBIA) disorders, such as Phospholipase A2G6-Associated Neurodegeneration (PLAN) and Pantothenate Kinase-Associated Neurodegeneration (PKAN), are a group of rare early-onset, genetic disorders characterized by neurodegeneration and iron accumulation inside of the basal ganglia (BG) accompanied by progressive motor symptoms. In order to address the limitations in available models of NBIA, a B6.C3-Pla2g6m1J/CxRwb mouse model of PLAN was characterized. This model demonstrated key hallmarks of the disease presentation in NBIA, including a severe and early-onset motor deficit, neurodegeneration inside of the BG including a loss of dopaminergic function and the formation of abnormal spheroid inclusions as well as iron accumulation inside of the substantia nigra (SN). The capture of these hallmarks makes this an ideal research model for NBIA. Exploration of candidate systemic biomarkers of NBIA was performed in a case study of a patient with PLAN and in a cohort of 30 patients with PKAN.

These investigations demonstrated reductions in transfer and slight, but not significant elevations in soluble transferrin receptor. No significant difference was seen in serum iron parameters. A systemic disease burden including chronic oxidative stress; elevated malondialdehyde and inflammation; elevated C-reactive protein (CRP), IL-6 and TNFα was noted in both investigations. A number of candidate protein biomarkers including: fibrinogen, transthyretin, zinc alpha-2 glycoprotein and retinol binding protein were also identified. These markers correlated with measures of the severity of iron loading in the globus pallidus (GP); based on R2* magnetic resonance imaging (MRI) and the severity of motor symptoms (Barry-Albright Dystonia Rating Scale) making them potential candidates markers of dysfunction in NBIA. In the patient with PLAN, 37 weeks of therapy with the iron chelator deferiprone (DFP) as well as 20 months of therapy with the antioxidants alpha lipoic acid (ALA) and n-acetylcysteine (NAC) were efficacious in reducing the systemic oxidative and inflammatory disease burden, but it did not significantly alter the progression of the disease. In the antioxidant therapy, this efficacy was primarily due to ALA. When the cohort of patients with PKAN were treated
with DFP for 18 months it was highly efficacious in lowering brain iron accumulation in the GP. No significant reduction in the speed of disease progression was seen in DFP treated patients compared to placebo based on initial analysis. Similar to the PLAN patient, DFP also mitigated the systemic disease burden in PKAN patients. In both cases DFP was well tolerated and had minimal impact on serum iron levels, TIBC and transferrin saturation. Collectively these investigations provide valuable insights into disease progression in NBIA. They also provide tools to aid further investigations in the form of a well-characterized B6.C3-Pla2g6m1J/CxRwb model of PLAN, which robustly captures the disease presentation seen in patients, as well as a panel of systemic blood-based markers of disease burden in NBIA and candidate markers of dysfunction in NBIA: which were used to assess two novel therapies in NBIA chelation with DFP and antioxidant therapy with ALA and NAC.