Quality Award Winner (Non-Trainee Category):

**Systems Pharmacology Modeling to Support Clinical Development of Anti-CD20/CD3 T-Cell Dependent Bispecific Antibody**

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**Objectives:** To develop and apply a quantitative systems pharmacology (QSP) model to support clinical trial design for anti-CD20/CD3 TDB in non-Hodgkin lymphoma (NHL).

**Methods:** We developed a mechanistic model to describe the dynamics of B- and T-lymphocytes and their interactions in multiple physiological compartments (peripheral blood, tumor, and lymphoid tissues including the spleen, lymph nodes, and bone marrow) in the presence of an anti-CD20/CD3 T-cell dependent bispecific antibody (CD20-TDB) and the CD19-targeting bispecific T-cell engager blinatumomab (a molecule with similar mechanism, approved for ALL). The model is based on physiological, mechanistic, pharmacokinetic, and pharmacodynamic data and includes: 1) multiple activation states of CD8\(^+\) T-cells; 2) CD19\(^+\)CD20\(^-\) (pro-B), and CD19\(^+\)CD20\(^+\) (pre- to mature-B) B-lymphocytes; and 3) the pharmacokinetics of CD20-TDB and blinatumomab and their mechanistic effects (activation of CD8\(^+\) T-lymphocytes and consequent killing of CD20\(^+\) and CD19\(^+\) B-lymphocytes, respectively).

**Results:** The model was calibrated using *in vitro* potency data and circulating cell measurements in cynomolgous monkeys treated with CD20-TDB [1]. Preclinical and translational validation was performed using additional CD20-TDB preclinical data and blinatumomab clinical data [2, 3]. The model replicated the effects of CD20-TDB on cell dynamics in circulation, and predicted CD20-TDB preclinical data at lower doses and in tissues, and blinatumomab clinical data in patients with ALL and NHL (Fig. 1). The model will be used to evaluate and propose dosing strategies for CD20-TDB in patients with NHL and to inform other clinical development considerations.

**Conclusions:** The mechanism-based systems model accurately captures and predicts the pharmacodynamics of CD20-TDB in cynomolgous monkeys and in patients with ALL and NHL. The model provides a novel approach for evaluation of clinical dosing strategies for CD20-TDB and can be extended to related molecules and/or other B cell malignancies.

**References:**