Research

Parkinson Society Canada
National Research Program Awards
for 2006-2008 Cycle

Granting period
July 1, 2006 – June 30, 2008

Pilot Project Program Grants

FRIEDMAN PILOT PROJECT GRANT
Researcher: **Brian E. Staveley**
Name of Project: **Preliminary analysis of PINK1 (PARK6) and LRRK2 (PARK8) in Drosophila models of Parkinson's disease**
Institution: Memorial University of Newfoundland
Amount Year One: $45,000
Amount Year Two: n/a – one year grant
Total Awarded: $45,000
Lay Summary: Parkinson's disease (PD) is due to the loss of neurons that produce dopamine in the brain. A number of genes, some key to the destruction of toxic proteins, have been associated with inherited forms of PD. Selective protein detoxification is a common biological mechanism shared by humans and fruit flies. Using fruit fly models, our laboratory investigates the cellular functions disrupted in PD.
Our laboratory has demonstrated that increased expression of the *parkin* gene, responsible for targeting harmful proteins for destruction, can reverse Parkinson's disease-like symptoms in fruit flies. Recently, we have shown that *parkin* can prevent by cell death caused by elevated levels of Gal-4, a foreign protein. With the recent discovery of two novel genes responsible for PD in humans, *PINK1 (PARK6)* and *LRRK2 (PARK8)*, we direct our attention to understanding the biological role of these novel genes. We will generate conditional transgenic lines of standard and mutant forms of *PINK1* and *LRRK2* to evaluate their expression in neurons. To complement these studies, we intend to generate loss-of-function mutants of both genes through the standard techniques of P element transposition. In time, we will characterize the relationship of *PINK1* and *LRRK2* to □*-synuclein* and *parkin* in Drosophila models of PD.

Researcher: Mandar Jog
Name of Project: **Network level changes in the basal ganglia in a rodent model of dyskinesia**
Institution: London Health Sciences Centre
Amount Year One: $45,000
Amount Year Two: n/a – one year grant
Total Awarded: $45,000
Lay Summary: Parkinson's disease is complicated in its later stages by the development of excessive abnormal movements termed dyskinesias. The treatment of this symptom is complicated and many new options are being tried. Research done so far has told us that changes occur in many levels of the brain, and especially in the area termed the basal ganglia, as the dyskinesias develop. The basal ganglia functions as a network of interconnected structures and therefore it is highly likely that the changes are occurring also at the network level. Our laboratory had developed expertise in studying and analysing the electrical properties of networks of neurons. We feel that by using our techniques, we will be able to better understand

how dyskinesias change the electrical properties of the basal ganglia. In addition, the research will provide a work-bench to test new treatments and their impact on the network of brain cells within the basal ganglia.

Researcher: **William D. Hutchison, Jonathan O Dostrovsky, Mojdan Hodaie & Andres M. Lozano**
Name of Project: **Pathological oscillations in basal ganglia and synaptic plasticity**
Institution: Toronto Western Hospital
Amount Year One: $40,924
Amount Year Two: n/a – one year grant
Total Awarded: $40,924
Lay Summary: The basal ganglia are a group of nuclei that receive input from higher levels of the brain (cortex) and direct their output to lower motor centres (brainstem and thalamus). Parkinson's disease results from the loss of dopamine supply to the basal ganglia input, and this leads to abnormal rhythmic activity of the neurons there. How these abnormal rhythms affect the output neurons and lead to the motor symptoms is still not understood. The implantation of chronic indwelling deep brain stimulation electrodes in the STN can be very effective for treatment of severe cases of PD. During this operation we can monitor and test the responsiveness of the output neurons to small electrical currents. One test measures at the same time the response of the neuron to excitatory input as well as the level of activity at the output. Our research proposes to stimulate these output neurons with a rhythm that mimics the abnormal activity to see what changes occur in the output neurons. This work will give us a much clearer picture of the mechanisms at work so that specific drugs can be developed to change or prevent these alterations.

Researcher: **Philippe Seguela & Edward Fon**
Name of Project: **ASIC-mediated Excitocity in Parkinson's disease**
Institution: McGill University Amount Year One: $45,000
Amount Year Two: n/a – one year grant
Total Awarded: $45,000
Lay Summary: Parkinson's disease (PD) is the most common neurodegenerative movement disorder. The loss of dopamine neurons underlies the symptoms of PD. In some patients PD is inherited. It is estimated that up to 50% of young-onset PD cases are due to parkin mutations. However, how parkin mutations impinge on dopaminergic neuron survival remains unresolved. We propose to test the hypothesis that parkin protects the midbrain dopamine neurons from cellular stresses. This work could provide a mechanism explaining how mutations in the *parkin* gene lead to neurodegeneration and point toward novel therapeutic targets in PD.

Researcher: **Francesca Cicchetti & Frederic Calon**
Name of Project: **Effects of dietary omega-3 polyunsaturated fatty acid on pesticide-induced neurotoxicity**
Institution: Laval University Medical Center (CHUL)
Amount Year One: $45,000
Amount Year Two: n/a – one year grant
Total Awarded: $45,000
Lay Summary: Recent evidence suggests that the fat we eat may have an impact on brain health. This could be especially true in the elderly when fat metabolism might be impaired. Indeed, low dietary consumption of omega-3 fatty acids is associated with a higher risk of other neurodegenerative diseases such as Alzheimer. Omega-3 fatty acids are essential nutriment that the body cannot produce but that are found in food such as fish and canola oil or in dietary supplements. Our hypothesis is that these types of fats play a role in many pathological processes that might underlie neuronal death in Parkinson's disease (PD). Therefore, we propose to feed rodent with diets containing low or high omega-3 fats to see if this diet alone impacts the animal susceptibility to neurotoxin modeling parkinsonism. If this diet alone impacts the animal susceptibility to neurotoxin modeling parkinsonism. If successful, the results of these studies should give us new clues on how to prevent PD in humans by manipulating fats in the diet or by other means. Because n3PUFA are cheap, safe and widely available and PD incidence is high in our aging population, increased

n3PUFA intake could feasibly be considered as a preventive tool for PD.

Researcher: **David Park**
Name of Project: **The role of the base excision repair geneAPE/Ref-1 in dopamine neuron loss in an animal model of PD**
Institution: **University of Ottawa**, Ottawa Health Research Institute
Amount Year One: $45,000
Amount Year Two: n/a – one year grant
Total Awarded: $45,000
Lay Summary: Parkinson's disease is a movement disorder characterized by death of a specific population of brain cells that secrete the neurotransmitter dopamine. Accordingly, an important therapeutic strategy for treatment of PD involves blocking biochemical signals which lead to death of these brain cells. However, the events which control such death are not fully understood. We had recently shown (in studies supported by PSC) that a specific protein called cdk5 was essential for death to occur in an animal model of PD. However, the manner by which this protein controls death is not very well understood. We presently propose that a gene important in repair of our DNA (APE/Ref1) is important in the process. We have preliminary evidence that cdk5 can modify and reduce the repair capacity of APE. This makes sense since DNA damage is known to be important in Parkinson's disease. If true, our research would provide important insight into how the capacity of DNA repair in neurons might be impaired in Parkinson's leading to its symptoms. It would also provide good indications that enhancement of DNA repair capacity might improve survival of these dopamine producing neurons.

Researcher: **Michel Panisset, Brigitte Stemmer & Alain Dagher**
Name of Project: **Neurobiology of gambling in patients with Parkinson's disease**
Institution: Hotel-Dieu du CHUM
Amount Year One: $45,000
Amount Year Two: n/a – one year grant
Total Awarded: $45,000
Lay Summary: A group of people with Parkinson's disease who take dopaminergic agonists have been shown to develop pathological gambling (PG). Although this situation appears relatively frequent, very little is known about its cause and we cannot predict patients at risk. We plan to study people with PD who have developed PG with the use of a modified MRI (functional MRI or fMRI) and a modified electroencephalogram that have been used in the study of addictive and gambling-related behaviours. These tools and the use of neuropsychological testing will help us better understand how the brain of people with PD and PG works. We also hope to be able to detect those patients who could develop such devastating behaviours.

Researcher: **Harold A. Robertson**
Name of Project: **Neuroprotective strategies in Parkinson's disease: the role of microglia**
Institution: Dalhousie University
Amount Year One: $44,597
Amount Year Two: n/a – one year grant
Total Awarded: $44,597
Lay Summary: Parkinson's disease is diagnosed at early stages of the disease and therefore halting progression is a priority. MPTP produces Parkinson's disease and is the best animal model for the disease. Ginseng, even when administered 24 hours later, blocks the bad effects of MPTP. Ginseng is safe for patients. To determine the site of action, we have begun gene screening studies to see which genes are increased or decreased after treatment with MPTP or PTPT plus ginseng. This screen suggested that neuroinflammation and cells called microglia are involved. Microglia have been implicated in Parkinson's disease. Some microglia reside in the brain while others move from the blood after injury. The microglia from blood are thought to produce damage. We will test this in a mouse which has the blood microglia labelled with a green-coloured protein. MPTP causes microglia to move to the brain. Because they will be green, we will be able to see them. We think ginseng will prevent the green microglia from entering the

brain. There is also a suicide gene in the green microglia. Once they are in the brain, we can reverse their effects. This will give us important information for a clinical trial for Parkinson's disease.

New Investigator Award Program

Researcher: **Julie Messier**
Name of Project: **Sensorimotor integration and adaptation-learning in Parkinson's disease**
Institution: University of Montreal
Amount Year One: $45,000
Amount Year Two: $45,000
Total Awarded: $90,000
Lay Summary: Parkinson's disease (PD) is characterized by tremor, bradykinesia and postural instability. Increasing evidence suggests disorders in sensory integration and adaptation-learning in PD. The specific nature of these sensorimotor deficits and the ability of L-dopa to correct them is an under-explored issue. We will use a 3D virtual reality environment to create novel sensorimotor situations and measure movement abnormalities to examine the deficits of PD patients in sensorimotor integration and learning and to determine the selective effects of L-dopa on these dysfunctions. This knowledge will shed light on limiting factors interfering with quality of life and help shape novel rehabilitation strategies.

Researcher: **Julie Desbarats**
Name of Project: **A proteasomal mechanism for Fas-mediated neuroprotection in Parkinson's disease**
Institution: McGill University
Amount Year One: $45,000
Amount Year Two: $45,000
Total Awarded: $90,000
Lay Summary: Parkinson's disease (PD) is caused by the degeneration of dopamine neurons in the brain. At present, there are no proven ways of protecting neurons from degeneration to halt disease progression. We have recently discovered that Fas, a molecule found on the surface of neurons, can protect dopamine neurons from degenerating in an animal model of PD. We will investigate how Fas protects neurons from degenerating, at the molecular level, by examining whether Fas can speed up the breakdown of abnormal protein in neurons. Our experiments may lead to new therapies to slow neuronal degeneration in PD patients.

Researcher: Quincy J. Almeida
Name of Project: **A research based evaluation of exercise rehabilitation for symptomatic and functional improvement in PD**
Institution: Wilfrid Laurier University, Movement Disorders Research Centre
Amount Year One: $45,000
Amount Year Two: $45,000
Total Awarded: $90,000
Lay Summary: Parkinson's disease (PD) has a progressive impact on our everyday movements, functional independence and quality of life. Yet, in Canada there are no scientifically-based recommendations for exercise to help individuals with PD. In fact, most exercise recommendations are primarily focused on avoiding the negative influences of inactivity, rather than developing a program that attempts to influence the underlying mechanisms that may cause motor impairments. This is critical in light of very recent research suggesting that exercise may stimulate and hence protect the specific neurons that normally deteriorate in PD. Thus, the potential to alter symptom progression is promising, if appropriate exercises are identified to access these neurons. Sensory information from muscles and joints can guide our perception of limb and body motion (called proprioception). Our own research suggests that movements driven by proprioception may be particularly effective in accessing the remaining neurons involved in PD. From a motor control perspective, this may be why *tai chi* and other alternative exercises appear to help in PD. We plan to

evaluate traditional aerobic and stretching exercises prescribed for PD, compared to a program that focuses on proprioception. Recommendations for an ideal exercise rehabilitation program for all Canadians with PD would be developed.

Basic Research Fellowships Program

Fellow: **Vladimir Rymar**
Name of Project: **Pitx3 determines vulnerability of subsets of dopaminergic neurons affected in Parkinson's disease**
Institution: McGill University, Montreal Neurological Institute
Amount Year One: $50,000
Amount Year Two: $50,000
Total Awarded: $100,000
Lay Summary: An important feature of dopaminergic neuronal loss in Parkinson's disease is that cell loss is limited mainly to a specific group of nerve cells. We wish to determine why some dopamine containing nerve cells are more vulnerable than others. In the brain a molecule known as Pitx3 is apparently expressed exclusively in this vulnerable subgroup of dopamine containing cells. We discovered that a mutant mouse which is not able to produce Pitx3, and which has selective loss of the vulnerable dopamine subpopulation during development. The pattern of dopamine cell loss bears a remarkable resemblance to that seen in Parkinson's disease. We will now determine whether Pitx3 is indeed expressed in vulnerable subpopulations in primate species including human, and determine whether Pitx3 containing dopamine neurons are indeed vulnerable in animal models of Parkinson's disease and in human. This work will give important new clues to the cause of Parkinson's disease, and lead to new discoveries aimed at preventing disease progression.

Fellow: Frank Jangsup Lee
Name of Project: DJ-1 response to oxidative stress regulates intracellular dopamine levels: implications toward Parkinson's disease
Institution: Centre for Addiction and Mental Health (Toronto)
Amount Year One: $50,000
Amount Year Two: $50,000
Total Awarded: $100,000
Lay Summary: Parkinson's disease (PD), characterized by resting tremor, slow movement, stiffness and postural instability, is caused by death of neurons that produce the neurotransmitter dopamine. While recent studies have identified genes involved in rare inherited forms of PD, the underlying cause of the more common forms of PD is unknown. However, understanding the function of genes involved in familial forms of PD will provide insight into the cause of sporadic PD. One such gene is named DJ-1. Although the normal function of DJ-1 is unknown, one possible role of DJ-1 is maintaining normal dopamine levels by altering the function of various dopaminergic proteins. We have evidence that DJ-1 can affect the dopamine transporter, which regulates synaptic dopamine levels. This interaction between DJ-1 and the dopamine transporter may lead to excessive dopamine accumulation that can cause cell death. Furthermore, we will examine the relationship of DJ-1 with other dopaminergic proteins (tyrosine hydroxylase, an enzyme that synthesizes dopamine, and the vesicular monoamine transporter-2, a dopamine packaging protein) and examine how the mutant forms of DJ-1 affect these interactions. This study will provide insight into the role of DJ-1 in maintaining normal dopamine neurotransmission and ultimately provide clues into the cause of PD.

Fellow: **Karim Mukhida**
Name of Project: **Neural transplantation**
Institution: Dalhousie University
Amount Year One: $52,500
Amount Year Two: $52,500

Total Awarded: $105,000
Lay Summary: Although the results of clinical trials of fetal cell transplants for the treatment of Parkinson's disease (PD) have been promising, the efficacy of neural transplantation has not yet reached the level to justify its use as a routine therapeutic option. While fetal dopaminergic cell transplants in multiple basal ganglia sites in the rodent PD model confer a more complete restoration of complex sensorimotor behaviours than striatal grafts alone, this recovery is incomplete. A contributing factor may be that these transplants do not reduce subthalamic nucleus overactivity. We hypothesize that inhibition of subthalamic nucleus overactivity using GABAergic transplants combined with dopaminergic cell-based restoration of nigrostriatal function by may be necessary to improve the efficacy of neural transplantation.

Fellow: **Elissa M. Strome**
Name of Project: **The effects of chronic L-DOPA on the blood-brain barrier in an animal model of Parkinson's disease**
Institution: Lund University, Lund, Sweden
Amount Year One: $40,000
Amount Year Two: $40,000
Total Awarded: $80,000
Lay Summary: Dyskinesia is a major complication of L-DOPA pharmacotherapy in Parkinson's disease (PD). In a rat model of PD we have obtained evidence that chronic L-DOPA treatment cause the formation of new microvessels with immature blood-brain barrier (BBB) properties in some brain regions. In this project we shall use a rat model of L-DOPA-induced dyskinesias (CID_) to examine (i) the functional status of the BBB using specific permeability tracers, and the (II) the anatomy and morphology of newly formed blood vessels in the brain. This project will further our understanding of how to treat and prevent dyskinesias in PD.

Fellow: **Dianbo Qu**
Name of Project: **Role of the antioxidant enzyme PRDX2 in dopaminergic loss in an animal model of Parkinson's disease**
Institution: University of Ottawa, Ottawa Health Research Institute
Amount Year One: $50,000
Amount Year Two: $50,000
Total Awarded: $100,000
Lay Summary: The reason why specific dopamine secreting brain cells die in Parkinson's disease (PD) is not clear. However, it has become imperative to understand the mechanisms that contribute to this degeneration to develop a potential therapeutic strategy for treatment of PD. Recently, a key role in brain cell loss for a specific protein called cdk5 has been reported. However, the way in which this this protein causes dopamine death is unknown. To start to address this problem, I recently discovered that another protein that is involved in antioxidant defense, PRDX2, physically interacts with cdk5. This is significant since oxidative stress is thought to be very important in the progression of PD. Equally tantalizing are other reports that PRDX2 is increased in PD patients. We believe that cdk5 directly modifies the PRDX2 by inhibiting its function. By doing so it prevents brain cells from properly handling the toxic oxidative insults present in dopamine brain cells. We will test this hypothesis in an animal model of Parkinson's disease.

Fellow: **Anna-Maria Szczesniak**
Name of Project: **Neurotransplantation/ neuroprotection**
Institution: Dalhousie University
Amount Year One: $40,000
Amount Year Two: $40,000
Total Awarded: $80,000
Lay Summary: The co-transplantation of fetal (dopaminergic) DA neurons with neural progenitor cells (NPCs) has been shown to increase the survival of transplanted DA neurons and attenuate abnormal motor behavior in Parkinsonian animals. In *vitro* experiments suggest these effects may be mediated by sonic

hedgehog (Shh), a signaling peptide released by NPCs. To investigate the effect of Shh on DA neuron survival, Parkinsonian rats will be transplanted with fetal DA neurons and NPCs cells capable (or incapable) of producing Shh. Gene expression studies will further elucidate the mechanisms of Shh actions and facilitate the further development of transplantation strategies in the treatment of Parkinson's Disease.

CLINICAL MOVEMENT DISORDERS FELLOWSHIP

Fellow: **Thomas Steeves**
Name of Project: **Clinical Movement Disorders Training**
Institution: Toronto Western Hospital, Movement Disorders Centre
Amount Year One: $45,000
Amount Year Two: n/a
Total Awarded: $45,000
Lay Summary: The clinical fellowship will consist of one year training with Dr. Anthony Lang and colleagues in the Movement Disorders Centre at the Toronto Western Hospital. Approximately 80% of the time will be devoted to patient care and 20% to clinical reach. As part of my clinical duties, I will evaluate and treat patients with Parkinson's disease and other movement disorders under the supervision of Dr. Anthony Lang. Additional clinical training may be acquired with faculty members at the Centre who have specific subspecialty skills and interests. As part of my research training, I will help develop and implement clinical trails for new pharmacological and surgical treatments of Parkinson's disease. The primary objective of the fellowship is to train Neurology sub-specialists to a standard of clinical excellence that will meet the needs of Canadian patients with Parkinson's disease and other movement disorders.

BOEHRINGER INGELHEIM CLINICAL MOVEMENT DISORDERS FELLOWSHIP

Fellow: **Andrew Edward Borys**
Name of Project: **Clinical Movement Disorders Training**
Institution: University of Manitoba, St. Boniface Medical Clinic
Amount Year One: $45,000
Amount Year Two: n/a
Total Awarded: $45,000
Lay Summary: This fellowship is a program approved by the University of Manitoba and consists of a one-year training period. The program is primarily supervised by Dr. Douglas Hobson, a Movement Disorder specialist, in conjunction with Dr. Jerry Krcek, a functional neurosurgeon. The bulk of the program focuses on seeing patients in a clinic setting, learning about all aspects of diagnosis and management of Parkinson's disease and other movement disorders. This will include playing a role in selecting patients for functional neurosurgery. There will be an emphasis on becoming involved with local community resources. In addition, there is time allotted to participate in related areas of Sleep Medicine, Behavioural Neurology, and Geriatrics. As part of the program, there will be involvement in ongoing and new clinical trials. The fellow will also prepare educational presentations for the multidisciplinary team and for the neuroscience community. It is the overall goal of the fellowship to provide the fellow with the skills needed to practice as a competent clinician in the field of Movement Disorders.

Parkinson Society Canada **provides this fellowship as a means to enhance the availability of high quality care for people with Parkinson's Disease and related movement disorders in Canada.**

The fellowship is a clinical training program for the subspecialty of Movement Disorders. This post-residency training is to provide expertise in the diagnosis and management of Parkinson disease and may include other movement disorders. Research may be a component of the program but the largest component is clinical training, (at least 80%). The training program is a two-year fellowship.