Development of a Psoriasis PhysioPD™ Platform to Evaluate a Novel Therapy and Identify Uncertainties Critical to Efficacy and Competitive Differentiation

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Introduction

- Psoriasis is a chronic, debilitating autoimmune skin disease affecting approximately 2% of the population with itching, thickened, red scaly skin, and more rarely rheumatoid arthritis
- Despite the therapeutic options including topical agents and systemic therapies, there is widespread under treatment due to lack or loss of response, safety concerns and tolerability
- Development of orally delivered novel drugs with fewer side effects may help overcoming these obstacles
- A small molecule that fulfills these criteria has been identified, but the specific enzyme isoform responsible for the mechanisms of action (MOA) remains uncertain
- Combining molecular biology, gene expression, and clinical data with computational mechanistic modeling (QSP) allowed evaluation of the effects of simulated inhibition of this individual isoform in the context of the disease

Objectives

- Identify mechanistic differences between the effects of **pan-enzyme inhibition** and **enzyme-specific inhibition** and to and to assess the potential efficacy of the specific inhibitor
- Provide insights into the **therapeutic potential of enzyme-specific inhibitors**
- Compare the efficacy of the pan-enzyme inhibitor at doses higher than currently administered with evaluation of enzyme-specific inhibitors
- Reduce risk for future stages of development by gaining new insights into the pathophysiology of psoriasis

Methods

The Psoriasis PhysioPD™ Research Platform is a mechanistic, quantitative model that represents key biological processes and component of psoriasis.

- The Psoriasis PhysioPD™ Platform is a graphical and mathematical model of the psoriatic disease processes and integrates data and knowledge from numerous sources into a single contextual framework
- Differential equations represent the dynamic processes associated with psoriasis and the response to treatments
- Platform was qualified by Rosa's Model Qualification Method (Figure 1)
- Key drivers of treatment efficacy were identified by **sensitivity analysis** (SA)
- **Virtual Patients** (VPs) were created to explore the impact of target-specific uncertainties
- **Target-specific uncertainties** were identified from a literature survey of enzyme subtype expression/functions

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

Results

The Psoriasis PhysioPD Research Platform represents the various biological components involved the pathogenesis of psoriasis as well as standard therapies.

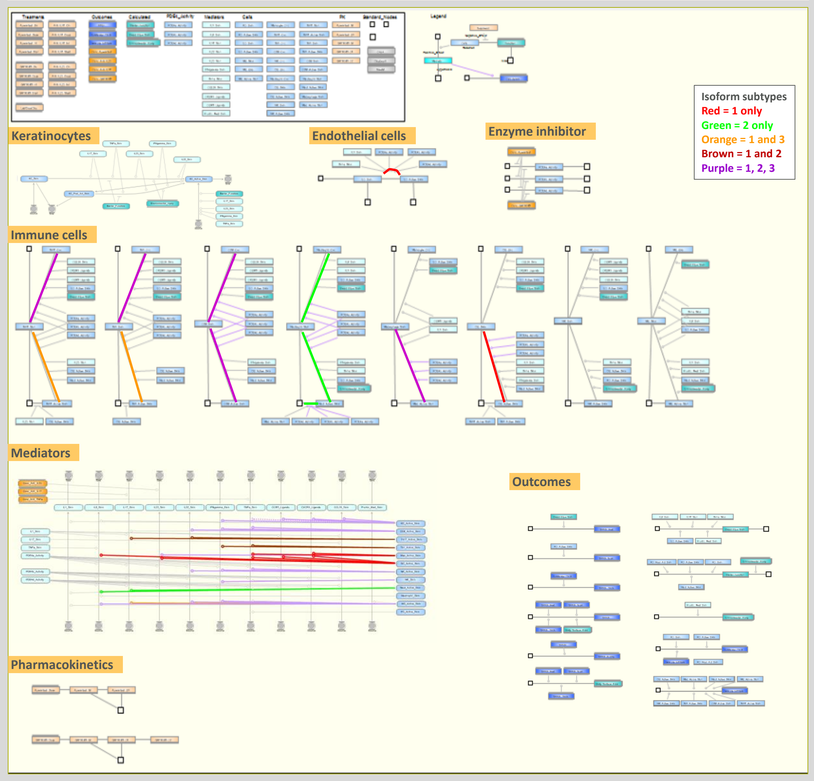

Figure 2. The Psoriasis PhysioPD Research Platform developed in JDesigner®.

- The Psoriasis PhysioPD Platform (Figure 2) was designed to represent the pathophysiology of a **single moderate/severe chronic psoriatic plaque**, incorporating:
  - Keratinocyte lifecycle and activation
  - Recruitment and activation of immune cells
  - Production and downstream effects of a variety of cytokines and chemokines
  - Clinical outcomes related to the SPASI score such as redness, scaliness, and epidermal thickness

The Platform was qualified to the expected behaviors based in literature and proprietary data.

- Platform was qualified to match baseline behaviors reported in the literature (e.g., provide a couple of examples) and the available preclinical data and clinical trial results for marketed therapies including, e.g., anti-TNFα, anti-IL-17, and anti-IL-23 treatments
- Prospective simulations were conducted to evaluate the efficacy of the enzyme-specific inhibitor under the various sets of target-related assumptions
- Therapy dosing and pharmacokinetics for the novel compound and the competitor drug were included in the Platform

Systematic SA highlighted the key pathways most critical in response to therapy.

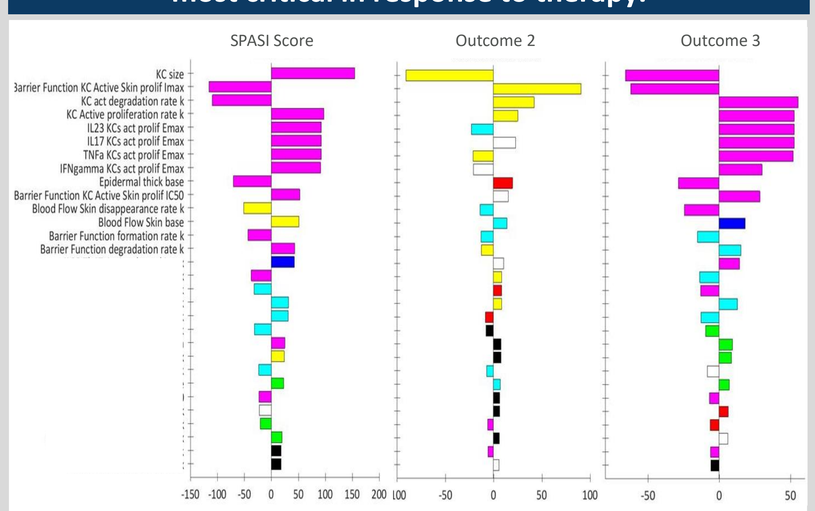

Figure 3. Tornado diagram showing ranking the effects of parameter perturbations on biological outcomes targeting disease pathogenesis. SPASI was a standard score used for sensitivity analysis and efficacy measures. Other treatment-specific outcomes were used in the research. Color coding was used to assign parameters to specific metabolic pathways or cell metabolism. This enables focus on the metabolic changes rather than a single parameter change.

Results

Virtual Patients were used to evaluate the effect of pathway uncertainties on drug efficacy.

- Two VPs were created to determine the range of efficacy (Figure 4)
  - Extremes of response were created by biasing all uncertainties in favor of, or against, the experimental therapy

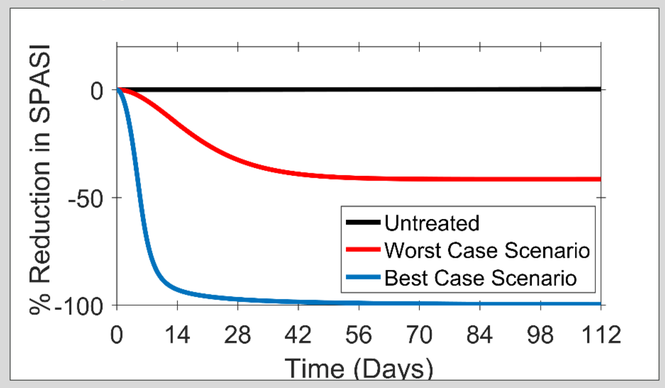

Figure 4. Clinical response of two Virtual Patients to experimental therapy illustrating the best and worst case scenario.

- Additional VPs explored the impact of specific groups of uncertainties on efficacy (Figure 5). Uncertainties explored were those determined to be the most significant according to the SA. These included TNFα activity, and Th17, Th1 cellular metabolism
- This analysis identified experiments most critical to de-risking development

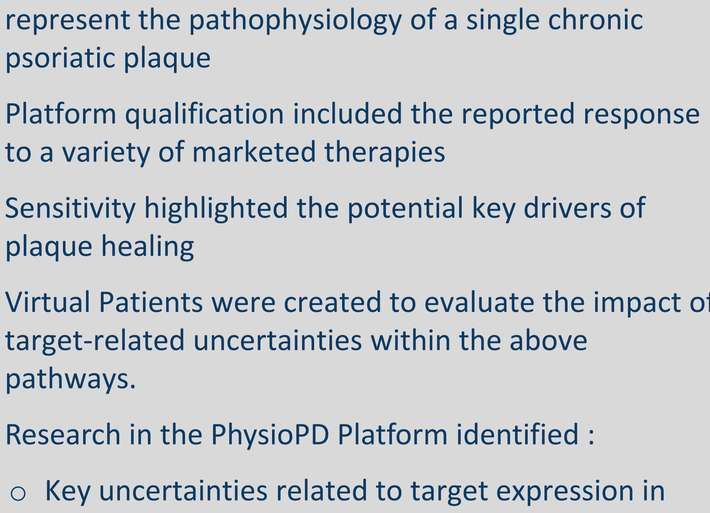

Figure 5. SPASI score of ten Virtual Patients treated with experimental therapy illustrating the the range of potential response response and the impact of specific uncertainties on predicted efficacy.

Conclusions

- The Psoriasis PhysioPD Platform was designed to represent the pathophysiology of a single chronic psoriatic plaque
- Platform qualification included the reported response to a variety of marketed therapies
- Sensitivity highlighted the potential key drivers of plaque healing
- Virtual Patients were created to evaluate the impact of target-related uncertainties within the above pathways.
- Research in the PhysioPD Platform identified :
  - Key uncertainties related to target expression in immune and skin cells
  - The follow-up experiments most critical to reduce risk throughout the development process
  - Conditions under which novel experimental drug would be superior to the standard of care

References

1. Friedrich, CM. (2016) CPT: Pharmacometrics & Systems Pharmacology 5, 43-53
2. Schmidt H, Jirstrand M. (2006) Bioinformatics 22, 514-5 (SimBiology)

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