Application of a Qualitative Model to Elucidate the Role of the Alpha-Synuclein System in Parkinson’s Disease.

CM Friedrich¹, W Zago², S Gardai², G Tonn², MJ Reed¹
¹Rosa&Co, CA, USA; ²Elan Pharmaceuticals, Inc, CA, USA

Introduction

- Alpha-synuclein protein is a major component of Lewy bodies, the hallmark features of Parkinson’s disease (PD).
- Alpha-synuclein’s is thought to be involved in vesicle formation, though its functions in healthy brains or in patients with PD are not well understood.
- Improper vesicle formation has been hypothesized to contribute to the pathophysiology of PD.

Objectives

- Provide insight into alpha-synuclein function in vesicle trafficking.
- Discover, discuss, and document the current state of knowledge within Elan.
- Formulate hypotheses for unknown or uncertain aspects of alpha-synuclein function.
- Identify future experiments to test hypotheses, resolve uncertainties and identify and prioritize potential targets.

Methods

- Explore the role of alpha-synuclein in vesicle formation and PD, by collaborating on the development of an Alpha-Synuclein PhysioMap®, a qualitative, graphical model of alpha-synuclein’s known and hypothesized functions.
- Engage in a participatory process of developing the Alpha-Synuclein PhysioMap to curate, discuss, and integrate existing public and Elan-proprietary data and knowledge.
- Facilitate identification of knowledge gaps, generation of hypothesis, and identification of assays to resolve uncertainties and test hypotheses.

Results

- The Alpha-Synuclein PhysioMap was designed and curated by a multidisciplinary team from Rosa and Elan to represent alpha-synuclein life cycle and function, including:
  - Alpha-synuclein synthesis and distribution within a neuron.
  - SNARE complex formation.
  - Phagocytosis.
  - Cytokine and neurotrophic factor release.
  - Mitochondrial function.
- Each process was represented as one of a series of inter-connected modules, or sub-systems (Figure 2).
- The graphical interface facilitated identification and discussion among the multi-disciplinary team of current knowledge, available data, data gaps, and hypotheses.

Conclusions

- Development of the Alpha-Synuclein PhysioMap facilitated:
  - Documentation and expansion of Elan’s institutional knowledge of alpha-synuclein.
  - Identification of key biological uncertainties and hypotheses.
  - Recommendations for focused laboratory experiments to further elucidate alpha-synuclein function in vesicle formation and PD.
- The Alpha-Synuclein PhysioMap could be expanded into a quantitative Alpha-Synuclein PhysioPD™ model, by adding mathematical relationships and parameters to the existing structure.
- An Alpha-Synuclein PhysioPD Platform would enable further in silico hypothesis generation and testing, including using simulation-based what-if explorations.

References