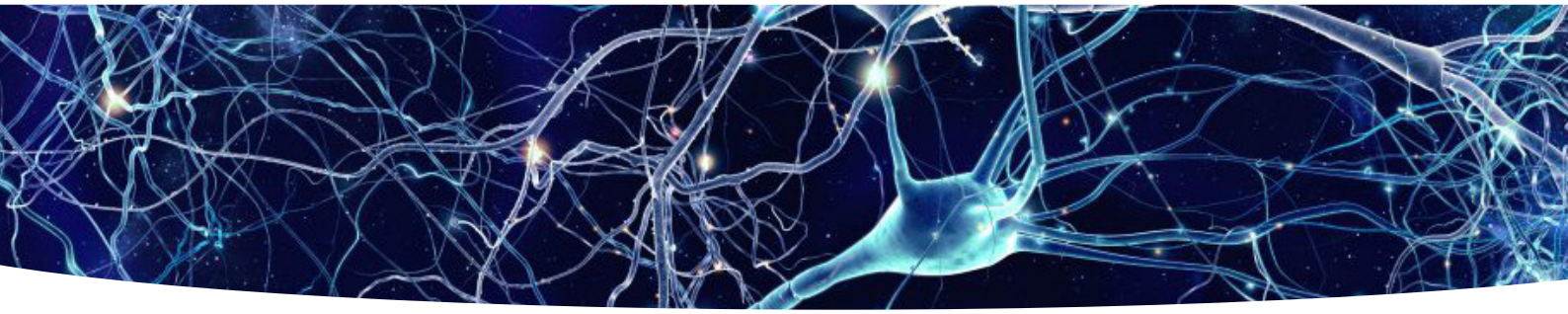
PD-MitoQUANT

Newsletter – August 2022



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. Funded by the Innovative Medicines Initiative (IMI), PD-MitoQUANT (www.pdmitoquant.eu) brought together 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. The project strived 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.

Closing Message from Coordinator Prof. Jochen Prehn

"We've now reached the end of the PD-MitoQUANT project. It's been an exciting challenge looking for new targets for Parkinson's over the last 31/2 years and seeing multiple teams with different expertise working together. We achieved very promising results, and as always, there is more to do! While the project is coming to a close, partners will continue to collaborate to gain more insight into mitochondrial dysfunction in Parkinson's using the rich datasets generated from both cultured cells and pre-clinical models. Multidisciplinary, cross-sectoral collaboration including bioinformatics and data science has been an essential element of our integrated approach and we look forward to continuing on this path in the future together."

Coordinator, Prof. Jochen Prehn

1 pathogenic αSyn

5 *in vitro* models

2 *in vivo* models

Several mitochondrial assays

2 high through-put validation platforms

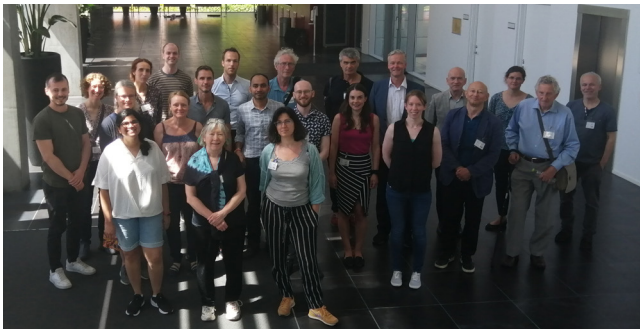
2 end point assays & signature validation platforms

16 publications, 37 conference participations, 8 public outreach events

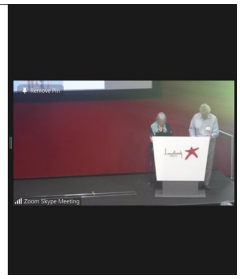
Final Project Meeting

Time has certainly flown! With the project formally ending in July 2022, project partners gathered in Copenhagen from 28 – 29 June for a final meeting, hosted by Lundbeck. Recent target validation results and future planning were the main focus of the meeting.

Young researchers also had a chance to showcase their results in a poster session, with the best poster prizes being taken home by ICM PhD students Noemi Asfogo for 'Impact of α-Synuclein fibril-dependent seeding on mitochondrial turnover' and Aurore Tourville for 'Modelling a-Synuclein aggregation and neurodegeneration with fibril seeds in primary cultures of mouse dopaminergic neurons'.



As always, lots of excellent research has been completed but there is still much more to do!



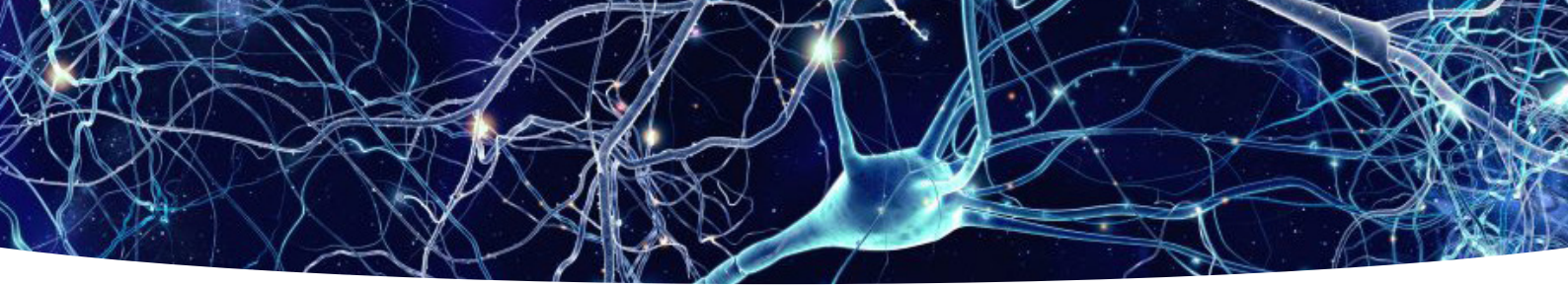
We've been privileged to have two people with Parkinson's join the consortium. At the final meeting, Richard Campbell and Paula Scurfield gave an inspirational farewell message, highlighting why continuing Parkinson's research is so important. You can see their final presentation and read more of their parting thoughts on our website (bit.ly/3yIZKNo).

Research into the basic causes of Parkinson's is needed to support future clinical advances. The science is spectacular, but it is important to keep such projects firmly fixed in reality: the aim is ultimately to benefit people with Parkinson's.

Richard Campbell

Listening to the researchers' passionate discussions is both intellectually inspiring and emotionally comforting. The past three years as a PPI volunteer for the PD-MitoQUANT study have been extremely enjoyable. We were quickly welcomed as an integral part of the team.

Paula Scurfield

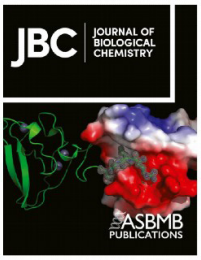


Publication Highlights

Partners have been actively publishing in scientific journals, with 15 publications so far. Our publications in 2022 to date include:

- Mechanisms and mathematical modelling of ROS production by the mitochondrial electron transport chain. S. Chenna, et al, *American Journal of Physiology-Cell Physiology* 10.1152/ajpcell.00455.2021
- Modelling α–Synuclein Aggregation and Neurodegeneration with Fibril Seeds in Primary Cultures of Mouse Dopaminergic Neurons. A. Tourville, et al., *Cells* 10.3390/cells11101640
- SGPL1 stimulates VPS39 recruitment to the mitochondria in MICU1 deficient cells. J. Jackson, et al. *Molecular Metabolism* 10.1016/j.molmet.2022.101503
- Sphingolipid changes in Parkinson L444P GBA mutation fibroblasts promote α-synuclein aggregation. C. Galvagnion, et al. *Brain* 10.1093/brain/awab371
- CEST-2.2 overexpression alters lipid metabolism and extends longevity of mitochondrial mutants. A. Piazzesi, et al. *EMBO Reports* 10.15252/embr.202152606

More publications are on the way - so keep an eye on our Publications page!



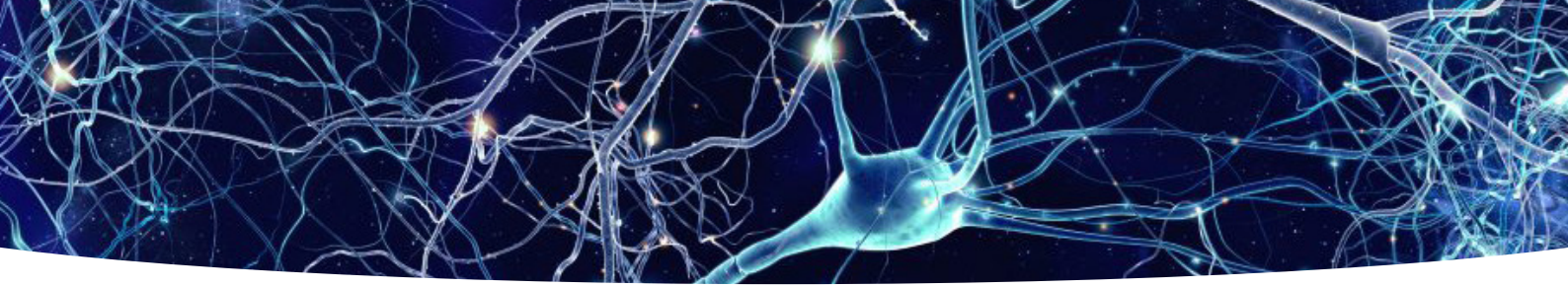
In collaboration with our Public Patient Involvement volunteer, Richard Campbell, many authors have written lay summaries to make our research accessible to the general public. For example, Prof. Ronald Melki explained results from 'The differential solvent exposure of N-terminal residues provides 'fingerprints' of α-Synuclein (αSyn) fibrillar polymorphs' (10.1016/j.jbc.2021.100737).

What did this study find?

We have demonstrated recently that different forms of αSyn aggregate into stacks that bind differentially to neurons, spread differentially in the brain of animal models and yield Parkinson's characteristic Lewy bodies or inclusions in oligodendrocytes (a type of cell that supports neurons) that are the hallmark of multiple system atrophy, another pathology associated with αSyn (synucleinopathy). In this study, we identified the surfaces of distinct αSyn stacks as they define binding to neurons and interaction with cellular proteins or organelles, in particular the mitochondria.

What is next?

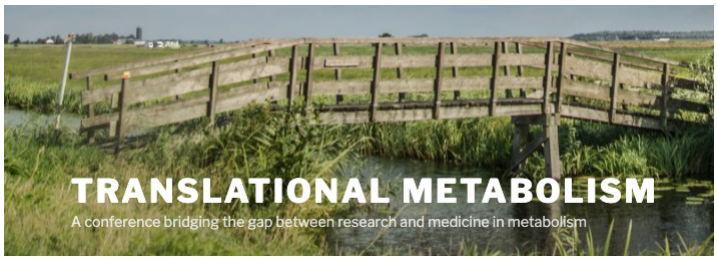
The differential recognition of different αSyn stacks has early diagnostic, as well as therapeutic, potential. We will be validating our finding in brain tissues donated by patients to brain bio-banks. We aim to develop specific binders for distinct alpha-synuclein pathogenic aggregates. In PD-MitoQUANT, we also aimed to identify the mitochondrial proteins that interact with the αSyn regions that we have identified in this paper.



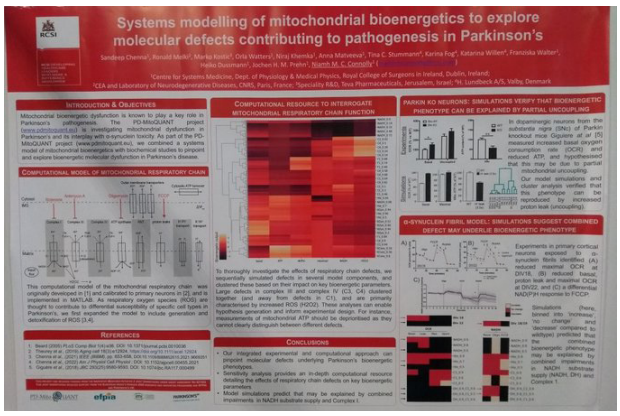
Dissemination Highlights

It's great to be back to in-person scientific meetings!

- At at the 2022 Dutch Translational Metabolism Conference, (June 2022), Dr. Shruti Desai (RUMC) presented 'PD-MitoQUANT: Quantification of Mitochondrial Morphofunction in hiPSC- derived Cortical Neurons' and Sandeep Chenna (RCSI) presented 'Systems modelling of mitochondrial bioenergetics and genome scale metabolic modelling to explore molecular defects contributing to pathogenesis in Parkinson's'.



- At the 13th FENS Forum of Neuroscience in Paris (July 2022), Dr. Patrick Michel (ICM) presented 'Cultured mouse dopaminergic neurons as a model system to study α–Synuclein aggregation and neurodegeneration in Parkinson's disease'.



Also, Dr. Niamh Connolly and Sandeep Chenna (RCSI) presented a poster on 'Systems modelling of mitochondrial bioenergetics to explore molecular defects contributing to pathogenesis in Parkinson's' and Noemi Asfogo (ICM) presented a poster on 'Studying Mitophagy in Neuronal Models of α–Synucleinopathy with the Fluorescent MitoRosella Reporter'.

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