A Quantitative Systems Pharmacology Model to Support Development of Combinational Therapy for Non-Small Cell Lung Cancer (NSCLC)

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Objectives: To develop a quantitative systems pharmacology (QSP) model to support development of anti-PD-1 centered combinational therapies for NSCLC. The model aims to facilitate mechanistic understanding of immune cell-mediated tumor killing, allow integrated analysis of in vitro, preclinical and clinical data, enable mechanism-based translation across species and predict outcome of immuno-oncology therapeutics in humans.

Methods: A mechanistic physiological QSP model was developed to capture key tumor and immune cell dynamics associated with NSCLC and in response to immunotherapy. The model focused on the blood and tumor compartments. CD8⁺ cytotoxic T cells (CTLs), CD4⁺ T regulatory cells (Tregs), natural killer cells (NK), and CD4⁺ T helper cells (Th cells) dynamics were represented by their infiltration into tumor, proliferation, elimination, activation and exhaustion in the tumor. Tumor cell dynamics were characterized by tumor cell life cycle and immune cell-mediated killing processes. Interplay between tumor and immune cells in the tumor microenvironment was incorporated by cell to cell contact and mediators such as PD-1/PD-L1, chemokines and cytokines. Processes were described using ordinary differential equations and implemented in Matlab SimBiology. Physiologically-based parameter values derived from literature were applied to the model. Dynamics of immune and tumor cells as well as tumor size at baseline, with anti-PD-1 or anti-PD-L1 monotherapy, and various combination therapies were examined and compared.

Results: The QSP model-based simulations showed anticipated tumor progression and immune response in NSCLC without treatment. After integrating pharmacokinetics/pharmacodynamics information of the therapeutics, model simulations were consistent with reported clinical data. Comparison of combination therapies versus monotherapy suggested possible enhancement of the antitumor effect by certain combinations. Sensitivity analysis was also conducted to identify factors important for tumor responses.

Conclusions: A mechanistic physiological QSP approach was developed to investigate the effects of immuno-oncology therapeutics, alone or in combination in NSCLC. The model provided a valuable tool to support development of effective immuno-oncology therapeutics.