Drug Development Advisors

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Mechanistic Physiological PhysioPD™ Models in Drug Development: A Proven Quantitative Systems Pharmacology (QSP) approach

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7th Annual Shanghai Symposium on Clinical and Pharmaceutical Solutions through Analysis

Innovative Approaches to Reduce Attrition and Predict Clinical Outcomes

Renaissance Shanghai Pudong Hotel
Shanghai, China
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Agenda

- High Level Overview of Rosa and PhysioPD Platform Creation Process

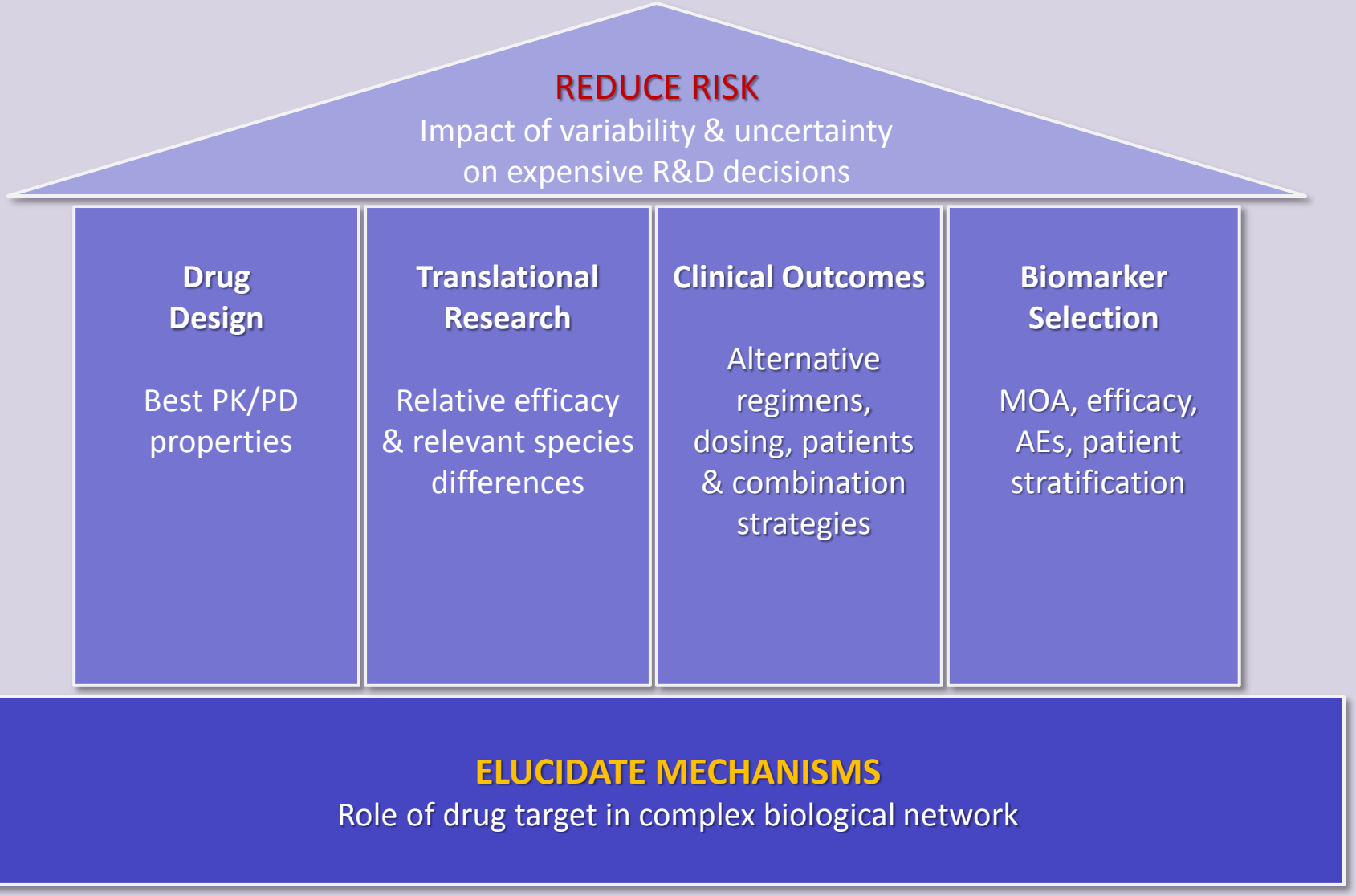
- 5 Select Highlight Case Overviews
  - Immuno-oncology
  - Psoriasis
  - Rheumatoid arthritis
  - Acute Lymphoblastic Leukemia
  - Support for FDA discussions

What are PhysioPD Research Platforms?

- ✓ Coherent mathematical representations of healthy and disease pathophysiology
- ✓ Built with diverse data, content, biological knowledge and hypotheses
- ✓ Capable of representing physiological variability
- ✓ Allow quantitative simulation of physiologic outcomes
- ✓ Carefully documented to enable future understanding, research, and extension

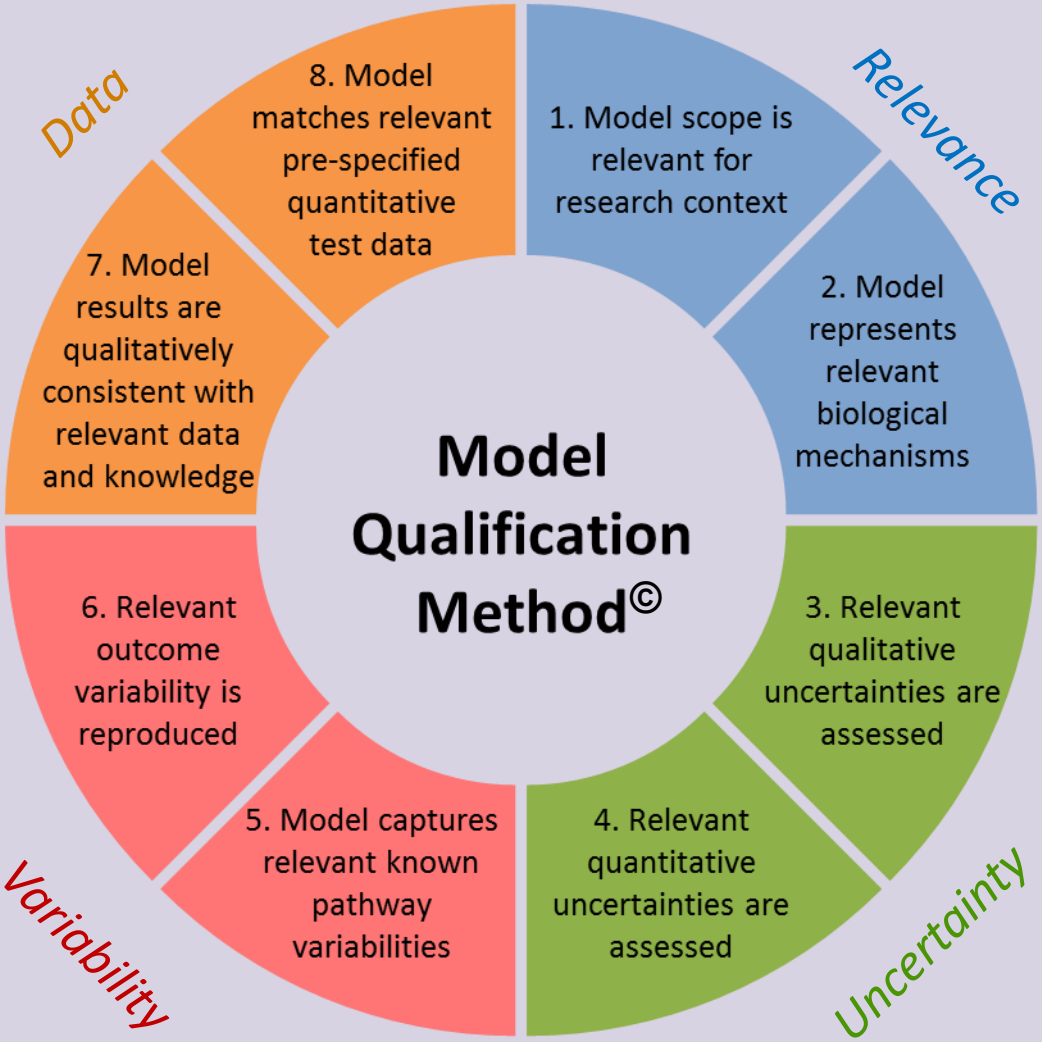
*Reviewed in Ramanujan, Gadkar, & Kadambi, "Quantitative Systems Pharmacology: Applications and Adoption in Drug Development" in *Systems Pharmacology and Pharmacodynamics*, Eds Mager & Kimko, in press.

Preclinical and Clinical PhysioPD Research Applications



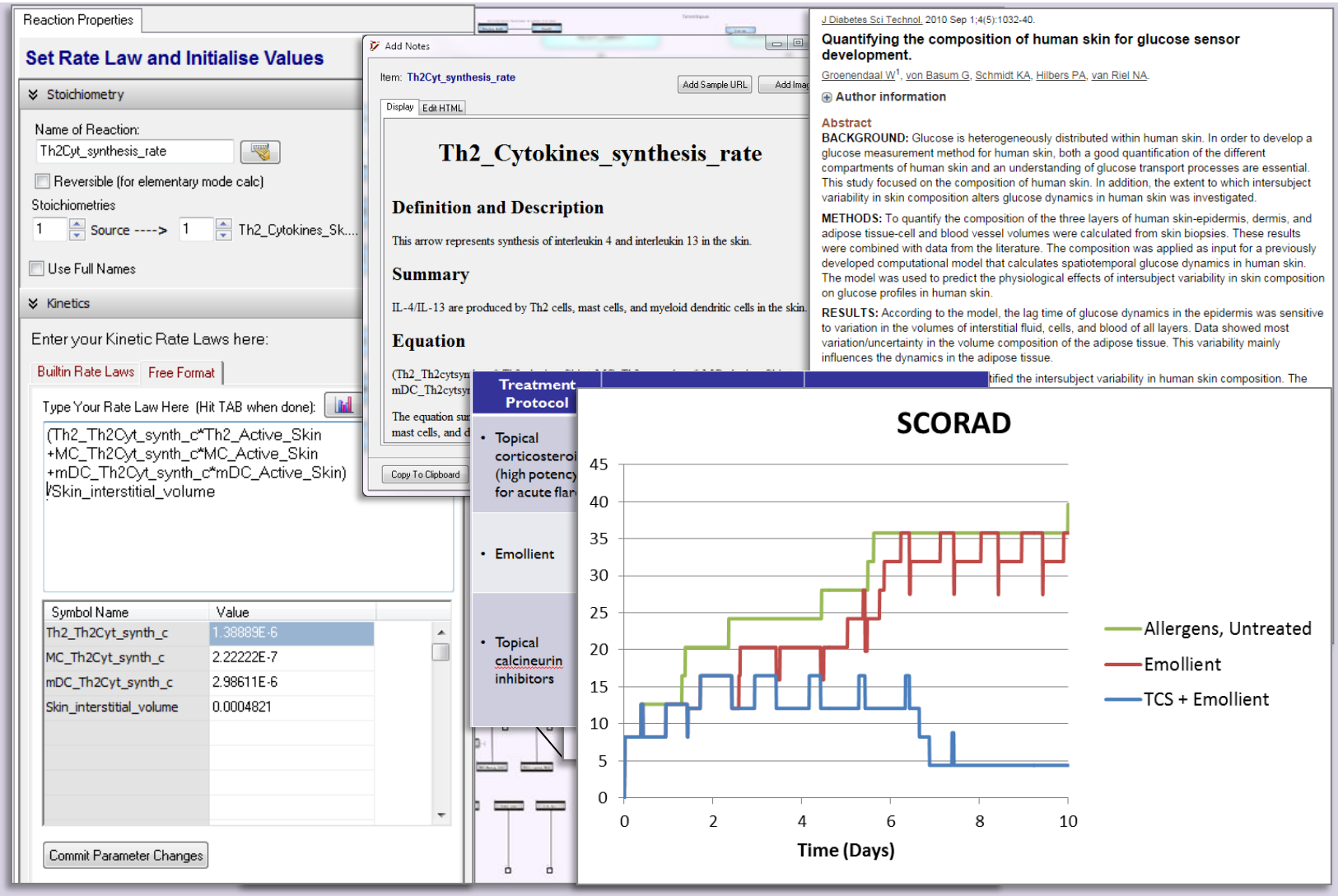
Rosa's Model Qualification Method (MQM)

Best Practice for Construction, Qualification, & Documentation



Ref: Friedrich, CPT Pharmacomet. Syst. Pharm. (2016)

PhysioPD Research Platforms include a graphical PhysioMap® and a quantitative representation of physiology: Inflammation Example



JDesigner can be obtained at http://jdesigner.sourceforge.net/Site/JDesigner.html

PhysioPD Research Platforms are built with the appropriate balance of research, curation, and integration of diverse information.

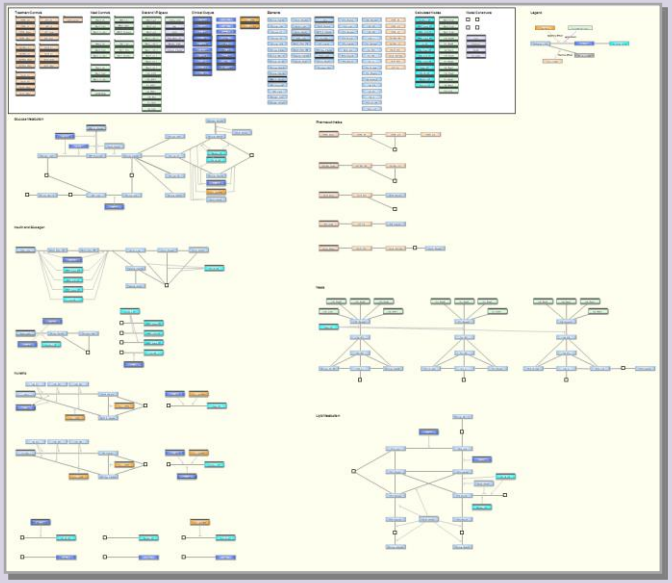
Physical Laws & Constraints

Healthy & Disease Physiology

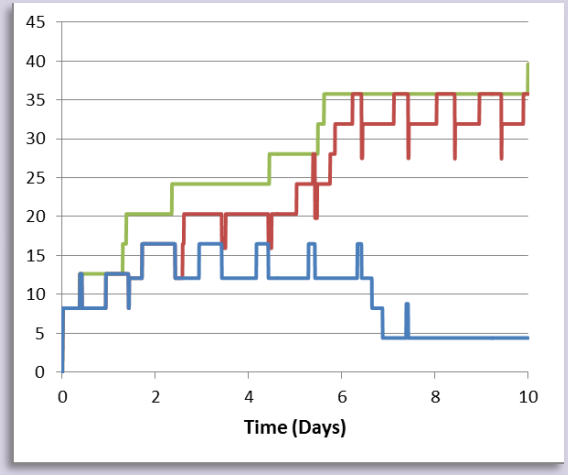
Target(s) & Drug Mechanism(s)

Preclinical Pharmacology

PhysioPD Research Platform



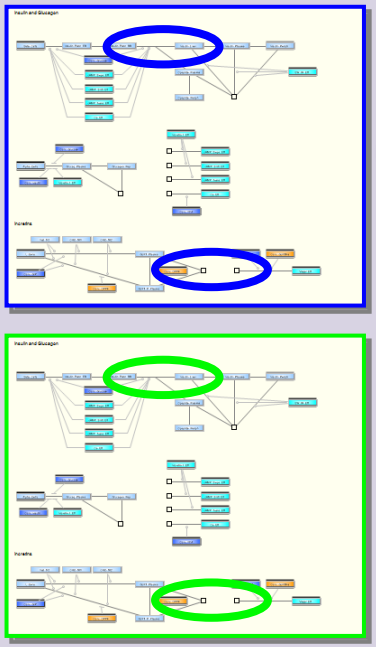
PhysioPD Research Results



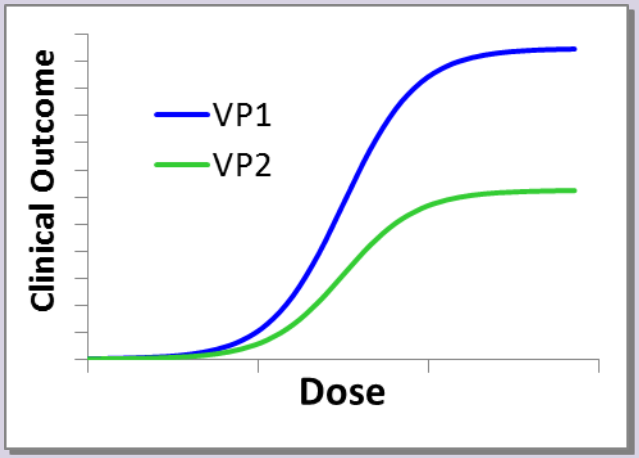
Virtual Patients facilitate exploration of how mechanistic differences may affect clinical outcomes.

Explore mechanistic hypotheses and known variability

Mechanisms



Outcomes



For Example:

- Which patient is most likely to respond well?
- What biomarkers are most informative?
- What enrollment criteria or protocol optimizes chances of clinical success?

Select Recent Case Overviews

- BMS & Rosa *Immuno-Oncology ASCPT 2015*
  - Development of a Quantitative Systems Pharmacology Platform to Support Translational Research and Clinical Development in Immuno-Oncology
- Stiefel (a GSK Company) & Rosa *Psoriasis IRA 2014*
  - Physiological model to investigate and prioritize targets for psoriasis
- MedImmune & Rosa *Rheumatoid Arthritis ASCPT 2014*
  - Quantitative Systems Pharmacology Modeling to Evaluate Clinical Response of an anti-TNFα/anti-Ang2 Bispecific Antibody in Rheumatoid Arthritis
- Amgen & Rosa *Acute Lymphoblastic Leukemia ASCPT 2014*
  - A Systems Pharmacology Model to Characterize the Effect of Blinatumomab in Patients With Adult B-Precursor Acute Lymphoblastic Leukemia
- PhysioPD™ Research to Support Client FDA Discussion (type 2 diabetes)

Case Study: Immuno-Oncology (I-O) PhysioPD™ Research Platform

Preclinical	Phase 1	Phase 2	Phase 3	Phase 4

- Research questions:
  - Identification of new targets
  - Evaluation of new drug combinations
  - Optimization of dosing strategies
- Research approach:
  - Developed I-O cycle Platform with selected therapy mechanisms of action, approved drugs, and novel targets
  - Created Virtual Patients with pathophysiological variability and simulated treatments
- PhysioPD research results:
  - Identified mechanistic determinants of non-response to approved therapies
  - Identified efficacious combination therapy dosing strategies
- Program impact:
  - Helped integrate and better understand the available data
  - Identified potential new targets and combination therapy strategies
  - Identified potential mechanisms of non-response and predictive biomarkers

Key Biological Elements in the Immuno-Oncology PhysioPD Platform

- Physiological compartments and processes
  - Blood
  - Plasma
  - Tumor
  - Lymph nodes
  - Angiogenesis
  - Metastatic potential
- Fundamental mechanisms underlying each step in the cancer-immunity cycle
  - Release of Cancer Antigens
  - Cancer Antigen Presentation
  - T Cell Priming and Activation
  - Immune Cell Trafficking
  - Tumor Infiltration
  - Cancer Cell Recognition
  - Cancer Cell Killing
- Drug Mechanisms of Action

I-O PhysioMap Overview: Functional Modules

Biomarker Outputs

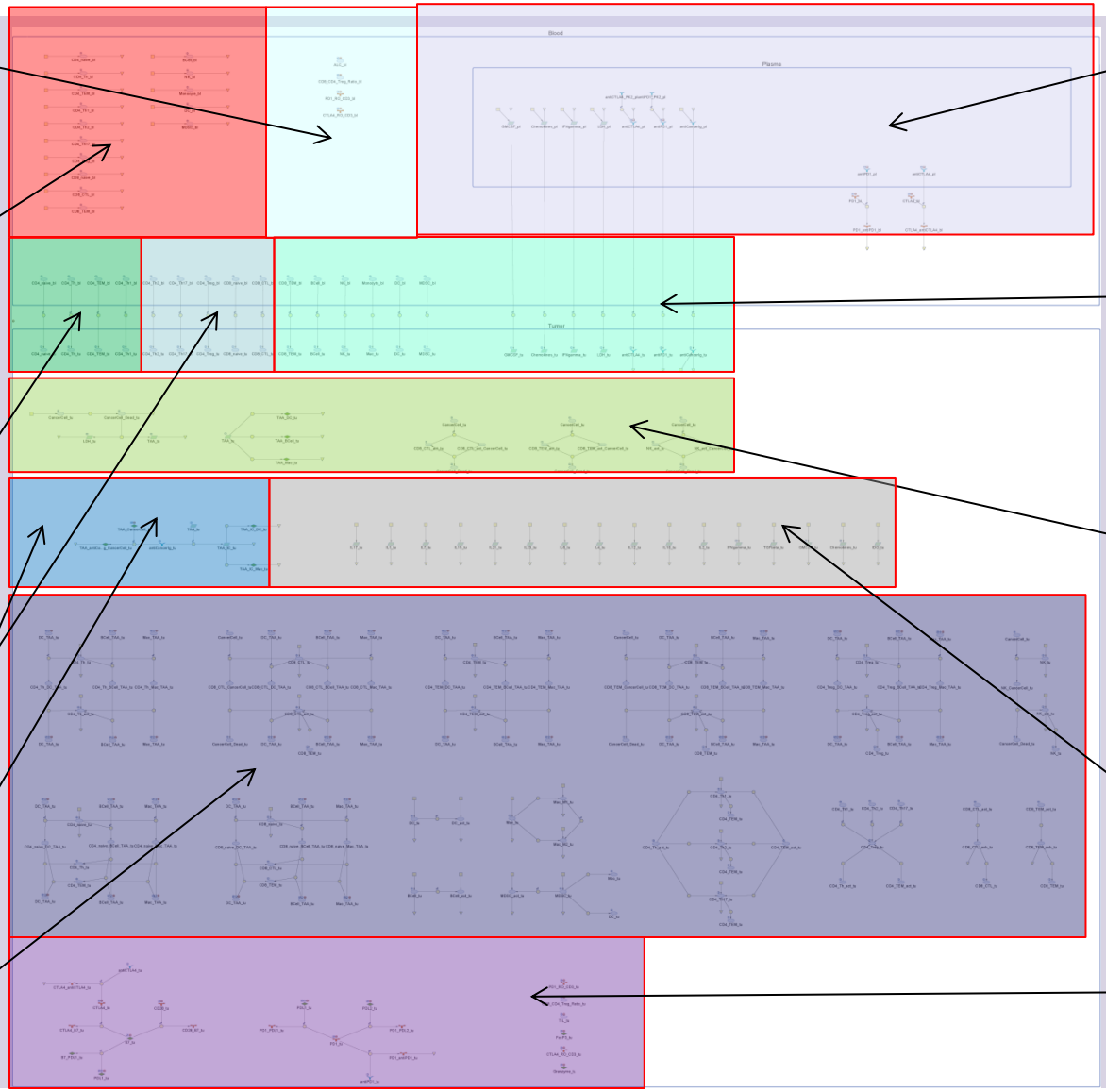
Cell Trafficking & Tumor Infiltration

Cancer Cell Growth, Death, & Release of Cancer Antigens

Antigen Presentation

T Cell Priming

Drug-Related Mechanisms



Drug Binding & Transport

Immune-Mediated Cancer Cell Killing

Cancer Cell Recognition & Effector Cell Activation

Immune Cell Signaling & Response

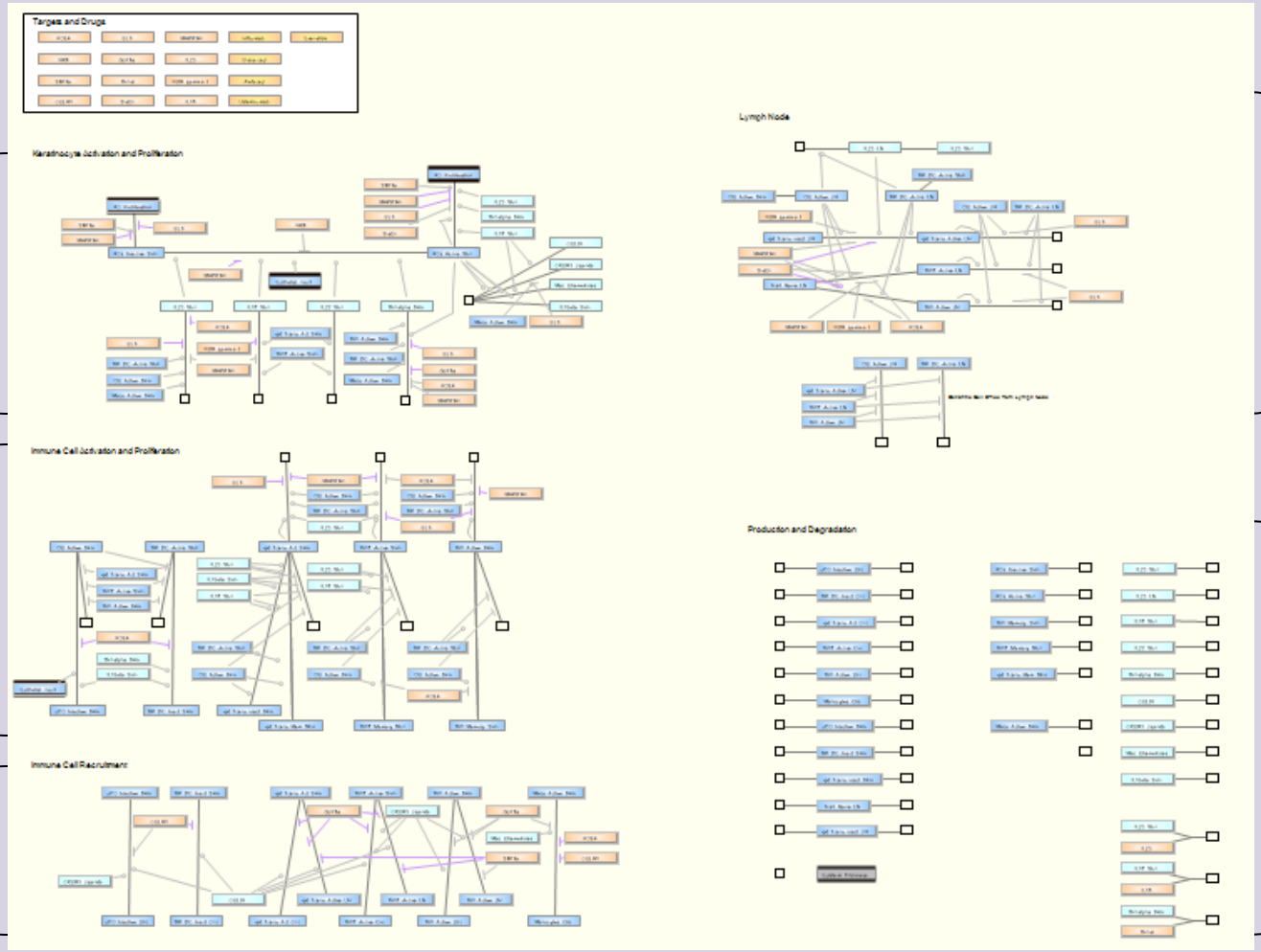
Drug-Related Mechanisms

Case Study: Development of a Psoriasis PhysioMap® to Prioritize Potential Therapy Targets

Preclinical	Phase 1	Phase 2	Phase 3	Phase 4

- Research questions:
  - Select, evaluate, and prioritize targets for early drug development
- Research approach:
  - Developed a Psoriasis PhysioMap® : the architectural blueprint that defines the disease and integrates the targets and Standards of Care
- PhysioMap research results:
  - Evaluated drug targets in disease pathways, their potential interactions, and relative efficacy contribution
- Program impact:
  - Informed target prioritization and selection
  - Consolidated institutional data and knowledge
  - Created the foundation for quantitative modeling

A Psoriasis PhysioMap® provides a method to prioritize and evaluate potential drug targets.



Keratinocyte Growth & Activation

Immune Cell Activation & Proliferation

Immune Cell Recruitment

Lymph Nodes

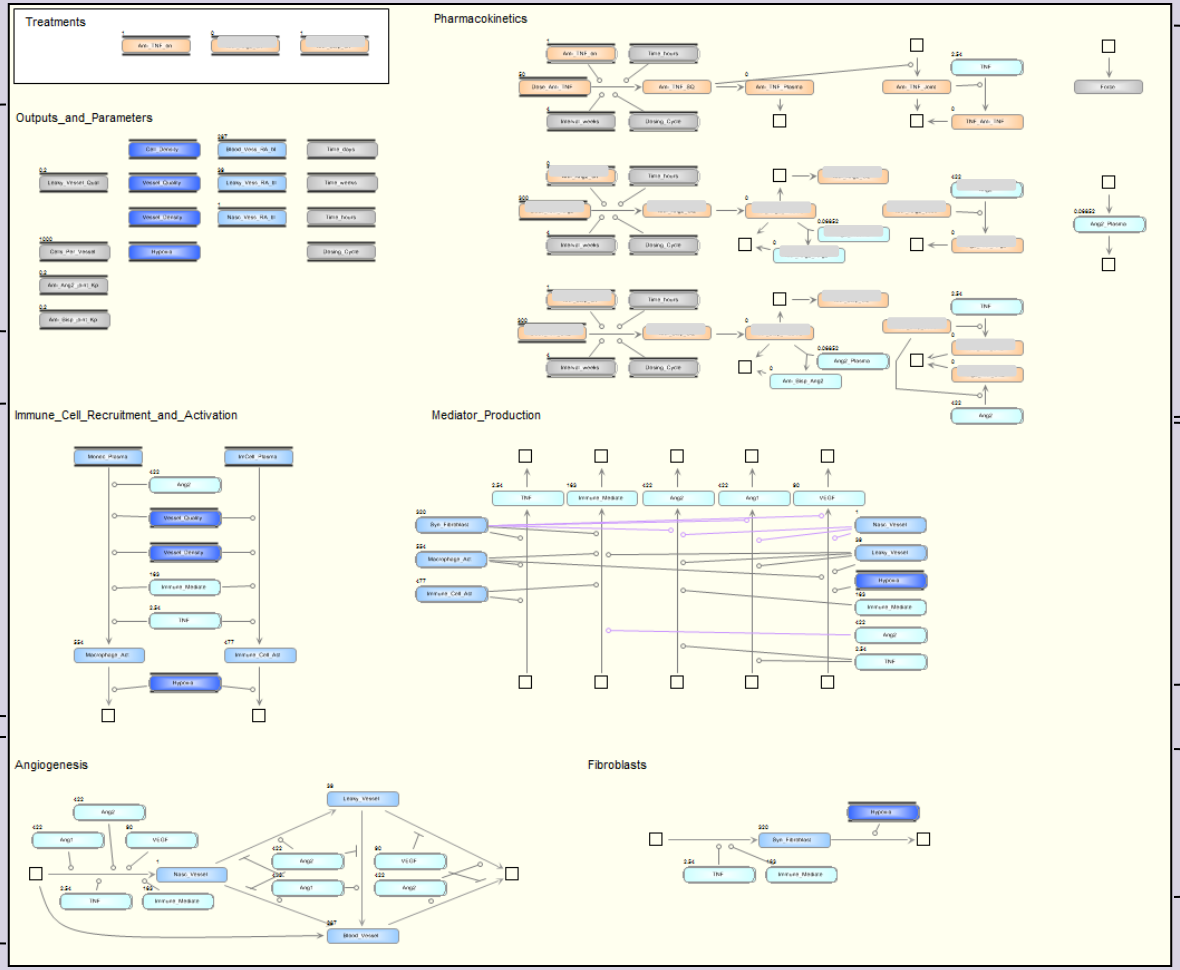
Metabolite Production & Degradation

Case Study: Development of a Rheumatoid Arthritis (RA) PhysioPD™ Platform to Optimize Drug PK and PD Characteristics

Preclinical	Phase 1	Phase 2	Phase 3	Phase 4

- Research questions:
  - Assess efficacy of novel, candidate drug (Compound R), which targets TNF-α and angiogenic pathways and compare to Standards of Care (SOC)
  - Evaluate trade-off between mechanism of action (MOA) and Compound R PK features
- Research approach:
  - Created a representative RA joint Platform
  - Represented PK and MOA of both SOC and Compound R
  - Simulated therapies in multiple Virtual Patients and predicted clinical outcomes
- PhysioPD Research results:
  - Clarified understanding of disease pathways and Compound R MoA
  - Illustrated how PK and PD characteristics of Compound R impacted clinical outcome
  - Identified multiple hypotheses that characterized Compound R best responders
- Program impact:
  - Results informed decisions for Compound R characteristics optimization

A Rheumatoid Arthritis PhysioPD™ Platform enables evaluation of candidate drug characteristics in different types of Virtual Patients.



Clinical Outcomes

Immune Cells

Angiogenesis

PK

Mediator Production

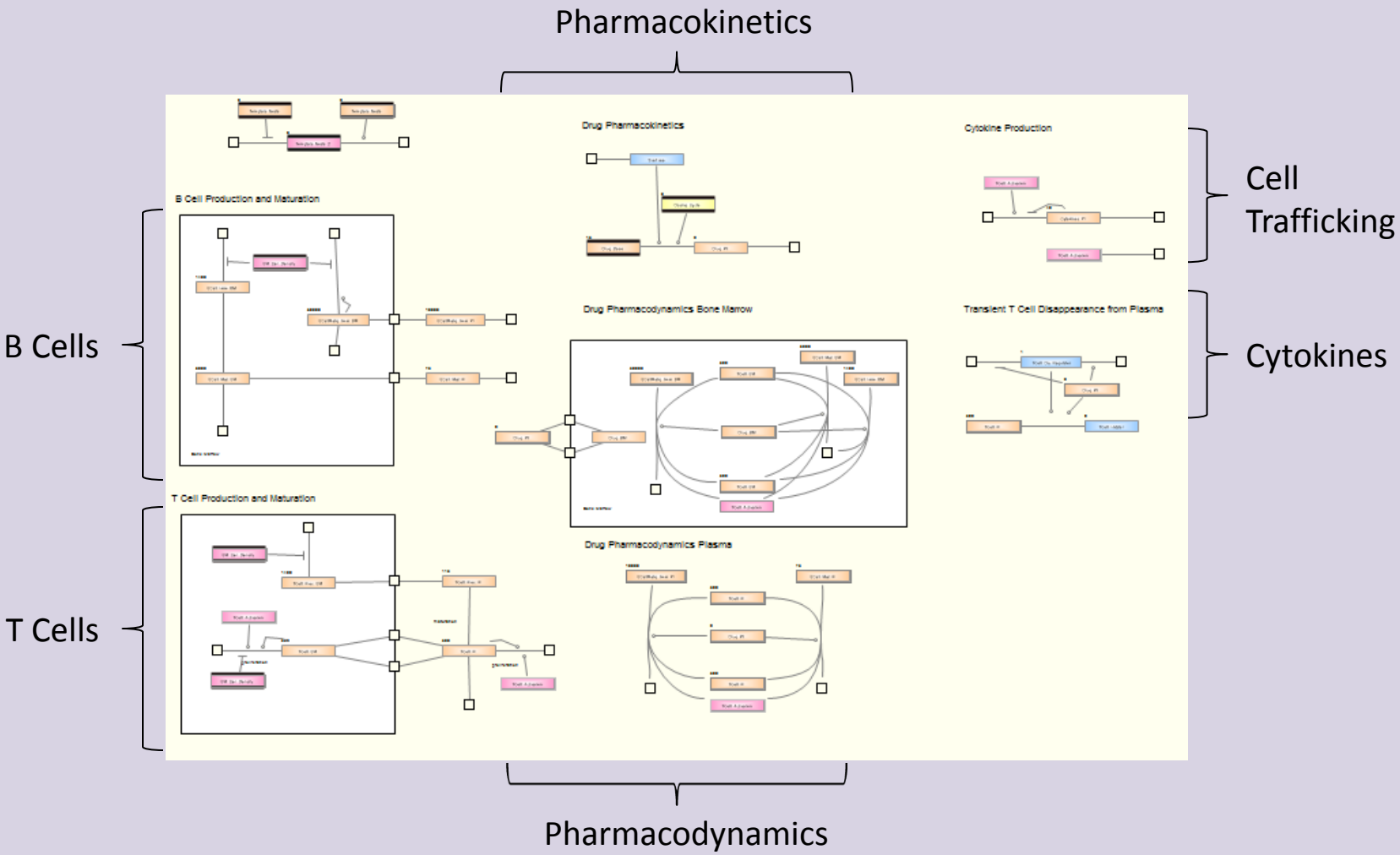
Synovial Properties

Case Study: Acute Lymphoblastic Leukemia (ALL)
PhysioPD™ Platform

Preclinical	Phase 1	Phase 2	Phase 3	Phase 4

- Research questions:
  - Understand mechanisms that underlie non-response to therapy
  - Determine dosing regimens to improve response
- Research approach:
  - Platform representing disease progression and therapy mechanisms of action
  - Create Virtual Patients with pathophysiological variability
- Research results:
  - Identified mechanistic determinants of non-response through simulation research
  - Identified potentially more efficacious dosing strategies for non-responders
- Program impact:
  - Identified several potential mechanisms that underlie non-response to therapy
  - Recommended dosing strategies to improve likelihood of response

Case Study: PhysioMap® of Acute Lymphoblastic Leukemia (ALL)



Case Study: *In vitro* to *in vivo* Translation for an anti-PCSK9 Antibody

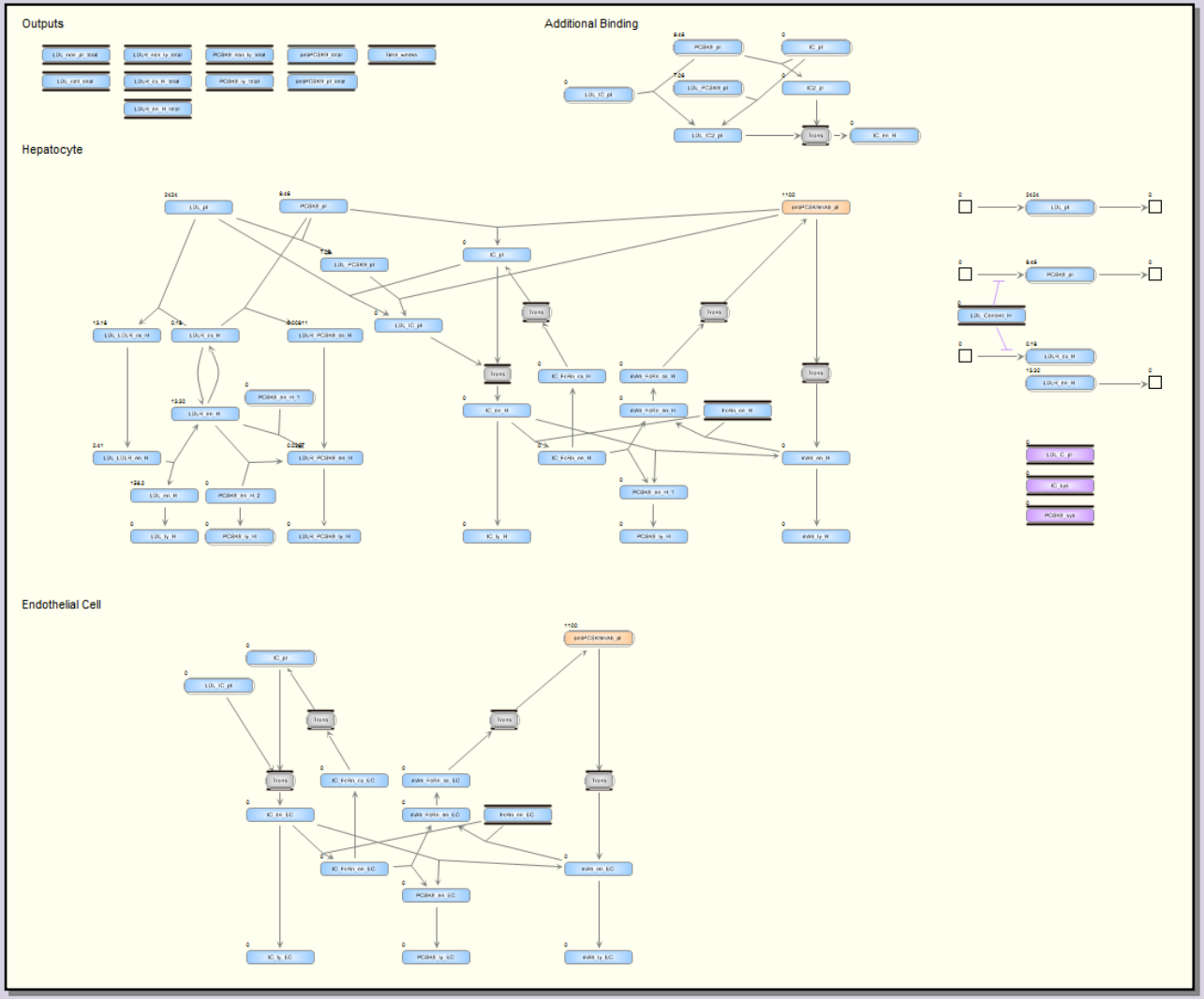
Preclinical	Phase 1	Phase 2	Phase 3	Phase 4

- Research question:
  - Understand how preclinical anti-PCSK9 data might translate to clinical efficacy
- Research approach:
  - Develop a Platform that represents *in vitro* and *in vivo* systems
  - Provide mechanistic insight into existing results and extrapolate to novel scenarios
- PhysioPD research results:
  - Confirmed mechanisms that drive *in vitro* and *in vivo* mAb efficacy and half-life
  - LDL:PCSK9 binding in plasma could affect *in vivo* dynamics and reduce mAb efficacy
- Program impact:
  - Provided a bridge from *in vitro* mAb characteristics to *in vivo* efficacy

Case Study: *In vitro* to *in vivo* Translation for an anti-PCSK9 Antibody

Hepatocyte

Endothelial Cell

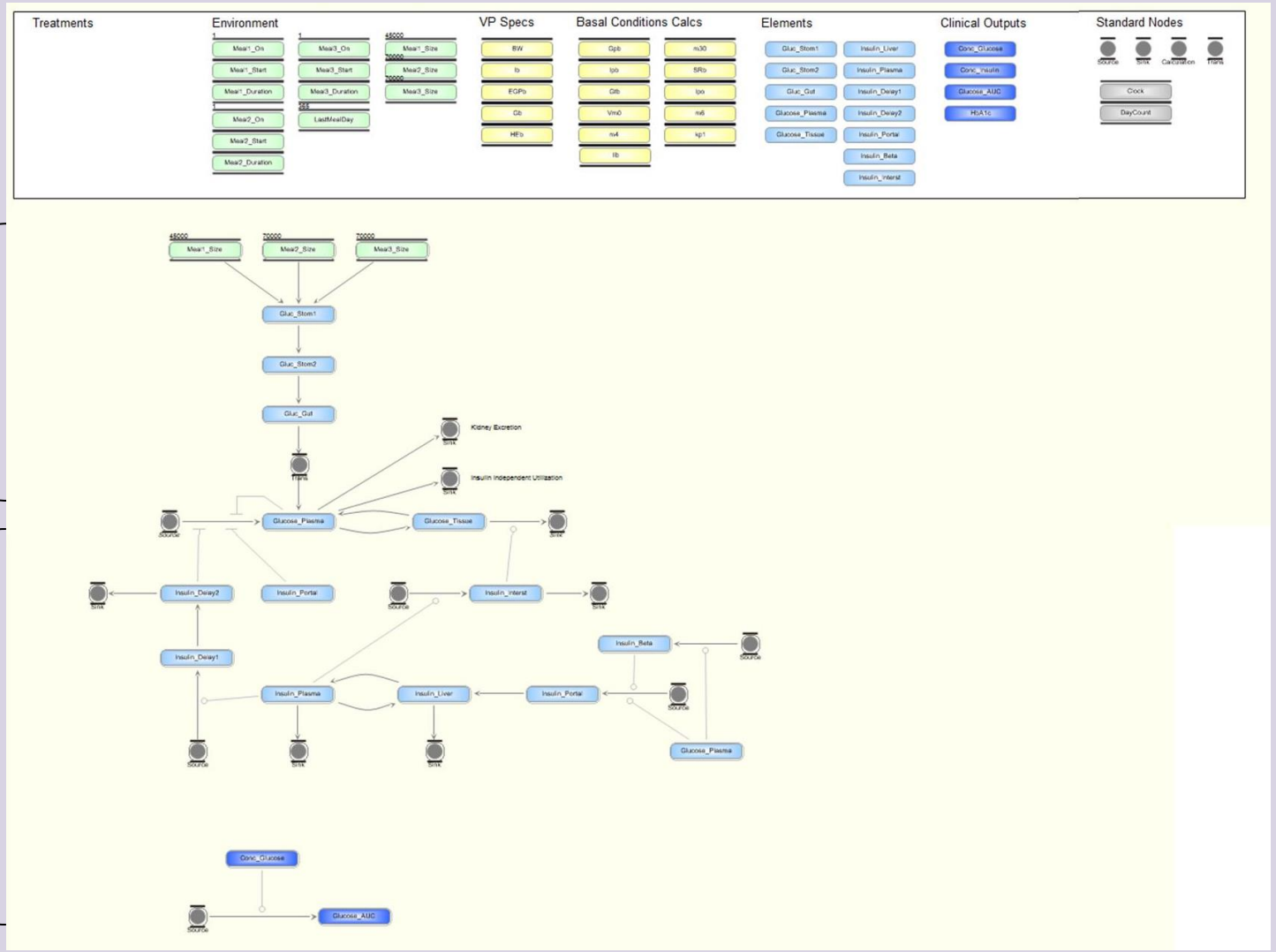


Case Study: PhysioPD™ Research for Hypothesis Generation to Support Client Discussion with FDA

Preclinical	Phase 1	Phase 2	Phase 3	Phase 4

- Research questions:
  - Drug with poorly characterized MOA showed reductions in A1C and plasma glucose
  - FDA review indicated a perceived inconsistency between A1C and average plasma glucose changes with no obvious explanation
- Research approach:
  - Develop a type 2 diabetes (T2D) PhysioPD™ Research Platform with Virtual Patients consistent with client Phase 3 trial data
  - Generate hypotheses to explain observed relationships between A1C and glucose
- PhysioPD research results:
  - Sampling time of fasting plasma glucose likely contributes to the perceived mismatch between A1C and glucose
  - Variability in dietary carbohydrate between clinical trial sites may impact observed response
- Program impact:
  - Informed client strategy for planned FDA discussions
  - Recommended strategies for future T2D drug trial design

Overview of T2D PhysioPD Platform



SUMMARY

- PhysioPD Platforms are “fit for purpose”
  - Each Platform is designed to research specific scientific questions
    - Target ID
    - Compound optimization
    - Mechanisms of response/non-response
    - Dosing strategies
    - Predictive biomarker identification
    - Clinical trial design
    - FDA discussion support
- PhysioPD Platform creation is applicable across all R&D Phases
- Projects can span from PhysioMap to multi-year Platform Development

100+ Staff Years PhysioPD & R&D Experience in all Major Tx Areas Enabling Scientific Insight & Impacting Program Decisions

- Rosa's Core Expertise: sufficient research investment to ensure scientific impact
  - Participatory Research Project Structure
  - Literature Curation and Extensive Platform Documentation
  - Fully-Integrated Rosa Scientific and Engineering Teams
  - "Fit for Purpose" PhysioPD Research Platforms Delivered to Client
  - Client-friendly Platform Software Selection (e.g., JDesigner, SymBiology)

Privately-held company founded in 2002

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