Using Mechanistic Physiological Models to Investigate Responder / Non-Responder Attributes Retrospectively and Prospectively to De-Risk Drug Development

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Objectives: To illustrate the use of Virtual Patients (VPs) in mechanistic physiological models to explore attributes of responder / non-responder patients.

Methods: Mechanistic physiological models, such as Rosa’s PhysioPD Platforms, are quantitative systems pharmacology (QSP) models that enable investigation of biological mechanisms giving rise to clinical outcomes. A central question in drug development is, will variability in the patient population limit my drug’s efficacy? This could occur, e.g., because the target’s involvement in pathophysiology may vary across patients. Mechanistic models support creation of multiple VPs to explore mechanistic variability that may underly responder and non-responder patients.

Results: We illustrate three cases in which VPs with variable responses to therapies of interest were used for research. In immuno-oncology, VPs were created with varying responses to blinatumomab, a bi-specific T cell engager therapy (BiTE). Interestingly, the research illustrated that some relapsing patients could become responders under an improved dosing protocol. In atopic dermatitis, VPs were created to better understand variability in response to dupilumab, an anti-IL4R antibody. By creating different VPs, including some that were relatively unresponsive to dupilumab, mechanistic modeling helped characterize a patient sub-population that may not be well served by this new treatment approach. Simulated response to alternative novel treatments under development could then be assessed in a range of VPs to ensure robustness of response under the novel treatment. In cardiovascular disease, VPs were created with variability in response to statins as reflected by serum and plaque biomarkers. These VPs were then used to systematically explore effects of PCSK9 inhibitor treatment on serum and plaque.

Conclusions: These examples illustrate that the use of VPs facilitates better mechanistic understanding of response or non-response to drugs on the market or in various stages of development. Such mechanistic insights can support clinical trial optimization, competitive differentiation, and identification of patient attributes or biomarkers that are likely to be predictive of response.