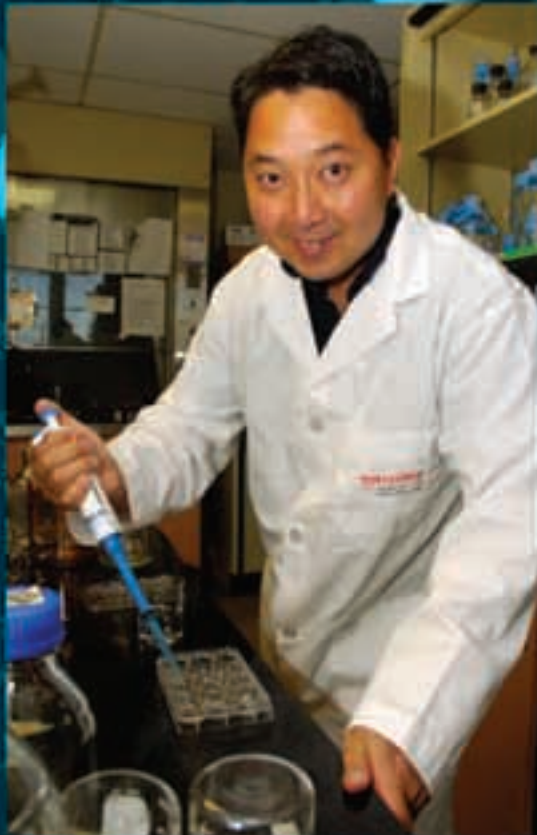


# Research

HIGHLIGHTS 2008

Parkinson  
Society  
Canada



Parkinson Society Canada  
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# Research

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## Message from the President & CEO, and Chair of the PSC Board

*At Parkinson Society Canada we are proud of our 27 year tradition of supporting research to find a cure for Parkinson's and to better understand the causes of this debilitating disease. Our research awards program seeks not only the brightest and most accomplished scientists, but also those with innovative ideas, a passion for Parkinson's and the seed of an idea that can grow.*

*PSC's National Research Program is a collaborative effort with our regional organizations. Our success is based on partnerships – partnerships with donors, charitable foundations and other granting agencies. Parkinson Society Canada does not receive any government funding but relies solely on the contributions of these donors and other granting agencies. PSC maximizes our funding capabilities by leveraging these funds through partnerships making it possible for us to increase our support of excellence in research.*

*Our goal is to build capacity in Parkinson's research – from Pilot Project Grants to Graduate Student Awards – from the pure science of basic laboratory research to psychosocial research that will enable us to better understand the significant impact this disease has on individuals and their day to day lives.*

*Parkinson Society Canada understands the importance of investing in Canadian Parkinson's disease research. Each year brings us closer to understanding the causes and discovering better treatments. Each year the scope of our understanding expands as do the hopes of the over 100,000 Canadians living with Parkinson's and their care partners. We are proud of our contribution to the science of discovery in the field of Parkinson's. Research is our hope. Our hope for a better life and a brighter future for people living with PD today, a world without Parkinson's tomorrow.*

*We salute the effort and contributions of the volunteers on our Research Policy Committee and Scientific Advisory Board as well as the hundreds of researchers whose work we have supported. Last, but certainly not least, we want to express our profound gratitude to our donors who share our vision and make this outstanding research possible.*



**Bob Ashuk**, Chair  
National Board of Directors



**Joyce Gordon**, President & CEO  
Parkinson Society Canada



## Message from the Chair, Research Policy Committee

*The RPC is a standing committee of the National Board of Directors of Parkinson Society Canada. Our mandate is to advise the Board on the most effective means to promote research into the cause(s), management and eventual cure of Parkinson's disease. Membership on the RPC includes a Chair, and representatives from the scientific community, non-MD health professionals engaged in the care of people living with Parkinson's and a patient advocate.*

*The National Research program is a cornerstone of PSC. It is one of the ways that PSC's stakeholders can judge the effectiveness of PSC in pursuing its mission. The RPC sets the ground rules for the program.*

*The RPC is a recognized professional body that promotes the relevance, credibility and viability of the research grant peer review process to PSC Board members, the scientific community and other stakeholders. The RPC strives to promote research that is meaningful to patients and caregivers. To that end we have created a new psychosocial research stream and we have performed a needs assessment so that we can better understand which research questions are of greatest importance to the Parkinson's community.*

*It is my pleasure to serve as Chair of the Research Policy Committee (RPC). My work in this capacity keeps me in touch with both new developments in Parkinson's and the excellent work of Parkinson Society Canada.*

**Dr. Anne-Louise Lafontaine**, Chair  
Research Policy Committee



## Message from the Chair, Scientific Advisory Board

*Each year Parkinson Society Canada's Scientific Advisory Board (SAB) reviews numerous research applications from across Canada that are received through the National Research Program's annual competition cycles. The SAB provides the highest quality of objective adjudication that is made possible through the significant efforts of a diverse volunteer panel of experts from the neurosciences field. These individuals, chosen not only for their expertise but also to ensure national representation, participate in a rigorous peer review process to determine scientific excellence and relevance to Parkinson's disease.*

*I am proud to Chair this panel working with my peers as part of a program that supports some of the best research and especially to be able to promote some of the most promising emerging young researchers in the country.*

**Dr. Jon Stoessl**, Chair  
Scientific Advisory Board

## Research Program at PSC

Parkinson Society Canada (PSC) understands the importance of investing in Canada's talented Parkinson's disease researchers. PSC supports the highest standard of excellence in research to enable progress in the effort to "ease the burden and find a cure". Through new discoveries and treatments, research improves the quality of life of all Canadians and reduces the economic burden of illness on the economy. Today's investment will go directly to research that is aimed at improving the health and lives of Canadians living with Parkinson's now and in the future.

In Canada, we are very proud to have some of the best Parkinson's researchers in the world. Canadians and visitors to Canada have contributed a disproportionate amount of knowledge to our understanding of the aetiology, progression and treatment of PD. Very few other countries in the world, if any, can make such a claim. As well Parkinson Society Canada is a national organization in Canada that specifically supports Canadian Parkinson's research and researchers.

## PSC's Research Funding Philosophy

Parkinson Society Canada strives to make an impact on the Canadian Parkinson's research community by working as investors in Canadian PD research potential. By funding meaningful and innovative projects and promising young researchers in their professional development, PSC aims to encourage continued growth and revitalization in the fields of Parkinson's research in Canada. Our "seed money" plants the seeds that will bear fruit tomorrow, ensuring that today's fresh ideas and innovative researchers become tomorrow's research breakthroughs and leaders in the field.

PSC awards research grants, fellowships and studentships on an annual basis. Grants are used to fund expenses associated with conducting a project and fellowships support the salary of a researcher who has completed doctoral training (an MD or a PhD) and who is pursuing specialized training in Parkinson's. Studentships support the salary of a graduate student at the masters or doctoral level who is at the start of their research career and have chosen to focus on Parkinson's research. PSC grants, fellowships and studentships range from one to two years in duration, creating a funding leap-frog pattern where two research cycles are funded at any given time.

PSC's Research Program is modelled on the Canadian Institutes of Health Research's four pillars of research and encourages a broad range of applications from biomedical, clinical, health services and systems research and population studies. PSC supports these four pillars of research with 75% of funding dedicated to biomedical research and 25% of funding directed to clinical, health services and systems and population studies.

## A proud funding tradition

Since 1981, PSC has invested more than \$15.6 million into Canadian Parkinson's research, granting over 300 basic research fellowships, clinical movement disorders fellowships, clinical research fellowships, pilot project grants, and new investigator awards.

In July 2008 Parkinson Society Canada announced its commitment to fund five research grants, seven fellowships and three studentships over the July 2008 - June 2010 Research Program cycle, for a total of \$946,950 over the next two years. This is in addition to the \$433,333 already committed to support existing 2007-2009 cycle awards in their second year.

More than ever, Parkinson Society Canada is committed to do more to support research, to search for the causes, to improve treatments, and to uncover the cure.

## Research Policy Committee

Dr. Anne-Louise Lafontaine (Chair)	Quebec
Dr. Pierre Blanchet	Quebec
Dr. Jim Emmett	Alberta
Dr. Edward Fon	Quebec
Dr. Mark Guttman	Ontario
Mr. Barry Johnson	Alberta
Ms. Liselotte Sawh	Nova Scotia
Dr. Frances Squire	Ontario
Dr. A. Jon Stoessl	British Columbia

## Parkinson Society Canada – Scientific Advisory Board 2007-2008

Dr. A. Jon Stoessl (Chair)	University of British Columbia
Dr. Pierre Blanchet*	University of Montreal
Dr. Therese DiPaolo*	Laval University, QC
Dr. Edward Fon	McGill University, QC
Dr. Susan Fox	University of Toronto
Dr. Alan Goodridge*	Memorial University of Newfoundland
Dr. Doug Hobson	University of Manitoba
Dr. Zelma Kiss	University of Calgary
Dr. Martin McKeown	University of British Columbia
Dr. Michel Panisset*	University of Montreal
Dr. David Park	University of Ottawa

\* Completed Terms on SAB June 2008

## New Scientific Advisory Board Members 2008-2009

Dr. Richard Camicioli	University of Alberta
Dr. Francesca Cicchetti	Laval University, QC
Dr. Alex Rajput	University of Saskatchewan
Dr. Harold Robertson	Dalhousie University, NS

## Donald Calne Lectureship

The Donald Calne Lectureship recognizes a distinguished neurologist of international reputation, whose work is primarily in the area of Parkinson's disease. Awarded annually, the recipient will deliver a "state of the illness" lecture on Parkinson's disease to the Parkinson community. This lectureship was established in 2002 to honour Dr. Donald Calne for his outstanding service to the Parkinson's community as Professor of Neuroscience, University of British Columbia and past chair and long time member of the Scientific Advisory Board, Parkinson Society Canada.

## Donald Calne Lectureship Awardees

**2008** Dr. J. William Langston Scientific Director of the Parkinson's Institute in Sunnyvale, California, U.S.A.

**2007** Dr. Anthony Lang, Director of the Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, Toronto, Ontario

**2006** Dr. Jon Stoessl, Director of the Pacific Parkinson's Research Centre at the University of British Columbia in Vancouver, British Columbia

**2005** Dr. Zbigniew Wszolek, Mayo Clinic Jacksonville, Florida, U.S.A

**2004** Dr. Oleh Hornykiewicz, The Brain Research Institute at the University of Vienna, Vienna, Austria

**2003** Dr. Yoshikuni Mizuno, Neurology Department, Juntendo University Medical School, Tokyo, Japan

# Research Programs

## PILOT PROJECT PROGRAM

**Duration** 1 year  
**Funding Amount** Maximum \$45,000

Through its Pilot Project grants, PSC aims to fund professionals engaged in novel, emerging, or innovative research in areas relevant to the cure, cause, prevention, improved treatment and/or understanding of Parkinson's disease and its impacts on society. This program is a strategic initiative to encourage established investigators to enter into the study of Parkinson's disease and to perform research in new, specifically targeted, high priority areas.

PSC is a committed supporter of Canadian research potential. PSC anticipates that funded projects in this program may lead to subsequent substantial grants from larger granting institutions. This critical "seed money" fosters new development and promises to "grow" new ideas and approaches to Parkinson's research.

## NEW INVESTIGATOR AWARD PROGRAM

**Duration** 2 years  
**Funding Amount** Maximum \$45,000 /year

During the initial period of their independent careers, new investigators are in a good position to formulate innovative and fertile research projects. New Investigator Awards provide researchers who have recently completed research training with an early opportunity to develop and demonstrate ability to initiate and conduct independent health research. This program is part of an active investment in the future of Canadian Parkinson's research, supporting promising individual researchers in their professional development.

## PSYCHOSOCIAL RESEARCH GRANT

**Duration** 2 years  
**Funding Amount** \$50,000 /year

This strategic initiative to encourage researchers specifically in the area of psychosocial research in Parkinson's disease helps PSC to better serve Canadians with Parkinson's, to foster Canadian Parkinson's research leadership internationally, and to support efforts to ease the burden and find a cure.

Research is directed towards closing the gap in understanding and treating non motor symptoms of Parkinson's.

Research topics identified as priority issues by Parkinson's Society Canada are:

1. Investigating the Psychological Well Being of People Living With Parkinson's, Partners and Families,
2. Evaluating the Benefits of Standardized care,
3. Assessing Medical Services,
4. The Economic Burden of Parkinson's.

## BASIC RESEARCH FELLOWSHIP PROGRAM

**Duration** 2 years  
**Funding Amount** \$40,000 - \$50,000 /year based on CIHR salary scale

The basic research fellowship program is a strategic initiative to encourage promising young scientists to enter the field of biomedical research into Parkinson's disease. Through the provision of this salary support, Parkinson Society Canada aims to attract new scientists to the field and to invest in their research training, offering promise for future work in the area of Parkinson's disease.

## **CLINICAL RESEARCH FELLOWSHIP PROGRAM (not awarded 2008-2010)**

**Duration** 2 years

**Funding Amount** \$50,000 /year

Relative to the needs of Canadians with Parkinson's, there is currently a shortage of leaders involved in Parkinson's service and clinical research programs in Canada. PSC believes that this shortage of medical specialists, neurologists or neurosurgeons with experience both in the critical management of Parkinson's and in its clinical research, has the potential to worsen in the next few years. The clinical research fellowship program, is a strategic initiative that redresses physician shortages by encouraging promising young scientists to enter the field of Parkinson's clinical research while simultaneously investing in research training that offers promise for future work in the area of Parkinson's disease.

## **NOVARTIS PHARMACEUTICALS CANADA CLINICAL MOVEMENT DISORDERS FELLOWSHIP**

**Duration** 1 year

**Funding Amount** \$50,000

Parkinson Society Canada wants to ensure that each Canadian with Parkinson's receives appropriate medical expertise, drug treatment, support services, continuous care, educational resources, respect, dignity, help and hope. This fellowship represents the first step in achieving part of our goal of ensuring that these critical elements in the day-to-day management of Parkinson's are accessible and available.

The Clinical Movement Disorders fellowship program is a strategic initiative to encourage promising young clinicians to enter into clinical training in the subspecialty of Movement Disorders, which will include Parkinson's disease. The purpose of this post-

residency training is to provide expertise in the diagnosis and management of Parkinson's disease and may include other movement disorders. Clinical training is the largest component of this hands-on program but it could include an element of research.

In this initiative, Parkinson Society Canada is also capitalizing on the potential of partnerships to support new programs and increase overall funding for our research program.

## **GRADUATE STUDENT AWARD**

**Duration** 2 years

**Funding Amount** \$15,000/ year\*

The Graduate Student Award Program is a strategic initiative to encourage promising young scientists to enter the field of Parkinson's research and to invest in research training that offers promise for future work in the area of Parkinson's disease. PSC wishes to encourage continued growth and revitalization in the fields of Parkinson's research in Canada by supporting talented young scientists and providing students with an opportunity to enter into the area of Parkinson's research during the early stages of their training.

\*Additional \$5,000 /year is contributed by the student's supervisor for a total award amount of \$20,000 per year.

## **Effects of genetically-induced conversion of brain n-6 PUFA into n-3 PUFA in a murine model of Parkinson's disease**

**One Year Award \$45,000**



### **Dr. Francesca Cicchetti**

Dr. Cicchetti received her BA from McGill University in Montreal and then moved to Laval University where she obtained her MS and PhD in Neurobiology. She then completed a post-doctoral fellowship at Harvard Medical School before returning to Laval University, where she is currently an Associate Professor and researcher.



### **Dr. Frédéric Calon**

Dr. Calon obtained his BSc, MSc and PhD from Laval University and completed his Post-Doctoral training at the University of California, Los Angeles (UCLA). He is currently an Associate Professor in the Faculty of Pharmacy at Laval University.

Omega-3 acids have long been touted as secret weapons in the fight against aging and illness. Now researchers at Laval University think they may also be important to preventing Parkinson's Disease.

Francesca Cicchetti and Frédéric Calon are studying n-3 PUFAs – otherwise known as Omega-3 polyunsaturated fatty acids – in mice genetically engineered to convert omega-6 into omega-3 in the brain. Their previous research has shown that mice fed diets low in Omega-3s and then exposed to a chemical implicated in Parkinson's Disease (MPTP) lose about 30 percent of their dopamine-producing brain cells. However, the dopamine-producing brain cells in normal mice that have been exposed to MPTP do not die if the mice are fed diets rich in Omega-3s.

"The implication is that they (the brain cells) were protected," says Calon.

Using the transgenic mice, Cicchetti and Calon are now studying the underlying mechanisms in the brain that are involved in this process, to determine how the Omega-3s prevent Parkinson's from developing.

If the researchers can figure out how the Omega-3s work to prevent the disease, the next step will be to conduct experiments to see if taking Omega-3s can slow down, stop, or even reverse the progression of Parkinson's Disease in people who have it.

"What's really fabulous about these results is that just by changing food intake and nutritional habits, one could potentially manage to prevent these diseases," says Cicchetti.

The research has already led Cicchetti and Calon to make changes in their own diets, even before their research reaches the stage of clinical trials in humans. Cicchetti takes an Omega-3 supplement three times a day; Calon eats salmon and tuna or other fish rich in Omega-3s twice a week.

Cicchetti's focus on Parkinson's Disease stems from her early interest in biology and neuropsychology, which led to research on Huntington's Disease, another neurodegenerative disorder, while she was taking her Master's and PhD degrees at Laval.

"Once you start investigating and exploring potential therapies for a disease, in this case Parkinson, you want to go in depth," she says. "After my first encounter with people with Parkinson's, I immediately wanted to do something for them."

"The good thing about Parkinson's is that we have better treatment options," she says. "There are steps that can be taken which will improve the quality of life for a significant number of years."

Calon's early interest in how the brain works and the complexity of the tiny brain cells that control movement progressed into research into the causes of both Alzheimer's and Parkinson's Disease. That research took a more personal focus when his first mentor, another scientist working on Parkinson's disease, was recently diagnosed with Alzheimer's.

His friend's illness gives Calon, who is also a pharmacist, even more motivation to find a treatment or cure for these degenerative diseases.

"I'm really interested in developing new therapeutic approaches to brain diseases in general, especially neurodegenerative diseases," he says.



### Dr. David Park

Dr. Park obtained his BSc at the University of Michigan and his PhD at Rutgers University in New Brunswick, New Jersey. He is currently an Associate Professor at the University of Ottawa, Co-Director of the Ottawa Parkinson Research Consortium and a Senior Scientist, at the Ottawa Health Research Institute (OHRI). Dr. Park is a well established and extremely productive scientist focusing on mechanisms of cell death in Parkinson's disease and stroke. Dr. Park's numerous personal awards include a Career Scientist from the Heart and Stroke Foundation.

### One Year Award \$45,000

For University of Ottawa Professor David Park, it's not enough to know that a specific gene is important to the survival of the dopamine-producing brain cells critical to Parkinson's disease. He wants to understand how and why that gene is important.

That's why Park is learning everything he can about DJ-1, a gene that has been linked to some familial forms of Parkinson's disease.

"It's relatively rare, even among the genetic causes for Parkinson's disease," Park says. "But we know if you have a deficiency of DJ-1, you are going to get the disease. So the question is, we know that it's important, but what is it doing? Why is it that the loss causes Parkinson's?"

DJ-1 may play a protective role by warding off stress that causes dopamine-producing cells to die, Park theorizes. By using DJ-1 to shine a spotlight onto familial forms of Parkinson's, Park hopes also to uncover clues as to what is causing symptoms of Parkinson's in general, and to the progression of the disease. He is also investigating the relationship between DJ-1 and VHL, another protein that plays a critical role in response to lack of oxygen in cells.

"We're now trying to figure out – do they really interact? If they do interact, what does that mean for the function of DJ-1 or for VHL, and what is that doing to the biology of the neurons?"

Ultimately, by figuring out the relationships and the pathways among genes and the proteins they express in brain cells, researchers including Park hope they will then be able to alter the processes that have gone askew, through drugs or gene therapies.

In animal models, Park has already been able to show that expressing more DJ-1 can protect their brains against the toxins that cause Parkinson-like symptoms in humans. Now he wants to see if that's valid for a broader – human – population.

The dysfunction and death of brain cells has long interested Park, who began studying these neurons in the mid-1990s. His close work as a co-founder of the Parkinson's Research Consortium in Ottawa brings him into close contact with people with Parkinson's, a community he says has been "tireless" in supporting the Consortium's research.

Their amazing attitude, and his work, has increased his optimism.

"Parkinson's is going to be one of those diseases where ... we will significantly improve management in the future," Park predicts. "It's a joy working on Parkinson's disease, because the people are just incredible in terms of the time and commitment they put forth."

## A new magnetic resonance imaging method (SWI) for assessing iron deposition in Parkinson disease

One Year Award \$44,500



### Dr. Martin J. McKeown

Dr. McKeown obtained his BEng in Engineering Physics from McMaster University, his MD at the University of Toronto, and trained in Neurology at the University of Western Ontario. He is currently an Associate Professor of Neurology at the University of British Columbia. Dr. McKeown's interests lay in various aspects of motor control, especially as it affects people with Parkinson's Disease (PD). He is particularly interested in compensatory mechanisms that may ameliorate some of the deficits in PD.



### Dr. Alexander Rauscher

Dr. Rauscher obtained his MSc in Physics and his PhD in MRI Medical Physics at the Technical University in Vienna, Austria, and the Friedrich Schiller University in Jena, Germany. He is currently a Research Associate at the University of British Columbia MRI Research Centre.

Dr. Martin McKeown likes to tackle problems that he can measure. That's why the neurologist – who is also an engineer – has joined forces with research associate Alexander Rauscher. Together, they're using MRI machines in a novel way, which may ultimately allow them to measure the progression of Parkinson's disease in the brain.

McKeown and Rauscher are using a unique method of imaging and a new analysis technique to track iron deposits in the brains of people with Parkinson's.

"We're trying to come up with a way to use modern engineering techniques to non-invasively assess Parkinson's," McKeown says.

Researchers have already linked excessive iron deposits in the brain to the death of dopamine-producing brain cells. But until now, analyzing those iron deposits could only be done through autopsies. So researchers were unable to use the information either to diagnose Parkinson's early on and possibly initiate therapies to prevent further cell loss, or to chart the progression of a patient's disease.

Now, Rauscher, a physicist originally from Austria, has brought this new way to program and analyze high-resolution magnetic resonance images to the University of British Columbia's MRI Research Centre.

"This MRI method is very sensitive to changes in magnetic susceptibility, which are associated with iron," explains Rauscher, who learned this new method in Germany. "That's why we think it will be more sensitive to changes in iron (in the brain) than conventional methods."

By following the patterns of iron deposits in the brain that the images show, and by mapping where those deposits occur in the brain, the researchers hope to distinguish between different types of Parkinson's disease, and, eventually, to measure whether or not new drugs are actually halting or even reversing the disease's progression.

Previously, researchers had tried to use another kind of imaging, known as PET (Positron Emission Tomography) scans, to see whether drugs were working. But there was a mismatch between what the imaging implied, and what patients were experiencing, says McKeown. The PET scans indicated the disease had slowed down, but patients were experiencing the same symptoms.

"No one really cares whether their scan is better – they just care whether their disability is worse," McKeown points out.

Unlike PET scanners, which are not widely available in Canada, MRI machines are in most major hospitals in Canada.

"That means that this could be done anywhere. It just needs the right sequence and analysis," McKeown says.

He and Rauscher hope their project will give patients a more accurate assessment of the disease and the effects of new drugs in treating Parkinson's.

For McKeown, the project is an excellent match of his engineering and medical skills – what he jokingly calls his "split personality."

## One Year Award \$45,000



### Dr. Guy Rouleau

Dr. Rouleau is currently a Full Professor at the Department of Medicine of the Université de Montréal. He is the Director of the Centre for Excellence in Neuromics as well as the Director of the CHU Sainte-Justine Research Center. Dr. Rouleau's work is focused on understanding the genetic basis of brain diseases and he has mapped more than 20 loci and made a major contribution toward the identification of more than 10 genes responsible for diseases as well as a better understanding of their pathogenesis.



### Dr. Nicolas Dupré

Dr. Nicolas Dupré received his Doctor of Medicine and Master of Surgery (MDCM) from McGill University in 1996 and enhanced his academic career by obtaining an MSc in Neurobiology and also Epidemiology from Laval University. He is currently an Assistant Professor in the Faculty of Medicine, at Laval. Dr. Dupré is also a Clinician-Scientist specializing in Neurogenetic Disorders at (CHAUQ), l'Hôpital de l'Enfant-Jésus.

In some cases, a single, powerful gene that has been damaged or mutated is all it takes to preordain the onset of an illness that people grapple with throughout their lives. But for other diseases, such as Parkinson's, it is likely that the interaction of several genes, combined with environmental factors, contribute to a person's susceptibility.

Using classic methods, geneticists have already identified some of the powerful genes, such as parkin, that are implicated in the familial form of Parkinson's. Now Dr. Guy Rouleau and Dr. Nicolas Dupré, both neurologists, are using cutting-edge high-throughput technology to screen and analyze genes in the parkin pathway of the brain, using blood samples from about 100 Parkinson's patients. Their goal is to discover the less powerful genes that are more elusive, but equally important in causing Parkinson's.

"It's not easy for classic genetic methods to find the genes that have moderate-to-small effects," explains Rouleau, who holds a Canada Research Chair in genetic disorders of the brain. "But it's thought that most genes that predispose to disease have moderate-to-small effects. It's these genes we are trying to find."

Finding these less powerful genes, as well as identifying the environmental triggers that may also play a role in the Parkinson's puzzle, is critical to developing a clear understanding of what causes Parkinson's and how it progresses. That's why the researchers are also collecting clinical histories and other risk factors, such as the type of job and other illnesses, from the patients in their study, says Dupré.

"If there's something striking, like a mutation in a given gene that is present only in people who have had a certain environmental exposure, then you can go back and do another study and collect samples only from people within that environment," Dupré explains.

The ambitious project will likely lead to future research to narrow down the causes of Parkinson's. Most people likely have a combination of genetic and environmental causes, says Dupré.

"One of the major aims is to be able to understand why one person gets it and one person does not, even with similar exposures (to environmental triggers)," says Rouleau.

Although there are good treatments for the symptoms of Parkinson's, often they only work for a time, something that frustrates their doctors.

"I've got lots of patients that medications are not helping that much anymore," he says. "If even at the beginning of the disease we could slow it down or stop it, that would be a huge advance."

Rouleau, whose father was also a doctor, always wanted to pursue medical research, he says, because of his interest in biology. His decision to specialize in neurology was born of his love for tackling problems.

"It's complicated – it's a lot of deductive reasoning and a lot of complexities, so I thought it was a bit of a challenge," he says.

Dupré's decision to go into medicine and research stemmed from his early love of science fiction and speculative writing about manipulating genes to control people in Orwellian worlds.

"I'm happy it never turned out that way (in real life)," he says, laughing.

## Understanding the action of the mitochondrial rhomboid protease in Parkinson's disease

Year 1 \$45,000 Year 2 \$45,000 Total Award: \$90,000



### Dr. Angus McQuibban

Dr. McQuibban obtained his PhD from the University of British Columbia and completed his Post Doctoral training under the supervision of Dr. Matthew Freeman at the MRC-Laboratory of Molecular Biology, Cambridge, UK. Dr. McQuibban is currently an Assistant Professor at the University of Toronto in the Department of Biochemistry.

Deep inside each cell, tiny powerhouses known as mitochondria provide the energy the cell needs to move, divide and grow. In a laboratory at the University of Toronto, molecular biologist Angus McQuibban is delving into the role that mitochondria play in the genes involved in Parkinson's disease.

Researchers already know that Parkinson's is caused by the degeneration of nerve cells inside the substantia nigra, the part of the brain that controls movement. They don't yet know exactly what causes those neural cells to degenerate, and they haven't identified all of the genes involved in the disease.

"The cell is a complicated place," says McQuibban. "It's uncommon for there to be a single (genetic) cause for a single disease. We do know that the mitochondria, as a sub-cellular engine, are very important in Parkinson's disease. That's one place to really start looking."

So that's what McQuibban is doing. He's focusing on one particular gene that makes a protein called rhomboid, that is found in the mitochondria of brain cells. Specifically, McQuibban is trying to uncover the role that rhomboid plays in interacting with another protein, the PTEN-induced putative kinase 1 (PINK) gene.

Other researchers have already identified mutations in the PINK gene that can cause the inherited, or familial form of Parkinson's. In animal models, fruit flies without a working PINK1 gene have defects in mitochondria. That results in muscle problems, and degeneration of the brain cells that produce dopamine.

The rhomboid protein cuts the PINK protein into two pieces and alters its activity. By unlocking the role that each of these proteins plays in the signalling cascade, or chain reaction that occurs within the brain of people with Parkinson's, McQuibban and other researchers hope to determine the exact genetic causes of the disease. If they can locate defects in the genes that lead to Parkinson's, they may eventually be able to produce new drugs.

"We think rhomboid will be one of these genes that can contribute to the disease but we have to prove it," McQuibban says.

McQuibban is motivated by his constant desire to understand how things work – from the bicycle he rode to work to the mitochondria in cells. His work on the mitochondrial rhomboid led him towards Parkinson's disease, but it may also eventually pay off for other neuro-degenerative diseases, including Alzheimer's.

Eventually, he hopes drugs will be able to "turn off or turn on" the genes and proteins needed to repair neural damage, or to prevent it.

## Psychosocial Research Grant

Co-funded by CIHR Institute of  
Neurosciences, Mental Health and  
Addiction.

# MRI and virtual navigational strategies in Parkinson's disease

**Year 1 \$48,388 Year 2 \$51,622 Total Award: \$100,000**



### Dr. Veronique Bohbot

Dr. Bohbot received her BA in Psychology from McGill University and obtained both her MA and PhD in the area of Experimental Psychology from the University of Arizona. She undertook her Postdoctoral training in Neuropsychology at the Montreal Neurological Institute. Dr. Bohbot is currently an Assistant Professor, Clinical Research at the Douglas Hospital Research Centre and is also a lecturer for the Departments of Psychology and Neurosciences, McGill University.

Psychologist Veronique Bohbot is an expert in how people use their brains to help them navigate the world.

She hopes to put that expertise to work to help people with Parkinson's strengthen one area of their brain.

Bohbot has used Magnetic Resonance Imaging (MRI) scans to discover that people use two different strategies, involving two different areas of the brain, to navigate. Some people create a mental map that shows them the relationship between where they are and where they are going. They visualize that map before they head home from work, for example. That spatial strategy involves using the part of the brain known as the hippocampus.

Imaging scans have demonstrated that people who use spatial strategies have more grey matter in their hippocampus than people who don't, Bohbot says.

Other people use what's called a stimulus response strategy to navigate – they simply memorize a series of left and right turns, and depend on travelling the same route. Stimulus-response strategies use the part of the brain called the caudate nucleus, located in the basal ganglia. People who rely on stimulus response strategies have more grey matter in the caudate nucleus than those who use spatial strategies.

Ideally, people should be able to shift between one strategy and the other, Bohbot says. "Both areas of the brain are important and we have to use them both," she says.

But often, people are so accustomed to relying on one strategy they don't know how to shift to another one. That's why Bohbot has developed a program to teach people who rely on stimulus response strategies (the caudate nucleus) how to shift to spatial strategies, giving their hippocampus some exercise. The program involves having people look at different landmarks, or details in their environment, estimate distances between them and visualize the relationships among them.

Bohbot is now using MRI scans to see if Parkinson's patients use these two different strategies – which she suspects they do. In some people with Parkinson's their hippocampus may have atrophied, because they are not using a spatial strategy to navigate.

Bohbot hopes to eventually train Parkinson's patients to use spatial strategies, thus strengthening their hippocampus, the same structure in the brain that's involved in building the relationships needed for good episodic memory, and for making associations among people, objects and places.

"If we have two different strategies, and we can train them (people with Parkinson's) to use one that is not dependent on the caudate nucleus, maybe we can help them have better lives," Bohbot says.

Bohbot became a researcher because she was inspired by Marie Curie, a role model who sparked Bohbot's interest in both physics and psychology. Eventually, psychology won out because Bohbot decided she wanted to work with people, rather than isolating herself in a laboratory. She was drawn to research involving memory because of her fascination with stories about patients with amnesia who learned complex tasks by repetition and automatic behaviour.

Recently, her father's diagnosis of Parkinson's has lent an additional poignancy to Bohbot's work. Although too late to help him, she hopes her plans to help people with this disease, by training and regaining the use of part of their brain, will make a difference in their lives.

## Characterization of a novel interaction between parkin and puromycin-sensitive aminopeptidase in Parkinson's disease

Year 1 \$50,000 Year 2 \$50,000 Total Award: \$100,000



### Dr. Antoine Duquette

Dr. Duquette obtained his MD from the University of Montreal in 2002. He continued immediately with his education and studied for his MSc in Neurological Sciences simultaneously with a residency in Neurology which he completed in 2005 and 2008 respectively. Dr. Duquette is currently a Post Doctoral Fellow training under the supervision of Dr. Edward Fon at the Montreal Neurological Institute.

Dr. Antoine Duquette recently had to tell the father of a close friend that he was in the early stages of Parkinson's disease. He remembers it vividly.

"It was hard," says Duquette, a neurologist who is working on his PhD during a basic research fellowship at McGill University. "It gets very frustrating to know that, when you're with a patient, you can help a lot with the symptoms, but you can't change the whole process that is active in those patients."

That frustration is one of the reasons Duquette turned to research into the causes of Parkinson's disease. The research provides both him and his patients with room to hope, even if a cure remains elusive.

Duquette's investigations focus around a poorly understood protein known as puromycin-sensitive aminopeptidase – PSA. Other researchers have already concluded that another protein – parkin – is responsible for inherited forms of Parkinson's disease. Duquette is looking at PSA because of its suspected interaction with parkin in brain cells affected by Parkinson's disease.

"What makes this protein very interesting is that it may also play a role in Alzheimer's disease and in another family of diseases which includes Huntington's disease," says Duquette. "It would be interesting and quite surprising if it was also implicated in Parkinson's disease."

PSA has been shown to play a protective role in fruit flies that have been genetically altered to display symptoms of Alzheimer's disease, by destroying toxic compounds in cells.

"Since it (PSA) possibly binds with parkin, which has been implicated in Parkinson's, maybe the toxicity that's associated with parkin can also be rescued by PSA," Duquette explains.

If that's true, researchers might then be able to design a drug that would increase the expression of PSA, to protect against the toxicity that appears to be killing dopamine-producing brain cells in people with Parkinson's.

Proteins are a critical focus of Parkinson's research because they are essential to every aspect of the human body's function. If a single protein in a cell or group of cells is damaged or stops working, the chain reaction among connected proteins can affect the entire system.

That's why Duquette's research into PSA is important to understanding – and eventually halting – the progression of Parkinson's disease.

"If we can demonstrate that it does play a role, it could be a therapeutic target," he says.

Year 1 \$40,000 Year 2 \$50,000 Total Award: \$90,000



### Dr. Thomas Jubault

Dr. Jubault received his MSc and PhD in Cognitive Sciences from L'Université Pierre et Marie Curie in Paris, France. He is currently a Post Doctoral Fellow at the PCAN laboratory at the Centre de Recherche de L'Institut Universitaire de Gériatrie de Montréal studying under the supervision of Dr. Oury Monchi.

One of the enduring mysteries surrounding Parkinson's disease is why some people with this illness develop dementia, while the cognitive functions of others are not affected. At the Institut Universitaire de Gériatrie de Montréal, Thomas Jubault is using new imaging techniques to try to answer this question.

"There clearly exist different subtypes of Parkinson's disease," says Jubault, a post-doctoral fellow in neuro-imaging. Those subtypes would include the 30-40 percent of patients who eventually develop dementia, and the other patients who do not.

"We know it has to be related to some kind of different evolution of the illness," he says. But researchers don't yet know which pathways in the brain are involved in the various subtypes.

Jubault will follow a group of people with Parkinson's for three years, using two new kinds of brain imaging techniques to map the pathways, or communication channels, among cells in the substantia nigra, the region of the brain where Parkinson's occurs.

The first technique is called Diffusion Tensor Imaging – DTI – and the second is Magnetization Transfer Imaging – MTI. The new techniques will give Jubault access to data about the health of brain cells at the micro-structural level, so he can analyze whether cell membranes are intact or beginning to deteriorate.

Along with the non-invasive brain scans, Jubault's team will also administer a battery of neuropsychological tests to assess the memory, language, and executive brain functions of the people in his study, to see how well they plan and strategize. Combining those test results with the brain imaging scans will help to separate the subtypes and relate them to different types of deterioration in the brain, Jubault says.

Eventually, Jubault hopes the imaging techniques can be used as a tool to diagnose Parkinson's earlier before the onset of the tremors, rigidity or other motor function problems that are actually later symptoms of the disease, but are usually the ones that first trigger a diagnosis.

The researcher also hopes his findings will contribute to the growing body of knowledge about Parkinson's that will eventually lead to a cure.

Jubault, who has a cousin with Parkinson's disease, is motivated by his dedication to help people with this illness.

He's also encouraged by the speed with which research in Parkinson's is progressing, he says. "I'm quite optimistic."

Year 1 \$37,500 Year 2 \$50,000 Total Award: \$87,500



### Dr. Dianbo Qu

Dr. Qu received his BSc from Wuhan University, and his MSc in Molecular Biology at the Institute of Biotechnology in China. He completed his PhD in Neurobiochemistry at the National University of Singapore and is currently a Post Doctoral Fellow training under the supervision of Dr. David Park at the University of Ottawa.

Unlocking the puzzle of Parkinson's disease is all about relationships – the relationships among genes, proteins and pathways in the brain. At the Ottawa Health Research Institute, neuroscientist Dianbo Qu is examining the relationship between proteins that may protect against the death of critical brain cells.

The targets of Qu's investigation are two proteins: cdk5 and PRDX2, and their relationship with a gene called DJ-1, whose mutation results in early onset Parkinson's disease.

Qu, a specialist in neurobiochemistry and neuropathology, is trying to determine how cdk5 and PRDX2 regulate each other and work with DJ-1 to rescue the dopamine-producing brain cells whose death contributes to Parkinson's disease.

In animal models, over-expressing the protein PRDX2 can stop the death of brain cells affected by MPTP, a chemical known to induce Parkinson-like symptoms.

Qu believes PRDX2, working with DJ-1, is part of a natural repair process in cells that is triggered when they come under stress. If the dopamine-producing neurons that are under stress cannot remove all of the toxicities, then the neurons die. That results in Parkinson's disease. That stress might come from the cells' response to neurotoxins, or to mutations in genes. Researchers don't yet know the exact mechanism is that triggers each part of the process that reacts to the stress and produces the repair function.

"We hope if we can identify the relationship between PRDX2 and DJ-1, we can find the exact pathway to regulate neurodegeneration," Qu says.

Mapping the mechanisms and the relationship might also give the researchers the clue to how to trigger the repair process when they need to turn it "on."

Their hope is to find a potential target for drug therapy in the future.

Qu came to Canada from Singapore, where he had done initial research on cdk5, which plays an important role in neurodevelopment and neurodegeneration. He was interested in why cdk5, like Jekyll and Hyde, plays opposite roles. When he discovered that David Park – another Parkinson's grant recipient – was working on cdk5's function in Parkinson's disease, he came to Canada and joined him for a post-doctoral fellowship to unravel the mysterious cdk5.

His interest in biology and in understanding the nature of human beings led him to his work on the brain and to Parkinson's disease research.

"To know the nature of ourselves – that is what I like," Qu says.

## Investigation of how $\alpha$ -synuclein forms Lewy bodies and how mutations in $\alpha$ -synuclein gene promote PD pathology

Year 1 \$40,000 Year 2 \$40,000 Total Award: \$80,000



### Dr. Hamid Qureshi

Dr. Qureshi obtained his BSc and MSc at the University of the Punjab and an MPhil at the University of Agriculture in Pakistan. Dr. Qureshi was a visiting scholar in Dr. Hemant Paudel's laboratory at the Lady Davis Institute for Medical Research in the Departments of Neurology and Neurosurgery and completed his PhD at the University of Montreal with Dr. Zafarullah. He is currently a Post Doctoral Fellow training under the supervision of Dr. Paudel.

Hamid Qureshi's inspiration for researching the causes of Parkinson's disease comes from the public struggles of two celebrities grappling with the illness: former World Heavyweight Champion Mohammed Ali, and actor Michael J. Fox.

Even in Qureshi's native Pakistan, Ali is well-known, and he learned about Fox when he came to North America. Both men, who have spoken publicly about Parkinson's and, particularly in Fox's case, worked hard to raise money for research, made Qureshi want to focus his skills on defeating the disease, he says.

At the Lady Davis Institute, housed in Montreal's Jewish General Hospital, Qureshi is exploring the way that two proteins, tau and alpha-synuclein, interact to contribute to the death of dopamine-producing brain cells in people with Parkinson's. He's particularly interested in the role the proteins play in the formation of Lewy bodies, the abnormal clumps of fibrous structure found inside the neurons of people with Parkinson's.

One of the components of the Lewy bodies is the alpha-synuclein protein. Qureshi's goal is to determine how mutations in the genes that regulate these proteins promote the formation of Lewy bodies in animal and cell models, by observing three different mutations of alpha-synuclein as they occur.

"To understand the molecular mechanism is very important," Qureshi says. "Then we will be able to design some new therapies."

Those new therapies would be designed to disrupt the reaction that produces the Lewy bodies, which could be either a protective response to damage to the cells, or the cause of the cell death itself.

Qureshi came to Canada to earn his Ph.D. in biomedical sciences and to pursue research.

"I've always been fascinated by medical science. I wanted to help people suffering from disease," Qureshi says.

## Characterizing Parkinson's-linked SNCA gene expression by GATA transcription factors

Year 1 \$40,000 Year 2 \$40,000 Total Award: \$80,000



### Dr. Julianna Tomlinson

Dr. Tomlinson completed an Honours BSc and PhD in Biochemistry at the University of Ottawa. She is currently a Post Doctoral Fellow at the Ottawa Health Research Institute in the Division of Neurosciences training under the supervision of Dr. Michael Schlossmacher.

Never underestimate the influence of a co-operative learning placement. That's what sparked Julianna Tomlinson's interest in a career in biochemistry and neuroscience.

Tomlinson was still in high school when she accepted a placement in Robert Haché's laboratory at the University of Ottawa. There, as she ran small experiments and helped other scientists with their projects, Tomlinson began her first research into the mechanisms that regulate gene expression. She's particularly interested in transcription – the process of turning on a gene to express more of that gene product.

Today, at the Ottawa Health Research Institute, Tomlinson is putting that expertise to work to identify the mechanisms in the brain that regulate the expression of alpha-synuclein, a critical protein that has been linked to the development of Parkinson's disease.

"There's a strong genetic link between how many copies of that gene an individual carries and the development of the disease," says Tomlinson. The more alpha-synuclein that a person's brain produces, the greater chance they have of developing Parkinson's disease, she adds.

"But very little is known about how the gene is regulated – how it's turned on or off."

Tomlinson's current research builds on work her supervisor, Dr. Michael Schlossmacher, and his colleagues did to identify a family of proteins that regulate the production of alpha-synuclein. These proteins are called the GATA proteins.

Working with a bank of brain tissue from Parkinson's patient and comparing that to tissue from the brains of people who did not have Parkinson's, Tomlinson will try to better characterize the role of the GATA proteins and their relationship to alpha-synuclein. It's an excellent use of the gene transcription skills she first began to develop as a high school co-op student.

"If we can understand how the expression of alpha-synuclein is regulated, then we may be able to interfere with this process and reduce alpha-synuclein production. Targeting the players involved in this pathway could potentially lead to new therapeutic approaches designed to lower alpha-synuclein production in patients with Parkinson's disease."

Since coming to work on this project with Dr. Schlossmacher, Tomlinson has met people with Parkinson's disease and learned about the realities of their lives. That has solidified her determination to use her skills to work toward the challenge of finding a cure.

"It's been really rewarding," she says.

## Basic Research Fellowship

Partially supported by the Catherine and Maxwell Meighen Foundation

# The role of the interaction between feritin and alpha synuclein ( $\alpha$ -syn) in Parkinson's disease

Year 1 \$50,000 Year 2 \$50,000 Total Award: \$100,000



### Dr. Naomi Visanji

Dr. Visanji received her Honours BSc in Neuroscience at the University of Nottingham in the UK in the Department of Biomedical Science. She completed her PhD in Pharmacology at the University of London. From 2004-2007 she was a Post Doctoral Fellow at the Toronto Western Research Institute. Dr. Visanji is currently training under the supervision of Dr. Anurag Tandon at the University of Toronto.

When Naomi Visanji was eight years old, living in her native Winchester, England, her favourite toy was a chemistry set. Today, as a post-doctoral fellow at the University of Toronto, she's still preoccupied with chemistry – the chemistry of the brain.

Visanji, now a neuroscientist, is investigating the interaction between two proteins considered important to understanding the cause and progression of Parkinson's disease. The first protein is alpha-synuclein, which is always present in brain cells, but clumps together in the neurons of people with Parkinson's disease.

"The jury is still out on whether the clumps themselves are toxic, or whether the cells have put them into these clumps to help deal with the excess of the synuclein," says Visanji.

Researchers at the University of Toronto have recently discovered that alpha-synuclein binds to other proteins, including feritin, the second protein on Visanji's agenda. Feritin stores iron, to release it when a cell needs it. But too much iron is dangerous – and the dying dopamine-producing cells implicated in Parkinson's disease have also been found to be much richer in iron than the average cell.

"A major theory at the moment is that the amount of iron in those cells is what makes them vulnerable and what makes them die," Visanji explains.

By figuring out how feritin and alpha-synuclein interact, Visanji hopes to find a common pathway that leads to the death of the dopamine-producing cells.

"By doing that, we may be able to find ways to stop that happening," she says.

Along the way, Visanji may uncover mechanisms that shed light on another disease that produces symptoms similar to Parkinson's. Neuroferritinopathy is a movement disorder caused by a genetic mutation in the feritin protein. The disease, which is rare, provides more evidence of the important role of iron metabolism in these kinds of neurodegenerative diseases.

Visanji believes the interaction between alpha-synuclein and feritin may be key to unlocking both diseases.

Longterm, Visanji is hoping to uncover a mechanism that can be targeted to prevent the degenerative process that is Parkinson's disease. She is fascinated by Parkinson's – just as she was by her chemistry set – because of the scope of the problem. The small, relatively specific area of the brain that degenerates and the relatively small cell population involved make it seem possible to figure out and prevent the cause or causes of the disease.

"It feels like it's curable," she says.

## One Year Award \$50,000



### Dr. Amitabh Gupta

Dr. Gupta obtained his PhD from Harvard Medical School in Biological and Biomedical Sciences and completed his Post Doctoral Fellowship at Harvard School of Public Health. He then received his MD from Ruprecht-Karls-Universitaet Heidelberg, Germany and completed a Medicine Internship at Johns Hopkins Bayview Medical Center in Baltimore. As the recipient of a Clinical Movement Disorders Fellowship, Dr. Gupta is working under the supervision of Dr. Tony Lang at the Morton & Gloria Shulman Movement Disorders Centre.

Dr. Amitabh Gupta is not just interested in understanding why dopamine-producing brain cells die. He wants to know how the death of those brain cells affects the lives of each of the patients with Parkinson's he treats.

That's why the movement disorders fellowship Gupta is completing at Toronto Western Hospital is so important from the perspective of a neurologist and a researcher. Treating patients at the hospital's clinic gives him the chance to "see and smell Parkinson's, to get a feel for the disease, to understand how to treat it and how my treatment affects the patients."

Gupta, who came to Canada after doing research into Parkinson's disease at the Johns Hopkins University in Baltimore, is well-versed in the importance of finding the genetic causes for the illness. He intends to focus on several genes implicated in Parkinson's during his fellowship. But first, he's eager for the chance to spend a year focusing on patients, because he understands that understanding and managing Parkinson's is a great skill.

"It's like a little detective story every single time you see a patient," Gupta says.

The clinical side of his practice is also helping to confirm Gupta's theory that instead of being a single disease, Parkinson's is actually a cocktail of diseases. He believes different gene mutations may produce different types of Parkinson's disease, and those forms may require either drug cocktails or drugs specific to each form.

Patients whose parkin gene is mutated exhibit slightly different symptoms from patients with sporadic forms of the disease, or those whose alpha-synuclein gene is damaged, he says.

"Maybe the pattern of cell destruction is different in their brains – producing more dementia here, more dystonia there," he says. There may be a genetic reason that some patients have more trouble sleeping than others, why some experience depression, and some cognitive problems, while others do not.

While the majority of researchers focus on the motor problems, Gupta wants to turn his attention in a different direction.

"Maybe what is relevant for the patient is a better effort in understanding the non-motor symptoms, because that's what really matters for the patients," he says. "A lot of scientists just know how a cell dies, but they don't understand what goes beyond it."

Gupta became a doctor because of his desire to help people, and focused on neurology as his specialty because he finds the brain "fascinating."

Eventually, he hopes to pair the clinical knowledge he is gaining about these diverse symptoms with his research skill to design drug trials that focus on the problems that matter most to the patients, he says.

"I'm not just working on a molecule ... I'm working on something Mr. or Mrs. Smith would love to get so they can sleep well. It's a completely different outlook," he says.

## How Parkin mutations result in Autosomal Recessive Juvenile Parkinson's disease

Year 1 \$15,000 Year 2 \$15,000 Total Award: \$30,000



### Ventzislava Hristova

Ms. Hristova obtained her Honours BSc in Chemistry and Biochemistry in 2004 from the University of Western Ontario and is currently a PhD student studying under the supervision of Dr. Jane Rylett and Dr. Gary Shaw in the Department of Biochemistry also at the University of Western Ontario.

Ventzislava Hristova was just four years old when her grandfather died from Parkinson's disease, back in her native Bulgaria. The knowledge that the disease affected her family prompted Hristova's determination to discover its origins – and spawned a promising research career.

Hristova, 26, is working on her doctorate in biochemistry at the University of Western Ontario in London, Ont. She's concentrating on characterizing a protein called parkin that is implicated in the cause of Autosomal Recessive Juvenile Parkinson's (ARJP), a type of Parkinson's disease that appears in people at an early age.

Many people with ARJP, who may begin experiencing the tremors, muscle spasms and rigidity that are symptomatic of Parkinson's in their 20s, have a mutation in the park2 gene. That gene is responsible for producing parkin.

Proteins are three-dimensional structures. Hristova's research involves learning about the physical structure of parkin, and how mutations affect its three-dimensional fold, which then prevents it from carrying out its normal activity in a cell.

"The question is what this (mutated) parkin protein does to cause the death of the neurons in a certain region of the brain (the substantia nigra)," says Hristova.

"If we learn more about how the protein is folded and what it does in neuronal cells, we will have an idea of how the various mutations affect protein structure and activity."

When researchers figure that out, "we will learn how the neural degeneration begins and how the death of these cells is triggered," Hristova says. "Once we learn the cause and the mechanism of the neural degeneration behind AJRP, we can learn how to treat and manage it and hopefully even prevent it."

The structure of the protein is critical, because that will eventually become the target of any new drug, says Hristova. Any drugs that are developed and tested will target the pathways with which the parkin protein is involved.

For Hristova, whose family moved to Canada when she was 14, joining the legions of researchers working on Parkinson's is a way of contributing to the illness that has affected her family. Although she doesn't know what form of Parkinson's her grandfather had or whether it is an inherited type, the possibility that one day she or someone else in her family could be affected is always in the back of her mind. She hopes her work will help solve the puzzle and eventually lead her into clinical trials and drug-testing.

"I realize thousands of people are working on Parkinson's disease, but in the long run my little contribution will contribute to bettering the lives of those people affected by Parkinson's disease," she says.

## The role of Pitx-3 in the survival of midbrain dopamine neurons that are afflicted in Parkinson disease

Year 1 \$15,000 Year 2 \$15,000 Total Award: \$30,000



### Mr. Khanh Nguyen

Mr. Nguyen received his BSc in Physiology and Neuroscience, and his MSc in Neurological Sciences both from McGill University. He is currently a PhD student in Neurological Sciences at McGill University studying under the supervision of Dr. Abbas Sadikot.

Ken Nguyen has always believed that to truly understand something, he must first take it apart and learn the function of each component. Only then can he put it back together and know how each part works in unison.

It's a principle Nguyen used to fix his bicycles. Now he's applying the same method to understand the human brain.

Nguyen, a doctoral candidate in neurological sciences at the Montreal Neurological Institute, is studying the reason that dopamine-producing neurons die in Parkinson's disease. He's doing that by "taking apart" a component in those neurons: a protein known as Pitx3.

"This protein is expressed only in the dopamine neurons and not in any other neurons in the brain," says Nguyen. "This piques our interest."

The Pitx3 seems to control other proteins that help the dopamine-producing brain cells survive, says Nguyen. Researchers theorize that Pitx3 may be activating survival systems specifically in these brain cells. Mutations in Pitx3 may fail to activate the survival systems, causing the dopamine-producing brain cells to die, and resulting in Parkinson's.

If Nguyen can help to establish Pitx3's importance, it could become an important target for drug or gene therapy. Increasing the amount of Pitx3 that is expressed, or boosting its function, might then protect the dopamine neurons.

"Several papers have shown that Pitx3 in humans is genetically related to Parkinson's disease and increases the susceptibility to Parkinson's disease," Nguyen says. His goal is to establish that relationship more firmly, to decipher the workings of the Pitx3 and the survival systems in dopamine-producing neurons, and to find a highly specific avenue for treatment.

Nguyen was motivated to study Parkinson's disease because of his desire to take apart and repair things, starting with the brain, the most vital of human organs. Because in Parkinson's one main area of the brain – the substantia nigra – is involved, Nguyen was drawn to the well-defined scope of the research.

"It seems that we have a firm understanding at least of where the major problem lies, and we can (already) fix it to some extent," Nguyen says. "I believe that with this research we are doing we can fix it in a more targeted manner."

Just like his bicycle.

## The role of Parkin in regulating mitochondrial morphology and its importance in Parkinson's disease

Year 1 \$15,000 Year 2 \$15,000 Total Award: \$30,000



### Mr. Pierre Robinson

Mr. Robinson obtained his BSc in Medical Biology from the Université du Québec à Trois-Rivières and went on to complete his MSc in Biophysics and Cellular Biology at the same institution. He trained as a PhD student at McGill University studying under the supervision of Dr. Edward Fon.

Pierre Robinson knows all too well the pain of watching a loved one struggle with a degenerative brain disorder. His grandfather, Jean-Baptiste Mimeault, had Alzheimer's disease for 10 years before he died.

"It was pretty bad," says Robinson, now a Ph.D. candidate at the Montreal Neurological Institute.

Before Mimeault died, he recognized his grandson. He grabbed Robinson's hand, shed a tear and exchanged a last lucid look before he was gone again.

"He knew I was there at the end," Robinson says.

His grandfather's illness prompted Robinson to wonder about the causes of brain disorders, sparking his interest in neuroscience and a bachelor's degree in medical biology. After an internship with a researcher working on Huntington's disease – another neurodegenerative disorder – Robinson is now studying the role that dysfunctional mitochondria play in Parkinson's disease.

Mitochondria are tiny molecular structures within cells that provide their energy. Emerging research is now focused on mitochondria's role in the respiratory complex chain of proteins that are vital for the brain cells involved in Parkinson's disease. They may either contribute to the health of those cells, or be responsible for their premature decay.

Robinson is particularly focused on the parkin gene, which is believed to be involved in regulating the integrity of mitochondria. He is studying the shape and structure of mitochondria in embryonic mouse cells.

"It has been shown that when mitochondria are smaller and fragmented, it's not good for the cells," Robinson says. The damaged mitochondria mean the cells will eventually die because of a lack of energy, he explains.

In fruit flies where the parkin gene was knocked out, the mitochondria in neural cells were deeply damaged, pointing to a link between parkin and mitochondria. Robinson hopes to solidify the evidence of that connection. He is also tracking the specific proteins that help mitochondria fuse and divide.

Eventually, Robinson hopes to come up with a drug target or gene therapy that would either activate or turn off the proteins involved in unusual mitochondria fragmentation.

"This could provide supporting energy for the neurons to live longer," he says.

If the mitochondria stayed intact, they could help keep dopamine-producing brain cells healthy.

Despite his initial personal interest in neurodegenerative diseases, Robinson is happy that he is now focusing on Parkinson's research.

"The research that's being done on Alzheimer's Disease to me is going in a circle," he says. "I was more interested in what Parkinson's disease was doing because it's more specific and more promising ... in the near future."

## New Investigator Award

Second year of two year award 2007-2009

# Role of cytoskeleton-associated proteins in Parkinson's disease and L-DOPA-induced dyskinesia

Year 1 \$45,000 Year 2 \$45,000 Total Award: \$90,000



### Dr. Michel Cyr

Dr. Cyr is an Assistant Professor in the Neuroscience Research Group in the Department of Chemistry Biology at the Université du Québec at Trois-Rivières. He is also a Junior 1 Scholar in the FRSQ Neuroscience Research. Dr. Cyr began his education at the University of Quebec at Trois-Rivières and received his PhD at the University of Laval. He then went on to complete his Post-Doctoral training at Duke University in the USA.

When it comes to his scientific life, Michel Cyr has set himself a single goal: finding a better treatment for Parkinson's disease.

As a molecular neuropharmacologist investigating the function and interactions of proteins in the brain, Cyr is aware that his goal may take time to reach. But at 34, he has a long career ahead of him, and is already on the path to alleviating one of the most distressing symptoms for Parkinson's patients: involuntary movements.

In his laboratory at the Université du Québec à Trois Rivières, Cyr is deciphering the link between the activation of dopamine receptors in the brain and cytoskeletal proteins. Cytoskeletal proteins are structural proteins within cells that affect the general function and interconnections between neurons.

"We always thought these proteins just gave the shape of the neurons, but now we realize they are also implicated in the function, and perhaps the memory, of cells," says Cyr.

When people with Parkinson's are treated over a long period of time with L-DOPA, a chemical that is converted to dopamine in the brain, one of the side-effects is dyskinesia, or involuntary movements.

Cyr believes that the death of dopamine-producing neurons, which causes Parkinson's, and the dyskinesia that L-DOPA causes both affect the cytoskeletal proteins. He wants to find out exactly what the connection is and how these proteins affect involuntary movements and cell memory.

Cyr is also looking at the way L-DOPA is delivered, to see if a continuous infusion of the drug, rather than intermittent injections, can reduce dyskinesia. He thinks the current treatment may be over-stimulating dopamine receptors, causing other proteins to malfunction and produce the involuntary movements.

"Maybe we're giving too much L-DOPA," Cyr says.

Injections produce peaks of dopamine. By using a mini-pump, a patch or another slow-release form of delivery to provide the medication continuously, it may reduce the side-effects, Cyr hopes.

Cyr has always been interested in the brain and how it controls movements, he says.

He spent much of his childhood in his own world, analyzing and pondering questions – although not necessarily the subjects his teachers thought he should consider. Fortunately for Parkinson's patients, the questions Cyr considers today are exactly on track to helping reduce the depression and withdrawal that dysfunctional movement can provoke.

"If we can remove the emergence of this dyskinesia just by adapting the treatment – we can give these people a more comfortable life," he says.

## New Investigator Award

Second year of two year award 2007-2009

# Neuroprotective effects of the cytokines interleukin-6 and interleukin-10 in a paraquat model of Parkinson's disease

Year 1 \$45,000 Year 2 \$45,000 Total Award: \$90,000



### Dr. Shawn Hayley

Dr. Hayley is an Associate Professor in Psychology, CIHR Canada Research Chair and Director of the Institute of Neuroscience at Carleton University. He received his PhD in 2002 from Carleton University, in the Department of Psychology and his Doctoral research received the Governor General's Medal. Dr. Hayley's work investigates the link between disturbed immune system functioning and the development of neurological and psychiatric conditions, particularly Parkinson's disease and depression.

Shawn Hayley was an undergraduate student at Newfoundland's Memorial University when he first encountered patients with a disease that would become the focus of his research career.

He was volunteering on the dementia and Parkinson's wards in the local hospital, where he saw the profound effects of neurodegenerative diseases on people's lives.

"It's a terrible way to end one's life," says Hayley. "We just know so few good long-term treatments, that it's a motivation."

That motivation drives Hayley, who now holds a Canada Research Chair in Behavioural Neuroscience at Carleton University, to look for the causes of Parkinson's disease in its links to the immune system.

Accumulating evidence now suggests that inflammation in the brain can contribute to some aspects of Parkinson's disease. Hayley and the members of his lab are exploring ways to dampen that inflammation and prevent the loss of the dopamine-producing brain cells that die in Parkinson's disease.

To do that, they are using an animal model based on a common pesticide and herbicide called Paraquat. Hayley's lab, as well as labs in the United States, have already demonstrated that Paraquat kills dopamine neurons, just as Parkinson's does. Since Parkinson's has been linked to exposure to environmental toxins, Hayley is focusing on Paraquat as a possible trigger that kills the brain cells, by over-activating inflammatory nerve cells called microglia.

Hayley's theory is that Paraquat's interference with the microglia, those inflammatory nerve cells, releases an inflammatory response that damages the dopamine-producing neurons in the brain that regulate movement and motor control.

With his grant from Parkinson Society Canada the neuroscientist plans to look at the specific signalling mechanisms in the brain that could be killing the dopamine-producing neurons.

Normally, microglial cells release inflammatory factors and reactive oxygenated molecules, called free radicals, as an immune response to fight off infection, such as bacterial or viral meningitis that can attack the brain. But if there is no infection, and the inflammation is being triggered without cause, those free radicals and other inflammatory factors can damage or kill otherwise healthy brain cells.

"We're speculating that environmental toxins may be on thing that's triggering this release – and one of these environmental toxins looks like it's Paraquat," Hayley says.

Instead of using general anti-inflammatory drugs, such as Ibuprofen, to try to reduce the inflammatory response in the brain, Hayley's lab is targeting two particular proteins, called cytokines, which are being inappropriately triggered to fight off infections or stress.

The two anti-inflammatory cytokines are called Interleukin-6 and Interleukin-10. Hayley's research involves administering these proteins to mouse models that have been exposed to Paraquat, to see if they can reduce the damage that the pesticide does, by triggering an anti-inflammatory response. "They're very powerful proteins, or molecules," says Hayley. "We're looking at ways to therapeutically harness their potential."

If Hayley's hypothesis works, and Interleukin-6 and Interleukin-10 counter the effects of Paraquat exposure on the brain, the results of his research will provide new treatment options for Parkinson's that target these molecules and their anti-inflammatory properties.

"Any experiments that get at the basic mechanisms on how these neurons could be dying are beneficial," says Hayley.

## New Investigator Award

Second year of two year award 2007-2009

## Proteomic analysis of parkin ubiquitin-ligase substrates

Year 1 \$45,000 Year 2 \$45,000 Total Award: \$90,000



### Dr. Thibault Mayor

Dr. Mayor obtained his BSc from the University of Geneva in Switzerland, his PhD from the University of Geneva and Max Planck Institute of Biochemistry in Germany, and completed his Post-Doctoral training at the California Institute of Technology. He is currently an Assistant Professor in the Department of Biochemistry and Molecular Biology at the University of British Columbia.

In another lifetime, Thibault Mayor might have explored new worlds. He thrives on the excitement of beginning an expedition into a previously unknown region.

Instead, Mayor is a biochemist whose expeditions take place in areas of the brain, like the substantia nigra that is so critical to understanding Parkinson's disease.

Mayor's research at the University of British Columbia's Department of Biochemistry and Molecular Biology focuses around the ubiquitin proteasome system, or UPS, a delivery system in the cells that breaks proteins down into smaller pieces.

"It's a little bit like a garbage system," Mayor explains. "It says which system needs to be degraded (or discarded), adds a little tag, and the protease system breaks it into little pieces."

When proteins get damaged or age, becoming less efficient, they need to be replaced. The UPS in cells is a natural process for destroying and recycling materials.

Researchers believe that for some reason, however, the UPS is unable to degrade the damaged or mutated genes linked to Parkinson's disease. The UPS has been linked to familial forms of Parkinson's disease.

"We don't really know why these cells cannot degrade these proteins," says Mayor.

When aggregates of these damaged proteins clump together in cells, such as the dopamine-producing cells in the brain that regulate motor function, the cells begin to have problems. Mayor's research is concentrated on discovering why UPS has broken down. He's particularly interested in the parkin ubiquity ligase, an enzyme that can attach ubiquitin to other proteins – like a signal, or a tag, that tells the proteasome system which proteins to degrade.

Mayor is using a technique involving mass spectrometry, equipment that can detect the mass of proteins, allowing him to purify them and remove them from cells. He can then inject the cells with a detector to allow him to identify the protein he is examining. He's comparing cells where the parkin enzyme is mutated to those where it has not.

Once Mayor understands the role parkin is playing in these cells, the proteins might eventually be used as diagnostic markers, or drug targets.

This research project is the first time Mayor, who grew up in Geneva, Switzerland, has directed his work on the ubiquitin protease system towards Parkinson's disease. He hopes it will give him the opportunity to continue his explorations amongst the brains' cellular network.

## **Migration of new neurons in the adult parkinsonian brain**

**Year 1 \$45,000 Year 2 \$45,000 Total Award: \$90,000**



### **Dr. Armen Saghatelian**

Dr. Saghatelian holds the Canada Research Chair on Postnatal Neurogenesis at the University of Laval. He is also an Assistant Professor in the Department of Psychiatry in the Faculty of Medicine. He completed his BSc and MSc at Yerevan State University in Armenia and then relocated to Germany where he obtained his PhD at the University of Hamburg.

Almost two decades ago, researchers demonstrated that the adult brain can regenerate some cells – shattering the belief that humans’ central nervous system was incapable of repairing itself.

At Laval University, Armen Saghatelian is studying the olfactory bulb in the brain, one of the two regions, along with the hippocampus, where the brain can regenerate cells. The olfactory bulb is at the front of the brain, and receives input from the nose, which is critical for detecting odours. He is trying to figure out how the brain not only produces new cells in the olfactory bulb, but what enables them to migrate, and what controls their movement.

Saghatelian’s dream is to understand the mechanisms that redirect these brain cells. One day, he hopes to be able to use that knowledge to redirect the new cells to other regions in the brain that have been damaged by Parkinson’s disease or other neurodegenerative disorders.

“If we know this mechanism, we’ll be able to control their dispersal,” Saghatelian says of the new cells.

Other researchers have already tried to transplant stem cells into the brains of Parkinson’s patients, in the hope that those cells would move to the damaged areas of the brain and would halt or repair the areas affected by disease. Unfortunately, the transplanted cells did not disperse – they stayed at the site where they were placed.

Saghatelian’s work could be the key to understanding how to get those cells to the locations in the brain where they are most needed.

At the moment, Saghatelian is working with animal models, trying to redirect endogenous stem cells from the brain to the basal ganglia. By understanding the basic mechanism of migration, he hopes to be able to control the movement of stem cells from the striatum into the substantia nigra, a neighbouring region in the brain. His hypothesis is that the new cells would release dopamine and compensate for symptoms of the disease.

“That’s our hope, that the brain will heal itself,” Saghatelian says.

Saghatelian, who is originally from Armenia, was always fascinated by how the brain is constructed and how we are able to perform difficult tasks. His work on integrating new cells into damaged areas of the brain takes that interest to a whole new level.

“Since we are looking at the birth and development of new cells in the adult brain, I think we have to use this knowledge for some treatment, for cell replacement therapies,” he says.



### Dr. Thomas Durcan

Dr. Durcan received an Honours BSc in Cell and Molecular Biology from the University College of Dublin, Ireland, and is a graduate of Biological Sciences from the University of Notre Dame, IN. He is currently a Post Doctoral Fellow at the Montreal Neurological Institute training under the supervision of Dr. Edward Fon.

Year 1 \$40,000 Year 2 \$40,000 Total Award: \$80,000

In a laboratory at the Montreal Neurological Institute, Thomas Durcan is studying the role three proteins play in the signaling pathways in the brain. Understanding how these proteins interact could help identify the causes of Parkinson's disease, and shed light on another progressive illness.

Machado Joseph Disease is a rare, hereditary disorder linked to cell degeneration in the cerebellum, the brain stem and the upper part of the spinal cord. People with the disease walk with a staggering, lurching gait, may have involuntary eye movements, difficulty speaking and swallowing, and rigidity. Recently, scientists have learned that the Ubiquitin, Parkin and Ataxin 3 proteins are involved in both Parkinson's and Machado Joseph.

Ubiquitin is a small protein made up of 76 amino acids, or molecules, contained within our cells; Durcan describes it as a kind of 'tag'. When attached to other proteins, such as Parkin or Ataxin3, ubiquitin tells the brain either to degrade the cell, sending it off to die, or it sends the protein on in the signaling system. Attached to Parkin, ubiquitin sends the proteins on; added to Ataxin, it takes on the opposite function, signaling the cell to degrade.

Now Durcan and his colleagues have discovered that Ataxin 3 and Parkin can bind to each other.

"It was pretty novel, because it's actually two separate proteins in two separate diseases that are able to interact," Durcan says of the discovery. "It indicates that these two diseases might have an overlapping, underlying cause."

A better understanding of the molecular causes of these diseases could suggest a new pathway for treatment, says Durcan, a way, for example, to use Parkin to counteract the effect of Ataxin, which when over expressed can lead to the degeneration of brain cells.

"Up until this point, people know about the diseases but they don't really know what causes them," says Durcan. "We're trying to get to the 'why' behind them before we can outline targets for future work."

Durcan, who is originally from Dublin, came to Canada to work at the world-renowned Institute in Montreal after completing his Ph.D in cellular molecular biology. Even as a kid, he enjoyed biology.

Designing experiments just seemed like a natural extension of his early curiosity, he says.

"It takes an inquisitive nature!"

## CDK5 & its role in the cascade of signals that cause death of dopamine – producing brain cells

Year 1 \$40,000 Year 2 \$50,000 Total Award: \$90,000



### Dr. En Huang

Dr. Huang studied for his Bachelor of Medicine at Fudan University School of Medicine in China, and completed his PhD in anatomy at National University of Singapore. He is currently a Post Doctoral Fellow in the Department of Neuroscience at the Ottawa Health Research Institute under the supervision of Dr. David Park.

In the world of research into Parkinson's disease, it's vital to understand the role of each protein involved in the cascade of signals that lead to the death of dopamine-producing brain cells.

En Huang, a post-doctoral fellow in neurobiologist David Park's lab at the University of Ottawa, is tracking the role of CDK5, a protein that is central to that signal cascade.

Huang and Park already know that CDK5, a type of protein called a kinase, promotes the death of the dopamine neurons. What they don't know is how or why.

Within each cell there is a whole universe of proteins, which act and react to one another in an intricate dance. CDK5 appears to be binding to another protein, called APE1. APE1 plays a protective role, by keeping genetic information in a cell intact and warding off damaging oxygen molecules, called free radicals. The protein is therefore essential for cell survival – and for some reason, CDK5 is interfering with that important role.

When CDK5 becomes abnormally active, it shuts down the protective cells. Even this slight alteration in a cell causes neurons to get sick and die. Huang's research into the roles of these proteins, using cell cultures and animal models, is an attempt to figure out these subtle cell mechanisms.

Eventually, he hopes to discover a drug or another therapy that will inhibit CDK5, allowing APE1 to recover.

"So it will be a protection – it can repair DNA and protect against cell death," says Huang, who came to Ottawa from Singapore last year, and is originally from China.

"If we can use a CDK5 inhibitor, it will be for the benefit of the patients."

Huang, whose PhD is in anatomy, has enjoyed science since he was a child. He's particularly pleased that cloning techniques have now made it easier for the researchers to create a mutant protein that may be able to alter CDK5. That's what the Parkinson Society fellowship will help him to investigate.

"You get a sense that in a cell, a whole lot of things are happening," says Park, who has welcomed Huang's expertise in his lab. "We have to figure out what all these things are, and find their common points that we can target."

## Evaluation of the role of Monoamines in Electroconvulsive Therapy in an animal model of Parkinson's disease

Year 1 \$13,333 Year 2 \$13,333 Total Award: \$26,666



### Dr. Anne M. Landau

Dr. Landau began her education at McGill University, where she received her Honours BSc, MSc and PhD in the Department of Physiology. She is currently a Post Doctoral Fellow at Pacific Parkinson's Research Centre at the University of British Columbia in Vancouver, working under the supervision of Dr. Doris Doudet.

Anne Landau was just finishing her Master's degree when her grandmother's Alzheimer's Disease worsened. Watching Czernia Kegel, a Holocaust survivor, endure the pain of believing herself trapped back in Poland during the Second World War drew Landau into the field of neurodegenerative diseases.

"You see how devastating it can be to the person who is suffering, and to the family, and to society. I wanted to be able to help," says Landau.

The neuroscientist quickly became involved in research on Parkinson's disease, which like Alzheimer's involves the progressive degeneration of brain cells. Today, Landau spends a third of her time in Aarhus, Denmark, where she is investigating why electro-convulsive therapy (ECT), once known as shock therapy, helps people with Parkinson's.

Originally, doctors were using ECT to relieve depression in people with Parkinson's. About 30 percent of patients with depression do not respond to medication, but do respond to ECT. The doctors discovered that in addition to lifting their depression, the treatment also alleviated their patients' rigidity and other motor symptoms – for up to six months. But no one yet understands why ECT works

Landau is using an animal model – pigs – to try to figure out how ECT is changing neurotransmitters and their receptors in the brain.

"What we want to look at is the changes to the dopamine, serotonin and norepinephrine levels at the receptor level, to see what could be occurring that cause the improvement both for depression and for Parkinson's disease," says Landau.

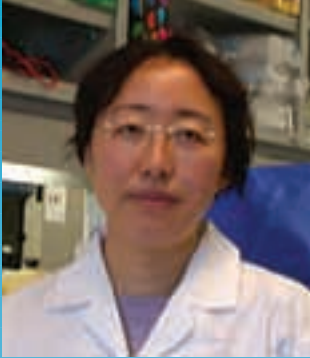
She hopes that understanding why ECT works and explaining why it can be beneficial will help dispel the stigma that surrounds the treatment, which is tarnished by the conditions and experiments under which it was administered in the 1950s and 1960s.

"The only side-effect or drawback is transient memory loss for a few weeks after the treatment," says Landau. "If we do more research on this, people might be more open-minded and more funding would come, and there would be a chance to treat more of these people."

Landau has always been interested in science, and began working in the lab of a friend of the family when she was 17.

"I was interested in the brain and how it works, and how the tiniest changes to the brain can cause huge changes in the behaviour of the motor system," she says. "The smallest thing can be off-balance in the brain and you can get such a huge change – that always really fascinated me."

Year 1 \$50,000 Year 2 \$50,000 Total Award: \$100,000



### Dr. Wenjing Ruan

Dr. Ruan began her training by completing her MD in clinical medicine at Lanzhou Medical College in China. She worked as a physician in the Department of Respiratory Systems at the People's Hospital of Gansu in the Province of Lanzhou, China and also as an acupuncturist in London, UK. She then obtained her MSc and PhD in Neurobiology at the Research Institute of Montreal General Hospital. Dr. Ruan is currently a Post-Doctoral Fellow at McGill University and has received training under the supervision of Dr. Julie Desbarats and Dr. Edward Fon.

Researchers studying Parkinson's disease are increasingly focusing on the role that particular proteins play in the degeneration of dopamine-producing brain cells. At McGill University in Montreal, Dr. Wenjing Ruan is concentrating on one of those proteins, which she believes has protective powers.

Fas is a cell surface molecule that stops dopamine neurons from degenerating – at least in mice. Ruan, who came to Canada in 1997 after obtaining her medical degree in China, wants to know exactly how Fas works.

"In our mice model, if the mice have a deficiency in Fas, it makes them very susceptible to Parkinson's Disease," Ruan explains. She hypothesizes that people with Parkinson's may have mutations in Fas that control its ability to switch 'on' or 'off', affecting the way it can regulate other proteins.

Previously, researchers thought that an accumulation of Fas in brain cells caused the cells to degenerate. Now, Ruan believes an accumulation of the protein actually serves a protective function, slowing the accumulation of another abnormal protein that is causing the brain cells to die.

As part of her research, she is testing the blood of Parkinson's patients to see whether they have an Fas deficiency. Eventually, Ruan hopes her work will lead to a new drug or therapy, consisting of small molecules that resemble Fas. Those could be administered to patients to slow down the death of critical brain cells.

"There is a lot to be studied in this field – there's so many molecules involved in these pathways," says Ruan. "We just try to figure out how they interact with each other. It's very challenging."

Part of the challenge comes from the fact that different neurons respond differently to Fas. Figuring out why one combination works differently than another is important.

In China, Ruan specialized in respiratory diseases. In Canada, she is working in neurobiology and neuroscience, in research rather than medicine. But she's all too familiar with the effects of Parkinson's, from which a close friend's father suffers.

"It's a dreadful disease," Ruan says.

"I really hope I can resolve at least this Fas mechanism, to find out why Fas in the neural system and in the nervous system mediates protection."

## A proposed novel mechanism underlying the inhibitory action of deep brain stimulation

Year 1 \$50,000 Year 2 \$50,000 Total Award: \$100,000



### Dr. Damian Shin

Dr. Shin completed his BSc and MSc in Zoology at the University of Western Ontario and his PhD in Zoology at the University of Toronto. Dr. Shin is currently a Post Doctoral fellow at Toronto Western Research Institute training under the supervision of Dr. Peter L. Carlen.

Damian Seung-Ho Shin loves not knowing exactly how the basal ganglia portion of the brain works.

That's because Shin, a neurophysiologist at Toronto Western Hospital, believes that the more complicated a problem is, the better. He's driven to find the answers. That trait comes in handy right now, since he's studying parts of the basal ganglia to find out what happens when neurologists use deep brain stimulation to relieve symptoms of Parkinson's disease.

For 40 to 60 percent of Parkinson's patients who undergo deep brain stimulation, the procedure to stimulate portions of the basal ganglia with electrical impulses, relieves their symptoms. But for the remaining percentage of patients on which the procedure is performed, it doesn't work. No one knows why, and doctors do not yet have a way to screen patients to determine when the operation will be successful.

"My research is looking at ways to improve deep brain stimulation, by understanding how it works," says Shin, a postdoctoral fellow at Toronto Western Hospital. "No one has concrete evidence as to how it works."

Shin's research is focused around the involvement of an ion channel in the brain called I-H, and its relationship to potassium. An ion channel is a core in brain cells that allows currents or ions to pass through – the signals that allow cells to communicate with one another.

When researchers stimulate brain tissue, potassium increases. Shin's theory is that the increased potassium enhances the I-H ion channel, which dampens the hyperactivity of cells in the GPI portion of the basal ganglia, nullifying the effect of the electrical stimulation.

If he can prove his hypothesis and demonstrate the role that potassium and the ion channel play in deep brain stimulation, Shin may be able to help devise a way to improve the way the procedure works, opening up the treatment option for more patients with Parkinson's.

## **Genetic screen for suppressors of $\alpha$ -synuclein-mediated death of dopaminergic neurons**

**Year 1 \$50,000 Year 2 \$50,000 Total Award: \$100,000**



### **Dr. Satoshi Suo**

Dr. Suo completed his BSc in the Faculty of Agriculture at the University of Tokyo, Japan. He then went on to complete his MSc and PhD in the Department of Biotechnology at the Graduate School of Agricultural and Life Sciences also in Tokyo. Dr. Suo is currently training under the supervision of Dr. Joseph Culotti as a Post Doctoral Fellow at the Samuel Lunenfeld Research Institute, Mount Sinai Hospital in Toronto.

The humble roundworm, better known as *C. elegans*, is not the kind of high-tech device normally associated with cutting-edge genetic research into the causes of Parkinson's disease.

But for molecular biologist Satoshi Suo, the roundworm is an essential tool in his efforts to discover the reason that a particular protein is implicated in the death of dopamine-producing brain cells, or neurons.

Suo is investigating the role of the alpha-synuclein protein. In families with inherited forms of Parkinson's, a mutated form of this protein aggregates, or clusters together, within the dopamine-producing neurons. Alpha-synuclein is also implicated in the death of dopamine neurons in people with sporadic Parkinson's.

"It's not known how these clusters of alpha-synuclein kills the cells," says Suo.

By introducing mutated forms of various proteins into the roundworms that are an animal model of Parkinson's disease, Suo is performing a genetic screen to determine whether or not he can turn the genes that are the suspected culprit in killing the neurons "on" or "off." If he can find a way to do that, he will have discovered another possible target for drug or gene therapy that could arrest the progression of Parkinson's.

One of the tricky parts of the research is finding a way to measure the activity of the dopamine-producing neurons.

"You need to have something that reports on what's going on inside (the cells)," says Suo. He has developed a system in which he uses fluorescent proteins to introduce genetic mutations and observe their interactions with the dopamine-producing neurons and with alpha-synuclein proteins.

If he finds the mutation or discovers the function of whatever is interfering with alpha-synuclein, researchers may be able to design a drug that keeps the protein from becoming toxic and killing the dopamine-producing neurons.

For Suo, unravelling the dopamine system in roundworms – and in the human brain – flows naturally from his life-long interest in basic science.

"It's interesting to know how things work, and what the mechanism is of what you see," says Suo.

"Dopamine is involved in human behaviours and control of mood, and that was something that I wanted to work on."

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