IMPRiND First Publishable Summary

March 2017—February 2018

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 2030 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 and tau assemblies between neurons. Our programme is collaborative and mobilizes diverse expertise in order to deliver physiologically relevant phenotypes suitable for screening and validation platforms in cellular systems of increasing complexity as well as 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 first year, we have made significant progress in fostering collaborations between groups and delivering on our objectives. This has been facilitated by regular teleconferences that are coordinated by the project management team and three Consortium meetings. The first two (kick-off and 6 months) were primarily focused on planning research activities whereas the third (12 months) was comprised of a series of research presentations (11) and posters (17) summarizing the scientific progress made by the (24) of junior researchers (post-docs and PhD students) that have been recruited to work on the project. In addition, **IMPRiND** has incorporated a new partner, Cellular Dynamics, who will contribute to the work in iPSC-based modelling and established an Advisory Board for independent input and oversight on potential for translation to therapeutics.

The research efforts in the first year were focused on three main areas: (i) optimization of protocols for isolation or generation of proteopathic assemblies from human brain, (ii) generation of focused libraries for targeted screens and development of disease-relevant readouts in cell lines and (iii) initial characterization of validation models. Specific progress along these lines that also demonstrates our collaborative approach include the following:

- A major effort has been invested in the identification of the most optimal method to isolate brain-derived tau assemblies from AD brain. To this end cases of AD tissue were distributed from the Oxford Brain Bank to Eli Lilly, Janssen and LMB and collaborative work at the three sites has led to a consensus on how to optimally extract, quality control and quantify tau assemblies for screening and validation platforms. Progress on

α-synuclein assemblies include the successful amplification of brain-derived seeds in tissue from PD cases that was not seen in control brains by CNRS. In addition CNRS has provided well-characterised recombinant α-synuclein assemblies to facilitate testing and if necessary running genetic screens and the development of validation models. Based on these results, the first milestone set at 12 months has been reached.

- Eli Lilly has generated a list of gRNA sequences focused on proteostasis. gRNAs oligonucleotides were synthesized and subcloned as pooled oligos into lentiviral vectors by UOXF. These libraries have been sequenced by Novartis and are now in production for the initial CRISPR/Cas9 screen by UOXF using human cell lines.

- A number of neuronal and animal models are in the initial stages of characterization by a number of partners. CNRS has delivered α-synuclein assemblies to a number of partners to investigate their properties on validation models. These include iPSC-based (UOXF), primary neurons (HLU, UBX), organotypic cultures (DZNE) and in vivo models in mice (HLU, BRFAA), and zebrafish (Servier). Initial planning for the primate tau propagation model (UBX) has also started. VIB in collaboration with AbbVie is developing a model of tau propagation in Drosophila for screening of modifiers that will be validated in tau iPSC models in culture or in vivo after transplantation of iPSC into mouse models.

These efforts are buttressed by the creation of a roadmap for a FAIR-driven data management policy with input from all members of the consortium. UOXF has performed two surveys followed by a study registration standard operating procedure for **IMPRiND** researchers to record planned experiments, provide longitudinal insight into the execution of their work over the course of the project that will eventually enable sharing of datasets or dissemination following publications.

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

Through genetic screening and validation platforms **IMPRiND** will define critical steps in the propagation of α-synuclein and tau assemblies between neurons that could inform the development of mechanism-based future therapeutics.

IMPRiND

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