

Webinar | IMI2 - Call 7

Identification of druggable targets modulating misfolded proteins in Alzheimer's and Parkinson's diseases

Kenneth Thstrup
14.01.2016 • IMI webinar

Need for public-private collaboration

- High need for new disease modifying treatments for Alzheimer's (AD) and Parkinson's (PD) diseases
- A β , tau and alpha-synuclein have been known to play a major role in the pathology for years
 - Lack of understanding of how these proteins affects pathology has limited the identification of new targets
- Recent hypothesis that these proteins display prion-like properties enables the identification of new druggable targets related to AD and PD
- A successful project demands strong understanding of fundamental biological processes and access to disease models and tools only available through broad public-private collaborations

Objectives of the full project

- Identify druggable targets modulating misfolded proteins
 - Set up *in vitro* and *in vivo* model systems for spreading and seeding processes of tau and alpha-synuclein
 - Use *in vitro* assays to conduct genetic or small molecule screens to identify targets and mechanisms involved in these processes
 - Based on key mechanisms identified in screens validate targets in selected *in vitro* and *in vivo* assays
 - Investigate druggability of targets by more broadly characterizing the implications of modulating the targets

Pre-competitive nature

- The consortium will be working in precompetitive landscape and tools and results will be made available to the public
- To achieve the highest impact collaboration and synergies with other relevant global initiatives and consortia will be considered
- The consortium consisting of academia, SMEs and EFPIA aims to
 - Develop tools that will be freely shared between partners and scientific community
 - Share existing knowledge to accelerate PD and AD research
 - Disseminate results to the public
- Regular meetings and workshops will be held to openly discuss results and progress

Expected impact on the R&D process

- Several outputs from the project may contribute to the R&D process of developing new therapies against PD and AD.
 - Establishing a common preclinical platform of assays based on the hypothesis of turnover / aggregation / spreading of misfolded pathological proteins is important to reach a consensus of how new treatment principles can best be evaluated and substantiated.
 - Such a platform can form the basis for identification of new druggable targets which would open up for development of new innovative treatments against PD and AD.

Suggested architecture of the project (1)

WP1: Governance and project management

WP2: Establish tau and alpha-synuclein assays



WP3: Target identification based on established assays



WP4: Target validation and druggability evaluation

WP5: Data and knowledge management

Suggested architecture of the project (2)

- **Work Package 1:** Governance and project management
 - grant administration; project plan; dissemination results.
- **Work Package 2:** Establishing *in vitro* and *in vivo* assays for tau and alpha-synuclein uptake, seeding and aggregation and aggregate-dependent toxicity
- **Work Package 3:** Identification of targets using genetic based and small molecule based screening in cellular assays established and selected from Work Package 2
 - Available validated assays can be used directly if agreed by the consortium.
 - Run genetic screens by modulating specific targets in cellular models with defined mechanistic or phenotypical endpoints;
 - Identify targets and mechanisms of uptake/seeding/aggregation.

Suggested architecture of the project (3)

- **Work Package 4:** Target validation and evaluation of druggability using *in vitro* and *in vivo* assays
 - modulate selected targets and/or pathways and study effects on alpha-synuclein and tau and their down-stream cellular response and disease phenotype
 - investigate druggability of targets and more broadly characterizing the implications of modulating the target(s).
- **Work Package 5:** Data and knowledge management
 - establish data format and content standards for data collection, data management and data sharing in order to ensure interoperability to quality standards and optimal use of IMI
 - develop data and knowledge management plan.

Expected contributions of the applicants

- Project management and integration of drug discovery expertise
- Expertise in Alzheimer's and Parkinson's disease and related tau and synucleinopathies
- Expertise in other neurodegenerative diseases beyond AD & PD with pathologies based on similar misfolded proteins (e.g. FTD and MSA), might be a further asset
- Expertise in protein clearance, uptake/endocytosis/exocytosis mechanisms and cell responses to misfolded proteins
- Expertise in and application of relevant models, screening systems and tools making them available for other members of the consortium as needed

Expected (in kind) contributions of EFPIA members

- Project Management
 - Joint scientific leadership / experience in drug development & AD and PD preclinical and clinical research
 - Fostering collaborative and focused joint efforts to achieve goals.
- The EFPIA in kind contribution will be EUR 4 685 000; the indicative matching IMI 2 contribution will be of similar amount
- Indicative tools (Transgenic animals and samples thereof: alpha-synuclein and tau. Cellular tau and alpha-synuclein seeding/spreading models, iPSCs. Bioinformatics. High content imaging. Drug screening in cellular assays. Tool compound collections and ADME/PK

What's in it for you?

- Funding of research initiatives
- Involvement in international consortium consisting of academia and Pharma for an indicative period of 4 years
- Access to tools from diverse sources to progress research and close collaboration with leading EFPIA companies in the field of PD and AD
- Identification of new targets on which future innovative new medicine can be developed against AD and PD
- Establishing and sharing precompetitive research and development tools for the scientific community to progress AD and PD research

Key deliverables of the full project

- A platform consisting of:
 - robust *in vitro* assays for tau and alpha-synuclein uptake and seeding/aggregation useful for target identification
 - established model systems for *in vitro* and *in vivo* validation of targets modulating seeding and spreading of disease associated forms of tau and alpha-synuclein proteins
- Conducted genetic based screens on either seeding, spreading or clearance to identify targets in the relevant druggable genome
- Tools to modulate targeted genes and identify suitable reagents to quantify effect of knock-down or overexpression;
- Findings validated by gene knock-down or over-expression studies in widely accepted preclinical models *in vitro* and *in vivo*
- Druggable targets reducing the spreading of tau or alpha-synuclein

Questions?

Contact the IMI Programme Office
infodesk@imi.europa.eu • www.imi.europa.eu

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