Advancing QSP Technology to Address the Most Complex Areas of Drug Development

Certara's Publications on the use of Quantitative Systems Pharmacology modeling for Immunogenicity, Immuno-oncology, and Neurodegenerative Disease Rated Top 10% of All Downloaded Papers in Leading Peer-reviewed Journals

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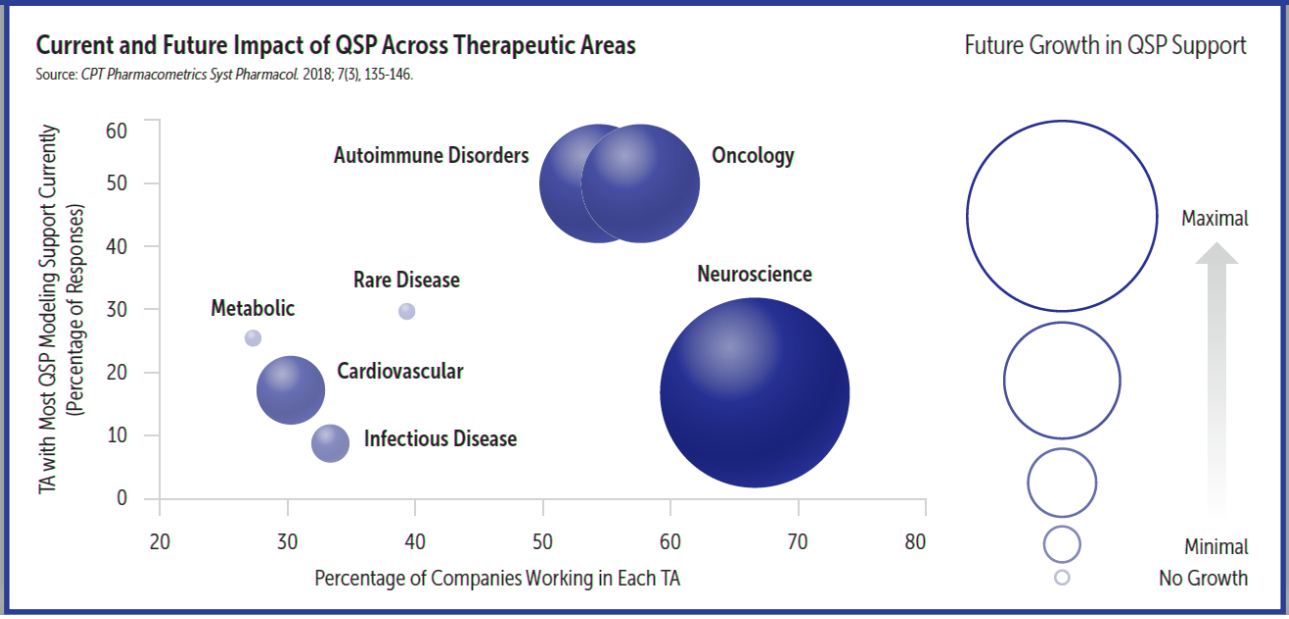
Introduction

Beginning with the seminal 2011 paper, "*An NIH White Paper by the QSP Workshop Group, the discipline of Quantitative Systems Pharmacology (QSP)*" has demonstrated significant impact on our understanding of many drug development mysteries. QSP combines computational modeling and experimental data to examine the relationships between a drug, the biological system and the disease process. By integrating quantitative drug data with knowledge of its mechanism of action, QSP can predict how drugs modify cellular networks along with how they affect and are impacted by human pathophysiology. Additionally, QSP facilitates the evaluation of complex, heterogeneous diseases such as cancer, immunological and neurodegenerative diseases that tend to require combination therapies.

Figure 1: Benefits of QSP across key therapeutic areas



QSP enables drug developers to ask and answer pivotal questions, including:

- In a given biological pathway, what is the **best target and modality** for pharmacological intervention to treat a given disease
- How can we improve the therapeutic effectiveness of an existing drug through **combination therapy**
- Can we predict the effect of a drug in a **special population/other indication**
- Can we individualize **dosing regimen** based on patient characteristics
- Can we predict human response (dose) to a **novel mechanism** based on preclinical data
- How can we **optimize clinical trials** by accounting for pharmacodynamics interactions with comedications and genotypes
- Which **biomarkers** do we require to answer the above questions

Wiley, the publishers of the three American Society for Clinical Pharmacology & Therapeutics (ASCPT) journals, recently announced the top 10% most downloaded papers for 2019, citing the research impact those papers have had on the industry. Four Certara papers on QSP were included in this category—a summary of each follows.

1 Immunogenicity

COMMENTARY

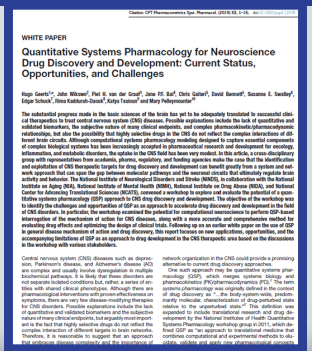
Immunogenicity in Clinical Practice and Drug Development: When is it Significant?

2 Best Practices in QSP Model-building

WHITE PAPER

Best Practices to Maximize the Use and Reuse of Quantitative and Systems Pharmacology Models: Recommendations From the United Kingdom Quantitative and Systems Pharmacology Network

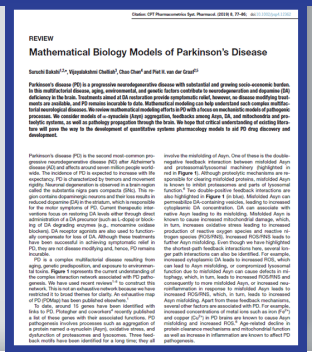
3 Neuroscience Drug Discovery & Development



WHITE PAPER

Quantitative Systems Pharmacology for Neuroscience Drug Discovery and Development: Current Status, Opportunities, and Challenges

4 Parkinson's disease Case Study



REVIEW

Mathematical Biology Models of Parkinson's Disease

1 Immunogenicity

Biologic drugs offer high efficacy and targeted delivery with fewer side effects, with the exception of immunogenicity (IG). IG is defined by the FDA as the propensity of the therapeutic protein to generate immune responses to itself and to related proteins. The development of antidrug antibodies (ADA) against these protein-based therapies is a challenge in both drug development and clinical practice. Our first paper, "*Immunogenicity in Clinical Practice and Drug Development: When is it Significant?*" focuses on this issue.

Initially delivered during a workshop at ASCPT, this paper expands that discussion to provide a rationale for ongoing research into this topic. IG considerations in clinical practice, IG testing and current limitations, IG risk assessment and mitigation, and the use of QSP model to address these IG challenges are covered.

In drug development, a tiered assay process is used to evaluate IG risk assessment. However, this approach has limitations with regard to incidence rates or intensity of response, and certainly the ability to compare between different therapeutic proteins or the same protein that used different assays. There are also inconsistencies in analytical methodologies used to assess the incidence of ADA formation and the impact of immune reactions. In clinical practice, the long-term outcomes of diseases treated with biologics may be severely impacted by immune responses to them, an issue of great concern for pediatrics.

Per regulatory guidance, there are two principal options for ADA mitigation: induction of immune tolerance to the therapeutic protein once in clinical development, or de-immunization of the protein therapeutic via use of predictive algorithms and in vitro studies to identify and remove immunogenic epitopes while maintaining product activity prior to or during product development. As our knowledge of IG has expanded, so has our ability to leverage a newer, in silico approach to understanding and mitigating this challenge: QSP.

In 2017, a number of leading pharma companies working with Certara recognized that development of a QSP platform focused on the pre-competitive issue of IG was a prudent method for advancing knowledge on the topic. A consortium with six pharma companies and a multidisciplinary team of 50 scientists have been working for the past three years to develop a QSP platform and Simulator for IG risk assessment (figure 2). This IG Simulator integrates literature-based, mechanistic models of immune response and ADA synthesis with a physiologically based pharmacokinetic (PBPK) model of biologics, using the Simcyp® Simulator. The IG Simulator predicts ADA impact on pharmacokinetics (PK) in different patient populations. It outputs virtual trials, where the effect of different dosing regimens, patient characteristics, and co-therapy can be evaluated. The QSP platform can integrate of a wide range of in vitro assays, clinical data, and bioinformatics predictions, including sources of 'big data.' As a drug development program progresses, the QSP model can be further informed by clinical data and used for extrapolation to later stages and special populations. During development and post-marketing, the platform is also used to evaluate combination therapies.

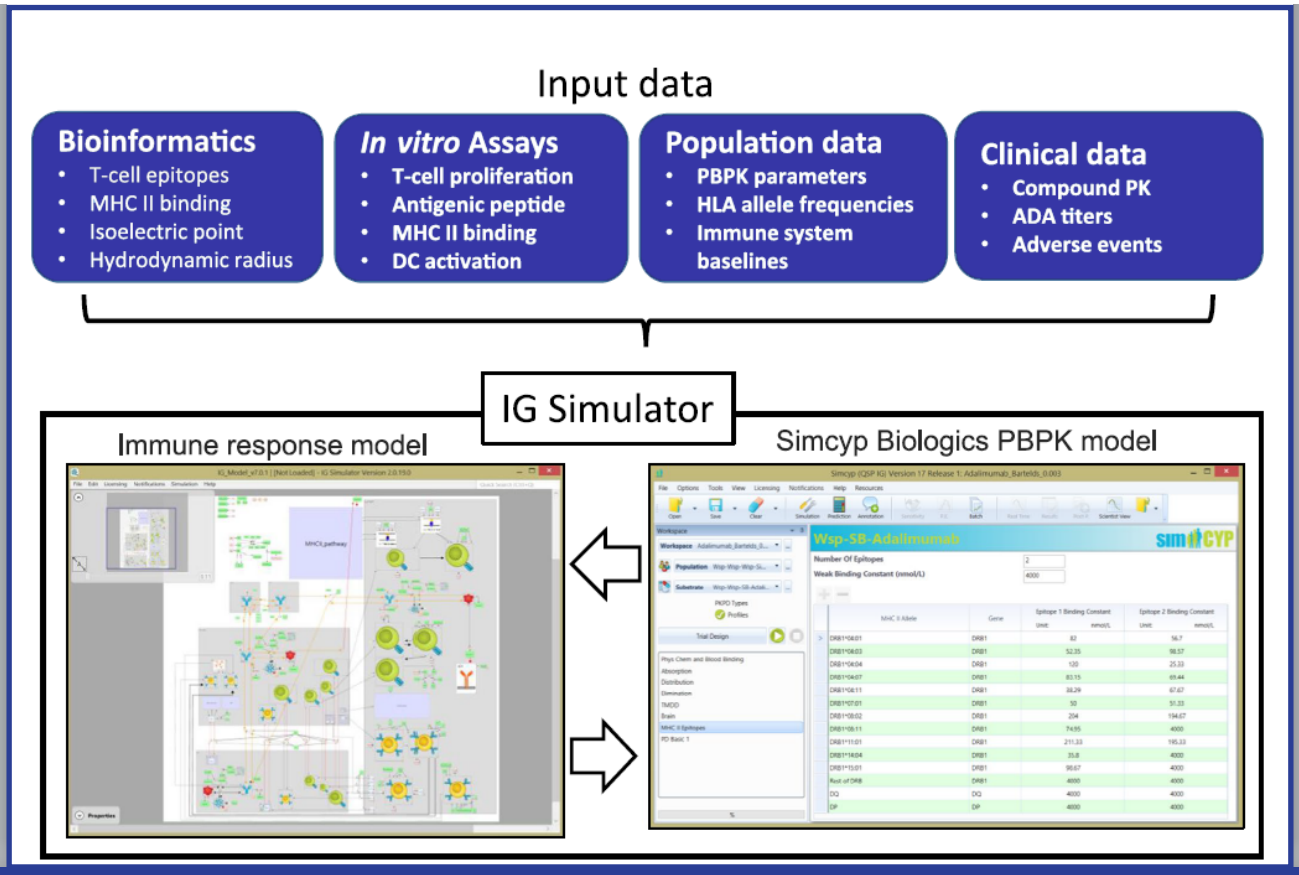


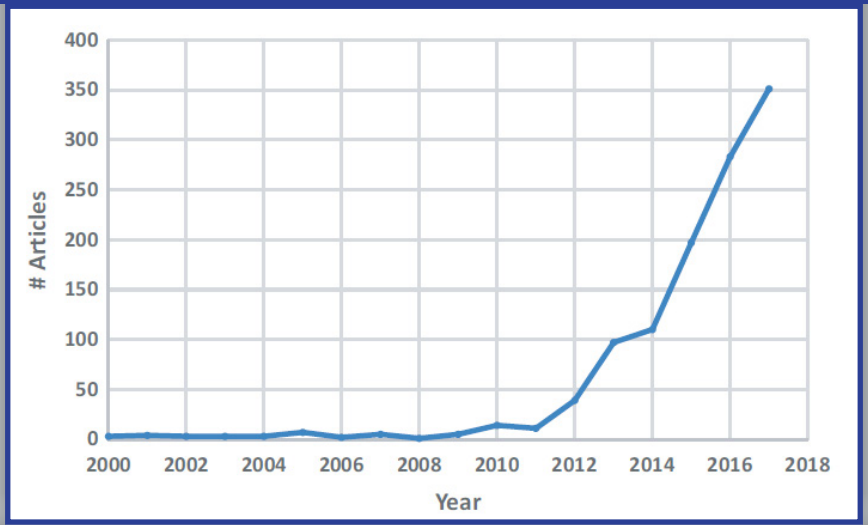
Figure 2: Overview of the IG Simulator.
The Quantitative Systems Pharmacology model includes mechanistic model of the immune response and Simcyp Biologics physiologically based pharmacokinetics.

2 Best Practices in QSP Model-building

Modeling & simulation methods such as pharmacokinetic/pharmacodynamic (PK/PD) or PBPK have followed a similar pattern to gain acceptance in drug development, beginning in academia and progressing through to regulatory approval. These approaches have achieved that latter status after demonstrating adherence to well-understood tenets of software development, such as reproducibility, standardization, reusability, quality assurance, and model verification. Our second highly read paper, "*Best practices to maximize the use and reuse of quantitative and systems pharmacology models: recommendations from the United Kingdom Quantitative and Systems Pharmacology Network*" addresses this topic. The article's viewpoint is that it is time for QSP to cross that chasm and establish a set of recommendations to guide scientists working on these models such that their work can provide maximum value to projects and stakeholders.

QSP use in drug development has been growing, as evidenced by the citations in PubMed (**Figure 3**). A benefit of QSP is that it is integrative and modular, such that new models can be derived from reusing existing models. However, since most of the published models are not standardized, the ability for others to reproduce and reuse, expand or reduce, or otherwise alter the model to meet new objectives is hampered. Common issues affecting this situation include a lack of purpose, scope or underlying assumptions, missing data or other quantitative information, and justification for model impact.

Figure 3: Annual number of PubMed abstracts containing the term "systems pharmacology"



This paper, authored by The United Kingdom Quantitative and Systems Pharmacology Network provides recommendations on how to address this challenge, focusing on how to document QSP models when published, inclusive of a minimal set of standardization requirements. It provides a set of computational and mathematical recommendations and literature references for each of the six challenges:

- Purpose and context of the model
- Model structure and model methodology
- Input data, knowledge and assumptions going into the model
- Model verification
- Model validation
- Model results, application and impact

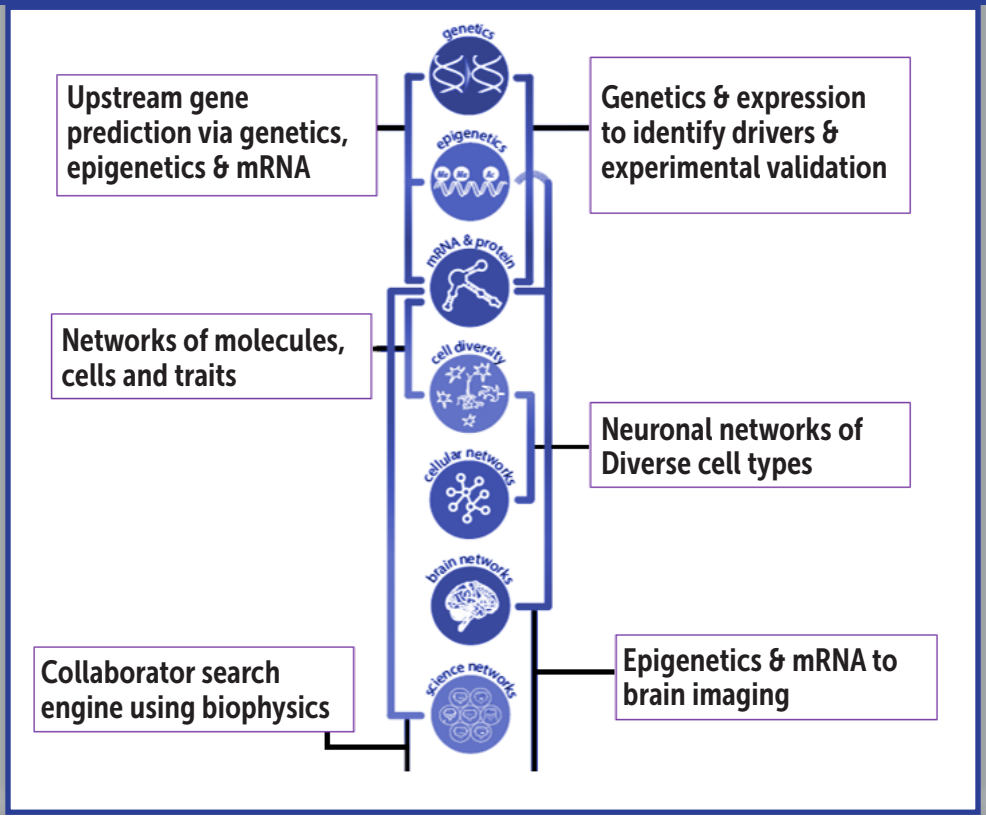
QSP holds enormous promise for extrapolating the results of drug treatment between diseases with common underlying mechanisms and in the evaluation of optimal drug combinations. It can play a sizeable role in addressing the challenges in target validation, modality selection, and dose assessment, especially for pediatrics and vulnerable populations. Further, these multiscale models can be leveraged to study how an observed variability in patient response can be explained by, for example, variables influencing trial design, variation in disease-specific covariates (not exclusively pharmacokinetics), or the complex pathway modulation that can be produced by drug combinations.

3 Neuroscience Drug Discovery & Development

Often called the 'holy grail' of drug development, developing safe and effective treatments for neurodegenerative diseases (NDD) is the most vexing drug development challenge today. The lack of quantitative and validated biomarkers, the subjective nature of many clinical endpoints and the complex PK/PD relationships add to the conundrum, along with the enormous complexity of interactions that occur between brain circuits.

NDD are complex and usually involve dysregulation in multiple biochemical pathways. Moreover, while there are pharmacological interventions with proven effectiveness on symptoms, there are few disease-modifying therapies available for patients. Our third paper, "*Quantitative systems pharmacology for neuroscience drug discovery and development*: *current status, opportunities, and challenges*, contends that NDD requires a different approach—one that integrates the complex interactions of different brain circuits across multiple biophysical scales (**figure 4**). This paper identifies QSP as a path forward toward better understanding of NDD to create effective therapies.

Figure 4: QSP enables the coupling and integration of multiple biophysical scales that can guide the complexities inherent in neurodegenerative diseases



Typically, drug discovery projects focus on a single biophysical scale. The connections across these scales are obscured by the complexity of biological systems, causing an obstacle to building coherent disease models. QSP facilitates the coupling of these biophysical scales, which allows the 'scaling up' of molecular findings to the level of cognitive processes.

QSP provides many benefits in NDD development, ranging from target selection and safety assessment to evaluation of individual subject variability in clinical trials (**Figure 5**). Because the QSP approach is based on the implementation of pharmacology, target engagement, and neurophysiology, it is ideally suited for the simulation of these PD interactions.

In the case of chronic NDD, often many comorbidities converge in the elderly brain. In addition, genetic studies suggest a large number of pathways involved in the pathology. Therefore, it is unlikely that selective interventions focused on a single pathway will be able to provide a substantial clinical improvement. By merging systems biology and PK/PD approaches in a QSP framework, we could greatly facilitate drug discovery and development for complex diseases that have not been defined by a single molecular target. In this context, systems biology would identify the most likely network of genes, proteins, or neural pathways from large data sets with a variety of environmental, chemical, orgenomic perturbations.

Figure 5: List of major impacts of QSP on key decision points in the development of a CNS drug and comparison with traditional research and development

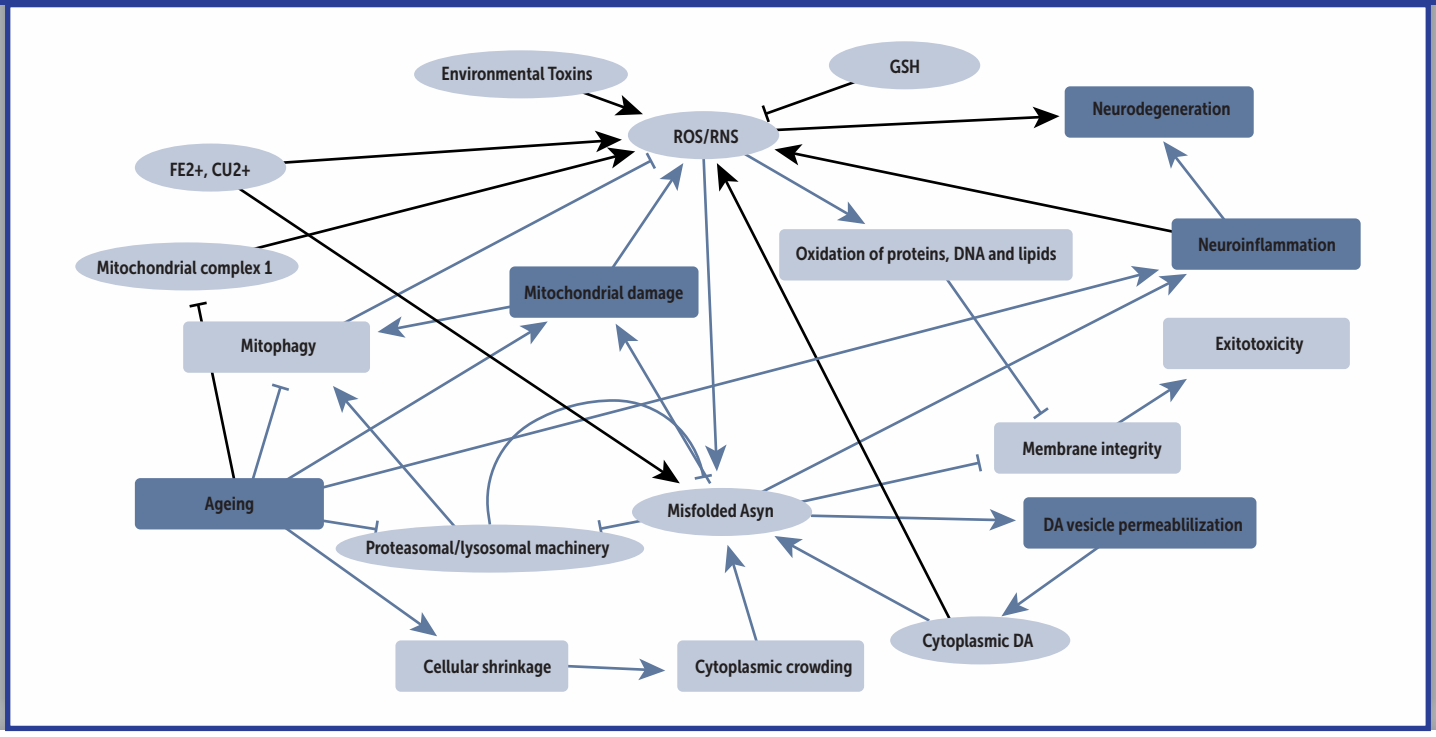
Decision Point	Current approach	QSP
Target Selection	Use of clinical-genetic data, and preclinical information	Target(s) identification with biggest impact on network and circuit outcome
Single vs. multitarget profile	Usually single target based on mostly genetic and biological information	Combination of targets based on biological information
Clinical candidate selection	Usually highly selective (avoiding side effects)	Can be rationally designed multitarget drug or drug combination
Proof of concept dose selection	Allometric calculations combined with vitro-in vivo modelling	Can identify optimal dose in nonlinear dose response
Impact of comedication on clinical outcome	Tested when applicable	Effect predicted based on non-linear interactions between medications
Impact of genotypes on clinical outcome	Tested when applicable	Effect predicted based on non-linear interactions with physiological effect from human imaging studies
Analysis of clinical trials	Statistical post hoc analysis; data "binning" needed for statistical power	Virtual patient analysis taking into account individual patient profile

4 Parkinson's disease Case Study

Parkinson's disease is the second most-common progressive neurodegenerative disease after Alzheimer's disease and affects around seven million people worldwide. In this multifactorial disease, aging, environmental, and genetic factors contribute to neurodegeneration and dopamine deficiency in the brain. Treatments aimed at dopamine restoration provide symptomatic relief, however, no disease modifying treatments are available, and PD remains incurable to date. The final paper cited by CPT, "*Mathematical Biology Models of Parkinson's Disease,*" demonstrates how QSP can help in the understanding of this complex multifactorial neurological disease.

A biological map of Parkinson's disease (**Figure 6**) resulted in our decision to focus on α-synuclein (Asyn) aggregation, feedbacks among Asyn, DA, and mitochondria and proteolytic systems, as well as pathology propagation through the brain. 15 genes have been identified with links to PD, its pathogenesis involves processes such as aggregation of the Asyn protein, oxidative stress, and dysfunction of proteasomes and lysosomes. Many involve the misfolding of Asyn, known to cause increased mitochondrial damage, which, in turn, increases oxidative stress leading to increased production of reactive oxygen species and reactive nitrogen species (ROS/RNS). Increased ROS/RNS leads to further Asyn misfolding. As a multi-factorial disease, there are several other factors beyond Asyn associated with Parkinson's disease.

Figure 6: Biological map of Parkinson's disease pathogenesis for constructing a QSP model



Parkinson's disease models can be either mechanistic or phenotypic, the latter will includes models that quantitatively describe some aspect of motor symptoms, such as tremors or gait disturbances or electroencephalography characteristics, using signal processing. This enables us to identify quantitative differences between healthy and diseased subjects. Our work addresses the mechanistic models of Parkinson's disease, primarily Asyn aggregation, but also pathogenesis and pathology propagation models. In total, we classified 32 pharmacodynamic models based on Parkinson's disease pathology.

We believe that a critical understanding of existing literature will pave the way to the development of QSP models to aid Parkinson's disease drug discovery and development. Since the publication of this paper, we have progressed the Asyn model for specific client company targets.

Summary

During the past decade, QSP has gained traction within the pharmaceutical industry and for regulators as a modeling method to quantitatively and mechanistically describe diseases and the complexity of drug action. It aims to understand the behavior of the system as a whole, as opposed to individual processes. By combining disparate data into coherent mechanistic models, QSP is becoming a key tool for picking the right dose for first-in-human trials and optimizing clinical trial designs. In short, QSP improves confidence in both the compound and the target.

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