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Physiological modeling offers a valuable tool in early drug development for acne targets

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Combining molecular biology, clinical data, and informatics technologies with computational modeling can aid comprehensive understanding of complex diseases such as acne.We have developed a quantitative physiological model depicting acne pathophysiology to enable effective evaluation of targets and pathways via systematic integration and analysis of existing data and knowledge.We created a mechanistic disease **map** of acne describing relevant biological pathways and their interactions.The mechanisms of action of current standard of care (SOC) therapies were included to support model qualification. This **map** was converted to a quantitative pharmacodynamic model, the Acne PhysioPD™, using proprietary and published data.The contributions of sebum production, *P. acnes* growth, hyperkeratinization of infundibulum, and inflammation were integrated to represent an acne lesion of moderate severity and allow evaluation of target effects at the biological and clinical level. Rosa's Model Qualification Method was used to document the design, testing criteria, uncertainties, and patient variability. Integration of existing data and knowledge into a mechanistic model offered new insights into the pathophysiology and SOC therapies of acne and identified knowledge gaps. Simulated responses to SOC therapies were in agreement with published data. Analysis of the mechanistic pathways driving the clinical benefits of oral isotretinoin therapy indicated that reduction in sebum production is a key driver of efficacy, while effects on keratinocyte life cycle were immaterial to clinical efficacy. Subsequent literature analysis confirmed these findings. Simulations also suggested a potential role for IL-17 in the sebaceous follicle hyperkeratinization process. Use of quantitative modeling improved mechanistic understanding of acne and provided a novel tool for evaluation of the therapeutic potential of new drug targets.

Keyword: Acne, physiological model.

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