

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

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**Objective:** In order to improve the understanding of the alpha-synuclein system and its role in Parkinson's disease, Elan and Rosa collaborated in the development of a Synuclein PhysioMap<sup>®</sup>, a graphical model to support hypothesis generation and testing. The objectives of the project were to provide insight into alpha-synuclein function in vesicle trafficking by creating a PhysioMap, memorialize and communicate the current state of knowledge within Elan in a Synuclein Model Qualification Method Document (MQM), and to recommend experiments to test hypotheses, resolve uncertainties, and identify and prioritize potential targets.

**Background:** Elan was developing inhibitors of alpha-synuclein formation for the treatment of Parkinson's disease and wanted to improve the design and interpretation of *in vitro* assays to evaluate candidate compounds.

**Methods:** The PhysioMap was developed using both publically available literature and proprietary Elan data. The Synuclein PhysioMap was designed and curated by a multidisciplinary team to represent synuclein synthesis and distribution within a neuron, SNARE complex formation, phagocytosis, cytokine release, neurotrophic factor release, and mitochondrial function.

**Results:** During the development of the PhysioMap, the team identified key biological uncertainties and hypotheses and recommended focused laboratory experiments to gain a better understanding of synuclein function in Parkinson's disease.

**Conclusion:** Development of the PhysioMap helped provide insight into the alpha-synuclein system and its function in Parkinson's disease, and helped identify a more efficient experimental path for evaluating therapeutic compounds.

Previously presented at the World Parkinson Conference, Portland, Oregon, 2016