Development and application of a Quantitative Systems Pharmacology (QSP) model of complement pathway to evaluate treatments for autoimmune diseases

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**Objectives**: Complement system acts as a first line of defense against infections, however dysregulation of the complement pathway is associated with various infectious, inflammatory and autoimmune diseases [1]. A QSP model of the complement pathway has been developed to evaluate dosing tractability of novel targets in GSK to treat diseases caused by complement over-activation.

**Methods**: The QSP model incorporates complement activation in the blood and on the cell surface (classical and alternative pathways) leading to formation of membrane attacking complexes (MAC) resulting in cell lysis (terminal pathway). In addition to MAC and cell lysis, a number of other complement fragments (C3a, Ba, iC3b) that are used as biomarkers for complement activation have been implemented along with regulators of the pathway (e.g. properdin, Factor I, CR1). The model was validated using in-vitro data generated within GSK and comparing the known effects of existing treatments with model predictions.

**Results**: The levels of complement fragments predicted by the model for healthy individuals matches well with the reported values. The model has also been used to understand dosing requirements for existing anti-complement treatments e.g. anti-C5 antibody: Soliris. Clinical data [2] suggests that the therapeutic doses of Soliris lead to complete blockade of terminal pathway which matches with model predictions (Figure 1).

![Figure 1 Model predictions for a) C5 inhibition (solid blue line) and b) MAC inhibition (solid blue line) on Soliris treatment at the clinical dose for treatment of aHUS (900 mg weekly for 4 weeks then 1200 mg every 2 weeks). Black dashed line: 50% inhibition, Blue dashed line: 90% inhibition](image)

**Conclusions**: A QSP model of complement pathway has been developed by integrating literature and in-house knowledge of pathway and data from multiple scales (in-vitro, in-vivo, biomarker levels) and validated by comparing model predictions to patient level responses. It has been used to understand the effect of existing anti-complement therapies and has been crucial in evaluating dosing requirements of small/large molecule compounds for novel targets in GSK.