How to Ensure Your QSP Model is Useful – Illustrative Examples and Lessons Learned

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Rosa Impact Webinar Series

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What is Quantitative System Pharmacology (QSP)?

Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms

An NIH White Paper by the QSP Workshop Group – October, 2011

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Quantitative and Systems Pharmacology (QSP) is an emerging discipline focused on identifying and validating drug targets, understanding existing therapeutics and discovering new ones. The goal of QSP is to understand, in a precise, predictive manner, how drugs modulate cellular networks in space and time and how they impact human pathophysiology. QSP aims to develop formal mathematical and

ultimately span knowledge of molecules, cells, tissues and patients will be particularly critical for pre-clinical and clinical research teams evaluating target selection and testing therapeutic proof of concept. QSP draws on several existing disciplines, including classic pharmacology, chemical biology, biochemistry and structural biology, molecular genetics and genomics, pathology, applied mathematics, and medicine, and has an intrinsic and extensive experimental component that incorporates approaches

approaches. QSP will accelerate drug discovery and development by helping to identify and validate targets (and druggable) networks, uncover drug-response biomarkers, design better drugs and drug combinations, select appropriate doses and dosage regimens and identify those patients most likely to respond to new therapeutic agents and combinations. It will therefore become a core discipline of

www.rosaandco.com/uploads/primary/QSP-What-is-in-it-for-me-and-case-studies.mp4

(Dr. Valeriu Damian, GSK)

QSP helps reduce risk by improving understanding of how drug activity influences clinical outcomes.

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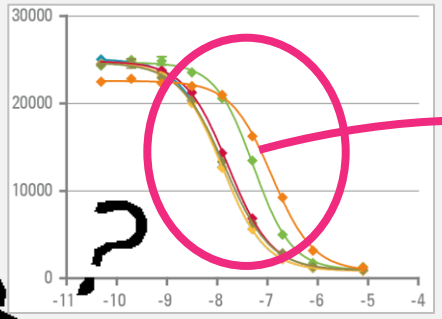
Preclinical Evidence



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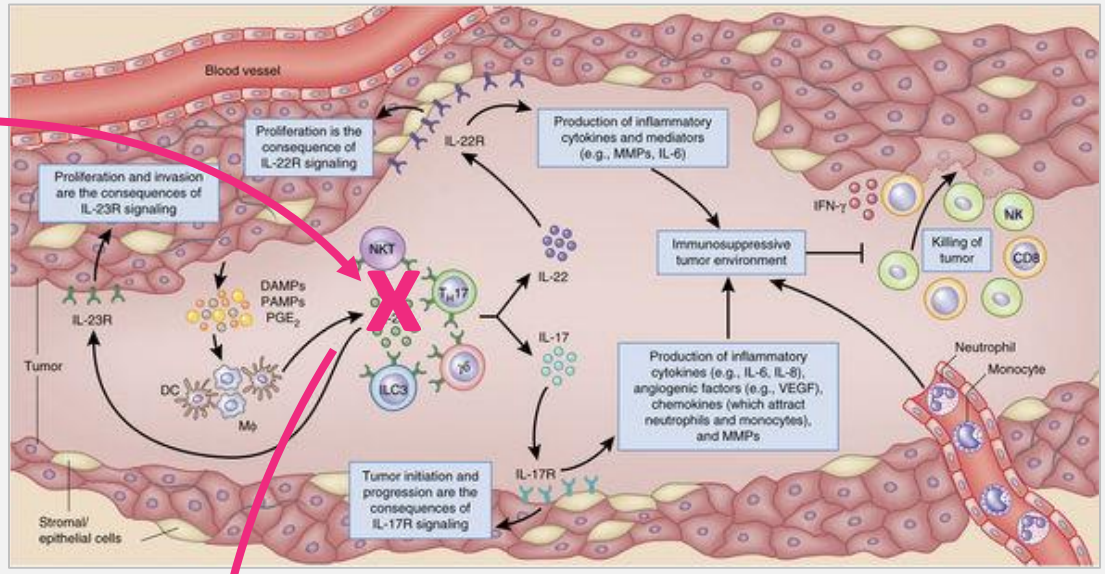
Mechanistic Understanding



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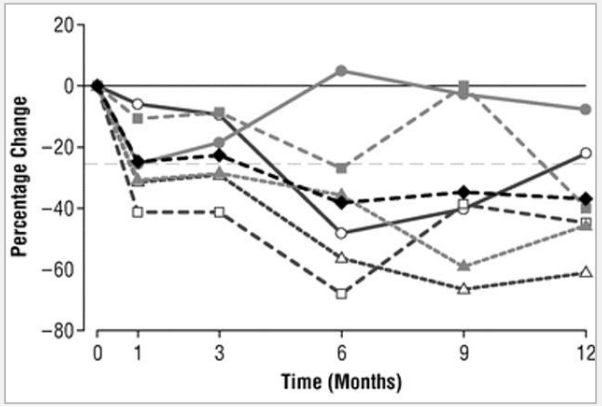
Clinical Outcome



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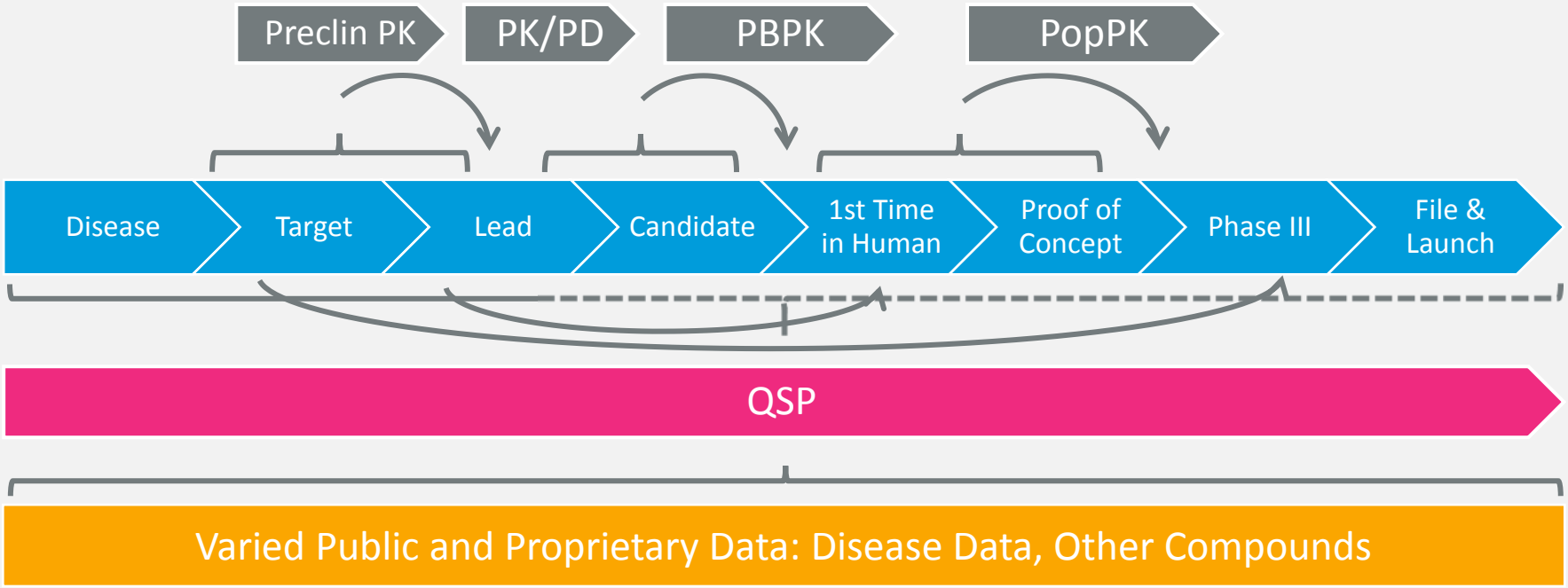
Mechanistic QSP models are especially helpful for evaluating novel scenarios before data are available.

- Other modeling techniques use data generated during development to inform next steps



- QSP modeling draws on a broader range of data to support farther extrapolation
  - E.g., prioritize targets by potential clinical efficacy given everything else we know

Mechanistic QSP Research: Elucidating Mechanisms Reduces Risk.

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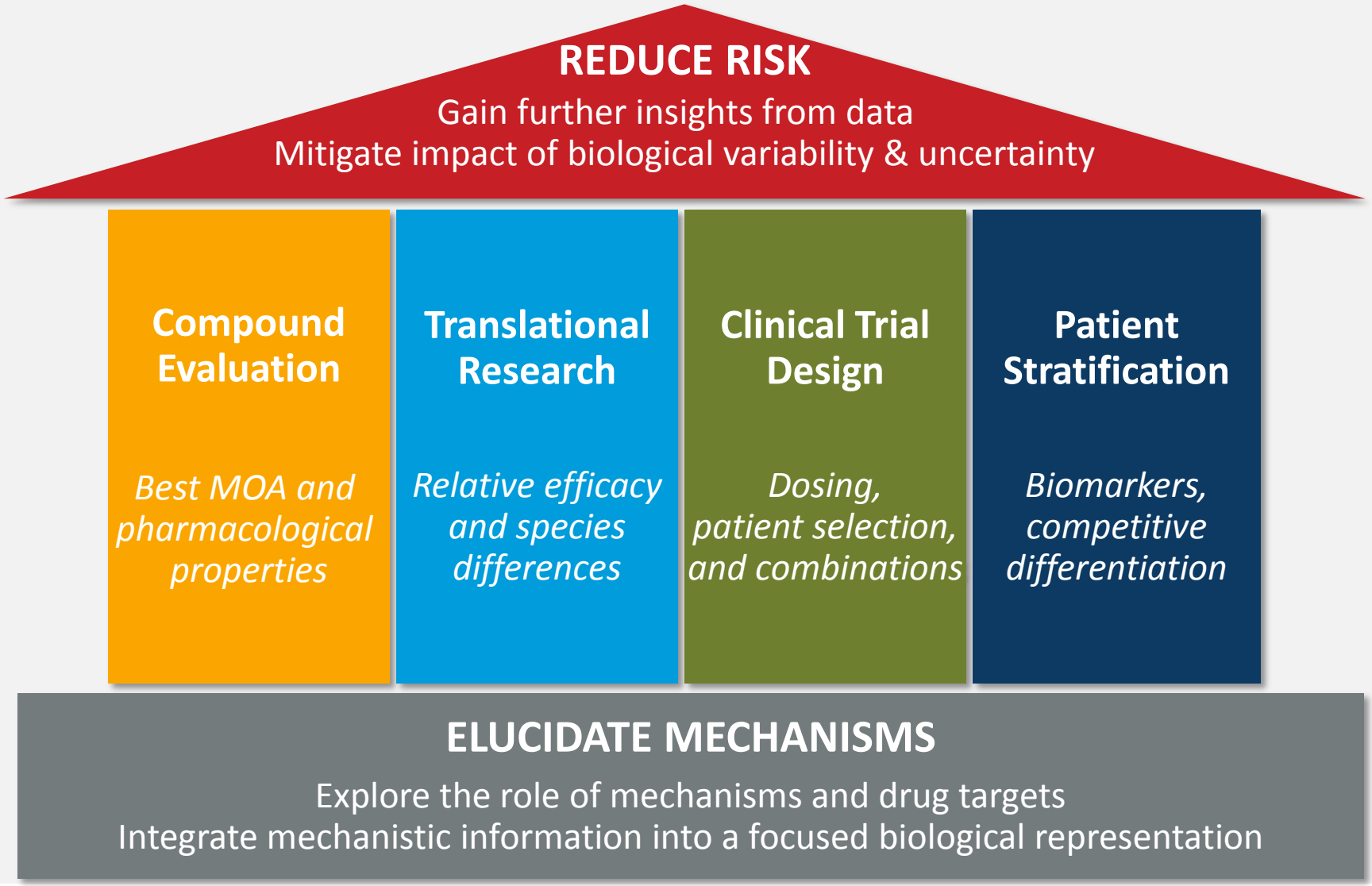
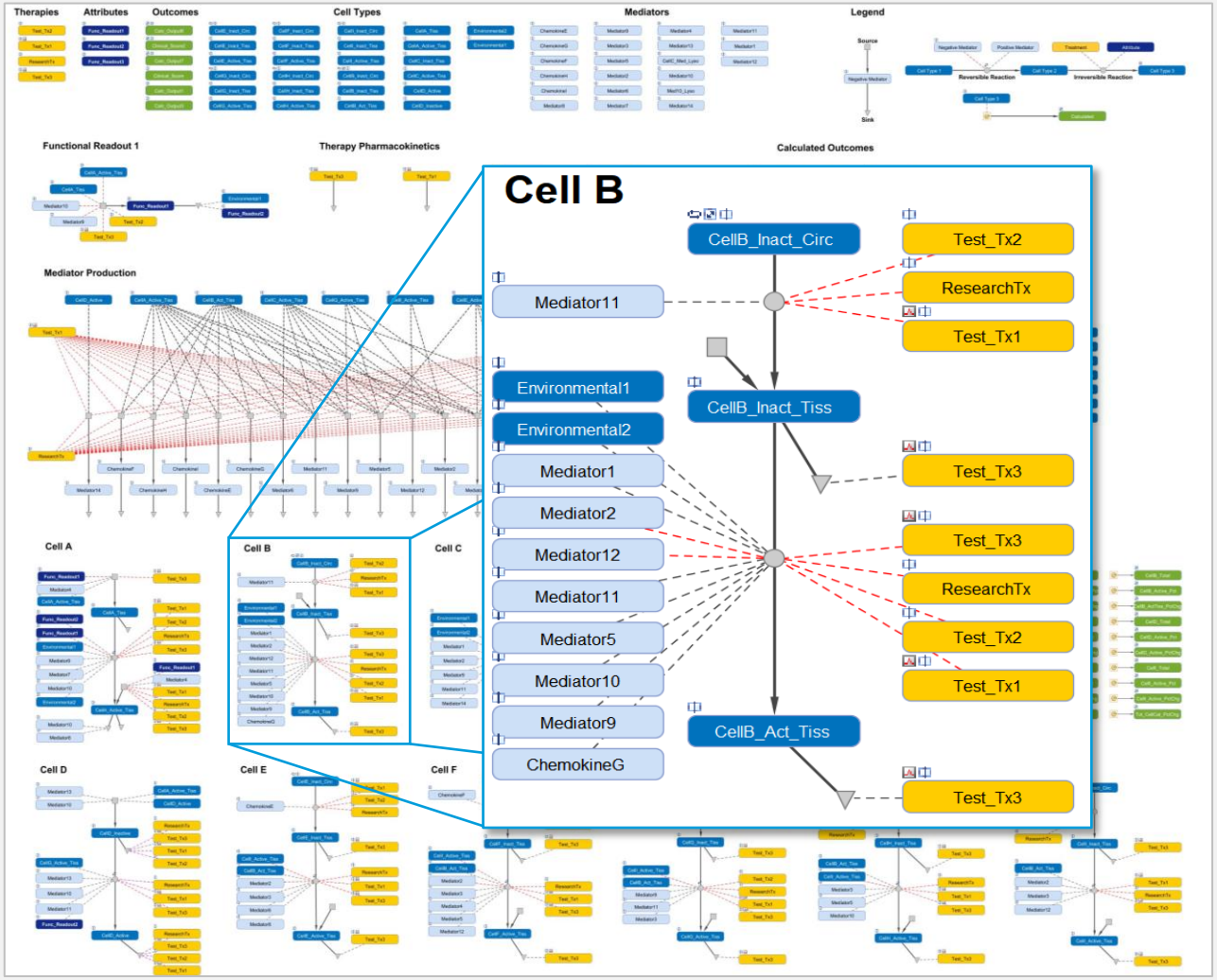


This example mechanistic QSP model includes cells, mediators, and therapies of interest.



Example PhysioMap and PhysioPD Platform are implemented in MathWorks' SimBiology software.

Strategies to avoid common failure modes and inefficiencies.

1. *Focus on scientific understanding, not just on data points*
2. *Right-size your model to answer your question*
3. *Explore biologically informed hypotheses of variability, not just error bars*

The goal of mechanistic modeling is to understand.

- Fitting all data does not guarantee a good model
- Mechanistic models should reflect scientific understanding, not just fit data points
  - Decisions should be guided by scientific insight
- Life science experts are essential for this goal
  - Trained in identifying, interpreting and contextualizing data
  - Can compare model fidelity to the scientific state of knowledge
  - Can help avoid missing the forest (knowledge and understanding) for the trees (data)
- Improved mechanistic understanding supports extrapolation to new scenarios

Various types of data are used in model development.

Data type	Used for…	Check that…
In vitro/ ex vivo data	• Choosing equation forms • Setting parameters • Subsystem testing (e.g., cell numbers)	• Parameters are physiological • Model subsystems match data
Animal model data	• Understanding disease mechanisms • Qualitative testing	• Model response is qualitatively consistent with expectations
Untreated disease	• Qualitative and quantitative testing	• Model simulation with no treatments reproduces outcomes and biomarkers
Clinical treatment data (marketed and test compound)	• Qualitative and quantitative testing	• Model simulation with treatment (PK and MOA) reproduces outcomes and biomarkers

- Data are vital for building understanding
- Data from disparate sources may not fit together seamlessly

Example: Taking in vitro data too literally can lead you astray.

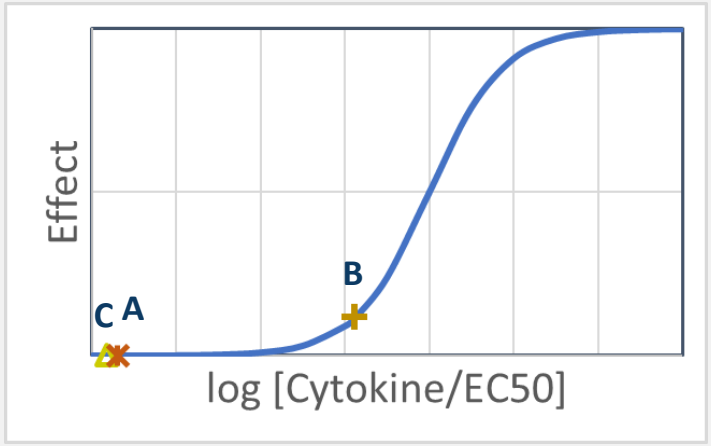
Tissue concentration data

Mediator	Tissue Concentration	Reference
Cytokine A	2×10^{-1}	Pub 1
Cytokine B	8	Pub 2
Cytokine C	3×10^{-2}	Pub 1

EC50 values for downstream effect of cytokines

Mediator	EC50	Reference
Cytokine A	1×10^{3}	Pub 3
Cytokine B	6×10^{1}	Pub 3
Cytokine C	2×10^{2}	Pub 4

Tissue concentration on dose response



Can we conclude with confidence that cytokine B is driving the effect in vivo?

- Consider assay conditions – often designed to show relative effects, not absolute levels
- Cross-reference absolute AND relative values
  - E.g., is cytokine B consistently expressed at ~300x higher level than cytokine C?
- Look for related data (e.g., how does inhibition of each cytokine affect the effect?)

Lesson 1: Build the model to facilitate understanding, and let this guide your use of data.

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- Use scientific judgment, consider big picture, draw on context from other diseases
- Do not treat in vitro data as gospel – at best, it's an approximation of truth!
- Make use of sub-system constraints
  - E.g., rates of cell proliferation, recruitment, and clearance must balance out to produce the appropriate cell numbers
- Cross-check data and model against multiple different protocols
- Use qualitative testing if data are not appropriate for quantitative testing
  - E.g., for related but not identical population, animal models, or for what-if scenarios
- Communicate model results in scientific terms, avoid modeling speak

Strategies to avoid common failure modes and inefficiencies.

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"Can you build me a model of disease X?" is the wrong question

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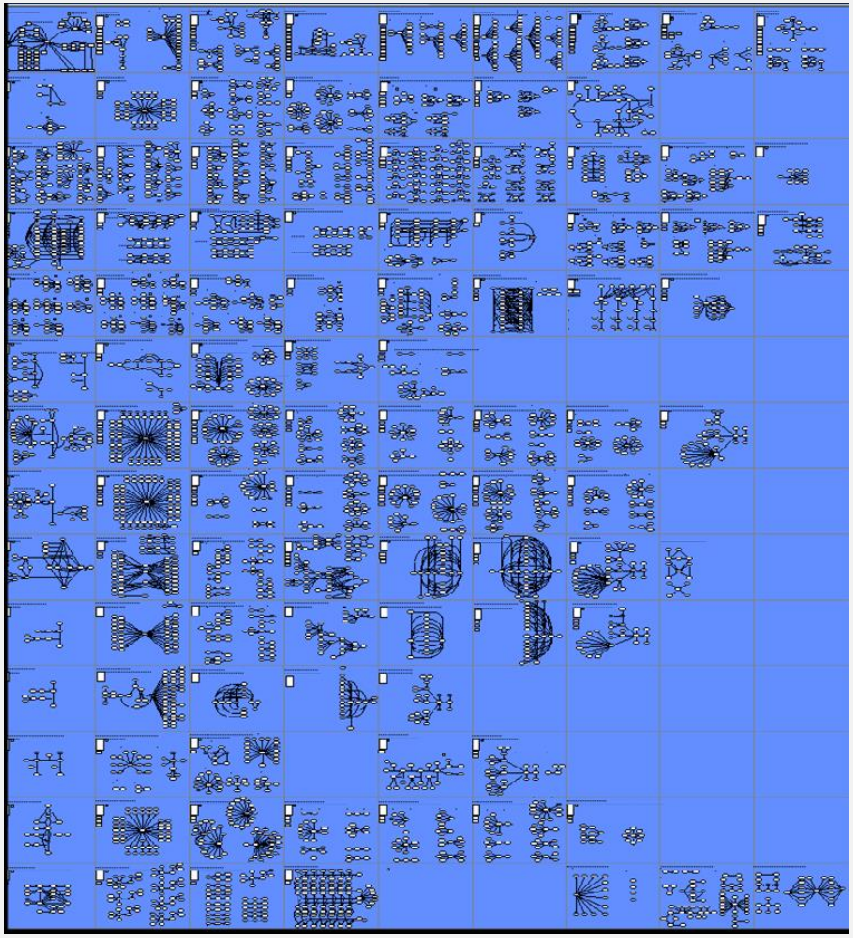
- To build a useful model, modelers must understand the research context
  - What are your research questions?
    - What decisions do you need to make?
  - What data are available to inform the research?
  - How much time do you have?

- Develop the most parsimonious model for the research context
  - Answers the question in the shortest time possible
  - Easier to communicate so results will be actionable

- Rosa has built models for a wide variety of research contexts
  - Diabetes models ranging from 12 to >80 ODEs
  - Rheumatoid arthritis models ranging from 11 to >60 ODEs
  - IO models ranging from 10 to >100 ODEs

How big is too big?

Entelos Rheumatoid Arthritis PhysioLab®



- Depends on the research context
- Models of this scale may be impractical for most purposes
  - Long development time
  - May miss opportunities to influence program decisions
  - Lack of focus on a research context makes simplifying assumptions more difficult to explain and defend
  - Simulation times may be prohibitive

If the biology is so complicated, how can you make the model simpler?

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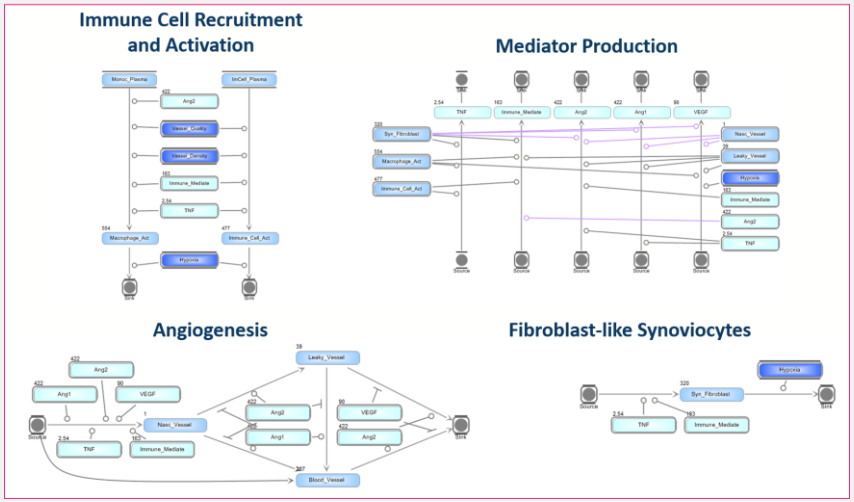
- Scope can be managed by:
  - Focusing on biological species that play a key role in pathophysiology and/or response to treatment
  - Grouping species functionally, e.g., “pro-inflammatory mediators”
  - Modeling one prototypical site, e.g., one joint in RA, one patch of skin in dermatology
    - Mechanistically informed extrapolation to clinical level outcomes is usually possible
  - Modeling on relevant time scales, e.g., assume equilibrium solutions for fast processes

- All scope decisions are made with consideration of the research context

Can a model be too small?

- This version of an RA model focused on the differences between anti-TNFα and a bi-specific antibody
- This model was built and yielded insights on a timeframe relevant for program decisions
- It would have been “too small” for a broad-ranging exploration of possible new RA targets
  - Note, however, that mechanistic models can be expanded as needed, e.g. to add detail for a new target

A Rheumatoid Arthritis PhysioPD Research Platform Developed by Rosa with MedImmune



Lesson #2: First figure out the research context, then design the model scope.

- Clarity about the research context helps limit scope
  - A written description of the research context is helpful to ensure team alignment

- A mechanistic model intended as a broad program support platform generally merits larger scope and greater detail than a model built for a focused investigation

Strategies to avoid common failure modes and inefficiencies

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3. *Explore biologically informed hypotheses of variability, not just error bars*

Mechanistic models offer an opportunity to elucidate mechanistic causes of clinical response variability.

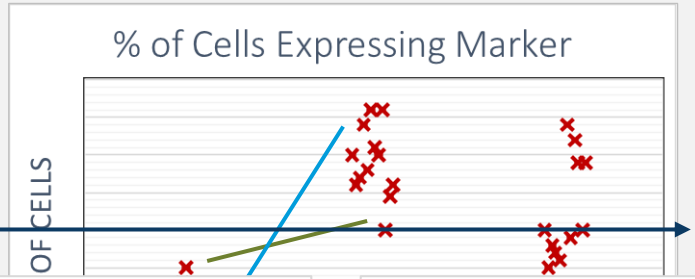
- Will more people respond better to new drug A than to standards of care (SOCs)?
- This may depend on:
  - PK and compound properties
  - The **underlying mechanistic causes of variability** in response to SOCs
  - The **expected mechanistic causes of variability** in response to drug A
- Mechanistic causes of variability may not be fully known, even for SOCs
- The question is not, is my model the best model for describing existing SOC data…
- …the question is, **do my simulations account for mechanistic variability that may impact response to drug A?**
- Effective exploration of mechanistic variability means testing biological hypotheses
  - Variability at the parameter level alone may not capture mechanistic diversity

Example: Hypothesis supported by biomarker data was used to create a mechanistically diverse Virtual Population.

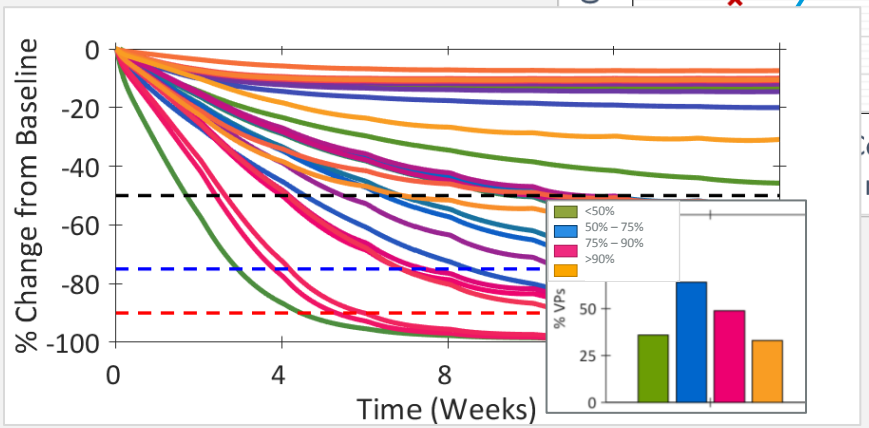
Hypothesis: Patients with highly polarized expression of A vs. B are mechanistically different from less polarized patients

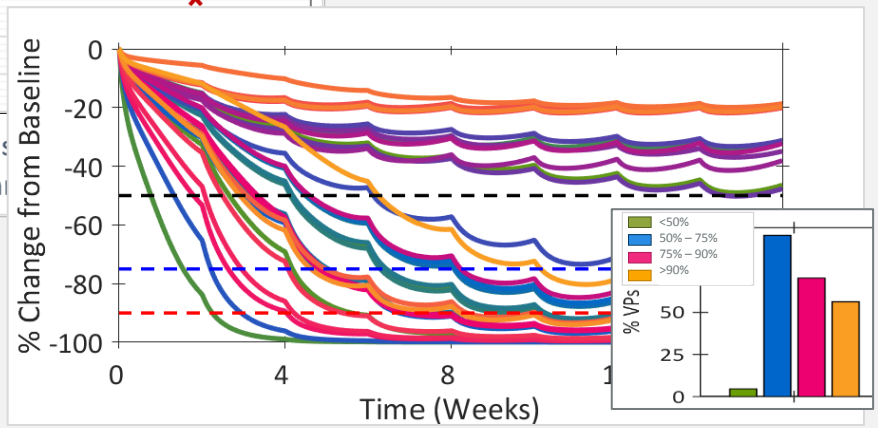
Created VPs with variability in cell type distribution (and other scientifically supported differences)

Simulated responses of VPs to SOCs match clinical data



Simulated responses of VPop to drug A reflect mechanistic hypotheses





- The Virtual Population reproduced variability seen for marketed treatments AND the variability reported in the biomarker biopsy data
- The mechanistic model connects the biomarker data to response to drug A and allows you to anticipate responder/ non-responder behaviors

Lesson #3: Alternative mechanistic hypotheses are not just error bars.

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- Inter-subject biological variability can create a range of responses to therapies
- Mechanistic models offer an opportunity to understand sub-classes of patients
- Mechanistic modeling should focus on identifying biological modulators of response to therapies and creating Virtual Patients that:
  - Are as mechanistically different as possible while still meeting data constraints
  - Jointly reproduce the range of responses seen in existing clinical data
- Parameter-level variability and statistical sampling can be introduced on top of the mechanistic variability as desired for additional analysis

Summary: Three Strategies for Success

- Mechanistic QSP models should reflect biological understanding
  - Putting data together is not enough – knowledge and hypotheses must play a part
  - Uncertainties and assumptions should be documented and assessed for impact
- Clarity about the research context will help you select the right scope
- Use virtual patients to explore meaningful mechanistic diversity, not just to create error bars

The Model Qualification Method (MQM) is a framework to implement strategies for success.

- Focus on relevance to research context ensures efficiency
- Systematic qualification ensures credibility and impact

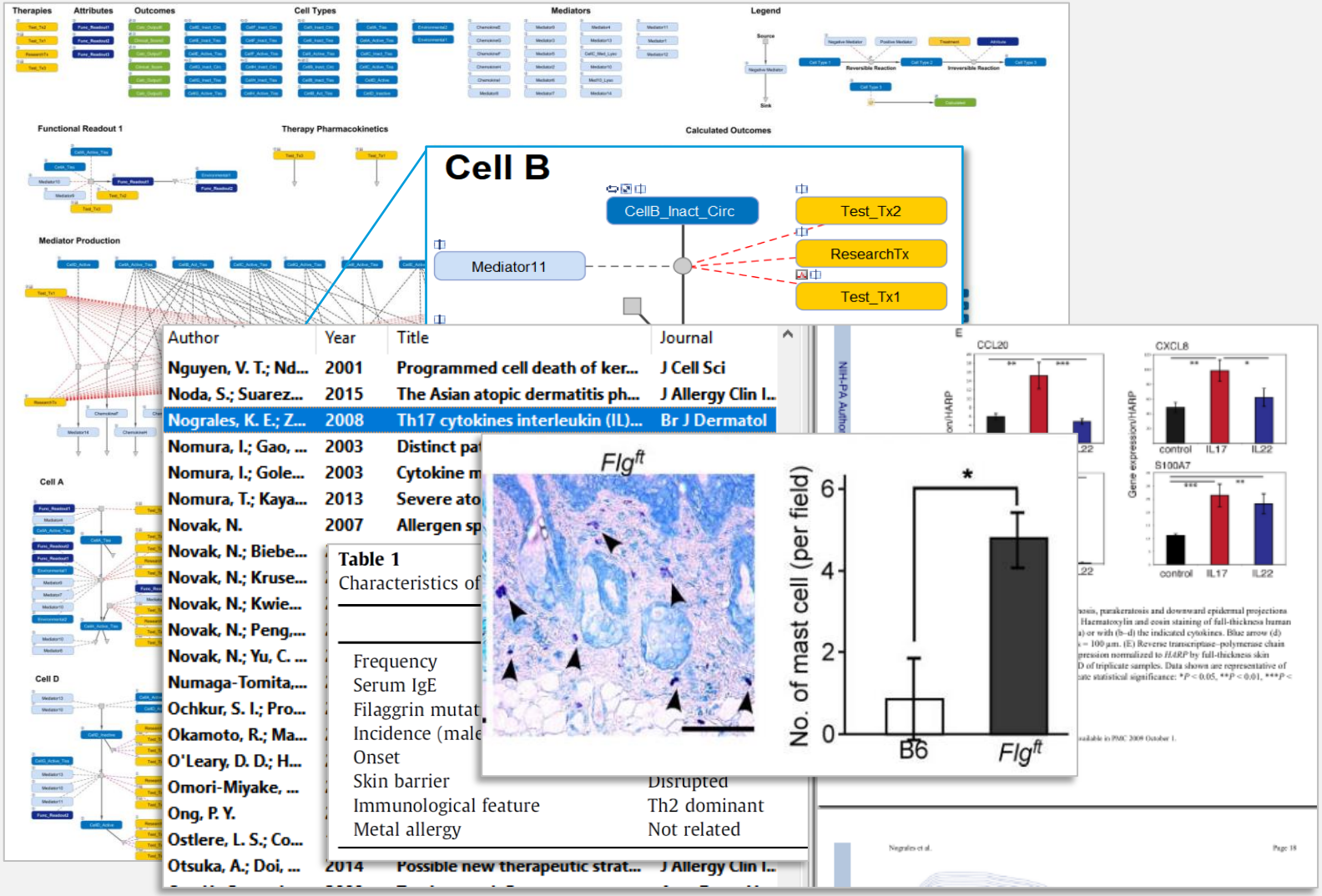
Reference: Friedrich, C. M. (2016). CPT: Pharmacometrics & Systems Pharmacology **5**(2): 43-53. PMID:26933515

https://www.rosaandco.com/uploads/primary/Rosa-MQM-webinar.wmv (2011)

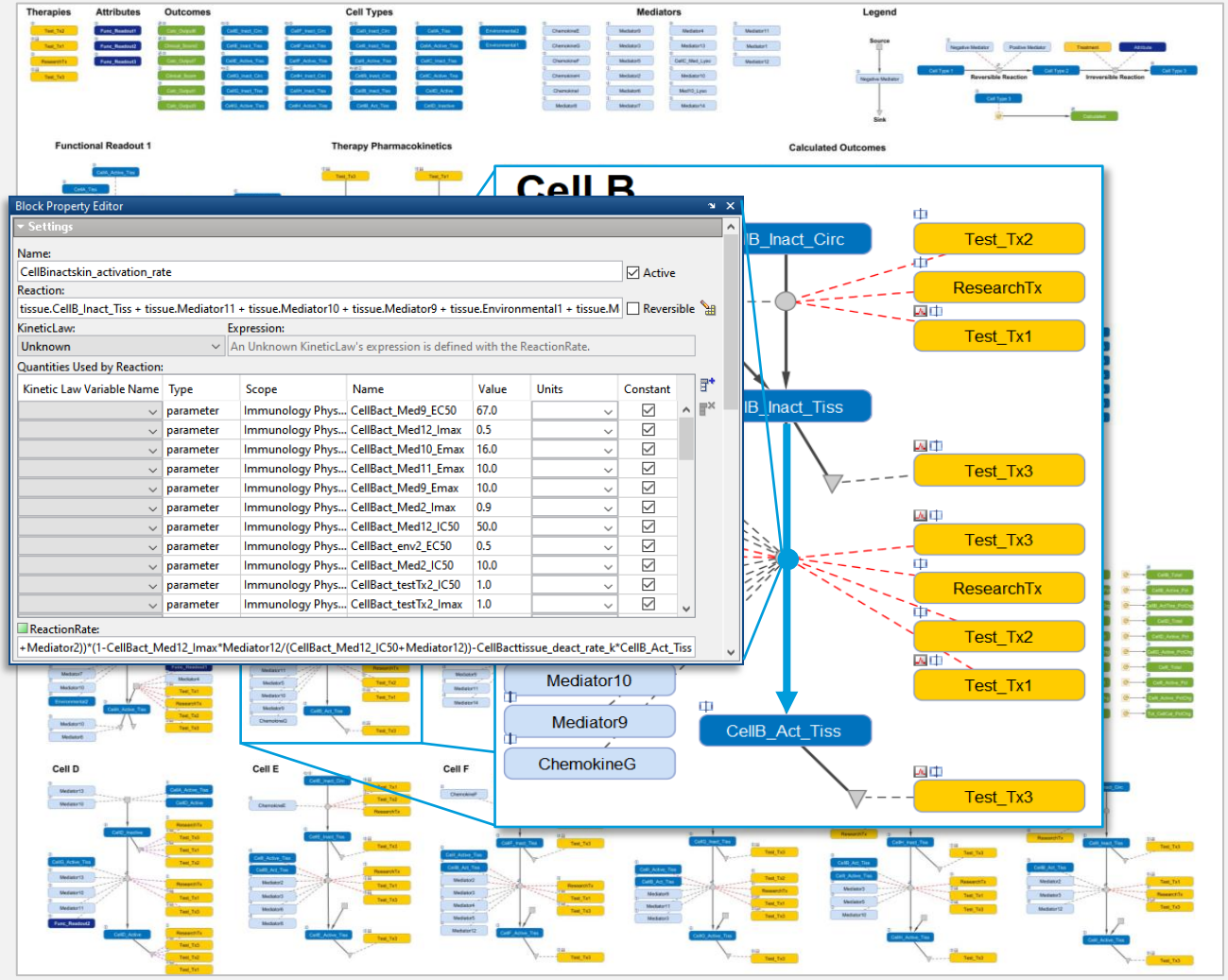
https://www.rosaandco.com/uploads/primary/MQM-Learnings-webinar.wmv (2013)

THANK YOU

Extensive literature research informs the development at every stage.



PhysioPD™ Research Platforms combine PhysioMaps® with embedded mathematical relationships.



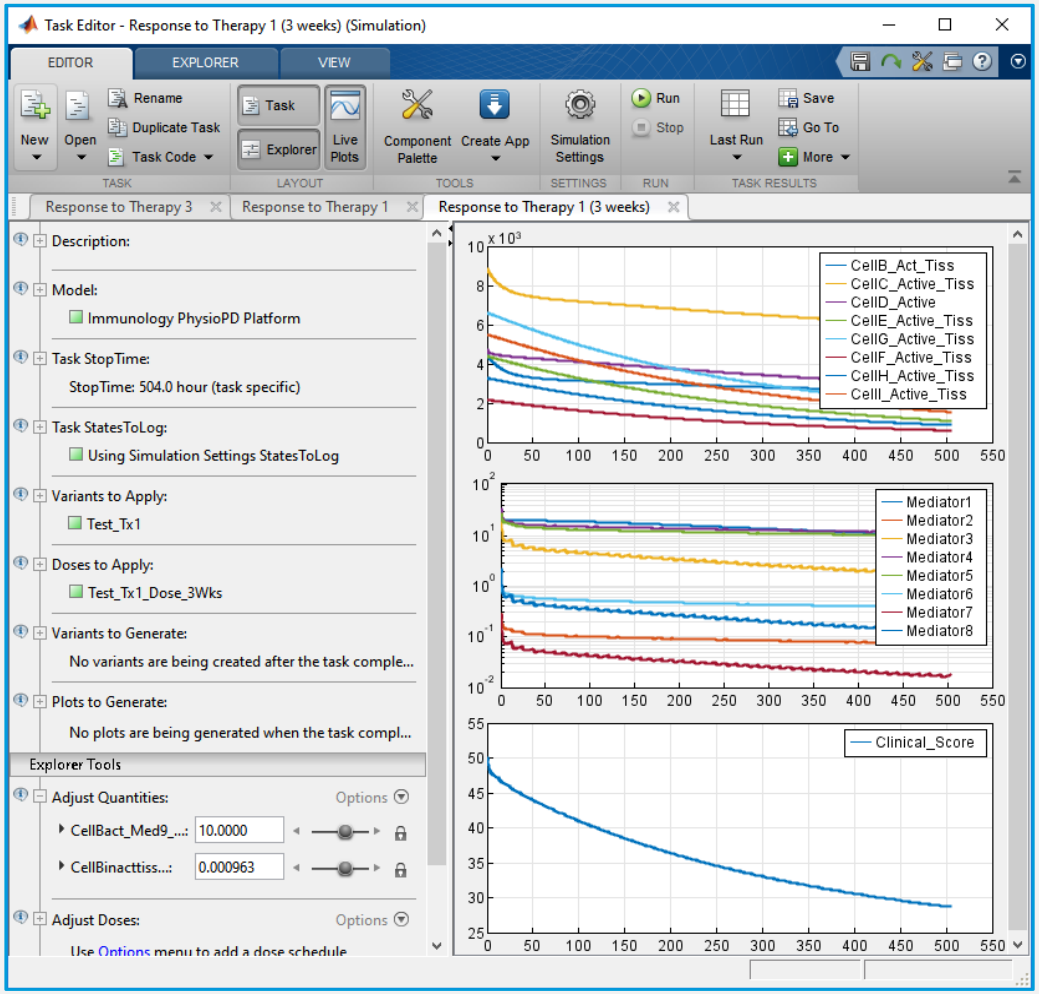
Virtual experiments are used to simulate known and novel protocols.

How do I know that the model responds like a real patient?

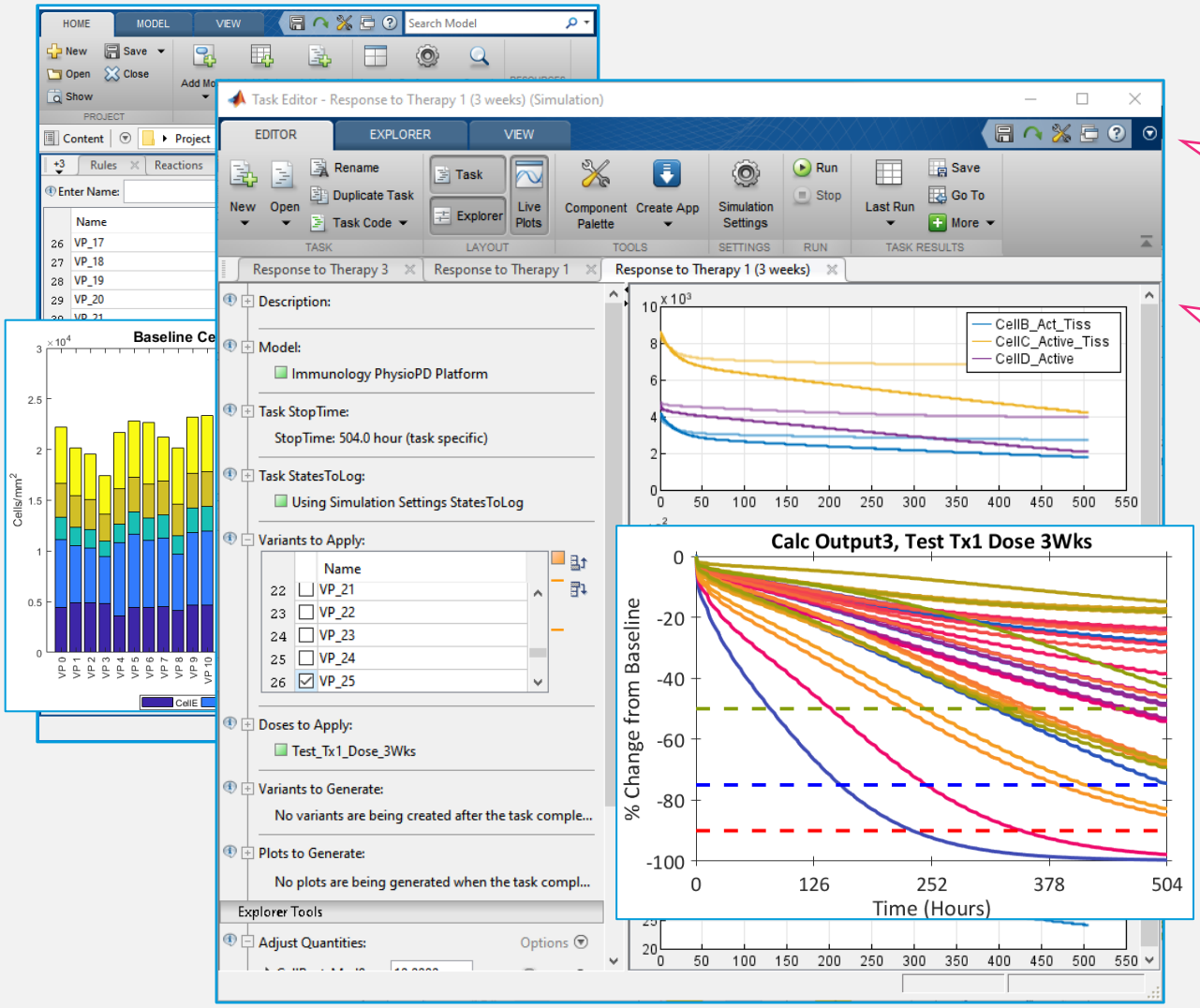
Encode known protocols and check the results!

Can I simulate "what if" protocols?

Yes!



Virtual Patients are used to explore variability and alternate hypotheses.



How do I explore biological variability?

What if parts of the biology are not known?

Explore multiple Virtual Patients!

Virtual Patients (VPs) facilitate exploration of how mechanistic differences affect outcomes.

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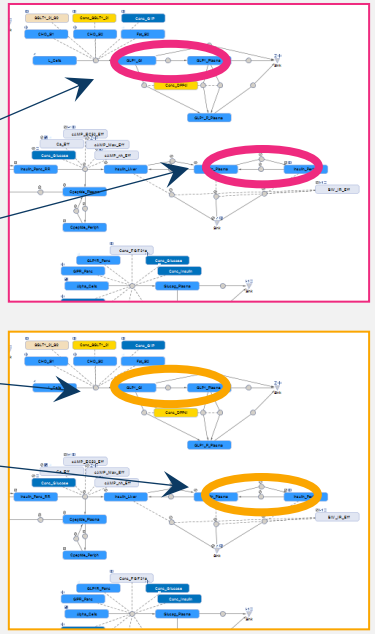
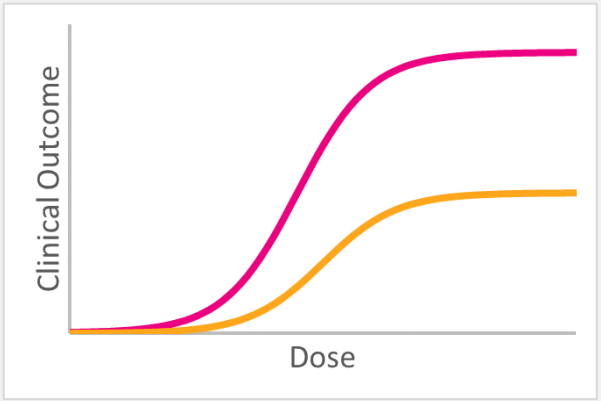
Virtual Patients



Mechanistic differences between VPs relevant for the research context

Outcomes



Example questions to explore:

- What preclinical experiment is highest priority?
- What biomarkers may be most informative?
- What patients are likely to respond?