

Parkinson

Research Consortium



October 4, 2005

Update on the PRC

It has been a very productive year since the official launch of the PRC one year about. We started this initiative with three main visions

- 1) To build a comprehensive Center focused around the science of understanding the genetic susceptibility factors and cell biological processes which contribute to PD progression.
- 2) To provide a scientific forum which will readily link the goals of basic and clinical scientists in the treatment of PD.
- 3) To use this virtual center of excellence in Ottawa as a springboard to build a cohesive national Canadian effort in PD research.

Vision 1

To accomplish our first vision we decided to explore 5 main scientific projects.

- a) Identification of genetic determinants of dopaminergic neuron development and death in the *C. Elegans* worm. The work on this project is being lead by Drs. D. Park and A. Colavita. The main focus is to study the effect the inserting the Parkinson's disease causing genes DJ-1, PINK1 and LRRK2 into the *C. Elegans* worm.
- b) Zebrafish as a powerful vertebrate genetic model for the study of PD. The two scientists leading this project are Drs. M. Ekker and V. Trudeau. They have set up screens to identify genes which are required for dopamine functioning in two separate fish models.
- c) Use of drosophila to determine pathways of dopaminergic loss in PD. Drs. M. Sonnenfeld and D. Park have begun work at inserting the Parkinson's disease causing gene LRRK2 to study it's affect on the fly's dopamine cells.
- d) Delineation of the molecular mechanisms of dopaminergic loss in mammalian models of PD. Drs. D. Park and J. Wolfe have been using both toxins (MPTP, 6-OHAD, etc) and genetic models (synuclein, DJ-1 and Nurr1) of Parkinson's disease in mice to understand the basic mechanisms of the disease process.

e) Identification of novel genes or gene mutations in individuals with Parkinson's disease. Drs D. Bulman, and D. Grimes have been exploring the role of PD genes in patients with Parkinson's. Dr. J. Ngsee has been studying the Parkinson's causing gene LRRK2.

The PRC has been able to provide funding for: 1) graduate students in the labs of Dr. Park, Dr. Ekker and Dr. Trudeau 2) research technicians in the labs of Dr. Bulman/Grimes, Dr. Ngsee, and Dr. Albert and 3) a summer student in the lab of Dr. Wolfe.

Vision 2

The PRC has been holding bimonthly scientific meetings to discuss our projects and to present new data that has been generated in our labs. These meetings are attended by not only basic scientists but clinicians involved in the care of individuals with Parkinson's disease. We have also had three external scientists come and share their work in Parkinson's disease research. These meetings have been used as a forum to discuss important initiatives as well as the direction of research that the group wants to focus on. We have been able to generate interesting ideas and discuss ways to link our findings to patients with the disease.

In order to disseminate our new knowledge to a wider audience, we have worked with the Parkinson Society Ottawa giving evening lectures to individuals with Parkinson's and their families. These have occurred approximately every six months. We published our first newsletter and have used this in an effort to raise awareness of the importance of research in Parkinson's disease and what is being done in Ottawa to better understand the disease.

An important goal of the PRC has been to attract new scientists and clinicians into Parkinson's. We have advertised in international journals to recruit individuals and have a very prominent American researcher interested in coming to Ottawa. This recruitment would not have been initiated if not for the formation of the PRC. This researcher will be coming for a second visit this month and we hope will want to join our group. The PRC funding will play a key role in making Ottawa an attractive choice.

Vision 3

Already we have made efforts to broaden the scope of the PRC to a more national basis. A grant has just been submitted to The Networks of Centres of Excellence program for funding of a Canadian Parkinson Network. This is a federal program administered jointly by the Natural Sciences and Engineering Research Council(NSERC), the Canadian Institutes of Health Research (CIHR) and the Social Sciences and Humanities Research Council (SSHRC) in partnership with Industry Canada. The goals of the Canadian Parkinson Network are to organize and integrate the expertise of Canada's already considerable cadre of PD experts to address the needs of the PD community. The proposed focus of the Network was to first develop a "best practices" strategy for treatment of PD patients, the second was to generate the synergisms of scientists across Canada to push forward PD research to better understand the disease process and third was translate this information we discover to improve the quality of life for those with Parkinson's. Since the submission of this grant, we have been contacted by many researchers from across Canada who were not part of the initial grant but are keen to join.

Despite having only just launched the PRC we have already been able to measure our success in concrete ways. We have received \$210,500 in funding support from donors plus an additional \$77,500 due to be received this month. We have a commitment from the Department of Medicine of \$80,000 to help the recruitment of a Parkinson's clinician scientist and have a very strong candidate as discussed above interested in coming to Ottawa from the United States. Dr John Wolfe and Dr David Park have just received operating grants of \$45,000 from Parkinson Society Canada and Dr. Park has just obtained fellowship funding for two post doctoral positions (one from the Parkinson Society Canada and another by the Parkinson's Disease Foundation in the United States). In addition, investigators in our group have generated six papers stemming from work in part sponsored by the PRC.

1. MPTP Induces Intranuclear Rodlet Formation in Rat Nigral Dopaminergic Neurons. Wiplove Lamba, David G Munoz, Wendy Prichett-Pejic, **David Park**, **John Woulfe** (accepted to **Brain Research**)
2. Central nature of interferon-gamma in microglial mediated loss of dopaminergic neurons. Matthew P. Mount, Arman Lira, Shawn Hayley, **David Grimes**, Patrice D. Smith, Sylvie Faucher, **Ruth Slack**, Hymie Anisman & **David S. Park** (submitted)
3. Calpain regulated p35/cdk5 plays a central role in dopaminergic neuron death through modulation of the transcription factor MEF2. Patrice D. Smith, Matthew P. Mount, Raj Shree, Steve Callaghan, Ruth S. Slack, Hymie Anisman, Inez Vincent, Xuemin Wang, Zixu Mao, and **David S. Park** (accepted to J. Neurosci.)
4. Differential Roles of Nuclear and Cytoplasmic Cdk5 in Apoptotic and Excitotoxic Neuronal Death. Michael J. O'Hare, Neena Kushwaha, Yi Zhang, Hossein Aleyasin, Steven M. Callaghan, **Ruth S. Slack**, **Paul R. Albert**, Inez Vincent, **David S. Park** (in press J Neurosci)
5. Screening of the neurofilament M Gene Gly336Ser mutation in a French-Canadian population with Parkinson's disease. F Han, **DE Bulman**, M Panisset, **DA Grimes**. Can J Neurol Sci. 2005 Feb;32(1):68-70
6. A translated mutation in the Nurr1 gene as a cause for Parkinson's disease. **DA Grimes**, F Han, M Panisset, **DE Bulman** (in press Movement Disorders)

Appendix,

Current active members:

David Park-OHRI, -neurodegeneration

David Grimes-OHRI, neurologist

John Woulfe-OHRI, neuropathologist

Dennis Bulman-OHRI, genetic disorders

Paul Albert-OHRI, dopamine signalling

Johnny Ngsee-OHRI, cell trafficking

Ruth Slack-OHRI, stem cell/development

Antonio Colavita-OHRI, worm genetics

Mark Ekker-U of Ottawa, fish genetics

Vance Trudeau-U of Ottawa, environmental science

Margaret Sonnenfeld-U of Ottawa, fly genetics

Jagdeep Sandhu, NRC, neurodegeneration

Marianne Sikorsky, NRC, neurodegeneration

Shawn Hayley, Carleton University, inflammation/stress