ABSTRACT

Huntington disease (HD) is an adult onset neurodegenerative disorder that is characterized by motor dysfunction, cognitive impairment and neuropsychiatric disturbances. HD patients exhibit progressive and selective neurodegeneration primarily in the striatum and cortex. There is currently no treatment that can prevent the development of HD or alter its progression. The major objectives of this thesis were to determine which symptoms of HD are recapitulated in YAC transgenic mouse models of the disease, to develop a standardized protocol for therapeutic trials in these mice and to investigate potential treatments for HD.

Two transgenic mouse models of HD were examined that express huntingtin (htt) with either 72 (YAC72 mice) or 128 (YAC128 mice) glutamines from a yeast artificial chromosome transgene. While YAC72 mice exhibit a mild phenotype, YAC128 mice show quantifiable abnormalities that recapitulate the motor and cognitive deficits in HD. Importantly, YAC128 mice also exhibit selective and progressive degeneration in the brain, including neuronal loss.

To determine the feasibility of genetic modulation of the disease phenotype, we investigated the ability of over-expression of wild type htt to prevent striatal neuropathology in YAC128 mice based on a putative pro-survival function of wild type htt. We demonstrate for the first time that wild type htt is neuroprotective in the brain. In YAC128 mice, over-expression of wild type htt prevented atrophy of striatal neurons but did not significantly improve striatal volume or striatal neuronal numbers.

To determine the feasibility of pharmacologic therapeutic trials in YAC128 mice we treated mice with cystamine, a transglutaminase inhibitor with other beneficial characteristics. While cystamine treatment did not improve motor symptoms, this treatment ameliorated striatal volume loss, striatal neuronal loss and striatal neuronal atrophy. This trial validates the use of YAC128 mice in therapeutic trials for HD as we reproduced all of the differences between YAC128 and WT mice in this therapeutic trial. Overall, this thesis demonstrates that the YAC128 mouse model of HD recapitulates the progressive motor dysfunction, cognitive deficits and selective neurodegeneration of HD. As such, these mice can be used for studies of HD pathogenesis and in preclinical therapeutic trials for HD.
BIOGRAPHICAL NOTES

Born: October 17, 1975, Maple Ridge, B.C.

Academic Studies: B.Sc. (Hon. Biochemistry), University of B.C., 1997
M.Sc. (Medical Sciences), McMaster University, 1999

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Field of Study: Huntington disease

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MEDG 520 Advanced Human Molecular Genetics Carolyn Brown
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2004-2005 Landmark Graduate Award for HD research
2001-2004 CIHR Doctoral Research Award
2001-2004 MSFHR Doctoral Trainee Award
2001-2002 Kearns Award for HD Research
1999-2001 NSERC PGS B Scholarship
1999-2001 UBC Faculty of Medicine Grant Supplement Award
1997-1999 NSERC PGS A Scholarship
1997-1999 McMaster Entrance Scholarship
1996-1997 University of British Columbia Wesbrook Scholar
1993-1997 University of British Columbia Chancellor’s Scholarship
1993-1997 Canada Scholarship in Science and Engineering
1995-1997 Charles and Jane Banks Scholarship for Science
1996-1997 Canada Scholarship Corporate Award
1993-1997 Dean’s Honours List University of British Columbia
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The Final Doctoral Examination
For the Degree of

DOCTOR OF PHILOSOPHY
(Medical Genetics)

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Tuesday, September 6, 2005, 12:30 pm
Room 200, Graduate Student Centre

“Characterization and Treatment of Mouse Models of Huntington Disease”

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