From translational PKPD models to quantitative system pharmacology in neurodegeneration drug development

Co-Chairs

Sreeraj Macha and Li Li

Description

The ISoP/C-Path Neuro-Pharmacometrics Community of Practice (NeuroCoP) was launched at ACoP7 2016. Within the community, the Alzheimer disease (AD) and Parkinson disease (PD) working groups share/develop modeling methods and tools applied to different stages of drug development programs. This session will focus on utility of quantitative systems pharmacology and translational approaches to inform early stage drug development. Neurodegenerative diseases are characterized by progressive loss of structure, function and eventually death of neurons. The lack of disease modifying therapies and a rapid increase in the prevalence of these diseases poses a significant socioeconomic burden worldwide. The complex pathophysiology of neurodegenerative diseases continues to be a great challenge to identify therapeutic targets. In addition, the lack of animal models and predictive biomarkers reflective of disease condition amplify the challenges facing the research community resulting in a relatively greater attrition rates in the neuroscience area. Recent advances in understanding the biology and pathophysiology of various neurodegenerative diseases led to greater success in identifying new targets to address unmet medical need. These new developments also helped to develop robust quantitative systems pharmacology approaches integrating in vitro, animal and human data. This session will focus on the latest quantitative approaches integrating diverse data from in vitro and in vivo models to understand target engagement and inform early clinical development.

Learning Objectives

This session will address the challenges facing drug development in the neuroscience area and provide an overview on the latest strategies to implement quantitative approaches integrating biology, pathophysiology, and biomarkers to inform go/no-go decisions. A few case studies will be discussed highlighting the integrated approaches to model diverse data to inform dose selection and trial design.

Session Speakers and Presentations

Piet van der Graaf - Quantitative Systems Pharmacology for Neuroscience drug discovery and development: current state, opportunities and challenges

Application of quantitative pharmacology (QSP) approaches in neuroscience has been lagging behind most other therapeutic areas, which in part can be explained by a wide-

spread belief that the brain may be "too complex to model". However, the low success rates in neuroscience R&D has exposed the urgent need for novel approaches and in recent years there has been a marked increase in the application of model-based approaches. This talk will provide an overview of the current state of neuroscience QSP and a perspective of the opportunities and challenges, illustrated with case studies.

Tatiana Karelina - Quantitative systems pharmacology model for amyloid pathology investigation

Translational quantitative systems pharmacology (QSP) model of amyloid beta (Ab) distribution and aggregation allows for investigation of therapy efficacy on different amyloid species (soluble, insoluble) under different mechanisms of action and clinical trial design and evaluation of Ab toxicity hypotheses. The model mechanistically describes Ab production, clearance and pathways of Ab aggregation in the brain. It was verified using data available from the literature. Model describes accumulation of insoluble and soluble Ab species during AD and results of published clinical trials (gamma- and beta-secretase inhibitors, immunotherapy). It demonstrates that only early therapeutic intervention would prevent accumulation of toxic species.

Li Li - Mechanistic PKPD modeling to understand the uncertainty in predicting CSF target engagement

Biomarkers, such as soluble abeta and tau, have been collected from both plasma and CSF to demonstrate target engagement for Alzheimer Disease drug development. However, due to practical difficulties, CSF sample collection is often limited to a single lumbar puncture or a short duration catheter collection. Therefore, while plasma PKPD models can be developed with data collected from intensive sampling, the parameters in CSF compartment may have to rely on published physiological values or animal data. The presented simulation re-estimation excise will demonstrate that which CSF parameters are most sensitive and how they impact the CSF target engagement predictions.

Hugo Geerts - Turning the tide of failed trials. Re-engineering R&D using quantitative systems pharmacology

Developing successful Neurology and Psychiatry drugs remains a tremendous challenge, but applying computer-based modeling approaches as is standard in other engineering disciplines is a possible solution. Quantitative Systems Pharmacology applies concepts of neuropharmacology to biophysically realistic computer models of humanized neuronal circuits. Clinical studies are used to implement the pathology and further constrain system parameters. Practical examples include predicting clinical effects at the individual patient level with multiple medications, the biology underlying responders to a specific antipsychotic, the biological explanation for the multiple failures of amyloid therapies in Alzheimer’s Disease and drug repurposing for treatment of Parkinson’s Disease tremor.

Malidi Ahamadi - Disease progression model platform to inform efficient clinical trial design for Parkinson's Disease

Poster abstract speaker - Poster T-061 Tuesday 8-9 AM