Working Towards a Physiologically-based Mathematical Model for Predicting Treatment Outcomes in a Prostate Cancer Mouse Model

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Objectives: The objective of our work is to develop a physiologically-based mathematical model to describe the interplay between the key components of the therapeutic agent, host immune system and prostate cancer cells for predicting treatment outcomes.

Methods: The initial step was to first examine a mechanism-based mathematical model developed by Peng et al. [1] which had been used to explore the interactions between prostate tumor and immune microenvironment. The model predicted treatment efficacy with androgen deprivation therapy (ADT), dendritic cell vaccines, regulatory T cells (Tregs) depletion and/or Interleukin-2 (IL-2) neutralization in a prostate-specific Pten−/− mouse model. Extensive literature search was conducted to determine the physiological ranges and values of 18 out of the 25 initially model-derived parameters. The updated model was used to fit observed mouse data following various treatments and to examine the biological relevance of other estimated model parameters. First order conditional estimation with interaction (NONMEM® V7.2.0) was used to fit longitudinal mouse data simultaneously from 5 different compartments, including tumor size, Tregs and cytotoxic T cells (CTLs) in prostate tissues and prostate-draining lymph nodes in 7 mono-therapy and combination treatment groups reported by Peng et al. [1].

Results: The Peng et al. model was first verified by comparing simulated versus observed data using previously estimated parameter values. Then, the model was updated by replacing over 10 parameters using physiological values from the literature search. The updated model converged successfully with covariance step completed. All treatment groups have reasonable model prediction for all compartments. Next, sensitivity analysis was performed on a series of parameters for determining impact on estimating other parameters and overall model fitting. Further, the established model was used to predict the outcomes for untested combined treatments.

Conclusions: This study highlighted the potential role of physiologically-based mechanistic modeling under a framework of systems pharmacology approach in studying tumor immunotherapy and rational selection of therapeutic interventions.

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