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

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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

PK & PD Mechanism(s)

Biological System

Research Simulations

Simulate in vitro or in vivo studies or clinical trials

Target MOA and/or compound pharmacology
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

**Guide Experimental Study Design**

**Drug Design**
- Best PK/PD properties: binding, half-life, target tissue?

**Translational Research**
- How do *in vitro* and/or animal results translate to humans?

**Patient Stratification**
- Who are (non) responders and how do we identify them?

**Biomarkers**
- How to determine efficacy, AEs, population segments?

**Understand Mechanisms**
- How does complex biology interact in a system?
  - Is the target viable?
  - Is there risk associated with uncertainty and patient variability?
Rosa’s Model Qualification Method ensures that the Platforms are fit for purpose.

Ref: Friedrich, et al. (2011)
Process for Creating PhysioPD Research Platforms

1. Develop PhysioMap®
2. Generate Equations
3. Assign Parameter Values
4. Create Virtual Patients
5. Test and Refine Platform
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**

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

Examples of common equation forms:

- **First Order Equations**
  \[ \text{rate}_k \times S \]

- **Hill Equation Modifier – Potentiation**
  \[ 1 + E_{\text{max}} \times \frac{L^{nh}}{EC50^{nh} + L^{nh}} \]

- **Hill Equation Modifier – Activation**
  \[ E_{\text{max}} \times \frac{L^{nh}}{EC50^{nh} + L^{nh}} \]

- **Hill Equation Modifier - Inhibition**
  \[ 1 - I_{\text{max}} \times \frac{L^{nh}}{IC50^{nh} + L^{nh}} \]

\(E_{\text{max}}, I_{\text{max}} = \text{maximum activation or inhibition effect (} E_{\text{max}} \geq 0, \ 0 < I_{\text{max}} < 1\)\)

\(L = \text{amount of ligand present}\)

\(EC50, IC50 = \text{ligand amount at 50\% effect}\)

\(nh = \text{Hill coefficient}\)

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

\[
\text{rate of UGE (mg/min)} = \begin{cases} 
\text{GFR (dl/min)} \times (PG (mg/dl) - RT_G (mg/dl)) & \text{if } PG > RT_G \\
0 & \text{if } PG \leq RT_G 
\end{cases}
\]
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Parameter values in a Platform are identified by literature survey and data analysis, local fitting, or hypotheses.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Tissue</th>
<th>Disease status</th>
<th>Type or Specie</th>
<th>Amount</th>
<th>Units</th>
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<td>41.3 L/min</td>
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<td>Sherwin et al., 1974</td>
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<td>whole body</td>
<td>healthy</td>
<td>human</td>
<td>0.13 L/min</td>
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</tbody>
</table>
Process for Creating PhysioPD Research Platforms

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

- Pancreatic function
- Glucose metabolism
- Incretin production
- Meal inputs and OGTT

Pharmacokinetics

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy</th>
<th>VP1</th>
<th>VP2</th>
<th>VP3</th>
<th>VP4</th>
<th>VP5</th>
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<td>ISR_scale_k</td>
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<td>Glucose_glucagon_Imax</td>
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</tr>
</tbody>
</table>
VPs facilitate exploration of how mechanistic biological differences may affect clinical 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?
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A Platform is tested against multiple datasets describing subsystem behaviors and refined if necessary.

- 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.

- Plasma Glucose (mM)
- Plasma Insulin (pM)
- C-peptide (mM)

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

Gray shaded area indicates inter-subject variability
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?

Mechanisms ➔ Outcomes
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.
VPs were created to simulate clinical trials with the compound.
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

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

<table>
<thead>
<tr>
<th>Marker</th>
<th>Correlation</th>
<th>P-Value</th>
</tr>
</thead>
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<tr>
<td>Marker 2</td>
<td>-0.107</td>
<td>0.4323</td>
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<tr>
<td>Marker 3</td>
<td>0.548</td>
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<td>Marker 4</td>
<td>0.004</td>
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<td>Marker 6</td>
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<td>Marker 7</td>
<td>-0.058</td>
<td>0.6872</td>
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<tr>
<td>Marker 8</td>
<td>0.254</td>
<td>0.0587</td>
</tr>
</tbody>
</table>

Individual VPs
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.

Platform research results:
- 18 hr AUC for low responders
- 18 hr AUC for high responders

Clinical trial results:
- 18 hr AUC

Glucose AUC (Percent change)

Dose (mg)
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