Drug Development Advisors

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Creating and Performing Research with PhysioPD™ Research Platforms: Process and Case Study

QSP Congress Europe 2015
Basel, Switzerland
28 April 2015

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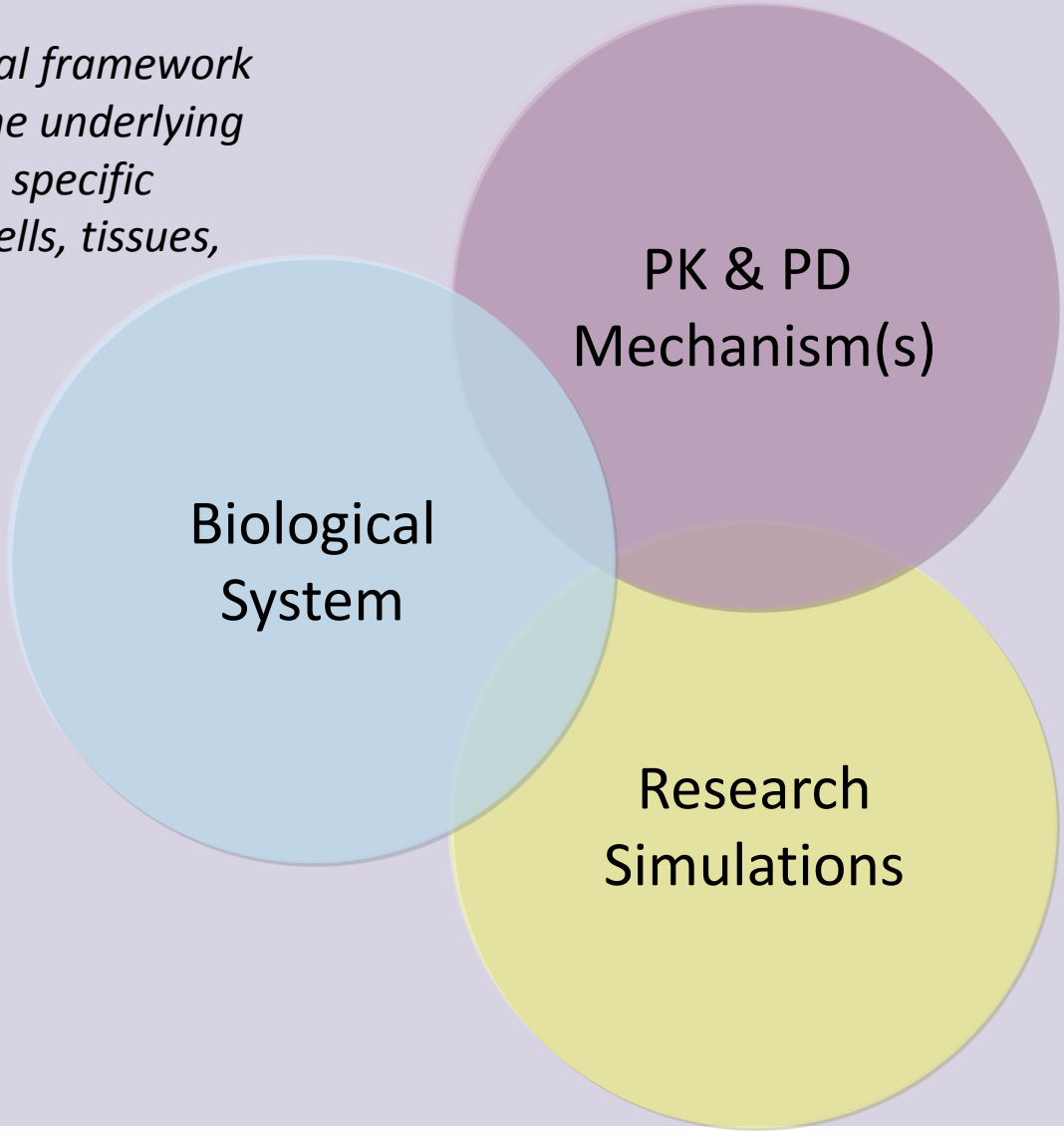
Summary

- The PhysioPD research approach is designed to impact client decisions and has been successful in many, diverse therapeutic indications
- PhysioPD Research Platforms are Quantitative Systems Pharmacology (QSP) models that are designed with multidisciplinary client team input
- I will describe the process of creating and conducting research using PhysioPD Research Platforms to drive scientific innovation in the pharmaceutical industry

PhysioPD™ Research Platforms incorporate biological mechanisms, pharmacology, and simulation capabilities.

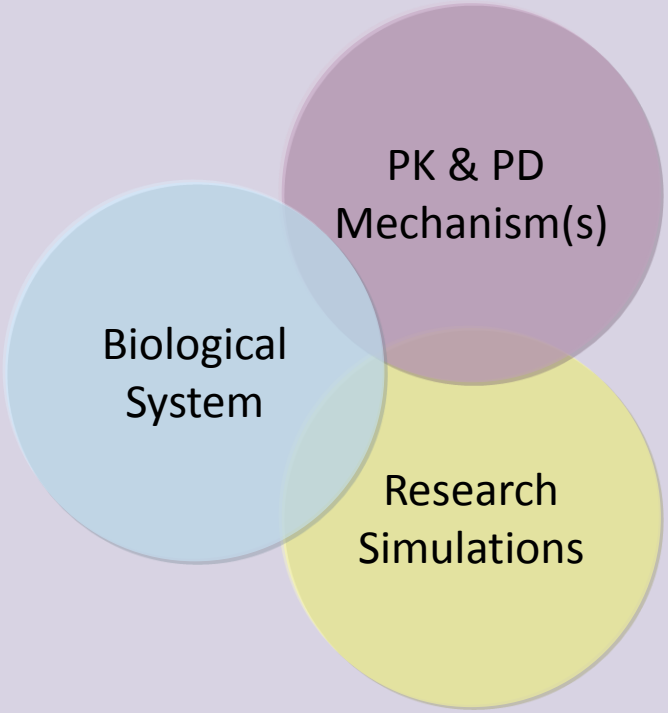
Mathematical framework describing the underlying biology, e.g., specific mediators, cells, tissues, organs



Target MOA and/or compound pharmacology

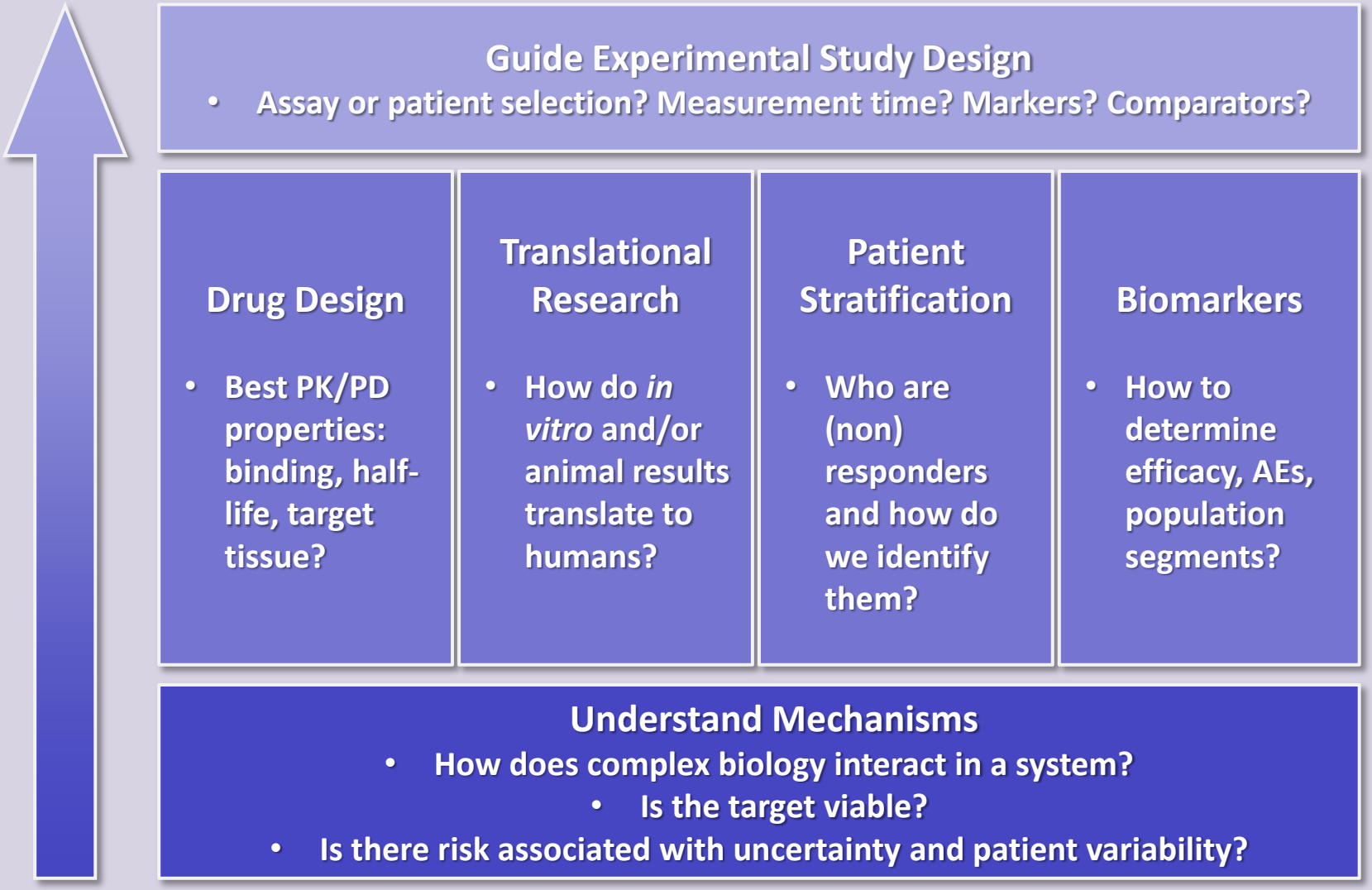
Simulate in vitro *or* in vivo *studies or clinical trials*

PhysioPD Research Project Objectives support fundamental goals essential for effective R&D.

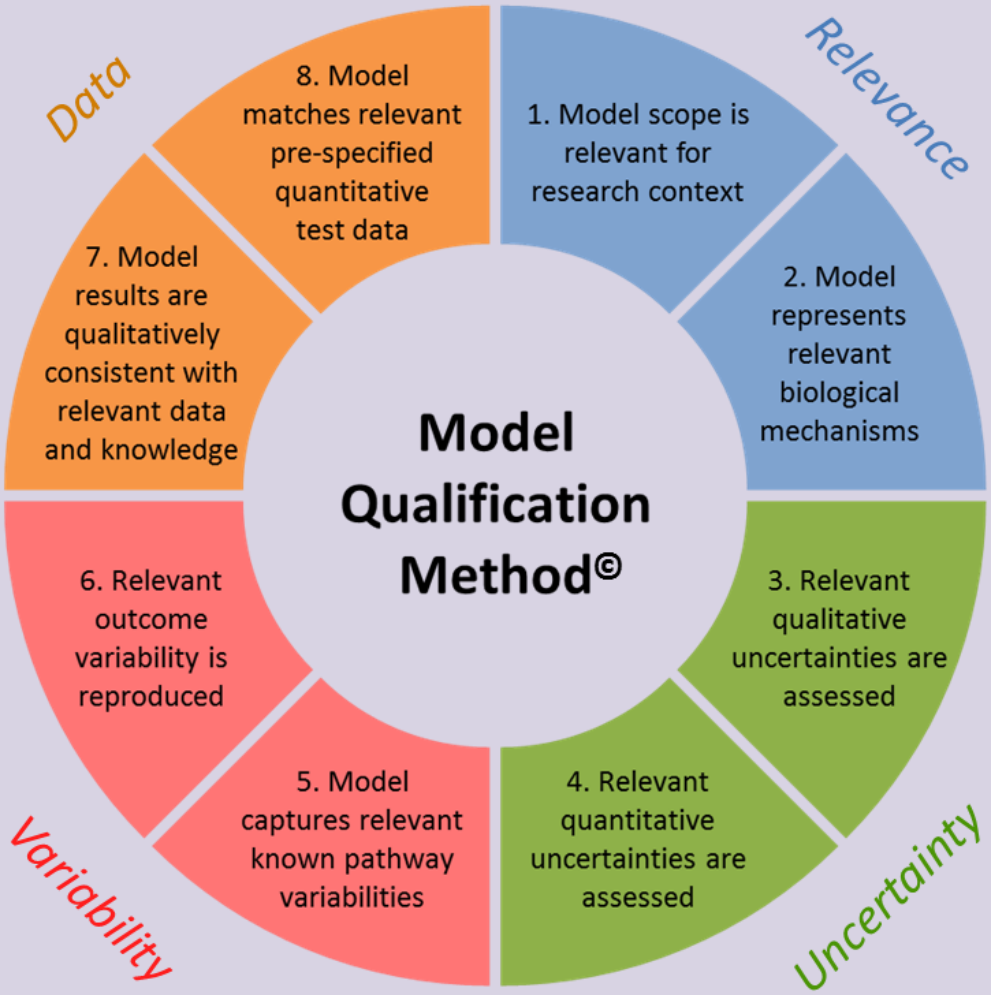


- ARTICULATE non-obvious implications of known biological behaviors
- UNDERSTAND the impact of biological uncertainty
- PRIORITIZE and FOCUS experimental design and interpretation

PhysioPD Research Objectives: Connecting Mechanisms to Outcomes

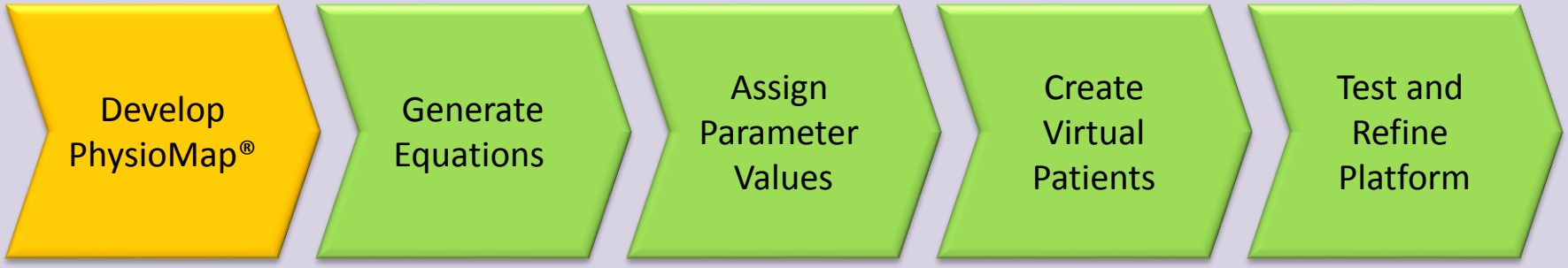


Rosa's Model Qualification Method ensures that the Platforms are fit for purpose.

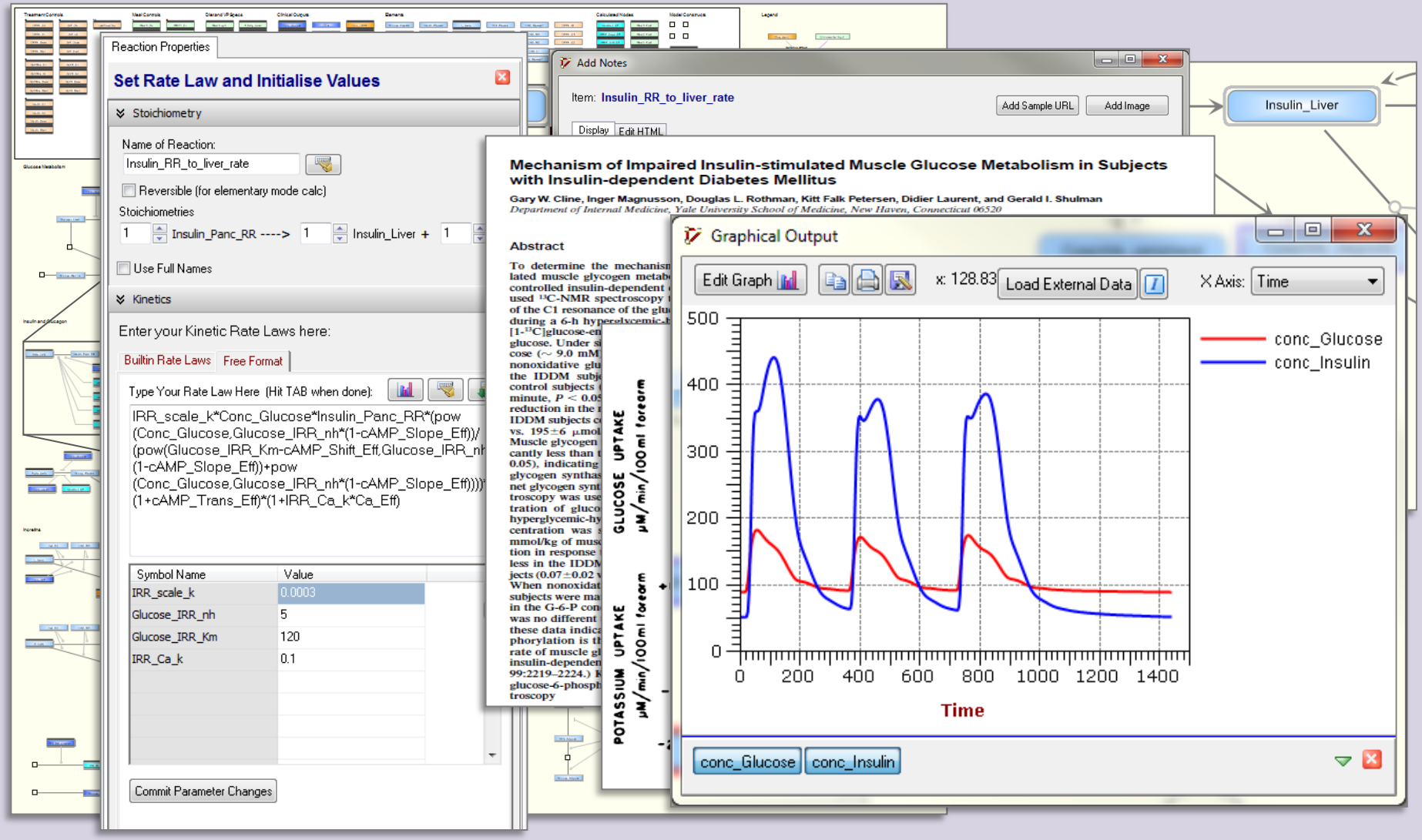


Ref: Friedrich, et al. (2011)

Process for Creating PhysioPD Research Platforms



A PhysioPD Research Platform includes a PhysioMap® and a mathematical representation of biology: Metabolism Example

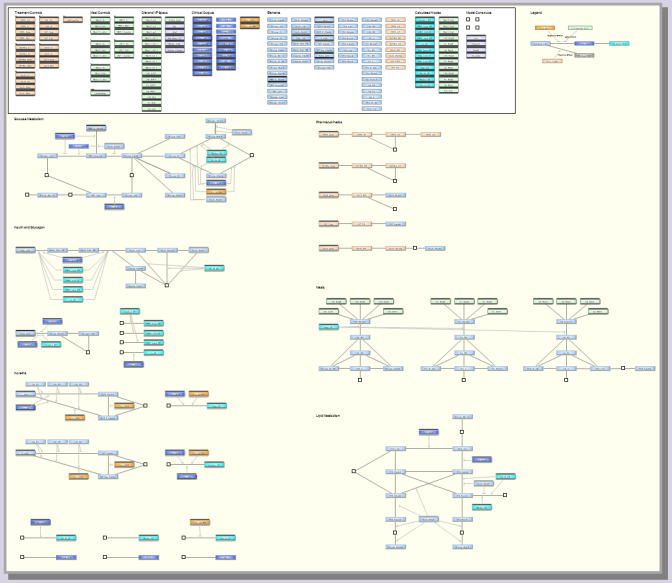


JDesigner can be obtained at http://jdesigner.sourceforge.net/Site/JDesigner.html

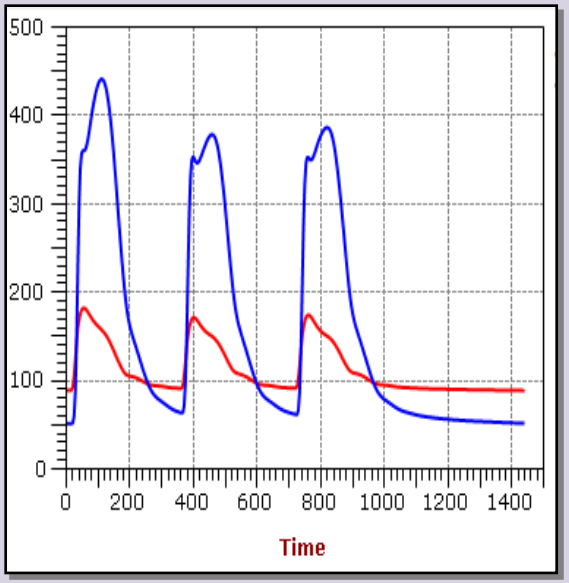
PhysioPD Research Platforms are built with extensive research, curation and integration of disparate information.

- Physical Laws
- Healthy & Disease Physiology
- Target(s) & Drug Mechanism(s)
- Preclinical Pharmacology

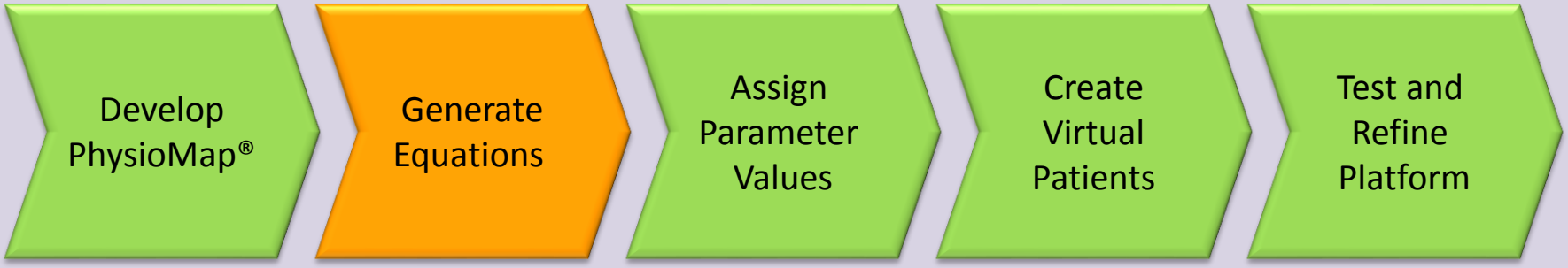
PhysioPD Research Platform



PhysioPD Research Results



Process for Creating PhysioPD Research Platforms



Rate arrows in a Platform are quantified using standard engineering techniques to represent biological interactions.

Examples of common equation forms:

- First Order Equations

  $rate\_k*S$

- Hill Equation Modifier – Potentiation

$$1 + Emax \times \frac{L^{nh}}{EC50^{nh} + L^{nh}}$$

- Hill Equation Modifier – Activation

$$Emax \times \frac{L^{nh}}{EC50^{nh} + L^{nh}}$$

- Hill Equation Modifier - Inhibition

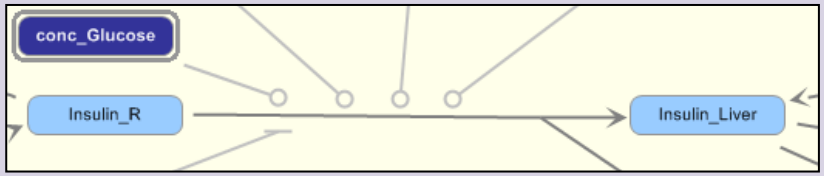
$$1 - Imax \times \frac{L^{nh}}{IC50^{nh} + L^{nh}}$$

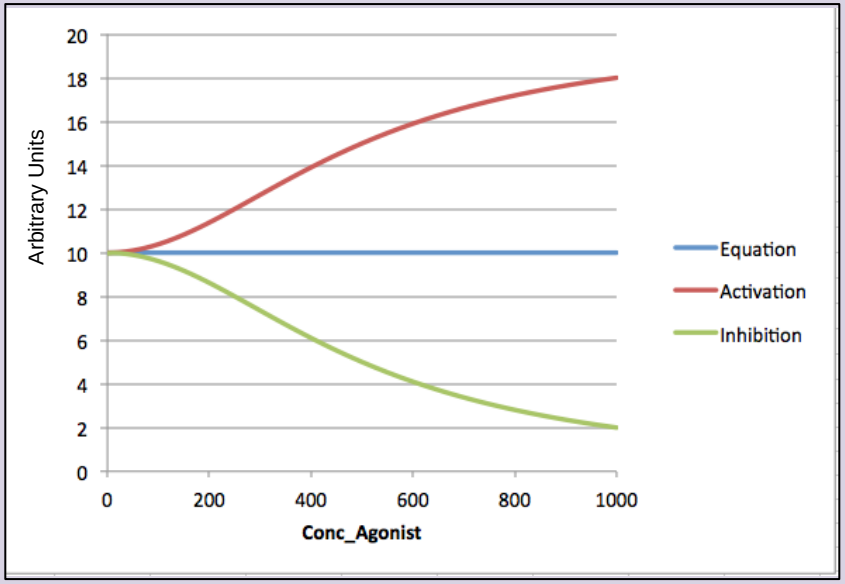
Emax, Imax = maximum activation or inhibition effect (Emax ≥ 0, 0≤ Imax ≤1)

L = amount of ligand present

EC50, IC50 = ligand amount at 50% effect

nh = Hill coefficient

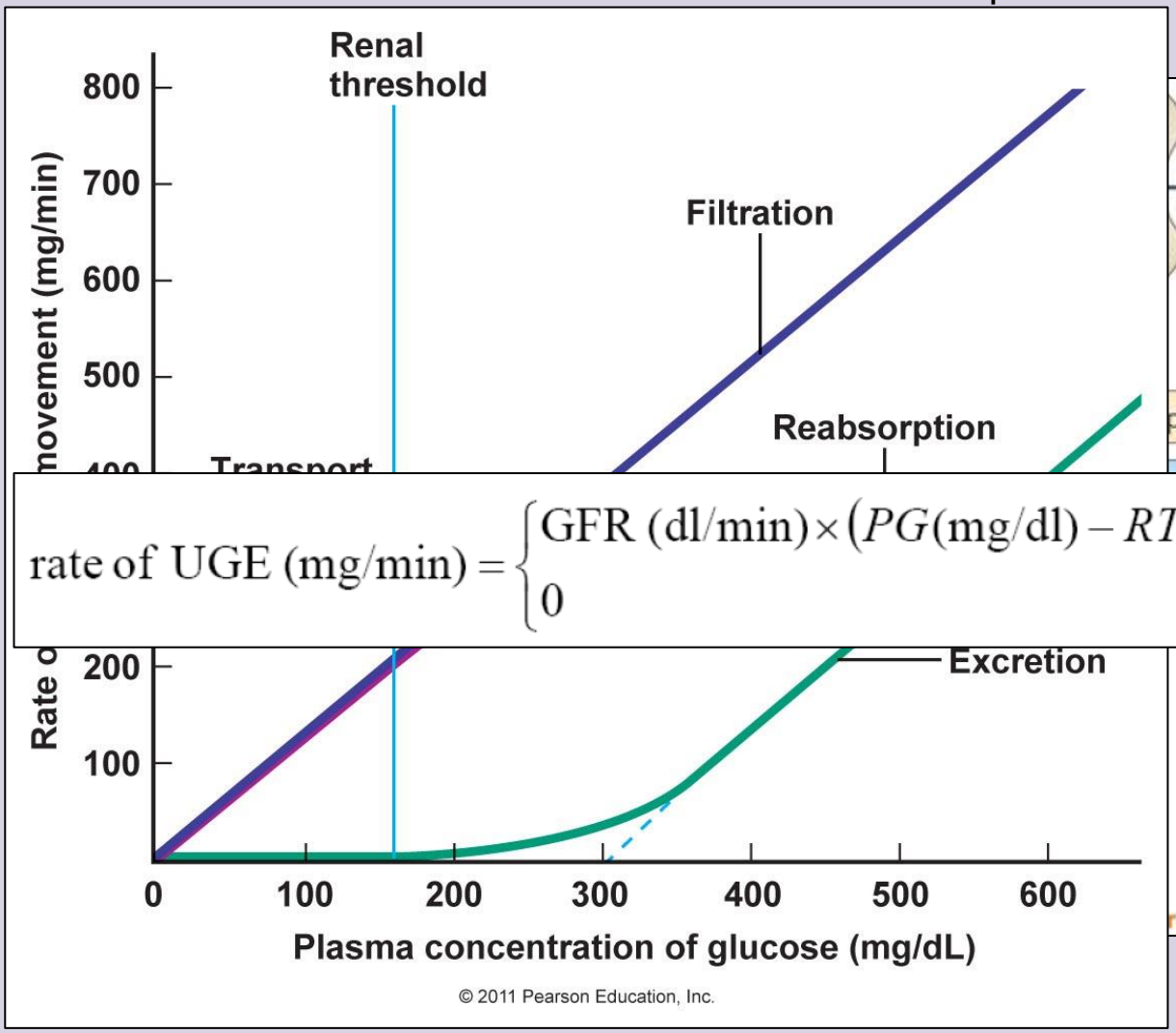




Example: modeling of mediator effects.

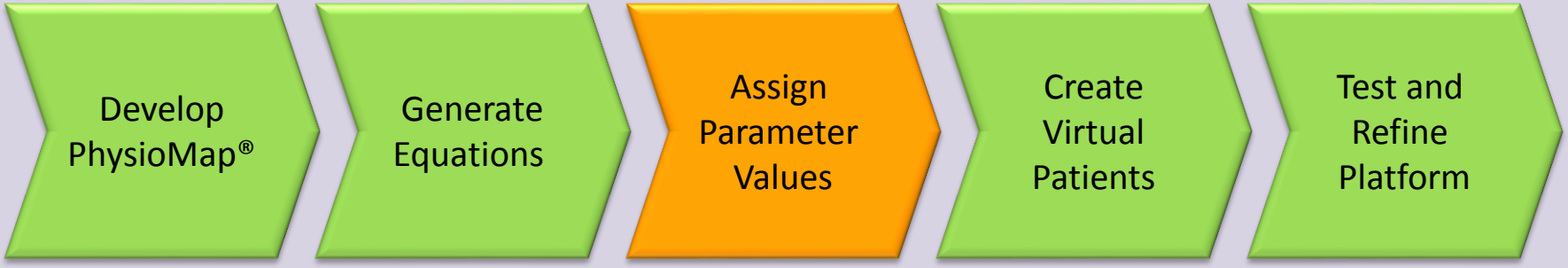
Equation forms may be derived from first principles, locally fitted to mechanistic data, or created by hypothesis.

Renal Glucose Reabsorption



$$\text{rate of UGE (mg/min)} = \begin{cases} \text{GFR (dl/min)} \times \left(PG(\text{mg/dl}) - RT_G(\text{mg/dl})\right) & \text{if } PG > RT_G \\ 0 & \text{if } PG \le RT_G \end{cases}$$

Process for Creating PhysioPD Research Platforms

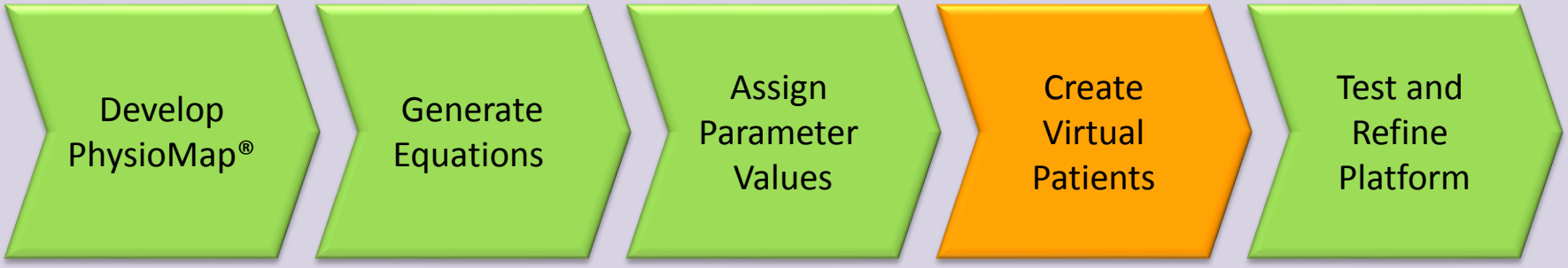


Parameter values in a Platform are identified by literature survey and data analysis, local fitting, or hypotheses.

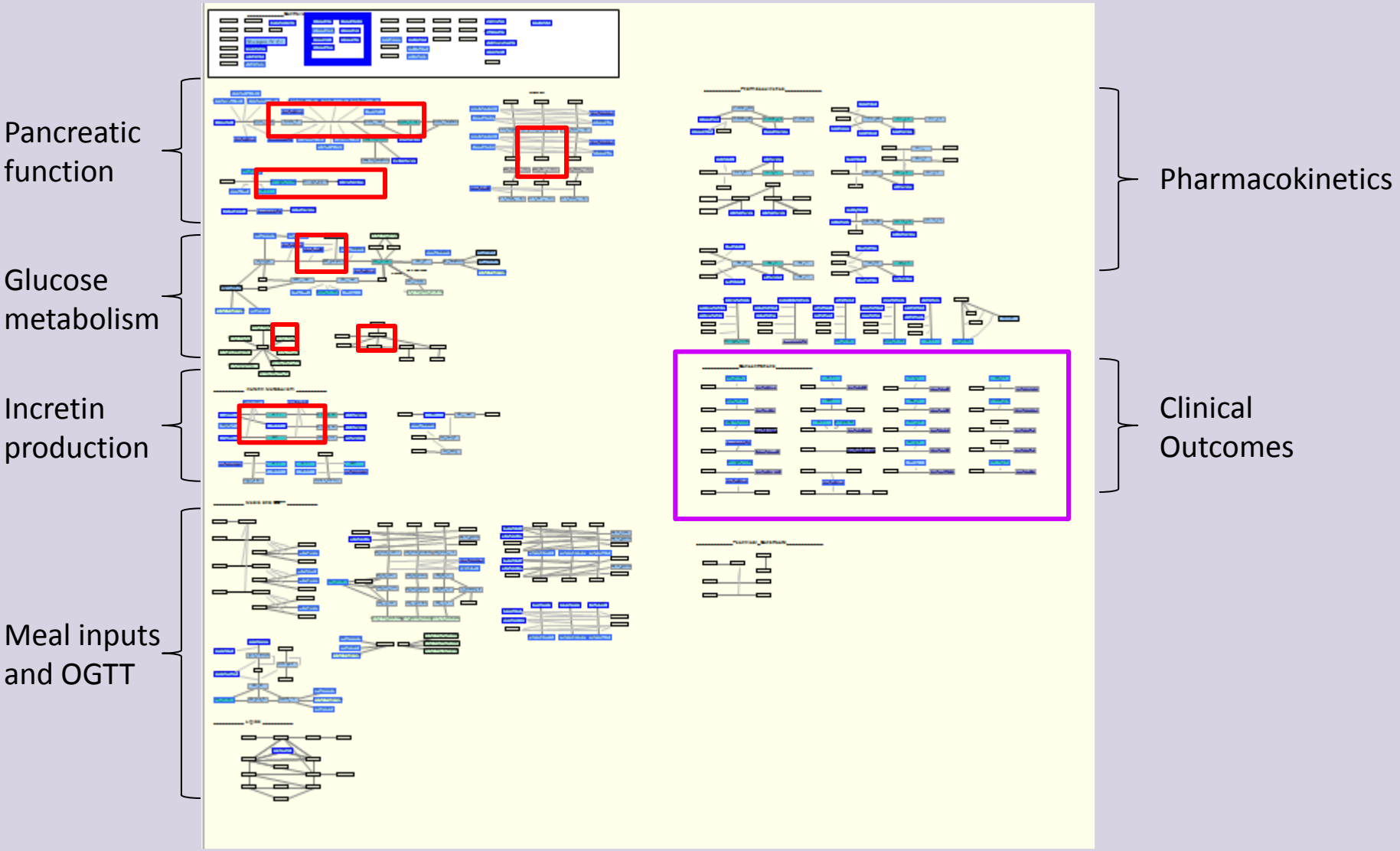
Reference	Description	Tissue	Disease status	Type or Specie	Amount	Units	Amount in Model Units	Model Units
Insulin kinetics								
Insulin clearance								
Tura 2001	hepatic insulin extraction	liver	healthy	human	41.3	L/min	41.3	L/min
Tura 2001	Hepatic insulin clearance	liver	healthy	human	0.66	L/min	0.66	L/min
Sherwin et al., 1974								
Sherwin et al., 1974								
Polonsky 1988								
Tura 2001								
Sherwin et al., 1974								
Sherwin et al., 1974								
Sherwin et al., 1974								
Krützfeldt 2000								
Sherwin et al., 1974								
Insulin								
Not healthy								
Tura 2001								
Tura 2001								
Polonsky 1988								
Tura 2001								
Tura 2001								

Description	Tissue	Disease status	Type or Specie	Amount	Units
in extraction	liver	healthy	human	41.3	L/min
lin clearance	liver	healthy	human	0.66	L/min
tion hepatic	liver	healthy	human	47	%
nce hepatic	liver	healthy	human	400	ml/min
c insulin extraction	liver	healthy	human	53.1	%
ulin clearance	whole body	healthy	human	1.19	L/min
tion peripheral	Whole body	healthy	human	20	%
sma flow	Whole body	healthy	human	660	ml/min

Process for Creating PhysioPD Research Platforms

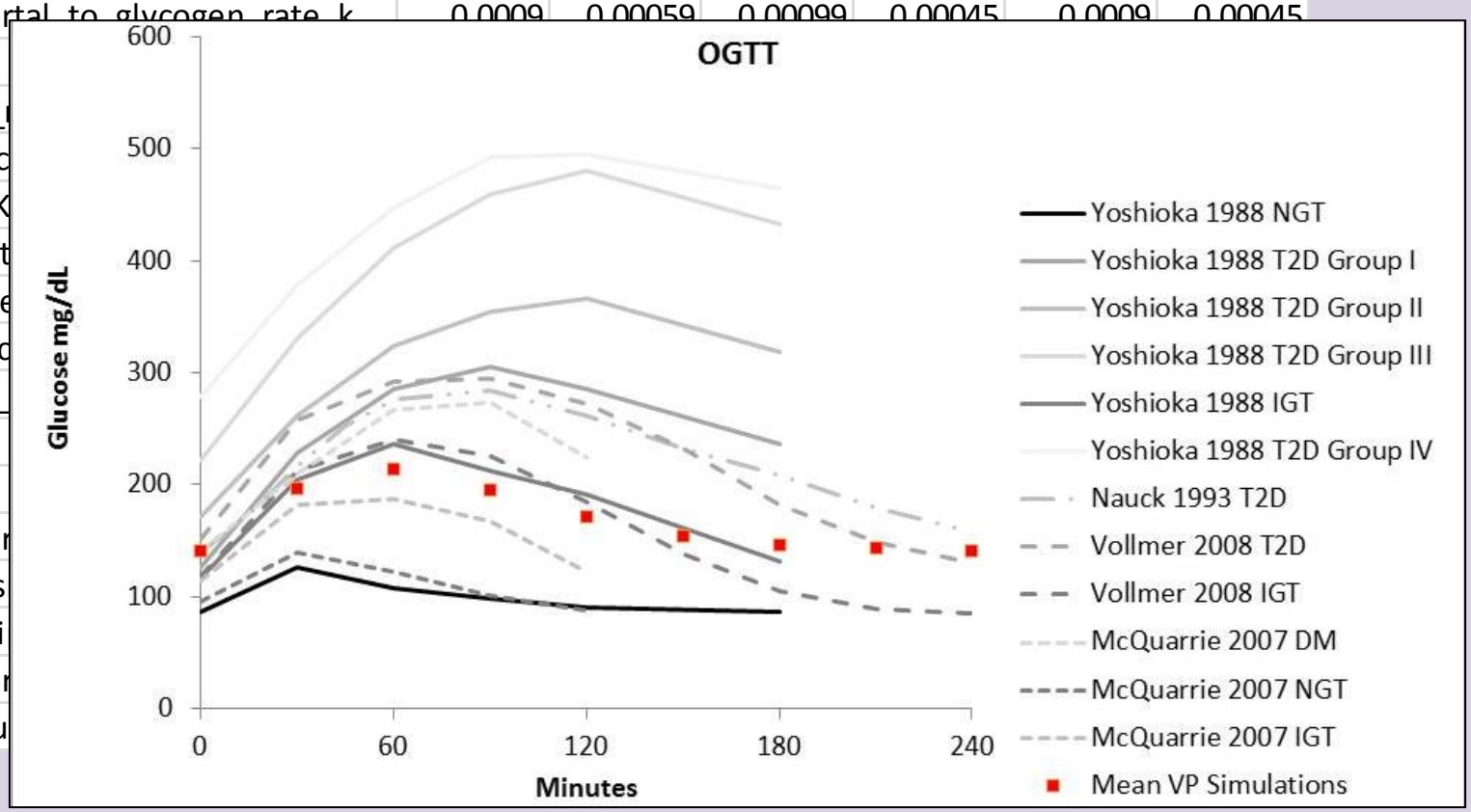


Specific parameters in a Platform are adjusted to create Virtual Patients (VPs) with different pathophysiology or phenotypes.



Alternate VPs are created with biologically plausible parameter values that are constrained by data and system behaviors.

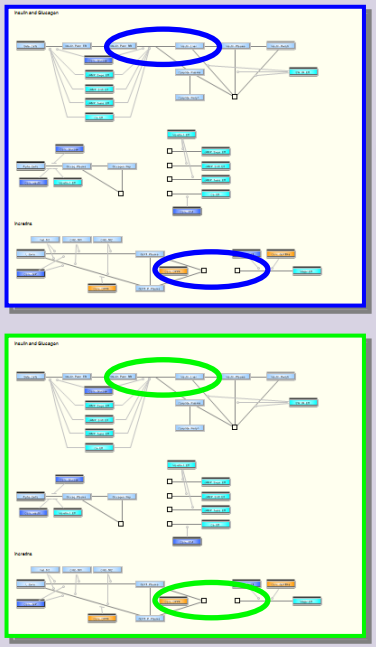
	Healthy	VP1	VP2	VP3	VP4	VP5
Gluconeog_rate_max	106.9	116.9	126.9	185	126.9	250
Gluconeog_Shift	90	110	95	135	101	210
Glycogenolysis_rate_k	1.6	1.8	2.1	1.5	1.6	2.555
Body_weight	70	127	75.3	108.9	81	123
G6P_periportal_to_glycogen_rate_k	0.0009	0.00059	0.00099	0.00045	0.0009	0.00045
GK_Liver						
Insulin_GK_						
G6P_to_glyc						
G6P_Liver_K						
G6P_to_met						
Glucose_live						
Insulin_Gluc						
Glucose_SE_						
ISR_Shift						
ISR_scale_k						
Insulin_liver						
Insulin_plas						
Insulin_peri						
Glucagon_pr						
Glucose_glu						



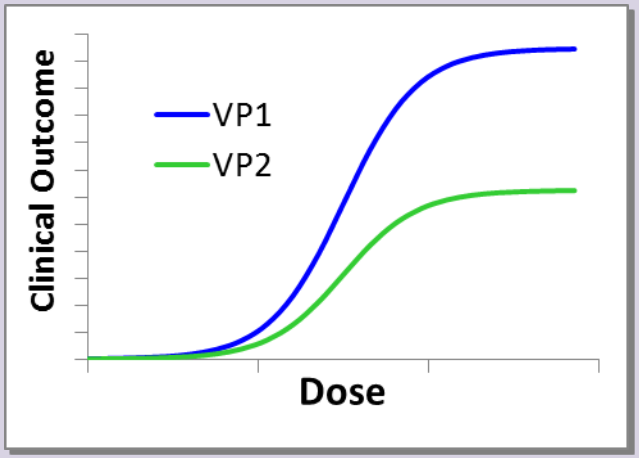
VPs facilitate exploration of how mechanistic biological differences may affect clinical outcomes.

Explore mechanistic hypotheses and known variability

Mechanisms

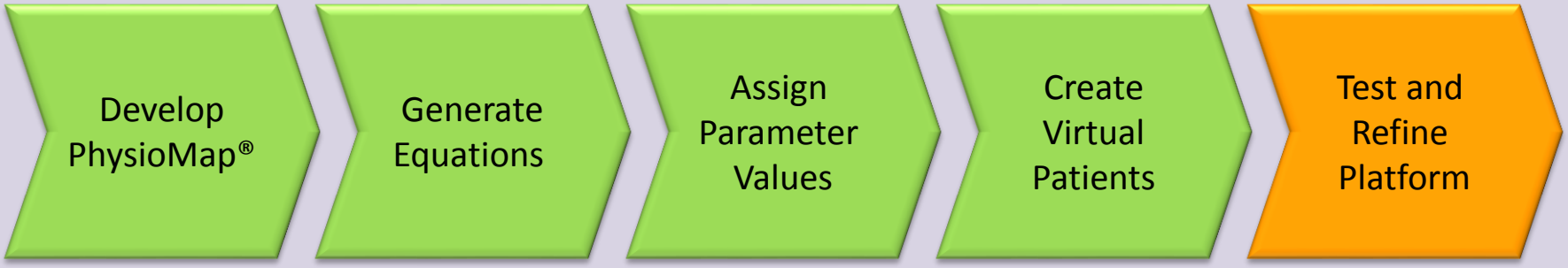


Outcomes



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

Process for Creating PhysioPD Research Platforms



A Platform is tested against multiple datasets describing sub-system behaviors and refined if necessary.

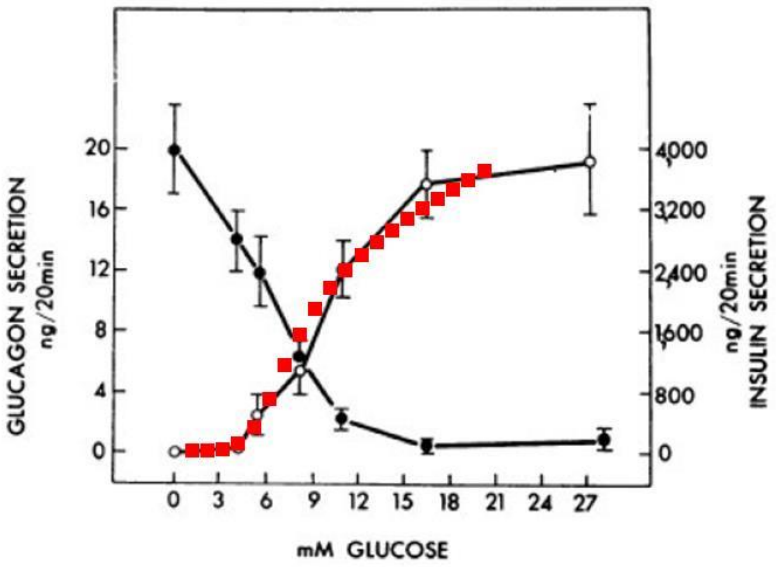
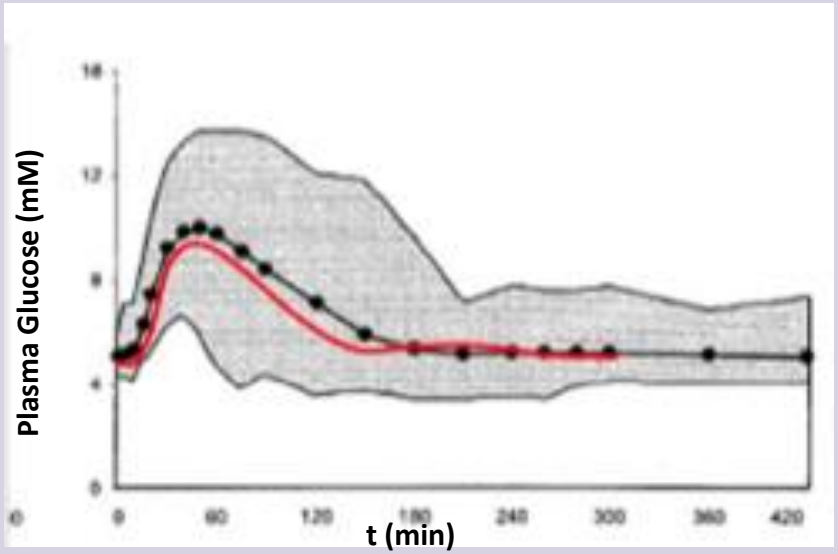
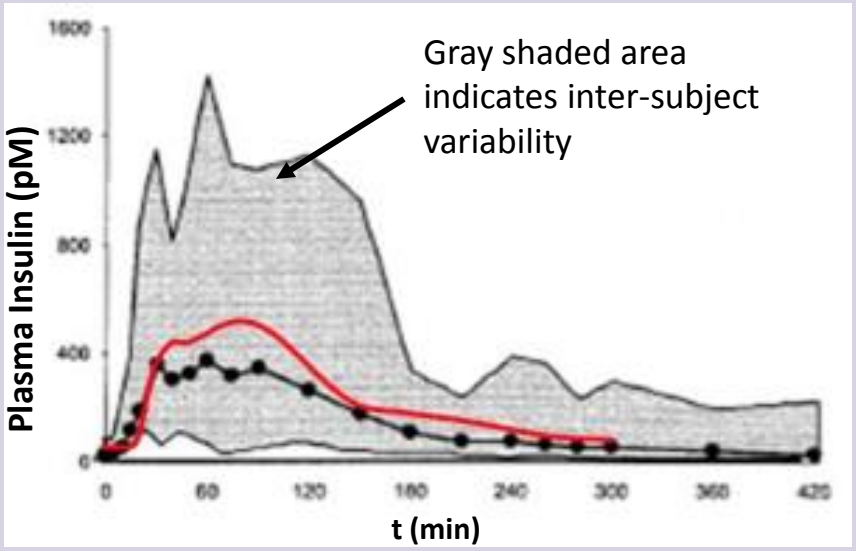


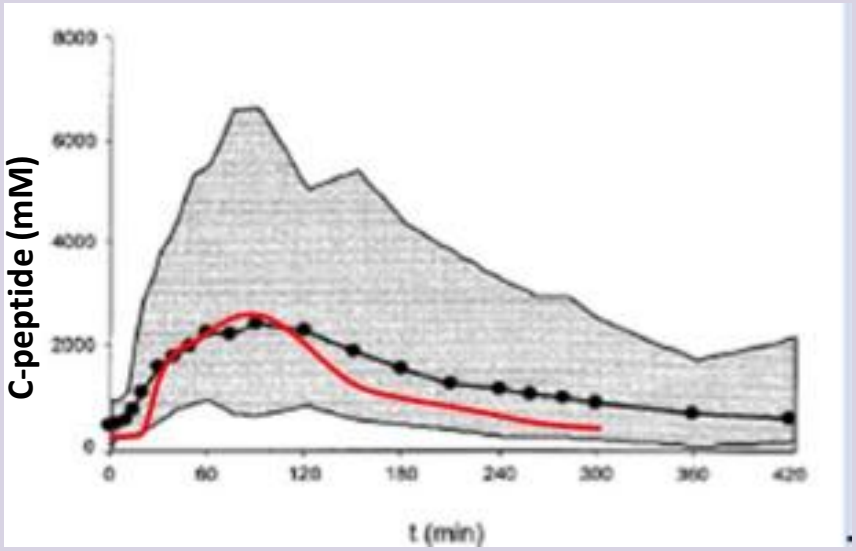
FIGURE 2 Comparison of effects of various concentrations of glucose on glucagon (●) and insulin (○) release from the in vitro perfused rat pancreas. Each point ($n = 6$) represents the total hormone released during a separate 20 min infusion of glucose, mean ±SE.

- The simulated insulin secretion rate as a function of glucose concentration (red squares) is in agreement with experimental data (Gerich, et al. 1974)

A Platform is then tested against multiple datasets describing whole-system behaviors and refined if necessary.







- Red line is simulation
- Data from Dalla Man (2005)

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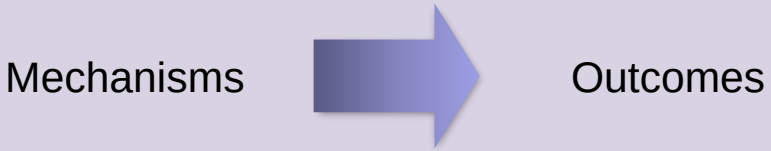
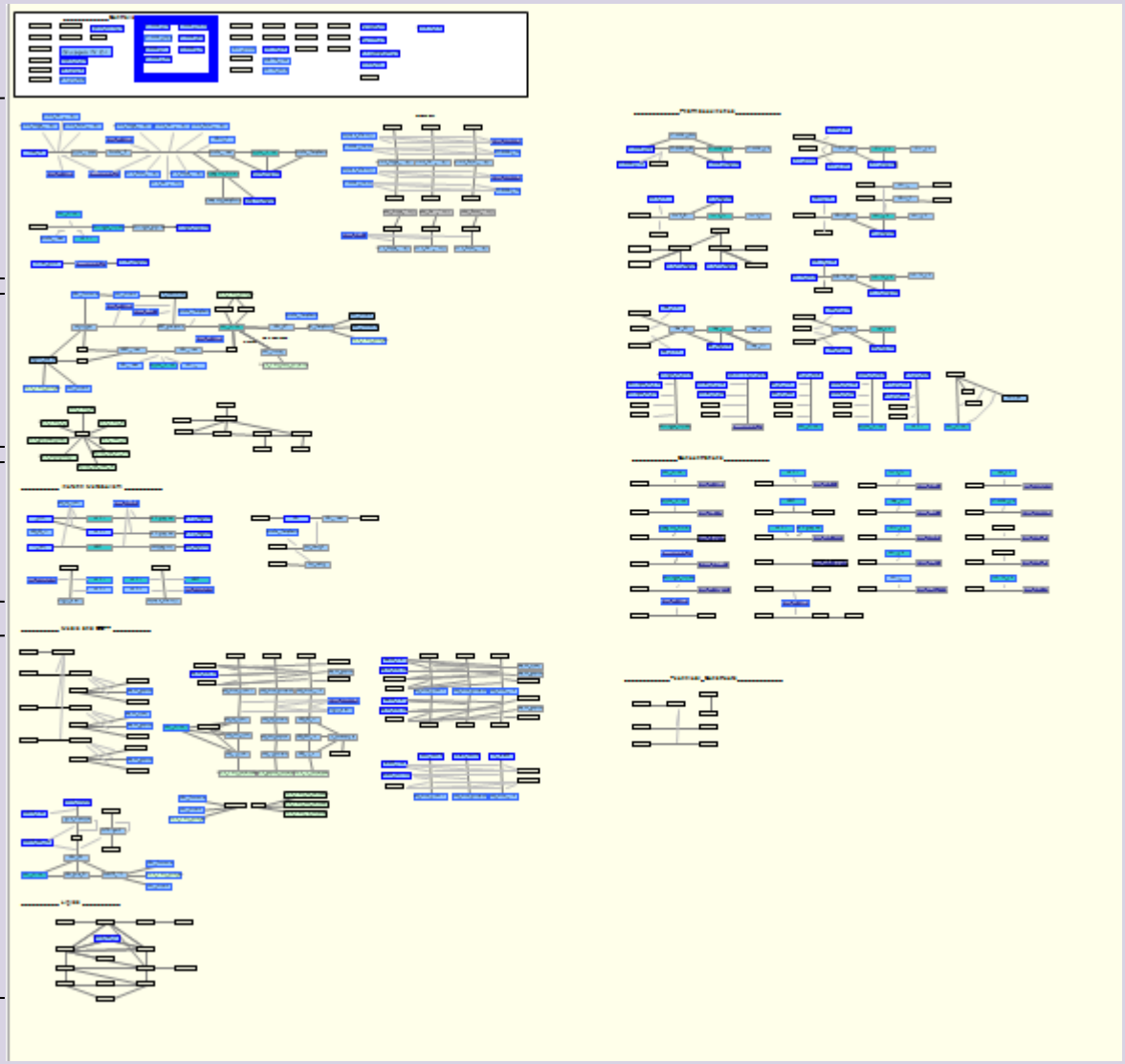
Case Study

Critical questions for a program entering clinical development

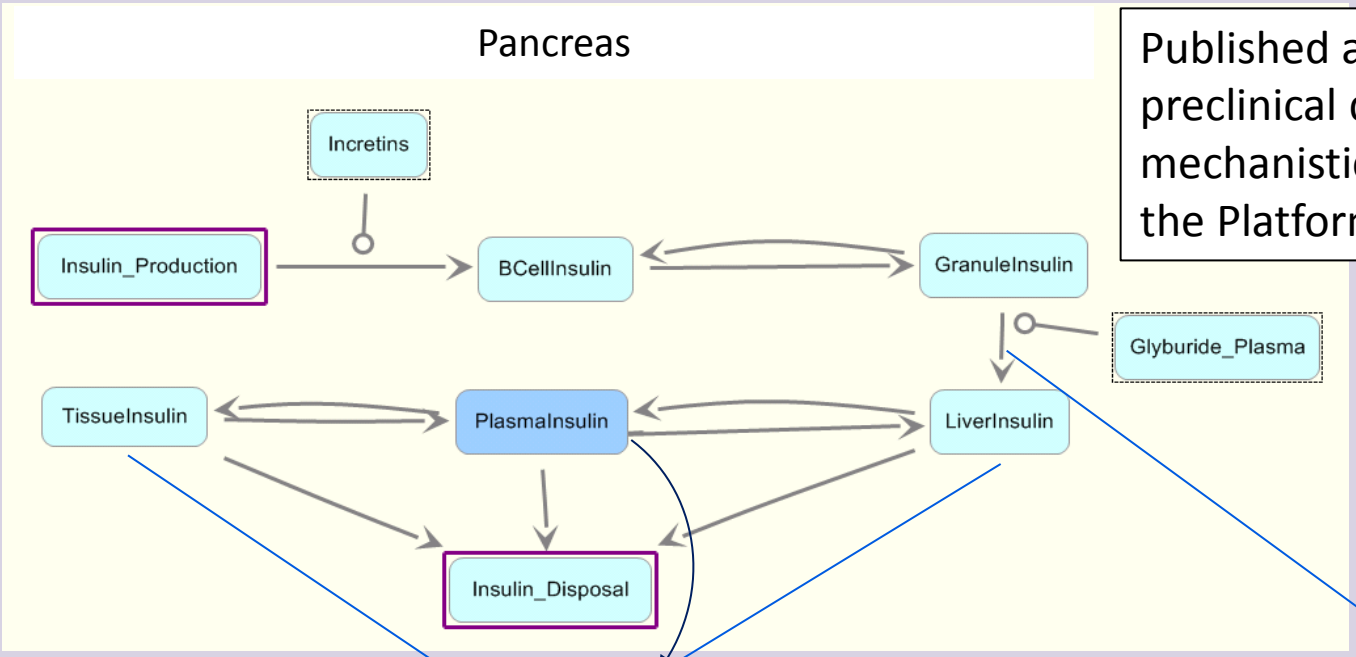
- Target evaluation
  - Will a compound against this drug target be efficacious in humans?
  - Which mechanisms of action are critical for efficacy?
- Translational medicine
  - Are our preclinical data predictive of efficacy in humans?
- Clinical trial optimization
  - How will different types of patients respond to the compound?
  - Can we prospectively identify patients likely to respond?
  - What is the most efficient trial design to demonstrate treatment effects?



A Disease PhysioMap represented the key aspects of the biology relevant to type 2 diabetes and the research questions.

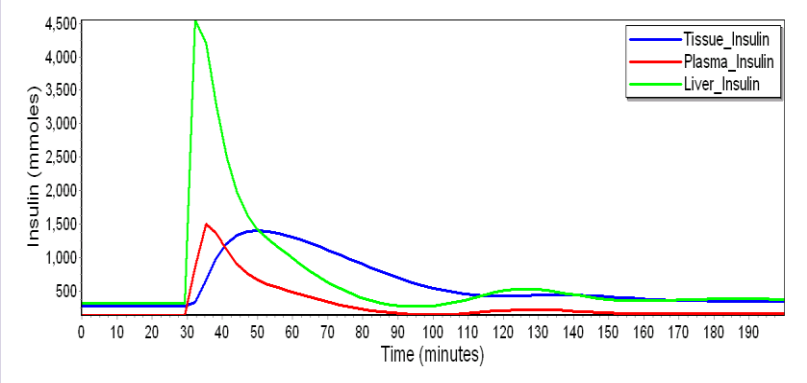


A PhysioPD Platform represented the quantitative relationships between elements of the biological system.

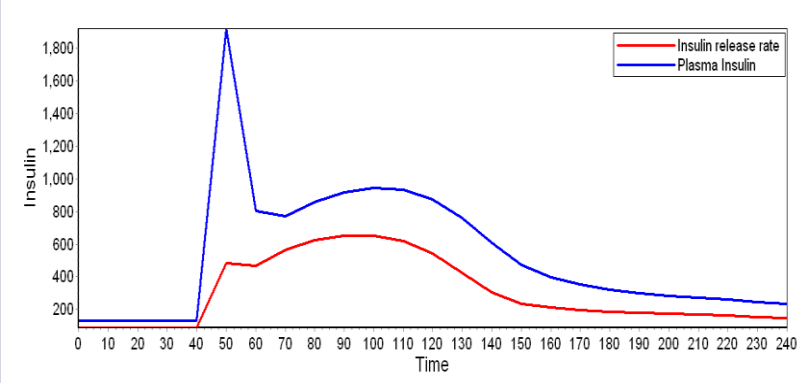


Published and proprietary preclinical data provided key mechanistic information to build the Platform.

Changes in insulin compartments

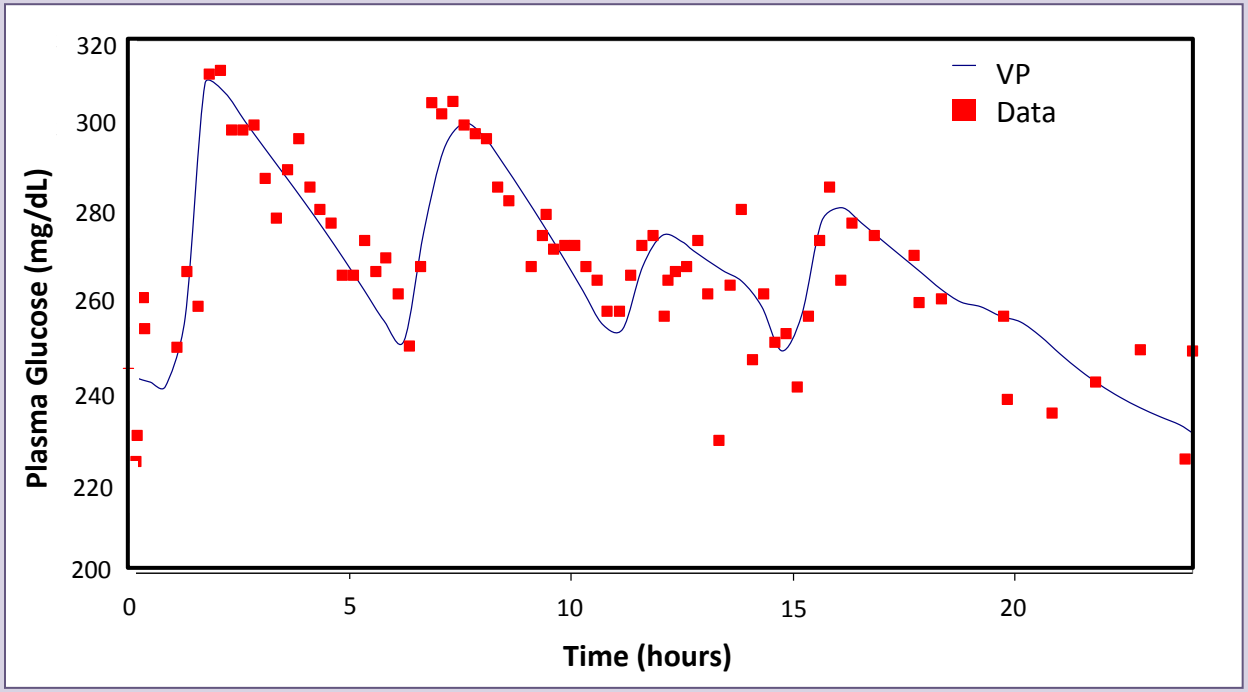


Changes in insulin release rate



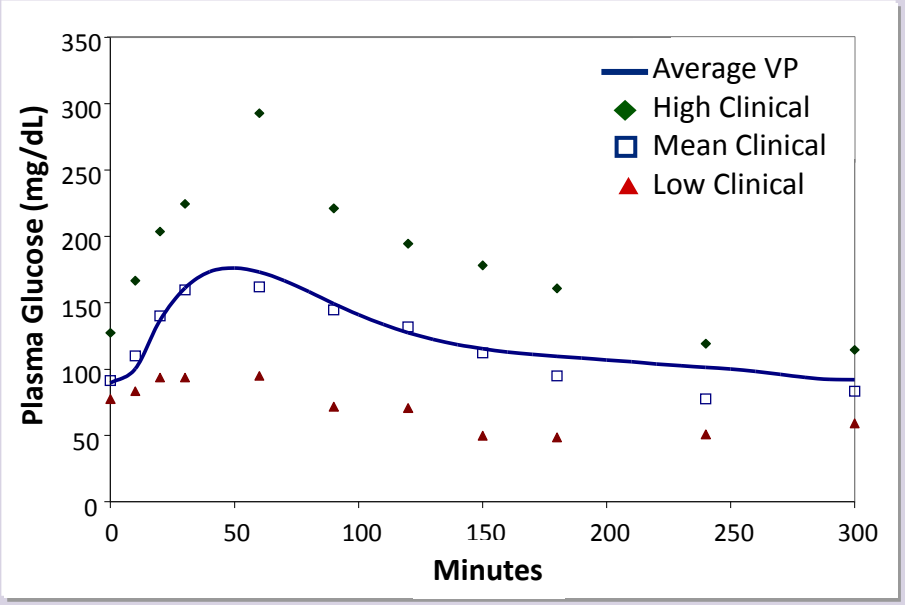
VPs were created to simulate clinical trials with the compound.

Single Virtual Patient compared to data

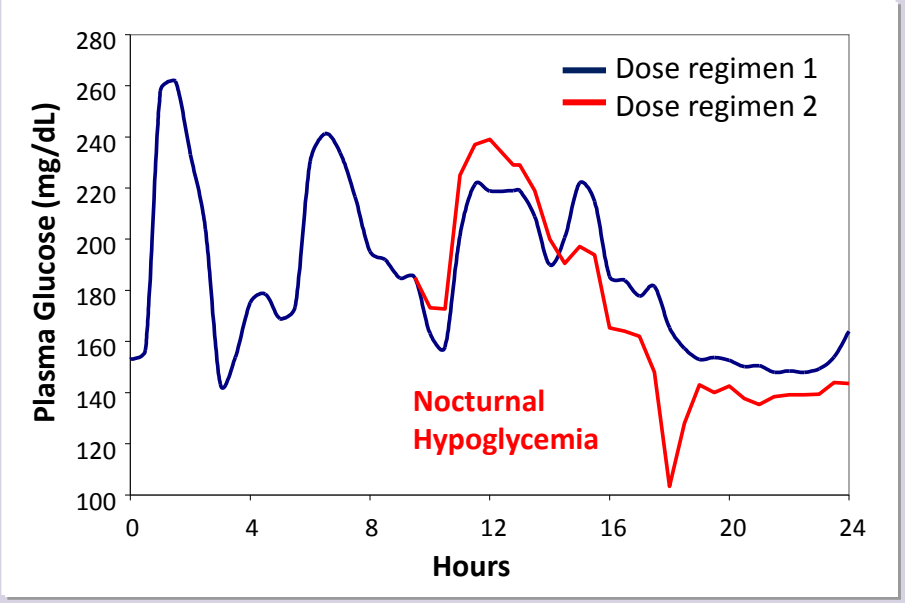


A wide range of protocols under consideration were simulated to guide the design of the clinical trial.

Ave. model OGTT compared to public literature

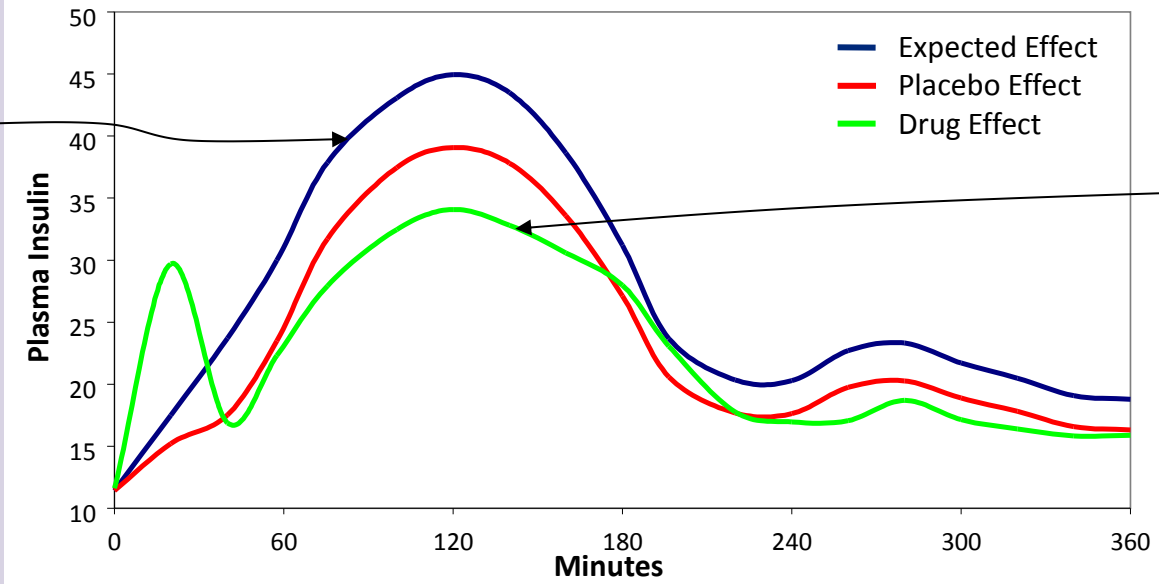


Multiple meals, snacks, complex dosing



Contrary to client expectations, PhysioPD research showed that compound administration would lower plasma insulin.

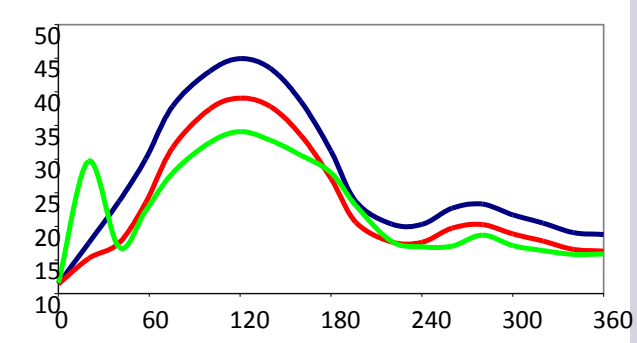
Expectation

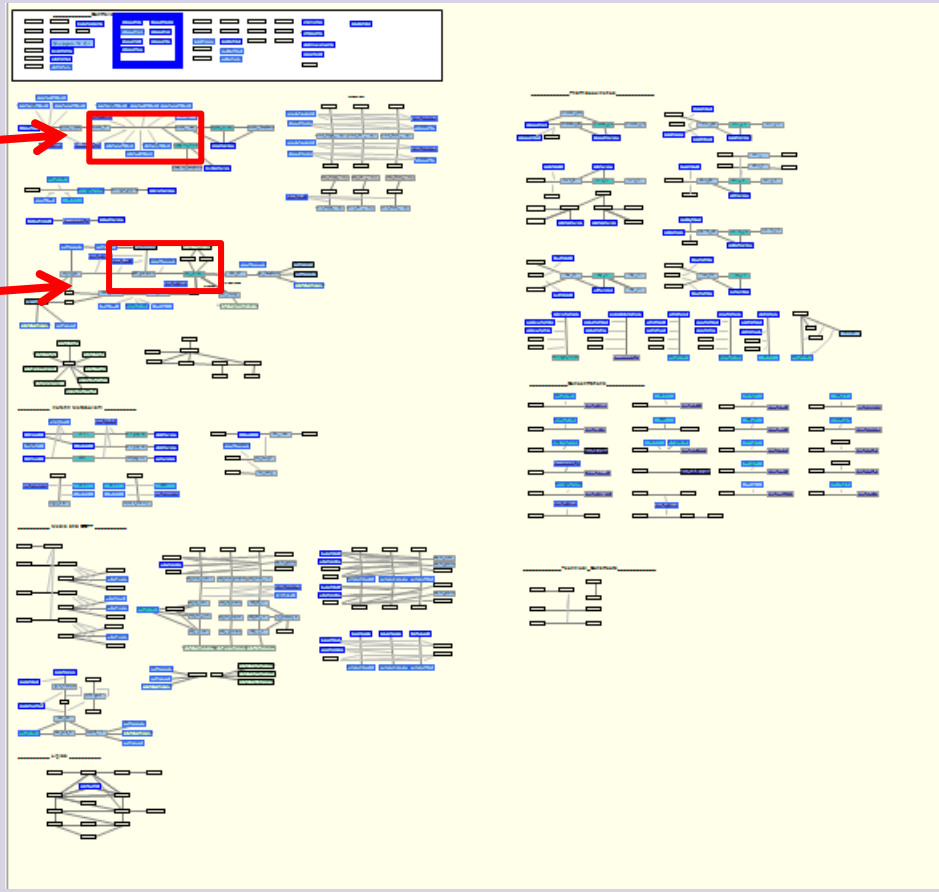


Actual simulation result

PhysioPD research provided a mechanistic rationale for the unexpected behavior of the compound.

- The PhysioMap process identified multiple hypothesized compound effects
- These effects have opposite effects on insulin secretion

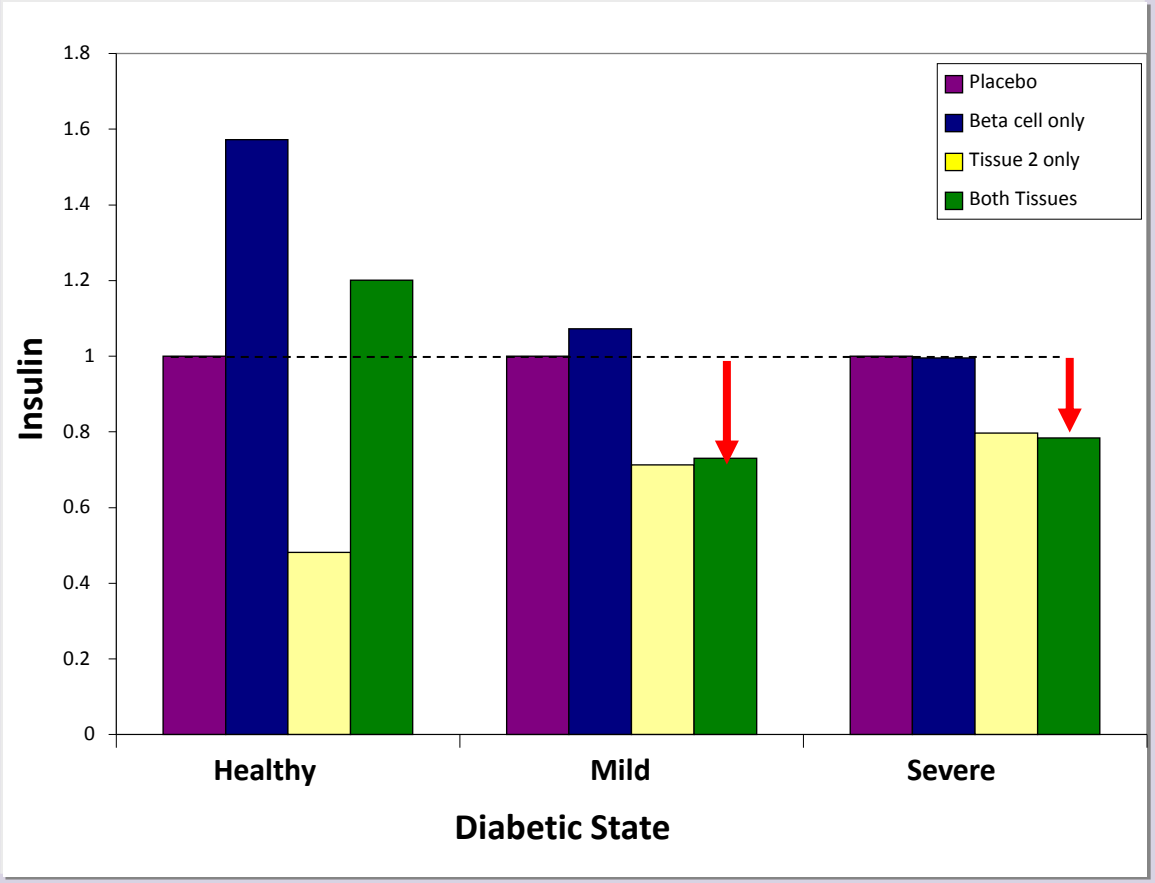




- This complex behavior was not previously identified using non-mechanistic PK/PD modeling

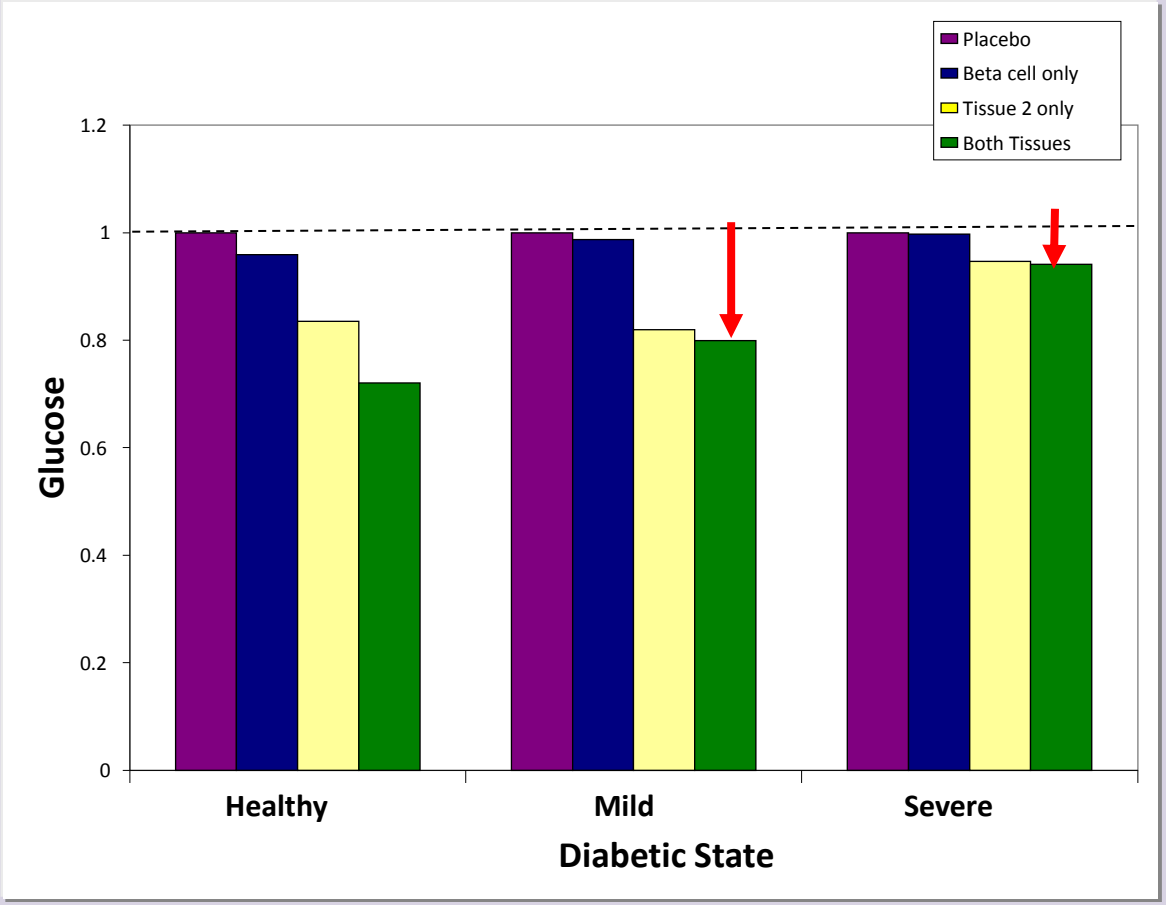
Simulations highlighted the relative impact of each hypothesized compound effect.

- Compound effect in the beta cell alone increased or maintained plasma insulin
- Compound effect in another tissue alone reduced plasma insulin
- The combination of these effects resulted in lower plasma insulin in diabetic VPs



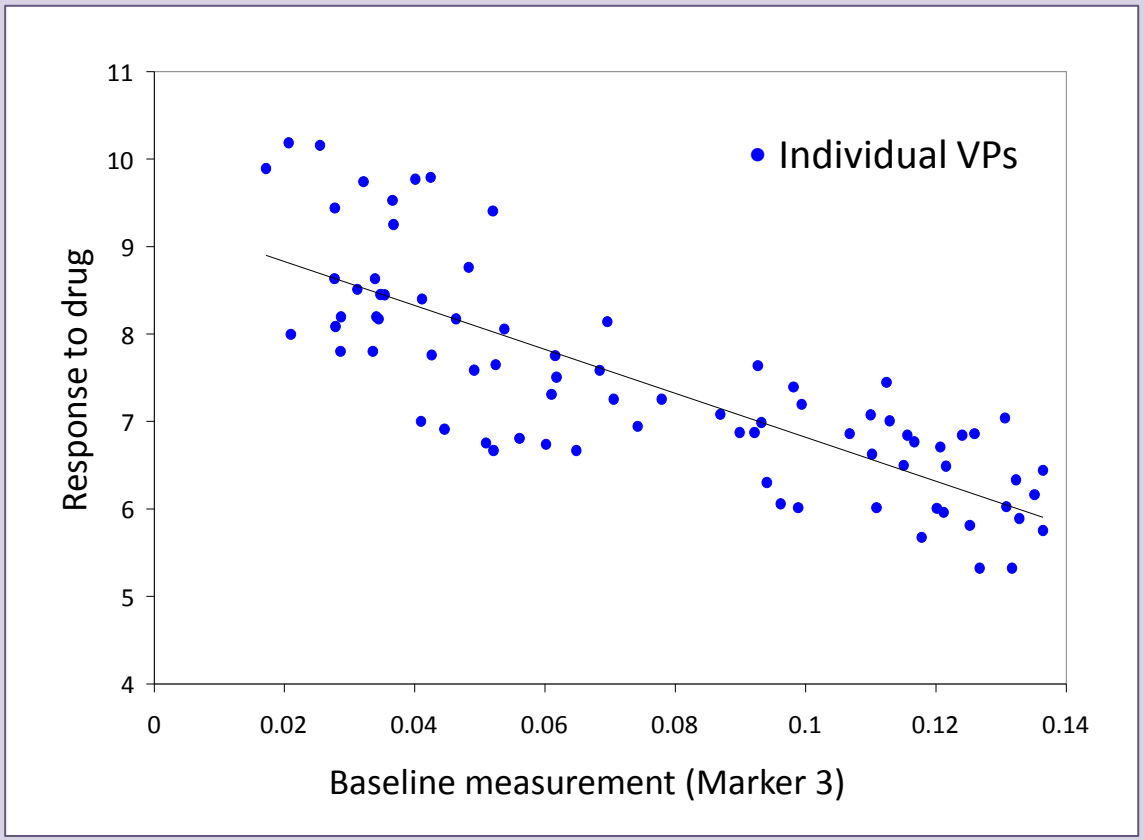
Simulations in multiple VPs revealed that efficacy was also dependent on patient phenotype and pathophysiology.

- Compound was less efficacious as diabetes severity increased
- PhysioPD research suggested this was due to reduced insulin secretory capacity



PhysioPD research identified a potential mechanistic biomarker distinguishing high responders from low responders.

Simulated biomarker 3 relationship to response

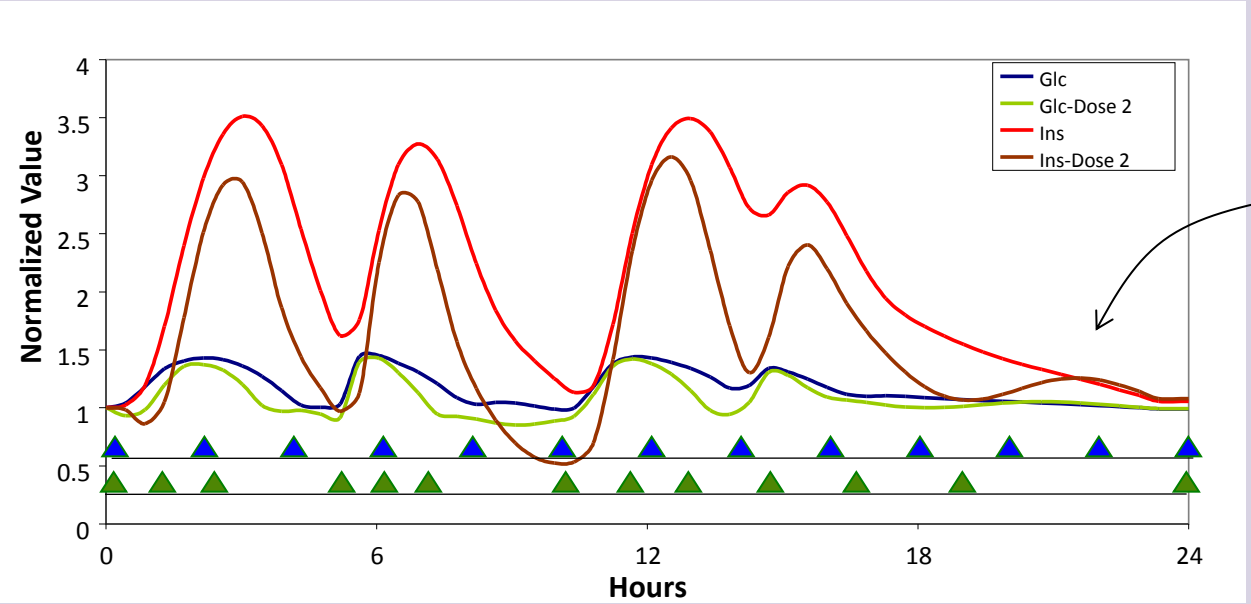


Marker	Correlation	P-Value
Marker 2	-0.107	0.4323
Marker 3	0.548	0.0083
Marker 4	0.004	0.9739
Marker 6	0.392	0.0026
Marker 7	-0.058	0. 6872
Marker 8	0.254	0.0587

PhysioPD research identified improvements for the proposed clinical trial design.

- Dose times relative to meals were optimized to increase sampling when treatment effect was greatest.
- Nighttime sampling was reduced without impacting trial predictive power.

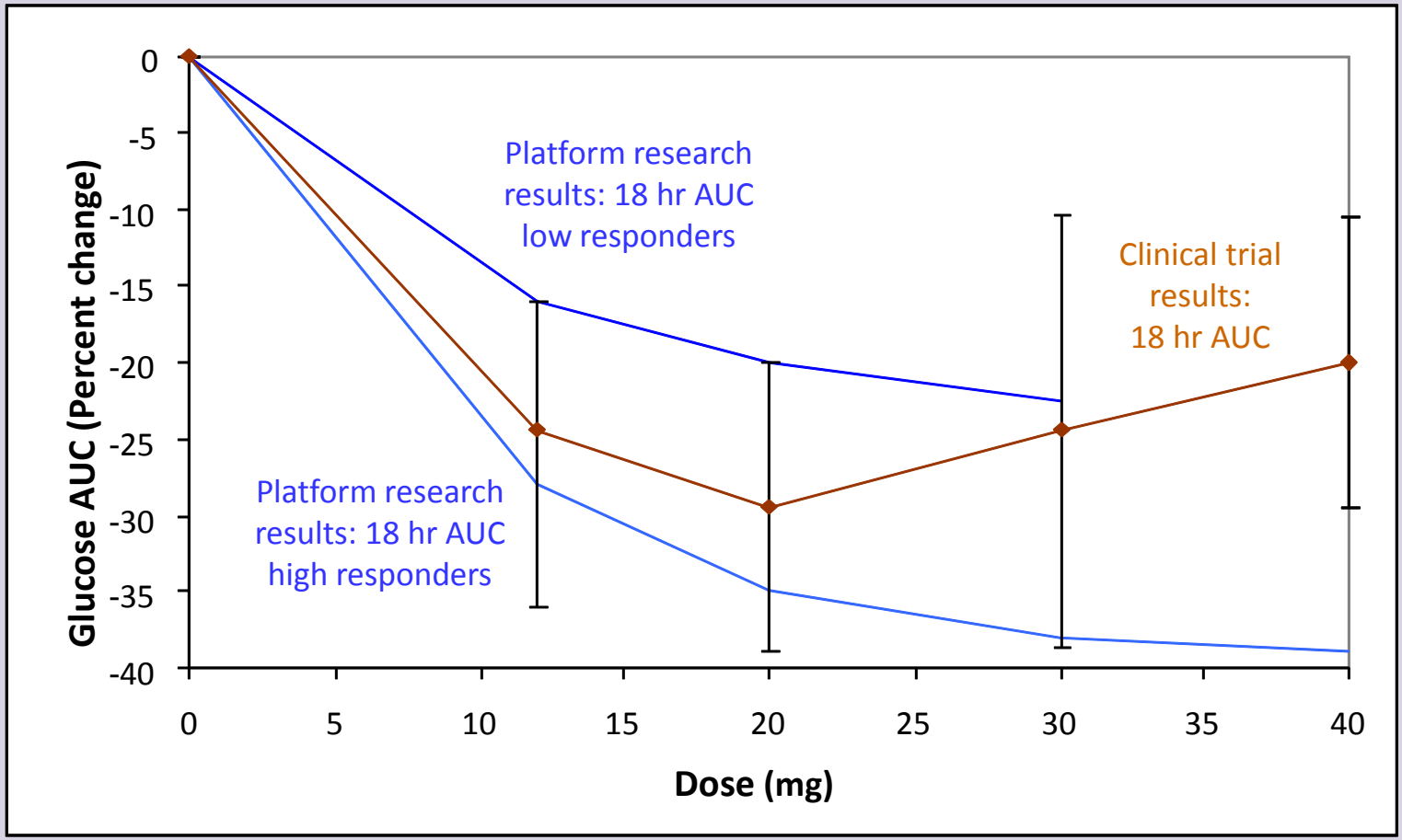
Glucose and insulin time course



Fewer samples needed at night

▲ Planned collection
▲ Revised collection

PhysioPD research resulted in the design of a successful first in human clinical trial.



Case Study Conclusions

- PhysioPD research gave critical mechanistic insight and guidance that optimized the clinical trial design and accelerated compound development
  - Aided interpretation of preclinical pharmacodynamic data
  - Identified responder and non-responder characteristics to guide patient inclusion criteria
  - Identified potential efficacy biomarker
  - Optimized sampling frequency to maximize opportunity to demonstrate treatment effect

Summary and Conclusions

- PhysioPD research makes more complete use of existing data and biological knowledge, creates a bridge from mechanisms to outcomes, and facilitates:
  - Improved clarity and quantitative understanding of existing information
  - Efficient hypothesis generation and testing
  - Experimental designs that resolve key uncertainties and address variability

- By focusing on improving decisions, PhysioPD research has successfully impacted drug development in many, diverse therapeutic indications

THANK YOU!