PARKINSON'S NEWSLETTER

DECEMBER
2023

**John van Geest Centre for Brain Repair,
Department of Clinical Neurosciences,
University of Cambridge**

IN THIS ISSUE

INTRODUCTION

Welcome to the 2023 Parkinson's newsletter! We hope you will enjoy this update about our research. In the 'Meet the Team' section, you will see that lots of new faces have joined us this year. You will meet some of them in the clinic, but others are working hard behind the scenes in the lab to help us better understand what happens in the body and the brain to drive the progression of Parkinson's – which in turn guides development of new treatments that we are testing in clinical trials.

Many of our studies are now focusing on the role of the immune system in Parkinson's, which has become a really 'hot topic' in Parkinson's research over the past few years. **Our theory is that over-activation of the immune system might lead to more rapid disease progression**, and we are testing this idea with a wide range of studies which look at blood and spinal fluid samples and brain scans, as well as tissue from post-mortem brains. We are also trying to better understand how the immune system interact with cell transplants - which is critical given the recent advances in our research in stem cell transplant therapy. **We are excited to announce that the STEM-PD transplant trial has begun this year, and future cell therapy trials are planned for 2024...** watch this space!!

A big thank you to all of you who have participated in our research this year and generously given up so much of your time. You are absolutely essential to our research and we couldn't make progress without you! Please do get in touch with your feedback about the studies you have been involved with, and our research more generally. We are always keen to hear from you.

Professor Roger Barker & Dr Caroline Williams-Gray

MEET THE TEAM

Prof Roger Barker
Professor and Honorary
Consultant Neurologist

Dr Caroline Williams-Gray
Principal Research Associate and
Honorary Consultant Neurologist

Julia Greenland
Clinical Research Associate

Marta Camacho
PD Cohort Studies Coordinator
and PhD Student

Bina Patel
Acadmic Clinical
Fellow

Evridiki Asimakidou
PhD Student

Ju Ribeiro
Research Assistant

Molly O'Reilly
Clinic Administrator

MEET THE TEAM

Lenni Spindler
Postdoctoral Research Associate

Reiss Pal
Postdoctoral Research Associate

Lakmini Kahanawita
Research Assistant

Shaline Fazal
Research Manager

Anna Curle
Postdoctoral Reseach Associate

Annelies Quaegebeur
Cambridge Brain Bank
Research Director

Katie Andresen
Clinical Trials Coordinator

Browen Harry
Clinical Trials Coordinator

Amy Evans
Clinical Trial Assistant

OUR PD RESEARCH CLINIC

We run our Parkinson's Disease Research Clinic every Friday at the John Van Geest Centre for Brain Repair, where **we welcome people with PD as well as companions without the condition as 'control' participants.** The research clinic is the gateway to many of our other research studies.

We have recently been focusing on recruiting individuals with a recent diagnosis of PD and we are delighted to have welcomed so many new participants to our research programme. Clinic visits involve a combination of questionnaires, physical assessments, neuropsychological tests to evaluate memory and thinking, and collection of blood samples to look at genetic and other biological factors which might be contributing to differences in symptoms and rates of disease progression between individuals.

Caroline Williams-Gray

Bina Patel

Marta Camacho

Ju Ribeiro

Molly O'Reilly

We are also continuing to follow participants up from our long-term cohort studies "CamPaIGN", "PICNICS" and "ICICLE-PD". **We are excited to announce that we have now completed 20 years of follow-up of the "CamPaIGN" study,** making this one of the longest running studies of PD progression in the world!

Individuals who have been assessed in the research clinic may be eligible to go on to be involved in a range of other research studies or clinical trials. We will be in touch about more opportunities to get involved!

The Parkinson's Research Clinic and all of our clinical research studies are supported by the National Institute of Health Research Cambridge Biomedical Research Centre.

THE GUT AND PARKINSON'S DISEASE

Marta is studying **the role of the gut in Parkinson's**. She asked many of you to complete the **Blue Poop Challenge** and 82 participants and their household controls kindly ingested a blue food dye to measure gut transit time (length of time between ingestion of the dye and first appearance of a blue-coloured stool).

People with Parkinson's had significantly slower transit time compared to their companions without Parkinson's and approximately 12% of PwP had a transit time of over 100 hours, passing a blue stool up to 9 days later.

Marta is also running a long-term study of gut symptoms in a group of people with Parkinson's, controls living in the same household, and people who have a sleep disorder called RBD that puts them at high risk of developing PD. (RBD, or REM Sleep Behaviour Disorder, is a condition in which people act out their dreams, which leads to them shouting and thrashing about in their sleep.) Participants have donated blood and faecal samples and we are currently analysing the relationship between gut symptoms, changes in bacteria in the faeces (the 'microbiome') and measures of inflammation in the blood. The aim is to understand whether changes in the gut cause inflammation and faster progression of Parkinson's disease.

Marta Camacho

We hope that this study will tell us more about **whether therapies directed at improving gut health might have benefit for Parkinson's disease**.

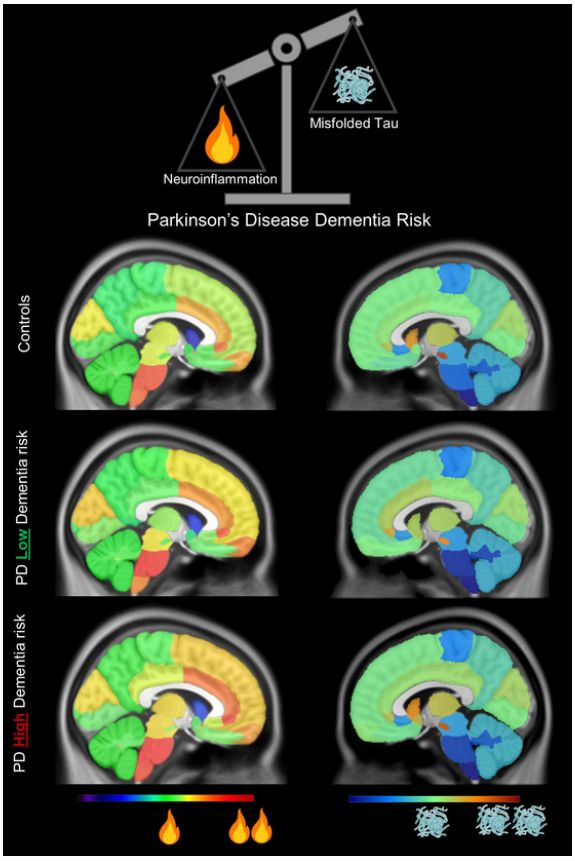
This work is being funded by the Evelyn Trust, and a pilot funding award from the NIHR Cambridge Biomedical Research Centre Dementia and Neurodegeneration Theme.

NET-PDD – USING PET BRAIN SCANNING TO STUDY THE CHANGES THAT LEAD TO DEMENTIA IN PARKINSON'S

We are using a **brain scanning** technique called Positron Emission Tomography (PET) **to measure changes in the brains of people with Parkinson's**. This technique involves injecting a radioactive tracer which travels via the blood stream to the brain and binds to specific proteins. The scanner shows us where the tracer binds - allowing us to visualise biological processes in the brain.

We are using tracers for: i) **brain inflammation**; and ii) a protein called "**tau**", which can becomes sticky and form toxic tangles. Both of these processes are known to affect brain function and can lead to brain cell death. **Our NET-PDD (Neuroinflammation and Tau Accumulation in PD) study is the first study to assess these brain changes over time in Parkinson's.**

Participants with early Parkinson's and healthy control volunteers have had 2 sets of scans, 3 years apart. We are still analysing the results but we have already been able to show that in people who have more memory/thinking problems, and are at greater risk of developing dementia, inflammation is higher – whereas we have not seen early changes in tau protein accumulation. We are confident that more interesting insights will be gained from this study to help inform development of new treatments to slow down the onset of memory problems and dementia in Parkinson's.



PET brain scan signals differ in different groups of participants in the NET-PDD study: those with greater cognitive difficulties have more brain inflammation (left column) than those with less cognitive issues, or healthy controls. For tau accumulation (right column) there are no differences between the groups.

Lenni Spindler

Caroline Williams-Gray

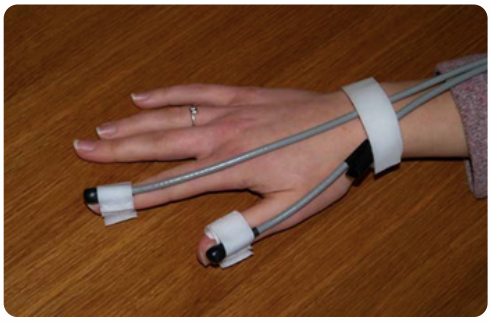
This study is funded by the Evelyn Trust and the Medical Research Council .

THE AZA-PD CLINICAL TRIAL

Although there are many good treatments for the symptoms of Parkinson's disease, **there is currently no treatment to slow down disease progression.**

Work done by our group has implicated activation of the immune system in this progression. It is a critical system for protecting the body from infections, but can become inappropriately activated in certain diseases, including Parkinson's, leading to inflammation and damage to brain cells.

We are therefore running a clinical trial of an immunosuppressant drug called azathioprine.



Electromagnetic sensor used to measure movements at different timepoints in the trial.

Half of the trial participants are receiving azathioprine tablets and half are receiving placebo tablets (or 'dummy pills'), with the treatment being taken once daily, for one year. The trial is double-blinded, so that neither the participants nor the researchers know who is taking the active drug. Detailed assessments are being carried out at the beginning of the trial, and at regular intervals, until 6 months after the treatment is completed. These include clinical measures looking at the impact of the trial treatment on movement, memory and thinking, and day-to-day life. We are also looking at blood and spinal fluid tests to assess immune activation, and brain scans to measure inflammation. We will compare how these measures change over the course of the trial in the group who have taken azathioprine compared to those who have received the placebo..

The trial is now in its final stages, with the last patient visit scheduled for February 2024, and **results expected in summer 2024.**

Julia Greenland

Caroline Williams-Gray

This work is being funded by the Cambridge Centre for Parkinson's Plus, and by Cure Parkinson's.

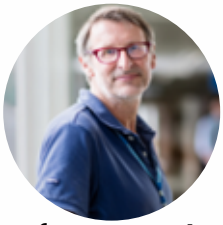
THE TRANSEURO STUDY

TRANSEURO is a large multicentre European study which includes a **dopamine cell transplantation trial** and an observational component.

The observational study has been ongoing for nearly 13 years. It involves 6-monthly appointments looking at movement, memory, thinking and mood. There are 42 participants still involved: 17 in Cambridge, 13 in Lund (Sweden), 11 in London and 1 in Cardiff. The aim is to gather detailed information on how Parkinson's disease behaves and progresses over time and to provide a comparison group for the transplant study.

The transplant study involves surgical transplantation of dopamine producing cells into the striatum, a part of the brain which is known to be affected by PD. 11 patients were grafted in Cambridge and Lund, Sweden from 2015 to 2018. The study was completed in December 2022. We are currently in the process of analysing the results and hope to publish them soon.

The goal of TRANSEURO is to help **develop safe cell-based treatments for PD**, particularly for patients whose symptoms are not well controlled with standard medications. It is a stepping stone for future cell transplant studies, and has led to a new stem-cell transplant trial, STEM-PD, which you can read more about on the next page.



Prof Roger Barker

Katie Andresen

Amy Evans

This study is funded by an EU FP7 grant and the Cure Parkinson's Trust.

STEM CELL DERIVED DOPAMINE CELL TRANSPLANTS FOR PD: THE STEM-PD CLINICAL TRIAL

One exciting new treatment option that we have been working on for many years with our colleagues in Lund in Sweden is to repair some of the critical damage caused in Parkinson's disease by **replacing the lost dopamine producing nerve cells with new ones made from human stem cells**.

The STEM-PD trial is investigating this using a new human stem cell therapy, called STEM-PD, in people with mild-moderate Parkinson's. The STEM-PD cells are generated from human embryonic stem cells and have been designed to mature into dopamine-producing nerve cells once implanted into the human brain.

The focus of the trial is to assess: (a) whether the STEM-PD cells are safe to use in people with Parkinson's; (b) exactly how many cells should be transplanted; and (c) the extent to which the cells develop and go on to produce dopamine in the brain after transplantation. **This is the first time the STEM-PD cells will be given to people**.

The trial started in Sweden in December 2022, and we have recently been granted permission from the UK authorities to start in Cambridge. So far 4 participants, out of the target of 8, have received transplants of STEM-PD cells. The transplanted cells are expected to mature over a period of at least 1 year, with expected maximal benefit after 2-3 years.

Visit our website for updates on the progress of this research: stem-pd.org

Prof Roger Barker

Browen Harry

The STEM-PD trial is funded by a research grant from Novo Nordisk.

THE IMMUNE RESPONSE TO DOPAMINE CELL TRANSPLANTS IN PD - WHAT TO EXPECT AND HOW TO CONTROL IT

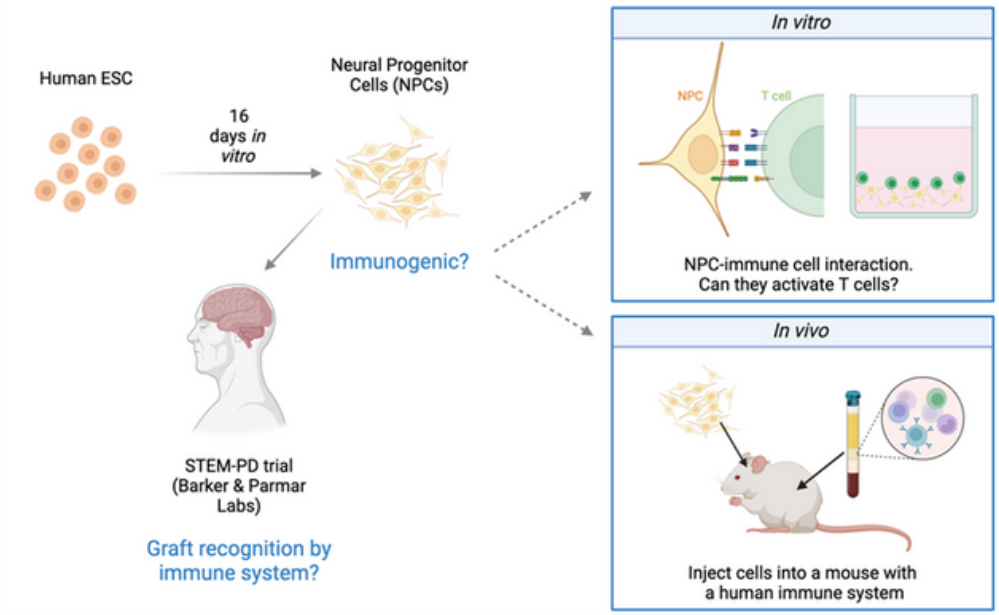
We have been working to understand whether stem cell treatments such as the treatment used in the STEM-PD trial (dopaminergic neural progenitor cells; or "NPCs") is likely to cause an immune response in patients that could result in rejection or impair the success of the treatment.

Starting "in vitro" or "in the dish", we looked at whether NPCs express proteins on their surface that might allow them to be recognised by, and interact with, immune cells. Then, we mixed the NPCs with immune cells and examined their capacity to activate them.

Next, we moved "in vivo" (animal models). We injected the NPCs into the brains of mice that have been given a human immune system (working with Sarah Howlett, who is part of the Jo Jones lab here in Cambridge). We are now using this model to answer two questions:

Do immune cells infiltrate into the brain after transplant?
If so, do they impact on survival of the transplanted cells?

This work is helping us to plan what type of immunosuppressive treatment to use in stem cell transplant trials in people with PD.



Anna Curle

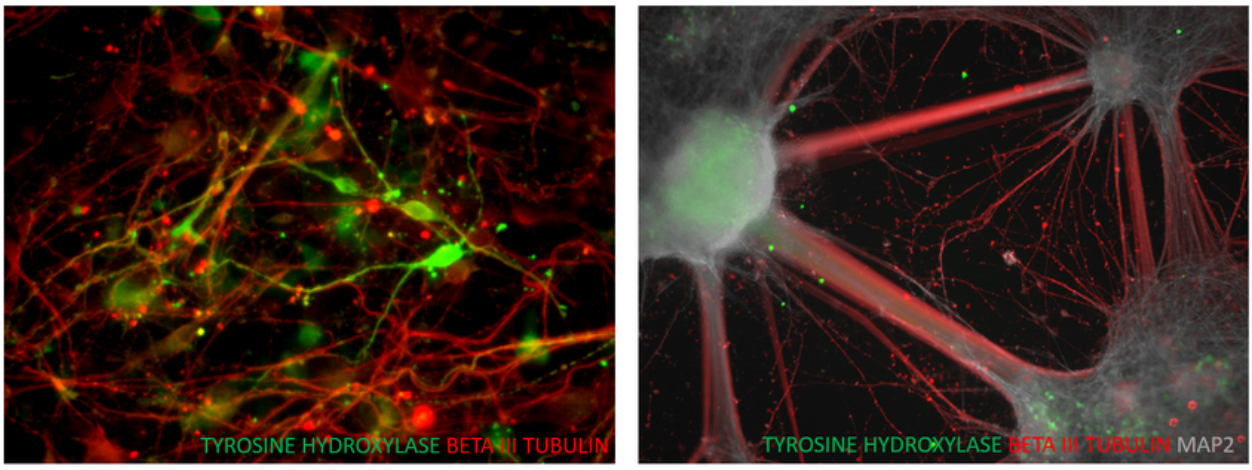
This study is funded by MRC-UKRMP (UK Regenerative Medicine Platform) and the Rosetree's Trust.

MODELLING PARKINSON'S IN THE LAB

In order to better understand Parkinson's disease, **we can study nerve cells grown in a dish**. We are particularly interested in studying nerve cells that produce dopamine, as these are the main cell type that is affected by Parkinson's disease.

We can make dopamine nerve cells from embryonic stem cells, and we have been studying how these nerve cells interact with microglia - the brain's inflammatory cells. We have looked at what happens when the dopamine nerve cells are grown with microglia in a dish in the laboratory, and found that the microglia do not react strongly - which is good news, given these nerve cells are similar to the cells that we are using for transplant in the STEM-PD trial.

DOPAMINERGIC NERVE CELLS DERIVED FROM EMBRYONIC STEM CELLS GROWN IN CULTURE FOR 45 DAYS AND 80 DAYS



The images show dopamine nerve cells that have been grown in the laboratory for 45 days (on the left) and 80 days (on the right), from embryonic stem cells. The green stain shows tyrosine hydroxylase, a marker of dopamine cells. Beta tubulin (red) and MAP2 (grey) are markers of nerve cells, and show the branching structure of these cells.

We are also working on creating **a human cell model of early Parkinson's disease.** This involves growing cells in a dish and adding toxic clumps of the protein alpha-synuclein repeatedly over time. These protein clumps are similar to those which can be found in the brains of people with Parkinson's and they are thought to be a major player in causing the disease, but we don't fully understand how they damage nerve cells. So far, this work has shown that the alpha-synuclein clumps damage the parts of the cell that are critical for providing energy - the mitochondria. We are continuing to develop these cell models to better understand how cells are damaged in PD.

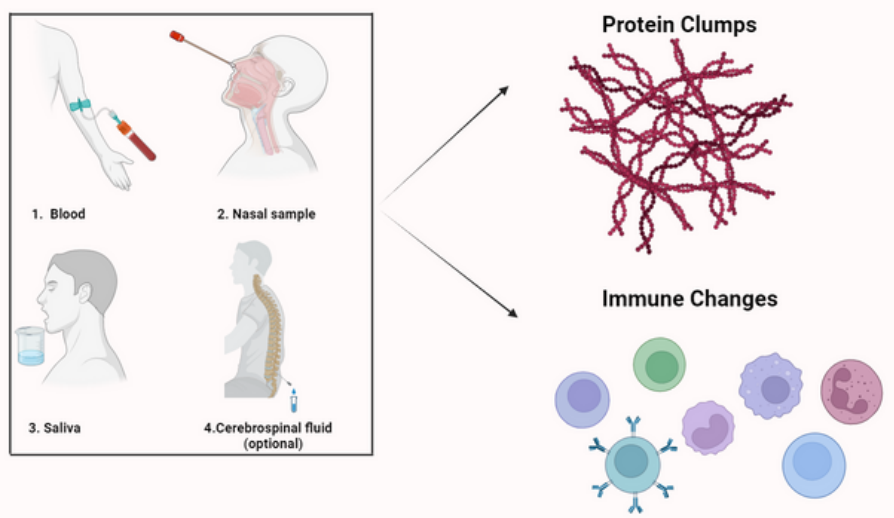
Shaline Fazal

These studies are funded by the EU Horizon 2020/ NSC-Reconstruct and MRC-DTP.

CAN WE USE NASAL SWABS AND SALIVA SAMPLES TO STUDY IMMUNE CHANGES IN PARKINSON'S?

Whilst we know that the immune system seems to be overactive in Parkinson's disease, critical questions that are unresolved are:
(i) what triggers the immune response?
(ii) whereabouts in the body does this happen?
(iii) when during the course of disease process does this happen?

To address this question, we are planning a new study involving people who are at high risk of developing Parkinson's, and people with both early- and late-stage disease, as well as healthy controls. From each participant, three types of samples will be collected: blood, nasal samples and saliva. In some participants, a sample of the fluid that surrounds the brain and spine, called cerebrospinal fluid, will also be collected. These samples will be analysed to measure immune cells, inflammatory markers, and proteins (including alpha-synuclein) which may trigger the immune response in Parkinson's.



This exciting new study will look at whether **easily accessible nasal swab and saliva samples** can provide a window into the immune activation that occurs in Parkinson's. We are also working with our colleagues in the department of Chemistry (David Klenerman's lab) to investigate how immune changes are linked to clumping of alpha-synuclein protein over the course of the disease. We will start recruiting participants for this study early next year.

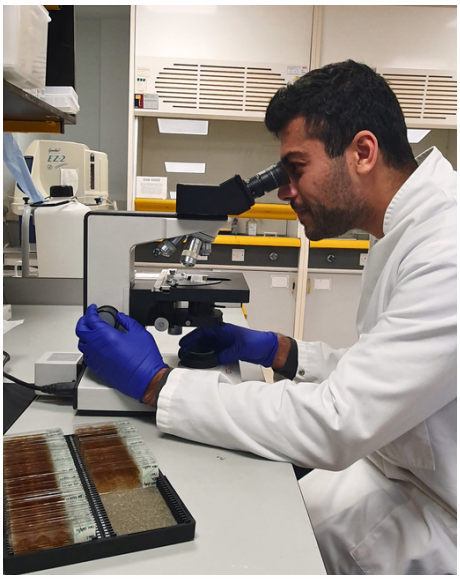
Evridiki Asimakidou

CAN WE TREAT PARKINSON'S DISEASE BY INHIBITING TOLL-LIKE RECEPTORS?

In Parkinson's disease, the **immune system contributes to the loss of brain cells that produce dopamine**. A specific set of immune cells, called mononuclear phagocytes, are critical for protection against infection. Mononuclear phagocytes have receptors on their surface called **'Toll-like Receptors' that sense and detect signals of damage and infection.** When these receptors are activated, the cells produce proteins called cytokines which amplify inflammation.

Our previous work has shown that levels of Toll-like Receptors are increased in the brain and blood of people with Parkinson's disease. We also know that alpha-synuclein, the protein that forms clumps in the brain in Parkinson's, can activate these receptors. This means that activated mononuclear phagocytes containing Toll-like Receptors may contribute to inflammation in Parkinson's.

Reiss Pal



Candesartan is a drug used to treat high blood pressure, but has also been shown to block Toll-like Receptors. Using blood samples donated by people with Parkinson's and healthy volunteers, we isolated immune cells and stimulated their Toll-like Receptors using alpha-synuclein or lipopolysaccharide (a bacterial toxin). We found that treatment of the cells with candesartan led to a reduction in the inflammatory response to stimulation.

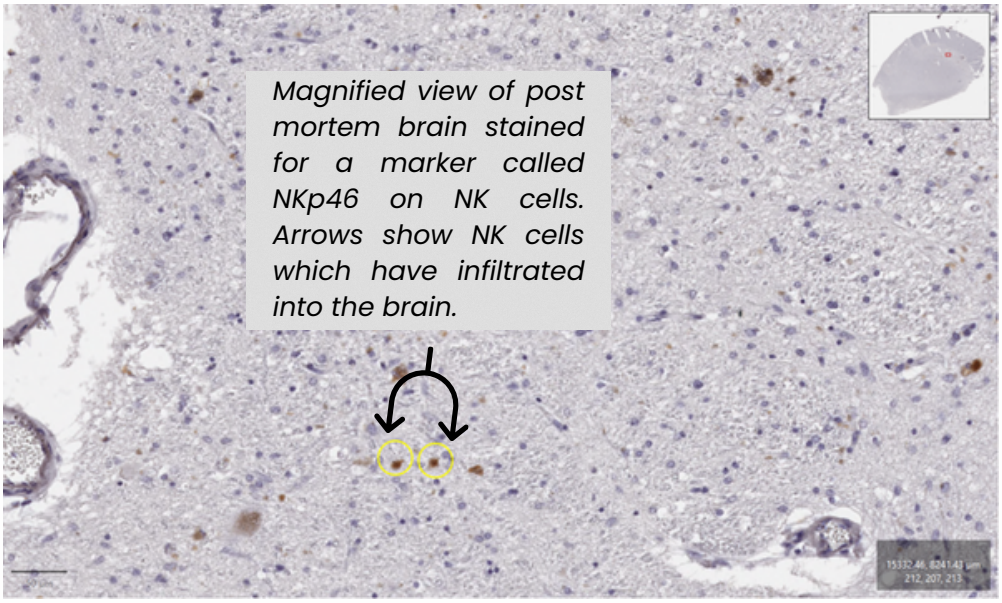
This early work suggests that candesartan might be able to reduce inflammation in Parkinson's. We are planning more studies in the lab and clinic to investigate whether repurposing this drug in a clinical trial may be beneficial for patients.

This study is funded by the Medical Research Council.

INVESTIGATING NATURAL KILLER CELLS IN PARKINSON'S

Natural killer (NK) cells are a type of immune cell. There is increasing evidence suggesting that these cells **might be important in the progression of Parkinson's disease**, but very little is still known about their exact role in the condition.

NK cells work by recognising 'damage' signals from cells which are unhealthy. They can move towards these damaged cells and release various proteins and chemicals which destroy them. This is important for protecting the body against processes such as cancer and infections. However, **NK cells might become abnormally overactivated in Parkinson's disease,** and contribute to an excess of inflammation - we are now exploring this theory.



Magnified view of post mortem brain stained for a marker called NKp46 on NK cells. Arrows show NK cells which have infiltrated into the brain.

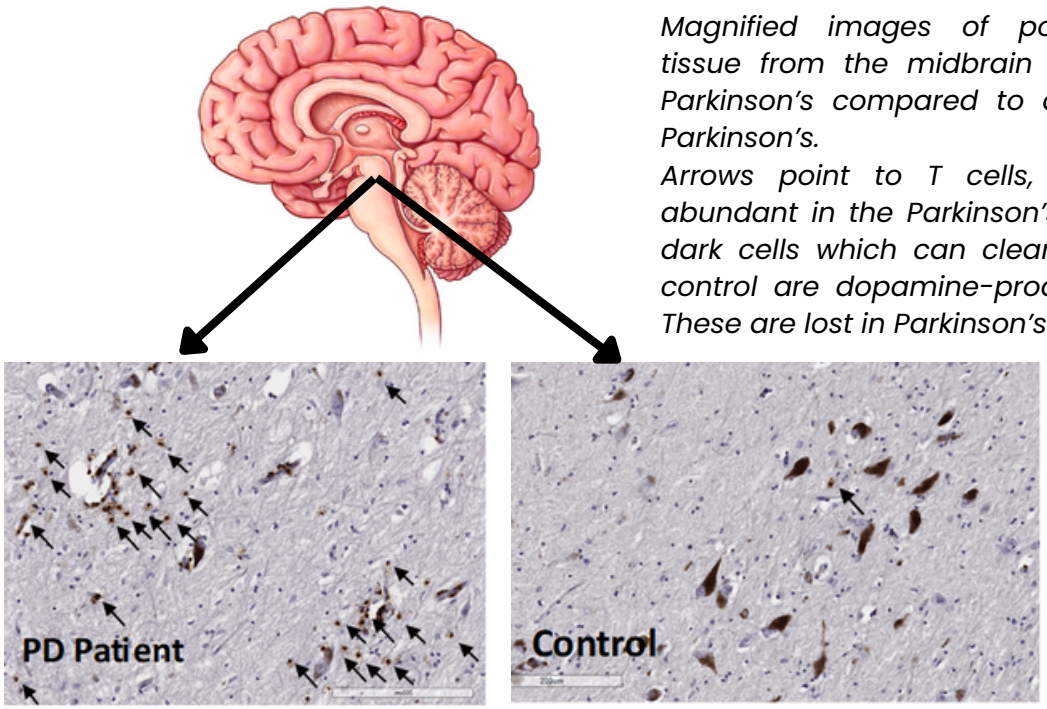
Our early work on this has shown **NK cells are increased in the blood of people with Parkinson's compared to those without**. We are now investigating whether NK cells infiltrate into the brain from the blood, where they might contribute to nerve cell damage. We are also investigating how NK cells interact with alpha-synuclein, the protein that accumulates in the Parkinson's brain. We are looking at whether the ability of NK cells to to digest this protein is abnormal in Parkinson's.

Lakmini Kahanawita

STUDYING IMMUNE CELLS IN THE BRAIN

Immune cells are not produced in the brain, but we know that they can travel there and may contribute to brain inflammation and nerve cell damage. **We are trying to understand more about the role of immune cells that travel into the brain in Parkinson's.**

Monocytes and T cells are types of immune cells involved in our body's response to infection and injury. When these cells make their way into the brain, it is thought they could have a toxic effect and contribute to the loss of brain cells, which in turn leads to Parkinson's symptoms.



Magnified images of post-mortem brain tissue from the midbrain of a patient with Parkinson's compared to a 'control' without Parkinson's.
Arrows point to T cells, which are more abundant in the Parkinson's brain. The larger dark cells which can clearly be seen in the control are dopamine-producing brain cells. These are lost in Parkinson's.

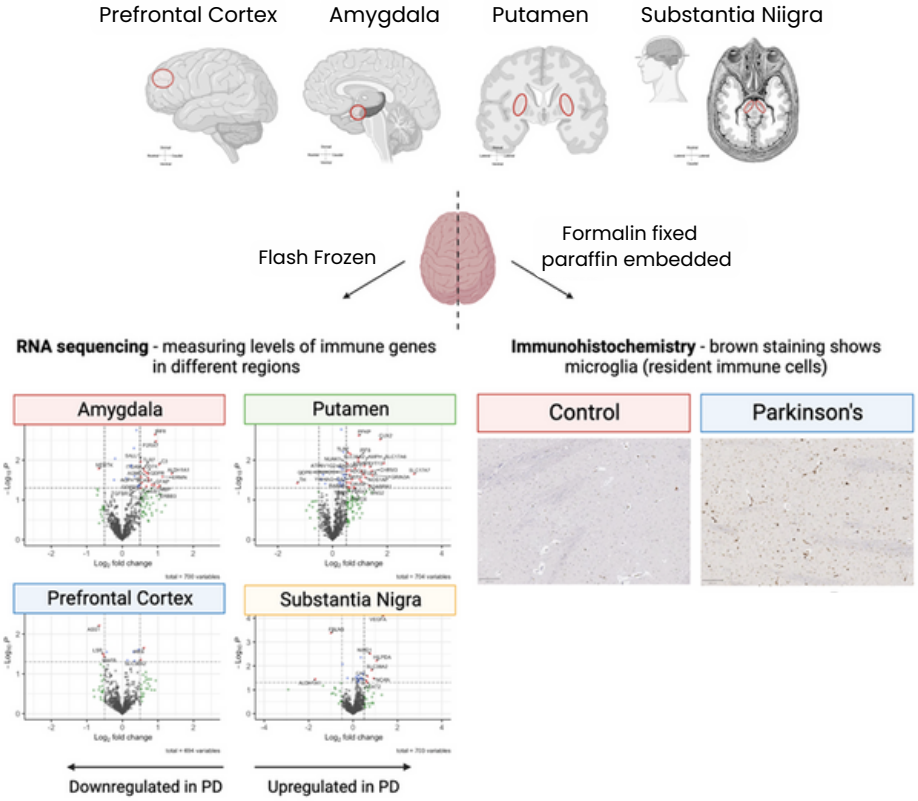
Bina has been looking at post-mortem brain tissue from 14 people who had Parkinson's and 5 controls without the condition, to see whether there is a difference in the number of T cells and monocytes infiltrating into different regions of the brain. Her results so far suggest that **people with Parkinson's have more of these immune cells in regions of the brain responsible for movement compared to healthy controls**. Bina will also investigate whether there is a relationship between the number of these cells in the brain and the severity of the disease during life.

Bina Patel

EXPLORING INFLAMMATION ACROSS DIFFERENT BRAIN REGIONS

We are working with teams in Sweden (Johan Jakobsson) and America (Molly Gale-Hammel), who are interested in specific elements of our genetic code called Transposable Elements, and how they might trigger inflammation in the brain.. Supported by Annelies Quaegebeur at the Cambridge Brain Bank, we have been **studying tissue from four regions of the brain** from donors with and without Parkinson's.

We are comparing the substantia nigra, the putamen, the amygdala and the frontal cortex. The substantia nigra is the region where we see the most nerve cell damage in Parkinson's. This region is linked to the putamen which is involved in control of movement. The amygdala and frontal cortex are important in memory and thinking. We are using a number of different techniques to study inflammation, including measuring which inflammatory genes are switched on (RNA sequencing), and staining cells of interest so that we can see them under the microscope (immunohistochemistry). So far we have found that the amygdala and putamen are the most inflammatory regions in the Parkinson's brains compared to controls. This work is helping us to understand how **inflammation might play different roles in different parts of the brain**, as well as identifying specific inflammatory genes which are involved - which might ultimately help us to find new drug targets.



Anna Curle

Annelies Quaegebeur

This study is funded by the Aligning Sciences Across Parkinson's (ASAP) consortium.

BRAIN DONATION: THE CAMBRIDGE BRAIN BANK

You are probably familiar with organ donations of the heart, kidneys or eyes to sustain the health or even the life of people in need. Brain donation for research is a precious and unique gift. Scientists can learn and understand more about disease processes such as Parkinson's when they are able to work on donated tissue. Ultimately, we hope that scientific work of this kind will lead to better and more effective treatments and that future generations will benefit from the help of brain donors.

Registering to donate the brain and other parts of the nervous system is a big decision and needs to be discussed with family and friends. Advice is available from the Cambridge Brain Bank team who would be very happy to discuss any concerns or questions you or your family may have. Email brbank@addenbrookes.nhs.uk for further information, or visit the website: www.cuh.org.uk/tissue-bank.

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THANK YOU TO OUR FUNDERS

DONATIONS

If you would like to donate to any of our research projects, then please do contact us on 01223 331160 or send any donations (payable to University of Cambridge) to either Professor Roger Barker or Dr Caroline Williams-Gray at the John Van Geest Centre for Brain Repair, University of Cambridge, Forvie Site, Robinson Way, Cambridge, CB2 0PY.