THU-014

How does mechanistic QSP modeling reduce R&D risk in data-poor disease areas such as central nervous system (CNS) diseases?

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Problem Statement

- Neurodegenerative CNS diseases present unique challenges for drug development:
  - Significant uncertainty about pathophysiology
  - Slow disease progression
  - Limited data and biomarkers
- How can mechanistic QSP models be useful under these conditions?

Methods

- Analyze QSP modeling projects in CNS diseases
- Identify attributes that allowed the modeling projects to support development decisions

Conclusion

In data-poor diseases such as CNS, QSP modeling is ideally suited to **improve scientific understanding**, systematically **explore hypotheses**, **prioritize experiments**, and **de-risk** next steps.

Results

- The successful CNS QSP projects shared attributes:
  - Appropriate scoping and framing
  - Opportunity to direct empirical experiments
  - Appropriate expectations – improved understanding and more confident next steps vs. predictive precision
- Most useful modeling approaches:
  - In-depth scientific discussions
  - Quantitative integration of disparate data
  - Hypothesis exploration using what-if simulations
  - Sensitivity analysis to identify material uncertainties
  - Virtual patients to explore impact of variability
  - Extrapolation from biomarkers to disease scores

Case: Parkinson's Disease

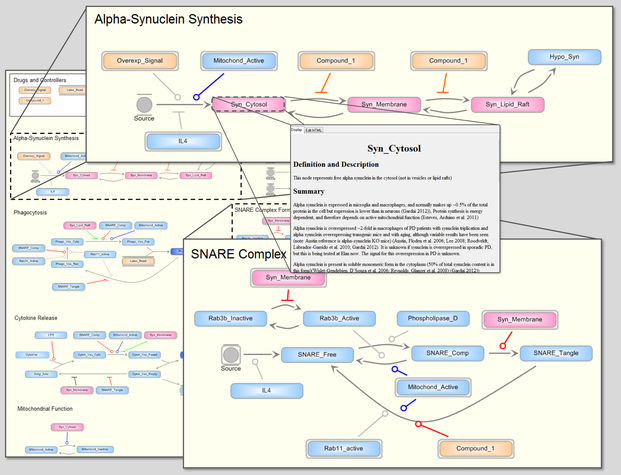

Figure 1. An α-synuclein PhysioMap®.

Case: Frontotemporal Dementia

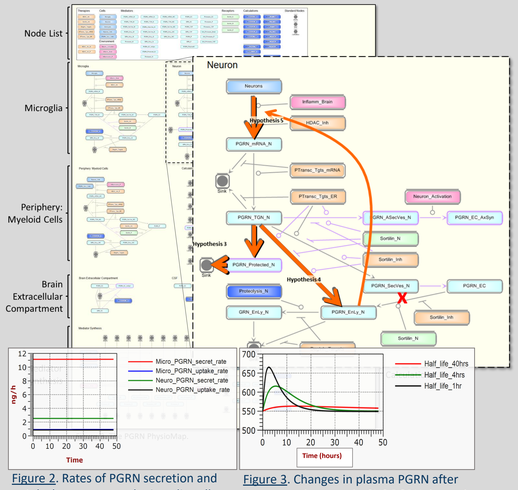

Figure 2. Rates of PGRN secretion and uptake by neurons and microglia cells.

Figure 3. Changes in plasma PGRN after temporary increase in CNS PGRN depend on plasma PGRN half-life.

Case: Schizophrenia

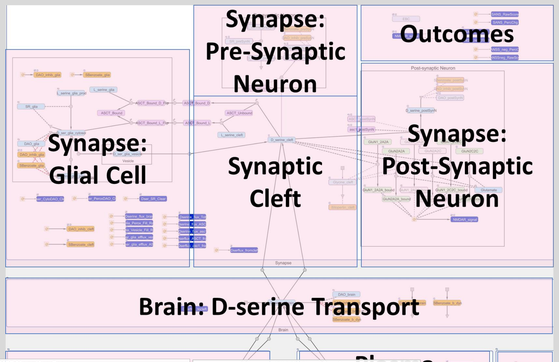

Figure 4. PANSS negative score in VPs vs clinical data for D-serine administration.

Figure 5. PANSS neg score prediction for one VP under three different therapies.

Figure 6. Schizophrenia PhysioMap (SimBiology® software)

Case: Alzheimer's Disease

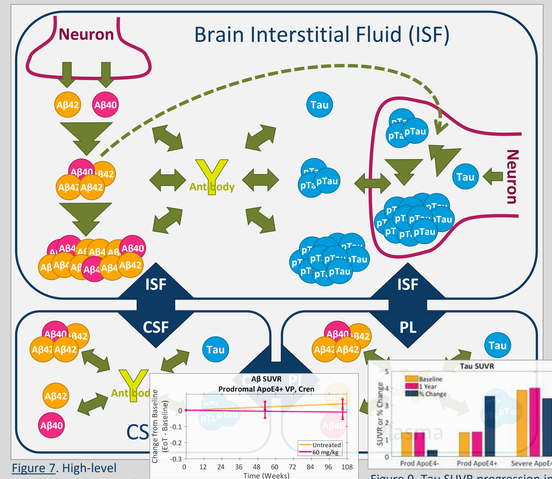

Figure 7. High-level scope of an Alzheimer's Disease PhysioPD Platform.

Figure 8. Clinical outcomes for anti-Aβ therapy.

Figure 9. Tau SUVR progression in three virtual patient phenotypes.

Research Question	What hypotheses of α-synuclein effects are consistent with data?
Context	Discovery, low risk, sparse data, high uncertainty, first-in-class
QSP Research Methods	Graphical model of known and hypothesized pathways In-depth discussions with client scientific experts
Actionable Results	Formulated novel hypotheses for uncertain aspects of α-synuclein function Suggested incisive experiments to test hypotheses, resolve uncertainties, and identify and prioritize potential targets

Research Question	What intracellular pool of progranulin should be increased for efficacy?
Context	Preclinical, low risk, some good proprietary in vitro and preclinical data, high uncertainty, first-in-class
QSP Research Methods	Quantitative model to integrate data sets In-depth scientific discussions In silico "what-if" hypothesis explorations Sensitivity analysis
Actionable Results	Demonstrated contradiction between current understanding and client's data, formulated novel testable hypotheses Identified likely biomarkers of efficacy

Research Question	How much will DAAO inhibitors improve schizophrenia negative symptom scores?
Context	Translational, competitor data for similar MOA, high uncertainty
QSP Research Methods	Quantitative model to integrate mechanistic and clinical competitor data Sensitivity analysis and virtual patients to explore robustness of conclusions Bridging from biomarkers to PANSS score
Actionable Results	Demonstrated that despite uncertainty, the DAAO inhibitor is expected to outperform competitors

Research Question	Can a model that integrates Aβ and tau pathology support R&D?
Context	Range of contexts, clinical data for anti-Aβ, mechanistic data for tau
QSP Research Methods	Quantitative model that reproduces known Aβ outcomes and facilitates extrapolation/exploration in VPs Future extensions to bridge to mental status outcomes
Actionable Results	Hypothesis generation and testing Predictions of Aβ and tau outcomes for new treatments under different hypotheses

This poster and additional details about these case studies are at https://www.rosaandco.com/publications.

www.rosaandco.com

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