

## ABSTRACT

Huntington disease (HD) is a progressive disorder characterized by involuntary movements, emotional disturbances, and memory loss. The cardinal neuropathological feature of HD is loss of medium spiny neurons within the striatum. There is currently no cure for HD and the disease is ultimately fatal. Accumulating evidence has implicated excitotoxicity, a process in which excessive signaling via the glutamate receptors results in neurotoxicity, in the selective neuronal loss in HD. The main aim of the studies presented was to evaluate the potential of small molecule therapeutics known to target excitotoxicity-related pathways in the YAC128 transgenic mouse model of HD. Induction of a heat shock protein (HSP) response has been shown to be neuroprotective in acute excitotoxicity models and in models of polyglutamine-induced neurodegenerative disease. We examined whether treatment with arimocloamol, a compound shown to enhance the HSP response by prolonging the activation of heat shock factor 1 (Hsf-1), can improve the phenotype of the YAC128 HD mice. Our findings demonstrate that treatment with arimocloamol does not lead to up-regulation of an HSP response or rescue of the behavioural and striatal deficits in the YAC128 HD mice. We next examined whether treatment with memantine, a clinically well-tolerated NMDA receptor antagonist currently used to treat patients with moderate to severe Alzheimer's disease, can improve the phenotype of YAC128 HD mice. We demonstrated that treatment with memantine results in improvements in motor function and rescues the striatal deficits in a dose-specific manner. Rasagiline is a selective inhibitor of monoamine oxidase type B (MAO-B) clinically approved for the treatment of Parkinson's disease that has been shown to protect against a number of neurotoxic stimuli. We demonstrate that treatment with rasagiline protects against striatal lesioning in acute models of excitotoxicity and improves the motor function of the YAC128 HD mice. Finally, we demonstrate that treatment with a combination of memantine and rasagiline yields greater benefit than obtained with either compound alone, providing early and sustained improvements in motor function and rescuing striatal deficits in the YAC128 HD mice. Our findings suggest that targeting excitotoxicity may be a viable therapeutic approach in HD.

## BIOGRAPHICAL NOTES

Born: September, 14, 1979, Kuwait

Academic Studies: B. Sc. (Honours) McMaster University, 2001  
M. Sc. McMaster University, 2004

## GRADUATE STUDIES

Field of Study: Translational research on excitotoxicity as a therapeutic target for Huntington disease

### Courses

MEDG520 Advanced Human Molecular Genetics  
MEDG530 Advanced Human Genetics  
MEDG545 Current Topics in Medical Genetics  
MEDG548 Directed Studies

### Instructors

Dr. A. Brooks-Wilson &  
Dr. C. Brown  
Dr. J. Friedman  
Dr. W. Robinson  
Dr. M.R. Hayden

## AWARDS

2010 Ripples of Hope Award in Biotechnology & Entrepreneurship  
2009 Canadian Institutes of Health Research Brain Star Award  
2009 CHDI HD Therapeutics Conference Oral Presentation Prize  
2008 UBC Medical Genetics Research Day Senior Poster Prize  
2007 UBC Medical Genetics Research Day Senior Poster Prize  
2004-2008 Canadian Institutes of Health Research Doctoral Research Award  
2006-2007 Michael Smith Foundation for Health Research Doctoral Trainee Award  
2004-2007 University of British Columbia PhD Tuition Award

## SELECTED PUBLICATIONS

**Pouladi MA**, Xie Y, Skotte NH, Ehrnhoefer DE, Graham RK, Kim JE, Bissada N, Yang XW, Paganetti P, Friedlander RM, Leavitt BR, Hayden MR. 2010. Full-length huntingtin levels modulate body weight by influencing insulin-like growth factor 1 expression. *Human Molecular Genetics*. 19: 1528–1538.

Okamoto S\*, **Pouladi MA\***, Talantova M\*, Yao D\*, Xia P, Ehrnhoefer DE, Zaidi R, Clemente A, Kaul M, Graham RK, Zhang D, Vincent Chen HS, Tong G, Hayden MR, Lipton SA. 2009. Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. *Nature Medicine*. 15: 1407–1413.

**Pouladi MA**, Graham RK, Karasinska JM, Xie Y, Santos RD, Petersén A, Hayden MR. 2009. Prevention of depressive behaviour in the YAC128 mouse model of Huntington disease by mutation at residue 586 of huntingtin. *Brain*. 132: 919-32.

Milnerwood AJ, Gladding CM, **Pouladi MA**, Kaufman AM, Hines RM, Boyd JD, Ko RW, Vasuta OC, Graham RK, Hayden MR, Murphy TH, Raymond LA. 2010. Early Increase in Extrasynaptic NMDA Receptor Signaling and Expression Contributes to Phenotype Onset in Huntington's Disease Mice. *Neuron*. 65: 178–190.

Graham RK, **Pouladi MA**, Joshi P, Lu G, Deng Y, Wu NP, Figueroa BE, Metzler M,



André VM, Slow EJ, Raymond L, Friedlander R, Levine MS, Leavitt BR, Hayden MR. 2009. Differential susceptibility to excitotoxic stress in YAC128 mouse models of HD between initiation and progression of disease. *Journal of Neuroscience*. 29: 2193-204.

Becanovic K, **Pouladi MA**, Lim RS, Kuhn A, Pavlidis P, Luthi-Carter R, Hayden MR, Leavitt BR. 2010. Transcriptional changes in HD identified using genome-wide expression profiling and cross platform analysis. *Human Molecular Genetics*. 19: 1438–1452.

**Pouladi MA**, and Hayden MR. 2007. "Introduction to Huntington's Disease" in *Huntington's Dementia*, first ed.

**Pouladi MA**, Bezprozvanny I, Raymond LA, and Hayden MR. 2006. "Molecular Pathogenesis of Huntington's Disease: The Role of Excitotoxicity" in *Genetic Instabilities and Neurological Diseases*, second ed, pp 251-260.

Hayden MR, **Pouladi MA**, and Kremer B. 2006. "Basal Ganglia Disorders" in *Emery & Rimoin's Principles and Practice of Medical Genetics*, fifth ed, pp 2703-2736.

\* These authors contributed equally to this work.

**SELECTED PRESENTATIONS**

**Pouladi MA**, Hayden MR. Trial of memantine in the YAC128 mouse model of HD. In Memantine and HD Meeting, 2010, Oslo, Norway.

**Pouladi MA**, Graham RK, Bertram L, Dar Santos R., Xie Y, Schwab C, Zapala M, Metzler M, Leavitt BR, and Hayden MR. A controlled trial of memantine, an NMDA receptor antagonist, in combination with the propargylamine rasagiline in a mouse model of Huntington disease. In 4th Annual Huntington's Disease Therapeutics Conference: A Forum for Drug Discovery & Development, 2009, Cannes, France.

**Pouladi MA**, Graham RK, Karasinska J, Xie Y, Dar Santos R, Petersén Å, and Hayden MR. Prevention of cleavage of mutant huntingtin by caspase-6 alleviates the depressive behaviour in the YAC128 mouse model of Huntington disease. In Pacific Northwest Chapter Meeting of the Society for Neuroscience, 2008, Vancouver, BC.

**Pouladi MA**, Xie Y, Leavitt B, and Hayden MR. Role of Huntingtin in Body Weight Regulation. In The 1st Reisensburg Workshop—The Metabolic System as a Therapeutic Target in HD, 2008, Gunzburg, Germany.

**Pouladi, MA**, Bertram L, Stämpfli M, and Hayden MR. Inflammation and Huntington Disease Pathogenesis. In RCAI International Summer Symposium, 2006, Yokohama, Japan.

**SUPERVISORY COMMITTEE**

- Dr. Michael R. Hayden, Research Supervisor (Medical Genetics)
- Dr. Yu Tian Wang (Neuroscience)
- Dr. Jon Stoessl (Neuroscience)
- Dr. Lorne Clarke (Medical Genetics)

**PROGRAMME**

The Final Oral Examination  
For the Degree of

DOCTOR OF PHILOSOPHY  
(Medical Genetics)

**MAHMOUD A. POULADI**

B. Sc. (Honours) McMaster University, 2001  
M. Sc. McMaster University, 2004

Wednesday, July 21, 2010, 9:00 am  
Room 203, Graduate Student Centre

**"On the Modulation of Excitotoxicity as a Therapeutic Approach for the Treatment of Huntington Disease"**

**EXAMINING COMMITTEE**

Chair:  
Dr. Peter Graf (Psychology)

Supervisory Committee:  
Dr. Michael R. Hayden, Research Supervisor (Medical Genetics)  
Dr. Yu Tian Wang (Neuroscience)

University Examiners:  
Dr. Anthony G. Phillips (Neuroscience)  
Dr. James G. McLarnon (Neuroscience)

External Examiner:  
Professor David Rubinsztein  
Department of Medical Genetics  
Cambridge Institute for Medical Research  
Cambridge, England  
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