

Our research offers vital new insights into Parkinson's

We have some important new results to share from our largest ever project - **The Monument Discovery Award at the University of Oxford** - which is improving our understanding of Parkinson's and driving us closer to a cure.

A key part of the project is studying more than 750 people in the early stages of Parkinson's, alongside up to 300 brothers and sisters of those with the condition and 300 people without Parkinson's, across the Thames Valley.

The team is collecting huge amounts of information which has already helped them to uncover some vital new insights into this complex condition:

Important differences between men and women

For the first time, this study has highlighted important gender differences in Parkinson's:

- Men are more likely to experience problems with memory, postural hypotension (dizziness on standing) and sleep problems.
- Women tend to experience more problems with posture and balance.

Age matters

Older people with Parkinson's tend to experience more symptoms at an earlier stage in the condition.

These include mobility problems like tremor, stiffness and slowness, as well as non-motor symptoms like problems with memory and constipation.

Acting out dreams – a common early symptom

REM sleep behavior disorder, a condition which causes people to act out their dreams, is common in the early stages of Parkinson's. Having REM sleep behavior disorder is often associated with other non-motor symptoms and a reduced quality of life.

Spotting thinking and memory problems early

People with Parkinson's may experience thinking and memory problems at some stage during the condition but these can be subtle and difficult to identify, especially in the early stages.

This study shows that a test called the 'Montreal Cognitive Assessment' may be more sensitive than another common test – the mini-mental state exam (MMSE) for detecting early changes in thinking and memory in Parkinson's.

Building a better understanding of Parkinson's



Dr Michele Hu (above, left) is leading the study:

“This study is helping us to build a much more detailed picture of Parkinson's and how it develops from the earliest stages. It will help us understand why the condition varies so much between individuals and how it progresses. And this knowledge will ultimately help us to develop diagnostic tests and better treatments and therapies to help those living with Parkinson's and their families.”

Reference:

Szewczyk-Krolkowski K et al. **The influence of age and gender on motor and non-motor features of early Parkinson's disease: Initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort.** *Parkinsonism and related disorders*. 2013 ([Link](#))

Rolinski M et al. **REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease.** *Journal of Neurology, Neurosurgery & Psychiatry*. 2013 ([Link](#))

Hu M et al. **Predictors of cognitive impairment in an early stage Parkinson's disease cohort.** *Movement Disorders Journal*. 2013 ([Link](#))



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ABOUT OPDC

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“ After my visit to the OPDC I gained renewed hope that one day soon the crucial piece of soil in the Parkinson’s field will be lifted to reveal a cure for this devastating disease. ”



Dr Jonathan Stevens
Parkinson's sufferer
and blogger

Digging for a cure at the OPDC

Extracted from the blog by Dr Jonathan Stevens

The OPDC is an interdisciplinary research centre, which means that clinicians (investigating better ways to diagnose and treat Parkinson's), brain scientists (investigating the nerve cell networks that go wrong), cell biologists (investigating what goes wrong in cells) and, linking these approaches together, mouse geneticists (investigating Parkinson's in mice) are under one roof. This ensures the links between human patients and the knowledge generated from cells, nerve cell networks and model organisms is as close as possible. In other words, they are busying digging in multiple parts of the Parkinson's field and increasing the chances of finding that vital clue.

From skin cells to nerve cells – Induced Pluripotent Stem Cells (iPSCs)

Dr Wade-Martin's lab investigates cells and mouse models of Parkinson's. Researchers in the lab know enough to take skin cells from human patients and convert these into nerve cells, which are the same as those cells that go wrong in Parkinson's affected brains. Look at your skin...the **tissue that covers your body can be changed into nerve cells! Amazing!** These cells are incredibly valuable because they **contain all the genetic changes (known and unknown) that cause Parkinson's**. Therefore, understanding and treating what goes wrong in these nerve cells will give a more comprehensive view of what goes wrong in Parkinson's. Studies using these cells will be a huge leap forward in understanding and treating human patients.

The role of LRRK2 in autophagy

One of the genes known to cause Parkinson's is LRRK2. Sergey Brin, one of the founders of Google, has a mutation in this gene and therefore has an increased chance of developing Parkinson's. LRRK2 normally passes messages to other proteins in the cell and these proteins carrying out processes in the cell; LRRK2 is sort of the manager in a factory. In Sergey Brin's brain (and other affected by Parkinson's), LRRK2 becomes hyperactive and gives out messages to everyone, causing chaos; cells normally work by keeping calm and balanced.

LRRK2 has been implicated in a process called **autophagy**. Imagine the cell is a chemical factory, producing vital chemicals to make sure the cell functions properly. However, like a real chemical factory it produces waste products. Autophagy is the process whereby the cell cleans up after itself and chucks away the rubbish it generates.

Mutations in LRRK2 can disrupt the cleaning regime of the cell; eventually accumulated rubbish makes the cell become chaotic and it does not function properly. Eventually the cell begins to malfunction and it dies, therefore causing a reduction in dopamine levels and the symptoms of Parkinson's.

Work in the lab is trying to discover which part of autophagy LRRK2 controls; is it when the cell is preparing to clean (induction), getting the bin bags ready (autophagosome formation), picking up the rubbish (lysosome fusion) or throwing the bin bags away (autophagosome breakdown). This is important to know because it tells us which drugs to potentially use to correct the process.

Treating alpha-synuclein?

Another major gene implicated in Parkinson's is alpha synuclein; **alpha synuclein protein clumps together to form Lewy bodies in Parkinson's affected cells**. Dr Wade-Martins lab published some work this year (Janezic et al, *PNAS*) showing they created a mouse with three copies of the alpha synuclein gene (normally mice have one copy). This forces the cell to make 3x the amount of alpha synuclein protein; Lewy body formation (common in Parkinson's) is therefore more likely in these mice. Indeed these mice show symptoms of late-onset Parkinson's. There are humans who also have three copies of the alpha synuclein gene and develop Parkinson's. Members of the lab have been trying to use drugs to break up the Lewy bodies, prevent cell death and stop Parkinson's from developing. It is early days but this work demonstrates the benefit of having multiple specialists in the same research centre: cell work can lead to mouse work which can lead to testing drugs to stop what is happening in the cells of the mouse, and ultimately human sufferers.

Jonathan died over the Christmas holidays in 2013 before this article was published. He has been a passionate believer in spreading knowledge & awareness of Parkinson's.

Jonathan graduated from Oxford in 2012 with a DPhil in genetics & was diagnosed with early onset Parkinson's that year. He wrote a detailed online blog of living with Parkinson's: <http://dialoguewithdisability.blogspot.co.uk/>

Article about Jonathan published on York press: www.yorkpress.co.uk/news/10947224.Tributes_paid_to_Dr_Jonathan_Stevens_who_has_died_aged_34/?ref=twtr

Donations to Parkinson's UK in Jonathan's memory www.justgiving.com/inmemoryofjonathanstevens

Reference:

Stephanie Janezic et al. **Deficits in dopaminergic transmission precede neuron loss and dysfunction in a new Parkinson's model.** *Proc Natl Acad Sci USA*. 2013 ([Link](#))

TAKING PART:

Perspectives from 'healthy controls'

Many research studies invite people known as 'healthy controls' to take part so results can be compared with those of people living with the condition being studied.

Hubert Allen and Fraser Old are members of 'Friends of DeNDRoN', a NHS panel of patients, carers and members of the public interested in improving research into Parkinson's, dementias, and other neurological conditions. Friends of DeNDRoN offer their help and advice in a variety of ways to support local research activity and make studies more relevant to patients and carers.

Hubert and Fraser are both taking part in the Discovery study. They offer here some views on participation.

What is your interest in Parkinson's?

Hubert: "I cared for my wife who had dementia for more than 10 years. We desperately need a better understanding of the brain through research. It strikes me how little we know about the brain, when it's arguably the most important organ of all."

How has your experience of the research study been so far?

Fraser: "The doctor I saw was very approachable – he explained the background in detail. I then spent a pleasant hour with a research nurse completing assessments and doing manual dexterity tests. The whole experience was very smooth and interesting. I was even lucky enough to find a parking space!"

Why did you decide to take part in the Monument Discovery study?

Fraser: "My interest in Parkinson's is general. I understand that some researchers are moving towards a view that many neurological conditions are sub-sets of the same family. We do have a friend who lost a husband to Parkinson's. My main consideration was the time commitment, which in the case of the study was perfectly acceptable."

Hubert: "I am now in my 80s. I don't feel there is much I can do, but taking part in this study gives me the satisfaction of being of some help."



Dr Kieran Breen (left), Director of Research and Innovation at Parkinson's UK, explains why the Discovery study team is recruiting male controls:

"We have recruited enough men over forty with Parkinson's for the research, but now need to cross match with this particularly hard to reach group of men who may not normally consider volunteering in this way."

News in brief

➤ **Royal Institution Lecture :**
"Clinical Trials & Parkinson's: What does it take to find a cure?"

Dr Richard Wade-Martins gave a lecture on clinical trials and their impact at the event organised by Parkinson's UK at the world famous Royal Institution on Wednesday 20 November 2013. Watch his lecture on Parkinson's UK youtube channel at:
<http://bit.ly/1gp7R1Z>

➤ **Parkinson's UK Oxford Walk**

The OPDC team took part and raised over £800 for the Oxford Walk organised by the Oxford Branch, Parkinson's UK on Sunday, 27 October 2013.



Funds raised will go towards supporting the work at OPDC in investigating a cure for Parkinson's.

➤ **Oxford Parkinson's Open Afternoon**

Drs Michele Hu, Elizabeth Hartfield, Stephanie Cragg and Richard Wade-Martins gave talks at the Public Open Afternoon on Thursday, 17 October 2013, covering the multidisciplinary research undertaken at the Oxford Parkinson's Disease Centre.

➤ **BBC Interview: Hope for Parkinson's**

Dr Sarah Threlfell was interviewed by the BBC News about her Parkinson's UK-funded optogenetics work. This work focused on studying how genetically engineered nerve cells respond to light and why they stop working as Parkinson's disease progresses was featured on BBC South News on 16 April 2013.



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New International/EU Research Projects

EU Human Brain Project (HBP)

Professor Chris Ponting is the Principal Investigator in sub-projects on mouse brain data and management. HBP is a 10-year, large-scale European research initiative, currently funded by EU 7th Framework Programme, to understand the human brain and its diseases & ultimately to emulate its computational capabilities.

EU NoTremor Project

Dr Michele Hu is the Co-Principal Investigator for the EU STREP Award project which aims to provide patient specific computational models of the coupled brain & neuromuscular systems which will be subsequently used to improve the quality of analysis, prediction & progression of Parkinson's disease

EU StemBANCC

Drs Sally Cowley and Richard Wade-Martins lead Work Packages 4 and 8 respectively in this 5-year research programme funded by the EU Innovative Medicines Initiative (IMI) with contributions from industry partners across 11 countries. The objective of this programme is to develop human induced pluripotent stem cells as a platform for cellular phenotypic drug screening in drug discovery.

Wellcome Trust New Investigator Award

Dr Peter Magill has won a prestigious Wellcome Trust New Investigator Award for research designed to explain how different types of nerve cell in the basal ganglia (a brain region severely affected in Parkinson's) control voluntary movement.

TAKING PART (continued from page 3)

If you are a man over 40 without Parkinson's, we would like to hear from you.



The research team is looking for men over the age of 40 who:

- do not have Parkinson's or another neurodegenerative condition
- do not have any biological relatives with Parkinson's

Taking part involves visiting the nearest clinic for a simple blood test and a range of assessments of sense of smell, thinking and memory and mobility. The research team will monitor participants through brief phone calls every eighteen months during the 5 year study.

Getting involved will help our researchers towards the development of tests that can diagnose the condition before symptoms appear, and lead us ever closer to a cure.

The study is running at clinics in 11 different sites across the Thames Valley region, including Amersham, Ascot, Aylesbury, Banbury, Henley, Kettering, Milton Keynes, Newbury, Northampton, Oxford and Reading.

If you interested in taking part please call the team at Oxford on **01865 234892** or email Parkinsons.Discovery@nhs.net

Find out more:



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Information on all our current research activities can be found on our website www.opdc.ox.ac.uk and in the 'Monument Discovery Project' section of Parkinson's UK website www.parkinsons.org.uk/content/monument-discovery-project



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