A Quantitative Systems Pharmacology Model of Asthma

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**Objectives**: To develop a Quantitative Systems Pharmacology (QSP) Model of the major inflammatory pathways in the context of asthma for the *in silico* simulation of potential drug design parameters and identification of target patient sub-populations for anti-IL5/IL13 antibodies

**Methods**: The model was designed as a system of ODEs (197 reactions, 87 species) and parameters were fitted using experimental in-vitro, ex-vivo and clinical data. The model includes the following sub-modules:
- Life cycles of main asthma effector cells (eosinophils, neutrophils and mast cells) and their modulation by endogenous and exogenous factors
- Cytokine and leukotriene production by relevant cells and their dependence on endogenous and exogenous factors
- Leukotriene and cytokine distribution and clearance
- Pharmacokinetics of anti-IL5 monoclonal antibodies (mAbs), anti-IL13 mAbs, 5-lipoxygenase inhibitors, CysLT1 receptors antagonists and anti-IL5/IL13 bispecific antibodies
- Variants describing different groups of virtual patients according to their asthma phenotype, disease severity and environmental factors
- Complex clinical endpoints such as FEV1, exacerbation risk score and exhaled NO.

**Results**: A QSP model was developed with all parameters identified. The model was qualified and adequately predicted clinical observations across a wide range of targets and drug treatments (figure 1). It was used to simulate the stratified responses of asthmatic patients to anti-IL5 and anti-IL13 treatments.

**Figure 1. Example of model qualification. Simulation of blood eosinophils dynamics during mepolizumab treatment. Administration is subcutaneous once every 4 weeks (experimental data from [1])**
Conclusions: The in silico QSP model of the IL-5 and IL-13 pathways in the context of asthma can be used to test and optimise a therapeutic hypothesis in terms of target molecule, target patient population and dosing regimen. In addition, it can be used as a platform for the development of expanded QSP models in the context of asthma.