# 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; 20-30% of psoriatic patients may develop psoriatic arthritis
- There are numerous anti-psoriatic treatments; however, there is widespread under-treatment due to lack/loss of response, safety concerns, and development of treatment tolerance
- Novel, orally delivered drugs with few side effects may help to overcome some of these obstacles
- A small molecule that fulfills these therapeutic 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) facilitated evaluation of the role of specific isoforms in the disease and treatment response

## Objectives

- Identify mechanistic differences between the effects of **pan-enzyme inhibition** and **isoform-specific inhibition** on the disease response
- Provide insight into the **therapeutic potential of isoform-specific inhibitors**
- Evaluate the potential efficacy of a select **isoform-specific inhibitor,** a candidate for **the novel treatment**
- Reduce risk for future stages of research and development by gaining new insights into the pathophysiology of psoriasis

## Methods

**The Psoriasis PhysioPD™ Research Platform is a mechanistic, quantitative model representing key biological mechanisms involved in the pathophysiology of psoriasis and response to treatments.**

- The Psoriasis PhysioPD Platform is a mathematical representation of a single moderate-to-severe psoriatic plaque
- The Platform represents the dynamics of keratinocytes, immune cells, key cytokines and chemokines, as well as the pharmacokinetics and pharmacodynamics of various therapies (Figure 2)
- Data and scientific knowledge from numerous sources are integrated into a single contextual framework
- Rosa's Model Qualification Method was used to ensure the model was fit-for-purpose (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/function


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

## References

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3. Micali et al. (2016) Skin Research & Technology, 22, 341-348
4. Reddy et al. (2010) J Dermatol 37, 413-425
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## Results

**The Psoriasis PhysioPD Research Platform represents the biological components involved the pathogenesis of psoriasis, mechanisms of anti-psoriatic therapies, and clinical outcomes.**

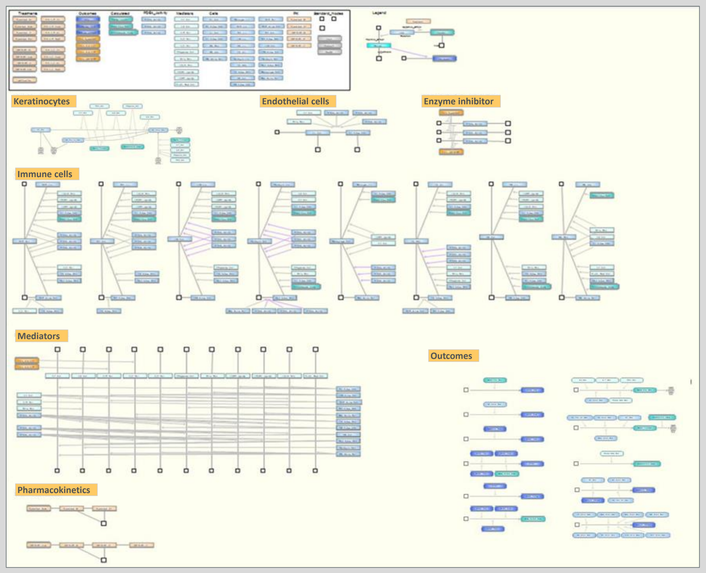


Figure 2. The Psoriasis PhysioPD Platform (Figure 2) represents the pathophysiology of a **single moderate/severe chronic psoriatic plaque,** including keratinocyte lifecycle and activation, recruitment and activation of immune cells, production and downstream effects of a key mediators involved in the pathophysiology of the disease, and response to treatments

The Platform includes mechanisms of action for existing treatments (e.g., anti-TNF$\alpha$, anti-IL-17, and anti-IL-23, and pan-specific enzyme inhibitor), pharmacokinetics and dosing of the novel compound and the competitor drugs, and clinical outcomes related to the SPASI score such as redness, scaliness, and epidermal thickness

The Platform was developed using System Biology Workbench JDesigner®

**The Platform was qualified to meet expected behaviors based on available public and proprietary data.**

- Platform was qualified to match behaviors reported in the literature (e.g., epidermal thickness, immune infiltrate, SPASI score etc.) under placebo and standard of care (SOC) treatments

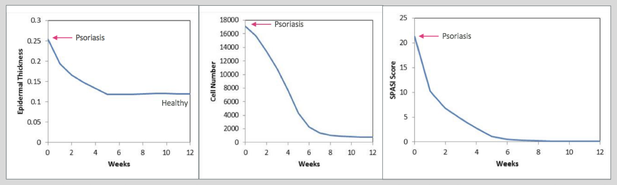


Figure 3. Example of Platform qualification: epidermal thickness (mm), inflammatory infiltrate (e.g., T cells, neutrophils, macrophages) and SPASI score decrease with simulated anti-IL-23 therapy in a psoriatic Virtual Patient. Simulated results are consistent with reported data. Over 50% decrease in epidermal thickness with anti-IL-23 treatment has been reported [4,5]. Immune infiltrate is also strongly inhibited [4,5]. Reduction is SPASI score has been shown to be >75% [4,6].

**Sensitivity Analysis highlighted the key pathways most critical in the disease pathophysiology.**

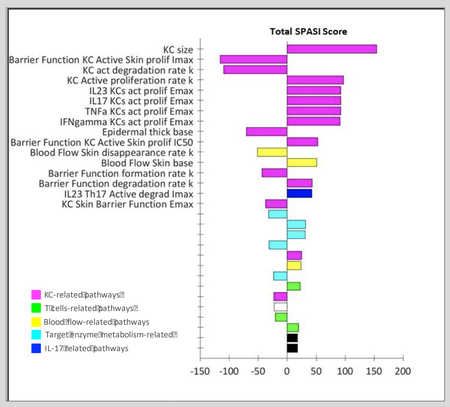


Figure 3. Biological pathways most highly affecting the SPASI score are related to KCs, T cells, blood flow, IL-17, target enzyme effects.
Tornado diagram shows ranking the effects of parameter perturbations on biological outcomes (e.g. SPASI score shown). Other treatment-specific outcomes were evaluated. Color coding was used to assign parameters to specific metabolic pathways or cell processes.

## Results

***In silico* research in Virtual Patients identified conditions under which a novel compound would be superior to the SOC treatments.**

- VPs, each representing alternative parametrizations of the model, were created to evaluate the effect of pathway uncertainties on novel compound efficacy
- Extremes of response were created by biasing all uncertainties in favor of or against the efficacy of the experimental therapy in two VPs (Figure 4)

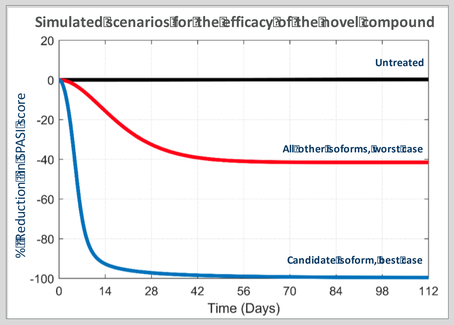


Figure 4. Simulated change in SPASI score in two VPs illustrates the best and worst case scenarios for the efficacy of the novel treatment. For the best case scenario, all pathways in the Platform with uncertainties related to the candidate enzyme isoform were completely inhibited by the novel treatment. Under the worst case scenario, regulation was attributed to other enzyme isoforms.

- The key uncertainties with biggest impact on clinical outcomes were determined by SA, and included TNFα activity, and Th17, Th1 cellular effects
- Additional VPs were used to explore the impact of specific key uncertainties on the new compound efficacy (Figure 5)
- Changes in clinical outcomes under experimental therapy in VPs with different underlying assumptions illustrate the range of potential response on predicted efficacy of the novel compound
- This type of analysis identified critical uncertainties that can be resolved by additional laboratory research, reducing drug development risk

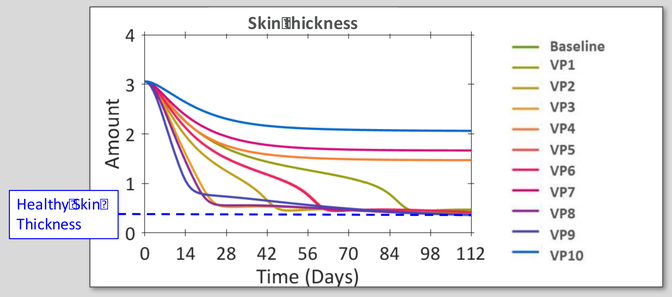


Figure 5. Simulated SPASI scores reflect differential responses of ten VPs, treated with simulated experimental therapy

## 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 analysis highlighted the potential key drivers of disease and plaque healing
- Virtual Patients were created to evaluate the impact of target-related uncertainties
- Research in the PhysioPD Platform identified:
  - Key uncertainties related to target expression and function in immune and skin cells
  - Conditions under which novel experimental drug would be superior to the standard of care

**For more information about this work, please contact:**
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