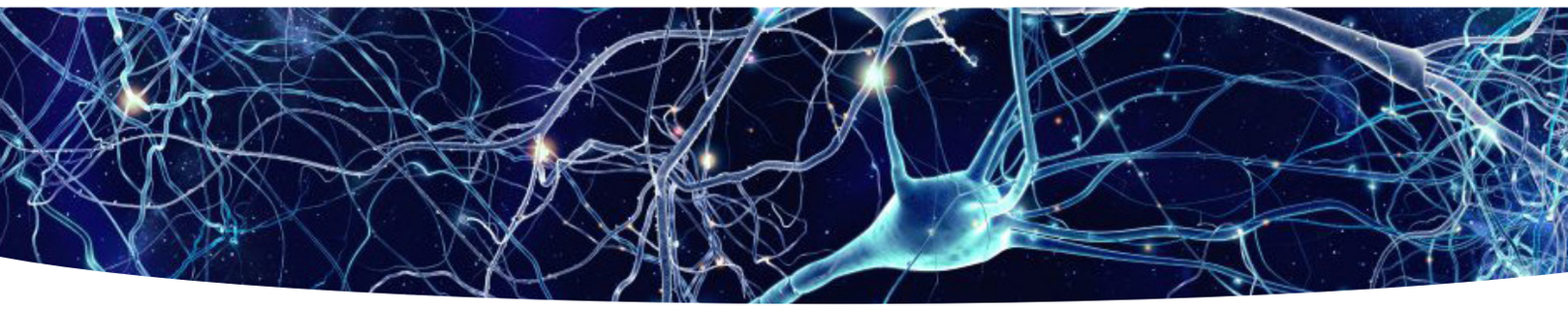
PD-MitoQUANT

Newsletter – August 2021



Learning more about the role of mitochondrial dysfunction in Parkinson's to help develop better therapies

New, more effective treatments are urgently needed for the more than one million people living with Parkinson's in Europe today. PD-MitoQUANT (www.pdmitoquant.eu) is an Innovative Medicines Initiative (IMI) project investigating the role of mitochondrial malfunction in Parkinson's. Academic experts, Small/Medium Enterprises (SMEs), pharmaceutical companies from the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the patient advocacy organisation, Parkinson's UK have assembled in this project to: (i) improve our understanding of mitochondrial dysfunction in Parkinson's, (ii) validate molecular drivers and mechanisms, (iii) develop improved models for study, and (iv) discover novel therapeutic targets for future therapies.

Message from Coordinator Prof Jochen Prehn

Coordinator, Prof. Jochen Prehn

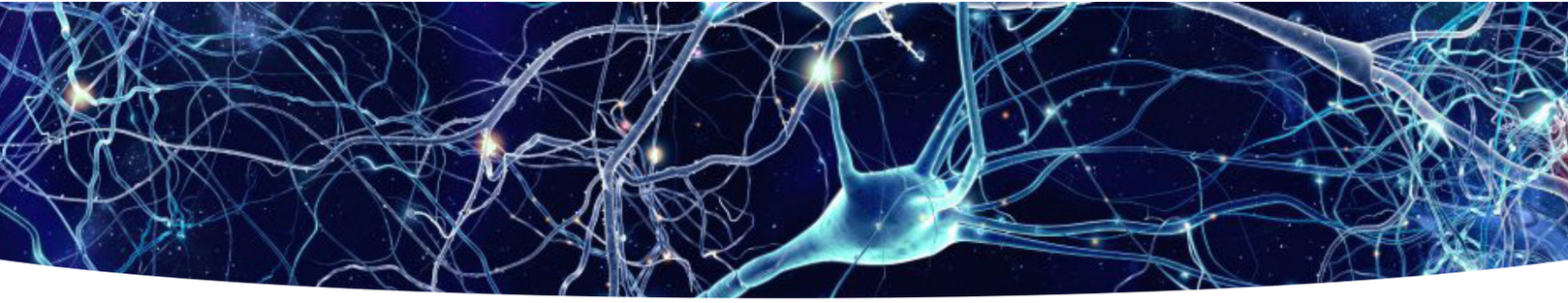
"We're well into year 3 of PD-MitoQUANT and the models, protocols and assays developed by the consortium have been used to generate an impressive collection of datasets from both cultured cells and pre-clinical models.

Work continues in studies exploring if a novel form of α-synuclein (αSyn) affects the production and use of energy in mitochondria (RCSI, UCL), and whether αSyn alters protein import into mitochondria or the degradation of damaged mitochondria (ICM, RUMC). Data has also been generated on the effect of αSyn on signal transmission between neurons (Teva), and proteins present in mitochondria (CNRS, RCSI). The effects of αSyn on different brain regions and on markers related to disease progression have also been measured at longer time points in vivo (ICM, DZNE, Lundbeck).

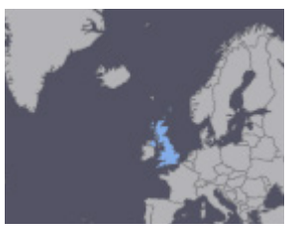
Using the data generated so far, bioinformatics and network analyses are on-going to identify potential targets and signatures (RCSI, GENEXPLAIN, UCB). We have started planning validation studies for the targets and signatures in 3D 'Organ-on-a-Chip' models (Mimetas), directly reprogrammed neurons (CNR), in vivo models (DZNE, ICM) and patient samples (PUK, UCB)."

Keep an eye on our Publications page for all our latest papers!

You can also meet some of our early- and mid-stage researchers in our Researchers profiles.



Partner Spotlight - University College London



University College London (UCL, https://www.ucl.ac.uk/) is ranked 10th in the 2021 QS World University Rankings. The Institute of Neurology is a top ranked neuroscience institution and is one of the most highly ranked clinical neuroscience institution in the UK. The institute's mission is to translate neuroscience discovery research into treatments for patients with neurological diseases.

Within PD-MitoQUANT, UCL will:

- quantitatively investigate mitochondrial bioenergetics, and
- investigate mitochondrial dynamics, including fusion/fission.

Prof. Abramov

Prof. Andrey Abramov, UCL Institute of Neurology, has an international reputation in cell physiology and pathophysiology. He has contributed significantly to the role of mitochondria, bioenergetics, oxidative stress and protein misfolding in Parkinson's and other diseases.

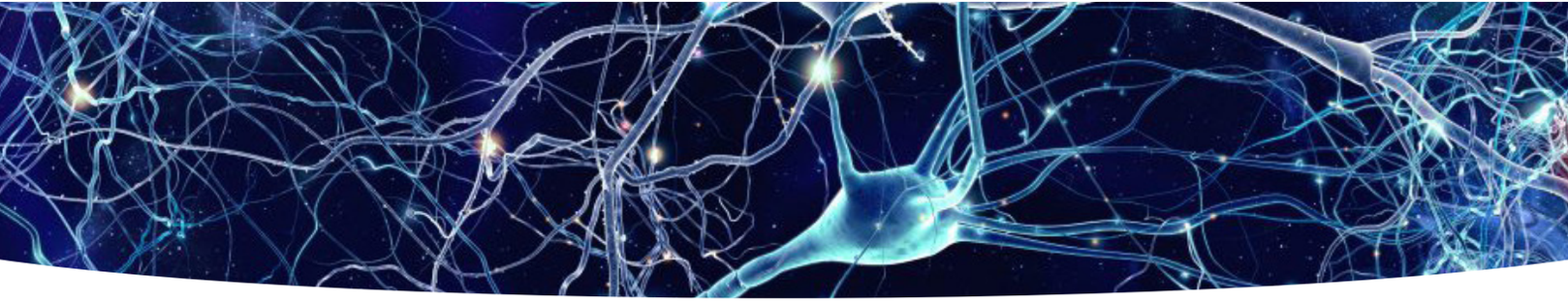
What do you find most interesting about mitochondria?

Although mitochondria are the 'powerhouse' of the cell, they do more than produce ATP. They possess complex functionality that includes a number of interdependent processes and loss of function, which can lead to cell death. So, it is not surprising that mitochondrial 'dysfunction' has been implicated in a variety of diseases. The number of mitochondria varies between different cells and tissue types, but neurons are particularly dependent on mitochondrial function. The brain represents only ~2% of the total body weight, yet accounts for more than 20% of the total consumption of oxygen. Furthermore, long-lived neurons, where mitochondria must be maintained for an entire lifetime, have very high energy requirements. Neuronal mitochondria, through their trafficking, ATP production and calcium buffering functions, play a crucial role in the function of synaptic vesicle pools and neurotransmission. Thus, neurons are vulnerable to mitochondrial dysfunction. However, it is still not clear if there is any specific mitochondrial function/dysfunction which leads to neurodegeneration in Parkinson's. The research of this consortium is focused on this important scientific question.

Recent Dissemination Highlights

Conferences have gone virtual and so have our researchers!

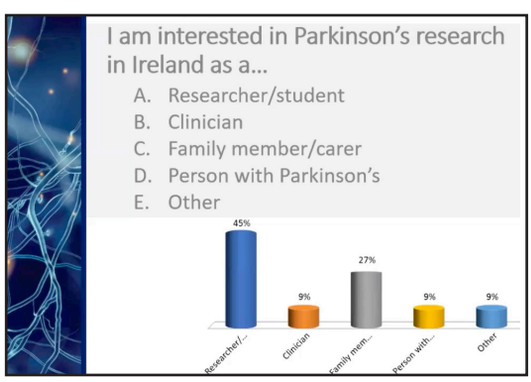
- Dr. Patrick Michel (ICM) shared his results with colleagues at the ICM PI Progress Report session in March 2021, speaking about "In vitro modeling of αSyn aggregation in dopamine neurons with fibril seeds."
- Dr. Daniele Bano (DZNE) spoke about "Respiratory supercomplexes and single-cell assessment of mitochondrial bioenergetics" at the Spring Symposium of The Netherlands Society for Biochemistry and Molecular Biology organised by RUMC's Dr. Werner Koopman and Dr. Merel Adjobo-Hermans.



Parkinson's Research in Ireland Event Series

The RCSI University of Medicine and Health Sciences (www.rcsi.com) hosted two public virtual lecture series on Parkinson's Research in Ireland in November 2020 and April 2021. The series covered research from the PD-MitoQUANT project, as well as a range of clinical, applied and basic research from academic and industrial organisations. Parkinson's advocates also presented their perspectives and hopes for research leading to better treatments, and ultimately a cure.

- Gary Boyle, Parkinson's Association in Ireland,
- Prof. Jochen Prehn, RCSI University of Medicine and Health Sciences,
- Dr. Eilis Dowd National University of Ireland in Galway,
- Caitriona McLoughlin, Dublin Neurological Institute, Mater Misericordiae University Hospital
- Prof. Suzanne Timmons, University College Cork,
- Dr. Jeremy Skillington, Inflazome,
- Richelle Flanagan, PD Avengers, World Parkinson's Congress 2022 Ambassador and Parkinson's Assocation Ireland Member,
- Prof. Madeleine Lowery, University College Dublin,
- Prof. Maeve Caldwell, Trinity College Dublin,
- Andrew Phelan and Cecelia Reyes, Beats Medical.



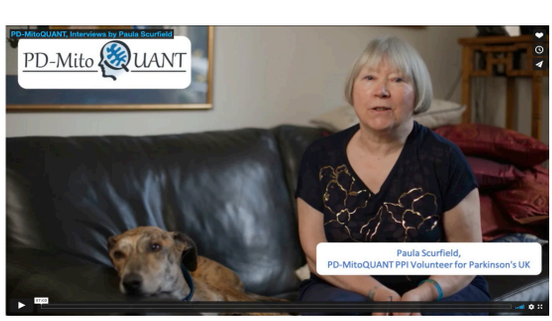
Attendees came from equally broad backgrounds, leading to lively and engaging Question & Answer sessions!

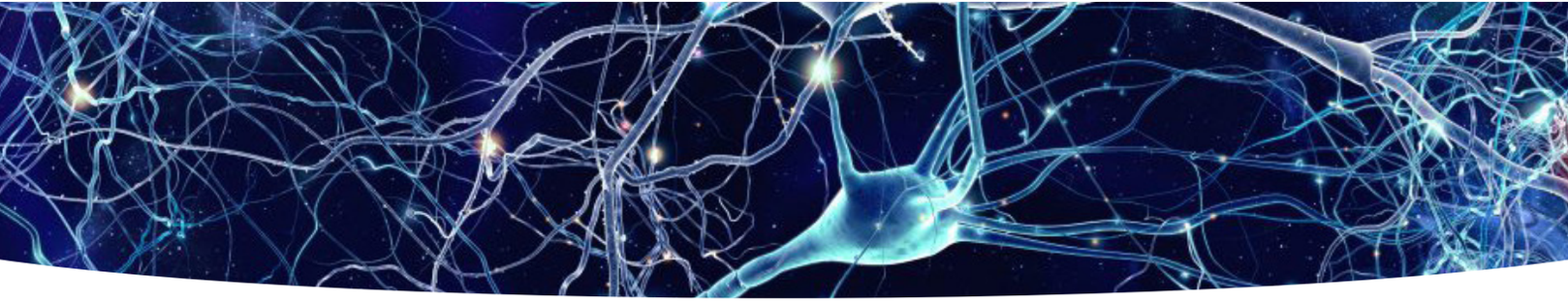
Videos of the event are available on the project website: https://www.pdmitoquant.eu/media/

World Parkinson's Day Video

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

For World Parkinson's Day on 11th April 2021, we released a video from one of PD-MitoQUANT's Public-Patient Involvement (PPI) volunteers, Paula Scurfield (https://vimeo.com/534329659). Paula interviewed Dr. Werner Koopman from the Radboud University Medical Center and Dr. Alexander Kel from GeneXplain GmbH at a project meeting in 2019. In her video, she shares her perspective on the project and its importance for people with Parkinson's. Parkinson's UK have developed tools for PPI involvement in lab-based research projects like ours (https://bit.ly/2R20quj).





Partner Spotlight - Centre National de la Recherche

The Centre National de la Recherche (CNRS, http://www.cnrs.fr/) is a large multidisciplinary research institution. Internationally recognised for the excellence of its scientific research, the CNRS is a reference in the world of research and development, as well as for the general public. The Life Sciences Institute of the CNRS is composed of over 300 research units.

Within PD-MitoQUANT, CNRS:

- has generated robustly characterised human and mice αSyn strains for *in vitro* and *in vivo* assays across the partner laboratories, and
- will identify the fibrillar αSyn mitochondrial protein interactome by a proteomic approach.

Dr. Melki

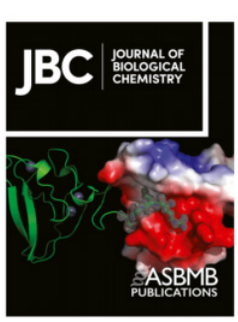
Dr. Ronald Melki is a first class Director of Research at CNRS, who has been active in the prion field since 1999. He demonstrated that fibrillar huntingtin and αSyn assemblies propagate from cell to cell in a prion like manner, as well as established a structure-function relationship for distinct synucleinopathies.

What is the most interesting thing about αSyn?

αSyn was discovered nearly 30 years ago and found in Lewy bodies a year later. We still do not know what is the exact function of this abundant protein. Usually, a protein has a given form or shape. αSyn is remarkably flexible. It adopts millions of forms. Among the many shapes, some stack to form deleterious aggregates that look like noodles in the electron microscope. My team established that different stacks cause different synucleinopathies. We also showed that the stacks found in the brain of a patient suffering from Parkinson's are different from those found in the brain of a patient suffering from other synucleinopathies.

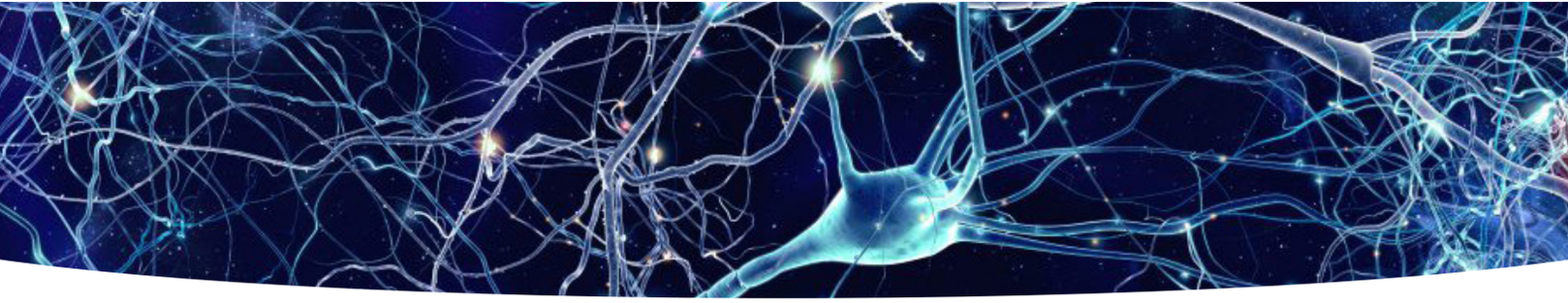
After documenting the damages caused by αSyn stacks at the neuronal membrane, we aim to identify and understand, with our partners within PD-MitoQUANT, what defects those stacks cause to mitochondria.

Latest Project Publication



In April 2021, CNRS published 'The differential solvent exposure of N-terminal residues provides 'fingerprints' of alpha-synuclein fibrillar polymorphs' in the Journal of Biological Chemistry (https://doi.org/10.1016/j.jbc.2021.100737). In this paper, polypeptides exposed on the surface of distinct αSyn fibrillar polymorphs were found to be like fingerprints. The findings have the potential to inform the development of future diagnostic assays and therapies for diseases that involve synucleinopathies.

For a full list of project papers, visit our Publications page!



Partner Spotlight - Consiglio Nazionale delle Ricerche

At the National Research Council (CNR), (https://www.cnr.it/), the Neuroscience Institute is the largest Italian Institution for research on the nervous system and related diseases. The institute includes more than 60 different research groups located in 4 different cities, with around half located in Milano.

Consiglio Nazionale delle Ricerche

Within PD-MitoQUANT, CNR has:

- validated pluripotency in Parkinson's patient-derived human induced pluripotent stem cells (iPSCs) and isogenic controls, and
- generated induced dopaminergic neurons by direct reprogramming of aged fibroblasts and is now characterising their molecular signature.

Dr. Broccoli

Dr. Vania Broccoli has pioneered new approaches for direct neuronal reprogramming and their use for modelling and new translational approaches for Parkinson's. His group has generated a biobank of iPSCs from genetic and sporadic Parkinson's with a particular interest in studying mitochondrial dysfunctions related to this pathology. He spoke with Richard Campbell from our patient advocacy partner Parkinson's UK about CNR's work.

What is the focus of your laboratory's work?

We work to strengthen and optimise *in vitro* models of Parkinson's. The best way for us to do this was to use patient cells to generate induced pluripotent stem cells (iPSCs). We do this by reprogramming patient skin fibroblasts or blood cells to become stem cells that can then be differentiated in the lab to become neurons. So, we then have patient-derived neurons, in particular dopaminergic neurons, which are the type of neurons that die in Parkinson's. We can use these neurons to study why they are vulnerable in Parkinson's.

PD-MitoQUANT Partners

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