Mechanistic Modeling of Co-stimulatory and Co-inhibitory Surface Molecules Effect on Cell-to-cell Interactions

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Objectives: To derive formula describing effect of co-stimulatory/co-inhibitory surface molecules on processes associated with cell-to-cell interactions, and to explore the ways of integration of the formula in systems pharmacology models of immune response and identification of their parameters against in vitro data.

Methods: The formula was derived within the framework of quasi-equilibrium approach and represent an upgrade of surface molecules description implemented in Immune Response Template database [1]. Parameters of the formula were fitted against in vitro data from multiple sources using the Hook-Jeeves method as implemented in the DBSolve Optimum package [2]. To check the ability of new formula to describe the surface molecules interaction, in vitro data on interferon gamma production during culturing of T cells with dendritic cells in presence of different concentrations of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) were used.

Results: Different ways of description of surface molecules and its effect were proposed. The rate laws were derived within the framework of the mechanistic approach. Derived equations were able to describe the variability of response of T cells purified from blood of different patients to different concentrations of nivolumab and ipilimumab in vitro.

Conclusions: The approach allows to successfully describe effect of co-stimulatory and co-inhibitory surface molecules on processes associated with cell-to-cell interactions of immune cells. This approach could be used further for development of quantitative systems pharmacology models of particular diseases.