NEWSLETTER

Issue 6, Autumn 2015

Oxford Parkinson's Disease Centre

National Institute for Health Research
Clinical Research Network Thames Valley and South Midlands

Oxford Biomedical Research Centre
Enabling translational research through partnership

Funded by PARKINSON'S UK
CHANGE ATTITUDES. FIND A CURE. JOIN US.

Discovery Cohort Update: October 2015

Clinical OPDC team: *Top row L-R: Samuel Evetts, Anita Foster, Taryn Talbott, Fahd Baig, Claudio Ruffman, Michal Rolinski, Christine Parker*
Bottom row L-R: Research volunteer, Michele Hu, Liz Templeman

Since September 2010, a total of 1,076 people with Parkinson's, 297 control subjects, 107 relatives of people with Parkinson's, and 99 people with rapid-eye movement sleep behaviour disorder (RBD) have been recruited to the Discovery cohort. This incredible number reflects the willingness and generosity of participants to get involved and support the study across the Thames Valley, underlining its importance in tackling Parkinson's. Because of your involvement, the cohort is now making a world-leading contribution to research aimed at:

1. Predicting the onset of Parkinson's in at-risk individuals;
2. Improving the accuracy of earlier diagnosis;
3. Predicting and measuring progression on an individual basis following diagnosis.

A high point in 2015 was securing funding from Parkinson's UK to continue to follow up the cohort over the next 5 years. This funding reflects the key significance our international reviewers placed on the cohort and its central role in tackling Parkinson's. ***Continued overleaf.***

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UNIVERSITY OF OXFORD

ABOUT OPDC

Website: www.opdc.ox.ac.uk

Phone: 01865 282358

Email: opdc.administrator@dpag.ox.ac.uk

Twitter: @OxfordPDcentre

To contact the research team:

Tel: 01865 234892

Email: Parkinsons.Discovery@nhs.net

Moving forward, as of October 2015 we will no longer be recruiting new people with Parkinson's to the study. Instead, we will focus on how Parkinson's develops over time through our 18 month follow-up visits in the 1,076 individuals so far recruited. The information we collect will be critical to understanding why individuals progress at different rates and respond to medications differently. **The longer each person with Parkinson's can stay in our study, the more valuable the data we collect, and the more meaningful the conclusions we can draw.** This is because we can go back and look at both the clinical information as well as test markers in blood samples to see which factors predict how the disease changes over time. **The value of this research is far greater if we can maintain a high follow-up rate.**

I would really encourage participants to continue to attend the 18 monthly follow up visits over the next 5 years, as the information we collect will be critical for our research aims. We appreciate that coming to clinics can be difficult, so we will also be offering the option of telephone visits for those unable to attend clinic visits. This will allow us to collect some of the data but is obviously less valuable than a clinic visit where we can collect more detailed information. We also realise that individuals and their families may change where they live over time. We would be very grateful if you could let us know new contact details if you relocate as otherwise we won't be able to keep in touch.

We will continue to recruit and follow-up individuals with RBD sleep problems to the cohort over the next 5 years, as we believe this group is key to furthering our understanding of the earliest changes leading to Parkinson's. Relatives of individuals with Parkinson's will also be followed up, and control participants will be asked if they are willing to attend clinic for a second visit when convenient over the next few years. **Thank you all once again for your tremendous support.** The research team and I look forward to working with you over the next 5 years of this exciting endeavour!

Dr Michele Hu, Discovery Cohort Lead

"The longer each person with Parkinson's can stay in our study, the more valuable the data we collect, and the more meaningful the conclusions we can draw... The value of this research is far greater if we can maintain a high follow-up rate... I would really encourage participants to continue to attend the 18 monthly follow up visits over the next 5 years, as the information we collect will be critical for our research aims... Thank you all once again for your tremendous support".

Dr Michele Hu

Research Participant Perspective

Cathi Grainger lives in Great Kingshill, Buckinghamshire and was diagnosed with Parkinson's disease in 2012. Cathi is very passionate about finding a cure for Parkinson's, and a few months after her diagnosis became a research participant, along with her husband who is a control subject. Cathi has so far taken part in two of the three sessions and sees how our longitudinal study will help us monitor how Parkinson's develops over time.

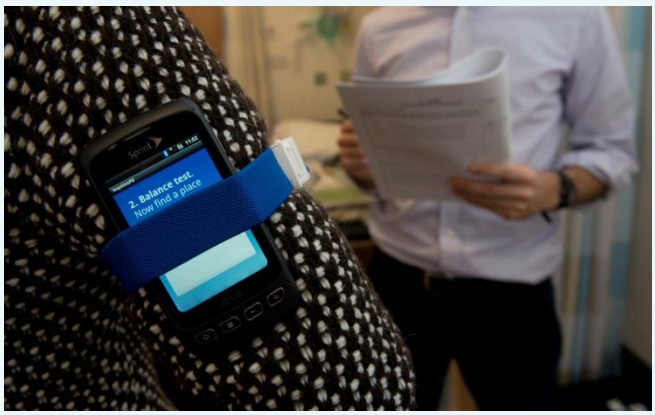
Why did you take part in the Monument Discovery Study?

"It was an opportunity for me to ask questions to find out more about this disease and how I could help myself."

What has been your experience of the study so far?

"The tests were all done in a very relaxed way with my approval to continue sought at each stage, so I didn't feel under any pressure. Between the two study sessions I gave up work and was able to exercise more, spend time with the local support group and attend various classes to improve my wellbeing. I noticed an improvement in several of the tests on the second study which gave me great pleasure, as I felt that I was being proactive for my own good and that what I was doing was working."

Why are you eager to continue supporting the study?



"I think this study asks all the right questions and takes all the necessary tests to build an enormous database of information for researchers. This disease is wide-ranging in its symptoms with sufferers being diagnosed at different stages and different degrees of degeneration – all of which make it difficult to analyse. The longitudinal nature of the study will continue to add information on the development of the disease and can improve data that is currently available.

The study has also developed, for example, it now uses modern technology – in the first study, the rate of tremor was made as a visual assessment, whereas now it is measured by smartphone to increase accuracy."

Is there anything you would like to say to encourage other participants?

"I would hope that those involved in the study will make it a priority to continue with it as their information is vital to building up the data needed to find a cure, see how different drugs work and examine their side effects."

"I think this study asks all the right questions and takes all the necessary tests to build an enormous database of information for researchers. … I would hope that those involved in the study will make it a priority to continue with it as their information is vital to building up the data needed to find a cure".

Cathi Grainger, Monument Discovery Project Participant

Update: Recent OPDC publications

OPDC investigates the non-motor or 'invisible' symptoms of Parkinson's disease

Too much focus on tremor may be leaving people with Parkinson's under-treated for non-motor symptoms like depression, sleep problems and pain. Studies have shown that these symptoms are common in established Parkinson's, but far less is known about the early and pre-motor phases.

We looked at more than 750 people in our cohort recently diagnosed with Parkinson's and found that 99% had at least one 'non-motor' symptom, and many suffered five or more. A number of these symptoms were apparently untreated, despite the availability of effective treatments. For example, only one quarter of people with Parkinson's and significant depression were being treated with medication.

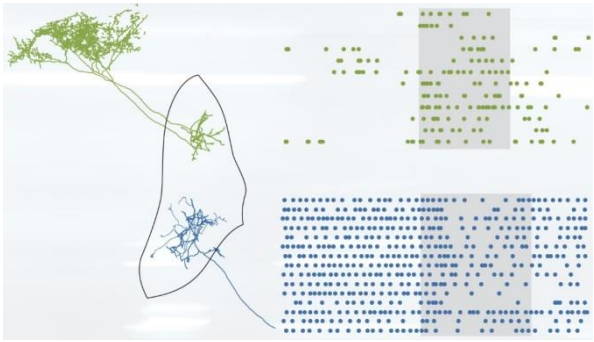
We found that pain, depression, anxiety and fatigue had the largest impact, and that overall these non-motor symptoms impacted quality of life more than tremor and movement problems. Careful characterisation of these features, which we have now published in the Movement Disorders Journal, could improve clinical care and better our understanding of the disease.

Reference: Fahd Baig *et al*., (2015) Delineating nonmotor symptoms in early Parkinson's disease and first-degree relatives. Movement Disorders, in press.
http://www.ncbi.nlm.nih.gov/pubmed/26179331

OPDC scientists map the origins and activities of neurons important for movement

Neurons in a brain region called the external globus pallidus (GPe) are essential for proper movement. To fully understand the movement difficulties of people with Parkinson's disease, it is important to define the code of electrical impulses used by GPe neurons in the healthy brain.

We have discovered that the electrical activities of two types of GPe neuron signal movement, but the patterns of their impulses are strikingly different. To examine potential causes for these differences, our researchers traced the embryonic origins of the two cell types and found that they are generated in different parts of the developing brain. These findings demonstrate how the origins of different types of neurons shape their function in the adult brain, and provide important new clues as to how inappropriate signalling of these cells in Parkinson's disease might result in movement difficulties.



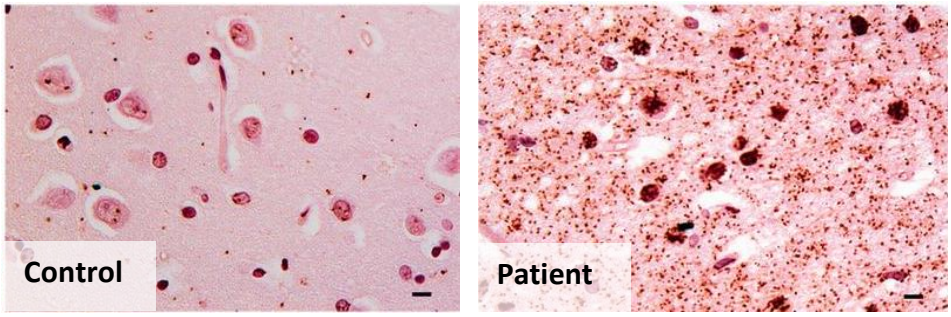
The OPDC has discovered divergences in the way that different types of neurons signal movement.

Reference: Paul Dodson *et al*., (2015) Distinct Developmental Origins Manifest in the Specialized Encoding of Movement by Adult Neurons of the External Globus Pallidus. Neuron 86, p501–513.
http://www.ncbi.nlm.nih.gov/pubmed/25843402

OPDC develops new method to look for biomarkers of Parkinson's

The OPDC aims to understand the earliest events in the brain that lead to the development of Parkinson's disease. We have made exciting discoveries about the role of alpha-synuclein oligomers in Parkinson's in a study of post-mortem brain tissue from people with Parkinson's disease and healthy controls.

During the development of Parkinson's, the protein alpha-synuclein begins to function abnormally and clumps together to form small clusters, known as oligomers. Oligomers are present at the early stages of the disease and are thought to cause damage to neurons which results in their degeneration. The oligomers can further cluster and compact together to form Lewy bodies, which are associated with the late stages of Parkinson's. Our understanding of how alpha-synuclein oligomers cause Parkinson's has been hindered by the absence of a technique to detect the oligomers.



AS-PLA staining in post-mortem brain sections

We have developed a new technique called the alpha-synuclein proximity ligation assay (AS-PLA), which specifically detects alpha-synuclein oligomers. For the first time, we have shown in post-mortem Parkinson's disease brain tissue that alpha-synuclein oligomers are located in brain regions that do not have Lewy bodies, a late sign of the disease. This suggests that using the AS-PLA technique will allow us to detect earlier signs of Parkinson's in the brain. Alpha-synuclein oligomers therefore represent a promising biomarker of Parkinson's and we are currently investigating the association between alpha-synuclein oligomers in other tissues and the early stages of Parkinson's.

Reference: Rosalind Roberts *et al*. (2015) Direct visualization of alpha-synuclein oligomers reveals previously undetected pathology in Parkinson's disease brain. Brain 138: 1642-1657.
http://www.ncbi.nlm.nih.gov/pubmed/25732184

News in brief

Oxford Fun Run for Parkinson's UK

In May, OPDC researchers took part in the 5km Oxford Fun Run, in Oxford University Parks. The team ran in support of Parkinson's UK and were also joined by a great team from Masud Husain's lab. Chair of the Oxford Parkinson's UK branch, Sally Bromley, also led a team round the course who between them exceeded the 5 km race course winning a special achievement trophy for their impressive effort.

Team OPDC

Oxford Walk for Parkinson's

On Sunday 25th October 2015, a team of 20 OPDC researchers and supporters took part in the Oxford Walk for Parkinson's, organised by Parkinson's UK. The walk was started by Principal Investigators Richard Wade-Martins and Michele Hu and completed by Parkinson's UK supporters to raise money to support our research at the OPDC. We would like to thank everyone who completed the walk and raised money to fund our research.

Team OPDC

Parkinson's UK visit OPDC members to discuss the use of animals in research

OPDC members Paul Bolam, Peter Magill and Paul Dodson recently hosted a group of staff and lay members of Parkinson's UK who have a particular interest in the use of animals in biomedical research. The visit took place at the Medical Research Council Brain Network Dynamics Unit (MRC BNDU), and was co-organised by Paul Bolam and Claire Bale, Head of Research Communications and Engagement at the charity.

The visit began with Peter Brown (MRC BNDU Director) and Peter Magill highlighting how research using animals has advanced research into, and treatments for, Parkinson's disease, as well as some other benefits arising from the mutual exchange of ideas and discoveries made in the clinical and "basic" research fields. The open discussion session then focused on why, how and when animals are used in Parkinson's research and, more generally, how animal use in scientific procedures is regulated in the UK.

During a tour of the MRC BNDU, led by OPDC Senior Research Fellow Paul Dodson and early-career scientists, the visitors were shown new results from work in animals on the structure and function of dopamine-releasing nerve cells, which are especially vulnerable in Parkinson's. The visitors were also shown mouse models of Parkinson's disease that were generated at the OPDC.

OPDC scientists and members of Parkinson's UK discuss the use of animals in biomedical research.

The Parkinson's UK Brain Bank

Join our Parkinson's UK Brain Donor Register and help us to find a cure and improve life for everyone affected by Parkinson's.

Studying human brain tissue is an essential part of Parkinson's research to understand the condition and develop new and better treatments. But this work is completely dependent upon the generosity of people with and without Parkinson's who pledge their brains to research.

To find out more about the Parkinson's UK Brain Bank or to request an information pack:

Visit www.parkinsons.org.uk/brainbank

Call 020 7594 9732

Email brainbank@imperial.ac.uk

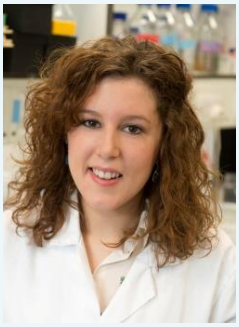
OPDC scientists update Parkinson's UK members of current research

Throughout October, OPDC scientists presented an update of the research taking place within the centre at forums across England, organised by Parkinson's UK.

Dr Caleb Webber is an OPDC Investigator and presented a talk entitled **"How can skin cells help us find therapeutics for Parkinson's?"** at The Gateway Conference Centre in Aylesbury on the 8th October. Caleb presented some exciting work taking place in the OPDC of developing neuronal models of Parkinson's disease that are made from induced pluripotent stem cells, which are derived from patient skin samples. Caleb explained how this research is helping us both to understand the disease and to identify new potential therapeutics.

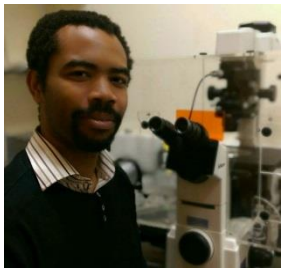
Professor Paul Bolam is an OPDC Investigator and presented at The Hilt in Chandler's Ford on the 14th October. Paul presented an overview of the research that is taking place at the OPDC.

Dr Laura Parkkinen is an OPDC Senior Research Fellow and presented at The Dunchurch Park Hotel in Rugby on the 20th October. Laura gave an overview of the research at OPDC and then focused on the neuropathology branch of OPDC research, which Laura leads. Laura spoke about the biomarker research taking place in our centre, where we are trying to develop new techniques that allow us to measure pathological protein species in gut samples, cerebrospinal fluid and nasal brushings. She also spoke about the importance of examining risk genes in human brains and the need for brain tissue donations. Identifying Parkinson's risk genes and biomarkers will ultimately allow us to detect Parkinson's earlier, when treatments might be more effective.

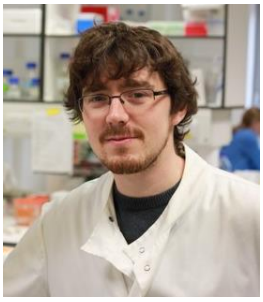


Dr Natalie Connor-Robson is an OPDC Career Development Fellow and presented a talk entitled "**Modelling Parkinson's**" at The Ark Centre in Basingstoke on 23rd October. Natalie spoke about the OPDC's induced pluripotent stem cell models and how we are using them to identify early changes that happen in Parkinson's disease cells. Natalie also explained how we use our animal models and aim to identify new drug targets by using a combination of both stem cell research and rodent models.

OPDC welcomes new Career Development Fellows



Dr Dayne Beccano-Kelly is investigating the cellular mechanisms of Parkinson's. Dayne uses a combination of novel techniques. This involves the use of stem cells, where neurons are generated from skin samples that have been generously donated by participants of the OPDC Discovery Cohort; electrophysiology to assess the electrical cross-talk between neurons; and molecular biology to investigate how communication differs between Parkinson's disease neurons and healthy control neurons.



Dr Brent Ryan focusses on identifying the changes in neurons that occur early on in Parkinson's and develops assays to measure these changes. Brent uses dopamine neurons (generated from stem cells) and both genetic and toxin models of Parkinson's to investigate how biochemical processes, such as energy production, are altered. These changes can be used as the basis for high-throughput screens to identify drugs to correct alterations in neurons and treat Parkinson's.

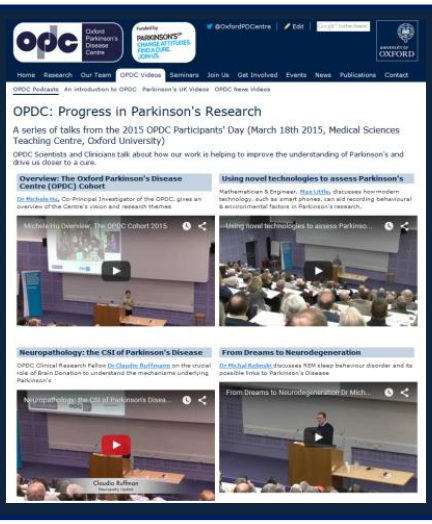
Dr Siddharth Arora is investigating the efficacy and feasibility of remote technologies for detecting and monitoring the symptoms of Parkinson's disease. Siddharth's work involves developing mathematical algorithms to analyse data for motor and non-motor symptoms collected via smartphones. The aim of his study is to develop remote, non-invasive and objective tests that can be used to support expert diagnosis.

OPDC Podcasts: Progress in Parkinson's Research

A series of talks from the OPDC Participants' Day (18th March 2015) held at the University of Oxford are available online.

OPDC scientists and clinicians talk about how our work is helping to improve our understanding of Parkinson's and drive us closer to a cure.

www.opdc.ox.ac.uk/opdc-podcasts



Find out more:

Information on all our current research activities can be found on our website **www.opdc.ox.ac.uk** and in the 'OPDC' section of Parkinson's UK website **http://www.parkinsons.org.uk/content/oxford-parkinsons-disease-centre**

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THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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