Quantitative Systems Pharmacology Modeling to Evaluate and Prioritize Targets (CD19, CD20, CD22) for Bispecific Antibodies and CAR-T in Acute Lymphoblastic Leukemia

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**Objectives:** To develop and apply a quantitative systems pharmacology (QSP) model to evaluate and prioritize targets such as CD19, CD20 and CD22 for acute lymphoblastic leukemia (ALL) treatment with bispecific antibodies and chimeric antigen receptor T-cell therapy (CAR-T).

**Methods:** QSP model of ALL treatment with bispecific antibodies and CAR-T was developed on the basis of Immune Response Template presented at ASCPT 2016 \cite{1}. Model describes hematopoiesis of normal B cells, leukemic blasts, different subsets (naïve, TCM, TEM, TEMRA or Th1, Th2, Treg) of CD4 and CD8 T cells, NKT cells, different cytokines (IL-2, IL-6, TGF\textbeta, TNF\alpha and other) in physiological compartments (bone marrow, blood/plasma). Model describes pharmacokinetics and pharmacodynamics of blinatumomab (CD3/CD19 bispecific antibody), KTE-019 (CD19 CAR-T). Model was calibrated and validated against different types (in vitro, clinical) of data.

**Results:** Model is able to describe clinical data on leukemic blasts, different subsets of T cells and cytokines dynamics during treatment of ALL patients with blinatumomab and CAR-T. Model shows that CD19 and CD20 are better targets than CD22 for treatment with bispecific antibodies and CAR-T due the higher numbers of these molecules on the surface of leukemic cells. Due to the high variability of CD19, CD20 and CD22 expression on leukemic blasts of ALL patients, different surface molecules could be effective as a target for treatment of particular patients.

**Conclusions:** Developed model accurately captures available clinical data. Model shows the importance of CD19, CD20 and CD22 expression as a potential predictive biomarkers and key biomarkers to choose the right target for the therapy. Model could be used as a tool for optimization of ALL patients treatment with bispecific antibodies and CAR-T.

**References:** \cite{1} Antonina Nikitich, Oleg Demin Jr, Oleg Demin. 2016. ASCPT. San Diego, CA.