PARKINSON'S NEWSLETTER 2024

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

DECEMBER 2024

IN THIS ISSUE

INTRODUCTION

Welcome to the 2024 Parkinson's newsletter! We hope you will enjoy this annual update about our research.

Our team has continued to expand this year and you will see some new faces in the 'Meet the Team' section. As well as our clinic-based researchers who you will meet when you come along to take part in our studies, we have a strong team of researchers who work in the laboratory on a range of projects aimed at better understanding the underlying factors that influence the onset and progression of Parkinson's disease. We also have a fantastic team of support staff without whom our research would not be possible.

The John van Geest Centre for Brain Repair

INTRODUCTION

A central theme of our research is trying to understand why Parkinson's disease is so variable between individuals. We know that people with Parkinson's have a broad range of symptoms which differ between individuals, and people differ in terms of how quickly their Parkinson's progresses over time. Our studies are investigating whether activation of the immune system is a factor which drives this variability, and looking at how this is linked to changes in the brain. We have also been exploring how gut health is linked to changes in the progression of the disease. Our main goal is to translate what we are learning into new treatments for Parkinson's - and we are running an active programme of clinical trials. This year we have completed a trial of an immune-suppressing drug for Parkinson's, and for 2025, we are planning more trials targeting inflammation and the immune system as well as gut health. Another major focus of the lab over the last few years has been cell transplant therapy. Our STEM-PD transplant trial is now underway and making good progress, and we continue to work on developing new stem cell treatments for Parkinson's.

A huge thank you to all of you who have participated in our research this year. You are absolutely essential to our research and we couldn't do it without you! Please do get in touch with any feedback about the studies you have been involved with, or any questions about our research. 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

Dr Julia Greenland
Clinical Research Associate

Dr Marta Camacho
Postdoctoral Research Associate

Dr Bina Patel
Clinical Research Associate

Dr Alexander Peattie
Postdoctoral Research Associate

Clotilde Tournerie
PhD student

Molly O'Reilly
Clinic Administrator

Emma Cutting
Senior Trial Coordinator

Miriam Schaepers
Clinical Research Assistant

MEET THE TEAM

Sara Crooks
PhD student

Alex Friend
PhD student

Dr Shaline Fazal
Research Manager

Dr Anna Curle
Postdoctoral Reseach Associate

Katie Andresen
Clinical Trials Coordinator

Dr Saeed Kayhanian
Clinical Research Associate

Amy Evans
Clinical Trial Assistant

Kerry Dresser
Clinical Trials Coordinator

Dr Annelies Quaegebeur
Cambridge Brain Bank Research Director and Consultant Neuropathologist

Florence Layburn
PhD student

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 recruit people with a recent diagnosis of PD to come along to the clinic, and continue to follow them up with assessments every couple of years to look at how their PD changes over time. Visits to the clinic involve a combination of questionnaires, physical assessments, neuropsychological tests to evaluate memory and thinking, and collection of blood samples as well as other sample types to look at the biological factors which might be contributing to differences in symptoms and rates of disease progression between individuals.

Caroline Williams-Gray

Bina Patel

Marta Camacho

Miriam Schaepers

Molly O'Reilly

We also continue to follow participants up from our long-term cohort studies "CamPaIGN", "PICNICS" and "ICICLE-PD". We have now completed over 20 years of follow-up in the "CamPaIGN" study and 10 years of follow-up in the PICNICS study, providing essential information about long-term outcomes in PD and what influences these.

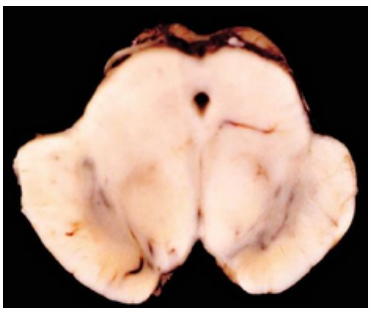
Individuals who have been assessed in the research clinic may be eligible to take part in a range of other research studies or clinical trials. We will be in touch about more opportunities to get involved as and when they arrive.

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.

DO ANCIENT VIRAL INFECTIONS LEAD TO ABNORMAL BRAIN INFLAMMATION IN PARKINSON'S DISEASE?

Recently we are joined forces with the team of Johan Jakobsson at Lund University in Sweden to investigate whether one of the reasons the immune system is activated in the brain in Parkinson's is due to the reactivation of ancient viral remnants called transposons.

These transposons are made up of bits of viral DNA that have become incorporated into the DNA of the host brain cells many years ago in evolution. They make up to over 50% of our DNA and it has long been thought that they simply represents junk DNA and do nothing. However, Johan has shown that these transposons can be reactivated in the brain under certain conditions and when they are, the brain sees them as an invading virus and so mounts an immune response to try and kill them off.



Section of midbrain of a patient with Parkinson's disease shows paleness of an area called the "substantia nigra" which reflects loss of nerve cells in that area. We are using these brain sections to study the processes driving this progressive degeneration.

We have now started looking at this in the post-mortem brains of people with Parkinson's disease using sophisticated techniques to study different cells in different brain regions. We have found that some transposons do seem to be reactivated in some cells of the brain in Parkinson's and this is associated with an immune response within the brain.

We are now trying to work out exactly how this happens, when in the disease course, how this relates to the alpha synuclein pathology and also how we can stop it and by so doing slow down the disease process.

Roger Barker

Annelies Quaegebeur

Joanne Jones

Shaline Fazal

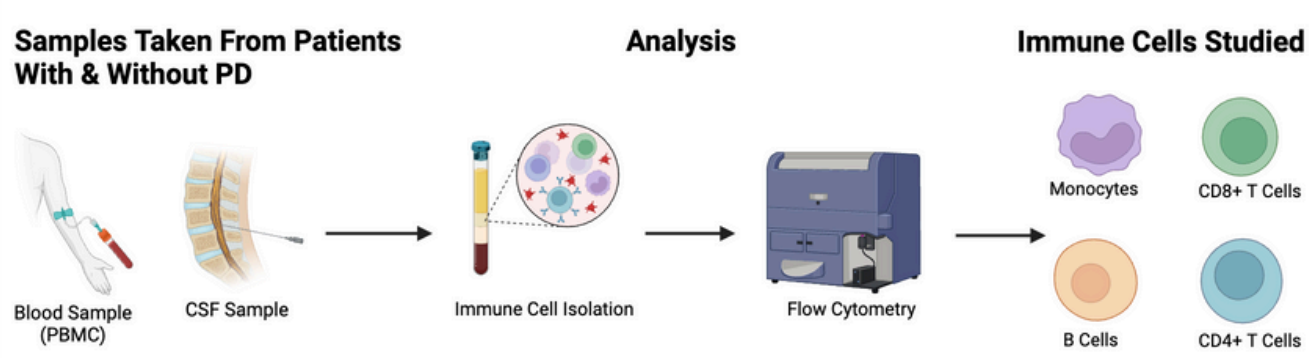
Anna Curle

This work is funded by a grant from the Aligning Science across Parkinson's Initiative funded through the Michael J Fox Foundation.

STUDYING IMMUNE CHANGES OVER TIME IN PARKINSON'S

The immune response in Parkinson's is thought to lead to inflammation in the brain, which exacerbates nerve cell damage. However it is not known whether or how the immune response changes over the course of the disease. Understanding when the immune response is most prominent is important to help us detemine the best time to intervene with treatments to dampen inflammation.

Our NET-PDD (Neuroinflammation and Tau Accumulation in the development of Parkinson's Disease Dementia) study is one of the first studies in the world to track immune changes over time. The project, which involves 80 participants, is looking at how immune changes relate to disease progression and development of cognitive symptoms. During the study, people with Parkinson's and individuals without PD have donated blood and cerebrospinal fluid (CSF) samples at repeated timepoints, in addition to having brain scans to look at inflammation and accumulation of tau protein. Using a technique called flow cytometry we can identify the levels of specific immune cells within blood and CSF samples. After finding some interesting differences between people with PD and those without PD in the baseline samples, Alex Friend (PhD student) is analysing results from the 3 year samples, and we are now collecting more samples at the 7-year timepoint. We hope to identify specific immune changes that we can target with treatments to slow disease progression, and find out when in the disease course we should use these therapies.



Alex Friend

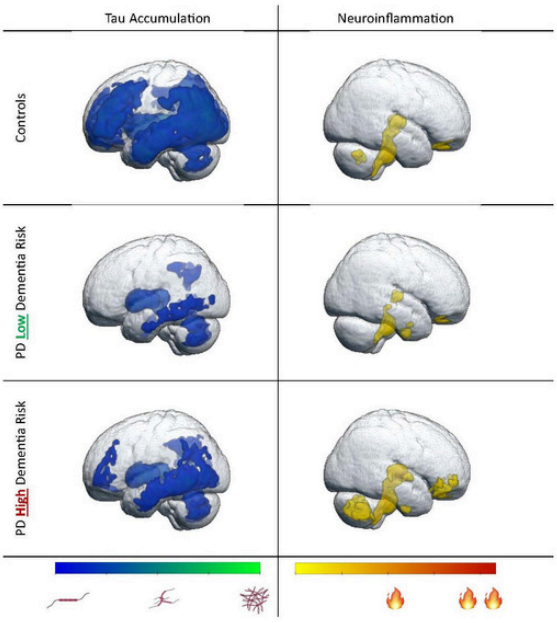
This work is funded by the Medical Research Council .

USING PET BRAIN SCANNING TO INVESTIGATE MEMORY AND THINKING IN PD

We are using a brain scanning technique called Positron Emission Tomography (PET) to measures the changes that happen in the brains of people with Parkinson's disease. This technique uses an injected radioactive tracer which travels via the bloodstream to the brain and binds to specific proteins. The PET scanner allows us to detect where these tracers bind, so we can visualise biological processes in the brain.

We use tracers to track: 1) brain inflammation; as well as 2) a protein called "Tau" which can clump together and form toxic tangles. Together, these processes are known to cause cell damage, adversely affect brain function and cause memory and thinking problems. Our NET-PDD (Neuroinflammation and Tau accumulation in the development of Parkinson's Disease Dementia) study is investigating these brain changes in Parkinson's over time.

Participants with early Parkinson's and control volunteers without Parkinson's have had 2 sets of scans, 3 years apart. The results from the baseline scans showed that people with PD who had a higher risk of developing dementia had more more widespread inflammation in the brain compared to those at low risk of dementia, and compared to controls. In contrast, tau accumulation in the brain was not different between the three groups. This work was published earlier this year in the journal 'Brain'. Alexander Peattie (postdoctoral reseach associate) is now analysing changes in inflammation and tau on the scans over time and looking at how this is linked to the development of memory and thinking problems as well as progression of other Parkinson's symptoms. We hope that insights from this study will help in the development of new treatments to combat the onset of memory problems and dementia in Parkinson's disease.



PET brain scans signals differ between groups of participants in the NET-PDD study at the 3 year timepoint:. Those with a greater risk of developing cognitive problems have more brain inflammation (right column) compared to those with a lower risk of developing cognitive problems and healthy controls. Tau accumulation (left column) was more prominent in people without PD, but was also higher in people with PD at greater dementia risk than those at low risk.

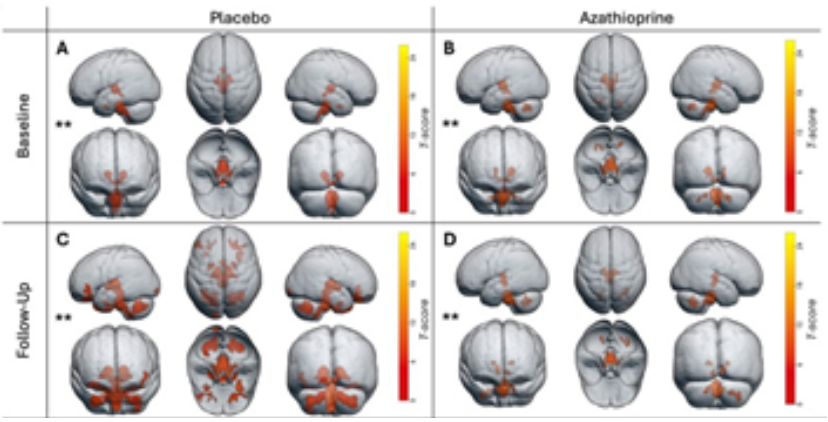
Alexander Peattie

This study has received funding from the Evelyn Trust and the Medical Research Council

THE AZA-PD CLINICAL TRIAL

Building on our research suggesting that immune activation plays a role in Parkinson's, we have conducted a clinical trial of an immunosuppressant drug called azathioprine. The AZA-PD trial began in April 2021 and recruited 66 participants with early-stage Parkinson's disease who were treated with either azathioprine or placebo for 12 months, and then followed up for a further 6 months. The main aim of the trial was to assess whether azathioprine treatment had a beneficial effect on the progression of clinical symptoms of PD. The trial visits were all completed earlier this year. Overall, the treatment was well tolerated with no unexpected safety concerns. Analysis of the trial data is now being finalised and we hope to release the main clinical results of the trial very soon.

In addition to clinical assessments, blood and lumbar puncture samples were collected over the course of the trial. We have measured immune cells and markers in these samples and found that azathioprine reduces immune cells both in the blood and cerebrospinal fluid. We also used PET brain scans to measure inflammation pre and post treatment. The results suggest that inflammation levels in the brain increased over 12 months in people who were taking placebo, but remained stable in those were treated with azathioprine. These results are really encouraging, and suggest that azathioprine had the biologically desired effect of reducing immune activation and inflammation in PD. The trial results will show us whether this is linked to a clinical improvement in PD symptoms.



PET brain scanning using the ligand [11C]-PK11195 showed that inflammation became more widespread over 12 months in people with PD taking placebo (left column) but did not progress in people with PD taking azathioprine (right column).

Julia Greenland

Caroline Williams-Gray

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

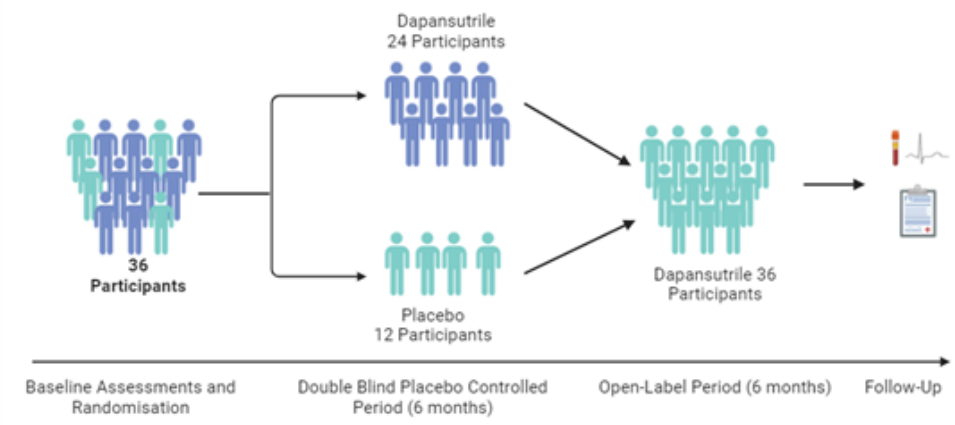
THE DAPA-PD CLINICAL TRIAL

Our previous research suggests that an overactive immune system contributes to the progression of Parkinson's disease. The inflammasome is a key part of the immune system that detects threats and triggers inflammation to protect against harm. It can become excessively activated by abnormal proteins in Parkinson's disease and this can lead to chronic inflammation, contributing to the nerve cell loss seen in the brain of people with Parkinson's disease.

Dapansutrile is a new drug, developed by Olatec Therapeutics, which is designed to stop the overactivation of the inflammasome. Currently it is being tested for its potential use in several diseases.

With funding from Cure Parkinson's and the Van Andel Institute, we are now setting up a new clinical trial of dapansutrile for Parkinson's disease. The trial will recruit 36 people with PD, who will take either dapansutrile or a placebo ('dummy drug') for a duration of six months. During this period, participants will undergo various assessments to help us evaluate the safety of this new drug and its effects on inflammation. These assessments will include specialized brain scans, blood tests, and spinal fluid tests.

After the initial six months, all participants will be offered dapansutrile for an additional six months so that we can continue to measure how it impacts on inflammation and Parkinson's symptoms in the longer-term.



We are currently setting up the trial and hope to begin recruiting participants early next year.

Bina Patel

Caroline Williams-Gray

This work is being funded by Cure Parkinson's and the Van Andel Institute

THE STEM-PD CLINICAL TRIAL

We are very excited to be working on Europe's first clinical trial of a stem cell derived dopamine cell replacement therapy for Parkinson's disease. This trial, being run jointly with colleagues from Lund University in Sweden, is investigating whether dopamine cell transplants into the brain can replace and restore the lost dopamine cell circuits seen in Parkinson's . These circuits are essential for controlling the body's movement and are lost over time in people with Parkinson's.

The STEM-PD cells are generated from human embryonic stem cells that are matured into precursor dopamine-producing nerve cells in the laboratory. These are then implanted into the critical area of brain which is missing dopamine signalling in people with Parkinson's. This surgical implantation is precisely guided using a three-dimensional frame that is attached to the head during the operation and lined up with a scan of the brain, similar to how Deep Brain Stimulation (DBS) surgery for Parkinson's disease is guided.

The focus of this first-in-human trial is to understand whether the STEM-PD cells are safe to use in people with Parkinson's and to help work out exactly how many cells should be transplanted to produce a therapeutic benefit.

The trial started in Sweden in December 2022, aiming to recruit 8 participants. The trial has now completed recruitment, with two UK participants receiving cell transplants in Autumn 2024. The first results from this study will be available after all participants have been followed up for 12 months after transplantation, so in late 2025.

Roger Barker

Saeed Kayhanian

Amy Evans

The STEM-PD cells being drawn up into the surgical implantation device during an operation.

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

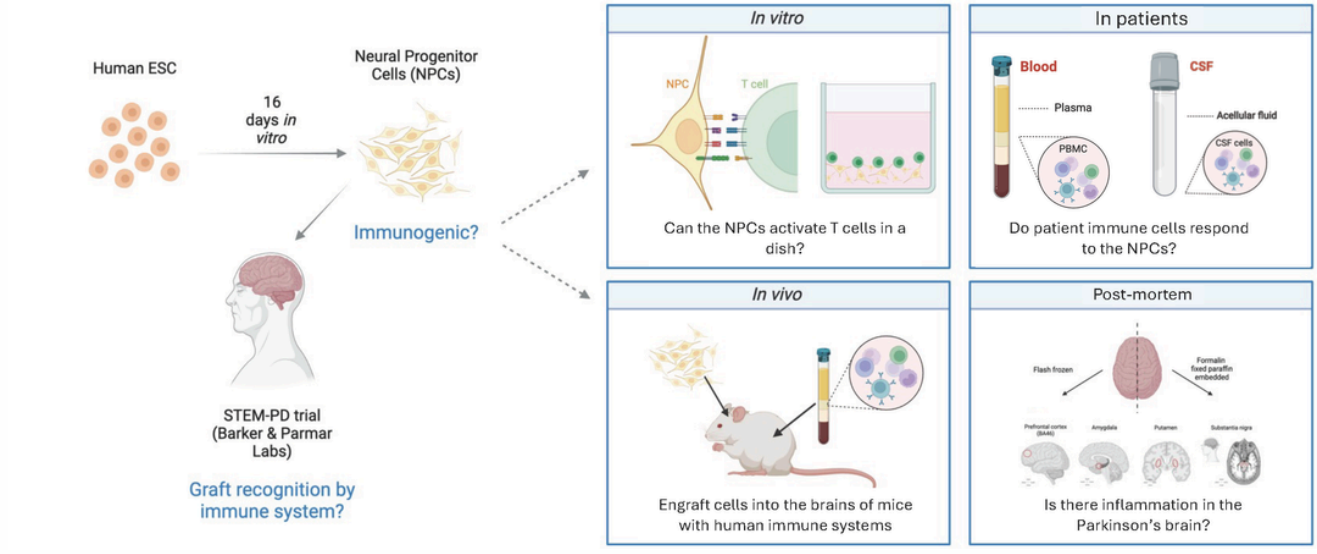
THE IMMUNE SYSTEM IN PD: FROM NEUROPATHOLOGY TO TREATMENT

To understand the immune environment of the brain in Parkinson's disease and how the STEM-PD cell therapy interacts with the immune system, we are using cutting-edge technologies including single-cell and spatial transcriptomics. The "transcriptome" is like a snapshot of all the active molecules in a cell, showing us its function. Single-cell transcriptomics examines individual cells, while spatial transcriptomics reveals how cells interact as networks of cells visualised in a single brain region

We are analysing post-mortem brain tissue donated by people with Parkinson's to explore brain inflammation, focusing on microglia, the brain's immune cells. This is helping us to better understand the environment that the STEM-PD cell therapy is going into. Then by studying blood and cerebrospinal fluid from STEM-PD trial participants, we look for signs of immune activation after receiving cell therapy.

In the lab, we are using models to mimic the cell therapy process. "In vitro" models involve cells grown in a dish, while "in vivo" models use humanised mice (with a human immune system) to closely replicate how the human body responds to transplants. These models allow us to study interactions between transplanted cells and the immune system in a controlled way.

This research aims to improve understanding of the immune system's role in cell therapy and predict how patients may respond. Insights from these studies may help enhance the effectiveness of cell therapies for PD.



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

Anna Curle

METHANE LEVELS AND GUT ORGANISMS

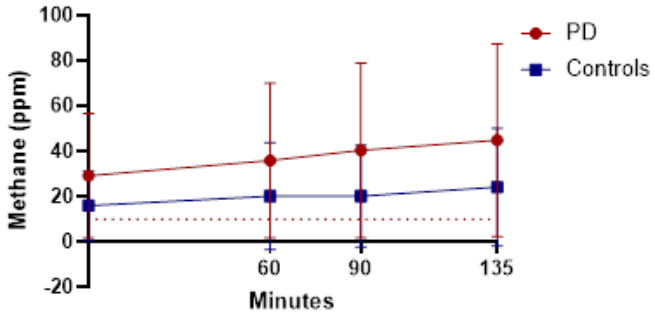
Gut microbes are important players in gut health by producing chemicals, proteins, hormones and gases. Whilst much attention has been dedicated to the role of gut bacteria in Parkinson's disease, other less known microorganisms such as archaea, which produce methane in the gut, might also be contributing to the disease process.

Marta Camacho has been leading a new research study investigating methane levels in Parkinson's using breath testing. 20 people with PD and 20 controls without PD were asked to blow into glass vials every 15 minutes for 135 minutes and their breath was analyse for methane levels. They also donated a stool sample, a blood sample and had a clinical assessment.

Marta found that methane levels in the breath were associated with slower gut transit times and higher levels of archaea in the stool samples. Higher methane levels were also linked to worse memory scores. Marta would now like to explore in more detail how changes in methane-producing archaea are linked to PD symptoms.

In a new study, we are aiming to include a larger group of people with PD, people at high risk of developing PD, other neurodegenerative disorders with memory problems, and controls to determine whether overproduction of methane is specifically linked to development of cognitive problems as well as gut problems and other symptoms. Marta will also be investigating how diet might alter gut methane production, and looking into whether reducing methane levels might be beneficial for the disease.

Breath testing kits



Graph showing that methane levels in the breath are higher in people with PD than those without PD

This work was supported by the Evelyn Trust and the NIHR Cambridge Biomedical Research Centre

Marta Camacho

EXERCISE, THE GUT & PARKINSON'S

We have recently welcomed Fu Miao Tan to the team, an MPhil student who will be working with us this academic year. His project is focusing on the effects of exercise in Parkinson's disease. It is already well known that people who do more exercise have better long-term outcomes in Parkinson's, but the reasons for this are not well understood.

Recent results from our GUT-PD study (led by Marta Camacho) suggest that exercise is a strong protective factor against constipation in PD - and constipation is a known risk factor for accelerated disease progression. We therefore think that changes in gut function might be one of the ways that exercise has an impact in PD. However, the effect of exercise on gut function, the gut microbiome and associated inflammation in PD has not been properly investigated.

Fu Miao will be using data already collected through the GUT-PD study to investigate whether and how levels of exercise are associated with gut symptoms, blood markers of gut function and inflammation, microbial changes in the stool, and PD progression.

We look forward to learning how different types of exercise (sports, walking, playing an instrument) relate to changes in the gut in PD, and to PD symptoms. We hope tthat this will help us to give better management advice around exercise, and to understand how we might combine this with other treatments targeting gut health.

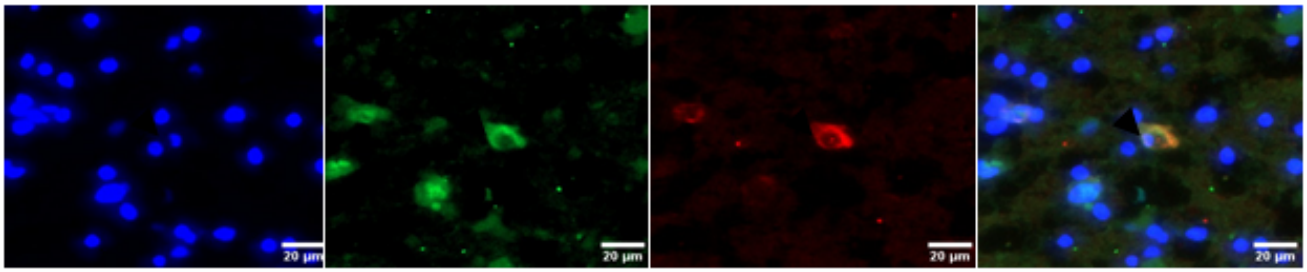
Fu Miao Tan

USING NASAL AND SALIVA SAMPLES TO STUDY THE INNATE IMMUNE SYSTEM IN PD

In an ongoing effort to better understand the involvement of the immune system in Parkinson's disease, we have designed a new study to look at how different immune cells are involved at different stages of the disease. We will be looking specifically at natural killer (NK) cells, monocytes and neutrophils which are three different types of immune cells which form part of the innate immune system. The usual role of the innate immune system is to defend us from infections and injury, but in Parkinson's disease it may have a detrimental role by causing excessive brain inflammmation.

Clotilde Tournerie (PhD student) will be working on this study, which will involve people with PD at early and late stages of disease, as well as healthy controls. We will also invite people who have a condition called REM Sleep Behaviour Disorder which is associated with a high risk of developing PD, so that we can see whether immune changes happen even before PD develops. We typically study immune cells in blood samples, but in this study we will also collect nasal and saliva samples, because we know that the disease process in PD affects cells in the nose and salivary glands from an early stage. Clotilde will measure changes in immune cells in these samples, as well as alpha-synuclein protein, which is linked to cell damage in PD. In doing this, she hopes to show that these easily accessible biosamples can be used to measure immune markers, and that these markers change from early to late stage disease.

Clotilde is also looking whether the same types of immune cells are infiltrating into the brain in PD, by staining post-mortem brain tissue with fluorescent markers which label different immune cell types. Overall, this study aims to fill important gaps in our understanding of the involvement of innate immune cells in Parkinson's, as well as to provide new avenues for developing immune-related markers of disease progression, and immune-targeting therapies.



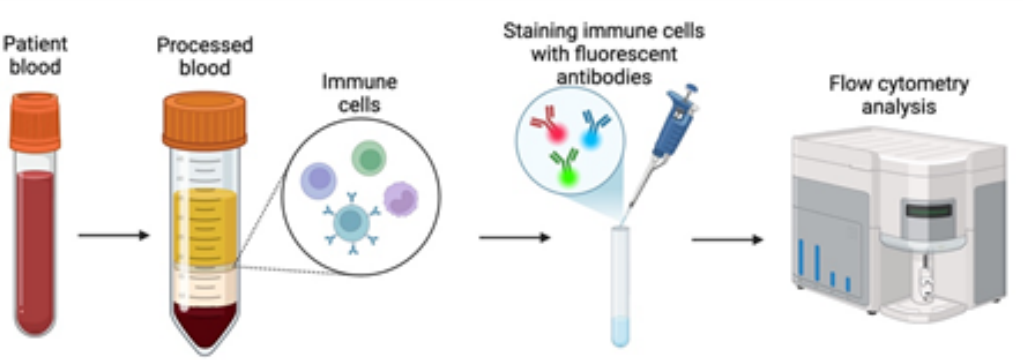
Post-mortem brain tissue stained with fluorescent markers to detect NK cells

Clotilde Tournerie

Clotilde's work is supported by the MRC-DTP PhD programme

UNDERSTANDING THE ROLE OF T REGULATORY CELLS IN PARKINSON'S DISEASE

Another immune cell type of interest in Parkinson's disease are 'T regulatory cells' (Tregs). These make up a small proportion of the immune cells in the blood, but play a very important role in regulating immune responses and preventing excessive inflammation. There has been some evidence from work done at other research centres which suggests that Tregs might not function properly in PD, but this is unclear and not well studied. Understanding whether Tregs are dysfunctional in PD is of great interest because it may be possible to deliver therapies which boost their function. The hope is that this might reduce inflammation and slow disease progression.



Sara Crooks (PhD student) is exploring the role of Tregs in PD in depth, assessing whether there are changes in these cells in the blood of people with PD compared to healthy controls. This work includes:

-Extracting Treg cells from blood samples and looking at cell markers which tell us their characteristics such as how stable or activated they are, and whether they can move into other tissues or the brain. This uses a technique called spectral flow cytometry.

-Looking at how these Treg cells function, for example how well they can suppress the activity of other immune cells in the blood. This involves looking at how Treg cells behave and interact with other immune cell types using experiments in the laboratory.

-Looking for evidence of infiltration of Tregs in the brain, by examining post-mortem brain samples and using markers which bind to Tregs and allow us to visualise them.

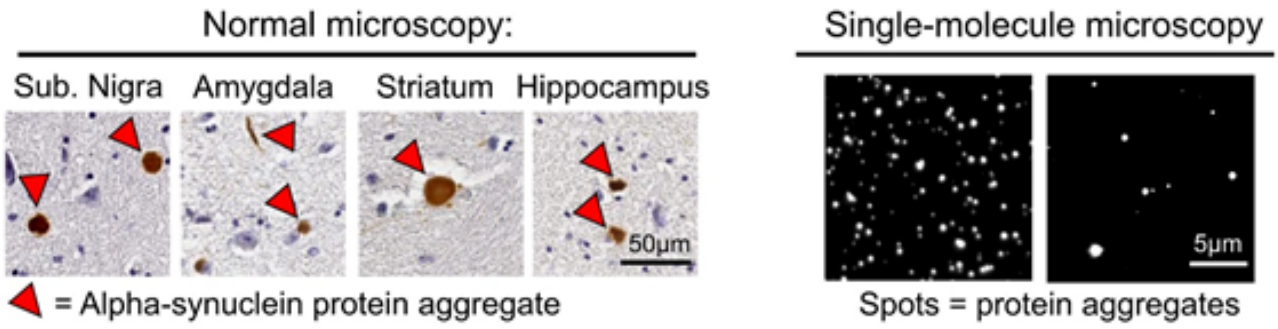
Sara's work is supported by the MRC-DTP PhD programme

Sara Crooks

EXAMINING PROTEINS IN THE BRAIN IN PD USING SINGLE-MOLECULE MICROSCOPY

In Parkinson's disease and many other neurological diseases, large clumps of protein in the brain can be seen under the microscope. The specific protein that aggregates into clumps helps us differentiate between various diseases, for example, in Parkinson's, a protein called alpha-synuclein forms clumps, whereas in Alzheimer's diesase, two proteins called tau and amyloid-beta are involved. However, it is now becoming clear that not just alpha-synuclein, but a combination of proteins, might be relevant in Parkinson's disease. We are trying to characterise these different protein clumps in post-mortem human brain tissue from people with Parkinson's to help us better understand what causes brain cell damage.

Florence Layburn, a PhD student who is based in Professor Sir David Klenerman's lab in the University of Cambridge Department of Chemistry, is using a new technique based on single-molecule microscopy to visualize protein aggregates in the brain. This technique allows her to measure the size, number, and composition of protein aggregates that are too small to be seen using a standard microscope. Florence is measuring small protein aggregates of various types from five different brain regions including the hippocampus, amygdala (both involved in memory), the frontal cortex (thinking and planning), occipital cortex (visual information processing), and striatum (movement control). Her early results suggest that tau protein has a larger influence in Parkinson's than previously thought, and she is now investigating how small tau aggregates might be linked to inflammation in the brain.



Different appearance of protein aggregates using normal microscopy techniques compared to single-molecule microscopy. The scale is 10 times higher in single-molecule microscopy (5µm compared to 50µm), so we are able to measure very small aggregates.

Florence Layburn

This study is funded by the Medical Research Council

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. Tissue donation can also be valuable for research.

Brain donation for research is a precious and unique gift. Scientists can learn and understand more about brain diseases 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 add-tr.cambridgebrainbank@nhs.net for further information, or https://www.cuh.nhs.uk/patient-information/the-donation-of-brain-pituitary-tissue-and-cerebrospinal-fluid-after-death/

Ann Mary Alias
Specialist Brain Bank Research Nurse

THANK YOU TREVOR!

Trevor was diagnosed with Parkinson's disease 5 years ago. In his own words 'it was devastating at first' but he made a commitment to himself to keep active and not give up on camping and hill walking as his main hobbies, and he walks his dog, Sam, 10km every day. Since his diagnosis, he has been an enthusiastic research participant. He is involved in our PD Research Clinic, the NET-PDD study, exercise for Parkinson's study, and others. Through these, he realized how research studies are constrained by budgets and funding, and, in June 2024, he organized a 120km walk along Hadrian's Wall from Newcastle to Carlisle to raise money for our PD research programme at the Cambridge Centre for Brain Repair and to promote awareness of what it is like to live with Parkinson's. Through this incredible challenge, he raised over £2000. He will be talking about this experience in our next PD Open Day and sharing his plans for his next adventure - walking on volcanos for Parkinson's disease!

Trevor and Sam before their 120km walk.

CONTACT US

Facebook: The Barker/Williams-Gray Lab

Telephone: 01223 331160

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.

UPCOMING EVENTS

Check out the website at www.wpc2026.org

THANK YOU TO OUR FUNDERS

NIHR | Cambridge Biomedical Research Centre

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

CURE PARKINSON'S

European Commission

MRC Medical Research Council

Cambridge Centre for Parkinson-Plus

novo nordisk

BRITISH COUNCIL

NSC-Reconstruct
Horizon 2020 European Union Funding for Research & Innovation

Rosetrees Trust
Supporting the best in medical research

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

asap
Aligning Science Across Parkinson's

UK Regenerative Medicine Platform

wellcome trust

The Evelyn Trust

The Academy of Medical Sciences