CERTARA

Certara QSP Designer Technology

User-driven, graphical workspace to optimize collaboration for all stakeholders

Tapping the Power of QSP to Make Smarter Decisions

While still a relatively new discipline, Quantitative Systems Pharmacology (QSP) has already had a sizeable impact on drug development. QSP combines computational modelling and experimental methods to explore the relationship between a drug, human biology, and the disease process. It leverages large quantities of biological and pharmacological data to increase scientific knowledge of disease pathophysiology and facilitate the investigation of different therapeutic approaches in virtual patients in virtual clinical trials. As virtual patients are used instead of real people, QSP modeling saves time and money and allows more drug doses and drug combinations to be investigated than could be practically and ethically evaluated in clinical trials.

QSP modeling can help to identify and validate a new drug target or biomarker, select the optimal drug dose for a specific and vulnerable patient population or an individual patient, predict clinical efficacy and/or toxicity, repurpose an existing on-market drug for a different indication or develop a new combination therapy.

Democratizing QSP for all Stakeholders (Modelers and Non-modelers Alike)

Combining the disciplines of systems biology with pharmacokinetics-pharmacodynamics (PKPD), QSP examines the mechanistic relationships between a drug, the biological system, and the disease process using computational modeling. QSP models can quickly become quite large and complex with numerous equations and variables, which can be overwhelming, especially for non-modelers. Yet for QSP to deliver on its great potential, the multidisciplinary scientists within drug development teams need to be able to ask and answer questions about the drug, target, pathway, disease, and patient from all their scientific perspectives.

Typical QSP workflows involve discussion of biology, supported by graphical diagrams ("biological maps"), followed by construction of mathematical models, typically using ordinary differential equations (ODEs) models. QSP Designer facilitates this process by providing enhanced graphical notation, which enables hierarchical presentation with modules and handling of combinatorial complexity with diagram node arrays. Whereas the software includes a simulation engine, a major feature is full model code generation in MATLAB, R, C, and Julia to support multiple modeling communities.[1]

QSP Answers Key Development Questions

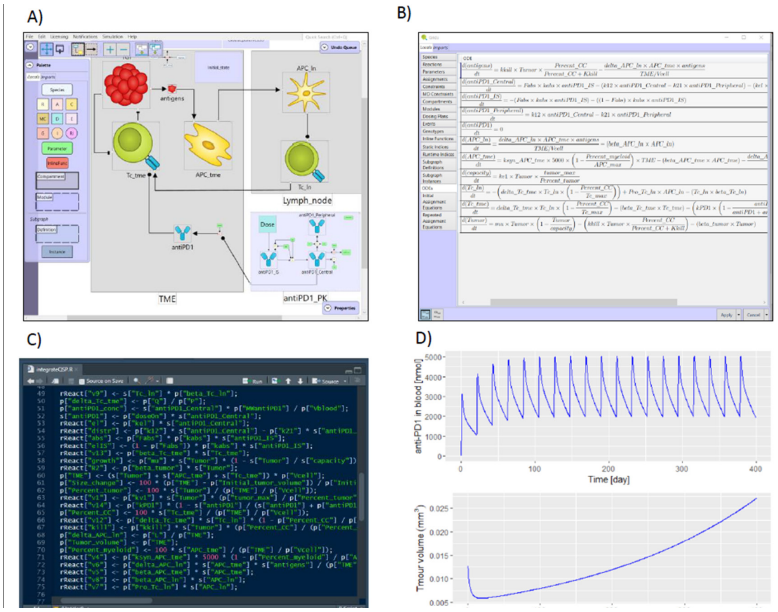
- ✔ New Modalities
- ✔ Dose Selection & Optimization
- ✔ Combination Therapy
- ✔ Compound Repurposing
- ✔ Biomarker Determination
- ✔ Target Selection
- ✔ Target Engagement
- ✔ Discovery
- ✔ Disease Triage
- ✔ Portfolio Strategy

Introducing QSP Designer

QSP Designer is the first-of-its-kind QSP tool that meets the needs of modelers and non-modelers. The backbone of the tool is the graphical user interface (GUI), which has evolved from the concept and great utility of the biological map, which is then converted into a mathematical model. All key QSP modeling functionality (virtual populations, parameters estimation, sensitivity analysis etc) are integrated into a single environment. The model is continually updated and calibrated with new data, providing ongoing 'learn and confirm' cycles with the larger drug development team. The key to collaboration and enhanced decision-making of both modelers and non-modelers is via the GUI, which democratizes QSP and gives the full team access to the tremendous power of QSP. A tutorial with three case studies is available.

Certara's QSP Designer Technology has been built in a user-driven workspace environment that enables both modelers and non-technical stakeholders to ask and answer questions about specific drug, patient, and trial characteristics.

- QSP Designer has a graphical user interface that facilitates the creation and editing of a biological process map of a given compound. This allows for close and continuous involvement of all stakeholders.
- Model reusability and exportability to any software language ensures that the final model is regulatory submittal ready.
- By seamlessly integrating QSP and physiologically-based pharmacokinetics (PBPK, using Simcyp Designer), you can answer questions related to individual patients, dose regimens, co-medication and morbidities, trial design, and issues of safety and effectiveness.



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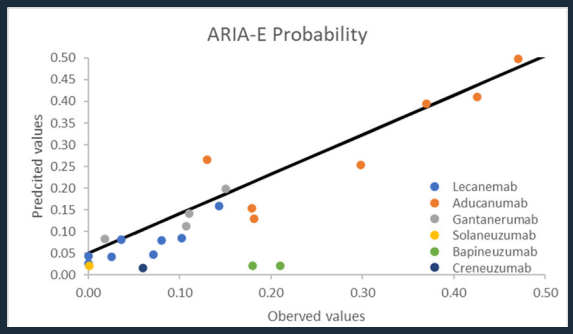
QSP Designer Case Study: Neurodegeneration platform

A complex and growing disease with a long history of drug development failures, there are currently >140 drugs in the pipeline for Alzheimer's Disease (AD). Key to success is understanding the disease and its pathology and the use of reliable biomarkers that can be used to chart patient outcomes.

Certara's virtual modeling technology (QSP) was leveraged for predicting safety and biomarker outcomes for lecanemab, the recent regulatory approved drug for AD. Based on the drug's PK properties and pharmacology, Certara's model correctly predicted efficacy biomarker outcomes and generated a new hypothesis for the relatively lower Amyloid-Related Imaging Abnormalities (ARIA-E) liability of lecanemab. The model also predicted changes in peripheral fluid biomarkers, identifying a less expensive and invasive approach to positron emission tomography (PET) scans.



Certara's QSP platform is particularly well suited to studying AD because it reflects the underlying biology of the amyloid aggregation pathway from the monomeric form to the plaque form. It is a mechanistic, realistic platform that integrates relevant biology and clinical data, and strikes a good balance between data- and mechanism-driven approaches. In addition, it allows the identification of "virtual biomarkers," which are (currently) inaccessible biomarkers driving the pathology that help to make the link to functional clinical outcomes for amyloid therapeutic agents. Today, this platform is used to predict the anticipated clinical effects of various amyloid antibodies with regard to differentiation on biomarker changes, as well as the simulation of dosing options, patient populations and trial designs.

QSP Designer Case Study: Inflammatory Bowel Disease (IBD) platform

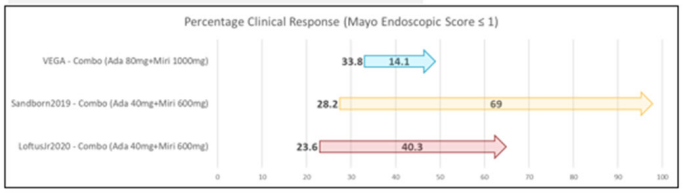
IBD is a term that describes disorders involving chronic inflammation of tissues in the digestive tract, specifically Crohn's disease (CD) and ulcerative colitis (UC). Certara built into its QSP Designer platform a mechanistic, multistate, mathematical model including key biological mechanisms in blood and gut, cell differentiation, cytokine production, and clinical biomarkers[2]. This model was used to simulate both CD and UC using the same underlying biological mechanisms and expanded with relevant biology of key cells and biomarkers in the blood and gut. The output of that model was linked to clinical endpoints to enable the investigation of targets, dosing regimen, and patient types with a novel disease activity score predictor.

Subsequently, we leveraged Certara's artificial-intelligence/machine-learning (AI/ML) technology to integrate with the mechanistic model and compared to clinical data from known therapies for these diseases. That work showed that results from public trials could be improved by increasing dose and/or adding a second therapy. The calibrated model can next be used to simulate virtual trials and virtual patients, guiding efficacious dosing regiments tailored to distinct trial characteristics. We are now using this same model for assessing novel targets for IBD and helping companies prioritize portfolio assets.

Predict Clinical Scores

Therapy	MES score probability				MES prediction
	0	1	2	3	
Untreated UC	0	0	0	**1**	3
Adalimumab 80mg	0.08	**0.75**	**0.16**	0.01	1
Mirikizumab 600mg	0.004	0.18	**0.65**	0.16	2
Ada 80mg + Miri 600mg	**0.5**	**0.48**	0.017	0	1

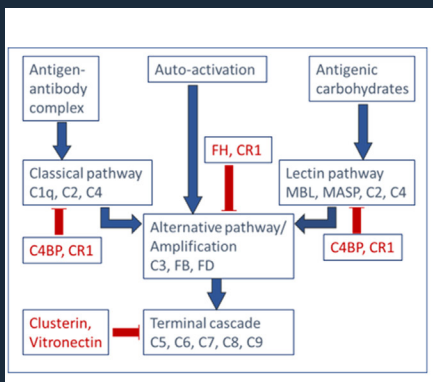
Guide Clinical Trial Design

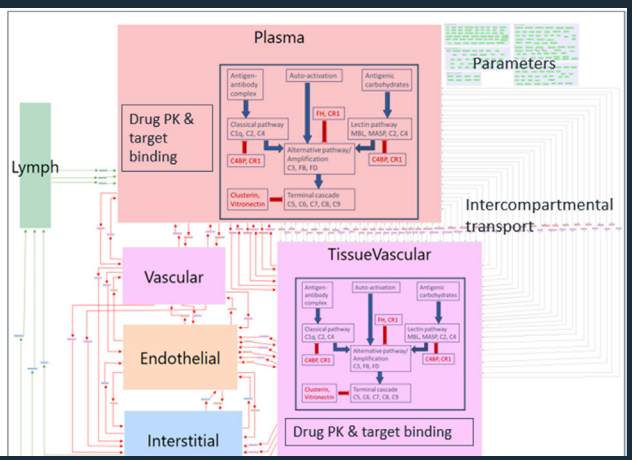


QSP Designer Case Study: Complement System platform

The front line of defense for the immune system, the complement system activates proteins to defend against injury and illnesses brought by viruses and bacteria. The proteins (about 50) that make up the body's complement system are created in the liver and move to tissue and the bloodstream. It can be activated via three different pathways: classical, lectin and alternative.

We built a mathematical model of the complement system (3 activation pathways + inhibitors) and set it in the framework of a minimal PBPK model for biologic drugs. The in vivo model was calibrated using healthy volunteer data on levels of complement components. This model can either be used to simulate ex vivo Wieslab assays or in vivo PKPD experiments, enabling the comparison of targets against competitor compounds. It offers a convenient tool to translate experimental IC50 measurements at diluted sera to physiological serum concentrations. It can be used to aid lead optimization, as in silico studies can be used to predict the impact of different binding properties of drugs on pathway inhibition. The model can be easily extended to include disease-like state in vivo and can be calibrated with systemic biomarker readouts in healthy vs diseased states.





Summary: Unlocking Drug Development's Future with QSP Designer

Certara's QSP Designer redefines the landscape of drug development by seamlessly merging computational brilliance with biological insights. This groundbreaking tool not only simplifies the complexities of QSP but also democratizes its understanding. With an intuitive graphical interface, QSP Designer empowers both seasoned modelers and non-experts to explore intricate drug interactions, predict clinical outcomes, and optimize therapeutic approaches. By facilitating collaborative decision-making and real-time data updates, QSP Designer isn't just a tool—it's the key to a future where innovation knows no bounds and where every drug development decision is fortified with unparalleled knowledge. Welcome to a new era of pharmaceutical exploration, where Certara's QSP Designer stands as the guiding beacon into uncharted scientific territories.

References

1. Matthews, R, Hollinshead, D, Morrison, D, van der Graff, P, Kierzek, A. "QSP Designer: Quantitative systems pharmacology modeling with modular biological process map notation and multiple language code generation," CPT Pharmacometrics Syst Pharmacol. 2023; 12:889-903

2. Rogers et al. 2021. https://doi.org/10.1111/cts.12849)

About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions and regulatory agencies across 62 countries.

For more information, visit **www.certara.com**.