Mechanistic Physiological Modeling as a Tool for Enhancing Dermatology Research.

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Introduction

- Skin diseases range from benign to life threatening and affect a majority of people at some stage in their lives
- Despite recent advances, many mechanistic details of etiology and pathogenesis remain to be elucidated
- Limited NIH funding points to a need to increase research efficiency for new skin treatments
- Mechanistic physiological modeling can help to meet this need

Objectives

- Provide an overview of PhysioPD™ Platforms developed to support research in dermatological indications
- Show **three concrete examples of impact** on development decisions
- Illustrate the utility of the approach to support 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)
- Simulated experiments can be used to test hypotheses and explore the efficacy and toxicity for existing or novel treatments
- With industry clients, we have conducted **over a dozen projects** in **acne, atopic dermatitis, psoriasis, skin aging,** and **erythema**
- Three examples are highlighted here

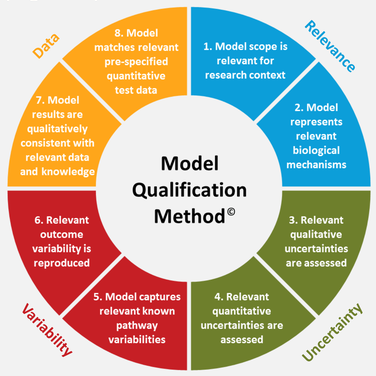

Figure 1. Rosa's Model Qualification Method[1]

Results

Three examples of model-informed development of dermatological treatments illustrate the impact of PhysioPD Platform research.

- Atopic Dermatitis:
  - **Clarified mechanisms of action** in context of disease processes
  - **Prioritized acquired assets** with insight about likely efficacy
  - **Elucidated the biological connections** between biology and **clinical outcome score (SCORAD)**
- Acne:
  - Identified **key drivers of pathophysiology**
  - Supported **prioritization** of new compounds, comparison to SOC
- Skin Aging:
  - **Identified** potential key drivers of skin aging
  - Created **Virtual Consumers** with different response profiles
  - Tested novel anti-aging protocols and identified **promising anti-aging approaches**

Results: Atopic Dermatitis

Modeling supported repurposing decision for acquired portfolio of assets.

- The client had acquired a portfolio of assets and needed to prioritize them for development for atopic dermatitis
- An Atopic Dermatitis PhysioPD Platform provided a graphical and mathematical model of disease processes and target involvement
- The SCORAD ("SCORing Atopic Dermatitis") clinical score was implemented by connecting it to immunological markers such as cell and mediator concentrations
- By implementing "virtual compounds" and simulating likely effects on immune cells and on SCORAD, the client was able to **prioritize assets for development with better clarity about likely efficacy**

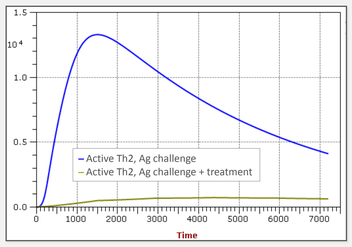

Figure 2. The effect on Th2 cell activation of a compound under consideration.

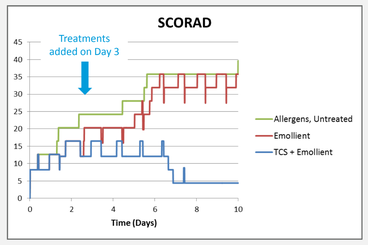

Figure 3. SCORAD under allergen challenge, Emollient, and topical corticosteroid (TCS) + Emollient treatment.

A Portion of an Atopic Dermatitis PhysioPD Research Platform including atopic dermatitis pathophysiology and drug mechanisms of action.

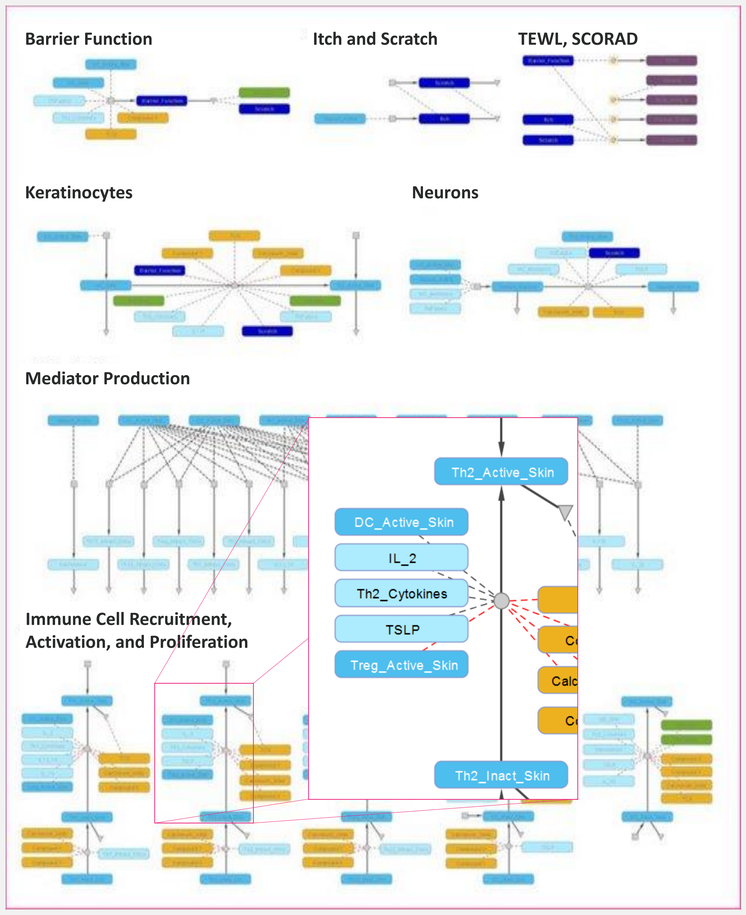

Figure 4. This Atopic Dermatitis PhysioPD Platform captures disease processes involved in the pathophysiology. The graphical and mathematical representation of targets or compounds of interest facilitates exploration of the interaction between target mechanisms and outcomes.

Results: Acne

Testing of Virtual Compounds in multiple Virtual Patients ensures robustness of new treatment approaches in a diverse population.

- Acne pathophysiology is complex and existing acne treatments focus on different aspects (Table 1)
- Patients differ in the extent to which their acne is driven by different aspects of disease biology, e.g., *P. acnes* bacterial load varies
- Research in the Acne PhysioPD Platform clarified what combinations of pathophysiological factors lead to acne in different patients
- This enabled creation of diverse Virtual Patients and **simulation of existing and novel acne treatment effects** (Figure 5)

Table 1. Mechanisms of Action of acne treatments.

Treatment	Anti-bacterial	Anti-lipogenic	Normalize KC life-cycle	Anti-inflamm.	Comedolytic
Clindamycin	✓✓✓	✓✓		✓✓	
Isotretinoin	✓✓	✓✓✓		✓✓	
Topical RA	✓	(?)	✓✓✓	✓✓	✓✓
BPO	✓✓✓			(?)	✓
SA	✓✓			✓	✓✓

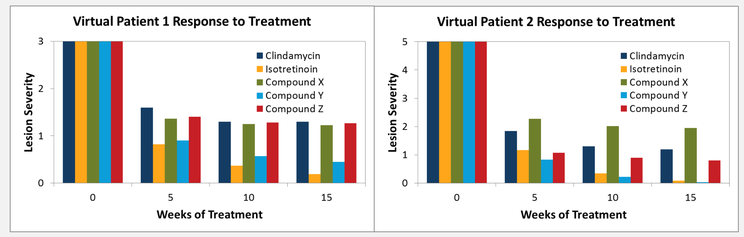

Figure 5. Response of two Virtual Patients to SOC and novel therapies.

Results: Skin Aging

Systematic Sensitivity Analysis highlighted the key drivers of improvement in skin appearance in response to application protocols

- The Skin PhysioPD Research Platform facilitated exploration of mechanisms involved in skin aging
- Standard of care and **novel anti-aging protocols were tested** in a variety of Virtual Consumers (Figure 6)
- Sensitivity analysis was used to assess the impact of individual mechanisms on the response to anti-aging protocol applications
- Pathways identified as sensitive **may point to promising approaches for future anti-aging protocols**

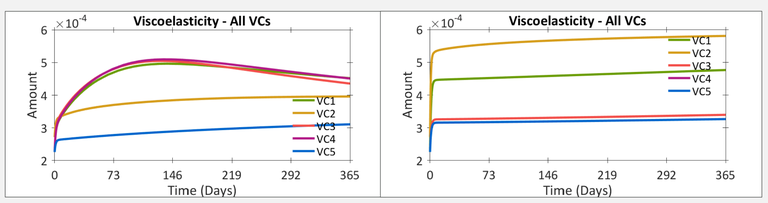

Figure 6. Response of five Virtual Consumers to two different anti-aging protocols.

Conclusions

- PhysioPD Research Platforms are graphical, mechanistic simulation models with **demonstrated impact** in drug and product development
- In dermatological indications, PhysioPD Platforms have been used to **clarify disease and drug mechanisms**, as well as the **connection between biological markers and clinical outcome scores**
- The three case studies illustrate that prospective **simulation research facilitates insights, enables focused allocation of resources, and reduces compound development risk**

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References

1. Friedrich, C. M. (2016) *CPT: Pharmacometrics & Systems Pharmacology* **5**, 43-53

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