Physiologically-based, Mechanistic Pharmacokinetic/Pharmacodynamic Modeling to Support Development of T Cell Redirecting Bispecific Agents

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Objectives: Engineered bi-specific agents that combine tumor antigen recognition with CD3-mediated T cell recruitment are highly potent tumor-killing molecules. However, the exceptional efficacy comes with a price. Excessive activation of immune system can cause cytokine release syndrome, which sometimes can be fatal. The objective of this study was to develop a physiologically-based, mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model to characterize drug PK, target engagement at the site of action, and the resulting target cell (tumor) killing and cytokine release. The model aimed to help bridge the gaps between in vitro/preclinical models and clinical scenarios, assess the efficacy and safety of the bi-specific agents and provide rational human dose projection.

Methods: A physiologically-based mechanistic PK/PD model was developed by integrating published in vitro cytotoxicity data, in vivo PK, target cell depletion, and cytokine release data of blinatumomab as well as key human disease-related physiological parameters into a single, unifying model structure.

Results: The developed model suggested that bispecific agent-mediated tumor killing effect is driven by the numbers of “CD3-bispecific agent-tumor epitope” complexes formed on each target cell, and the clinical efficacious dose of blinatumomab was successfully predicted with in vitro cytotoxicity information. The developed model also successfully characterized the attenuation of blinatumomab induced cytokine release in patients following intra-subject dose escalation by linking the magnitude of cytokine release to the total numbers of CD3-bispecific agent-tumor epitope complexes formed in the body after treatment.

Conclusions: This physiologically-based mechanistic PK/PD model holds great potential in providing rational human dose projection and dose optimization in patients, thus supporting the development of T cell redirecting bispecific agents.