Oxford Parkinson's Disease Centre

NEWSLETTER

http://opdc.medsci.ox.ac.uk

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Issue 1

Welcome to the first newsletter of the Oxford Parkinson's Disease Centre (OPDC). In this first edition we introduce you to the group of scientists who are leading this new initiative, describe some of the exciting work we will be doing, and invite you to the launch of the clinical arm of the project to be held at the John Radcliffe Hospital in Oxford on Friday 24th September.

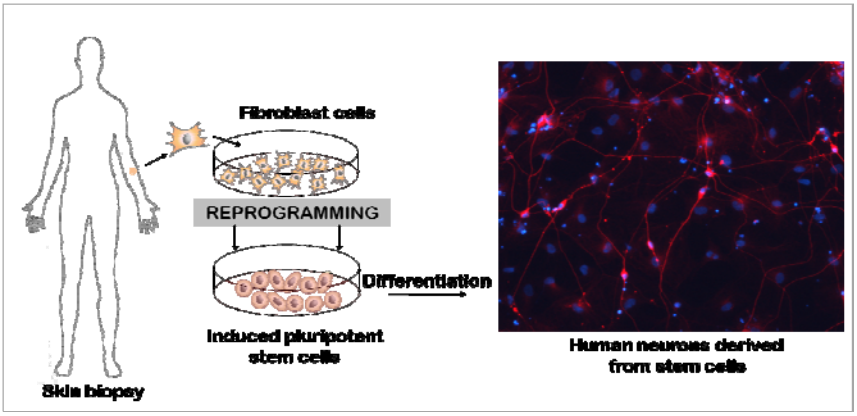
The OPDC is a unique interdisciplinary research centre focused on understanding the very earliest causes of Parkinson's disease (PD). It was founded by the £5m Monument Trust Discovery award from Parkinson's UK, and is the largest single research award funded by the charity. We have created an environment where internationally recognised scientists and clinicians with a combination of skills in molecular genetics, stem cells, brain structure and function, neuron biology and brain imaging will work closely together to better understand the biological pathways which lead to PD. Some of our work on stem cells and brain imaging is presented in this newsletter.

We will be recruiting between 1500 to 2000 new PD patients from the Thames Valley to take part In our clinical investigation into the causes of PD. Your next chance to find out more about the project and how you can become involved is to come along to the launch of the clinical arm of the study to be held at the John Radcliffe Hospital on Friday 24th September from 11am to 3pm. Further details are on the back of the newsletter. Information on all our current research activities can be found on our website www.opdc.medsci.ox.ac.uk.

Richard Wade-Martins

Induced Pluripotent Stem Cells: Converting Skin into Brain Cells

Stem cells have the ability to self-renew and can give rise to any cell type within the body. The human body contains hundreds of different cell types which originated from a single cell at fertilisation. This cell divides repeatedly during the development of the embryo and each cell is instructed to become part of the body via genetic and molecular developmental cues. For example, once a cell has been programmed to become part of the heart, that is its terminal fate and it cannot become anything else.



Revolutionary advances in cell biology have allowed the reprogramming of body cells into a 'stem cell-like' state from which they can be turned into a completely different cell type. These cells are called induced pluripotent stem cells (iPSCs) and offer great potential for research into human diseases. A small sample of skin (fibroblast cells) can be taken and reprogrammed into iPSCs. These cells can be grown into a large population in the laboratory and directed by the researcher to become the cell type of interest. In our case we are interested in generating brain cells (neurons) in order to study the pathology of Parkinson's disease (PD).

As you can understand, the availability of human brain cells from patients is extremely limited, and so iPSC technology allows human brain cells to be studied in much more detail in the laboratory. In PD, a specific group of neurons in the brain which make the chemical dopamine die. We aim to reprogram skin cells into these specific neurons and to study why these cells in particular are affected. By using this cutting edge technology, we will for the first time be able to understand the mechanism behind this cell loss. Increasing our understanding of what goes wrong can potentially lead to improved therapeutics to help suffers of this disease.

Elizabeth Hartfield

Richard Wade-Martins

OPDC Principal Investigator. Richard heads up the Molecular Neurodegeneration and Gene Therapy Research Group and leads the OPDC. Richard's work has two main interests: studying the molecular mechanisms of neurodegenerative diseases such as Parkinson's disease (PD) and related disorders, and developing novel viral and non-viral gene expression vectors as potential therapies. In the OPDC Richard will be generating the new transgenic rat and mouse models of PD and studying the cell biology of dopamine neurons.

Kevin Talbot

OPDC Co-Principal Investigator. Kevin is a consultant neurologist at the John Radcliffe Hospital with expertise in biomarkers and mouse models in neurodegeneration. His previous work to establish a 5-year program in biomarker research in motor neuron disease has provided a template for similar work under the OPDC. With Michele Hu, Kevin leads the OPDC clinical research theme.

Michele Hu

Michele runs a clinical Parkinson's Disease (PD) and movement disorders service in the NHS. Her research interests include studying brain function in PD patients using PET and MR spectroscopy. She is lead for PD research within the DeNDRoN Thames Valley Local Research Network. With Kevin Talbot, Michele leads the OPDC clinical research theme, which aims to recruit people with PD and their families from the Thames Valley area in the UK.

Chris Ponting

Chris is an international expert on computational analysis of genetic and genomic data working at the Medical Research Council Functional Genomics Unit. He has previously undertaken leadership roles in the International Human and Mouse Genome Sequencing Consortia. Chris has pioneered methods for pathway analysis to discover genes involved in neurodegenerative and neurodevelopmental disorders. His laboratory will now apply these methods as part of the OPDC to reveal the key early molecular mechanisms underlying PD.

J. Paul Bolam

Paul heads a group in the Medical Research Council Anatomical Neuropharmacology Unit devoted to understanding the function of a region of the brain called the basal ganglia in normal conditions and in models of Parkinson's disease. Working with Peter Magill, their range of expertise stretches from understanding the role of individual neurons, the function of neurons in circuits, and how the function and dysfunction of circuits affects behaving animals.

Olaf Ansorge

Olaf is Lead Clinical Neuropathologist in Oxford and Director of the Thomas Willis Oxford Brain Collection. His research interest is in the comparative study of human and mouse neuropathology of neurodegeneration and neurooncology. Within OPDC the neuropathology group will study mechanisms controlling regional variation of expression of PD genes in human brain, and investigate the pathological basis of new MRI biomarkers in PD. The group will also compare the neuropathology of newly generated PD models with that seen in human disease.

Yoav Ben-Shlomo

Yoav works at the University of Bristol and is an established neuroepidemiologist with wide-spread experience in both population and clinical cohort studies. He has been involved with clinical and pathological diagnostic studies of movement disorders and is part of UK and US working groups developing diagnostic methodology to improve the collection of common data elements for PD. Yoav will work with Kevin Talbot and Michele Hu to first design our clinical study and then interpret and analyse the resulting data.

Stephanie Cragg

Stephanie works at the forefront of understanding neuronal signalling dynamics in relation to the biology of neurodegenerative disease and addiction. Her research explores the regulation of neurons throughout the region of the brain termed the basal ganglia, including understanding the function and dysfunction of the dopaminergic neurons which die off in PD. Stephanie's laboratory will analyse the signalling of dopamine neurons in the rat and mouse models of PD we will develop.

William James

William oversees the Oxford Stem Cell Facility which works on the application of stem cell technology to understanding cell biology in health and disease. The Oxford Stem Cell Facility will generate induced pleuripotent stem cells (iPSCs; see accompanying article on the front page) from PD patients in the clinical cohort, and work with Richard Wade-Martins to turn these stem cells into patient-specific dopaminergic neurons for further study.

Clare Mackay

Clare heads a group which uses the latest neuroimaging techniques to study brain structure and function in healthy controls, individuals at risk of developing disease, and patient populations. In OPDC she will supervise the acquisition and analysis of MRI data for patients with PD and individuals at increased genetic risk of developing PD later in life. We will investigate whether measures of functional integrity in brain networks are sensitive to detect the earliest changes associated with PD (see accompanying article on the back page).

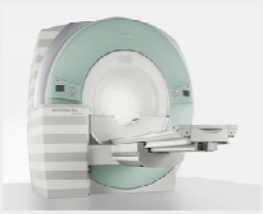
Peter Magill

Peter heads a group at the MRC Anatomical Neuropharmacology Unit that is devoted to understanding how the brain controls movement. His research is focused on defining the operation of brain regions called the basal ganglia, both in normal conditions and in models of PD. With Paul Bolam, Peter and his group will undertake a detailed analysis of new and improved rodent models of PD that are generated at the OPDC

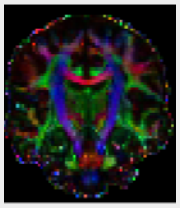
Matthew Wood

Matthew studies RNA biology and therapeutics for degenerative disorders of the nervous system. Interests of the group include the investigation of gene "knock-down" therapeutic methods for dominantly inherited PD caused by alpha synuclein and LRRK2 mutations, and investigating the role of newly discovered very short RNA molecules (microRNAs) in the normal growth and development of dopamine neurons and in the development of PD pathology.

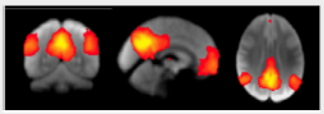
Brain Imaging and Parkinson's Disease



An MRI scanner



DTI colour map



Resting state network

Parkinson's Disease (PD) is characterized by progressive loss of dopamine-producing cells in a small region of the brain called the substantia nigra. As the substantia nigra deteriorates, less dopamine is produced and transported to the striatum, a part of the brain that controls balance and movements. Dopamine deficiency in the striatum eventually causes the debilitating symptoms of PD.

In the early stages when the symptoms are mild, PD can be difficult to diagnose. A correct early diagnosis of PD is essential for the initiation of appropriate treatment, as well as for the development of new therapies that might be most effective early in the course of the disease.

At the moment, diagnosis of PD is based on a set of clinical criteria that provides diagnostic accuracy of approximately 80% and is usually made when first motor symptoms occur. Recent studies suggest that brain imaging methods might help to improve diagnostic accuracy, and may even be able to identify cell loss in the substantia nigra before people develop symptoms.

Magnetic resonance imaging (MRI) is one of several imaging methods that may be useful in improving diagnosis for PD. The great advantage of MRI is that it does not use ionizing radiation or require injection of drugs. MRI uses a strong magnetic field and electromagnetic waves that can be used to obtain information about the structure and function of the whole brain in around an hour.

Conventional MRI cannot confirm a diagnosis of PD because the brain changes are very subtle. At the moment MRI is therefore mainly used to rule out other causes of the symptoms. During the past decade, however, more sophisticated MRI methods have emerged that are sensitive to subtle, microstructural changes in the brain. For example, a recently published study using an MRI technique called diffusion tensor imaging (DTI) was able to detect abnormalities in the substantia nigra in early stage PD patients with 100% accuracy.

MRI can also be used to measure blood flow changes in the brain that are caused by changes in neural activity (functional MRI, 'fMRI'). Our brains never stop working, and even when we are not instructed to do anything in particular we have patterns of fluctuations in the brain called 'resting state networks'. Resting state network analysis of individuals who are at-risk for PD may help identify a change in these patterns of brain activity years before the symptoms develop.

Within the framework of the OPDC we will apply DTI, resting state fMRI and other novel MRI methods to investigate early-stage PD patients, healthy controls subjects and individuals with an increased risk for developing PD in the future due to genetic and other risk factors. Repeated clinical follow-up investigations will reveal whether our MRI measures are able to help predict which 'at-risk' individuals are most likely to develop PD.

CLINICAL OPEN DAY:
NEW INITIATIVES INTO NEURODEGENERATION

Friday 24 September, 11am—3pm
Lecture Theatre 1, Academic Block,
John Radcliffe Hospital

Discussion topics include:

- Clinical launch of OPDC
- Imaging of the brain
- What post-mortem tissue can tell us about disease
- Making brain cells from skin cells
- Collecting our clinical cohort

Open to all: please register to attend by calling Katherine Lucas on 01865 234310 or by emailing k.lucas@nhs.net

OPDC CLINICAL CONTACT DETAILS

OPDC Webpage:
opdc.medsci.ox.ac.uk

Clinical studies contact:
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Please visit the patient involvement section of our web-site to read more about the study and / or to register an expression of your interest using the form provided there.

http://opdc.medsci.ox.ac.uk/patient-involvement