NEWSLETTER

Issue 7, Summer 2016

Oxford Parkinson's Disease Centre
National Institute for Health Research
Clinical Research Network Thames Valley and South Midlands
Funded by PARKINSON'S UK
CHANGE ATTITUDES. FIND A CURE. JOIN US.
Oxford Biomedical Research Centre
Enabling translational research through partnership

Discovery Cohort Update

Recruitment into the Discovery cohort continues to grow and up to May 2016 we have recruited 1,087 people with Parkinson's, 301 control subjects, 111 relatives of Parkinson's, and 133 people with rapid-eye movement sleep behaviour disorder (RBD). We have estimated that the total man/woman hours involved in seeing over 1600 participants for a single study visit (Participant, Nurse, Doctor, Administrator) is a **staggering 29,000 hours!** This incredible figure reflects the willingness and generosity of participants and researchers to get involved and support this study across the Thames Valley. **Thank You!** As a result of this colossal effort, the OPDC successfully obtained £5 Million in renewal funding in 2015, securing regular 18 monthly follow ups of the cohort until 2020.

Due to this additional funding award, we have managed to expand our dedicated Discovery Cohort support team, and would like to introduce several new key members. Jane Philips and Amandine Louvel started working with us full-time this year as research co-ordinator and administrator respectively, and have done an excellent job so far. Our new Clinical Fellow Dr Tom Barber started in February, and will be focusing on the REM sleep patients. Dr Shama Fernando started work this month as our new part-time project manager. Dr Fahd Baig and Claudio Ruffmann continue to do excellent work as Clinical Fellows, but sadly, will be leaving us in August, having completed their 3-year study period. Drs. Johannes Klein and Ludo Griffanti will continue to look after participants having an MRI brain scan and related MRI analysis. Sam Evetts capably manages the biobank in our lab, which houses in excess of 9000 specimens.


Claudio


Fahd


Tom


Johannes


Ludovica


Jane


Amandine


Sam


Shama

CONTENTS

ABOUT OPDC

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As we stopped recruiting more people with Parkinson's into the cohort last October, a crucial focus will be to make every effort to follow up all the enrolled individuals over the next 5 years of the study. We understand that some of you may no longer be able to attend clinic due to various reasons. Therefore, we have introduced the option of a **telephone visit instead of the clinic visit**, which can be completed with a family member, carer, or friend from your home or nursing home. We would encourage you to consider this option if a clinic visit becomes too difficult. We look forward to continue working with you over the next 5 years of this exciting project!

Dr Michele Hu, Discovery Cohort Lead

Dr Michele Hu

OPDC welcomes new researchers

Dr Robert Westphal (Career Development Fellow) is using neuroimaging technologies on genetically modified Parkinson's disease rodent models that were designed at University of Oxford to recapitulate the early stage of Parkinson's. Integrating these results with findings in human Parkinson's allows us to greatly refine the models we study and use them to probe disease mechanisms that are directly relevant to people with Parkinson's.

Dr Thomas Barber (Clinical Research Fellow) is investigating REM Sleep Behaviour Disorder (RBD), a condition that could be a precursor of Parkinson's. His work combines information from clinic assessments with new brain imaging techniques in order to understand the underlying mechanisms of RBD and identify markers that predict whether people will go on to develop Parkinson's in the future. Tom is also working on the development of new wearable devices that can facilitate diagnosis of RBD by detecting the symptoms in people's own homes.

Dr Jimena Monzon Sandoval (Career Development Fellow) is a computational biologist and is focusing on analysing large scale sequencing data generated from tissues and cells of people with Parkinson's, as well as from cellular and animal models of the disease. The main aim of Jimena's research is to guide further experiments to better understand and treat the disease. Jimena has a particular interest in coexpression changes that occur in Parkinson's and other neurodegenerative diseases.

Research Participant Perspective

Jenni Moss has taken part in the Monument Discovery Study since 2012. Jenni's brother was diagnosed with early-onset Parkinson's at the age of 37. Since then, Jenni has been passionate about contributing to Parkinson's research and decided to take part in the Monument Discovery Study as a sibling participant.

Jenni Moss, Monument Discovery Project Participant

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

"My brother had recently been diagnosed with early-onset Parkinson's which came as quite a shock to me; I hadn't expected it at all and I was dealing with a variety of emotions. I didn't know a huge amount about Parkinson's, particularly early-onset Parkinson's and so I was doing as much research as I could. A month after his diagnosis I was reading The Parkinson Magazine when I came across an article on the study. It immediately appealed to me because I had wanted to do something positive but I wasn't sure what. As this study was specifically looking for siblings it seemed like a brilliant opportunity to get involved with something practical that would hopefully have longer term benefits for my brother and all those diagnosed."

What has been your experience of the study so far?

"My experience has been really positive. I've found all the team involved really friendly, informative and engaging. The assessments have given me a great insight into some of the tests that my brother undertakes at his regular check-ups. Every step of the way the tests and the communication with me have been undertaken professionally and with a full insight as to what's involved. I've also learnt about some of the side-effects of drugs and elements of Parkinson's that I wouldn't have otherwise been aware of. It's been great to get updates on the study through the newsletters and my assessment visits and to see that my small part in the study is helping to build a bigger picture."

What do you hope to get out of your participation in the study?

"I've already got a lot out of it personally through understanding Parkinson's better and the knowledge that by simply giving up a couple of hours for assessments I can help the study reach its goals. On a broader scale I hope that my participation helps wider medical research into Parkinson's; the more we can learn about Parkinson's, the better, for those already diagnosed and those that will be in the future. Hopefully one day a cure will be discovered."

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

"Get involved - this is not a time consuming or invasive research study for participants and the more people that help then the better the results will be."

Leaving a gift in your will to OPDC

At the OPDC, we are working hard to understand Parkinson's and to develop new treatments. As we look to the future, we want to ensure that our work is sustainable, and that it can continue for years to come.

A Legacy gift will help the OPDC to continue vital research programmes, to find a cure and to improve the lives of everyone affected by Parkinson's. Large or small, your support will really make a difference to our work.

If you would like to know more about leaving a gift to the OPDC in your will, please contact our administrator Melanie Witt on **01865 282358** or **opdc.administrator@dpag.ox.ac.uk**

www.opdc.ox.ac.uk/giving

OPDC featured on BBC One

Paul Mayhew-Archer, one of the writers of Mrs Brown's Boys and The Vicar of Dibley, was diagnosed with Parkinson's disease five years ago. Paul has recently been involved in making an Inside Out programme on Parkinson's disease and has been on a quest to find out what is being done to develop treatments. In the last few months, Paul has visited the OPDC with a film crew to find out about our research.

On Saturday 5th March 2016, Paul visited BBC One Saturday Breakfast News to promote the Inside Out special, 'Parkinson's: The Funny Side', which was shown on BBC One on Monday 7th March and Wednesday 20th April. Paul was joined by Professor Richard Wade-Martins, Principal Investigator of the OPDC, who talked about our research using stem cell technology to grow and study dopamine neurons from skin cells. The skin cells are taken by simple biopsy from people with Parkinson's in our cohort to identify potential targets for treatments.

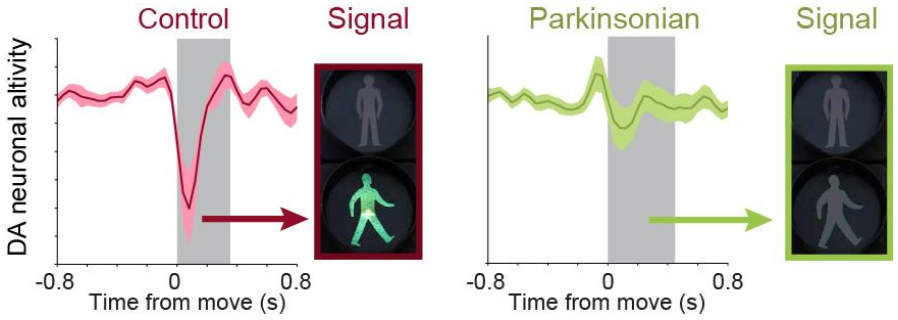
The programme also featured Dr Fahd Baig, OPDC Clinical Research Fellow, talking to Paul about the phone app that is used in our large Discovery Cohort Study. Researchers in our centre are using a smartphone app to understand how Parkinson's develops over time by collecting data on the progression of patients' symptoms. The app uses seven different tests to measure voice, balance, walking gait, dexterity, reaction time, resting tremor, and postural tremor. This data collected from the phone app is furthering our understanding as to how Parkinson's disease develops over time and affects people in different ways. In the future, it could be used to supplement clinical work by helping doctors to monitor patients' progress more accurately.

Top left: Professor Richard Wade-Martins and Paul Mayhew-Archer visited BBC One Saturday Breakfast News to promote the Inside Out special aired on BBC One. Top right: Paul visits one of the OPDC laboratories. Bottom left: OPDC Clinical Research Fellow Dr Fahd Baig talks with Paul about how a phone app is helping our research at the OPDC. Bottom right: Paul and Richard view dopamine cells generated from participants' skin cells under the microscope.

Update: Recent OPDC publications

Dopamine nerve cells pause to signal movement

Movement problems in Parkinson's arise when brain nerve cells releasing the signalling chemical dopamine stop working properly and die. Exactly how dopamine-releasing nerve cells control movement, and how their activity might be disturbed well before their death in disease, are unknown. To address these key issues, Paul Dodson and colleagues at the MRC Brain Network Dynamics Unit and OPDC recorded the electrical activity of dopamine nerve cells in mice on a running wheel. They discovered that the activity of a specific type of dopamine cell decreased ('paused') when normal mice began to move, compared to when the animals rested. However, in a genetic mouse model of Parkinson's, the dopamine cells did not pause their activity, suggesting this pattern helps with movement precision. This research gives the first detailed insights into how the precisely-timed electrical and chemical signalling of dopamine brain cells is altered in early Parkinson's, with important implications for therapies aiming to correct nerve cell function in disease.



A pause in activity of dopamine nerve cells in control mice signals the onset of movement. This signal is lost in Parkinsonian mice.

Reference: Paul Dodson *et al.* (2016) Representation of spontaneous movement by dopaminergic neurons is cell-type selective and disrupted in parkinsonism. PNAS 113, E2180–E2188. http://www.ncbi.nlm.nih.gov/pubmed/27001837

Parkinson's model shows progressive motor impairment and changes to normal dopamine function

Changes in the LRRK2 gene are known to be one of the greatest genetic contributors to Parkinson's. We created rat models with the forms of LRRK2 found in people with Parkinson's in order to characterise the changes that occur in the early stages.

We found that rats that had these LRRK2 genes had clear motor and cognitive impairment, and this only occurred in aged rats and not young rats. This motor impairment was corrected using L-DOPA, the current standard treatment for Parkinson's. We also demonstrated that in aged LRRK2 rats there was a reduction in the release of dopamine, the key neurotransmitter that is depleted in Parkinson's. This was accompanied by changes in the electrical signalling of dopamine producing nerve-cells in the brain. All of these changes occurred in the absence of cell loss in the substantia nigra, a key region of the brain affected in Parkinson's. This suggests that the early changes that occur in Parkinson's centre around dopamine dysfunction which happens prior to the cell loss that is seen in the later stages of the disease.

Reference: Max Sloan *et al.* (2016) LRRK2 BAC transgenic rats develop progressive, L-DOPA-responsive motor impairment, and deficits in dopamine circuit function. Human Molecular Genetics 25, p951-963. http://www.ncbi.nlm.nih.gov/pubmed/26744332

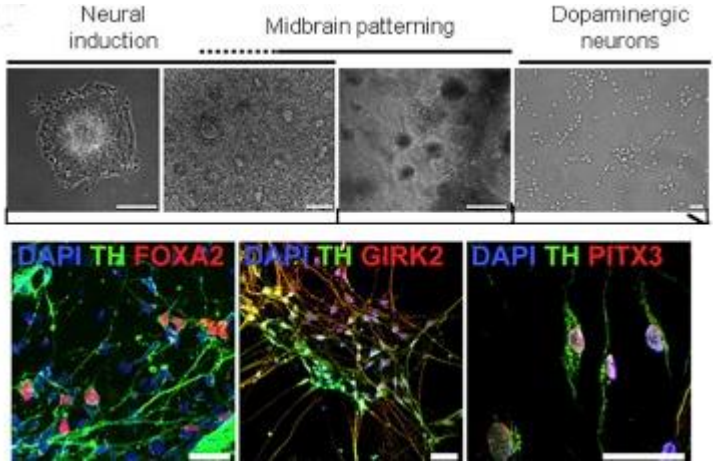
Modelling Parkinson's in a dish using patient derived neurons

A major limitation for research in our field is that the brain cells most affected in people with Parkinson's (dopamine neurons) are deep inside the brain and are not accessible while a person is alive. To overcome this, we make use of a recently developed technology (induced pluripotent stem cells - iPSCs) that allows us to grow dopamine producing neurons in a dish via the skin cells kindly donated by our participants in skin biopsies.

One of the most common genetic risk factors for Parkinson's is a mutation in a gene called GBA, yet the reasons for this are poorly understood. In this study we generated dopamine neurons from multiple OPDC participants carrying GBA mutations, which were compared to neurons derived from participants without Parkinson's.

We found that neurons from those with GBA mutations had altered levels of several key proteins involved in important cell clearance and cell stress mechanisms, which might be relevant for Parkinson's.

Overall, these neurons grown in a dish offer a unique insight into the early dysfunction in Parkinson's, and might offer new possibilities for therapeutic screens.



Images showing dopamine neurons grown in the lab.

Reference: Hugo Fernandes et al. (2016) ER Stress and Autophagic Perturbations Lead to Elevated Extracellular α-Synuclein in GBA-N370S Parkinson's iPSC-Derived Dopamine Neurons. Stem Cell Reports 6, p342-356. http://www.ncbi.nlm.nih.gov/pubmed/26905200

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

Discovery Participant raises money for the OPDC and Parkinson's UK

In February 2016, Monique Warham completed an amazing fundraising challenge – having her hair shaved to raise money for Parkinson's research and to support those living with the condition.

In September 2014, Monique was officially diagnosed with Parkinson's. Monique said: "It was a shock and the treatment hit me hard as well as having to give up my job which I loved. It is still a shock and it is still hard but we never give up on living."

"I am sure that thanks to this campaign, a few more people will be sympathetic of our situation… Too many people misunderstand this condition.

"We live with it and we might be a little wobbly, speak and walk slowly, and sometimes have the shakes but we never lose our sense of humour!"

Monique raised over £3000, with half of it donated towards funding the clinical theme of research at the OPDC and the other half donated to Parkinson's UK. Well done Monique!

Peter's Parkinson's Pilgrimage

A participant from the Monument Discovery Project, Peter Charles, who has been taking part in our research study for the last four years, is currently doing an incredible fundraising walk totalling more than 1,500 miles.

Peter aims to raise £250,000 for Parkinson's UK, which will be split 90% towards finding a cure for Parkinson's and 10% for respite care. The pilgrimage started on Sunday 14 February from St John the Baptist, Little Missenden, Buckinghamshire and will finish around the end of October. Peter has walked 260 miles from Little Missenden across the south of England to Cornwall. After a Ferry to Roscoff, he is walking more than 700 miles down the west side of France to the Pyrenees. At the time of writing, Peter has completed over 620 miles of his 1500 mile walking challenge. In Spain, Peter will take the Camino del Norte coastal route, which will take him more than 500 miles to his destination at Santiago de Compostela. Peter aims to walk an average of 10 miles a day.

Peter is 70 years of age and has had Parkinson's for 6 years. If you would like to support him in this huge challenge or follow his progress you can visit his branch webpage:
http://www.parkinsonsahw.org.uk/peterspilgrimage/

OPDC Discovery Participants' Open Day

On the 6th May, we held our annual OPDC Discovery Participants' Open Day at the John Radcliffe Hospital, Oxford. OPDC scientists and clinicians gave a series of talks to update the cohort on our recent findings at the OPDC. Speakers included Dr Michele Hu, Dr Claudio Ruffmann, Dr Fahd Baig, Dr Thomas Barber and Professor Richard Wade-Martins, with representatives from Parkinson's UK.

The talks were filmed and will soon be made available as podcasts on our website:
www.opdc.ox.ac.uk/opdc-podcasts

We would like to thank everyone who completed our **open day questionnaire** which was conducted to find out how the top 10 research priorities of the Discovery Cohort compared with those of the Priority Setting Partnership for Parkinson's http://bmjopen.bmj.com/content/4/12/e006434.full.pdf+html.
The top 10 priorities of our cohort as numbered in the questionnaire were:

- Finding a cure for Parkinson's [Q4]
- What is the best type and dose of exercise (physiotherapy) for improving muscle strength, flexibility, fitness, balance and function in people with Parkinson's [Q20]
- What helps improve the dexterity (fine motor skills or coordination of small muscle movements) of people with Parkinson's so they can do up buttons, use computers, phones, remote controls etc. [Q22]
- What training to improve knowledge and skills do informal carers (family and friends) need in order to best care for people with Parkinson's? [Q26]
- What is helpful for improving the quality of sleep in people with Parkinson's? [Q7]
- What is the best treatment for stiffness (rigidity) in people with Parkinson's? [Q24]
- Can medications be developed to allow fewer doses per day for people with Parkinson's? [Q21]
- What best treats mild cognitive functions such as memory loss, lack of concentration, indecision and slowed thinking in people with Parkinson's? [Q8]
- What approaches are helpful for reducing stress and anxiety in people with Parkinson's? [Q11]
- What interventions are effective for reducing or managing unexplained fatigue in people with Parkinson's? [Q14]

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Team OPDC

Oxford Fun Run 2016 for Parkinson's UK

On the 7th May, members of the OPDC/Wade-Martins Research Group took part in the 5km Oxford Fun Run, around Oxford University Parks. Ruth Faram, Ryan Patterson, Serena Cerritelli and Claudio Ruffmann ran in support of the Oxford and District Branch of Parkinson's UK. Chair of the branch, Sally Bromley, was there to cheer us on!

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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 'OPDC' section of Parkinson's UK website
http://www.parkinsons.org.uk/content/oxford-parkinsons-disease-centre

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