**Systems Pharmacology Multiscale Model to Optimize Mono- and Combination-Therapy Regimens for Immune Checkpoint Inhibitors and Identify Potential Biomarkers**

Oleg Milberg1, Chang Gong1, Bing Wang2, Paolo Vicini3, Rajesh Narwal4, Lorin Roskos4, and Aleksander S. Popel1

1Departments of Biomedical Engineering and Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland; 2MedImmune, Mountain View, California; 3MedImmune, Cambridge, United Kingdom; 4MedImmune, Gaithersburg, Maryland

Immunotherapy is revolutionizing the treatment of various cancers; however, there are many unanswered questions regarding identification of patients best suited for a particular treatment and the selection of an optimal regimen. Biomarkers for patient selection and optimal treatment regimens can be potentially predicted through the use of multiscale systems pharmacology modeling.

We have developed such a model focusing on simulating the immune response following the administration of immune checkpoint inhibitors against PD-1, PD-L1 and CTLA-4 either as mono- or combination therapies. In total, the model comprises 337 species and 855 parameters and consists of a mix of 220 algebraic equations, 267 ODEs, and 10 discontinuous equation sets. The model was implemented in MATLAB using the SimBiology plug-in. Parameters were derived from a range of experimental and computational literature sources, and chosen to simulate the treatment of melanoma and NSCLC. However, the model framework is flexible and allows simulation of the response of other tumor types to these immunotherapies.

In silico simulations using this model have identified that administration of 1-10 mg/kg (prescription dosage) of anti-CLTA-4 promotes both an increase in the activation levels of the effector T cells, and an extended life span of the antigen presenting cells (APCs), which altogether may produce a therapeutic response. The dose-response relationship to anti-CTLA-4 therapy is more clearly delineated in comparison to what is seen for anti-PD-1 and anti-PD-L1 therapies, administered at 1-10 and 1-20 mg/kg, respectively. Furthermore, we compared the simulations with anti-PD-1 and anti-PD-L1 therapies and found the results in qualitative agreement with reported clinical response data. Overall, as a confirmation of the predictive power of the model to aid in the design of combination therapies, model simulations showed, in correlation with the results of a recent clinical trial, that sequential administration of anti-PD-1 therapy prior to anti-CTLA-4 results in a better tumor response than the reverse. Lastly, it suggests that resistance to immunotherapy may play a major role in the loss of response and the balance of treatment response and tumor progression is additionally a function of several different factors, including the size of T cell clones, the strengths of the antigens, and levels of expression of the appropriate target receptors. Future work will focus on correlating model-predicted immune cells with those observed in patients undergoing immunotherapies for further model calibration and potential treatment optimization.