CERTARA

Gene Therapy Platform using Certara's Virtual Twin™

Proven, *In-silico* Dose Optimization Technology for Gene Therapies

The Promise of Gene Therapy

Gene therapy, the replacement of defective genes with healthy ones, holds enormous promise for addressing the millions of patients with genetic-based diseases. Gene therapy works by replacing a gene that is missing or dysfunctional or turning off genes that are causing medical problems. Oftentimes, the defective gene is missing from birth, but it can also mutate later in life. Gene therapy can be a one-time treatment which would permanently change the medical health of the patient. It does this by reversing or halting the disease, eliminating the underlying cause of that disease. Gene editing, which directly edits pieces of DNA within the cell is a type of gene therapy.

Key Challenges in Gene Therapy Drug Development

As gene therapy is a new drug modality, successful development requires new types of expertise:

- The inherent manufacturing challenges in gene therapy can slow clinical trials,
- As many gene therapy candidates are for rare disease, patient recruitment can be difficult,
- Working with regulators and gaining approval for novel clinical plans is often a new paradigm,
- The single-dose delivery of gene therapy cannot be determined using traditional dose determination methods, such as PK/PD,
- Dose escalation with each patient is not feasible because of the immunogenicity response.

Getting the Dose Right

In most cases, you have one chance to deliver gene therapy to a patient. Considered personalized medicine, each 'therapy' is based on individual patient data detail to repair or enhance faulty genes. Because each patient is different, the dose and administration of that gene therapy must differ as well. So, if you are too cautious and give too low a dose, a patient may not receive any benefit of the treatment. On the other hand, giving too high a dose can be very dangerous, since any side effects may be irreversible and may last for years if not decades. In short, the definition of a narrow therapeutic index takes on a completely new meaning in gene therapy.

Dose selection for gene therapy is like hitting a bullseye—too little will inhibit efficacy and too much can cause a serious safety issue.

Certara's QSP Virtual Twin Technology

Certara's Virtual Twin technology creates a computer-simulated model of each patient, replicating the patient's various attributes that affect a drug's fate in their body and hence its effects. Virtual Twin allows drug developers and clinicians to predict the optimal drug dosing regimen for an individual patient – one that maximizes therapeutic benefit while minimizing side effects – by evaluating the impact of different drug doses, schedules, and combinations in the patient's *in silico* 'virtual twin' first. This technology is a component of Certara's industry-leading Simcyp™ physiologically based pharmacokinetic (PBPK) and quantitative systems pharmacology (QSP) platforms, and has determined dosing and other label claims on many approved novel drugs.

There are currently >3,000 IND submittals for cell and gene therapy under FDA review. Each IND must include a projection for pharmacologically active doses in humans and provide input into the first-in human (FIH) dose selection. Certara's QSP-based biosimulation in silico models focus on biological effects rather than clinical safety margins across these new modalities, benefiting:

- Translational research: pre-IND
- Guiding FIH dose selection
- Selection and application of biomarkers
- Predicting immunogenicity
- Addressing the needs of special populations (i.e. pediatric and geriatrics)
- Optimizing trial design through virtual patients
- Precision dosing using virtual twins
- According to the IQ Consortium of leading pharmaceutical companies: QSP/Model Informed Drug Development can:
  - Accelerate regulatory approval by as much as 2 years
  - Reduce cost of drug development by $30-70M

Gene Therapy Case Study Using Virtual Twin

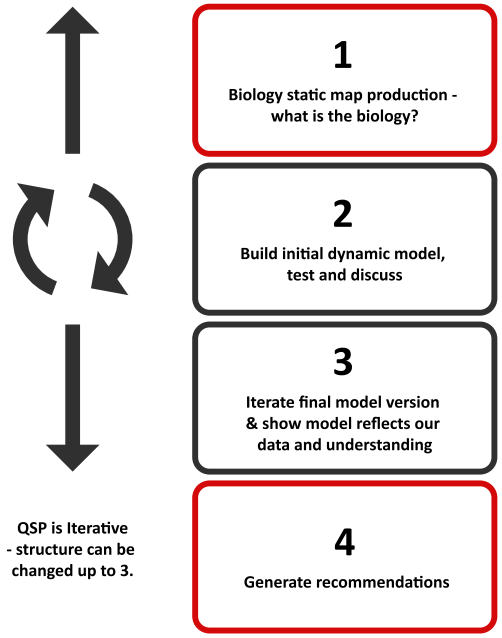
A mechanistic model (using QSP) gene therapy platform was developed and further adapted for the rare disease treatment under investigation. Inputs to the platform included patient morphology factors such as age, including pediatrics, gender, weight, height and varying doses. We then predicted organ and plasma volumes from the morphology as well as several uncertainty factors and ran the simulations in the platform. Based on those outcomes, we provided individualized dosing recommendations (from virtual twin) tested in early clinical studies. Each of these dosing predictions were successfully applied to individual patients in the phase 1/2 trial. The model was then used to generate virtual trials to determine the dosing approach for the phase 3 clinical study submitted within the regulatory package.

> "Traditional PK study designs are generally not feasible for CGT (cellular gene therapy) products; thus, such data are not available to guide clinical trial design. Due to various issues, such as species specificity and immunogenicity, extrapolation from a CGT product dose administered in animals to a clinical dose can be less reliable than the customary allometric scaling typically used for small-molecule pharmaceuticals."
>
> *- per US FDA guidance*

Application Across a Range of Gene Therapy Modalities

QSP predictive modeling is applied to answer a specific development question but can grow in value throughout the lifecycle of programs using a regulatory-approved 'learn and confirm' approach. A typical gene therapy program is initially focused on guiding translational research with regards to human efficacious dose/dose regimen selection and therapeutic index, incorporating any biomarker information. Programs begin with the creation of a detailed biological map that graphically represents all compartments, variables and interactions. Pre-clinical data—in vitro, mouse, non-human primate and other is integrated into these bottom-up predictive models. The approach used has been applied across a range of gene therapy programs, including:

- AAV based gene therapy
- Ex-vivo, in vivo, in situ
- Lysosomal storage
- LNP-based RNA
- Gene editing
- CRISPR/Cas9
- CAR-T

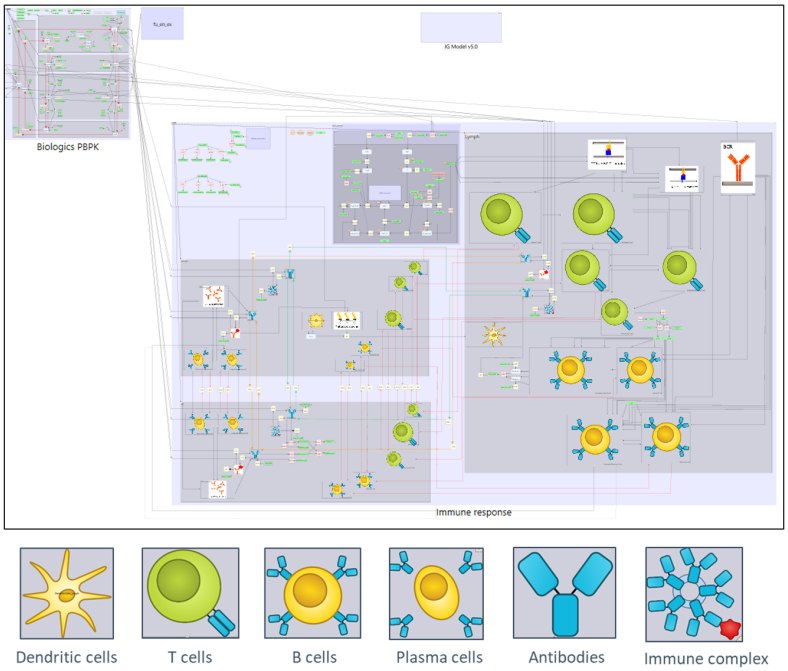


Certara's model development process

Addressing Immunogenicity (IG)

Undesired immunogenic response to AAV vector administration is one of the major challenges in gene therapy development programs. A patient's humoral antibody immune response against the viral vector can prevent entry into cells and establishment of therapeutic gene expression. Moreover, immune memory typically prevents repeated administration of the therapy to the same patient. Development of a cellular immune response to the vector has been associated with loss in transgene expressing cells.

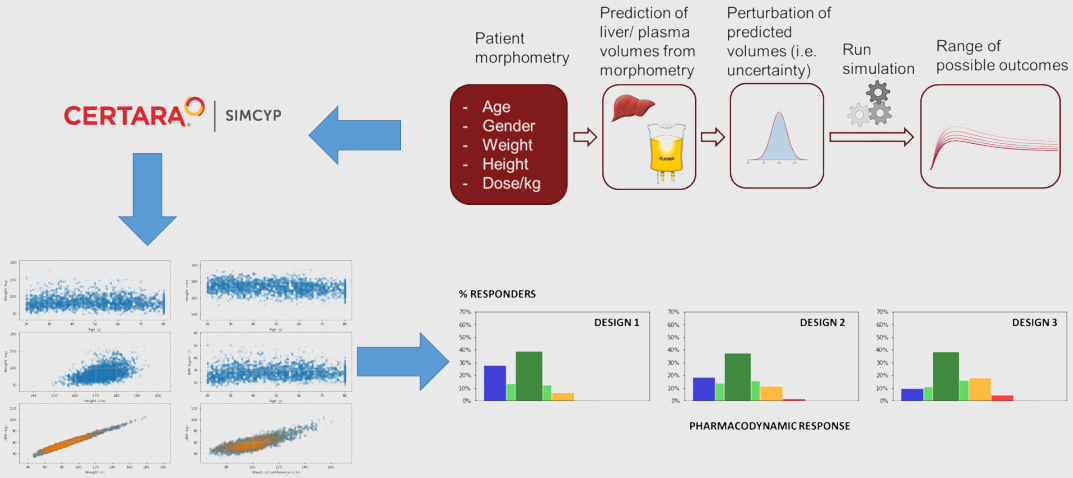
Certara's IG Simulator has been developed for the prediction of the anti-drug antibody response to therapeutic proteins and has also been used to predict the clinical response to >20 biological products, including gene therapy and COVID-19 vaccines. The IG Simulator, which was developed with seven leading pharmaceutical companies via a consortium was expanded to enable the prediction of antibody and cellular anti-capsid immune response. The US FDA is a licensee of the IG Simulator.



Variables	Lymph compartment	Vascular compartment	Plasma compartment
T cells	Naïve	Naïve	Naïve
	Activated from naïve	X	X
	Memory	Memory	Memory
	Activated from memory	X	X
	Functional	Functional	Functional
B cells	Naive	Naive	Naive
	Activated from naive	X	X
	Memory	Memory	Memory
	Activated from memory	X	X
DC cells	Matured	X	X
	Immature	Immature	X
ADA	IgG	IgG	IgG
	IgM	IgM	IgM
IC	IgG-Ag	IgG-Ag	IgG-Ag
	IgM-Ag	IgM-Ag	IgM-Ag
Plasma cells	X	Long-lived	Long-lived
	Short-lived	X	X
Main modules of IG simulator			
• Minimal PBPK model • Bioinformatics input • Antigen presentation module (MHCII) • Cells circulation across compartments • Antibodies circulation across compartments • Antibody affinity maturation			

Certara's IG Simulator – Integrated with Gene Therapy Platform

Real-time, iterative and personalized dosing using Certara's Virtual Twin™ technology for gene therapy is here



The QSP model enabled us to create virtual twins to individualize the dosing for each patient and simulate virtual trials exploring different dosing regimens and trial designs. This QSP model-informed precision dosing approach was validated with real patients in early clinical trials and used for dose selection in phase 3 trial design.

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**.