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 (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. 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)

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