1. PUBLISHABLE SUMMARY

Summary of the context and overall objectives of the project (For the final period, include the conclusions of the action)

More than one million people live with Parkinson's in Europe and this number is forecast to double by 2030. New, more effective treatments are urgently needed. While there are treatments which help improve some Parkinson's symptoms, they do not improve all symptoms, nor do they slow or prevent disease progression.

Research has advanced our understanding of neurodegenerative diseases (NDs) like Parkinson's, but better understanding of key disease processes and improved disease models are needed to develop better therapies. Mitochondria are the 'powerhouses' of the cell, but also contribute to cell death and neurodegeneration when they malfunction. There is considerable evidence that mitochondrial dysfunction is involved in Parkinson's, but no effective treatments have been developed based on this knowledge. Researchers and companies developing new drugs need to know more about how mitochondrial dysfunction is involved in disease progression and new disease models need to be explored for drug discovery and development.

PD-MitoQUANT was an Innovative Medicines Initiative (IMI) project that brought together academic experts, small and medium-sized enterprises (SMEs), pharmaceutical companies from the European Federation of Pharmaceutical Industries and Associations (EFPIA) and patient advocacy organisation Parkinson's UK to:
(i) deepen our understanding of mitochondrial dysfunction in Parkinson's,
(ii) identify and validate molecular drivers and mechanisms in Parkinson's, and
(iii) discover innovative therapeutic targets that can be further progressed by the EFPIA partners in the future.

PD-MitoQUANT assembled world-leading experts in mitochondrial function, cellular and in vivo models of Parkinson's, advanced imaging, data-driven machine learning, and systems modelling. The team used innovative techniques to investigate the role of a key protein, alpha-synuclein (αSyn), in Parkinson's, looking specifically at mitochondrial dysfunction. The project aimed to identify novel targets for new treatments of Parkinson's and potentially other NDs. PD-MitoQUANT also developed new models to study Parkinson's and built on existing expertise by applying cutting edge technologies, such as super-resolution imaging, innovative microfluidics and 3D 'Organ-on-a-Chip' (OrganoPlate®).

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far (For the final period please include an overview of the results and their exploitation and dissemination)

Running over 3.5 years, PD-MitoQUANT developed and standardised key models, protocols and assays and applied them to studying mitochondrial dysfunction in Parkinson's. These are being shared with the wider research community through publications in peer-reviewed journals.

αSyn is a protein normally found in neurons and other cells, but in Parkinson's and other NDs it builds up and forms aggregates that affect how neurons work. p91 αSyn fibrils were selected for use in this project as they potently induced aggregation of endogenous αSyn in vivo and in vitro. High quality, well characterised batches of p91 fibrils were manufactured and distributed to partners.

Four different cell models of Parkinson's were optimised - primary cortical and dopaminergic neuron models, using harmonised cell culture protocols and treated with p91 αSyn fibrils; and human cortical and dopaminergic neurons derived from induced pluripotent stem cells (iPSCs) obtained from a Parkinson's patient with three copies of SNCA, the αSyn gene linked to Parkinson's. A 3D 'Organ-on-a-Chip' (OrganoPlate®) platform was also optimised as a more biologically representative alternative to traditional 2D models.

Four in vivo models were established: a mouse model where the levels of αSyn in the brain are increased by viral overexpression of human αSyn, a mouse model where injection of p91 αSyn fibrils causes aggregation of the endogenous αSyn and two models using fruit flies and roundworms with αSyn introduced genes.

Using these diverse models, partners looked at how aggregation or increased levels of αSyn affect mitochondrial function. Looking at how mitochondria produce and consume energy, partners identified reduced energetic capacity and altered calcium signalling in neurons. Experiments also found changes in neuronal firing, mitochondrial quality control, and uptake of the neurotransmitter dopamine. 2D and 3D high-resolution imaging of mitochondria in all models enabled exploration of changes in mitochondria shape and function. The mitochondrial pathology caused by αSyn aggregates was also studied in different brain regions, with a decrease in an important mitochondrial complex observed. An automatic pipeline for combined analysis of high-throughput 'omics data was also developed to identify master regulators and signalling pathways involved in the observed mitochondrial dysfunction. Combining the results from the various models, the consortium identified potential molecular signatures and targets for further exploration and validation in the in vitro and in vivo models, as well as in samples from people with Parkinson's. A number of druggable targets were identified for future exploration.

Progress beyond the state of the art, expected results until the end of the project and potential impacts (including the socio-economic impact and the wider societal implications of the project so far)

PD-MitoQUANT was an ambitious public-private partnership that brought together academic experts, SMEs, EFPIA companies and the patient advocacy organisation Parkinson's UK to improve our understanding of mitochondrial dysfunction in Parkinson's, identify and validate molecular drivers and mechanisms, and discover innovative therapeutic targets for future exploration. The project advanced the state-of-the-art by characterising and quantifying links between mitochondrial dysfunction and neurodegeneration, improving our understanding of NDs, and identifying novel regulators and therapeutic targets. As the project's methods and results are published, they can be taken up to revitalise industrial R&D in therapies for NDs, with novel tools available to facilitate progress in this challenging field, opening new avenues for therapy development.

A coherent innovation management strategy, which balances the protection of commercially valuable IP with open access to academic and industrial R&D communities was established to ensure maximal impact. Protected results will encourage investment in future work by the EFPIA partners, building on the initial IMI2 investment. SMEs have 'stress tested' their technologies in a non-competitive, open innovation environment, enabling integration of new knowledge to enhance their products/ services and opening new markets. For example, GENEXPLAIN further developed computational tools and created a unique expertise for causal multi-omics data analysis and Mimetas developed the PD-OrganoPlate® model.

Parkinson's is an important societal challenge, significantly impacting on the lives of people with Parkinson's, as well as carers and family members. The disease also consumes a growing share of

healthcare budgets. In the long-term, PD-MitoQUANT's results will contribute to the development of treatments that prevent, cure or slow the effects of Parkinson's, benefiting patients and carers, and reducing a growing burden on European and global healthcare systems. Importantly, PD-MitoQUANT included two people with Parkinson's, who kept these potential long-term benefits at the forefront, sharing their personal experiences of living with the disease and their hopes for people with Parkinson's in the future.

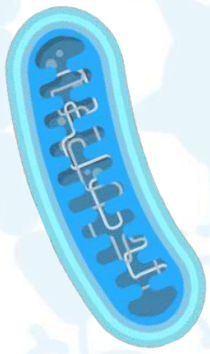
Address (URL) of the project's public website

https://www.pdmitoquant.eu/

Overview of PD-MitoQUANT project

In Europe, more than 1 million people live with Parkinson's

New, more effective treatments are needed



Mitochondria, the main energy supply in our cells, play a role in Parkinson's

Mitochondria may be a target for new therapies, but we need to learn more

Academia

Industry

PD-MitoQUANT

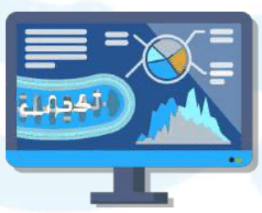
A public-private research partnership

Small & medium enterprises

Patient organisations

We will explore how mitochondria are affected in Parkinson's

We aim to develop new tools for drug discovery and better medicines



This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821522. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and Parkinson's UK.

PD-MitoQUANT partners

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Academic partners

RCSI

ICM Institut du Cerveau et de la Moelle épinière

cnrs

UCL

DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft

Consiglio Nazionale delle Ricerche

Radboudumc

EFPIA partners

teva | ucb | Lundbeck

Patient organisation

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

SME partners

MIMETAS
the organ-on-a-chip company

geneXplain

Project management

Pintail

efpia

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imi innovative medicines initiative PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.