PhysioPD™ Research Enhances Dermatology Research and Drug Development Using Mechanistic Physiological Modeling

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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® (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.

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.

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. acne 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.

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.

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.

References


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