Development of a Quantitative Systems Pharmacology Platform to Support Translational Research and Clinical Development in Immuno-Oncology

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ABSTRACT

Background: Mechanistic models capable of integrating datasets from the molecular, cellular, and tissue level to provide research predictions of tumor response are well-positioned to play a central role in translational research and clinical development for the emerging immunotherapy therapeutic paradigm. The availability of calibration and validation data from clinical trials from the first successful immunotherapy therapies such as nivolumab and ipilimumab (including CA184004, MDX1106-03, CA209005, CA209009) facilitates comparison of the simulated outcomes with clinical data.

Methods: A multidisciplinary team developed the biological scope of a mechanistic, ordinary differential equation-based simulation platform. The initial platform focuses on the interactions of multiple immune cell types, cancer cells, soluble mediators, cell-cell contact effects, checkpoint engagement effects, as well as nivolumab and ipilimumab therapies within the microenvironment of a prototypical simulated lesion and their effect on tumor shrinkage.

Results: The platform was calibrated, taking into account nivolumab and ipilimumab plasma concentrations, circulating absolute lymphocyte counts, trends in tumor cytokines, an IFN-gene expression signal, changes in tumor infiltrating lymphocytes, and lesion size data. In agreement with clinical observations, an enhancement in lesion response was observed with the combination therapy.

Conclusion: The platform recapitulates essential immune response pathways in a simulated lesion and exhibits qualitative agreement with patient response phenotypes to immunotherapy agents. Having demonstrated proof-of-principle with a preliminary calibration, the platform will serve as a framework to facilitate biomarker identification, integrate additional therapeutic mechanisms, propose new combination strategies, and serve as a sub-model within a broader simulation framework for the cancer-immune cycle.

BACKGROUND

- A new class of immune-stimulating agents show great promise for the treatment of cancers that have not responded well to other therapies. Nivolumab, the first biologic from the field of immunology, was approved by the FDA in 2011 for treating metastatic melanoma. Nivolumab monotherapy was approved by the FDA in 2014.
- Immunotherapy agents require checkpoint-mediated suppression of the immune response exploited by cancer or bind directly to activating receptors on the surface of immune cells to stimulate anti-tumor responses [1].
- New immunotherapy therapies are being developed, and mounting clinical evidence suggests combinations of immunotherapies will be an especially powerful treatment option. For example, an objective response at 1 year has been reported in over 50% of melanoma patients treated with a combination of ipilimumab and nivolumab [2]. A 2-year overall survival rate of 88% has been reported for patients receiving a concurrent regimen of 1 mg/kg nivolumab plus 3 mg/kg ipilimumab [3].
- Quantitative Systems Pharmacology (QSP) approaches facilitate key steps, outlined below, in drug development [4], which will also accelerate the successful development of new immunotherapy therapies and treatment regimens.
  - Target identification
  - Knowledge integration
  - Identification of knowledge gaps and hypothesis generation
  - Evaluation of new therapeutic combinations

METHODS: Model development team

A cross-function team of drug development scientists defined the QSP model scope and modeling objectives.

In addition to the core platform development team, subject-matter experts contributed in an ad-hoc fashion [4] to prioritize putative mechanisms for inclusion. Preclinical and clinical data sets, along with information from over 500 publications, were used to inform the platform design.

The model was constructed in accordance with Rosas’s Model Qualification Method [5] to ensure fit for purpose.

Figure 1: Expertise represented on development team

Figure 2: Diagram depicting included biological species and their dynamics

RESULTS: Response to nivolumab

(A) The VP exhibits a decrease in lesion volume with simulated nivolumab therapy.
(B) The cellular composition of the simulated lesion changes with therapy. Increases are observed in NK, CD8+, and also Treg cells.
(C) Relative changes in simulated cytokines are shown. The increase of IFN-g in the lesion is consistent with observations of IFN-g gene expression changes in patients with renal cell carcinoma [12], study CA209009.
(D) The density of cells in the simulated, shrinking lesion is shown. There is a large relative increase in the density of Treg cells, there remain 100-fold more CD8+ T cells.

RESULTS: Response to combination therapy

(A) A comparison of the response to alternate dosing strategies in the same VP is shown. The combination treatment is employed in a co-dosing stage of a concurrent regimen trial [2]. Note the simulated increased response to the combination relative to the monotherapies at the same concentrations.

METHODS: Model development team

- Nivolumab and an IgG1 antibody targeted to CTLA-4.
- Two proximal mechanisms of nivolumab were included:
  - Blockade of CTLA-4-mediated signaling effects
  - Release of IFN-g from tumor cells
  - Antibody-dependent cell-mediated cytotoxicity

METHODS: Nivolumab mechanism

Nivolumab is an IgG4 antibody targeted to PD-1.
- Mechanisms related to the release of checkpoint inhibition were included.
  - Binding of nivolumab blocked the inhibitory signaling through PD-1 mediated by PD-L1/PD-L2 expressed on macrophages, dendritic cells, B cells, and cancer cells.

REFERENCES

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