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

Exhibitor abstracts

- Online Research Conference 2020

- Poster 23 - Common Variants Co-Regulate Expression of GBA and Potential Modifier Genes to Delay Parkinson's Disease Diagnosis
- Poster 24 - Regional vulnerabilities in Parkinson's disease: investigating the role of SNCA gene copy gains in the occipital cortex.
- Poster 25 - IMMUNE EFFECTS OF DOPAMINERGIC AGENTS ON HUMAN CD4+ T LYMPHOCYTES: RELEVANCE FOR PARKINSON'S DISEASE
- Poster 26 - Investigating the impact of patient and public involvement on the readability of Parkinson's UK grant plain English summaries.
- Poster 27 - Glucocerebrosidase deficiency increases release of α-synuclein fibrils
- Poster 28 - Investigating LRRK2 Kinase activity and VPS35 function in human cell culture models of Parkinson's Disease
- Poster 29 - Differential in-vitro diagnostics of neurodegenerative dementias
- Poster 30 - Novel compounds modify mitochondrial deficits in Parkinson's models
- Poster 31 - Behavioural recovery after transplantation of hiPSC-derived dopamine grafts is dependant on neurite outgrowth.
- Poster 32 - Galvanic Vestibular Stimulation and Balance Control in Parkinson's Disease
- Poster 33 - Involving people with Parkinson's Disease in the co-design a trial investigating the effect of Galvanic Vestibular Stimulation on balance
- Poster 34 - Uncovering the Mechanisms of Mitochondrial Rescue with the use of a Novel Therapeutic Compound for the Treatment of Sporadic Parkinson's
- Poster 35 - The CloudUPDRS Smartphone Software in Parkinson's (CUSSP) study
- Poster 36 - Identification of candidate Parkinson's disease genes by integrating GWAS, expression and epigenetic datasets
- Poster 37 - Axonal translation in Parkinson's striatal dopamine neurons: Sequencing the 'translatome'
- Poster 38 - Single-cell sequencing of induced pluripotent stem cell (iPSC) dopamine neurons reconstructs disease progression and identifies HDAC4 as a regulator of Parkinson cell phenotypes
- Poster 39 - Neuropsychiatric differences and carer distress in Parkinson's disease, dementia with Lewy Bodies and Alzheimer's disease
- Poster 40 - Neuropsychological changes over the first 6 years of Parkinson's disease in the ICICLE-PD cohort
- Poster 41 - Using a high-throughput toxin-induced LUHMES neuronal model to screen for mitochondrial restorative compounds for Parkinson's disease.
- Poster 42 - Mass spectrometry based analysis of the biophysical properties of recombinant α-synuclein for the protein quality control and robust α-synuclein RT-QuIC
- Poster 43 - WNT and NFAT signalling changes in LRRK2 Parkinson's disease models
- Poster 44 - Visualising α-Synuclein oligomers using super-resolution microscopy
- Poster 45 - Spontaneous graft-induced dyskinesias correlate with graft inflammation, and are independent of 5-HT neurons and L-DOPA priming, in a xenograft model of Parkinson's disease
- Poster 46 - Predicting outcome using patient reported outcomes (PROs) in the UK Parkinson's Disease Tissue Bank.
- Poster 47 - REMOVED ON AUTHOR'S REQUEST
- Poster 48 - Quantitative chemical imaging of soluble α-synuclein and Aβ aggregates with Single Molecule Pull-down Assay in human Parkinson's brains
- Poster 49 - Characterising Sleep Quality in an Irish Parkinson's Cohort Using a Combination of Subjective and Objective Methods.
- Poster 50 - Using Actigraphy to Characterise the Relationship between Sleep, Quality of Life, and Depression in Parkinson's
- Poster 51 - Functional and axonal outgrowth deficits in tau-deficient human neurons
- Poster 52 - Human-specific levels of CDNF, MANF and ER stress in the pathological progression of Parkinson's disease
- Poster 53 - Human-specific transcriptomic profiling of ventral and dorsal midbrain dopamine neurons
- Poster 54 - Developing 31-phosphorus magnetic resonance spectroscopy (31P-MRS) as an imaging biomarker to identify mitochondrial dysfunction in Parkinson's disease
- Poster 55 - The UP study - Ursodeoxycholic acid (UDCA) as a neuroprotective treatment for Parkinson's disease
- Poster 56 - Investigating behavioural impulsivity and inhibitory control in Parkinson's and impulse control behaviours
- Poster 57 - Dose and time dependent effects of anle138b in transgenic MI2 mice expressing truncated human alpha-synuclein
- Poster 58 - How far can I reach? Perception of action capabilities in people with Parkinson's
- Poster 59 - Gabapentinoid drugs modify Ca2+ entry to striatal dopamine axons and promote dopamine release in a mouse model of Parkinson's

- Poster 60 - Universal latent axes capturing Parkinson's patient deep phenotypic variation reveals patients with a high genetic risk for Alzheimer's disease are more likely to develop a more aggressive form of Parkinson's.
- Poster 61 - A cellular model for sporadic Parkinson's disease
- Poster 62 - The role of pathogenic GBA1 mutations in the relationship between GBA1 and alpha-synuclein and the influence on Parkinson's disease.
- Poster 63 - Activity of the SERCA calcium pump is reduced in Drosophilaand human cell models of Parkinson's based onDJ-1 deficiency
- Poster 64 - Finding new drug targets for Parkinson's disease using genetics – Mendelian randomization of the druggable genome
- Poster 65 - Predicting the efficacy of exenatide in Parkinson's disease using genetics – a Mendelian randomization study
- Poster 66 - To investigate the hypothesis that raising proprioceptive awareness through specific movement-based exercise can support effective postural alignment for expiration during seated Parkinson's community choral sessions.
- Poster 67 - Genome-wide association studies of progression in Parkinson's disease
- Poster 68 - Multi-omic network analysis provides insight into exclusive and shared molecular signatures of neurodegenerative disorders
- Poster 69 - Exploring how people with Parkinson's watch dance with and without facial expressions
- Poster 70 - Generation of highly enriched hiPSC-derived midbrain dopaminergic neurons to model Parkinson's disease in vitro
- Poster 71 - A cellular atlas of human Substantia nigra enables the prediction of cell type-specific gene expression changes associated with Parkinson's disease risk
- Poster 72 - Bilateral Subthalamic Nucleus Theta-Frequency Stimulation Improves Episodic Category Fluency in Patients with Parkinson's Disease: A Double-Blinded Randomized Crossover Trial
- Poster 73 - Investigating the effects of staying at home during the COVID-19 pandemic on impulse control behaviours in people with Parkinson's
- Poster 74 - Investigating the impact of COVID19 on social interactions and technology use in people with Parkinson's

Exhibitor - Astex

Astex

Abstract TBC.

Exhibitor - Bial

Bial for Professionals

Abstract TBC.

Exhibitor - Boston Scientific Deep Brain Stimulation

Boston Scientific

Deep Brain Stimulation (DBS) is a surgical treatment which can help manage some movement disorder symptoms. DBS is typically used to treat people with advanced Parkinson's disease (PD), dystonia, and essential tremor (ET) whose symptoms are no longer controlled by medication. DBS is a well-established, safe, and effective treatment that helps improve day-to-day experiences and quality of life for these patients.

Exhibitor - Guarantors of Brain

Guarantors of Brain

The Guarantors of Brain is a charity that aims to promote teaching, education and research in neurology and related clinical-academic disciplines. The Charity was founded in 1955 with a body of Guarantors (Trustees) drawn from leading British Neurologists, Psychiatrists, Neurosurgeons, Neurophysiologists and Neuroscientists.

The official journals of the Guarantors of Brain are Brain and Brain Communications, published in partnership with Oxford University Press (OUP).

Exhibitor - Kinetikos

Kinetikos

Kinetikos is a digital health company on a mission to revolutionise the standard of care for movement disorders. We have developed a medical-grade tool for Parkinson's Disease treatment for accurate assessment of functional mobility and treatment monitoring. A telehealth tool for clinical care and clinical trials that quantifies mobility during daily living activities and improves quality of life through continuum healthcare. Our integrated solution is designed to help you improve patient care, drive clinical performance and lower costs.

Let´s get in touch to discuss collaborative research opportunities, the involvement in clinical trials or simply show you more about our products!

We currently support clinicians and researchers in Europe and America through our web-based clinical decision-making and analysis platform which combines artificial intelligence with accurate biomechanical models. The benefits are both higher accuracy-of and shorter time-to decision resulting in cost-effective services.

Some of our partners are: Queen Square Institute of Neurology, Madrid Parkinson Association, Columbia University in the city of New York.

Key Achievements:

- Regulatory-cleared: CE Mark Medical Device
- Scientific-validated: Clinical trial showing high usefulness and feasibility
- Key Opinion Leaders: PD customers in Lisbon, Madrid, London & NY
- Participation in EU projects

See you soon.

Exhibitor - Merz Therapeutics

Merz Therapeutics

Merz Therapeutics is a global pharmaceutical organisation with focus on patients with Movement Disorders. XEOMIN® Botulinum Toxin type A is the only treatment licenced for chronic sialorrhea (drooling) in adults due to neurological disorders[1]† including Parkinson's disease. XEOMIN® is recommended by NICE (TA605), within its marketing authorisation, as an option for this indication. It is recommended only if Merz provides it according to the commercial arrangement[2].

XEOMIN® is injected into the parotid and submandibular salivary glands providing a reduction in the patient's salivary flow rate for up to 4 months[3].

The Merz UK team are offering sialorrhea training and educational meetings both virtually and face to face for healthcare professionals managing Parkinson's patients with sialorrhea. For more information please visit the Merz conference booth or register your interest at XeominUK.com in the contact us section. Please click here for the XEOMIN® Prescribing Information.

[1] XEOMIN® Summary of Product Characteristics (SmPC)

[2] NICE Guidance. Xeomin (botulinum neurotoxin type A) for treating chronic sialorrhoea

[3] Jost WH. et al. Neurology. 2019 Apr 23;92(17):e1982-e1991. doi: 10.1212/WNL.0000000000007368. Epub 2019 Mar 27

† As of May 2019

Exhibitor - Symprove

Symprove

Founded in 2002, Symprove Ltd is committed to developing the understanding of the role of the gut microbiome through extensive research and testing. Our unique water-based food supplement called Symprove was launched in 2010 and contains four unique strains of live and active bacteria to support a healthy microbiome within the context of a healthy diet and lifestyle. Several studies have been carried out on Symprove, demonstrating its effective delivery system and looking at how gut function is impacted by the use of multistrain live bacteria.

Exhibitor - The UK Parkinson's Excellence Network

The UK Parkinson's Excellence Network

The UK Parkinson's Excellence Network is the driving force for improving Parkinson's care. It connects and equips all professionals to provide the services people affected by the condition want to see.

The Excellence Network offers free tools, education and data that are crucial for better services and professional development.

Parkinson's UK - Adapting research trials in light of COVID-19

Parkinson's UK Research Team

After many Parkinson's clinical studies had to be put on hold due to COVID-19, steps are now being taken to restart clinical research. It is vital that research resumes in a way that is safe, comfortable and convenient for people taking part. As researchers look to make adaptations to existing studies and plan for new ones, it is important that they take into account the views of people affected by Parkinson's.

Parkinson's UK have conducted a survey with people affected by Parkinson's to understand:

- how people feel about taking part in research in light of COVID-19
- what adaptations may need to be made to the way studies are carried out to help people feel safe taking part in research
- what support people may need to be able to take part in research studies, in light of adaptations

Here we present the results from the survey and recommendations for researchers, clinicians and pharmaceutical companies to help ensure studies are adapted and designed in a way that enables people affected by Parkinson's to remain active participants in research.

Parkinson’s UK - Improving research participation

The Parkinson’s UK Research Participation Steering Group

At Parkinson's UK we've had a workstream dedicated to improving research participation since 2015. The focus of this work has been to increase opportunities for people affected by Parkinson's to take part in research working with health care and research professionals.

To help give you an overview of the work we do, we have put together a schedule of conversation topics with members of the Participation Steering Group (the driving force behind this workstream):

Day 1

- 10:45 - 12:25: Introduction to the Participation Steering Group (PSG) - Laurel Miller
- 12:25 - 14:35: Introduction to the Take Part Hub -Alan Cameron
- 14:35 - 16:15: When people with Parkinson's want to know about research - Katherine Fletcher
- 16:15 - 17:45: The Participation Steering Group, a research professional perspective - Dr Tom Payne

Day 2

- 10:45 - 12:25: How we can help you recruit participants - Amelia Hursey
- 12:25 - 14:35: Continuous Engagement Project and poster - Jodie Keyworth
- 14:35 - 16:15: Your insight into how we can better support communication with participants - Amelia Hursey
- 16:15 - 17:45:The 'Communicating With Your Participants Toolkit' introduction and future plans - Julie Jones

If you would like to discuss anything else we are more than happy to do so

Parkinson's UK - Parkinson's Connect: Our information and support service

The Parkinson's UK Parkinson's Connect team

Find out more about Parkinson's Connect - a personalised information and support service from Parkinson's UK.

Parkinson's UK are designing a new support pathway, with people Parkinson's, their family friends and carers and healthcare professionals at its centre.

In the last 16 months the Parkinson's Connect team have spoken with over 100 people with Parkinson's and their family and friends, as well as health professionals across the UK, to explore what they want and need from a support service.

To ensure we are reaching everyone affected by the condition at diagnosis, three healthcare services are testing a new direct referral process.

Since direct referrals went live in January 2020, 63 newly diagnosed people with Parkinson's and 20 of their family members, have been referred to tailored content and support from Parkinson's UK.

Over the next 12 months we will be scaling our direct referral to more healthcare teams, to continue testing the process, learning, improving and reaching more people.

Parkinson's UK - Patient and public involvement (PPI) in research

The Parkinson's UK Patient and Public Involvement (PPI) team

We want all Parkinson's researchers to work in partnership (collaboration) with people affected by Parkinson's as much as possible. Involving people affected by Parkinson's in research leads to higher-quality research focused on what matters most to those living with the condition. Patient and public involvement (PPI) can also improve the recruitment and retention of participants to studies, leading to more efficient and successful research projects.

But we recognise that PPI can be a challenge, which is why we support researchers to carry out meaningful involvement that will add value, insight and relevance. Regardless of who you are funded by or applying for funding from, we can help you:

- understand when and how you should involve people affected by Parkinson's
- help you to plan and carry out relevant and meaningful involvement activities
- connect with people affected by Parkinson's and
- develop working relationships with PPI contributors

Visit the booth to learn more about our PPI programme and to hear from some members of the Involvement Steering Group, who design and oversee our programme.

Parkinson's UK - Research Grant Funding

The Parkinson's UK Research Grants Team

Parkinson's UK is the largest member-led charitable funder of Parkinson's research in Europe. So far, we've invested more than £93 million in groundbreaking research.

Our wide range of research grants offers support to Parkinson's researchers at every stage of their careers.

.

Parkinson's UK - Research Interest Groups

The Parkinson's UK Research Interest Groups

The Parkinson's UK Research Support Network (RSN) brings together people driven to help find a cure and better treatments for Parkinson's. Our Research Interest Groups (RIGs) up and down the UK are made up of people affected by Parkinson's, researchers and healthcare professionals, and they support us with our key aims at a regional level, including: increasing awareness and understanding of research, encouraging participation in research, and encouraging and supporting Patient and Public Involvement in shaping research.

If you're a researcher or healthcare professional interested in joining an existing group, or starting a new local Research Interest Group, please get in touch with Liz Nash, our Research Support Network Manager, at rsn@parkinsons.org.uk.

Parkinson's UK - The Edinburgh Parkinson's Lecture 2020

The Edinburgh Parkinson's Lecture 2020

The Edinburgh Parkinson's Lecture is organised by the Edinburgh Branch of Parkinson's UK. The Edinburgh Parkinson's Lecture has become a flagship annual event for the Parkinson's community in Scotland. The Lecture attracts internationally renowned experts to inform and educate a large live audience and to review progress in the fight against Parkinson's. This year for the first time the Lecture will take place as a live streamed online event. This means that we can reach out to a much larger audience.

We invite you to join us!

Parkinson's UK - The Parkinson's Virtual Biotech

The Parkinson's Virtual Biotech

The Parkinson's Virtual Biotech is the drug discovery and development arm of Parkinson's UK, focused on the timely delivery of novel therapies for People with Parkinson's. In this poster, we describe how we work and who we are, as well as providing an illustrative case history of one of our projects.

Poster 1 - Empirical evidence supports an aetiological role for changes in biometal pathways in Parkinson's disease

Amr Abdeen, Dr Benjamin Trist, Prof Kay Double

Brain and Mind Centre and Discipline of Pharmacology, School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

Iron overload and copper deficiency are characteristic of the degenerating substantia nigra (SN) in Parkinson's disease brains, however the evidence for causality between these pathological features has not been previously assessed. We gathered empirical evidence of metal changes in the Parkinson's disease SN using a systematic review, then employed the Bradford Hill model of causation to systematically assess whether the available evidence supports a causal relationship between metal alterations and neuron death in Parkinson's disease. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. An electronic search of articles published up to September 2019 was conducted in PubMed, EMBASE, Central Register of Controlled Trials and Scopus, and 8437 resultant articles were screened for pre-defined inclusion and exclusion criteria restricted to human research. The quality of the included 182 articles was assessed using our published Quality Assessment Scale and the NIH Quality Assessment tools; studies of limited quality were removed, resulting in 156 studies for final analysis. The Bradford Hill model evaluates a potential causal inference of one variable on another by assessing published evidence supporting and opposing each according to a set of nine criteria. Assignment of the final 156 studies to these nine criteria revealed that at least seven criteria support a causal role for alterations to iron and copper levels in nigral neuron death in Parkinson's disease patients. This study supports the development and clinical testing of current and future therapeutic interventions targeting metal alterations in Parkinson's disease.

Poster 2 - Plantarflexor muscle activity during a change in walking speed on a treadmill: Comparison between people with Parkinson's and physically fit controls

Mrs Esraa Aldayil, Mr Andrew Kerr

University of Strathclyde, Glasgow, United Kingdom

Background: Variable speed treadmill training may support the recovery of community walking in Parkinson's. This study aimed to determine the differences in plantarflexor activity during a change in treadmill speed between control and Parkinson's participants.

Method: Participants included control (n= 10, aged 31.7 (+/-17.9 years) and Parkinson's (n= 6, aged 67.3 +/-11.57 years) groups. Participants walked on a self-pacing treadmill linked to a virtual reality screen. Electromyography (EMG) captured the activity of gastrocnemius and soleus muscles during a planned increase in speed. Differences in contraction duration were compared before and during the speed change.

Results: Muscle excitation (area under curve) for soleus was increased in Parkinson's (+0.0029 mV %Gait cycle) but slightly decreased in controls (-0.0008 mV %Gait cycle) while in other muscles was broadly similar

Discussion: The muscle work associated with an increase in treadmill walking speed appears to differ between Parkinson's and physically fit controls. A longer contraction duration from the plantarflexors suggests these muscles provided (in part at least) the forward impetus in Parkinson's, this was particularly evident in substantially longer soleus activity which has been reported before in relation to gait initiation and may relate to heightened postural control.

Conclusions: A different motor strategy may be used by people with Parkinson's to increase walking speed on a treadmill. These preliminary findings should be further tested and compared to overground walking.

Poster 3 - Ochratoxin A induced chaperone-mediated dysfunction and alpha-synuclein accumulation in cell models

Dr Maria Izco[1], Dr Ariane Vettorazzi[2], Prof Adela Lopez de Cerain[3], Dr Lydia Alvarez-Erviti[1]

[1]Center of Biomedical Research of La Rioja (CIBIR), Logrono, Spain. [2]Universidad de Navarra, Pamplona, Spain. [3]University of Navarra, Pamploan, Spain

Objective: The aim of the present project was to determine the effect and mechanisms of Ochratoxin A (OTA) on alpha-synuclein in vitro in neuroblastoma cell lines.

Background: The primary cause of Parkinson's disease in the majority of patients is still unclear; however, several environmental factors have been associated with Parkinson's disease. Mycotoxins are a group of naturally-occurring fungal metabolites. OTA has shown neurotoxicity and striatal dopamine depletion in mice.

Methods: We established a neuronal (SH-SY5Y over-expressing alpha-synuclein) cell models. We assessed alpha-synuclein, LAMP-2A, hsc70 mRNA and protein levels, and alpha-synuclein turn-over. We evaluated miRNA levels after exposure to OTA.

Results: OTA treatment increased significantly alpha-synuclein levels due to an increased in alpha-synuclein half-life. Since the main pathway for alpha-synuclein degradation is CMA, we assessed LAMP-2A and hsc70 levels. None of the OTA concentrations significantly affected hsc70 protein or mRNA levels. OTA exposure induced a significant 45% decrease in LAMP-2A protein and a significant 48% decrease in lamp-2a mRNA.

A previous report showed that elevated miRNA levels lead to downregulation of LAMP-2A levels and compromised alpha-synuclein degradation. After OTA exposure 6 miRNAs were significantly upregulated and 4 miRNAs were significantly downregulated. A miRNA target analysis predicted hsa-miR-193a-3p to target lamp-2a mRNA. We transfected SH-SY5Y cells with a luciferase reporter constructs with the lamp-2a 3'UTR sequence and confirmed that hsa-miR-193a-3p caused a decrease in luciferase activity.

Conclusions: OTA increases alpha-synuclein levels due to a decrease in LAMP-2A protein caused by OTA induced miRNA dysregulation.

Poster 4 - Improving functional hand actions in Parkinson's through home-based observation and imagery training: a pilot randomised controlled trial of ACTION-PD

Dr Judith Bek[1], Dr Trevor Crawford[2], Professor Paul Holmes[3], Dr Stefan Vogt[2], Dr Ellen Poliakoff[1]

[1]University of Manchester, Manchester, United Kingdom. [2]Lancaster University, Lancaster, United Kingdom. [3]Manchester Metropolitan University, Manchester, United Kingdom

Objective: To investigate the acceptability and potential outcomes of a home-based intervention to improve everyday hand actions using observation and imagery.

Background: Action observation and motor imagery activate the sensorimotor system to facilitate movement, particularly when combined (watching an action while imagining performing it). Combined observation and imagery influence hand movements in lab-based studies in Parkinson's[1], but this has not yet been tested within an intervention. We have co-developed ACTION-PD, a home-based observation and imagery intervention, which is delivered via a tablet computer app[2].

Methods: A 6-week pilot randomised controlled trial in people with mild-to-moderate Parkinson's compared ACTION-PD (N=6) versus treatment as usual (N=4). The intervention involved video-based observation, imagery and physical practice of 5 functional actions (e.g., fastening buttons). Participants were asked to train for 120 minutes weekly. Pre- and post- assessments were conducted and participants were interviewed following training.

Involvement of people affected by Parkinson's: Through focus groups to inform intervention development, and as members of the research team.

Results: The target training dose was achieved and interviews indicated acceptability of the intervention. Preliminary outcomes suggested improvements in trained and untrained action performance, self-reported dexterity and reaction times. Qualitative data highlighted the need for a greater variety of actions, performance feedback, and additional support to engage in motor imagery.

Conclusions: Home-based training using observation and imagery is acceptable and may improve everyday hand movements in Parkinson's. The findings indicate that a larger trial of ACTION-PD is warranted, and support the use of observation and imagery in Parkinson's interventions.

1. Bek, J., Gowen, E., Vogt, S., Crawford, T.J., & Poliakoff, E. (2019). Combined action observation and motor imagery influences hand movement amplitude in Parkinson's disease. Parkinsonism and Related Disorders. https://doi.org/10.1016/j.parkreldis.2018.11.001

2. Bek, J., Webb, J., Gowen, E., Vogt, S., Crawford, T.J., Sullivan, M., & Poliakoff, E. (2016). Patients' Views on a Combined Action Observation and Motor Imagery Intervention for Parkinson's Disease. Parkinson's Disease. https://doi.org/10.1155/2016/7047910

Poster 5 - Assessing the impact of N-terminal acetylation on α-Synuclein's biophysical properties

Miss Rosie Bell, Miss Marta Castellana-Cruz, Dr Patrick Flagmeier, Dr Janet R. Kumita, Professor Michele Vendruscolo

University of Cambridge, Cambridge, United Kingdom

Objective(s): We aim to analyse the impacts of N-terminal acetylation on the biophysical properties of α-Synuclein (α-syn) at different stages of amyloidogenic cascade.

Background: α-Syn is a major component of Lewy Bodies, found in the brain of individuals suffering from Parkinson's Disease. In vivo α-syn has been found to be constitutively N-terminally acetylated (NTA).

Methods: We employ a three-pronged kinetic approach to compare acetylated-α-syn aggregation with that of the non-acetylated protein. We wish to examine the impact of NTA on the microscopic processes of amyloid aggregation (primary nucleation, secondary nucleation and fibril elongation). Through the kinetic measurements, an estimate of oligomer population can also be determined. The effects of NTA on lipid binding, fibril morphology, structure and stability will also be analysed using a variety of biophysical techniques. In vivo studies on α-syn toxicity and induction of oxidative stress in a neuroblastoma cell line will be done alongside.

Involvement of people affected by Parkinson's: To further study the impact of NTA on α-syn, the familial Parkinson's mutations H50Q and G51D are also studied.

Results: Our results have shown that NTA effects all stages of amyloidogenic aggregation as well as fibril morphology and structure.

Conclusions: As the complex pathway through which soluble, monomeric α-syn converts to amyloid-like fibrils results in the population of cytotoxic species in vivo, it is important to understand the effect of post-translational modifications, including NTA, on these processes. Mechanistic details of how NTA affects aggregation may open new avenues for therapeutic intervention.

Poster 6 - DNA methylome analysis in post-mortem brain tissue led to the identification of new α-synuclein partners in the pathogenesis of multiple system atrophy

Dr Conceição Bettencourt[1], Dr Yasuo Miki[1], Dr Ignazio Piras[2], Prof. Matt Huentelman[2], Prof. Janice Holton[1]

[1]UCL Queen Square Institute of Neurology, London, United Kingdom. [2]Translational Genomics Research Institute, Phoenix, USA

Objective: To investigate whether DNA methylation changes and downstream consequences in gene and protein expression contribute to the molecular processes altered in multiple system atrophy (MSA).

Background: MSA is a fatal late onset neurodegenerative disease, characterized by a variable combination of parkinsonism, ataxia and autonomic failure. Like Parkinson's disease, MSA is an α-synucleinopathy. The presence of α-synuclein within glial cytoplasmic inclusions (GCIs) in oligodendrocytes is the diagnostic hallmark of MSA. We have previously shown consistent DNA methylation changes in MOBP and HIP1 associated with MSA.

Involvement of people affected by Parkinson's: We have included Parkinson's disease as a comparison group.

Methods: We have investigated MOBP and HIP1 expression patterns using RNA-seq, and protein changes using immunohistochemistry and immunoblotting in cerebellar white matter tissue from MSA cases and controls. For immunoblotting, we have included Parkinson's disease, progressive supranuclear palsy and Huntington's disease cases as comparison groups.

Results: MOBP mRNA was downregulated in MSA and this was correlated with higher DNA methylation levels in MSA. No significant differences were detected for HIP1. While there were no changes in MOBP and HIP1 protein levels when compared to controls, there were significant differences with other neurodegenerative diseases. MOBP and HIP1 were mislocalized into GCIs in MSA where they appear to interact with α-synuclein.

Conclusions: Our results support a role for DNA methylation in regulating MOBP expression levels and point towards post-transcriptional mechanisms influencing its protein levels in MSA. We provide new insights into MSA pathogenesis by identifying MOBP and HIP1 as new α-synuclein interactors.

Poster 7 - The NeuroMotor Pen – An easily performed objective test of fine motor skill to support diagnosing Parkinson's disease

Dr Rutger Zietsma[1], Dr Sanja Bojic[1], Mr Arbinda Karki[1], Dr Roman Bauer[1], Prof Richard Walker[2]

[1]Manus Neurodynamica, Edinburgh, United Kingdom. [2]Department of Medicine, Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, North Shields, United Kingdom

Objective: The study assessed the ability of a handheld device intended to measure and analyze features of neuromuscular processes to diagnose Parkinson's disease, compared to current best practices (DaTSCAN). The overall objective is to assess the ability of the device to detect presence of disease (sensitivity) and absence of disease (specificity).

Background: We present an innovative diagnostic pen with multiple movement sensors that patients use to complete writing and drawing tasks. A set of automatic methods allows extraction of features to quantify motor symptoms with high accuracy.

Methods: Data was recorded to measure and analyze features of neuromuscular processes, in conjunction with other clinicopathological factors. The test was administered by healthcare professionals and compared with DaTSCAN and MDS-UPDRS scores. The analysis took place with proprietary algorithms.

Involvement of people affected by Parkinson's: 132 undiagnosed attendees with movement disorder symptoms at a movement disorders clinic, for which there was diagnostic uncertainty and DaTSCAN assessment was required for confirmation were examined.

Results: The classification accuracy was 80% (sensitivity 92% and specificity 74%). Seventy attendees were subsequently diagnosed with idiopathic Parkinson's. Previous validation on 92 patients with an established diagnosis resulted in classification accuracies of 82.0 % for essential tremor; 69.8 % for functional tremor and 72.2% for enhanced physiological tremor.

Conclusion: An early and accurate diagnosis is crucial to give patients access to the range of treatments and therapies available. The device may help specialists to reduce uncertainty of differential diagnosis, potentially avoiding the need for DaTSCAN, saving time and money.

Poster 8 - The prevalence of sarcopenia in people with Parkinson's Disease: A Scoping Review

Miss Danielle Brazier, Dr Emily Henderson, Dr Fiona Lithander

University of Bristol, Bristol, United Kingdom

Objective: To assess the evidence examining the prevalence of sarcopenia in Parkinson's Disease compared to the general population.

Background: Parkinson's can lead to a decrease in exercise tolerance and an increase in the risk of falls. One related factor is that of sarcopenia, defined as a progressive and generalised skeletal muscle disorder, characterised by loss of muscle strength and quality.

Methods: A search of PubMed, EMBASE, AMED and Cochrane databases was carried out on 17 July 2020 to identify English language papers relating to sarcopenia and Parkinson's.

Results: 164 papers were identified and 4 were included. Of these, three described a higher prevalence of sarcopenia in patients with Parkinson's compared to healthy controls, whereas one found no significant difference between groups. The reported prevalence of sarcopenia in Parkinson's ranged from 17.2%-70.7%, compared to healthy controls, which ranged from 8.2%-29.3%. It appears that sarcopenia is more prevalent in people with more advanced Parkinson's, and further findings suggest a direct association between pre-clinical Parkinson's and early stage sarcopenia.

Conclusion: Evidence describing the direct association between sarcopenia and Parkinson's and its prevalence in this population is emerging. The limitations of this review include the heterogeneity in the definition of sarcopenia in the papers that were examined, and a lack of age-matched control groups. In order to reduce significant complications of the disease, further research exploring the relationship between Parkinson's and sarcopenia may help delineate optimal methods for intervention and rehabilitation to positively impact the quality of life in this patient group.

Poster 9 - Exploring the pathogenic interaction between dRab39 and α-synuclein in Drosophila

Charlotte Smith[1], Carlo Breda[2], Susanna Campesan[1], Flaviano Giorgini[1]

[1]Department of Genetics and Genome Biology, University of Leicester, LE1 7RH, Leicester, United Kingdom.
[2]Department of Genetics and Genome Biology, University of Leicester, LE1 7RH and Leicester School of Allied Health Sciences, Faculty of Health and Life Sciences, De Montfort University, LE1 9BH, Leicester, United Kingdom

Objectives: We seek to identify the mechanisms by which RAB39B mutations lead to Parkinson's symptoms and Lewy body pathology.

Background: Mutations in RAB39B are associated with early onset Parkinson's featuring intellectual disability and Lewy body pathology. RAB39B is a member of the Rab GTPase family - the core regulators of cellular membrane dynamics. The function of RAB39B is not clear but it appears to be involved in trafficking of cargo to synaptic terminals. Notably, a-synuclein (aSYN) overexpression has a detrimental effect upon vesicle trafficking within neurons.

Involvement of people affected by Parkinson's: Throughout the grant application process and undertaking of the project we have involved people affected by Parkinson's. We also participate in the Project Engagement Volunteer (PEV) scheme.

Methods: We utilised the UAS-GAL4 system in Drosophila to knockdown dRab39 expression via RNAi and overexpress aSYN in specific neuronal populations. Several assays were employed for phenotypic assessment. Immunocytochemistry with an anti-tyrosine hydroxylase antibody was performed on Drosophila brains and dopaminergic neurons were scored. Mitochondrial respiration was measured using the Oroboros O2k-FluoRespirometer.

Results: dRab39 RNAi flies exhibited shortened lifespan, impaired locomotor ability, reduced mitochondrial respiration and neuronal loss, which was enhanced upon expression of aSYN. Furthermore, developmental toxicity was unmasked in aSYN dRab39 RNAi flies. Interestingly, we observed a significant rescue of aSYN induced mortality in flies overexpressing RAB39.

Conclusions: dRab39 knockdown flies exhibit neurodegenerative phenotypes relevant for Parkinson's. Our findings also indicate that Rab39 and aSYN functionally interact and may thus have overlapping pathogenic mechanisms.

Poster 10 - Can hESC-derived dopamine grafts improve non-motor impairments?

Miss Charlotte Bridge, Dr David Harrison, Miss Emily Stonelake, Dr Mariah Lelos

Cardiff University, Cardiff, United Kingdom

Objective: To investigate whether human embryonic stem cell (hESC)-derived dopaminergic (DA) grafts could alleviate non-motor symptoms (NMS) in 6-OHDA lesioned rats.

Background: NMS in Parkinson's have a significant impact on the quality of life for patients. Cell therapy products (CTP) can replace lost DA cells and alleviate motor symptoms. Human fetal ventral mesencephalic (hfVM) grafts can also alleviate NMS, such as visuospatial dysfunctions, in the 6-OHDA model. It is unknown whether NMS recovery could be achieved with hESC-derived DA grafts.

Methods: Rats underwent operant training on the lateralised choice reaction time (LCRT) task before receiving unilateral 6-OHDA MFB lesions, modelling late stage Parkinson's. Lesion-induced deficits were measured prior to receiving transplants of either hfVM or hESC-derived DA grafts differentiated according to two different in vitro protocols. Animals were kept for 21 weeks post-transplantation and tested on amphetamine-induced rotations and LCRT task before being perfused and brain tissue taken for immunohistochemical analysis.

Results: Grafts from all 3 CTPs alleviated amphetamine-induced rotational bias. However, only hfVM grafts improved visuospatial function on the LCRT task. Correlational analysis revealed association between more accurate visuospatial performance and deeper medial neostriatal innervation ($p=0.006$), lower TH+ neuron content ($p=0.008$) and a higher percentage of A10 neurons ($p=0.011$). Poorer visuospatial performance was associated with greater lateral neostriatal innervation ($p=0.007$).

Conclusions: The composition of the graft and extent of medial neostriatal innervation may underpin recovery of visuospatial deficits, highlighting that further optimization of hESC-derived DA grafts is required to develop a CTP capable of targeting the NMS.

Poster 11 - Label-free analysis of neuromelanin and associated iron deposits in Parkinson's disease brain tissue by synchrotron x-ray spectromicroscopy

Mr Jake Brooks[1], Dr James Everett[2], Dr Frederik Lermyte[1], Prof. Neil Telling[2], Prof. Joanna Collingwood[1]

[1]University of Warwick, Coventry, United Kingdom. [2]School of Pharmacy and Bioengineering, Stoke-on-Trent, United Kingdom

Objectives: Synchrotron spectromicroscopy was applied to imaging and spectral analysis of organic and inorganic material in Parkinson's disease brain tissue, providing outstanding specificity and sensitivity.

Background: Neuromelanin-pigmented neurons, which are highly susceptible to neurodegeneration in the Parkinson's disease substantia nigra, harbour elevated iron levels in the diseased state. Non-disruptive analysis of neuromelanin and associated metals is inherently challenging, since tissue processing and staining can significantly influence metal ion distributions and/or concentrations in tissues.

Methods: Post-mortem fresh-frozen substantia nigra was resin embedded, ultra-microtome-sectioned and analysed using Scanning transmission X-ray microscopy (STXM) at the carbon and oxygen K-edges, and the iron L_3-edge, using the I08 beamline, Diamond Light Source synchrotron (UK).

Involvement of people affected by Parkinson's: Brain tissues donated under informed consent from three Parkinson's patients were provided to this study by the Newcastle Brain Tissue Resource and by the former Canadian Brain Tissue Bank.

Results: Using STXM, a unique feature in the neuromelanin absorption spectrum was discovered, facilitating direct, label-free visualisation of neuromelanin in situ (Brooks et al., Angewandte Chemie, 2020). STXM also revealed evidence for a spectrum of oxidation states in neuromelanin-associated iron deposits in Parkinson's disease substantia nigra. The excellent sensitivity, specificity and spatial resolution of these STXM measurements demonstrated variation in iron oxidation state on sub-micron length scales.

Conclusions: STXM offers a label-free approach to characterising distributions of both organic and inorganic components in post-mortem human brain tissue, with particular utility for non-destructive analysis of metals associated with neuromelanin.

Poster 12 - Ca2+ Cellular Compartment Specific Deficits In iPSC-Derived Neuronal Models Of Parkinson's Disease

Ms Maria Claudia Caiazza, Dr. Charmaine Lang, Prof. Richard Wade-Martins

Oxford Parkinson's Disease Centre, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom

Objective: Study differences in Ca^{2+} dynamics in induced pluripotent stem cells (iPSC)-derived dopaminergic neurons (DAns) from Parkinson's patients.

Background: Parkinson's is characterised by the loss of DAns in the substantia nigra. Ca^{2+} is crucial in the regulation of many neuronal cellular processes. In particular, in DAns continuous Ca^{2+} waves occur, placing these neurons in an environment where even small alterations in Ca^{2+} homeostasis might impact on cellular function.

Method: Here we utilise iPSC-derived DAns harbouring mutations in the glucocerebrosidase gene (GBA-N370S and GBA-L444P). We employ Fura-2 to observe gross changes in Ca^{2+} dynamics and genetically encoded Ca^{2+}indicators (GECI) entrapped in the mitochondria and in the ER to trace down the source of such changes. Ca^{2+} imaging techniques are used in combination with drugs able to induce Ca^{2+} mobilisation in the cell to study Ca^{2+} dynamics in iPSC-derived DAns.

Results: Patient iPSC-derived DAns displayed a decreased response to ionomycin in a Fura-2 based assay. Moreover, patient iPSC-derived DAns showed decreased Ca^{2+} efflux from the ER in response to ionomycin and CPA while monitoring Ca^{2+} content with an ER-entrapped GECI. GBA-N370S DAns mitochondria displayed a decreased buffering ability in response to ionomycin. CCCP-induced Ca^{2+} release from the mitochondria was largely unaltered in all the disease lines.

Conclusions: We believe that studying Ca^{2+} dynamics and deficits in iPSC-derived DAn models of Parkinson's could shed some light on the pathogenic mechanisms associated with neuronal vulnerability and death in Parkinson's with the ultimate goal to identify new therapeutic compounds to treat Parkinson's.

Poster 13 - Variation in the Provision and Outcomes of Speech and Language Therapy for People with Parkinson's Disease in the UK

Katie Chadd[1], Kathryn Moyse[1], Professor Pamela Enderby[2]

[1]Royal College of Speech and Language Therapists, London, United Kingdom. [2]University of Sheffield, Sheffield, United Kingdom

Objective: To examine variability in current speech and language therapy practice for patients with Parkinson's disease and communication and swallowing difficulties.

Background: 90% of patients with Parkinson's disease experience a gradual deterioration of speech and intelligibility. A Cochrane review of speech and language therapy (SLT) for people with Parkinson's noted improvement but methodological flaws led to inconclusive results.

Methodology: The Therapy Outcome Measure for Rehabilitation Professionals (TOM) is based on the World Health Organization's International Classification of Functioning, Disability and Health, and was designed to be a simple, reliable, method of gathering psychometrically robust information on impairment, activity restriction, social participation and well-being. The Royal College of Speech and Language Therapists has developed a national database which supports SLT services to enter data on all their patients.

Results: Across a ten year period, SLTs from 6 NHS trusts have logged data on 1018 patients with Parkinson's disease and communication and swallowing difficulties. The results indicate variation across trusts in terms of: severity at start of treatment, the nature of improvement made, and changes in patient outcomes over time, indicating variation in practice and the care pathway.

Conclusion: Research is usually conducted on carefully selected patient groups and leads to some difficulty in generalising the results to clinical caseloads. Examining variation of current practice with non-selected patients along with research can assist in examining practice and identifying the most appropriate care pathways.

Poster 14 - Defining the Mechanisms of VPS35 and LRRK2 Parkinson's in vivo

Miss Rachael Chandler[1], Dr Patrick Lewis[2], Dr Eva Kevei[1]

[1]University of Reading, Reading, United Kingdom. [2]Royal Veterinary College, London, United Kingdom

Objectives: Using a new Caenorhabditis elegans worm model, with Parkinson's associated mutations engineered into Parkinson's associated genes VPS35 and LRRK2, we aim to investigate the mechanisms of neurodegeneration.

Background: A rare mutation of VPS35[D620N] has been identified in several families with late-onset inherited Parkinson's, but it is unclear how this mutation causes neurodegeneration. Emerging evidence suggests an interplay with LRRK2, mutations of which are the most common cause of inherited Parkinson's. Study of the C. elegans orthologues, VPS-35 and LRK-1 may shed new insight into these proteins.

Methods: We have developed multiple CRISPR/Cas9 genome engineered lines of C. elegans with Parkinson's associated and catalytic mutations in VPS-35 and LRK-1. We have characterised the effect of these mutations upon the biology of the worm, through a range of behavioural and molecular assays.

Involvement of People affected by Parkinson's: At the Parkinson's UK Research Support Network (RSN) Conference 2019, we held a marketplace stall to discuss our work with attendees. An RSN member is also involved in supervision of this project. We have participated in public outreach activities, including Pint of Science, Soapbox Science and a school talk.

Results: Our data suggests VPS-35 mutation acts through a toxic gain of function, consistent with alternate models and the hypothesis of LRRK2 interplay. C. elegans with Parkinson's associated mutations show impaired dopamine dependant behaviour and reduced mitochondrial health.

Conclusions: C. elegans VPS-35 and LRK-1 may be promising novel models to further understand VPS35 and LRRK2 functions.

Poster 15 - Molecular characterisation of a novel cell model of alpha-synuclein – the 3K

David Chau, Jack Sheppard, Tony Schapira

UCL, London, United Kingdom

Alpha-synuclein (A-SYN) plays a central role in Parkinson disease (PD) pathogenesis. We have characterized a novel cell model developed in the Selkoe lab known as 3K, that features A-SYN aggregation, inclusion body formation and neuronal death – the key pathological features of PD. The 3K combines the E46K mutation and 2 additional artificial mutations to abrogate physiological tetramers into disordered monomers therefore promoting aggregation. From SHSY5Y dopaminergic cells stably overexpressing the wild-type A-SYN protein, E46K and 3K mutant A-SYN, we demonstrated an increase in A-SYN aggregation using an HTRF-FRET immunoassay. Immunocytochemistry data suggest the presence of inclusion bodies in the 3K cells. Measurement of A-SYN serine-129 phosphorylation showed a significant increase in steady-state levels that was independent of kinase inhibition. Future studies can be used to explore the relationship between A-SYN aggregation and other genetic and biochemical abnormalities associated with PD.

Poster 16 - Peripheral Alpha-Synuclein Aggregates as Biomarkers for Parkinson's Disease and Dementia with Lewy Bodies

Dr. Shu Chen, Mr. Connor Bargar

Case Western Reserve University, Cleveland, USA

Parkinson's disease (PD) dementia with Lewy bodies (DLB) are characterized by the deposition of misfolded alpha-synuclein aggregates in the central nervous system (CNS). Previous efforts have focused on the development of CNS-proximal clinical biomarkers, including cerebrospinal fluid (CSF) measures. However, CSF is often acquired from patients with advanced disease, and involves complex and invasive procedure. Therefore, there remains an urgent need for reliable, inexpensive and minimally invasive peripheral biomarkers. Recent studies have revealed widespread peripheral involvement of synuclein pathology, often prior to clinical manifestations of the diseases. Indeed, alpha-synuclein deposits have been observed in peripheral tissues in PD and DLB, respectively. A formidable challenge is that the levels of these protein aggregates in peripheral tissues are extremely low and thus are not reliably detected using conventional immunoassays. Therefore, highly sensitive analytical platforms are required as the new generation of biomarker assays specific for protein aggregates and/or amyloid fibrils. The real-time quaking induced conversion (RT-QuIC) has emerged as a robust, rapid and ultrasensitive technology for template-assisted amplification of misfolded protein aggregates in neurodegenerative diseases. Using the RT-QuIC technique, our recent studies have shown that disease-associated alpha-synuclein aggregates are readily detectable in peripheral tissues of patients affected by PD and DLB, including skin, salivary glands, and colon. Our RT-QuIC assay of these easily accessible peripheral specimens have thus far yielded excellent sensitivity and specificity for PD/DLB (>95%). Development of peripheral biomarkers will enable sensitive and early diagnostic tests for PD and DLB, and accelerate clinical trials for disease-modifying therapies.

Poster 17 - Systems modelling of mitochondrial bioenergetics to explore molecular defects contributing to Parkinson's pathogenesis

Sandeep Chenna[1], Alvin Joselin[2], David Park[2], Jochen Prehn[1], Niamh Connolly[1]

[1]Royal College of Surgeons in Ireland, Dublin, Ireland. [2]University of Calgary, Calgary, Canada

Background: Mitochondrial bioenergetic dysfunction is known to play a key role in Parkinson's pathogenesis. We recently combined a systems model of mitochondrial bioenergetics with biochemical studies to identify pre-symptomatic glycolytic dysregulation in an animal model of Alzheimer's (Theurey et al., 2019).

Objective(s): As part of the PD-mitoQUANT project, we are further interrogating this systems model to identify and explore bioenergetic molecular dysfunctions in Parkinson's.

Methods: First, we expanded the model to include generation and detoxification of respiratory oxygen species. We next integrated experimental data from transgenic animal models to identify putative molecular defects explaining their bioenergetic phenotype. Finally, we performed sensitivity analysis to investigate the impact of wide-ranging defects in critical respiratory chain components on key bioenergetic parameters.

Results: We verified that bioenergetic defects observed in Parkin knockout brain tissue (Giguere et al., 2018) can be explained by partial mitochondrial uncoupling. Interestingly, only a combined defect in complex I and cytosolic ATP consumption/proton leak could explain the bioenergetic phenotype measured in neurons from PINK1 knockout mice. Our sensitivity analysis provides an in-depth resource detailing the effects of respiratory chain defects on key bioenergetic parameters.

Conclusions: In summary, we here expanded a systems model tool to explore putative bioenergetic molecular defects contributing to Parkinson's pathology. As part of the PD-MitoQUANT project, these techniques will now be used to investigate the effect of α-synuclein on mitochondrial bioenergetics.

Involvement of people affected by Parkinson's: The PD-mitoQUANT project involves two people with Parkinson's who regularly contribute to communication and dissemination activities.

Poster 18 - The Identification and Documentation of Delirium in People with Parkinson's

Dr Rachel Cullinan[1], Dr Rachael Lawson[2], Dr Louise Allan[2], Dr David Burn[2], Dr Sarah Richardson[2]

[1]Gateshead Health NHS Trust, Gateshead, United Kingdom. [2]Newcastle University, Newcastle Upon Tyne, United Kingdom

Objectives: Establish frequency of delirium symptom and diagnosis documentation in medical notes and discharge summaries of Parkinson's inpatients.

Background: Delirium is characterised by altered level of consciousness, confusion and impaired attention. The DETERMINE-PD Pilot study identified delirium is common in Parkinson's patients at admission and incidence increases during hospital stay, but is commonly missed.

Involvement of people affected by Parkinson's: People with Parkinson's and their carers were involved in study design.

Methods: The DETERMINE-PD pilot study assessed Parkinson's inpatients over 4-months. Delirium prevalence was classified using a standardised assessment at a single visit using DSM-5 criteria on the basis. Incident delirium was diagnosed using clinical vignettes and validated consensus method. Inpatient medical notes and discharge summaries of those identified with possible/probable delirium were reviewed for documentation of symptoms, diagnosis and follow-up.

Results: 37.9% of 30 patients with probable delirium had diagnosis documented. 72.3% Had symptoms documented. Older patients were more likely to be diagnosed with delirium(p=0.027). Previous cognitive impairment and delirium diagnosis showed no association(χ^2=1.0,p=0.79). Time from symptom documentation to diagnosis ranged from <24hours to 7days (mean 1.6±4.4 days). 11.5% Discharge summaries included delirium diagnosis and 7.7% had a relevant follow-up plan.

Conclusions: Documentation of delirium diagnosis is poor. Symptom documentation is more common, but still frequently fails to lead to a diagnosis. Improving identification and diagnosis of delirium could help reduce its impact on morbidity and mortality for those with Parkinson's, and identify patients at greater risk of dementia.

Poster 19 - Alpha-MSH: Could this anti-inflammatory mediator be the culprit in Parkinson's Disease?

Dr. Jay Dela Cruz

InTouch BioSolutions LLC, Moreno Valley, USA

We now show that key processes implicated in synuclein pathogenesis such as impairment of cellular autophagy and alpha-synuclein (α-syn) aggregation are induced by alpha-melanocyte stimulating hormone (alpha-MSH), a microglia-secreted anti-inflammatory mediator. Alpha-MSH is elevated in the cerebrospinal fluid of Parkinson's disease (PD) and multiple system atrophy (MSA) patients. We employed the pigmented melanoma cell line MNT-1 as a novel in-vitro cell model of melanin-containing dopaminergic neurons (DNs) of the substantia nigra (SN). Melanin levels serve as a reliable readout of autophagy in MNT-1 and exposure to alpha-MSH resulted in a decrease in melanin and a failure to slow down glucose consumption, which induced cell death by apoptosis. ASIP (agouti-signaling protein), the natural biologic inhibitor of alpha-MSH, blocked and reversed the effects of alpha-MSH. Mice administered intranasal alpha-MSH exhibited progressive decline in gait, a prevalent condition seen in patients with PD. Moreover, we observed what may be a-syn aggregation in the SN pars compacta (SNpc). SNpc and striatal tyrosine hydroxylase (TH) density showed very modest reduction in this animal PD model consistent with PD pathology at the very early stage of disease.

Fundamental questions addressed by this study:

1. What is the pathophysiologic link between neuroinflammation and impairment of autophagy in PD?

2. What microglia-derived mediator impairs autophagy and induces alpha-synuclein aggregation in dopaminergic neurons in PD?

3. What drives neurotoxicity that leads to oxidative stress and ROS-mediated cell loss in PD?

Poster 20 - The impact of the COVID-19 situation on people with Parkinson's

Dr Fiona Eccles, Dr Sandra Varey, Professor Carol Holland, Professor Jane Simpson

Lancaster University, Lancaster, United Kingdom

Objective: To find out the impact of the COVID-19 situation on people affected by Parkinson's.

Background: The impact of the COVID-19 pandemic and associated restrictions such as lockdown has been particularly concerning for those with pre-existing health conditions. We present the findings of qualitative interviews on the impact on people with Parkinson's during lockdown and the following months. These interviews complement the survey conducted by Parkinson's UK during lockdown and enable the journey of these participants through the following months to be elucidated.

Methods: 10 people with Parkinson's were interviewed during lockdown and in the subsequent months as the restrictions were lifted and the data were analysed using phenomenologically informed thematic analysis.

Involvement of people affected by Parkinson's: The interview schedule was constantly updated following feedback from people with Parkinson's in the interviews.

Results: Interviews during lockdown suggested that the COVID-19 situation amplified existing fears related to Parkinson's. People with Parkinson's tried to find ways of regaining control in an uncertain situation and there were worries about appraising and managing future risk. However, some positives of lockdown were noted. The findings of more recent interviews conducted during Summer 2020 as the lockdown in the UK is released will also be presented.

Conclusions: People with Parkinson's are living in an unpredictable situation with an unpredictable condition and negotiating these together presents specific challenges.

Poster 21 - Altered Synaptic and Astrocytic Proteins in Alpha-Synucleinopathies Associated with GBA Mutation

Mr Thamir Eid[1], Prof Thomas Warner[1], Prof John Hardy[1], Dr Rina Bandopadhyay[1], Prof Paul Francis[2]

[1]UCL Queen Square Institute of Neurology, London, United Kingdom. [2]KCL Institute of Psychiatry, Psychology & Neuroscience King's College, London, United Kingdom

Objectives: To investigate synaptic proteins in alpha-synucleinopathies with & without GBA mutations.

Background: Mutations in glucocerebrosidase gene (GBA) are a common risk factor for Parkinson's disease (PD) and Lewy body dementia (LBD). <70% of PD patients also develop dementia. To date, the molecular mechanisms underlying these diseases are unknown. Synaptic protein changes have been shown to correlate with cognitive decline in Alzheimer's disease (AD).

Involvement of People affected by Parkinson's: None.

Methods: Brain tissue was obtained from the Queen Square and South West Dementia Brain Banks. 119 PD cases were screened to identify GBA mutations. Synaptic marker proteins synaptophysin, SNAP25, PSD95, neurogranin, Rab3a, VAMP2 and VAMP3 were examined in 7 PD/LBD with GBA mutations, 21 PD/LBD without GBA mutations, and 10 controls. Four cortical regions were assayed using standard immunoblot procedures.

Results: Post-synaptic protein, neurogranin was significantly decreased in the frontal and parietal cortices of PD-GBA. Whilst the cingulate cortex showed a significant increase in PD/LBD compared to controls. Presynaptic protein synaptophysin was significantly increased in PD/LBD compared with control in cingulate cortex. SNAP25 was significantly increased in GBA group compared with both control and PD/LBD in frontal cortex. VAMP2 was significantly reduced in both diseased groups compared to controls in frontal cortex. Additionally, the astrocytic protein VAMP3 was significantly reduced in PD/LBD compared to both control and GBA groups.

Conclusion: Regional changes in synaptic proteins were observed in disease vs control groups. Altered pre-synaptic, post-synaptic and astrocytic proteins, could all play a role in PD pathogenesis.

Poster 22 - A shift in size changes the toxic behaviour of α-synuclein aggregates

Derya Emin, Evgenia Lobanova, Margarida Rodrigues, Zengije Xia, David Klenerman

University of Cambridge, Cambridge, United Kingdom

Neurodegenerative disorders such as Parkinson's disease (PD) are characterized by a loss of neurons. However, there is still a lack of understanding when it comes to the molecular mechanisms causing these diseases. In PD the misfolding and consequent aggregation of α-synuclein seems to play a central role. Recent research suggests that the small soluble aggregates up to 250 nm in size are likely to be the cytotoxic species.

Studying structural properties of small aggregates with traditional biophysical techniques is challenging due to their heterogeneity in structure and size and low abundance compared to the monomeric form. We approach this problem by separating α-synuclein by size and then confirm the successful separation using super-resolution fluorescence and transmission electron microscopy. To investigate the toxicity of different-sized aggregates, we apply two biological assays, which allow us to access both the ability of the aggregates to disrupt the membrane of single-liposomes and the production of TNF-α by an aggregate-treated microglial cell line. We later examine the soluble aggregates extracted from post-mortem brain tissue of PD patients.

We were able to determine that the fraction containing small aggregates (up to 150 nm), formed early in the aggregation process, are the most toxic species. Also, we compared our in vitro aggregates to endogenous α-synuclein. With this, we were able to assess regional variability by characterising the aggregates from different brain regions.

To our knowledge, this is the first time that this has been achieved and will provide new insights into the failure of protein homeostasis in PD.

Poster 23 - Common Variants Co-Regulate Expression of GBA and Potential Modifier Genes to Delay Parkinson's Disease Diagnosis

Miss Sophie Farrow[1], Dr William Schierding[1], Professor Martin Kennedy[2], A/Professor Antony Cooper[3], A/Professor Justin O'Sullivan[1]

[1]Liggins Institute, Auckland, New Zealand. [2]University of Otago, Otago, New Zealand. [3]Garvan Institute, Sydney, Australia

Objectives: To determine if common variants within the GBA locus regulate the expression of GBA and other genes, and to ascertain if they have a clinical impact.

Background: GBA coding mutations that impair GCase activity play a central role in PD. However, some Parkinson's patients lacking GBA mutations have reduced GCase activity, indicating a complex relationship between GBA and Parkinson's pathogenesis.

Methods: We used a computational pipeline (CoDeS3D) to identify variants at the GBA locus that modulate the transcriptional regulation of GBA and other genes.

Involvement of people affected by Parkinson's: Targeted Nanopore sequencing of the GBA locus in a longitudinal cohort of 229 clinically characterised Parkinson's patients.

Results: We identified three intronic genetic variants within GBA that both regulate GBA in peripheral tissues, and co-regulate 22 additional genes in the brain and peripheral tissues. These three variants form a haplotype that is associated with a mean delay in Parkinson's disease diagnosis of almost six years. In addition, we identified six common variants on different chromosomes that regulate GBA expression within the cortex and substantia nigra.

Conclusions: This work provides a new perspective on the regulation of GBA, with common SNPs within GBA contributing to modulation of the disease course. We further identified distant variants on other chromosomes that may collectively regulate GBA at a transcriptional level, and thus GCase activity. These findings broaden the GBA subtype, highlighting more individuals that may be suitable for GBA drug trials, as well as potential targets for therapy to slow disease progression.

Poster 24 - Regional vulnerabilities in Parkinson’s disease: investigating the role of SNCA gene copy gains in the occipital cortex.

Milda Folkmanaite, Dr Christos Proukakis

UCL, London, United Kingdom

Background: α-synuclein coded by the SNCA gene accumulates during Parkinson’s disease. It is hypothesized to spread through the brain but causes of spreading patterns and regional brain vulnerabilities (RBV) are mostly unknown. Since copy number gains can cause an increased gene expression, somatic SNCA mosaicism could lead to an increase in local α-synuclein levels causing RBV.

Objectives: Therefore, we aimed to investigate somatic SNCA mosaicism differences between brain areas, and Parkinson's patients and controls.

Involvement of people affected by Parkinson’s: To achieve this, tissue slides from Parkinson's patients supplied by Parkinson’s UK and Queen Square Brain Bank were tested.

Methods: Using fluorescence in situ hybridization, SNCA gains in the occipital cortex (OC) were quantified in Parkinson's and controls blinded to the disease status. Mosaicism levels were also correlated with previously published results of substantia nigra (SN) and cingulate cortex (CC).

Results: It appears that mean SNCA mosaicism is significantly higher in Parkinson's (3.99%) than controls (1.6%)(p=0.0418). Comparing SNCA mosaicism in OC with published levels in SN and CC in 7 Parkinson's patients shows a decreasing trend in mosaicism levels when moving from the OC towards SN.

Conclusions: Overall, higher SNCA mosaicism in Parkinson's OC than SN suggest that SN neurons affected by SNCA mosaicism and, therefore, by the disease the most might degenerate first sparing lower mosaicism regions. This results in a relatively higher mosaicism in OC than SN. Due to a small study sample size, further research on SNCA mosaicism is needed to validate these findings.

Poster 25 - IMMUNE EFFECTS OF DOPAMINERGIC AGENTS ON HUMAN CD4+ T LYMPHOCYTES: RELEVANCE FOR PARKINSON'S DISEASE

Alessia Furgiuele, Massimiliano Legnaro, Emanuela Rasini, Franca Marino, Marco Cosentino

Center for Research in Medical Pharmacology, University of Insubria, Varese, Italy

Objective: To test dopaminergic antiparkinsonian drugs on proliferation and proinflammatory cytokine production in human CD4+ T cells, which are key players in Parkinson's disease.

Background: CD4+ T cells as increasingly recognized as triggers of neuroinflammation and neurodegeneration in Parkinson's. Dopamine substitution is the mainstay of Parkinson's treatment, however little is known about the effects of dopaminergic antiparkinsonian drugs on CD4+ T cells, despite the established role of dopamine in peripheral immunity.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from buffy coats of healthy donors, and thereafter stimulated with anti-CD3/anti-CD28 Abs (2 µg/ml), alone or with 0.1 µM pramipexole (PPX), ropinirole (ROP) or rotigotine (ROT). Cell pellets and supernatants were finally collected and TNF-α and IFN-γ were measured by RT-PCR and ELISA. CD4+ T cell proliferation was assessed by flow cytometry.

Results: Stimulated PBMCs increased TNF-α and IFN-γ mRNA levels (by 4- and 8-folds, respectively), and TNF-α and IFN-γ secretion (from 35 to 2151 pg/mL and from 7 to 1597 pg/mL). ROT, ROP and PPX reduced TNF-α and IFN-γ mRNA levels (by 16-30% and 40%), however only ROT and ROP also reduced their extracellular secretion (by 35-50% and 29-34%). The effects of drugs on CD4+ T cell proliferation are currently under evaluation.

Conclusions: Dopaminergic antiparkinsonian drugs affect to different extent CD4+ T cell proinflammatory cytokines. In particular, ROT and ROP, but not PPX, result in reduced TNF-α and IFN-γ production. Further investigations in Parkinson's patients are warranted to assess the clinical relevance of such differences.

Poster 26 - Investigating the impact of patient and public involvement on the readability of Parkinson's UK grant plain English summaries.

Inez Gaczkowska[1], Sophie Griffiths[1], Dr Ellen Poliakoff[1], Dr Natasha Ratcliffe[2], Annie Amjad[2]

[1]University of Manchester, Manchester, United Kingdom. [2]Parkinson's UK, London, United Kingdom

Objectives: To investigate the impact of patient and public involvement (PPI) on the readability of plain English summaries.

Background: Plain English summaries are brief research summaries written in lay language so members of the public can understand it and input into funding decisions. It is recommended that researchers identify and change content difficult for laypersons to understand. Parkinson's UK has a network of PPI contributors - people affected by Parkinson's who have completed training about working with researchers to improve their work.

Methods: We compared 32 PUK lay summaries pre and post PPI input using readability formulae (Flesch Reading Ease, SMOG). Thirteen PPI contributors also rated the summaries.

Involvement of people affected by Parkinson's: Two people with Parkinson's were on the research team and PPI volunteers contributed ratings.

Results: Post-PPI versions were significantly easier to read as reflected by a higher mean Flesch score, but the SMOG scores were not significantly different. Over half the summaries had lower ratings post-PPI compared to pre-PPI, and fewer final versions were rated as 'excellent' compared to the first versions of the summaries.

Conclusions: The objective analysis provides some evidence of improvements in readability. However, this was not seen in the subjective measures, suggesting the measures of summaries refer to different concepts as numerical scores do not have the same value as PPI. Other factors should be considered when measuring improvement to lay summaries, such as the quality of the pre-PPI summaries and PPI feedback, and the researchers' responsiveness to the feedback.

Poster 27 - Glucocerebrosidase deficiency increases release of α-synuclein fibrils

Dr Matthew Gegg, Professor Anthony Schapira

UCL Queen Square Institute of Neurology, London, United Kingdom

Objective: Investigate if neurons with glucocerebrosidase (GCase) deficiency have increased intracellular accumulation and extracellular release of misfolded α-synuclein following treatment with preformed α-synuclein fibrils (PFFs).

Background: Mutations in the GBA gene, encoding the lysosomal enzyme GCase, are the greatest known genetic risk factor for developing Parkinson's. GCase deficiency impairs the turnover of α-synuclein by autophagy. α-synuclein pathology has been proposed to spread through the brain in a prion-like fashion leading to the progression of symptoms. Fibrillar forms of α-synuclein are thought to contribute to this spread, inducing endogenous functional α-synuclein to misfold, become insoluble and aggregate, like that observed in Lewy bodies.

Methods: Mouse cortical neurons and differentiated human dopaminergic SH-SY5Y cells treated with the GCase inhibitor CBE were incubated with PFFs to initiate α-synuclein pathology. Misfolded and aggregated a-synuclein was assessed by western blotting and dot blot. Coculture studies were performed to measure spread of α-synuclein pathology between cells.

Involvement of people affected by Parkinson's: None

Results: Neurons treated with PFFs had increased insoluble, aggregated α-synuclein species, that were phosphorylated at Ser129. GCase deficiency did not worsen intracellular α-synuclein pathology but did significantly increase the release of pathogenic α-synuclein fibrils from cells. When GCase deficient neurons preloaded with PFFs were co-cultured with naïve neurons, insoluble, aggregated α-synuclein was significantly increased in these naïve cells.

Conclusions: GCase deficient neurons increase the release of pathogenic α-synuclein fibrils, increasing the spread of α-synuclein pathology between cells. This might contribute to the earlier age of onset and increased cognitive decline observed in GBA-Parkinson's.

Poster 28 - Investigating LRRK2 Kinase activity and VPS35 function in human cell culture models of Parkinson's Disease

Miss Sophie Glendinning[1], Dr Yixi Chen[1], Dr Pawel Lis[2], Miss Telma Venturra[1], Dr Tilo Kunath[1]

[1]University of Edinburgh, Edinburgh, United Kingdom. [2]University of Dundee, Dundee, United Kingdom

Background: Mutations within LRRK2 are the most common cause of familial Parkinson's disease (PD), whereby most mutations increase its kinase activity. More recently a D620N mutation within VPS35, a component of the retromer complex, has been identified as an autosomal dominant cause of PD, and this mutation significantly increased LRRK2 kinase activity by an unknown mechanism. The Alessi lab have identified a subset of small Rab GTPases as substrates of LRRK2, and demonstrated that hyperactive LRRK2 variants G2019S-LRRK2 and R1441C/G-LRRK2 enhance phosphorylation of these Rab substrates. Moreover, the D620N-VPS35 mutation increased LRRK2-dependent Rab phosphorylation to a greater extent than the hyperactive LRRK2 mutations.

Objectives: Increasing evidence suggest a role of LRRK2 within immune cells such as macrophages. This project therefore aims to investigate the expression, activity and substrates of LRRK2 and VPS35 in human neurons and immune cells.

Methods: The developmental expression and activity of these proteins will be investigated in midbrain dopaminergic neurons, macrophages, and microglia-like cells differentiated from human pluripotent stem cells. Additionally, unbiased proteomics will be applied to determine bona fide substrates within these human cell types. Finally, within human dopaminergic neurons Lewy-like pathology can be initiated by seeding with pre-formed fibrils (PFFs) of recombinant α-synuclein. Using this well-established protocol we aim to investigate the effect of LRRK2 inhibitors on the formation of α-synuclein aggregates. These results will provide insight into LRRK2 and VPS35 function within neurons and immune cells, and their role in Parkinson's.

Poster 29 - Differential in-vitro diagnostics of neurodegenerative dementias

Dr. Vandana Gupta, Ms. Selene Lee, Dr. Laura Parkkinen

University of Oxford, Oxford, United Kingdom

Objective: To compare the various protocols for real-time quaking-induced-conversion (RT-QuIC) assay from different laboratories and assess their strengths and weaknesses.

Background: There is a vital unmet need for objective and sensitive diagnostic methods that would allow early and differential diagnosis of neurodegenerative dementias (NDs). RT-QuIC is one very promising method that can detect various aggregating proteins with high accuracy in patient's cerebrospinal fluid (CSF) as a surrogate of brain pathology. RT-QuIC was initially developed to detect prion-diseases but it has been successfully applied to detect alpha-synuclein (αSyn) aggregation in Parkinson's and Lewy body dementia and tau aggregation in Alzheimer's disease and other tauopathies.

Methods: RT-QuIC assays are multi-well plate-based reactions where intermittent shaking enhances the conversion of soluble recombinant protein into amyloid fibrils in the presence of pathological seed from patient-derived sample (e.g. CSF). These fibrils form bonds with Thioflavin T generating an easily measurable fluorescent signal.

Results: Among different laboratories, αSyn RT-QuIC exhibits specificity of 82 -100% and sensitivity of 70-100%. RT-QuIC protocols differ in terms of substrates, temperature, shaking/incubation cycles and buffers that all have an effect on the assay performance and make it difficult to compare the results. Moreover, RT-QuIC may hold potential to detect different conformational strains of the protein that would allow a better stratification of patients with different NDs. Although RT-QuIC is sensitive and specific, its quantitative nature needs to be established.

Conclusion: We recommend one standardised RT-QuIC procedure to be established as a routine diagnostic assay for NDs in the surveillance-centres worldwide.

Poster 30 - Novel compounds modifiy mitochondrial deficits in parkinsons disease models

Mr Christopher Hastings[1], Dr Heather Mortiboys[1], Dr Alex Weymouth-Wilson[2], Dr Gemma Packer[2]

[1]University of Sheffield, Sheffield, United Kingdom. [2]NZP, Reading, United Kingdom

Background: Mitochondrial dysfunction is well characterized in Parkinson's disease. This study aims to identify novel compounds which arace able to rescue mitochondria in sporadic Parkinson's patient tissue and elucidate the mechanism of action.

Methodology: The primary drug screen of over 200 novel compounds in Parkinson's patients' fibroblasts utilized high content imaging to determine mitochondrial membrane potential and cellular ATP assays. Oxygen consumption rate were measured in fibroblasts treated with five of the most potent compounds. The top performing compound was also investigated in a MPTP mouse model where complex I, II, IV activity were assessed in ex vivo mouse brain tissue. Cardiolipin assessment was conducted in both the cultured fibroblasts and ex vivo tissue homogenates.

Results: The primary screen identified several compounds with high activity at low nM concentrations. After subsequent screening, NZP437 was selected for in vivo testing. Complex I is decreased after MPTP treatment in mouse striatum; NZP437 increased complex I activity. Furthermore, NZP437 increased complexes II and IV activity. Reduced cardiolipin levels were found in patient fibroblasts and MPTP mouse brains; this was restored with treatment of NZP437.

Conclusions: NZP437 restores mitochondrial function in sporadic Parkinson's disease patient fibroblasts. NZP437 is also protective for complex I activity in a MPTP mouse model. Furthermore, a cardiolipin deficit was normalised with NZP437 treatment in both models. This compound is a promising drug candidate, which merits further evaluation.

Poster 31 - Behavioural recovery after transplantation of hiPSC-derived dopamine grafts is dependant on neurite outgrowth.

Ms Rachel Hills[1], Dr Andres Bratt-Leal[2], Professor Jeanne Loring[3], Dr Mariah Lelos[1]

[1]Cardiff University, Cardiff, United Kingdom. [2]Aspen Neuroscience, California, USA. [3]Scripps Research Institute, California, USA

Objective:

Poster 32 - Galvanic Vestibular Stimulation and Balance Control in Parkinson's Disease

Philip Hodgson[1], David Wilkinson[2], David Stephensen[3]

[1]Kent Community Health NHS Foundation Trust, Canterbury, United Kingdom. [2]The University of Kent, Canterbury, United Kingdom. [3]East Kent Hospitals University NHS Foundation Trust, Canterbury, United Kingdom

Objective(s): Study assessing acceptability and feasibility of Galvanic Vestibular Stimulation (GVS) to improve postural control for individuals with Parkinson's.

Background: Parkinson's disease is the most common neurodegenerative movement disorder worldwide, affecting 4% of those over 80. Common symptoms include tremor and muscle stiffness which impact on an individual's ability to maintain their balance, increasing the likelihood of falling. GVS may improve postural responses in individuals with Parkinson's however the optimal frequency for such intervention is unknown. This study aims to assess the acceptability and feasibility of two delivery timescales prior to larger-scale study.

Methods: Once recruited, participants will be divided into four groups.

- Physiotherapy + daily sham GVS,
- Physiotherapy + daily active GVS,
- Physiotherapy + weekly sham GVS, and
- Physiotherapy + weekly active GVS.

Each group will receive 5 sessions of GVS over 5 days or 5 weeks alongside a programme of exercises completed at home, with adherence assessed via participant diary entries. Participants will be re-assessed 2 and 4 weeks after the intervention period using clinically validated outcome measures.

Involvement of people affected by Parkinson's: Individuals with Parkinson's have been involved in the study design and preparation of participant documentation.

Results: Study to begin shortly following application for ethical approval.

Conclusions: This research will investigate the optimum frequency for therapeutic delivery of GVS through direct comparison of different delivery timescales. Given that balance and falls is currently the number one research priority of Parkinson's UK, now is the ideal opportunity to investigate this effect further.

Poster 33 - Involving people with Parkinson's Disease in the co-design a trial investigating the effect of Galvanic Vestibular Stimulation on balance

Philip Hodgson[1], David Wilkinson[2], David Stephensen[3]

[1]Kent Community Health NHS Foundation Trust, Canterbury, United Kingdom. [2]The University of Kent, Canterbury, United Kingdom. [3]East Kent Hospitals University NHS Foundation Trust, Canterbury, United Kingdom

Objective(s): PPI activity enabling the direction of future project to be led by service users.

Background: Symptoms of Parkinson's commonly affect individual's balance, increasing the likelihood of falling. Galvanic Vestibular Stimulation (GVS) may improve responses in Parkinson's however the optimal frequency for such intervention is unknown. Consultation provided pre-study feedback to ensure appropriate design before applying for ethical approval and committing funding.

Methods: PPI took place at Canterbury on 09/12/2019, led by a Physiotherapist within the research team. Participants were recruited through a Parkinson's UK affiliated exercise group and Parkinson's UK Canterbury.

The perception of people with Parkinson's were explored in relation to;

- Recruitment
- Intervention delivery
- Worries/concerns
- Acceptability
- Outcome measures

Involvement of people affected by Parkinson's: Individuals with Parkinson's were involved throughout.

Results: This session was attended by 8 individuals (5 individuals with PD, 3 relatives/friends/carers).

- All participants support further research in this area and felt GVS was an acceptable methodology.
- Main worries/concerns centred around potential side effects.
- Factors that may deter individuals from taking part were travel, accessibility, and flexibility around prior arrangements.
- Adaptations were made to the participant information sheet to include visual representation of the GVS device and further information on outcome measures.
- Participants unanimously felt that the proposed time commitment was acceptable.

Conclusions:

Individuals with PD (and their carers) are supportive of further work in this field, and were actively engaged in project design. Further work is required to carry out the project.

Poster 34 - Uncovering the Mechanisms of Mitochondrial Rescue with the use of a Novel Therapeutic Compound for the Treatment of Sporadic Parkinson's

Miss Rachel Hughes[1], Dr Gemma Packer[2], Dr Alex Weymouth-Wilson[2], Professor Oliver Bandmann[1], Dr Heather Mortiboys[1]

[1]The University of Sheffield, Sheffield, United Kingdom. [2]NZP UK Ltd, Reading, United Kingdom

Objectives: Previous work highlighted mitochondrial restoration properties of ursodeoxycholic acid (UDCA) in fibroblasts from people with Parkinson's (PwP), leading to a collaboration with an industrial partner. We aim to investigate cellular mechanisms altered by treatment with compound A in dopaminergic neurones derived from PwP.

Background: There is strong evidence of mitochondrial dysfunction in both sporadic and familial Parkinson's. Following a comprehensive drug screening program, we identified compound A, with potent mitochondrial restorative properties in Parkinson's patient cells and in vivo.

Methods: Neuronal and dopaminergic markers and mitochondrial membrane potential (MMP) were assessed in iNeurones. Basal mitophagy was assessed using live time-lapse fluorescent microscopy while induced mitophagy and alpha synuclein were investigated using immunocytochemistry. Experiments were conducted on iNeurones from controls and sporadic Parkinson's patients treated with vehicle, Compound A or UDCA.

Involvement of People Affected by Parkinson's: PwP were involved by using samples taken from participants. Also, a group was set up to discuss continuation plans for this project and has met twice face to face.

Results: iNeurones achieved approximately 90% tyrosine hydroxylase positive cells with no effect of compound A or UDCA. MMP increased following treatment with UDCA or compound A (73% and 100% respectively). Alterations were found between control and Parkinson's iNeurones in mitophagy and alpha synuclein content, however no drug effect was seen.

Conclusions: We continue to study the mechanism of compound A and future work will focus on in vivo models of Parkinson's and its effects on whole biological organisms.

Poster 35 - The CloudUPDRS Smartphone Software in Parkinson's (CUSSP) study

Dr Ashwani Jha[1], Dr Elisa Menozzi[1], Prof John C. Rothwell[1], Prof George Roussos[2], Prof Kailash P. Bhatia[1]

[1]UCL Queen Square Institute of Neurology, London, United Kingdom. [2]Birkbeck College, University of London, London, United Kingdom

Objectives: To determine the validity and accuracy of subject-level smartphone-based measures of severity in Parkinson's across a number of motor subitems.

Background: Digital assessments of motor severity could improve the sensitivity of clinical trials and personalise treatment in Parkinson's but have yet to be widely adopted. Their ability to capture individual change across the heterogeneous motor presentations typical of Parkinson's remains inadequately tested against current clinical reference standards.

Methods: We conducted a prospective, dual-site, crossover-randomised study to determine the ability of a 16-item smartphone-based assessment to predict subitems from the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) as assessed by three blinded clinical raters. Predictive performance was quantified as the leave-one-subject-out cross-validation (LOSO-CV) accuracy of a range of machine learning algorithms.

Involvement of people affected by Parkinson's: The software was iteratively co-designed with input from those affected by Parkinson's.

Results: We analysed data on 60 subjects (990 smartphone tests, 2628 blinded MDS-UPDRS III subitem ratings). A prespecified analysis averaged over 16 subtests classified 70.3% (SEM 5.9%) of subjects into a similar category to any one of three blinded clinical raters. This outperformed a random (36.7%; SEM 4.3%) baseline model. Post hoc optimisation of classifier and feature selection improved performance further (78.7%, SEM 5.1%).

Conclusions: Smartphone-based measures of motor severity have predictive value at the subject-level. Future studies should similarly mitigate against subjective and feature selection biases and assess performance across a range of motor features to avoid overly optimistic performance estimates.

Poster 36 - Identification of candidate Parkinson's disease genes by integrating GWAS, expression and epigenetic datasets

Dr Demis Kia, Mr David Zhang, Prof John Hardy, Prof Nicholas Wood

UCL Institute of Neurology, London, United Kingdom

Objectives: To identify genes that alter Parkinson's risk through changes in expression, splicing or methylation, and their important functional pathways and cell-types.

Background: Substantial genome-wide association study (GWAS) work has revealed an increasing number of loci associated with Parkinson's. Improved understanding of the underlying genes and mechanisms at these loci will be key to our understanding of Parkinson's pathogenesis.

Involvement of people affected by Parkinson's: This study is based on genetic data and brain donations kindly provided by Parkinson's patients to enable our study of the condition.

Methods: We comprehensively integrated Parkinson's GWAS data with expression and methylation data (derived from GTEx, Braineac and CommonMind consortia, and the Parkinson's UK brain bank). Candidate genes were further characterised by determining cell-type specificity, weighted gene co-expression (WGNCA) and protein-protein interaction (WPPINA) networks.

Results: 5 genes (WDR6, CD38, GPNMB, RAB29, TMEM163) were found to have expression changes associated with Parkinson's that replicated across all methods and datasets. A further 6 genes (ZRANB3, PCGF3, NEK1, NUPL2, GALC, CTSB) showed evidence of disease-associated splicing effects. Cell-type specificity analysis revealed that these genes were overall expressed more in glial cell-types compared to neurons. The WGNCA analysis highlighted catabolic processes related to protein ubiquitination, and processes regulating cell signalling. WPPINA analysis and simulations using random networks demonstrated that these candidate genes interact significantly more with known Mendelian Parkinson's proteins than would be expected by chance.

Conclusions: Together, these results point to a number of candidate genes and pathways that are driving the associations observed in Parkinson's GWAS studies.

Poster 37 - Axonal translation in Parkinson's striatal dopamine neurons: Sequencing the 'translatome'

Dr Peter Kilfeather, Dr Katharina Wagner, Dr Natalie Connor-Robson, Professor Stephanie Cragg, Professor Richard Wade-Martins

University of Oxford, Oxford, United Kingdom

Objective(s)

- To demonstrate axonal translation in dopamine neurons in mouse striatum.
- To compare the axonal and cell body 'translatome' in an alpha-synuclein-overexpressing Parkinson's mouse model and in ageing.
- To identify drivers of vulnerability and protection from degeneration in nigrostriatal dopamine neurons.

Background: Nigrostriatal dopamine neurons have long, highly arborised axons, indicating a requirement for axonal translation. The axonal 'translatome' will reflect the neuronal response to local stressors that precedes cell death in Parkinson's disease as well as revealing key transcriptional differences between protected and vulnerable dopaminergic populations. The translating ribosome affinity purification (TRAP) technique enables the capture of translating ribosomes specifically in dopaminergic neurons by expressing an eGFP-tagged ribosomal subunit driven by a cell type-specific promoter.

Methods: We have produced a novel transgenic mouse line by crossing a human alpha-synuclein overexpression model, previously generated by our lab, with a DAT-Cre driven TRAP line. We are collecting translating mRNA from dopaminergic terminals of 3 and 18-month control and Parkinsonian mice for sequencing. We use gene regulatory network analysis to identify drivers of gene co-expression that represent candidates for therapeutic intervention.

Results: We have optimised TRAP to obtain mRNA from dopaminergic axons for sequencing. We are now analysing data from healthy 3 and 18-month old mice and generating an aged Parkinsonian TRAP cohort.

Conclusions: This study is the first of its kind and will importantly reveal translation differences between vulnerable and protected dopaminergic populations as well as providing novel disease targets.

Poster 38 - Single-cell sequencing of induced pluripotent stem cell (iPSC) dopamine neurons reconstructs disease progression and identifies HDAC4 as a regulator of Parkinson cell phenotypes

Dr Charmaine Lang[1], Dr Kieran Campbell[2], Dr Caleb Webber[3], Dr Richard Wade-Martins[1]

[1]University of Oxford, Oxford, United Kingdom. [2]University of Toronto, Ontario, Canada. [3]UKDRI, Cardiff, United Kingdom

Objective: Our aim is to use iPSC models to unbiasedly uncover alterations in new unidentified pathways attributed to Parkinson's disease (PD) that may be therapeutically targeted by repurposed compounds.

Background: We developed an approach to obtain purified populations of iPSC-derived dopamine neurons from three control and three GBA-N370S PD patient lines by fluorescencet activated cell sorting for bulk and single cell RNA-seq analysis.

Results: Using single-cell transcriptomic analyses of iPSC-derived dopamine neurons we identified a progressive axis of gene expression variation. We hypothesise this axis represents the continuous progression of cells through a modelled disease-relevant process, moving from a control-like state to a PD-relevant state. We identified a robust set of 60 differentially expressed (DE) genes, that could be ordered along this disease axis. DE genes late in this disease axis are associated with increased ER stress, previously-characterised in PD. Early DE genes were down-regulated by HDAC4, a class IIa histone deacetylase and transcriptional repressor, which shuttles between the nucleus and the cytoplasm. HDAC4 was mislocalised to the nucleus in PD GBA-N370S iPSC-derived dopamine neurons and a subset of idiopathic PD patients, indicating HDAC4 as a potential upstream regulator of disease progression. Modulation of HDAC4 activity or localisation, with repurposed compounds, reversed the downregulation of the DE HDAC4 repressed genes and ameliorated PD cellular phenotypes, including ER stress, autophagic/lysosomal perturbations, and increased α-synuclein release.

Conclusions: This work demonstrates how we can exploit cellular heterogeneity and single cell RNA-seq to stratify patients and reveal new disease mechanisms and therapeutic targets.

Poster 39 - Neuropsychiatric differences and carer distress in Parkinson's disease, dementia with Lewy Bodies and Alzheimer's disease

Mr Daniel Smith, Professor David Burn, Professor Lynn Rochester, Dr Riona Mc Ardle, Dr Rachael Lawson

Newcastle University, Newcastle upon Tyne, United Kingdom

Objective: To identify neuropsychiatric symptom (NPS) profiles and carer distress in people with Parkinson's, Parkinson's with dementia, dementia with Lewy bodies, Alzheimer's and healthy older adult controls.

Background: Neuropsychiatric symptoms (NPS) are common and distressing in neurodegenerative disorders, and may present differently across conditions. Understanding NPS profiles will improve our understanding and could be useful to develop educational interventions to support coping carers.

Methods: A cross-sectional sample (n=187) of participants from the ICICLE-PD and GaitDem studies with Parkinson's, Parkinson's with dementia, dementia with Lewy bodies and Alzheimer's were compared with controls. The Neuropsychiatric Inventory (NPI) evaluated NPS. Backwards stepwise linear regression was used to identify which NPS symptoms were associated with NPI total and carer distress.

Results: NPI total was significantly higher across conditions compared to controls; people with Parkinson's had lower scores compared to those with Parkinson's dementia and dementia with Lewy bodies ($p<0.$), but not Alzheimer's ($p>0.05$). Regression analysis yielded four distinct NPS profiles across Parkinson's, Parkinson's, dementia with Lewy bodies, and Alzheimer's groups. A greater range of symptoms was significantly associated with carer distress across the conditions ($p<0.05$ for all, $R^2=0.62$-0.81).

Conclusions: NPS are more common and more severe in neurodegenerative disorders compared with normal ageing. A unique profile of NPS was associated with each condition, but carer distress was associated with a more diverse range of symptoms. These findings are an important first step to developing non-pharmacological interventions to support carers and reduce carer burden.

Poster 40 - Neuropsychological changes over the first 6 years of Parkinson's disease in the ICICLE-PD cohort

Dr Rachael Lawson[1], Dr Caroline Williams-Gray[2], Professor Roger Barker[2], Professor David Burn[1], Dr Alison Yarnall[1]

[1]Newcastle University, Newcastle upon Tyne, United Kingdom. [2]University of Cambridge, Cambridge, United Kingdom

Aim: To determine which neuropsychological tests are sensitive to change over time in people with early Parkinson's and dementia independent of ageing.

Background: Cognitive impairment is common in Parkinson's, with 80% cumulatively developing dementia over 20 years. However, it is unclear which neuropsychological tests are most sensitive to change over time in Parkinson's and dementia over and above normal ageing.

Methods: Newly diagnosed people with Parkinson's (n=212) and age-matched controls (n=99) completed a schedule of clinical assessments as part of the ICICLE-PD study and returned at 18 month intervals over six years. Participants completed detailed cognitive tests comprising global cognition (Montreal Cognitive Assessment, MoCA), verbal fluency and computerised tests assessing executive function, memory and attention. Changes in cognition across time points were determined using linear mixed effects models, adjusting for age, sex, education, depression and motor severity.

Results: Cumulatively, 45 (21.2%) Parkinson's participants developed dementia. Decline in attention scores was significantly faster in Parkinson's participants compared to controls ($p<0.05$). Participants who developed dementia with Parkinson's had a significantly faster rate of decline in MoCA, phonemic and semantic fluency, memory, attention scores ($p<0.05$ for all).

Conclusions: Attentional scores are sensitive to change over time in Parkinson's and those who develop dementia, but changes in executive function and memory were the most sensitive to change in participants who developed an early dementia. Our findings suggest that future studies should consider using specific tests of memory and executive function to detect changes in early dementia.

Poster 41 - Using a high-throughput toxin-induced LUHMES neuronal model to screen for mitochondrial restorative compounds for Parkinson's disease.

Tom Leah, Dr Irina Vazquez-Villaseñor, Prof Stephen Wharton, Dr Heather Mortiboys

University of Sheffield, Sheffield, United Kingdom

Objective(s):

1. To set up a high-throughput toxin-induced LUHMES-GFP+ cell model which can be used in a high content imaging screen.
2. To identify compounds which restore mitochondrial activity and neuronal morphology.

Background: Mitochondrial dysfunction is a key pathology of Parkinson's disease. Small molecules targeting mitochondrial restoration are an attractive target for drug discovery.

Methods: A high content imaging screen was designed using differentiated LUHMES-GFP+ neurons. Mitochondrial dysfunction was induced using rotenone treatment. Several mitochondrial and neuronal parameters were assessed for those which were robustly and reproducibly measured in the high content screen. Four parameters were selected based upon Z' and SW scores and used in compound screening. A compound library was screened using this model for small molecules which improve both mitochondrial function and neuronal morphology.

Involvement of people affected by Parkinson's: The project builds upon previous projects which involved close interaction with PwP, at the dissemination stage and in discussing options for continuation of the project. This project is one such continuation which was discussed and approved by PwP.

Results: Mitochondrial membrane potential, mitochondrial area, neurite length and neurite roundness were found to be reproducible and robust parameters in this toxin-induced LUHMES-GFP+ high content screen. Several compounds were shown to have significant recovery effects across these parameters.

Conclusions: The LUHMES neuronal model is a highly robust and reproducible high-throughput model for compound screening and assessment of mitochondrial and morphological parameters. The most promising candidate compounds can be processed further along the drug discovery pipeline towards clinical testing.

Poster 42 - Mass spectrometry based analysis of the biophysical properties of recombinant α-synuclein for the protein quality control and robust α-synuclein RT-QuIC

Miss Selene Lee, Dr Laura Parkkinen

University of Oxford, Oxford, United Kingdom

Objective: The objective is to develop a quality control method for recombinant α-synuclein to be used for RT-QuIC, which will provide a more rigorous RT-QuIC for the diagnosis of Parkinson's and α-synuclein research.

Background: Real-time quaking-induced conversion (RT-QuIC) is a protein amplification assay that can detect pathological α-synuclein in CSF and brain from patients with Parkinson's. Recombinant α-synuclein, the aggregation substrate, is an important variable in a RT-QuIC assay. Methods of producing recombinant α-synuclein vary significantly among different studies, possibly creating variability in RT-QuIC outcome.

Involvement of people affected by Parkinson's: Improved robustness of RT-QuIC will enable more reliable and accurate diagnosis of Parkinson's. Furthermore, studying the α-synuclein fibril products generated by RT-QuIC will provide a clearer understanding of the pathogenesis of Parkinson's.

Methods: We used native size exclusion chromatography - mass spectrometry (SEC-MS) to show that working recombinant α-synuclein exists in distinct charge states, suggesting the presence of definitive conformational species in a specific ratio that is optimal for RT-QuIC.

Results: Recombinant α-synuclein that results in a successful RT-QuIC reaction has a specific charge distribution pattern in the MS raw data. Repeats of freeze/thaw cycles and increasing the salt concentration of recombinant α-synuclein solution disrupted the charge distribution pattern and resulted in RT-QuIC false positives.

Conclusions: Specification of a detailed biophysical profile of working recombinant α-synuclein for RT-QuIC can set a criteria for rigorous α-synuclein RT-QuIC.

Poster 43 - WNT and NFAT signalling changes in LRRK2 Parkinson's disease models

Mr Si Hang Lei, Dr Andrea Wetzel, Dr Michael Hughes, Dr Ahad Rahim, Prof Kirsten Harvey

University College London, School of Pharmacy, London, United Kingdom

LRRK2 mutations are a major cause of sporadic and familial Parkinson's disease, but the exact mechanisms on how mutated LRRK2 causes Parkinson's disease still to remain unclear. However, there is accumulating evidence showing LRRK2 is a WNT signalling pathways component. G2019S is the most common mutation site, which contributes to 1-2% and 5% of sporadic and familial cases, respectively. Importantly, we previously reported that the G2019S Parkinson's disease mutation leads to reduction of WNT signalling activity. WNT signalling is important for synapse formation as well as neuronal maintenance.

In this project, we used wild type (WT), LRRK2 knock-out (KO) and G2019S knock-in (KI) mouse models. We identified WNT and NFAT signalling activities in different brain regions by transducing lentiviral biosensors into the brain at P0 and investigating the distribution of signalling activation by immunohistochemistry at 6 months. We also investigated mRNA and protein expression changes under basal condition via real-time PCR and western blotting, respectively. Primary neuronal cultures were used to study signalling activities under basal and stimulated condition.

Our preliminary data showed WNT signalling pathway activation in different brain regions with localised differences in WNT signalling component expression. These changes were also dependent on sex, LRRK2 genotype and cell types studied. However, the exact regulatory effects of LRRK2 mediated WNT signalling activities under physiological and pathological conditions requires further investigation.

Poster 44 - Visualising α-Synuclein oligomers using super-resolution microscopy

Mr Craig Leighton, Dr Tilo Kunath, Dr Mathew Horrocks

University of Edinburgh, Edinburgh, United Kingdom

Objective: To develop a method that will enable the characterisation of rare and highly heterogeneous αSyn oligomers at the nanoscale

Background: Currently, Parkinson's disease (PD) is clinically diagnosed, with confirmation made post mortem. The typical motor symptoms only manifest after approximately 50-60% of midbrain dopaminergic nerve terminals have been lost, which can start as early as 10-15 years prior to diagnosis. This highlights the need for an early diagnostic method.

αSyn is central to the aetiology of PD and evidence suggests that oligomers of the protein found in CSF are indicative of the disorder. These oligomers, however, are lowly abundant and highly heterogenous, making them challenging to study. By visualising molecules individually, single-molecule and super-resolution microscopy methods enable even the rarest of species to be characterised. We have focused on developing such tools with the aim of observing αSyn oligomers in PD patient CSF and correlating this with disease state.

Method: We can specifically isolate and immobilise αSyn oligomers and can image these using super-resolution microscopy methods, such as DNA-PAINT. We have demonstrated the success of this method using conditioned media collected from PD patient-derived mid-brain dopaminergic neurons.

Results: Following optimisation of our approach, we are now utilising it to analyse conditioned media collected from SNCA triplication vs. SNCA knockout cells. Single-molecule confocal microscopy and sandwich ELISAs are also being employed to detect αSyn species.

Poster 45 - Spontaneous graft-induced dyskinesias correlate with graft inflammation, and are independent of 5-HT neurons and L-DOPA priming, in a xenograft model of Parkinson's disease

Dr. Emma Lane[1], Dr Harri Harrison[1], Dr Agnete Kirkeby[2], Prof Malin Parmar[2], Dr. Mariah Lelos[1]

[1]Cardiff University, Cardiff, United Kingdom. [2]Lund University, Lund, Sweden

Background: A major challenge in progressing cell transplantation as a therapy for Parkinson's disease is understanding the spontaneous dyskinesia that emerged in some recipients of dopaminergic fetal grafts during early clinical trials. This has been, in part, due to the absence of a truly representative animal model.

Methods: In this study, rats with unilateral 6-OHDA lesions of the median forebrain bundle received intrastriatal grafts of human embryonic stem cells (hESCs) differentiated into either ventral midbrain dopaminergic progenitor cells (vmDA) or ventral forebrain cells (vFB). A subset of rats grafted with hESC-derived vmDA cells unexpectedly developed spontaneous contralateral rotational behaviours and abnormal involuntary movements (AIMs), which were chronic, stable and measurable with application of the AIMs scale.

Results: Pharmacological challenges demonstrated that these behaviours were exacerbated by amphetamine (2.5mg/kg) and inhibited by the D_2-like receptor antagonists eticlopride 0.03mg/kg and high doses of buspirone (5-HT_{1A} agonist, D_2-like receptor antagonist). They were not affected by more selective 5-$HT_{1A/1B}$ or 5-HT_6 agonist or antagonist activity. Post-mortem analysis demonstrated that the spontaneously dyskinetic rats had larger surviving dopaminergic grafts compared to non-dyskinetic rats. Histological comparison with hESC-derived vFB grafts indicated that the large vmDA grafts had significantly higher astrocytic and microglial activation. No grafts had serotonergic neurons present.

Conclusions: Findings from this study argue against current thinking and instead indicate that spontaneous post-transplantation dyskinesia can occur independently of L-DOPA exposure and are not always triggered by 5-HT neurons in the grafts. Instead, graft-induced dyskinesias may be linked also to high dopaminergic density and an inflammatory response to the graft.

Poster 46 - Predicting outcome using patient reported outcomes (PROs) in the UK Parkinson's Disease Tissue Bank.

Rebecca Leslie[1], Benison Tilley[1], Marina Romozzi[2], Steve Gentleman[1], Richard Nicholas[1]

[1]Imperial College London, London, United Kingdom. [2]Catholic University of Sacred Heart, Rome, Italy

Objectives: Investigate the utility of the United Kingdom Parkinson's Disease Tissue Bank (UKPDTB) patient reported outcome (PRO) for predicting survival in Parkinson's.

Background: Parkinson's has variable progression rates. Prognostic tools focus on physician's assessments. The UKPDTB has collected a 100-question PRO, the Imperial College London Donor Questionnaire (ICLDQ), since its inception. We investigated whether particular question(s) could predict survival.

Methods: Responses to the ICLDQ Likert scale (scored 0-3) were collected for a Parkinson's and a control group. Using logistic regression modelling we investigated the relationship between responses and survival in the Parkinson's group.

Involvement of people affected by Parkinson's: The ICLDQ was administered to participants in the UKPDTB. This included individuals with and without Parkinson's.

Results: 159 complete responses from people with Parkinson's and 203 from controls were analysed. 75 of those with Parkinson's and 0 controls had died since questionnaire completion. Responses were highly correlated for many questions. Cox regression produced a model of five questions for predicting survival (concordance=0.751). Questions were divided into symptom categories and two models were generated which were able to predict survival. One combined sleep and self-care (concordance=0.661), another combined self-care and autonomic dysfunction (R^2=0.1544). Higher frequency score of early Parkinson's symptoms correlated with shorter survival (R=-0.37, p=0.002).

Conclusions: PROs can predict prognosis in Parkinson's. High correlation between questions suggests an abbreviated questionnaire would be beneficial. Difficulties with self-care have previously been linked with poor survival, our findings support this.

Poster 48 - Quantitative chemical imaging of soluble α-synuclein and Aβ aggregates with Single Molecule Pull-down Assay in human Parkinson's brains

Dr Evgenia Lobanova, Derya Emin, Yu P. Zhang, Dr Rohan T. Ranasinghe, Professor Sir David Klenerman

Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Objective: Our aim is to quantify the spatio-chemical composition of individual toxic protein aggregates with spatial resolution down to 20 nm in post-mortem brain tissues of patients affected by Parkinson's.

Background: Toxic aggregates of α-synuclein (α-syn) and amyloid-β (Aβ) are both associated with the initiation and progression of Parkinson's disease. However, a quantitative single-molecule imaging of their individual protein chemical profiles in human Parkinson's brains at 20nm spatial resolution and up to picomolar concentrations is still under study.

Methods: Our study utilizes a recently developed Single-Molecule Pull-down (SiMPull) technique combining a conventional immunoassay with simultaneous single-molecule fluorescence imaging of the protein-specific aggregates pulled down to the chemically optimized glass surface using a mixture of the antibodies against α-syn and Aβ.

Involvement of people affected by Parkinson's: We examine both diffraction-limited and super-resolved images of soluble α-syn and Aβ aggregates soaked out from post-mortem brain tissues of Parkinson's patients.

Results: Our preliminary results demonstrate a proof-of-concept for SiMPull to detect the imaging concentration profiles of oligomeric/fibrillar α-syn aggregates from post-mortem human diseased brains with the significantly larger levels of α-syn in the amygdala compared to the occipital cortex. Together with SiMPull imaging of the super-resolved α-syn and Aβ aggregates which we are currently exploring, we hypothesise the relative contribution of α-syn and Aβ oligomeric species into the aggregates' content might be disease-dependant.

Conclusions: Our findings indicate that SiMPull assay has potential for accurate and ultra-sensitive diagnostic detection of early changes in the pathological aggregates' content from human biofluids.

Poster 49 - Sleep, Depression and Quality of Life in Parkinson's: An Investigation Using a Combination of Subjective and Objective Sleep Assessment Methods.

Dr Philip Mulryan, Dr Sean Affonso, Professor Aideen Sullivan

University College Cork, Cork, Ireland

Introduction: Sleep disturbances are among the most common of the non-motor symptoms of Parkinson's and are strongly associated with depressive symptoms and quality of life (QOL). Sleep quality can be assessed using both subjective and objective measures. Studies have shown that subjective sleep quality often differs from objective parameters. Few studies have used a combination of subjective and objective methods to explore the relationship between sleep, depression and quality of life in adults with Parkinson's.

Objectives: The aim of this study was to compare subjective and objective sleep measures and explore how these relate to depressive symptoms and QOL in a Parkinson's population.

Involvement of people affected by Parkinson's: Community-dwelling adults with a diagnosis of Parkinson's were invited to take part in this study.

Methods: Thirty-seven patients participated in this study. The Pittsburgh Sleep Quality Index (PSQI) and wrist-actigraphy were used to assess subjective and objective sleep quality, respectively. The Beck Depression Inventory (BDI) was used to measure depressive symptoms. The 39-Item Parkinson's Disease Questionnaire (PDQ-39) was used to measure QOL.

Results: Weak to non-significant correlations were found between PSQI scores and actigraphy-determined sleep parameters. BDI score was significantly related to PSQI subjective sleep quality ($r=0.62$, $p<.0001$), sleep latency ($r=0.53$, $p<.001$), sleep disturbances ($r=0.61$, $p<.0001$), daytime dysfunction ($r=0.51$, $p<.002$), and global score ($r=0.73$, $p<.0001$). BDI score did not correlate with any of the actigraphy-determined sleep parameters. PDQ-39 score correlated significantly with PSQI sleep disturbances ($r=0.466$, $p<.01$), and global score ($r=0.426$, $p<.01$). PDQ-39 score did not correlate with any of the actigraphy-determined sleep parameters.

Conclusions: These results suggest that a patient's perception of sleep quality is inconsistent with objective parameters. Interestingly, subjective measures were associated with depressive symptoms and quality of life while objective parameters were not.

Poster 50 - Using Actigraphy to Characterise the Relationship between Sleep, Quality of Life, and Depression in Parkinson's

Dr Philip Mulryan, Dr Sean Affonso, Professor Aideen Sullivan

University College Cork, Cork, Ireland

Background: Sleep disturbances are among the most common of the non-motor symptoms of Parkinson's Disease (PD) and have been shown to have a significant impact on quality of life. Few studies have used a combination of subjective and objective methods to assess sleep quality in those with Parkinson's. The aim of this study was to characterise sleep dysfunction in Irish adults with Parkinson's using both subjective and objective methods.

Methods: Forty community-dwelling adults with Parkinson's participated in this study. The Berlin Questionnaire, the Epworth Sleepiness Scale, and the Pittsburgh Sleep Quality Index (PSQI) were used to assess for sleep-disordered breathing, excessive daytime sleepiness, and sleep quality, respectively. The Innsbruck REM Sleep Behaviour Inventory was used to screen for REM sleep behaviour disorder (RBD). Actigraphy was used to objectively assess sleep over seven consecutive days. Measurements included total sleep time (TST), number of awakenings, and wake after sleep onset (WASO).

Results: Twenty-one patients (53%) were placed in the high-risk category for sleep disordered breathing. Twenty-two patients (55%) had probable excessive daytime sleepiness. Thirty-five patients (88%) had a PSQI score indicative of poor sleep quality. Sixteen patients (41%) had probable RBD. Mean TST was 437 +/- 80 min. Mean number of awakenings per night was 10.2 +/- 5.9. Mean WASO was 63.6 +/- 36 min.

Conclusion: Sleep dysfunction is highly prevalent in this Irish Parkinson's cohort.

Poster 51 - Functional and axonal outgrowth deficits in tau-deficient human neurons

Bryan Ng, Jane Vowles, Sally Cowley, Natalie Connor-Robson, Richard Wade-Martins

University of Oxford, Oxford, United Kingdom

Objective: The study objective is to understand the effects of tau depletion in human induced pluripotent stem cell (iPSC)-derived neurons.

Background: The MAPT gene encoding for the microtubule-associated protein tau is one of the major genetic risk factors for Parkinson's disease. Additionally, tau aggregation pathology could be detected in approximately 50 % of the post-mortem Parkinson's disease brains in the cortical regions and midbrain. Aged MAPT knockout mice have previously shown reduction in the number of TH-positive neurons as well as motor deficits. Yet, a tau-deficient human in vitro model has not been available to corroborate these studies.

Methods: Here we generated the first $MAPT^{-/-}$ human iPSC lines using the CRISPR-Cas9 technologies to study the effects of tau deficiency in human biological context. We also established a versatile and scalable cortical neuron differentiation protocol which successfully produced a heterogeneous population of functional neurons manifesting cortical identity in co-culture with rat astrocytes. iPSC-derived cortical neurons were aged for 80 days before imaging and electrophysiological experiments were carried out.

Results: iPSC-derived $MAPT^{-/-}$ cortical neurons exhibited lower firing amplitude and frequency compared to $MAPT^{+/+}$ neurons measured using the multi-electrode array system, while expressing similar number of synapses. The $MAPT^{-/-}$ neurons were also less capable in establishing network firing activities and achieving synchrony. Furthermore, $MAPT^{-/-}$ neurons demonstrated impaired axonal outgrowth over 5 days of live imaging.

Conclusions: Our data thus suggest that the absence of tau protein results in functional deficits and axonal outgrowth impairment in human iPSC-derived neurons.

Poster 52 - Human-specific levels of CDNF, MANF and ER stress in the pathological progression of Parkinson's disease

Dr Ilaria Poggiolini[1], Dominik Hrabos[1], Dr Paivi Lindholm[2], Dr Mart Saarma[2], Dr Laura Parkkinen[1]

[1]Nuffield Department of Clinical Neuroscience, Oxford Parkinson's Disease Centre, Oxford, United Kingdom.
[2]Institute of Biotechnology, University of Helsinki, Helsinki, Finland

Objectives: To establish whether levels of Endoplasmatic Reticulum (ER)-stress responsive neurotrophic factors, Cerebral Dopamine Neurotrophic Factor (CDNF) and Mesencephalic Astrocytes Derived Neurotrophic Factor (MANF) are altered during the progression of pathology in Parkinson's and whether these alterations are related to a-synuclein (aSyn)or ER-stress.

Background: The expression and secretion of CDNF and MANF increase with ER-stress, they protect dopamine neurons in animal models of Parkinson's and CDNF also decreases intracellular aSyn aggregation.

Methods: CDNF and MANF were analysed by sandwich ELISA, aSyn and phosphorylated/total eIF2a levels with automatized Western blotting and aSyn seeding with RT-QuIC. In addition, we analysed mRNA levels of above and other ER-stress targets. The levels were analysed 45 subjects selected from Oxford Brain bank in four brains regions: substantia nigra (SN), striatum, entorhinal cortex and occipital cortex (OccCx) and compared between three groups: 12 healthy controls without pathology, 19 cases with incidental Lewy body pathology (Braak stages 1-4) and 14 Parkinson's patients (Braak stages 5-6).

Results: Although we could not detect significant differences in MANF and CDNF protein levels between study groups, we were able to show that the levels of MANF significantly decreased in SN with immunohistochemistry during Parkinson's disease progression. aSyn seeding (but not total levels) significantly increased with the progression of Parkinson's pathology. MANF levels correlated with phosphorylated/total eIF2a but not with aSyn.

Conclusions: MANF but not CDNF levels are related to the extent of ER-stress in Parkinson's brain but not to aSyn levels.

Poster 53 - Human-specific transcriptomic profiling of ventral and dorsal midbrain dopamine neurons

Dr Jimena Monzón-Sandoval1[1], Dr Ilaria Poggiolini[2], Dr Richard Wade-Martins[3], Dr Caleb Webber[1], Dr Laura Parkkinen[2]

[1]UK Dementia Research Institute, Cardiff University, Cardiff, United Kingdom. [2]Nuffield Department of Clinical Neurosciences, Oxford Parkinson's Disease Centre, Oxford, United Kingdom. [3]Department of Physiology Anatomy and Genetics, Oxford Parkinson's Disease Centre, Oxford, United Kingdom

Objective: To identify intrinsic genetic differences that account for the differential vulnerability of the neurons in substantia nigra pars compacta (SNpc) in Parkinson's brain.

Background: Neuronal loss in the SNpc in Parkinson's brain is not uniform as dopamine neurons from the ventral (vulnerable) tier are lost more rapidly than those of the dorsal (resistant) tier.

Methods: We compared the transcriptional profiles of ~100 laser captured micro-dissected SNpc neurons from each tier obtained from seven healthy brain donors.

Results: Expression levels of dopaminergic markers were similar across the tiers while markers specific to the neighbouring ventral tegmental area were virtually undetected. After accounting for unwanted sources of variation, we identified 106 differentially expressed genes (DEGs) between the tiers. The genes upregulated in the dorsal/resistant SNpc tier neurons displayed coordinated patterns of expression, their protein products had more interactions than expected by chance and they demonstrated evidence of functional convergence. No significant shared functionality was found for genes upregulated in the ventral/vulnerable SNpc tier. Surprisingly, none of the identified DEGs were among the familial genes or genome-wide associated loci. Finally, we found some DEGs in opposite tier orientation between human and analogous mouse populations

Discussion: Our results highlight functional enrichments of vesicular trafficking, ion transport/homeostasis and oxidative stress genes showing higher expression in the resistant SNpc dorsal neurons. Furthermore, the comparison of gene expression variation in human and mouse SNpc populations strongly argues for the need of human-focused Omics studies.

Monzón-Sandoval et al. Ann Neurol 2020;87(6):853-868

Poster 54 - Developing 31-phosphorus magnetic resonance spectroscopy (^{31}P-MRS) as an imaging biomarker to identify mitochondrial dysfunction in Parkinson's disease

Dr Thomas Payne[1], Dr Matilde Sassani[1], Prof Iain Wilkinson[2], Dr Thomas Jenkins[1], Prof Oliver Bandmann[1]

[1]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom. [2]Academic Unit of Radiology, University of Sheffield, Sheffield, United Kingdom

Objective: To determine if ^{31}P-MRS can identify mitochondrial dysfunction in-vivo and if this correlates with in-vitro measures of mitochondrial function obtained from patient derived fibroblasts

Background: Sporadic Parkinson's is increasingly recognized as an aetiologically heterogeneous disorder. Identification of the distinct mechanism contributing to neuronal cell loss in an individual will be crucial to develop future "Precision Medicine" approaches. ^{31}P-MRS is a non-invasive tool that measures relative quantities of key compounds involved in energy metabolism, such as adenosine triphosphate and phosphocreatine.

Methods: ^{31}P-MRS scans will be undertaken in 35 people with Parkinson's and 25 healthy age and sex matched controls. All research participants will also be having a 3mm punch skin biopsy to establish fibroblast cell lines for functional mitochondrial assays. Clinical assessment includes widely utilised clinical rating scales, genetic analysis and the calculation of predicted risk of disease progression.

Involvement of people affected by Parkinson's: This study has been discussed with the local Parkinson's UK Research Interest Group.

Results: Interim analysis of baseline ^{31}P-MRS data reveals there is a significant difference in variance in ATP levels and Phosphocreatine/ATP ratio (an alternative bioenergetic measure) in the midbrain between Parkinson's and controls, with around a third of patients more than 2 standard deviations from the mean. Phosphocreatine/ATP ratio shows a significant linear relationship with predicted disease progression (linear regression $p=0.017$, $r^2=0.406$).

Conclusion: ^{31}P-MRS may help to identify a subgroup of Parkinson's with significant mitochondrial dysfunction. Future work includes completing the functional assessment of mitochondria in fibroblast cell lines and repeat ^{31}P-MRS for longitudinal data.

Poster 55 - The UP study: Ursodeoxycholic acid (UDCA) as a neuroprotective treatment for Parkinson's disease

Dr Thomas Payne[1], Dr Matthew Appleby[2], Dr Thomas Jenkins[1], Prof Thomas Foltynie[2], Prof Oliver Bandmann[1]

[1]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom. [2]Queen Square Institute of Neurology, University College London, London, United Kingdom

Objectives: To determine the safety and tolerability of Ursodeoxycholic acid (UDCA) in Parkinson's and explore its neuroprotective potential

Background: We previously undertook the first-ever drug screen in Parkinson's patient tissue and identified UDCA as a promising neuroprotective compound for Parkinson's. UDCA has been in clinical use for > 30 years for primary biliary cholangitis. It is well tolerated and safe.

Methods: We designed a two centre, phase IIa, randomised, placebo-controlled clinical trial to assess UDCA in 30 people with Parkinson's less than 3 years from diagnosis and a definite response to dopaminergic medication. Randomisation is 2:1 in favour of UDCA. Treatment duration is 48 weeks with reassessment after an 8 week washout. Primary outcome is safety and tolerability of UDCA. Secondary outcomes include the MDS-UPDRS, ^{31}Phosphorus Magnetic Resonance Spectroscopy (^{31}P-MRS) and sensor-based objective quantification of motor impairment.

Involvement of people affected by Parkinson's: This study has been discussed with the local Research Interest Group.

Results: Recruitment was completed in October 2019. Only 1/30 participants to date had to stop taking the medication due to swallowing problems and they were subsequently replaced. Mild, self-limiting diarrhoea for < 24h is the only treatment-related side-effect so far. ^{31}P-MRS has been optimised to reliably quantify ATP in both the substantia nigra and the striatum. Compliance with the use of motion sensors is excellent.

Conclusion: The UP study provides a successful example of academically led drug development. ^{31}P-MRS and sensor-based objective quantification of motor impairment could also be applied to assess the neuroprotective potential of other compounds.

Poster 56 - Investigating behavioural impulsivity and inhibitory control in Parkinson's and impulse control behaviours

Jade Pickering[1], Marta Majewska[1], Professor Iracema Leroi[2], Dr Jennifer McBride[1], Dr Ellen Poliakoff[1]

[1]University of Manchester, Manchester, United Kingdom. [2]Trinity College Dublin, Dublin, Ireland

Objective: To examine the effects of Parkinson's and additional impulse control behaviours on different facets of impulsivity and control.

Background: Whilst Parkinson's reduces dopamine availability in some brain areas, dopamine agonists increase the availability across all dopamine pathways. This lack of specificity can cause overstimulation of some pathways and increased impulsivity in the form of impulse control behaviours (ICBs). A systematic review of the literature (Pickering et al., in prep) revealed a lack of clarity as to which mechanisms associated with impulsivity and inhibitory (cognitive and motor) control are differentially affected in people with Parkinson's (PwP) and those who additionally experience medication-induced ICBs (PwP+ICBs). This may be due to heterogeneity in Parkinson's and publication bias in the literature.

Involvement of people affected by Parkinson's: The study was developed with PPI volunteers as part of a Parkinson's UK Research Involvement Award.

Methods: We recruited PwP, PwP+ICBs, and control participants to participate in a range assessments of impulsivity and inhibitory control: response inhibition/conflict (e.g. Stop Signal, Flanker task), task-switching, risky decision making (e.g. Iowa and Cambridge Gambling Tasks), delay discounting, and trait impulsivity.

Results: Data analysis was pre-registered and is ongoing. We will present findings for PwP, PwP+ICBs, and controls on the assessments mentioned above.

Conclusions: Collecting data from the same individuals in a broad range of tasks will greatly help to elucidate group differences, and provide a clearer picture as to the mechanisms that are affected in Parkinson's and ICBs.

Poster 57 - Dose and time dependent effects of anle138b in transgenic MI2 mice expressing truncated human alpha-synuclein

Dr. Katrina Albert[1], Dr. Michal Wegrzynowicz[2], Prof. Armin Giese[3], Prof. Christian Griesinger[4], Prof. Maria Grazia Spillantini[1]

[1]University of Cambridge, Cambridge, United Kingdom. [2]Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, Poland. [3]Ludwig-Maximilians-University Munich, Munich, Germany. [4]Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Objective: The goal of this study is to investigate the effects of different treatment times and amounts of anle138b in vivo in transgenic mice. The duration of the effect of anle138 was also evaluated.

Background: We have previously shown that MI2 transgenic mice, expressing human, aggregation-prone alpha-synuclein, develop alpha-synuclein aggregates, dopaminergic dysfunction, nigral neuron death and motor behaviour. The motor symptoms and dopamine neuron dysfunction and death, were rescued by treatment with anle138b, an oligomer-modifying compound synthesized by Andrei Leonov and Sergey Ryazanov (Wegrzynowicz et al. Acta Neuropathol 2019).

Methods: Different amounts of anle138b were administered in the food to MI2 mice for 2 or 3 months and the effect on alpha-synuclein aggregation, striatal dopamine release, nigral neuronal death and motor behaviour were analysed by immunohistochemistry, microdialysis, stereology, and gait analysis, respectively. Dopamine was measured by HPLC. The mice were followed up to 4 months post-anle138b administration.

Results: The pharmacodynamic experiments show that anle138b can rescue dopamine release at lower doses than the 2g/kg used in our published study. Lower dose and shorter treatment (2 months) obtained similar results to observations 3 months post-treatment. Ongoing behavioural studies and dopamine release measurements will assess whether the effect of anle138b is still present 4 months post-treatment interruption.

Conclusions: Anle138b is effective at lower doses compared to the amount previously used in in vivo studies. Compared to the 3 months used previously, the 2 months treatment is also effective. Ongoing work will determine whether anle138b's effects will persist after 3 month treatment interruption.

Poster 58 - How far can I reach? Perception of action capabilities in people with Parkinson's

Miss Megan Rose Readman[1], Dr Trevor Crawford[1], Dr Ellen Poliakoff[2], Dr Sally A. Linkenauger[1]

[1]Lancaster University, Lancaster, United Kingdom. [2]The University of Manchester, Manchester, United Kingdom

Objective: To analyse whether Parkinson's affects an individual's ability to accurately perceive the maximum extent to which they can perform reaching, grasping and aperture passing actions.

Background: Successful interaction within the environment relies upon one's ability to accurately perceive the range over which one can perform various actions, known as action boundaries. Healthy individuals are profoundly accurate in perceiving their own action boundaries. However, as Parkinson's reduces one's ability to perform actions and can lead to variability in perceptual-motor experience, it is important to ask whether Parkinson's affects the perception of action capabilities.

Methods: Participants completed 3 tasks measuring their judgment of the (i) farthest distance they can reach, (ii) largest object they can grasp and (iii) smallest size opening they can pass their hand through. Afterwards, participants' actual capability was measured.

Involvement of people affected by Parkinson's: This study recruited 30 patients with mild-to-moderate idiopathic Parkinson's and 30 healthy older adults.

Results: Individuals with Parkinson's perceptions of their action boundary for reaching ($p = .260$), grasping ($p = .882$) and aperture passing ($p = .760$) did not significantly differ from healthy older adults.

Conclusions: There was no evidence that perceptions of action capabilities were affected in Parkinson's. This indicates that despite the reduction in their ability to perform actions, and variability in perceptual-motor experience that occurs in Parkinson's, individuals' ability to accurately perceive their action boundaries is preserved. This suggests that they can use this knowledge to move safely within the environment.

Poster 59 - Gabapentinoid drugs modify Ca^{2+} entry to striatal dopamine axons and promote dopamine release in a mouse model of Parkinson's

Dr Katherine Brimblecombe, Dr Bradley Roberts, Prof Richard Wade-Martins, Prof Stephanie Cragg

Department of Physiology, Anatomy and Genetics and Oxford Parkinson's Disease Centre, University of Oxford, Oxford, United Kingdom

Objectives: To identify whether gabapentinoid drugs modify dopamine neurotransmission from nigrostriatal neurons in a mouse model of Parkinson's.

Background: Ca^{2+} entry via voltage-gated calcium channels (VGCCs) is critical for normal functioning of nigrostriatal dopamine neurons, but can generate excessive Ca^{2+} burden that promotes vulnerability to degeneration. Strategies to limit VGCC function can therefore be neuroprotective. VGCC function is dependent on α_1 pore-forming subunits, and on $\alpha_2\delta$ auxiliary subunits for channel trafficking and localisation. The $\alpha_2\delta$ subunits are the target of gabapentinoid drugs, which are used clinically for other neurological disorders. We tested whether gabapentinoids modify striatal dopamine release and VGCC function in dopamine axons, in order to explore their repurposing potential for Parkinson's.

Methods: We detected dopamine release in striatum in mouse brain slices (wild-type, and α-synuclein overexpressing, SNCA-OVX) using fast-scan cyclic voltammetry and assessed the effect of gabapentinoids during acute exposure (50 μM, 1hr) and after a clinically relevant chronic dosing regimens (pregabalin twice daily, 3 days, 30 mg/kg).

Results: Acute gabapentinoids reduced the contributions of L- and P/Q-type VGCCs to evoked dopamine release, yet slightly promoted dopamine release by increasing the efficiency of its coupling to Ca^{2+} sources. Chronic pregabalin significantly increased dopamine release in dorsal but not ventral striatum in male and female SNCA-OVX mice by up to 50%.

Conclusions: Gabapentinoids reduce sources of Ca^{2+} entry that are associated with neurotoxicity, and they also boost nigrostriatal dopamine release. Gabapentinoids might therefore have potential to offer both neuroprotection and symptomatic gain in Parkinson's.

Poster 60 - Universal latent axes capturing Parkinson's patient deep phenotypic variation reveals patients with a high genetic risk for Alzheimer's disease are more likely to develop a more aggressive form of Parkinson's.

Dr Cynthia Sandor[1], Dr Stephanie Millin[2], Pr Michele Hu[2], Pr Yoav Ben-Shlomo[3], Pr Caleb Webber[1]

[1]Cardiff University, Cardiff, United Kingdom. [2]University of Oxford, Oxford, United Kingdom. [3]University of Bristol, Bristol, United Kingdom

Objectives: The aim is to understand the mechanisms underlying the large variation in the clinical presentations and progression between Parkinson's disease (PD) patients.

Background: The generation of deeply phenotyped patient cohorts offers an enormous potential to identify disease subtypes but are currently limited by the cohort size and the heterogeneity of the clinical assessments collected across different cohorts. Identifying the universal axes of clinal severity and progression is key to accelerating our understanding of how disease manifests and progresses.

Involvement of people affected by Parkinson's: These universal axes would accelerate our understanding of how PD manifests and progresses through which patients may be appropriately compared appropriately stratified, and personalised therapeutic strategies and treatments can be developed and targeted.

Methods: We developed a Bayesian multiple phenotype mixed model incorporating the genetic relationships between individuals which is able to reduce a wide-array of different clinical measurements into a smaller number of continuous underlying factors named phenotypic axis.

Results: We identify three principal axes of PD patient phenotypic variation which are reproducibly found across three independent, deeply and diversely phenotyped cohorts. Together they explain over 75% of the observed clinical variation and remain robustly captured with a fraction of the clinically-recorded features. The most influential axis was associated with the genetic risk of Alzheimer's disease (AD) and involves genetic pathways associated with neuroinflammation.

Conclusions: Our results suggest PD patients with a high genetic risk for AD are more likely to develop a more aggressive form of PD including, dementia.

Poster 61 - A cellular model for sporadic Parkinson’s disease

Sebastian Schmidt, Dr. Daniela M. Vogt Weisenhorn, Prof. Dr. Wolfgang Wurst

Institute of Developmental Genetics, Helmholtz Zentrum München, 85764 Neuherberg, Germany

Background: Parkinson`s Disease is a progressive neurodegenerative disorder caused by a combination of genetic and environmental factors. Analysis of model systems carrying Parkinson`s Disease associated mutations have been harnessed to unravel the mechanisms contributing to disease etiology e.g. mitochondrial impairment. However, the etiology of sporadic Parkinson`s disease remains largely elusive.

Methods: To address impaired molecular mechanisms, we used induced pluripotent stem cells (iPSCs) derived from 7 sporadic Parkinson`s Disease and 5 control patients, which were cultivated in vitro for ~70 passages. Both low and high passage iPSCs were differentiated to neuronal precursor cells and further to dopaminergic neurons and screened for metabolic alterations.

Results: With similar mitochondrial mass and complex abundance, exclusively high passage neural cells derived from sporadic Parkinson`s Disease patients exhibited a reduced basal and maximal mitochondrial respiration as well as a clear complex I deficiency comparable to postmortem brain tissue. Furthermore, integrated analysis of transcriptome and metabolome data identified the citrate cycle as being impaired. The misexpression of involved genes hints towards a reduced citrate cycle flux and lower levels of citrate cycle metabolites. This may cause a substrate availability problem for the electron transport chain and explain the reduced mitochondrial respiration seen in sporadic Parkinson`s Disease.

Conclusions: Thus, long term in vitro cultivation affects specifically the mitochondria of high passage neural cells derived from sporadic Parkinson`s Disease patients. These show a deficit in the citrate cycle highly likely leading to a substrate availability deficit in their electron transport chain.

Poster 62 - The role of pathogenic GBA1 mutations in the relationship between GBA1 and alpha-synuclein and the influence on Parkinson's disease.

Laura Smith, Matthew Gegg, David Chau, Anthony Schapira

University College London, London, United Kingdom

Background: Mutations in the GBA1 gene are numerically the largest risk factor for Parkinson's disease. The GBA1 gene encodes for lysosomal hydrolase protein, GCase. Loss of GCase activity impairs lysosomal function. Some GBA1 mutations are misfolded and retained in the ER. Very little is known about the E326K mutation, despite it being one of the most common GBA1 mutations.

The key hallmark of Parkinson's is aggregation of alpha-synuclein within Lewy bodies and neurites. Alpha-synuclein is turned over by the lysosomal pathway. The aim of the study is to understand how GBA1 mutations increase the risk for Parkinson's, through influencing the relationship between GCase and alpha-synuclein.

Methods: The common GBA1 mutations E326K, L444P and N370S were investigated in homozygous form in fibroblasts. Mutant GBA1 was over-expressed in SH-SY5Y neuronal cells.

Involvement of people affected by Parkinson's: The fibroblast cells used were derived from patients with Parkinson's.

Results: Our data suggest that mutations in the GBA1 gene act through both loss-of-function and gain-of-function pathways. Unlike both L444P and N370S, the E326K mutation does not cause a significant reduction in GBA1 protein and activity levels. Furthermore, E326K mutations do not exhibit increased ER stress, unlike L444P. All mutant cell lines have increased insoluble alpha-synuclein levels, indicating the presence of aggregated alpha-synuclein, which may underlie the predisposition to PD.

Conclusions: The E326K mutation does not act the same as the other common activity mutations, L444P and N370S. However, in all these mutations alterations in alpha-synuclein metabolism are still evident.

Poster 63 - Activity of the SERCA calcium pump is reduced in Drosophila and human cell models of Parkinson's based on DJ-1 deficiency

Miss Cristina Solana-Manrique, Mr. Francisco José Sanz, Mrs. Verónica Muñoz-Soriano, Mrs. Nuria Paricio

Genetics and ERI BIOTECMED, University of Valencia, Valencia, Spain

Objective: Validation of SERCA as a promising target for future therapeutic avenues for Parkinson's.

Background: DJ-1, a causative gene for familial Parkinson's plays different activities, standing out its role against oxidative stress (OS). A Drosophila model of Parkinson's that harbors a mutation in the DJ-1β gene shows high levels of OS markers like protein carbonylation, which alters protein function. We performed a redox proteomic assay in DJ-1β mutant flies to identify potential biomarkers and processes underlying Parkinson's pathogenesis. Among the proteins identified, we found SERCA, which plays an important role in Ca^{2+} homeostasis. Several studies have supported the involvement of Ca^{2+} dyshomeostasis in Parkinson's. Thus, we decided to study the relation between SERCA activity and Parkinson's physiopathology.

Methods: We determined SERCA activity in the Drosophila and a human cell Parkinson's model, based in DJ-1-deficiency. SERCA function was also measured in both models after treatment with a specific SERCA activator, CDN1163.

Involvement of people affected by Parkinson's: None.

Results: Results show a high decrease in SERCA activity in both fly and human cell Parkinson's models. Consistently, CDN1163 was able to restore locomotor ability and increased viability in the Drosophila and human cell Parkinson's model, respectively, by increasing SERCA activity.

Conclusions: Reduced SERCA activity in both familial Parkinson's models suggests it may play a role in Parkinson's physiopathology and constitute a potential target for the disease. Furthermore, we demonstrate that CDN1163 could be a potential therapeutic compound to treat Parkinson's.

Poster 64 - Finding new drug targets for Parkinson's disease using genetics – Mendelian randomization of the druggable genome

Catherine Storm, Demis Kia, Mona Almramhi, Nicholas Wood

UCL, London, United Kingdom

Objectives: Identify new drug targets with genetic support for Parkinson's by applying Mendelian randomization (MR) to the druggable genome.

Background: The hunt for drug targets for Parkinson's is greatly limited by inefficiencies in the drug development industry. Drugs with genetic evidence may be more likely to succeed in clinical trials, and MR is a promising method to obtain such data.

Methods: Genes that encode drug targets are called "druggable genes", and we used genetic variants associated with expression of druggable genes to mimic exposure to medications. We used MR to predict whether increased expression of over 3000 druggable genes affects Parkinson's risk in two large cohorts, age at onset and several progression markers.

Involvement of people affected by Parkinson's: We recognise novel therapies as priorities for people affected by Parkinson's, and we focus on new ways to use data from ongoing large-scale genetic studies to aid drug development for Parkinson's.

Results: We propose 23 potential drug-targeting mechanisms for Parkinson's. Three are targeted by already-licensed drugs and may indicate repurposing opportunities. Our data suggest three currently-licensed medications that may increase Parkinson's risk or worsen progression. There is little overlap between MR-supported drug targets to prevent Parkinson's and reduce progression, suggesting that underlying mechanisms driving risk and progression may differ.

Conclusions: In this MR study, we provide compelling genetic evidence for 23 potential drug targeting mechanisms for Parkinson's, with the hope that this will help prioritise drug development efforts for Parkinson's.

Poster 65 - Predicting the efficacy of exenatide in Parkinson's disease using genetics – a Mendelian randomization study

Catherine Storm, Demis Kia, Nicholas Wood

UCL, London, United Kingdom

Objectives: Predict the efficacy of exenatide in Parkinson's and explore its mechanism using genetic data and Mendelian randomization (MR)

Background: Exenatide is a glucagon-like peptide 1 receptor (GLP1R) agonist used in type 2 diabetes mellitus, which showed promising results for Parkinson's in a phase II clinical trial. MR is a genetic technique that can predict the causal effect of an exposure (e.g. a drug) on an outcome (e.g. Parkinson's risk) (2).

Methods: We used genetic variants associated with expression of GLP1R to mimic exenatide, as well as 18 genes acting downstream of GLP1R or through alternative pathways. Using MR, we studies the effect of these on type 2 diabetes risk, Parkinson's risk and Parkinson's progression using several markers.

Involvement of people affected by Parkinson's: We recognise novel therapies as priorities for people affected by Parkinson's, and we focus on new approaches using data from ongoing large-scale genetic studies to aid drug development for Parkinson's.

Results: Raised GLP1R expression was associated with type 2 diabetes risk at nominal significance, but not Parkinson's risk or progression. Raised DPP4 expression was significantly associated with Parkinson's risk. DPP4 breaks down human GLP-1, and DPP4-inhibitors are used to treat type 2 diabetes mellitus. Toll-like receptor 4 expression was nominally significant for Parkinson's risk and age at onset.

Conclusion: The results of this MR study suggest that GLP-1 mimetics like exenatide may be effective in Parkinson's, but through a mechanism that is independent of GLP1R.

Poster 66 - To investigate the hypothesis that raising proprioceptive awareness through specific movement-based exercise can support effective postural alignment for expiration during seated Parkinson's community choral sessions.

Ms Elizabeth Drwal

University of Wales, Carmarthen, United Kingdom

Objectives: To develop a movement protocol that improves the clients' awareness of their seated alignment in a creative and socially inclusive way.

Background: Clinical research supports the positive effects of exercise on neuroplasticity in Parkinson's (Petzinger, 2013). Kinaesthetic remapping of posture and alignment through exercise impacts on expiration and ultimately resonance. Singing and movement have positive effects on mental wellbeing.

Method: A systematic literature review collected data from neurological, cognitive, and motor learning research focusing on the impact of Parkinson's on proprioception. Qualitative data was collated through a reflective journal, informal and semi-structured interviews. Audio-visual recordings analysed changes in participants' vocal quality and posture. A collaboration between the researcher and physiotherapist insured the integrity of the exercise programme.

Involvement of people affected by Parkinson's: Twenty-two early-stage Parkinson's volunteers took part in 12 singing for wellbeing classes. Their carers became an informal control group of similar-aged healthy adults. A creative movement protocol, incorporating key muscle groups, was choreographed, tested, and modified to accommodate the participants' needs.

Results: Participants demonstrated improved awareness and clarity of proprioceptive purpose. They reported feeling confident to sing longer phrases and felt vocal loudness improved. Social inclusion and personal identity became a strong motivation to attend sessions.

Conclusions: The programme's cross-disciplinary, social, and cultural setting motivated participants to practise exercises that support proprioceptive awareness. There are psychological, neural, and biomechanical benefits in attending therapeutically based wellbeing programmes for people with Parkinson's that can generate a cost-effective approach to preventive healthcare practice.

Poster 67 - Genome-wide association studies of progression in Parkinson's disease

Miss Manuela Tan[1], Dr Michael Lawton[2], Dr Donald Grosset[3], Dr Maryam Shoai[1], Professor Huw Morris[1]

[1]University College London, London, United Kingdom. [2]University of Bristol, Bristol, United Kingdom. [3]Queen Elizabeth University Hospital, Glasgow, United Kingdom

Objectives: To identify genetic variants associated with progression in Parkinson's.

Background: Case-control genome-wide association studies (GWASs) have identified variants associated with Parkinson's risk. However, in order to understand the biology of progression, it is necessary to also study phenotypes within patients. Progression in Parkinson's can be assessed in many different ways, therefore combining clinical scales may improve the accuracy of measuring underlying progression, as shown in Huntington's disease.

Involvement of people affected by Parkinson's: People with Parkinson's were involved in developing this project as a grant application.

Methods: We analysed three longitudinal, prospective cohorts: Tracking Parkinson's, Oxford Discovery, and the Parkinson's Progression Markers Initiative. We included clinical data for 3,364 participants with 12,144 observations and mean follow-up 4.2 years. We combined multiple assessments using principal components analysis to create scores for composite, motor, and cognitive progression. These were analysed in GWASs. We also performed a targeted analysis of the 90 Parkinson's risk loci from the latest case-control meta-analysis.

Results: There was minimal overlap between variants associated with Parkinson's risk and progression. The APOE e4 tagging variant, rs429358, was associated with the rate of composite progression and cognitive progression. There were no variants that were associated with the rate of motor progression, however we have reported nominally significant loci which need to be replicated in independent studies.

Conclusions: This new method in Parkinson's improves measurement of symptom progression. We provide strong evidence that APOE e4 drives progressive cognitive impairment in Parkinson's.

Poster 68 - Multi-omic network analysis provides insight into exclusive and shared molecular signatures of neurodegenerative disorders

James Tomkins[1], Nikoleta Vavouraki[1], Patrick Lewis[2], Claudia Manzoni[3]

[1]School of Pharmacy, University of Reading, Reading, United Kingdom. [2]Royal Veterinary College, London, United Kingdom. [3]UCL School of Pharmacy, University College London, London, United Kingdom

During the past two decades significant investments in human disease genetics has resulted in a wealth of genetic data relating to neurodegenerative disorders. However, utilising these data for improving our understanding of disease pathogenesis, biomarker discovery and therapeutic development remains to be fully harnessed. This study incorporates multiple omic data types to model the genetic and molecular landscapes of Parkinson's, Alzheimer's disease (AD), frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). This in silico approach is based around disease-specific protein interaction networks, which are analysed in the context of network topology, functional association and potential drug modulation, providing insights into commonality and exclusivity among these four disorders at a molecular level.

From protein interaction network mapping, numerous candidate proteins which are common to multiple disease networks were identified, providing leads for future investigation into common proteins and pathways involved in neurodegeneration. Functional profiling led to the discovery of differentially important biological processes in Parkinson's, AD, FTD and ALS pathogenesis, with particularly intriguing results centred on the immune response. Results were used to support prioritisation of candidate genes at GWAS loci suggesting, in particular for Parkinson's, a strong functional overlap between Mendelian and sporadic forms of disease. Such findings are guiding the direction of this study whereby current efforts are focussing on the nomination of disease biomarkers and the interrogation of drug repositories to identify potential therapeutic modulators of pathways impacted in these disease states.

Poster 69 - Exploring how people with Parkinson's watch dance with and without facial expressions

Ms Moudhi Al Twaijri, Dr Judith Bek, Dr Ellen Poliakoff, Dr Karen Lander

University of Manchester, Manchester, United Kingdom

Objective: To investigate where people with Parkinson's look while watching dance.

Background: Dance is increasingly used to promote physical activity and well-being in people with Parkinson's. Dance training and watching could help to improve physical movement and social interaction in people with Parkinson's. However, little is known about how dance is perceived by people with Parkinson's, particularly where people with Parkinson's look while watching dance, and how this is influenced by the dancer's facial expressions.

Methods: Eye movements were recorded while participants (13 with mild-to-moderate Parkinson's and 9 healthy controls) watched 16 dance clips, half with corresponding facial expressions, half without. After each clip, participants answered questions about their response, including their enjoyment, relaxation, energy, excitement and embodiment of the dance.

Involvement of people affected by Parkinson's: As participants.

Results: Both people with Parkinson's and controls looked more at the face and less at the body/torso during expressive dance compared to non-expressive dance. However, people with Parkinson's reported significantly less enjoyment compared to controls in both dance conditions. There was also a non-significant trend for lower ratings of excitement, relaxation and embodiment than controls.

Conclusion: This is preliminary evidence that people with Parkinson's are drawn to facial expressions similarly to controls. However, people with Parkinson's may have reduced enjoyment of watching dance. The findings suggest that observation of dance in Parkinson's should be explored further and could be used as an adjunct to physical dance training.

Poster 70 - Generation of highly enriched hiPSC-derived midbrain dopaminergic neurons to model Parkinson's disease in vitro

Mr Gurvir Virdi, Professor Sonia Gandhi, Professor Rickie Patani

UCL Institute of Neurology, London, United Kingdom

Objective: Develop a protocol to produce hiPSC-derived midbrain dopaminergic neurons which is rapid, efficient, cost effective, and generates highly enriched cultures.

Background: The development of human induced pluripotent stem cells (hiPSC) has greatly aided our ability to model neurodegenerative diseases. To date, there have been many protocols to differentiate hiPSCs to midbrain dopaminergic (mDA) neurons, of which a few are well established in the field. However, these protocols are often variable in their efficiency of enrichment and rely on the use of expensive growth factors to produce mDA neurons.

Methods: We developed a protocol to differentiate hiPSCs into enriched populations of mDA neurons using only small molecules in a timely fashion, to pattern hiPSCs to mDA neurons. We investigated the cellular pathology using single-cell imaging.

Involvement of people affected by Parkinson's: We used hiPSCs derived from patients with SNCA mutations which cause early onset autosomal dominant Parkinson's. By modelling the disease, we identified cellular pathological processes, which can be used to test disease modifying therapeutics.

Results: Our method generates >80% mDA neurons, that express the typical mDA neuronal markers, and display functional and electrophysiological neuronal properties. SNCA lines differentiated to produce functional mDA neurons. These neurons exhibited typical hallmarks associated with synucleinopathy including: aggregate formation, oxidative stress as well as mitochondrial dysfunction and impaired lysosomal dynamics.

Conclusions: We show that our novel protocol produces enriched mDA neurons, which can be used to successfully model Parkinson's, providing the potential to further elucidate molecular mechanisms contributing to disease development.

Poster 71 - A cellular atlas of human Substantia nigra enables the prediction of cell type-specific gene expression changes associated with Parkinson's disease risk

Dr Viola Volpato

UKDRI Cardiff, Cardiff, United Kingdom

Objective: We aim to prioritise Parkinson's disease (PD) genetic risk variants that likely alter the expression of target genes and pathways by disrupting cell-type specific regulatory elements. For this, we make use of single cell human substantia nigra (SN) maps to derive "in-silico" cell type expression quantitative trait loci (eQTLs).

Background: Genome-wide association studies have identified thousands of variants associated with PD, but their biological interpretation often remains unclear. Significant enrichment of disease-associated variants in regulatory regions suggests that many SNP-trait associations could act through gene expression regulation. While large-scale eQTL efforts on bulk human tissues, such as GTEx, exist, we lack similar resources at single cell level that can more precisely define the cellular contexts in which disease risk might affect gene expression.

Methods: We obtain robust cell type-specific gene expression signatures from a meta-analysis of single cell human SN datasets. We use these signatures to deconvolute 114 GTEx bulk RNAseq samples of human SN that we correlate with corresponding genotypes to obtain cell type eQTLs. We then apply eMAGMA to identify genes underlying PD genetic associations based on eQTL information.

Results: We prioritise a large number of PD-associated genes at cell type level that converge in pathways known to be involved in the disease. More importantly, we show that prioritisation through gene regulation highlights different cell type specificity of PD risk-associated genes than gene expression-based approaches.

Conclusions: Context specific analysis of PD risk regulatory variants helps to better understand the molecular and cellular mechanisms of the disease.

Poster 72 - Bilateral Subthalamic Nucleus Theta-Frequency Stimulation Improves Episodic Category Fluency in Patients with Parkinson's Disease: A Double-Blinded Randomized Crossover Trial

Mr Marcus Williams[1], Dr Jordan Lam[2], Dr Melanie Cohn[3], Dr Andrew Petkus[2], Dr Darrin J Lee[2]

[1]King's College London, London, United Kingdom. [2]Keck School of Medicine of USC, Los Angeles, USA. [3]University of Toronto, Toronto, Canada

Objectives: To evaluate the on/off effects of gamma and theta-frequency bilateral STN stimulation on cognitive function in Parkinson's disease.

Background: There is a paucity of research on the effects of frequency in deep brain stimulation (DBS) for Parkinson's disease. Recent evidence suggests a role of subthalamic nucleus (STN) theta frequency oscillations in cognition and suggests stimulation in this range could improve cognition in Parkinson's disease.

Methods: Twelve patients with bilateral STN DBS for Parkinson's disease underwent a double-blinded, randomized cognitive battery during stimulation at gamma (130-135Hz), theta (10hz) and off (0Hz). Verbal fluency, colour-word interference and random number generation were evaluated and compared between frequencies.

Involvement of people affected by Parkinson's: Participants were patients with Parkinson's disease that had previously underwent bilateral STN DBS.

Results: Episodic category fluency verbal fluency differed significantly between stimulation frequencies ($p=0.04$). Post-hoc testing revealed improved performance during 10Hz versus 130Hz stimulation ($p=0.02$) and a trend towards worse performance during 130Hz stimulation versus off stimulation ($p=0.09$). There were no significant differences between stimulation frequencies in phonetic or semantic verbal fluency, colour-word interference or random number generation ($p>0.05$).

Conclusions: We show improved episodic category verbal fluency during theta versus gamma-frequency stimulation, substantiating a role of STN theta oscillations in cognition. Further work is needed to explore if the concurrent use of theta and gamma-frequency stimulation can improve both motor and cognitive outcomes.

Poster 73 - Investigating the effects of staying at home during the COVID-19 pandemic on impulse control behaviours in people with Parkinson's

Elizabeth Yule, Jade Pickering, Dr Jennifer McBride, Dr Ellen Poliakoff

University of Manchester, Manchester, United Kingdom

Objective: We aimed to investigate the effects of the COVID-19 UK lockdown on impulse control behaviours (ICBs) in people with Parkinson's (PwP) and healthy control participants.

Background: Over a 5-year cumulative period, approximately 46% of PwP experience various forms of ICBs (e.g. gambling, over-shopping) and such behaviours have been associated with factors such as anxiety and trait impulsivity. Given that the UK lockdown has led to large changes in people's behaviour, we investigated how this affected ICBs in PwP and whether any changes were associated with changes in anxiety and other measured factors.

Methods: 132 PwP and 51 control participants living in the UK, completed an online survey including measures of ICBs, before COVID-19 and during lockdown, as well as anxiety, impulsivity, apathy, and social impact.

Involvement of people affected by Parkinson's: This study was informed by previous Patient and Public Involvement with Parkinson's and ICBs.

Results: 198 PwP and 60 controls completed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) in the survey. Scores on the QUIP changed significantly during the UK lockdown; 30.8% of PwP showed an increase in ICBs, whereas 12.1% showed a decrease. Further analysis to explore these changes is ongoing.

Conclusions: The findings show that PwP reported an overall increase in ICBs during lockdown. Further quantitative and qualitative analysis will examine the factors that may contribute to these changes. This will lead to a greater understanding of the factors that may underlie ICBs in PwP.

Poster 74 - Investigating the impact of COVID19 on social interactions and technology use in people with Parkinson's

Mr. Heng Zhang, Dr. Ellen Poliakoff, Prof. Bijan Parsia, Prof. Simon Harper

The University of Manchester, Manchester, United Kingdom

Objective: To investigate the smartphone usage and social behaviour of people with Parkinson's and the impact of COVID19.

Background: Parkinson's can lead to social withdrawal but little is known about how this changes with progression of the condition. Smartphones are now widely used and the hub of communications. Our initial aim was to explore the social withdrawal of people with Parkinson's unobtrusively using smartphone data. However, under social distancing because of COVID19, it provides an opportunity to observe how the pandemic impacts people with Parkinson's socially.

Methods: A specially designed application was installed on six smartphones of people with mild to moderate Parkinson's (age 63 -75, 2 females). It records all smartphone usage including calls, messages, application usage, etc. And smartphone sensors including Bluetooth, Wi-Fi, locations, microphones are utilized to infer social activities. An online questionnaire was used to measure the social impact and changes in technology use in the wider Parkinson's community (N =221).

Involvement of people affected by Parkinson's: As participants in the studies.

Results: Smartphone participants show decreased overall social interactions and spent almost all their time at home. Preliminary analysis shows 70.59% survey participants agreed that their social life had been affected and 55.66% use the phone more often. But only 29.86% reported that they feel more lonely and isolated.

Conclusions: COVID19 has had an inevitable impact on the social lives of Parkinson's patients. However, at least in this group able to engage with an online survey, technologies have brought them opportunities to maintain social connections.