

SELECTED PRESENTATIONS

Wagner, L.A., Lu, G., Thomas, M., Leavitt, B.R. (2007) Nuclear accumulation of huntingtin and other proteins in mouse models of Huntington Disease. Society for Neuroscience, San Diego, CA.

Wagner, L.A., Lu, G., Leavitt, B.R. (2007) Exploring gene therapy vectors for the treatment of Huntington Disease. BCRI Research Day, Vancouver, BC.

Wagner, L.A., VanRaamsdonk, J., Pearson, J., Schwab, C., Murphy, Z., Devon, R., Hayden, M., Leavitt, B.R. (2007) Huntingtin protects against epilepsy. Centre for Molecular Medicine and Therapeutics TGIF Lecture Series, Vancouver, BC.

Wagner, L.A., Lu, G., Leavitt, B.R. (2006) Exploring gene therapy vectors for the treatment of Huntington Disease. Medical Genetics Research Day, Vancouver, BC.

SUPERVISORY COMMITTEE

Dr. Blair R. Leavitt, Research Supervisor (Medical Genetics)

Dr. Louis Lefebvre, (Medical Genetics)

Dr. Cheryl Wellington (Pathology and Laboratory Medicine)

THE UNIVERSITY OF BRITISH COLUMBIA

PROGRAMME

The Defence
For the Degree of

MASTER'S OF SCIENCE
(Medical Genetics)

LAURA AMY WAGNER

B.Sc., University of Guelph, 2003

Date: Tuesday, June, 17, 2008

Time: 2:00 – 5:00 pm

Exam location: Room 2027, Centre for Molecular Medicine and Therapeutics, 950 W. 28th Ave

“Silencing Mutant Huntingtin by RNA Interference for the Treatment of Huntington Disease”

EXAMINING COMMITTEE

Chair:

Dr. Wyeth Wasserman

Supervisory Committee:

Dr. Blair R. Leavitt, Research Supervisor (Medical Genetics)

Dr. Louis Lefebvre (Medical Genetics)

University Examiner:

Dr. Tim O'Connor (Cellular and Physiological Sciences)

ABSTRACT

Huntington Disease (HD) is a dominantly inherited neurological disease attributed to a CAG expansion within the HD gene. The HD mutation gives rise to a polyglutamine expansion in exon 1 of the protein huntingtin (Htt). Since the discovery of the HD mutation in 1993, various HD gene mouse models have been developed to contain either fragments or full-length copies of the mutant HD gene. The existence of these HD mouse models enables focused therapeutic testing to develop potential treatments for HD. RNA interference (RNAi) therapy is a targeted gene silencing approach whereby synthetic RNA constructs are shuttled into the cell by viral vectors and used by the cells endogenous RNAi machinery to silence a gene of interest. RNAi therapy holds promise for mutant huntingtin (muHtt) allele-specific silencing as a treatment for HD. The purpose of this thesis was to develop the tools for pre-clinical testing of RNAi-mediated gene silencing of human muHtt in the YAC128 mouse model of HD. First, AAV vector serotypes were compared for delivery to striatal neurons, the neurons most affected in HD. From this work AAV serotype 1 was selected as the most effective serotype for construct delivery. Second, synthetic RNAi constructs including short-hairpin RNA (shRNA) and microRNA-based constructs (miR-shRNAs) were compared for silencing of human muHtt expression *in vivo*. Here miR-shRNAs were found to have increased gene silencing and improved tolerance in avoiding immune activation compared to shRNAs. Alternatively, the shRNAs induced dramatic immune activation and morbidity in some cases. Ultimately these findings will contribute to a pre-clinical trial in YAC128 mice investigating Htt RNAi-mediated gene silencing in the treatment of HD. This future work provides proof of principle for muHtt allele-specific silencing as a treatment of HD.

BIOGRAPHICAL NOTES

Born: August, 9, 1980, Kitchener, Ontario
Academic Studies: B. Sc. University of Guelph, 2003
Current Position: MSc candidate, UBC

GRADUATE STUDIES

Field of Study: Huntington Disease, Gene Therapy, and Mouse Models

Courses	Instructors
MEDG 505 Genome Analysis	Drs. P. Hieter, & S. Jones
MEDG 520 Advances in Human Molecular Genetics	Drs. A. Brooks-Wilson, C. Brown, R. McMaster, C. Ross, F. Rossi, E. Simpson, & W. Wasserman
MEDG 530 Advances in Human Genetics	Drs. L. Clarke, M. Harris, & B. Leavitt
MEDG 540 Seminar (Stem Cells)	Dr. F. Rossi
MEDG 545 Current Topics in Medical Genetics	Drs. L. Conibear, M. Kobor, & B. Leavitt
MEDG 548 Directed Studies	Dr. B. Leavitt

AWARDS

Michael Smith Foundation for Health Research, Trainee Award 2006-2008
Canadian Institute for Health Research, CGS-M 2006-2007
Huntington's Society of Canada, Travel Scholarship 2006
Medical Genetics Graduate Entrance Scholarship 2005

SELECTED PUBLICATIONS

Wagner, L.A., Menalled, L., Gourmeniouk, A., Brunner, D., Leavitt, B.R. (2008) Huntington Disease: Animal and translational models of behavioural disorders. Volume 2- Neurological Disorders. McArthur, R.A. and Borsini F. (Eds), Elsevier, New York. In Press.

Mazarei, G., Wagner, L.A. (2006) SCA8: A two-way street to pathogenicity. Clin. Genet. 70(5):382-83.

Wagner, L.A., Mazarei, G. (2006) Freeman-Sheldon syndrome and Sheldon-Hall syndrome: contracting new genotypes. Clin. Genet. 70(3):192