Using Mechanistic Physiological Models to Investigate Responder / Non-Responder Attributes Retrospectively and Prospectively to De-Risk Drug Development

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Introduction

- Variability in patient responses to drugs is a fact of life in the pharmaceutical industry
- Retrospective analysis may identify covariates associated with response, and population modeling approaches allow for extrapolation under appropriate conditions
- Only mechanistic modeling enables exploration of underlying biological drivers of variability **retrospectively** and **prospectively**

Objectives

- Provide an overview of mechanistic modeling and **Virtual Patients (VPs)** in Rosa's PhysioPD™ Platforms
- Show **three concrete examples** of using VPs to explore responder / non-responder hypotheses
- Illustrate the utility of this approach to de-risk efficient development of compounds and treatments

Methods

PhysioPD™ Research Platforms are mechanistic, quantitative models that elucidate the connection between mechanisms and outcomes.

- Rosa's PhysioPD™ Platforms are graphical, mathematical models of biology, a type of Quantitative Systems Pharmacology (QSP)
- PhysioPD Platforms combine **engineering approaches** and **scientific data analysis** to clarify complex physiology and drug interactions
- PhysioPD Platforms are qualified in accordance with Rosa's Model Qualification Method[1] (MQM) (Figure 1)
- Virtual experiments in VPs can be used to **explore the impact of biological variability on response to existing and novel therapy**
- This enables informed extrapolation of existing data to de-risk development

Figure 1. Diagram of Rosa's Model Qualification Method[1]

Results

Three examples of model-informed drug development using Virtual Patients illustrate the impact of PhysioPD Platform research.

- <u>Atopic Dermatitis (AD)</u>:
  - Identified key mechanisms driving response to the anti-IL4R antibody dupilumab
  - Created VPs with biological variability leading to **differential response to dupilumab**
  - Tested client's novel therapy on the range of VPs to assess robustness and risk
- <u>Immuno-oncology (IO)</u>:
  - Created VPs with **variability in key pathways driving response** to a bi-specific T cell engager therapy
  - Illustrated that relapsing patients may become responders under optimized protocol
- <u>Cardiovascular Disease (CVD)</u>:
  - Created VPs with **mechanistic differences underlying variable baseline LDL and response** to statins
  - Assessed VPs' response to PCSK9 inhibitor treatment

Results: Atopic Dermatitis

Modeling helped explore possible pathophysiological variability that may explain variable response.

- The client wanted to understand how a novel treatment may compare to dupilumab
- An Atopic Dermatitis PhysioPD Platform provided a graphical and mathematical model of disease processes
- A virtual population (VPop) with variability relevant for dupilumab and the novel therapy was developed
  - Hypotheses for possible mechanistic causes of variable response to dupilumab were generated with client input
  - All hypotheses were backed by extensive literature investigation
  - Model-based analysis identified the most sensitive variabilities
  - VPop virtual trial recapitulated results from Simpson, et al.[2] (Figure 2) and other relevant test therapies
- **Plausible variability relevant for the novel treatment** was also explored
  - Hypotheses were informed by nonclinical data as well as inferences from existing therapies with partially overlapping mechanisms of action (MOAs)
  - Individual VPs and VPop responses to existing therapies were simulated and compared to data

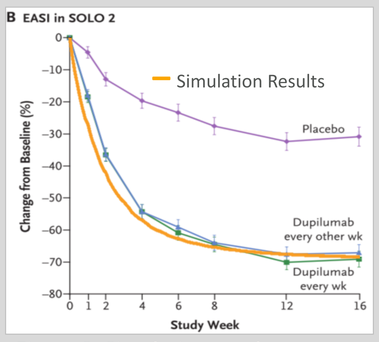

Figure 2. Simulation results (orange) overlaid on clinical data from Simpson, et al.[2]

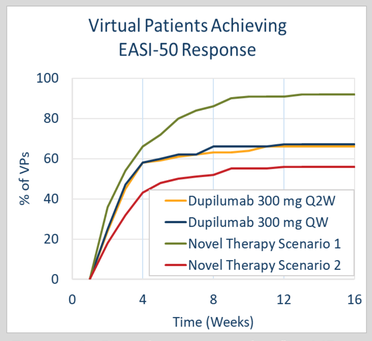

Figure 3. Simulation results for VPs achieving EASI-50 on dupilumab vs. novel therapy.

- Virtual head-to-head comparisons illustrate possible trial scenarios (Figure 3, results masked)
- The client gained insights into competitiveness and plausible mechanistic causes of variability

A Portion of an Atopic Dermatitis PhysioPD Research Platform including AD pathophysiology and drug MOA.

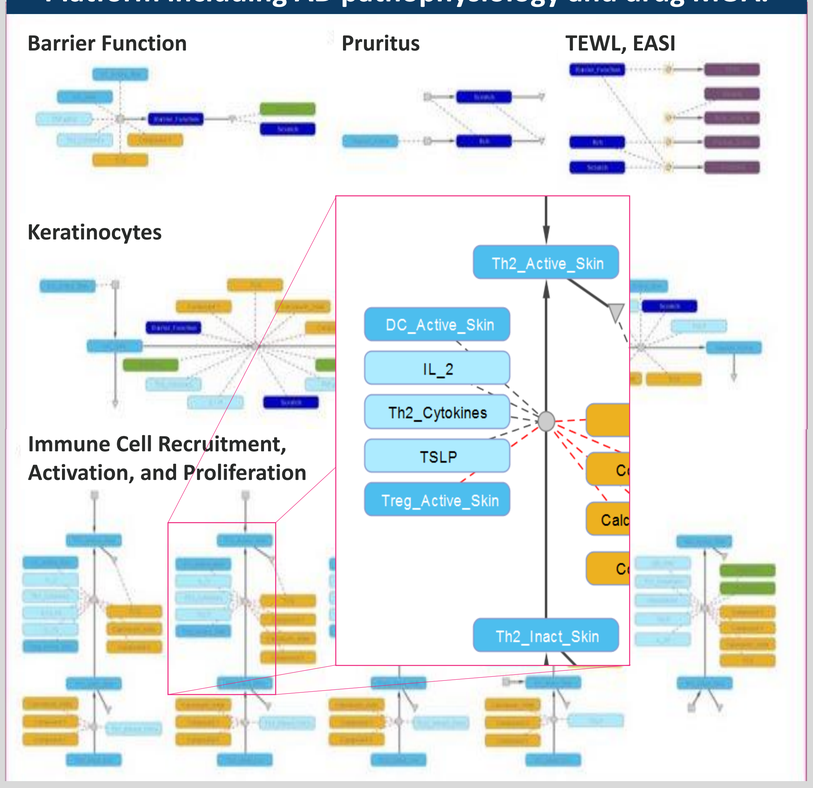

Figure 4. An AD PhysioPD Platform captures disease processes. The graphical and mathematical representation of targets or compounds of interest (yellow nodes) facilitates exploration of the interaction between mechanisms and outcomes.

Results: Immuno-Oncology

VPs illustrated possible differential treatment responses and facilitated exploration of alternate dosing protocols.

- A B-ALL PhysioPD Platform was constructed to explore variable response to blinatumomab, a bispecific antibody directing cytotoxic T cells to CD19-expressing B cells
- Sensitivity analysis identified parameters that impacted response to blinatumomab (Figure 5A)
- VP variability in sensitive parameters led to responder, non-responder, and relapser profiles (Figure 5B)
- VPs support protocol optimization and biomarker identification

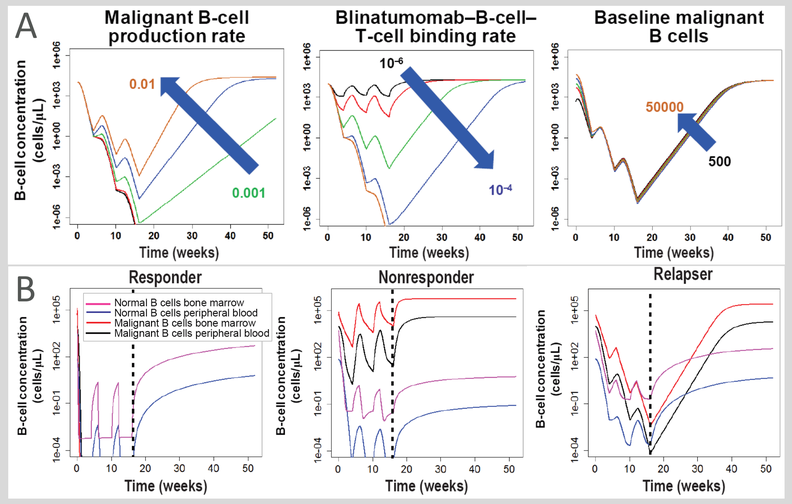

Figure 5. (A) Effect of varying individual parameters on B-cell populations under treatment. (B) Responder, Nonresponder, and Relapser VP B-cell profiles.

Results: Cardiovascular Disease

VPs with high / low statin and anti-PCSK9 responses supported investigation of LDL and plaque outcomes.

- A CVD Platform was developed as described in Ming, et al.[3] to investigate alirocumab effects on different patients
- A subset of 14 sensitive parameters was identified through biological reasoning and sensitivity analysis
- VPs differed from each other only in these 14 parameters and featured the desired response profiles (Figure 6)
- Each VP's parameters were within data constraints, and additional testing included other therapies and comparisons to plaque volume and composition data
- VPs could then serve to test a range of protocols and predict plaque outcomes not yet available for alirocumab

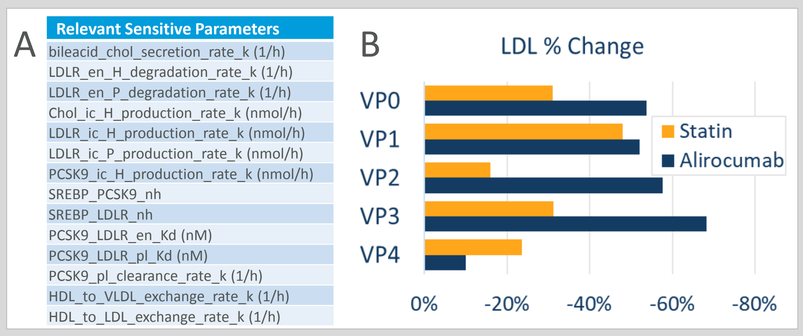

Figure 6. (A) Sensitive parameters that were varied between VPs. (B) Response to statin and alirocumab monotherapy across VPs.

Conclusions

- QSP models such as Rosa's PhysioPD Research Platforms enable exploration of the **mechanistic causes of clinical variability**
- Because Platforms draw on dozens of data sources to constrain VP parameters, such analysis can be conducted **before** clinical data become available
- Appropriate use of VPs to investigate possible causes of clinical variability reduces development risk

References

1. Friedrich, C. M. (2016) *CPT: Pharmacometrics & Systems Pharmacology* **5**, 43-53
2. Simpson, E. L., et al. (2016) *N Engl J Med* 375(24):2335-2348
3. Ming, J. E., et al. (2017) *Gene Regul Syst Bio* 11:1177625017710941

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