UPDATES IN PARKINSON’S DISEASE RESEARCH
WHAT IS PARKINSON’S DISEASE

Parkinson’s disease (PD) is a gradually progressive disorder of the brain that affects movement, causing tremors and stiffness. Other symptoms include issues with sleeping, loss of sense of smell, speech and swallowing problems, cognitive impairment, depression and anxiety.

The movement-related symptoms are caused by the progressive degeneration of brain cells (neurons) in the part of the midbrain that controls smooth, coordinated movement. When healthy, these neurons release dopamine, a neurotransmitter that stimulates the nerve cells that control the muscles. By the time symptoms appear, people with PD will have lost up to 80 per cent of their dopamine-producing cells.

The exact cause of PD is unknown. There may be genetic causes for some patients and environmental causes for others, such as exposure to herbicides and pesticides in farm workers, with a combination of environmental and multiple genetic factors contributing to the disease in the majority of patients.

SYMPTOMS

The movement-related symptoms of PD are initially mild, often beginning on one side of the body. As they progress, symptoms become more pronounced and appear in other parts of the body.

The characteristic Parkinson’s tremor can begin in the forearms, hands or fingers, especially when the limb is at rest. The foot, mouth and chin can also be involved. Over time, PD reduces the ability to move and slows voluntary movements (bradykinesia), such as standing up and sitting down. It becomes difficult to initiate walking and the gait of a person with Parkinson’s is marked by shuffling feet, lack of arm swing and with the head down.

Muscle stiffness can also limit the range of motion and cause pain. The person’s posture may become stooped, they may develop balance problems and fall more frequently. As it becomes harder to write, the handwriting may appear small.

In later stages as the automatic movements of the muscles become slower, people with Parkinson’s may develop changes to their speech, and difficulties with swallowing, passing urine and constipation. People with Parkinson’s also often have sleep problems and may act out their dreams. They may experience sudden drops in blood pressure, leaving them lightheaded. They may lose their sense of smell, feel fatigued and have pain in various parts of their bodies.

Later stage PD is often accompanied by depression, cognitive difficulties and dementia.

TREATMENT & PROGNOSIS

As there is no cure for Parkinson’s, the primary drug therapy aims to overcome the problem of depleted dopamine stores in the brain. Different drugs have different actions: some mimic the action of dopamine, and some enhance the action of the remaining dopamine stores.

Drugs for PD, however, often lose their efficacy over time, leading to a requirement for higher doses. Some drugs, such as Levodopa, also cause involuntary movements (dyskinesia). Other treatment side effects can include out of character behaviour, confusion, hallucinations, insomnia, nausea and gastrointestinal problems.

In severe cases, neurosurgery where lesions are made on parts of the brain may be necessary to relieve symptoms to interrupt involuntary movement. Deep brain stimulation (DBS), where an electrode is implanted in the affected area of the brain, may also help alleviate symptoms. DBS is most often offered to people with advanced Parkinson’s who have unstable medication responses as it can markedly improve movements. Although DBS may provide a sustained benefit for Parkinson’s symptoms, it doesn’t stop PD from progressing.

Although symptoms can be fairly well controlled, with exercise and physical therapy playing an important role, living with Parkinson’s can be extremely frustrating and depression is common. Being a carer for a person who has PD can also be very difficult.

GARVAN – A WORLD CLASS CENTRE FOR PARKINSON’S RESEARCH

The Garvan Institute recently became one of the first in the world to acquire technology that can sequence a whole human genome at high throughput and low cost. This gives the Parkinson’s disease research teams an unparalleled ability to undertake whole genome sequencing of patient DNA and animal models of PD, vastly increasing our understanding and leading to better, safer, more effective personalised medicine.

Did you know?

- There are about 80,000 Australians living with Parkinson’s disease.
- Parkinson’s disease is usually diagnosed around the age of 65, but one in 10 will be diagnosed before they are 45.
- Men have a somewhat higher risk of developing Parkinson’s than women.
National and international collaborators

- Eskitis Institute, Griffith University, Queensland, Australia
- Flinders University, SA, Australia
- Harvard Medical School, Parkinson Personalized Medicine Program, Massachusetts, USA
- Oxford University, Oxford, UK
- Neuroscience Research Australia, NSW, Australia
- Stanford University, California, USA
- St Vincent’s Hospital, Neurology Department, NSW, Australia
- University of Saskatchewan, Saskatchewan, Canada
- University of Sydney, NSW, Australia
- UNSW School of Medicine, NSW, Australia
UNRAVELLING PARKINSON’S DISEASE

Research into Parkinson’s disease (PD) at Garvan is multifaceted, focusing on early PD and its causes, new neuroprotection therapies to prevent progression, brain regeneration and repair and, of course, prevention. Two groups led by Associate Professor Antony Cooper (Neurogenomics) and Dr Daniel Hesselson (Neuroprotection) conduct innovative research in these areas using unique but complementary approaches. In a partnership with Cure-Parkinsons Trust’s Linked Clinical Trials program, Garvan is committed to holding clinical trials to provide Australians with the opportunity to trial potential neuroprotective drugs that may slow or stop disease progression and the associated worsening and additional symptoms.

Catching Parkinson’s Early

Associate Professor Antony Cooper, Head of Garvan’s Neuroscience Division and of the Parkinson’s Disease and Neurogenomics Laboratory, is focused on finding the cause(s) of PD to enable significantly earlier diagnoses and identification of therapies that will halt PD progression.

“We are working towards a future where an individual diagnosed at the earliest stage of PD (years before experiencing symptoms), and who receives disease-modifying treatment, may never progress to having symptoms, effectively providing a cure,’ said Associate Professor Cooper.

Identifying the underlying mechanism(s) of PD is key to the discovery and development of what will be the first neuroprotective or disease-modifying treatments to halt, or even reverse, disease progression. Biomarkers – molecular changes that indicate disease status – are also needed for both early diagnosis and to test the effectiveness of drugs in clinical trials – including testing existing drugs repurposed for PD.

Associate Professor Cooper and his team have recently performed large-scale RNA sequencing and analysis at the Kinghorn Centre for Clinical Genomics, allowing them to identify important RNA changes in the brain cells of PD patients to discover the causes and early dysfunctions of PD. RNA is the messenger that transfers instructions from our genes (DNA) to enable each cell to perform its many functions. The complete set of RNA for a cell is called the ‘transcriptome’.

‘By comparing the RNA transcriptome of brain samples from PD patients to those from healthy individuals, we have identified which genes are incorrectly on or off in PD patients and at what stage during the disease course. Identifying early changes will determine what cellular pathways/functions are first disturbed in PD allowing us to identify treatments to restore these pathways and halt disease progression. This approach will also identify treatments to benefit patients already showing symptoms. The RNA transcripts identified as changing in the initial stages of the disease are also excellent potential PD biomarkers for early detection.

‘Our recent research with combinations of RNA molecules in blood is showing very high diagnostic success and we are now looking to confirm the applicability of these blood biomarkers in giving a diagnosis before PD symptoms present themselves.

‘Our analysis has identified specific RNA transcripts involved in cellular pathways not previously associated with PD. In particular, we have discovered an RNA molecule, ‘PARNA’, with genetic links to PD. PARNA regulates up to 50 genes, some of which are in cellular pathways known to fail in PD and it is expressed in PD patients’ brains at only 20 per cent of the normal level in healthy individuals.

‘Low levels of PARNA are observed in PD patients and restoring PARNA levels in cell models of PD saved the cells from death. If we can restore PARNA levels in the brains of PD patients, we may be able to rescue cells from PD damage.’

Associate Professor Antony Cooper
Head, Neuroscience Division
Head, Neurodegeneration & Neurogenomics Program
Repurposing existing drugs to halt progression

Dr Daniel Hesselson is Head of the Beta Cell Regeneration Laboratory in the Diabetes and Metabolism Division where he and his team are focused on complex diseases. His PD work is in the area of neuroprotection and the prevention of progression by repurposing existing clinical drugs. He and his team are also investigating why diabetes is linked to a higher risk of PD.

‘DNA sequencing technology is transforming the analysis of human disease and as whole genome sequencing has become significantly cheaper it has empowered new experimental strategies that were previously not feasible, including the discovery of genetic risk factors for PD,’ said Dr Hesselson.

‘The zebrafish was established as a developmental model in the 1990s and using targeted genomic engineering we have produced a zebrafish strain called pink1 which has a mutation known to cause early onset PD and which is extremely sensitive to any chemical changes in their environment. Their small size and the fact that they can take up drugs from the water they live in makes them ideal for ‘whole animal’ screening, which can be far more effective than just testing single proteins or cell types.

‘In addition, with next generation sequencing, we now have the capacity to identify new disease modifying genes that improve our ability to understand PD risk and that can be targeted with new or existing drugs.’

Bernard McGrath

In October 1999, when trying to complete an auction contract, real estate agent Bernard McGrath suddenly noticed that his handwriting had become tiny. He was only 42, his health had been good and there was no trace of Parkinson’s disease in his family.

While the diagnosis was distressing to Bernard and his wife, Liz, they and their two children continued on as usual for the next few years, but by mid-2004 Bernard’s disease had deteriorated drastically. ‘Liz would have to dress me as my tremor left me unable to do up buttons or tie my shoe laces,’ said Bernard.

Bernard’s medication began with Sinemet, then Cabaser followed by Stelivo, Sifrol and Madapar, but he suffered with side effects from dyskinesia to compulsive behaviour. The compulsive behaviour effects of Cabaser in particular had a devastating impact on Bernard’s finances, causing him to start a new business when he should have been scaling down his work activities.

‘I wouldn’t listen to anyone and started working stupid hours which only exacerbated my illness. In 2008 we sold the business at a cost.’

In May 2008 Bernard underwent Deep Brain Stimulation (DBS). ‘The results were extraordinary and I was back at work a month later, this time as an employee, and continued working until 2011 when I retired aged 54.’

Bernard and his family then moved to Berry where he started to paint. Although he had no formal training, Bernard found that he could create vivid canvases and that the activity was a great form of therapy for his Parkinson’s disease. He believes that DBS stimulated a part of his brain that has triggered this imaginative outflow.

‘These days generally I feel very well, except that my speech and walking are poor. Otherwise I am good.

‘Even though DBS which made such a huge difference for me is not attributable to the Garvan, without such research institutions, there would never be any progress. The Garvan is at the cutting-edge of Parkinson’s research internationally and it is only through this continued work that there will eventually be a cure, or in the meantime other forms of treatment.’
Glenda Reichman

Glenda Reichman was 39 years old when she was diagnosed with Parkinson’s Disease in 2004. She was running a business and leading a happy, healthy life with her husband and two boys.

‘I noticed that my fingers on my right hand were not moving properly, they were quite stiff. I had difficulty waving and brushing my teeth’, said Glenda. ‘My handwriting had also become quite small.’

Like many others, Glenda had no family history of the disease or any clues as to why she might have developed it. ‘The diagnosis was obviously a huge shock to all the family, but as it was only slowly progressing with mild symptoms, life carried on as normal.

‘I’ve been on various regimes of tablets, all the gold standard of therapy. But after some time I began to battle to balance the side effects of the dopamine with the effects of the disease.

‘When the tablets wore off I struggled with slowness and stiffness. At the right dose, I became agitated, fidgety and my facial features changed to the point I found it hard to be with people. My speech was affected as well.’

In mid-March 2016 Glenda decided the time was right for DBS surgery.

‘It is now five months’ post-op and there are so many things that I can do now that I struggled with before. I know I still have a road ahead to full recovery, but I would not go back to the way I was before for anything.’

Glenda has written an ebook I Can Dance on her journey with young onset PD and DBS surgery to encourage others with PD and to let people that there are options.

‘I know that the Garvan is doing everything possible to find a cure or better treatment for PD. My frustration is that when I was diagnosed 12 years ago, I held onto the hope that some sort of breakthrough would happen and change the course of my illness. Never did I think that I would need surgery. We need money, resources, and exposure to find breakthroughs now for this awful illness.’

Because PD is typically a late-onset disease with a large environmental risk component, it has been difficult to effectively model this disease in animals. Like adult-onset PD in humans, pink1 zebrafish don’t exhibit PD symptoms at a young age. However, when they were exposed to even small doses of pesticide for 24 hours, Dr Hesselson’s pink1s were unable to move, whereas normal fish were able to tolerate doses at least five times higher.

‘Using this model for the combined effects of genetics and the environment, we screened the clinical collection of the US National Institutes of Health, a library of some 800 small molecules that includes drugs with a known safety profile from human clinical trials, and identified five possible drugs that could provide neuron protection in PD and slow or halt progression.

‘Now additional studies using human cells have shown that the drugs we identified are only active in damaged cells, suggesting that it may be possible to specifically target vulnerable neurons, without having unwanted effects on healthy tissues.’

‘Substantial progress has been made towards identifying PD at early stages, before the movement problems begin, indicating that there could be opportunities to intervene with neuroprotective therapies before patients reach the debilitating late stages of the disease. ‘Importantly, focusing on drugs that are already in use significantly accelerates the translation to the clinic environment.’

‘We are now very excited about combining our PD and diabetes models to investigate the effects of uncontrolled blood sugar on neuron survival. Because there are now many options for treating diabetes, we hope to use this system to establish which drug is the best for reducing the risk of PD.’
Throughout its more than 50-year history, Garvan researchers have been responsible for significant breakthroughs that have improved our understanding and the lives of people living with some of the most common, yet complex diseases affecting society today.

These include:
- Pancreatic cancer
- Hearing loss
- Lupus
- Obesity
- Alzheimer’s disease
- Osteoporosis
- Parkinson’s disease
- Arthritis
- Asthma
- Breast cancer

We are currently in the midst of the genomic revolution – using the information contained in an individual’s DNA to understand the basis of human development, help evaluate the genetic risk of disease, predict outcomes, and determine the most effective treatments for that individual.

I am proud to say that Garvan is one of the leading institutes internationally in the development and application of new genomic technologies to understand human disease and its prevention and treatment. The acquisition of the most advanced sequencing technology in the world has positioned Garvan as the human genomics hub for Australia and the region. It allows massive increases in genome sequencing capacity, accelerating medical research across the spectrum to include cancer, osteoporosis, autoimmune diseases, diabetes and neurological diseases.

Given Garvan’s exceptional research talent, combined with its innovative use of leading-edge technology, I am excited by the potential of our work to deliver real benefits to this generation and those to come.

Professor John Mattick AO FAA
Executive Director
Garvan Institute of Medical Research

### WHY INVEST IN GARVAN’S PARKINSON’S DISEASE RESEARCH?

- **Find a way to diagnose PD before the damage is done**
- **Fast-track better treatments for PD**
- **Discover how to repair damaged brain cells**

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For information about how you can help Garvan's researchers unravel the puzzle of Parkinson's Disease, contact:

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Web: www.giving.garvan.org.au
Front cover images:
Top: Dopamine neuron staining in brain cells. Courtesy Dr Daniel Hesselson, Beta Cell Regeneration Laboratory, Garvan Institute of Medical Research.
Bottom left: Dr Yuxi Zhang working with the zebrafish involved in Parkinson’s disease research.