A Quantitative Systems Pharmacology model of inhaled corticosteroids therapy for asthma

Authors: Justin Feigelman, Siddharth Sukumaran, Manoj Rodrigo, Fang Cai, Tracy Staton, Cynthia Stokes, Saroja Ramanujan, Heleen Scheerens, Kapil Gadkar

Affiliations: Genentech, Inc., San Francisco, CA

Objectives: Asthma is a disorder of the airway that impacts clinical measures such as lung function. Patients with moderate to severe asthma are commonly treated with inhaled corticosteroids (ICS), however not all patients achieve control necessitating more targeted therapies. We produce a quantitative systems pharmacology (QSP) model for ICSs yielding novel insights via *in silico* experimentation to facilitate therapeutics development.

Methods: We extend the previous QSP model (1) by adding ICSs such as fluticasone propionate, which act through multiple pathways to modulate the immune response to allergens, a driving factor for asthma (2). ICSs increases leukocyte apoptosis while inhibiting the anti-apoptotic effect of cytokines; reduce production of inflammatory cytokines and chemokines; reduce transcription of cellular adhesion molecules; inhibit secretion of histamine and leukotrienes; and globally drive the expression of anti-inflammatory genes, among other effects.

Results: We modeled the impact of ICS on clinical biomarkers (cell counts, cytokine/chemokine levels, FeNO, etc.) and endpoints such as FEV1. The model is calibrated using a collection of pre-clinical and clinical studies for different asthma subpopulations (mild vs. severe, type 2 high vs. type 2 low) with regards to clinical response to ICS therapy. Sensitivity analysis was performed for hypothesized model mechanisms. We investigated the impact of steroid background therapy and variability in steroids sensitivity and adherence across the clinical population.

Conclusions: These developed QSP model and evaluations will support clinical studies design, comparison of experimental therapeutics vs. steroids, and influence patient treatment decisions.

References: