IMPRiND Publishable Summary

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Summary of the context and overall objectives of the project

Over seven million people in Europe suffer from neurodegenerative diseases and this number is predicted to double by 2040 due to our increasingly ageing population with a dramatic impact on social services and potentially unsustainable financial burden on healthcare providers. Such urgent and currently unmet clinical need requires an unprecedented research effort that can only be achieved through a coordinated approach across leading European laboratories, the pharmaceutical industry and other international initiatives.

A growing body of data indicates that the propagation of pathogenic protein aggregates across neural systems could be mediated by misfolded protein seeds that are released and taken up by anatomically connected neurons causing disruption of their function. Therefore, blocking this process may help arrest the progression of Parkinson's (PD) or Alzheimer's (AD) disease. The Consortium **IMPRiND**, funded by the Innovative Medicine Initiative (IMI), is a group of European academic laboratories and members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) that aims to delineate and target critical steps in the propagation of α-synuclein (α-syn) and tau assemblies between neurons. Our programme is collaborative and mobilizes diverse expertise in order to deliver disease-relevant phenotypes suitable for high throughput screening and validation models using iPSC, organotypic cultures and animal models.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

Over the fourth year, we have made significant progress in delivering on our objectives. This has been facilitated by regular teleconferences and two virtual Consortium meetings.

The main research efforts of **IMPRIND** are focused on the following areas: (i) generation of brain-derived or amplified assemblies and their characterisation using biochemical techniques, (ii) cryo-EM structure of tau and α-syn assemblies, (iii) conduction of CRISPR screens in cell lines followed by cross-validation in primary neuronal screens, (iv) bioinformatic integration and analysis of screens based on druggability and gene expression data, (v) validation of prioritised hits in primary neurons, (vi) development of advanced cell-based models or animals for validation of selected targets and (vii) data dissemination.

- LMB, Lilly and Janssen have optimised and cross-validated protocols to isolate and quality control brain-derived tau assemblies from Alzheimer's disease brain. CNRS has established methodologies for amplification of proteopathic assemblies from brain homogenates of α-synucleinopathies.

- LMB has published the Cryo-EM structures of tau filaments isolated from Alzheimer's disease (Fitzpatrick et al., 2017), Pick's disease (Falcon et al., 2018) and chronic traumatic encephalopathy (Falcon et al., 2019) as well as Cryo-EM structures of MSA filaments (Schweighauser et al., 2020). CNRS has published the Cryo-EM structure of de novo generated α-syn fibrils (Guerrero-Ferreira et al., 2019).

- Development of assays suitable for high throughput screening and completion of primary screens were completed by UOXF, Novartis and HLU. These include focused CRISPR/Cas9 proteostasis screens for α-syn and tau, genome-wide CRISPR screens for tau, primary neuronal screens using siRNA for 300 targets for tau and the DUB screen for α-syn.

- Hits from these screens were further analysed in an integrated fashion by Lilly to prioritise targets for further validation in primary neurons.

- Validation of prioritised hits was performed by Novartis and HLU in primary neurons using siRNA or shRNA for tau and siRNA for α-syn. Further assessment of selected hits and additional targets for tau was performed at Janssen and has been planned for α-synuclein at Cellectricon.

- A number of advanced models have been fully characterised and their suitability for further use has been established. These include the iPSC-based dopaminergic neuronal model (UOXF), organotypic cultures (DZNE) and in vivo mouse (BRFAA and HLU models for α-syn. In vivo mouse tau seeding models have been established by Lilly and Janssen. The transplantation of iPSC-derived neurons for in vivo assessment of tau propagation and the tau drosophila model (both VIB) have also been completed. iPSC-based organoids (UCAM), hNP-based tau neuronal model (DZNE) and the primate model (UBx) are on-going. For the in vivo models different viral mediated silencing approaches were tested and characterized.

- We generated an on-line registry for critical reagents and initiated the deposition of data in public repositories to enable sharing of datasets or dissemination following publications. Website updates and news, social media messages, and a number of conference presentations and posters have completed the dissemination activities. We have also organised two international symposia during the biennial ADPD meeting

Progress beyond the state of the art, expected results until the end of the project and potential impacts

Through genetic screens **IMPRiND** has identified new targets that are now undergoing further validation in advanced cell models or animals. If confirmed, these could improve our understanding of disease-related molecular pathways and lead to the development of future mechanism-based therapeutics.

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