

Ask the Experts Session

**Thursday, 29th November 2007,
Westin Harbour Castle, Toronto**

SPEAKER: HEATHER D. DURHAM, PHD

BIOGRAPHY: Dr. Heather Durham obtained her Honours BSc in Physiology and Pharmacology and MSc in Pharmacology from the University of Western Ontario and PhD in Pharmacology from the University of Alberta. She subsequently moved to McGill University for postdoctoral studies in neurotoxicology and neuromuscular disease in the Department of Pharmacology and Therapeutics and subsequently in the Department of Neurology and Neurosurgery and Montreal Neurological Institute. In 1982, she became an independent investigator in the Neuromuscular Research Group at the MNI, where she now holds the rank of Professor of Neurology and Neurosurgery. Administratively, she has held several positions related to graduate studies and laboratory safety. Awards include CIHR postdoctoral fellowship, Chercheur Boursier of the Fond de Recherche en Santé du Québec (FRSQ) and Killam Scholar.

In her research career, Dr. Durham has specialized in motor neuron disorders. Her earlier studies involved toxic neuropathies induced by pesticides and organic solvents, but since the early 1990's her laboratory has focused on studies directly relevant to ALS. Her particular scientific interests and contributions relate to the physiological basis of motor neuronal vulnerability to disease, cellular stress responses, and mechanisms of toxicity of neurotoxic chemicals and mutant proteins. Her lab specializes in the use of primary culture models of motor neuron diseases to study these mechanisms and evaluate potential therapeutics. Her research laboratory has been funded by grants from the Canadian Institute for Health Research, ALS Society of Canada, Muscular Dystrophy Canada, ALSA, MDA, and the Johns Hopkins Centre for Alternatives to Animal Research.

Dr. Durham has been highly involved with charitable organizations, professional societies and government agencies. She is currently a member of the Board of Directors and Chair of the Research Policy Committee of the ALS Society of Canada and member of the Medical Advisory Committee for MDA. She previously held several positions on the Boards of Directors of the Society of Toxicology of Canada and the Canadian Federation of Biological Societies. Her expertise in neuromuscular toxicology has involved Dr. Durham in bio-chemical defence, serving as member and Chair of the Biological Chemical Defence Review Committee for the Department of National Defence (Canada) and member of the Advisory Committee on CBRN to the Minister of Health. She currently sits on scientific advisory committees for the Centre for Security Science (DND) and Agriculture Agri-Foods Canada.

TITLE OF PRESENTATION: BASIC RESEARCH: WHAT IS GOING WRONG WITH THOSE CELLS?

ABSTRACT: Good progress has been made in identifying specific abnormalities at the cellular level in ALS patients and in cell culture or animal models. The more holistic goal is to understand how these abnormalities relate to one another and how to target therapies to restore balance in the cells so they continue not only to survive, but to function. This view not only applies to what is going on inside motor neurons that contributes to their demise in ALS, but to the function of neighbouring glial cells. Deterioration of the relationship between neurons and glia takes considerable blame for the rapid progression of the disease once it starts.

Many structural and functional abnormalities have been observed at the level of the motor neuron including mitochondrial dysfunction, oxidative stress, accumulation of damaged proteins, defects in transporting materials, cytoskeletal abnormalities, attrition of dendrites, retraction of synapses, etc. In sporadic ALS, we don't know what initiates these changes or when they start, but in familial forms, cells express the mutant protein from conception; amazingly motor neurons and other cells form, develop and function before the most vulnerable start to fail and ultimately clinical symptoms appear in adulthood. It's not just being exposed to the initiator of the disease, but how cells react to the toxic challenge and defend themselves that determines outcome. In ALS, it is important to recognize multiple stages of disease at both the level of the cell and in the nervous system of an affected person that might require different types of intervention. In the first phase, cells are challenged, but still function. Many factors underlie the particular vulnerability of motor neurons, but one important consideration is the work required to maintain the extensive distribution of dendritic processes within the spinal cord and the long, large diameter axons of up to a meter in length that, in the case of spinal motor neurons, extend out to innervate muscle. As motor neurons lose their ability to cope, these distal extremities will be compromised, failing to maintain the connections that receive messages from other neurons or communicate the processed signal. In this phase, motor neurons are alive, but sick and not fulfilling their duties. At the cell body, signals of damage are sent out, the neighbouring cells are sensing trouble, and may be affected by the disease themselves. Instead of being supportive and nurturing, these glial cells may turn coat and secrete factors that contribute to the demise of not only the adjacent, weakened motor neuron, but those nearby.

Evolution has equipped us with the ability to withstand loss of a relatively high proportion of our motor neurons until a threshold is reached and motor function is compromised. Thus, both at the level of the cell and at the level of motor neuron pools, there are silent periods of damage before the appearance of clinical symptoms, which makes intervention difficult. However, not all pools of motor neurons are affected at the same time or to the same degree. Symptoms may present first in one area of the body and spread as the disease progresses. Thus, early in clinical disease there are likely to be neurons in the spinal cord and brain at different stages of malfunction from challenged but still functional, to alive but not working, to under attack by the neighbourhood. Each of these stages are conceptually amenable to therapy, but will require different types of interventions.

SPEAKER: GUY A. ROULEAU

Employment

Research Centre of the CHU Sainte-Justine	Director	2006-
Centre for excellence in neuromiccs	Director	2004-
Canada Research Chair in Genetics of the Nervous System		2004-
Université de Montréal	Full professor, Department of Medicine	2004-
McGill University	Adjunct Professor, Human Genetics	2004-
McGill University Medicine	Ass. Professor / Professor, Dept. of 1989-2004	

Honours

2007	Officier de l'Ordre national du Québec	
2007	Henry-Friesen Award	Royal College of Physicians and Surgeons of Canada
2006-	Member	Canadian Academy of Health Sciences
2005-	Award of Excellence	Department of Medicine, Université de Montréal
2002	Personnalité de la semaine	La Presse
2000	Michael Smith Award	Canadian Institutes of Health Research
1999	Prix Leo-Parizeau.	Association francophone pour le savoir (ACFAS)
1994	Un des Grands de l'année	Magazine l'Actualité
1993	Scientist of the Year	Société Radio-Canada

TITLE OF PRESENTATION: UPDATE ON GENETICS AND GENOMIC

ABSTRACT:

The state of research on ALS genetics has progressed rapidly over the past few years and has led to a better understanding of the genetic susceptibility to ALS. A new region has been identified where a gene causative for ALS and frontotemporal dementia exists on chromosome 9. A concerted effort is being put forward to identify this gene, as well as the genes responsible for other familial forms of ALS. Concurrently, a series of whole-genome association studies have been published which help point to subtle genetic variations and further candidate genes. This is particularly relevant in a disease like ALS where the large majority of cases do not have a strong familial component. The result is that new candidate genes are emerging, such as ITPR2, FLJ10986 and PON1-3. The functions of these genes can now be examined in the context of motor neuron degeneration. In addition, the cost of sequencing is decreasing at the same time as new sequencing techniques are emerging. This enables new and more comprehensive strategies to be employed to determine the genetic cause of ALS.

**SPEAKER: PROFESSOR ORLA HARDIMAN BSC MD FRCPI
FAAN**

BIOGRAPHY:

Orla Hardiman is a Consultant Neurologist at the National Neuroscience Centre, Beaumont Hospital Dublin, where she directs the National ALS service, Clinical Professor (Neurology) at Trinity College Dublin, and a Health Research Board Physician Scientist.

Prof. Hardiman was born in Dublin and is a graduate of University College Dublin, where she took a Bachelors degree in Physiology in addition to her medical degree. She underwent post graduate training in Neurology and Neuropathology in Dublin, and subsequently moved to Boston to undertake Neurology Residency training at Harvard Longwood Neurology Program (Brigham & Womens Hospital) where she was also Chief Resident in Neurology. Her Fellowship training was in the Day Laboratory for Neuromuscular Disease with Dr. Bob Brown at Massachusetts General Hospital and Harvard Medical School, Boston.

She returned to Dublin in 1991 as a Newman Research Scholar at University College Dublin, and was appointed first to position of College Lecturer in Physiology at UCD, and later to the post of Consultant Neurologist at the National Centre for Neuroscience. In 2004, she became the first Irish-based Neurologist to become a Fellow of the American Academy of Neurology. In 2007 she received a prestigious Physician Scientist Award, and was appointed as a Clinical Professor in Neurology at Trinity College Dublin.

Prof. Hardiman directs the Irish ALS Register, and has published extensively on clinical aspects of ALS, including the evaluation of respiratory dysfunction, quality of life, and eligibility criteria for clinical trials.

Her primary research interests include the epidemiology and pathogenesis of amyotrophic lateral sclerosis (ALS) with particular reference to the identification of genetic susceptibility factors. Her recent work has focussed on the clinical and genetic overlap between ALS and frontotemporal dementia. She currently holds research grants from the Irish Health Research Board, ALS Association (USA) and Muscular Dystrophy Association (USA).

Prof. Hardiman is an author of over 85 international peer-reviewed research articles, and a member of a number of national and international boards and advisory panels on ALS.

**TITLE OF PRESENTATION: CLINICAL TRIALS: WHY AREN'T THE
DRUGS WORKING AND CAN WE DO BETTER?**

ABSTRACT:

The selection of drugs and compounds as potential treatments for ALS can be based on a number of criteria. Some drugs are selected because they affect a biological process or pathway that is thought to be important in the death of motor neurones. Improving our understanding of the factors that lead to motor neurone death in ALS is therefore an important way to find new drugs. Other drugs and compounds are chosen because they seem to protect motor neurones from injury, or because they

seem to be effective in other related conditions. Many drugs are chosen for further development because they have a positive effect on survival in a mouse model of ALS. This mouse has been genetically engineered to contain a mutant SOD1 gene that causes ALS in humans, and the pathways leading to neurodegeneration in these mice have been examined in great detail. Many drugs have been selected because they seem to affect some of the known pathways that makes motor neurones degenerate in SOD1 mice.

However, there is now an increasingly long list of clinical trials that have been undertaken in good faith that have turned out to be of no benefit, and in some cases, to be injurious to patients. This is despite the fact that the majority of drugs looked very hopeful in the SOD1 mouse.

So why don't the drugs work in humans, and what new avenues should be pursued to find a cure, or at least to slow the progression of neurodegeneration in ALS?

It is becoming increasingly clear that the SOD1 mouse is an imperfect model for human ALS. It is important to recognize the differences between the mouse form of the disease, and that which occurs in humans. In most cases, SOD1 mice are treated with drugs before the illness is apparent – this is obviously much more difficult to do in humans. Finding very early markers of human disease would be very helpful.

It is also very likely that there is more than one cause of human ALS, and that some individuals will respond to particular drugs to a greater extent than others. Identifying these differences between patients will be very helpful in developing effective and tailored treatments.

While the experience to date in clinical trials has been disappointing to date, the current a re-assessment of and re-direction of our approach towards trial design, which will including the search for biomarkers and a re-organization of how we design clinical trials, is likely to yield a new panel of therapeutics that will slow and ultimately arrest the process of neurodegeneration.

**SPEAKER: WENDY JOHNSTON, MD, FRCP(C) ,
ASSOCIATE PROFESSOR, NEUROLOGY,
UNIVERSITY OF ALBERTA, EDMONTON,
ALBERTA, CANADA**

BIOGRAPHY:

Wendy Johnston, M.D., F.R.C.P. (C) is Associate Professor, Director of the ALS/Neuromuscular Program and Deputy Director of the Division of Neurology at the University of Alberta, Edmonton, Alberta, Canada.

Dr. Johnston graduated from the University of Toronto, Queen's University Medical School (Kingston, Ontario), and McGill University (Montreal, Quebec) including neurology residency and a neuromuscular fellowship under Dr. George Karpati.

In 1992, she started the ALS clinic and research program at Oregon Health Sciences University in Portland, Oregon. She has been principal investigator in multiple clinical trials, both pharmaceutically sponsored and investigator initiated, and became a member of the Western ALS Study group. Dr. Johnston was co-PI on studies of attitudes to assisted suicide (New England Journal of Medicine. 1998; 339 (14) 967-

973), and the prevalence of suffering and its correlates in patients with ALS (Neurology 1999, 52(7) 1434-1440). A follow up study found persistence of interest of assisted suicide (J Pain Symptom Manage. 24:312-217, 2002) The experiences of patients and caregivers in the last month of life with ALS were found to include unacceptably high levels of pain and suffering in spite of access to hospice care. (Neurology. 2002 Aug 13; 59(3): 428-31).

In 2000, Dr. Johnston joined the Neurology Division at the University of Alberta, and started a new ALS program that has now grown to include a multidisciplinary clinic, a research group that participates in clinical trials, as well as investigator initiated research in imaging , early diagnosis, quality of life and end-of-life issues., and collaboration with basic research in motor neuron diseases.

Dr. Johnston has authored or co-authored numerous articles on ALS, particularly related to end –of-life decisions, palliative care and quality of life in patient with ALS., and is a frequent speaker on these topics at local, national and international medical and neurological conferences.

TITLE OF PRESENTATION: TODAY’S PATIENT CARE CHOICES FOR SYMPTOMATIC AND PSYCHOLOGICAL SUPPORT

ABSTRACT:

There was a time when patients with ALS, and their loved ones, were routinely told that “Nothing can be done” when confronted by the diagnosis. In this presentation, and in the question and answer session, Dr. Johnston hopes to raise the expectations of those affected with ALS. A well informed person with ALS should expect patient-centred care, hopeful discussions about symptom management and interventions that improve quality of life. Those who feel in control of their medical care will achieve better quality of life. The challenge to families faced with ALS is how to apply their knowledge and get the care that makes a difference.

SPEAKER: DENISE A. FIGLEWICZ, PH.D.

BIOGRAPHY:

Denise Figlewicz received her B.S. in Biology, *Summa cum Laude*, and Ph.D. in Biochemistry & Biophysics, from Loyola University of Chicago. Her doctoral and postdoctoral studies centered on development of the myelin sheath in disease models and normal rodents, with focus on specific proteins and lipids. In 1985, as a Pierre de Bourghknecht fellow, she accepted the opportunity to travel to Switzerland and undertake studies of a mouse model of motor neuron degeneration. Since that time, her research has focused on studies of motor neuron degeneration and amyotrophic lateral sclerosis. In September of 2006 she joined the ALS Society of Canada as Research Director.

Dr. Figlewicz's studies of ALS/MND have been multidisciplinary, and highly collaborative. She was one member of the team of researchers who identified mutations in Cu,Zn Superoxide Dismutase (SOD-1) in familial ALS in 1993. Her subsequent studies employed approaches ranging from human molecular genetics, cell culture, protein biochemistry, and quantitation of gene expression to motor function testing of the mutant SOD mouse model of ALS. Her work has been funded by Muscular Dystrophy Association (USA), ALS Association (USA), and NINDS, NIAMS, and NIEHS institutes of the NIH. She is the author of over 80 peer-reviewed articles and book chapters.

In addition to research, Dr. Figlewicz has made important contributions in related areas. She enjoys teaching at all levels, and while an associate professor at the University of Rochester (NY) was awarded the Dean's Teaching Fellowship for her work with medical students, graduate students, Neurology residents, research fellows, and undergraduate students. She is a member of the Editorial Board of the ALS Journal and a regular reviewer for numerous neurology, neuroscience, and genetics journals. She has served on research advisory committees for MDA-USA and ALSA, and both regular and *ad hoc* scientific panels of NIH. She has participated in a number of community outreach opportunities – her volunteer activities have included demystifying molecular genetics for a ladies' church group and participating in middle school students' molecular biology day camps. However, most often, she participates in patient-oriented meetings sponsored by charitable organizations or private research foundations for patients, caregivers, friends and families.

She is particularly excited with her position at the ALS Society of Canada which allows her to pull together all these dimensions of her experience in the search for treatments for ALS/MND.

TITLE OF PRESENTATION: ALS RESEARCH: PROGRESS AND NEW DIRECTIONS

ABSTRACT

The joint opening session of the 18th International Symposium on ALS/MND provides the first glimpse of how research related to causes and development of treatments for ALS/MND continues along lines of investigation which have been underway for years, yet has expanded with some fresh perspectives and new methodological approaches. To begin with, the understanding of the clinical presentation of ALS/MND has broadened to acknowledge changes in cognitive function which may range from subtle to significant. Because of the potential impact this has on patient and caregiver choices, many approaches are being employed for assessment of frontotemporal dementia (FTD) in ALS. This includes overlap with what is already known about neuropsychology, neuropathology, and genetics of FTD itself.

Genetic studies have contributed the basis of many of the models for ALS/MND used in research during the past decade. However, new genetics approaches have contributed information about potential risk genes for ALS/MND, as well as whole-

genome portraits of sporadic ALS/MND patients. It might be expected that the results of these more recent studies will help us to test our current hypotheses about mechanisms of neurodegeneration in ALS/MND: excitotoxicity; oxidative stress; inflammation; problems with cytoskeleton and axonal transport; and handling of misfolded/ damaged proteins by the motor neuron; to name a few. In addition, the new results from genetics and gene expression studies should help us to construct new more comprehensive pictures about the multiple processes going on simultaneously during the course of the disease.

Identification of treatment strategies for ALS/MND has moved in parallel with understanding of mechanisms of disease suggested by basic research. The contribution of non-neuronal cells to both the support of motor neurons and the initiation of inflammatory reaction continues to be investigated in increasing detail. These cells may themselves serve as a target for experimental therapeutic approaches now being tested.

Challenges remain with respect to routes of delivery for therapies, to identification of most effective combinations of therapies, and to earliest possible confirmation of diagnosis to allow treatment(s) to be most effective. Thus, research into biomarkers from a variety of tissue sources which may serve as diagnostic hallmarks continues to be an important area of investigation. For the same reason, imaging studies and electrophysiology are also critical directions for recent research.

Progress on these many research fronts is accelerating. The Symposium provides the opportunity for us to assess the knowledge gleaned from the directions already being pursued, and to identify new areas of priority to focus additional research efforts.