Quantitative Systems Pharmacology (QSP) modeling as a systematic approach for drug combination evaluation in Immuno-Oncology (IO)

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Objectives: Multiple strategies for eliciting and enhancing antitumor immunity are currently being evaluated. However, a more systematic approach is needed, to analyze and translate such results into clinic practice, while rationally designing combination therapies based on mechanistic understanding of potential synergistic effects [1]. The objective of this study was to provide predictive QSP simulations capable of categorizing the types of synergistic effects which may arise from IO drug combinations, across realistic baseline conditions prevailing in the tumor microenvironment (TME).

Methods: A QSP model was developed and qualified using in vivo mouse data published in the literature. The following pharmacological modalities were calibrated: PD-L1/PD-1, CTLA-4 and CXCR2 inhibition, and OX40 agonism (Figure 1). Various combination scenarios were simulated for these modalities, at four baseline conditions prevailing in different syngeneic murine models.

Results: Simulated efficacy results were highly dependent on the baseline conditions. Several combinations and monotherapies were effective only within a specific baseline TME phenotype. These findings were in agreement with experimental data [2]. At baselines with higher levels of MDSC, best results were obtained for a PD-L1 mAb combined with either an OX40 agonist or a CXCR2 inhibitor, with 90% of complete responders. Anti (PD-L1 + CTLA-4) combinations showed high efficacy in Treg prevalence, but only moderate efficacy (22% complete responders), under baseline conditions of a dual (Treg + MDSC) immunosuppressive TME.

Conclusion: This work provides a quantitative modeling framework to comparatively predict responses to IO combinations, based on realistic baseline conditions prevailing in the TME, while revealing mechanistic interactions underlying such responses in IO combinations.


Figure 1. Schematic of the IO QSP model. Treg: Regulatory T lymphocytes. Teff: Effector T lymphocytes. DC(mature): Mature dendritic cells. MDSC: Myeloid-Derived Suppressor Cells.