



**Drug Development Advisors**

*Driving Scientific Innovation Since 2002*

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*

*April 20-22, 2016*

# 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

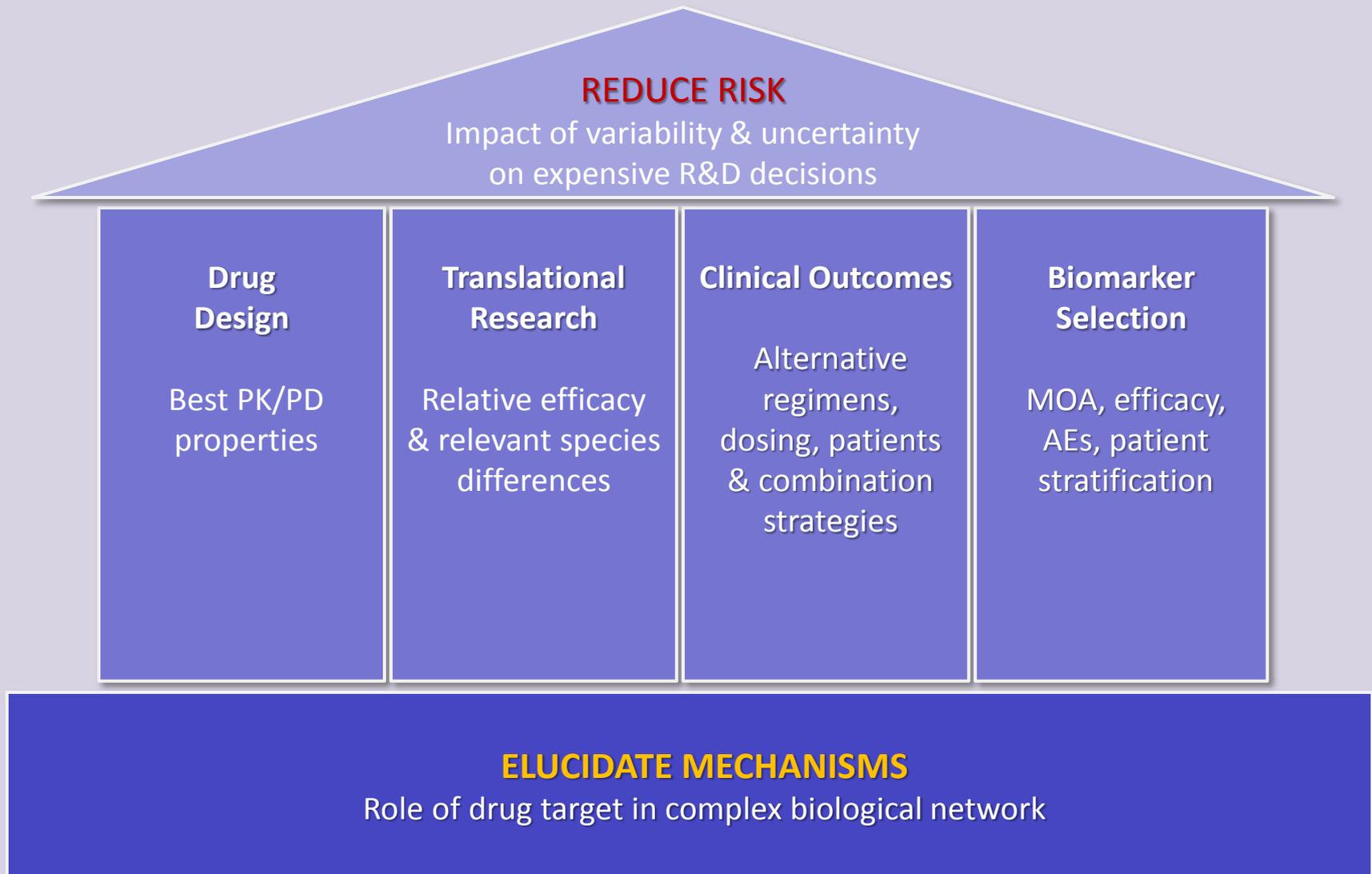


## What are PhysioPD Research Platforms?

- ✓ 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

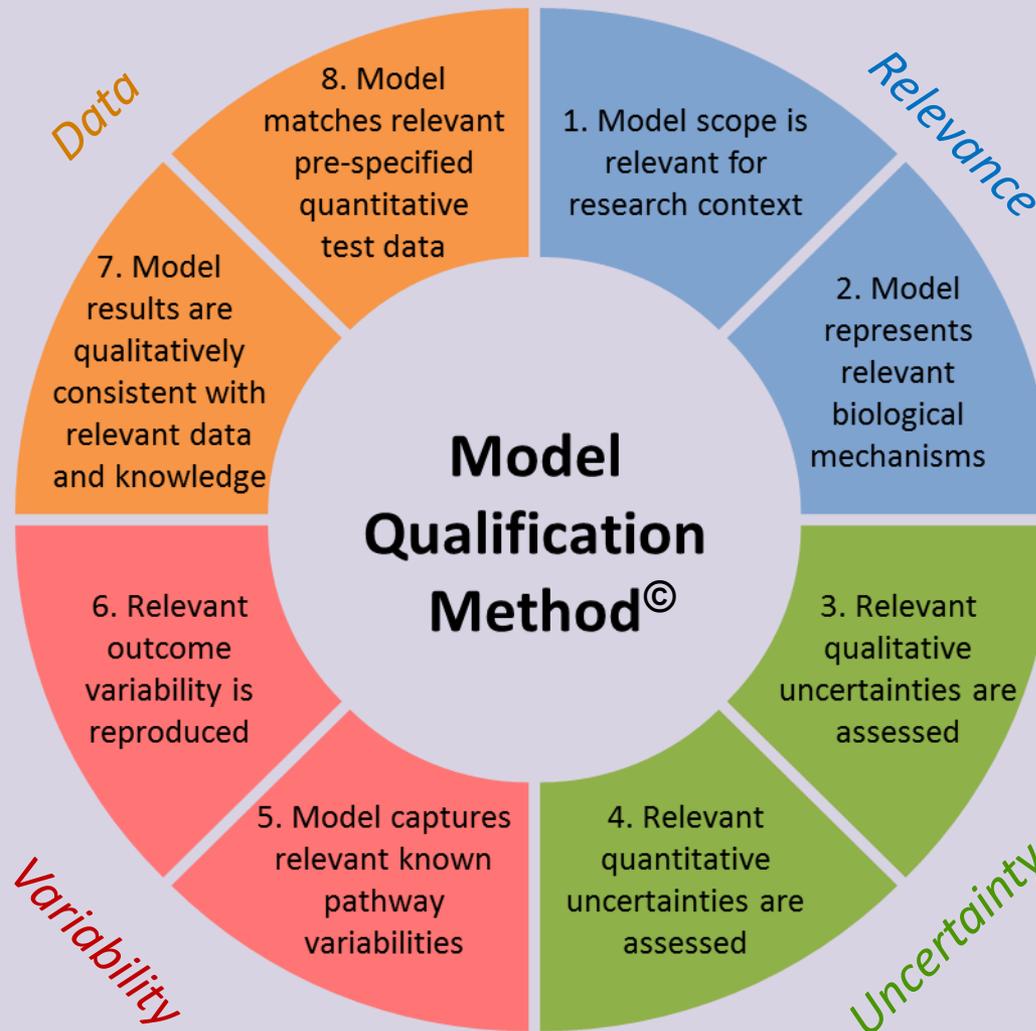
\*Reviewed in Ramanujan, Gadkar, & Kadambi, "Quantitative Systems Pharmacology: Applications and Adoption in Drug Development" in *Systems Pharmacology and Pharmacodynamics*, Eds Mager & Kimko, in press.

# 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<sup>®</sup> and a quantitative representation of physiology: Inflammation Example



### Reaction Properties

#### Set Rate Law and Initialise Values

**Stoichiometry**

Name of Reaction: Th2Cyt\_synthesis\_rate

Reversible (for elementary mode calc)

Stoichiometries: 1 Source ----> 1 Th2\_Cytokines\_Sk....

Use Full Names

**Kinetics**

Enter your Kinetic Rate Laws here:

Builtin Rate Laws Free Format

Type Your Rate Law Here (Hit TAB when done):

```
(Th2_Th2Cyt_synth_c*Th2_Active_Skin
+MC_Th2Cyt_synth_c*MC_Active_Skin
+mDC_Th2Cyt_synth_c*mDC_Active_Skin)
/Skin_interstitial_volume
```

Symbol Name	Value
Th2_Th2Cyt_synth_c	1.38889E-6
MC_Th2Cyt_synth_c	2.22222E-7
mDC_Th2Cyt_synth_c	2.98611E-6
Skin_interstitial_volume	0.0004821

Commit Parameter Changes

Add Notes

Item: Th2Cyt\_synthesis\_rate

Display Edit HTML

## Th2\_Cytokines\_synthesis\_rate

**Definition and Description**

This arrow represents synthesis of interleukin 4 and interleukin 13 in the skin.

**Summary**

IL-4/IL-13 are produced by Th2 cells, mast cells, and myeloid dendritic cells in the skin.

**Equation**

$(Th2\_Th2Cyt\_synth\_c * Th2\_Active\_Skin + MC\_Th2Cyt\_synth\_c * MC\_Active\_Skin + mDC\_Th2Cyt\_synth\_c * mDC\_Active\_Skin) / Skin\_interstitial\_volume$

The equation sum...  
mast cells, and d...

Copy To Clipboard

J Diabetes Sci Technol, 2010 Sep 1;4(5):1032-40.

### Quantifying the composition of human skin for glucose sensor development.

Groenendaal W<sup>1</sup>, von Basum G, Schmidt KA, Hilbers PA, van Riel NA

**Author information**

**Abstract**

**BACKGROUND:** Glucose is heterogeneously distributed within human skin. In order to develop a glucose measurement method for human skin, both a good quantification of the different compartments of human skin and an understanding of glucose transport processes are essential. This study focused on the composition of human skin. In addition, the extent to which intersubject variability in skin composition alters glucose dynamics in human skin was investigated.

**METHODS:** To quantify the composition of the three layers of human skin-epidermis, dermis, and adipose tissue-cell and blood vessel volumes were calculated from skin biopsies. These results were combined with data from the literature. The composition was applied as input for a previously developed computational model that calculates spatiotemporal glucose dynamics in human skin. The model was used to predict the physiological effects of intersubject variability in skin composition on glucose profiles in human skin.

**RESULTS:** According to the model, the lag time of glucose dynamics in the epidermis was sensitive to variation in the volumes of interstitial fluid, cells, and blood of all layers. Data showed most variation/uncertainty in the volume composition of the adipose tissue. This variability mainly influences the dynamics in the adipose tissue.

**Treatment Protocol**

- Topical corticosteroid (high potency for acute flare)
- Emollient
- Topical calcineurin inhibitors

## SCORAD

Time (Days)

Legend:

- Allergens, Untreated
- Emollient
- TCS + Emollient

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.



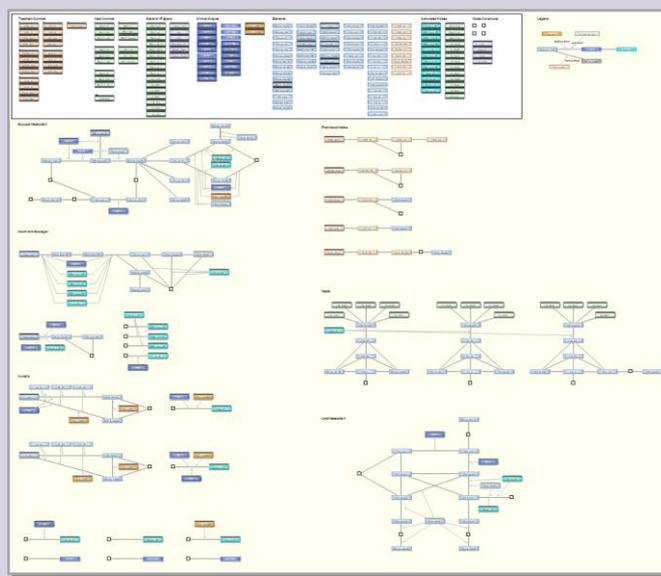
Physical Laws  
& Constraints

Healthy & Disease  
Physiology

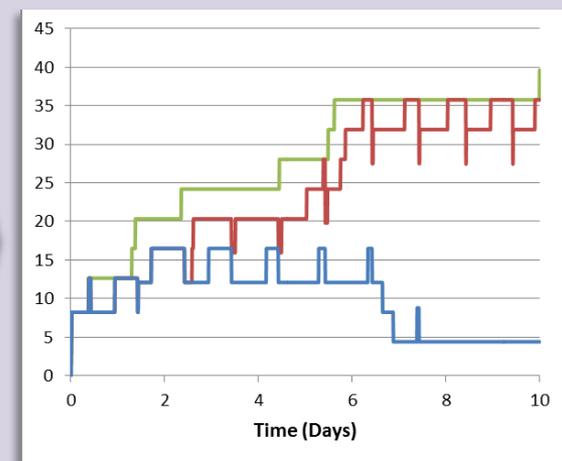
Target(s) & Drug  
Mechanism(s)

Preclinical  
Pharmacology

## PhysioPD Research Platform

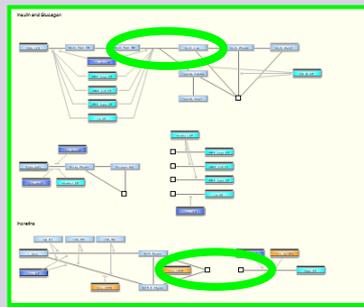
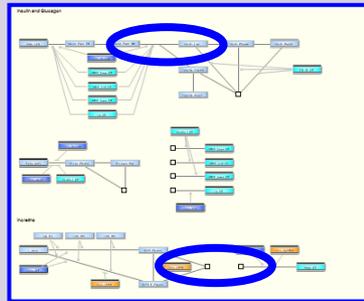


## PhysioPD Research Results



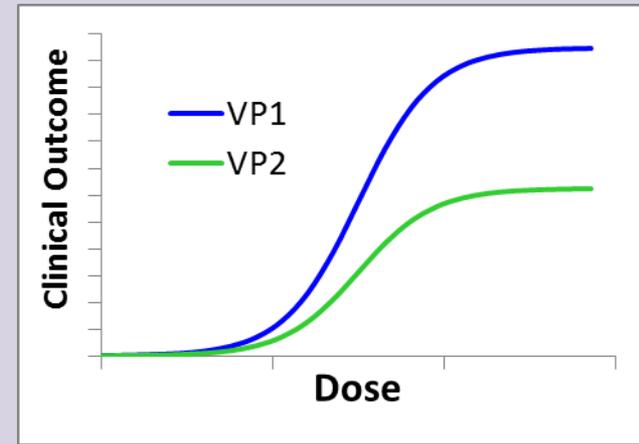
Virtual Patients facilitate exploration of how mechanistic differences may affect clinical outcomes.

## Mechanisms



*Explore mechanistic hypotheses and known variability*

## 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-TNF $\alpha$ /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
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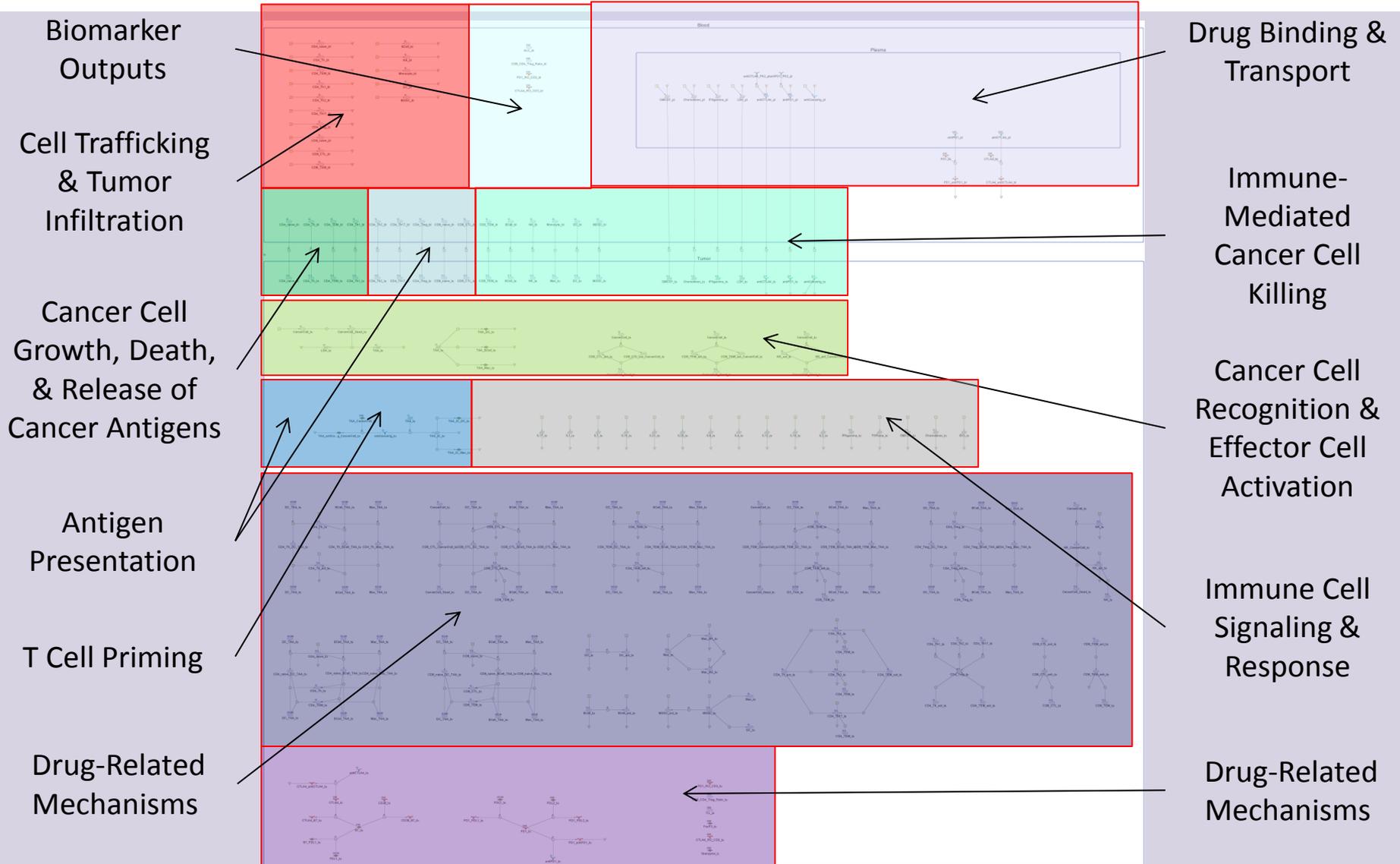
- Research questions:
  - Identification of new targets
  - Evaluation of new drug combinations
  - Optimization of dosing strategies
  
- Research approach:
  - Developed I-O cycle Platform with selected therapy mechanisms of action, approved drugs, and novel targets
  - Created Virtual Patients with 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



# Case Study: Development of a Psoriasis PhysioMap<sup>®</sup> to Prioritize Potential Therapy Targets



Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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- Research questions:
  - Select, evaluate, and prioritize targets for early drug development
- Research approach:
  - Developed a Psoriasis PhysioMap<sup>®</sup> : 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

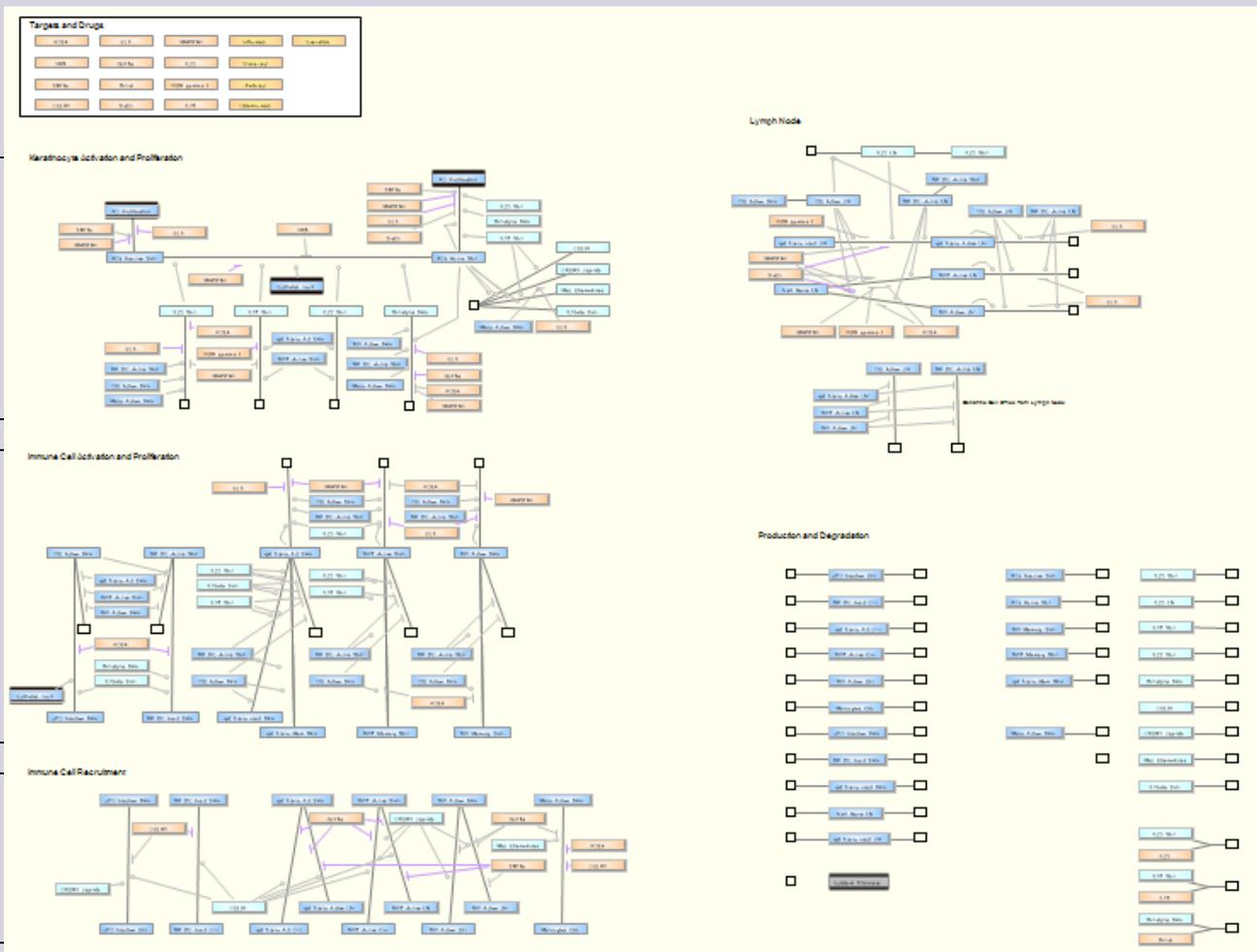
# A Psoriasis PhysioMap® provides a method to prioritize and evaluate potential drug targets.



Keratinocyte Growth & Activation

Immune Cell Activation & Proliferation

Immune Cell Recruitment



Lymph Nodes

Metabolite Production & Degradation

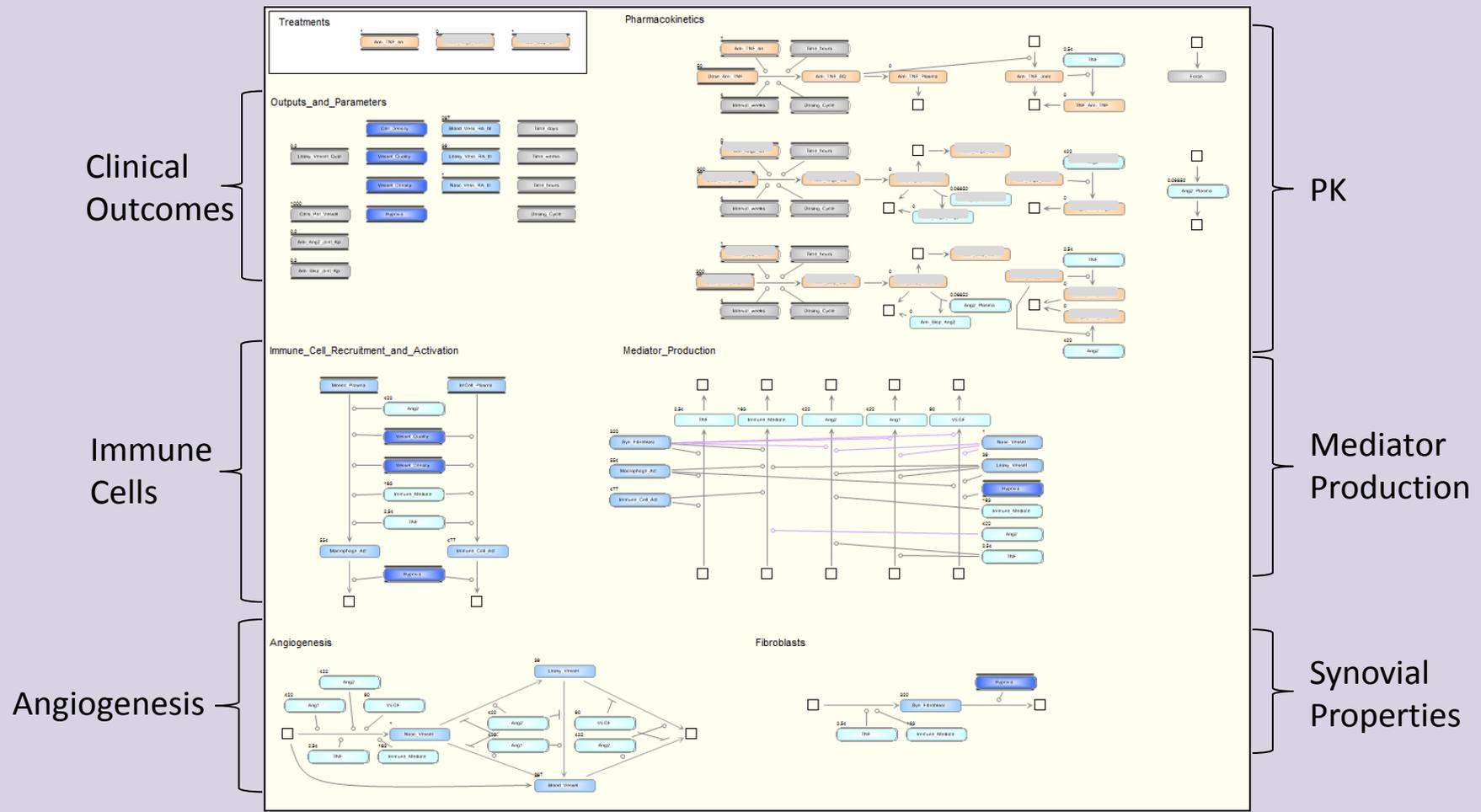
# Case Study: Development of a Rheumatoid Arthritis (RA) PhysioPD™ Platform to Optimize Drug PK and PD Characteristics



Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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- Research questions:
  - Assess efficacy of novel, candidate drug (Compound R), which targets TNF- $\alpha$  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.



# Case Study: Acute Lymphoblastic Leukemia (ALL)

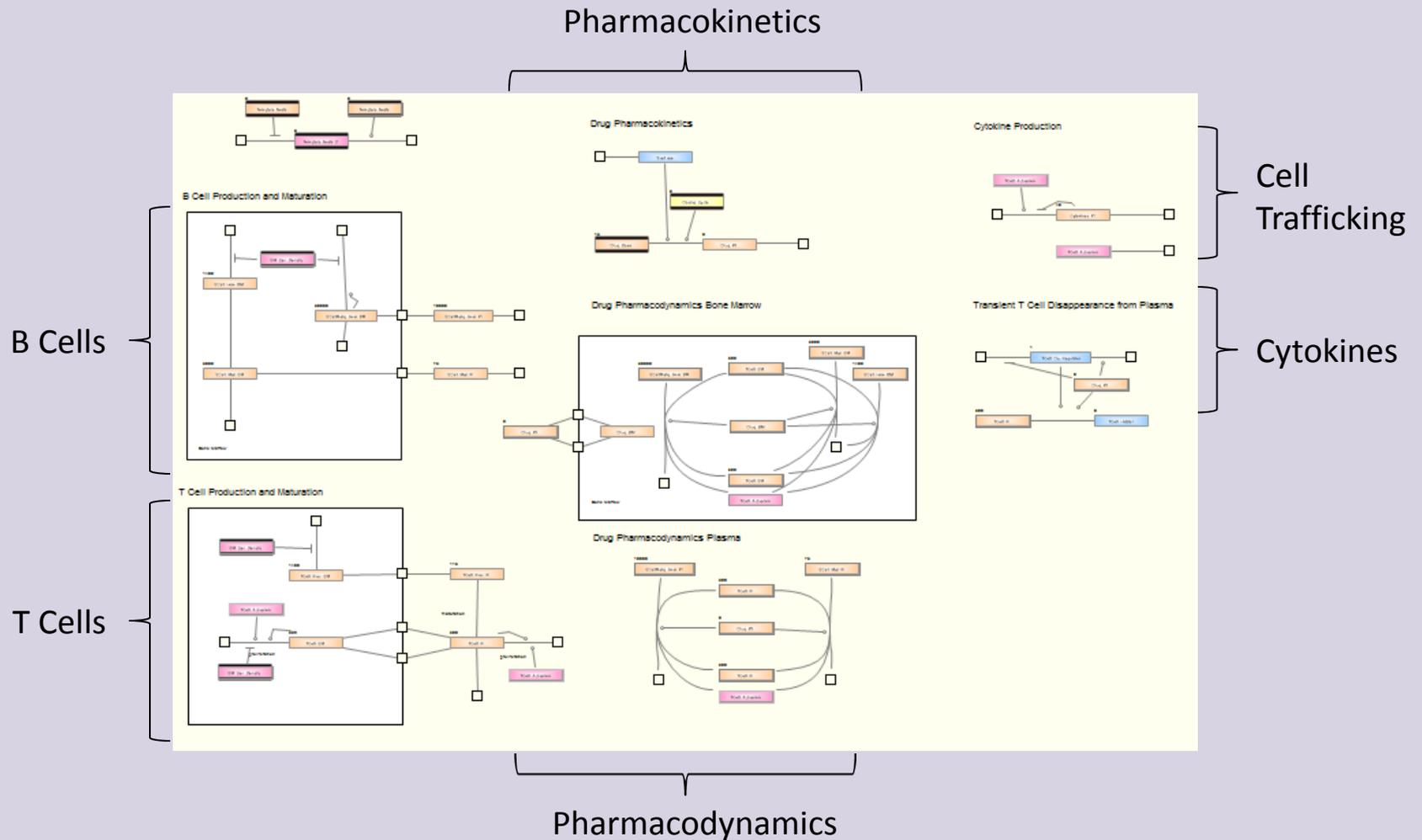
## PhysioPD™ Platform



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: PhysiMap® 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
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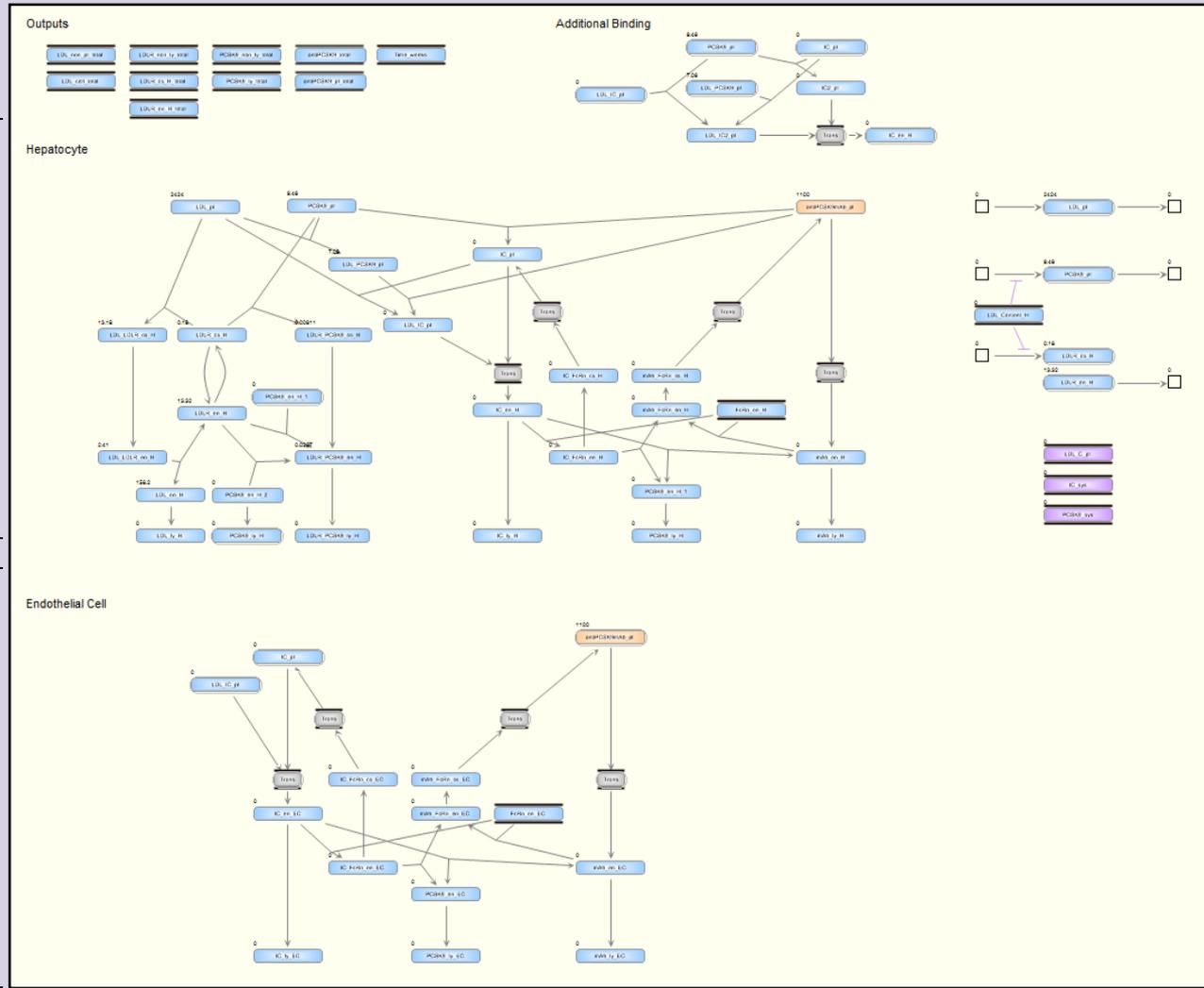
- Research question:
  - Understand how preclinical anti-PCSK9 data might translate to clinical efficacy
- Research approach:
  - Develop a Platform that represents *in vitro* and *in vivo* systems
  - Provide mechanistic insight into existing results and extrapolate to novel scenarios
- PhysioPD research 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



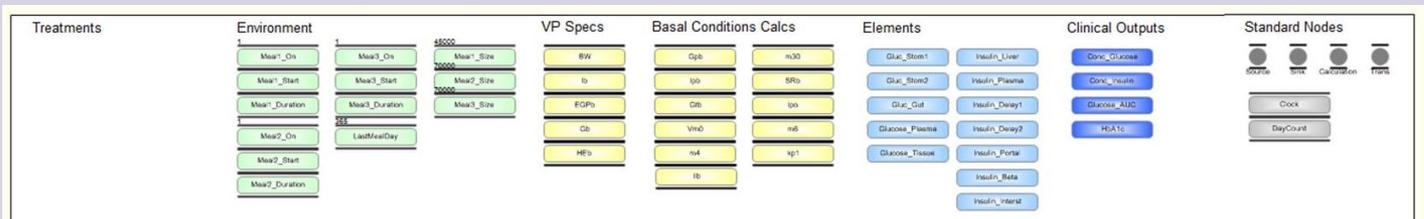
# Case Study: PhysioPD™ Research for Hypothesis Generation to Support Client Discussion with FDA



Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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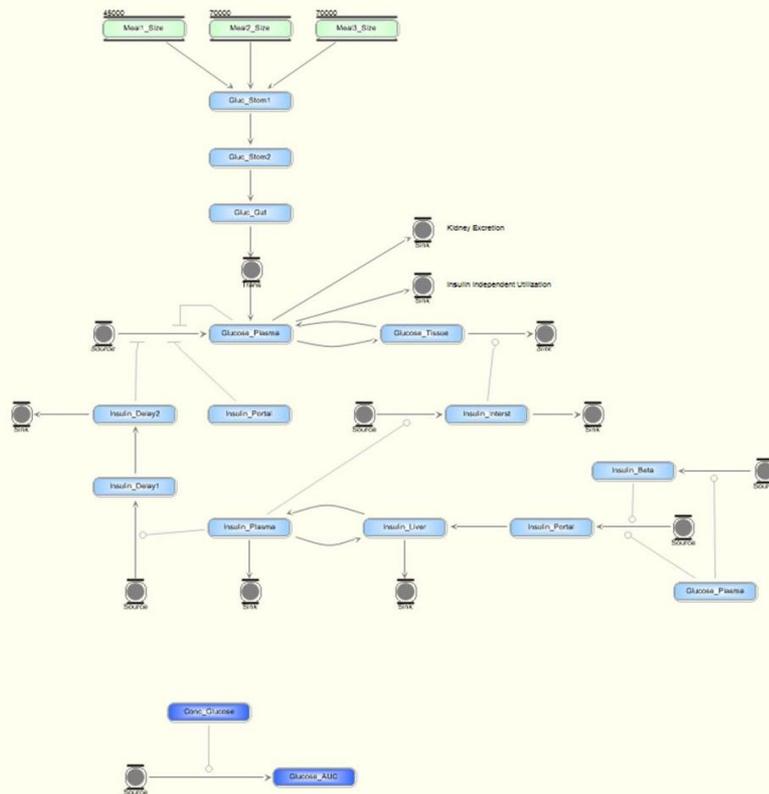
- Research questions:
  - Drug with poorly characterized MOA showed reductions in A1C and plasma glucose
  - FDA review indicated a perceived inconsistency between A1C and average plasma glucose changes with no obvious explanation
- Research approach:
  - Develop a type 2 diabetes (T2D) PhysioPD™ Research 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



Meals

Glucose & Insulin



## 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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*Driving Scientific Innovation Since 2002*

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

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