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 immuno-oncology therapeutic paradigm. The availability of calibration and validation data from clinical trials from the first successful immuno-oncology therapies such as ipilimumab and nivolumab (including CA184004, MDX1106-03, CA209004, 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 ipilimumab and nivolumab 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-γ 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 immuno-oncology 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-immunity cycle.

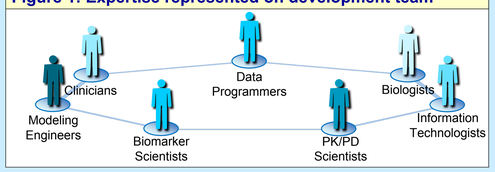
BACKGROUND

- A new class of immune-stimulating agents show great promise for the treatment of cancers that have not responded well to other therapies. Ipilimumab, the first biologic from the field of immuno-oncology, was approved by the FDA in 2011 for treating metastatic melanoma. Nivolumab monotherapy was approved by the FDA in 2014.
- Immuno-oncology agents relieve 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 immuno-oncology 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 immuno-oncology 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 Rosa's Model Qualification Method [5] to ensure fit for purpose.

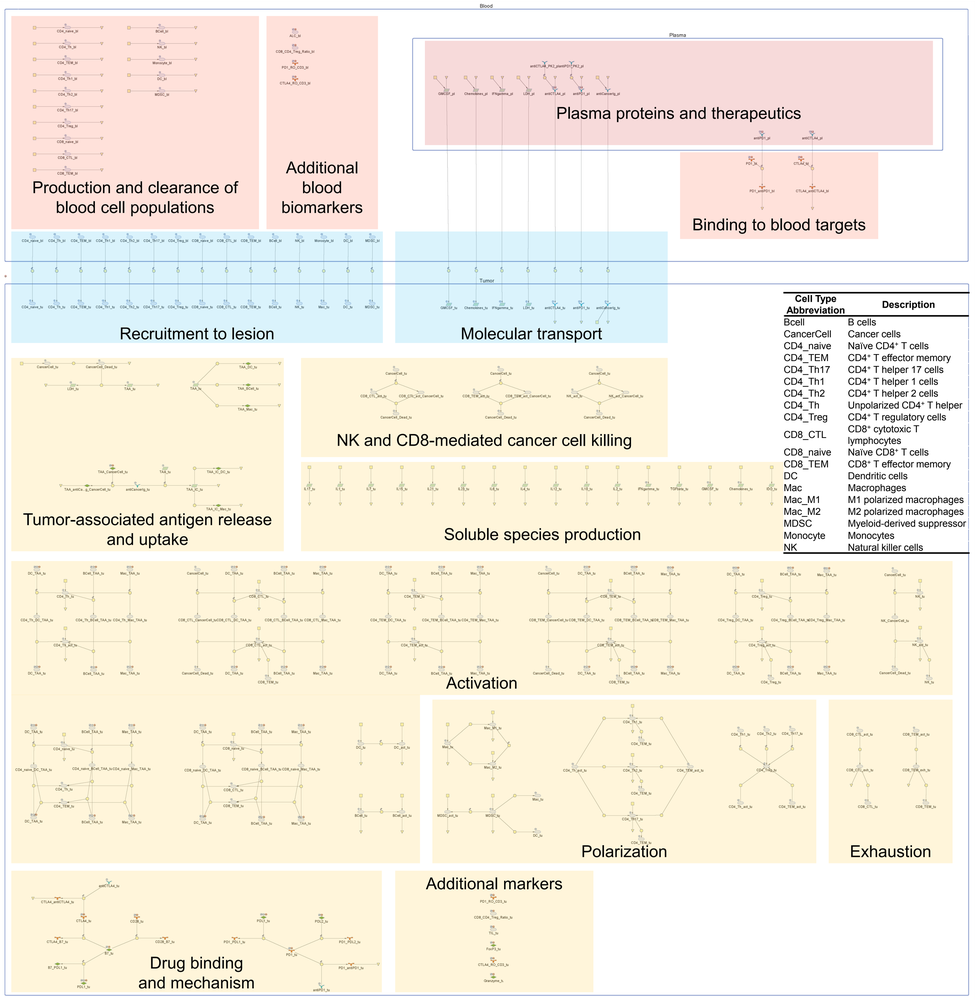
Figure 1: Expertise represented on development team



METHODS: Definition of objectives and biological scope

- The cancer-immunity cycle [6] was identified as an appropriate scope for creating a flexible platform for simulating the effects of immuno-oncology therapies with appropriate feedback mechanisms.
- Given the relative richness of data from the successful trials of immuno-oncology therapies, melanoma was identified as an appropriate cancer type for the first cycle of model development and parameterization.
- Initial model development was limited to represent a single melanoma lesion and salient blood and plasma species.
- Simulation time frames were limited to the initial 12-week induction phase of treatment.
- Ipilimumab, a CTLA-4 checkpoint inhibitor, and nivolumab, a PD-1 checkpoint inhibitor, were selected as clinically-approved therapeutics to include in the first round of model development.
- A single virtual patient (VP) was created to enable model development. Note that alternate VPs must be developed to characterize additional efficacy scenarios.

Figure 2: Diagram depicting included biological species and their dynamics



Cell Type Abbreviation	Description
Bcell	B cells
CancerCell	Cancer cells
CD4_naive	Naïve CD4⁺ T cells
CD4_TEM	CD4⁺ T effector memory
CD4_Th17	CD4⁺ T helper 17 cells
CD4_Th1	CD4⁺ T helper 1 cells
CD4_Th2	CD4⁺ T helper 2 cells
CD4_Th	Unpolarized CD4⁺ T helper
CD4_Treg	CD4⁺ T regulatory cells
CD8_CTL	CD8⁺ cytotoxic T lymphocytes
CD8_naive	Naïve CD8⁺ T cells
CD8_TEM	CD8⁺ T effector memory
DC	Dendritic cells
Mac	Macrophages
Mac_M1	M1 polarized macrophages
Mac_M2	M2 polarized macrophages
MDSC	Myeloid-derived suppressor
Monocyte	Monocytes
NK	Natural killer cells

METHODS: Ipilimumab mechanism

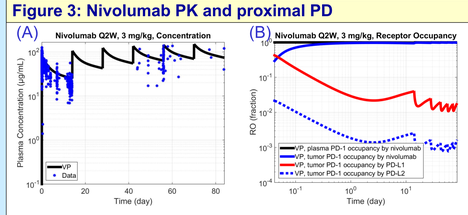
- Ipilimumab is an IgG1 antibody targeted to CTLA-4.
- Two proximal mechanisms of ipilimumab were included:
  - Blockade of CTLA-4 mediated signaling effects
    - Relieve competitive inhibition of B7 binding interactions and enable co-stimulatory signaling by CD28
    - Release of CTLA-4 mediated inhibition
  - 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.

METHODS: Nivolumab implementation

Figure 3: Nivolumab PK and proximal PD

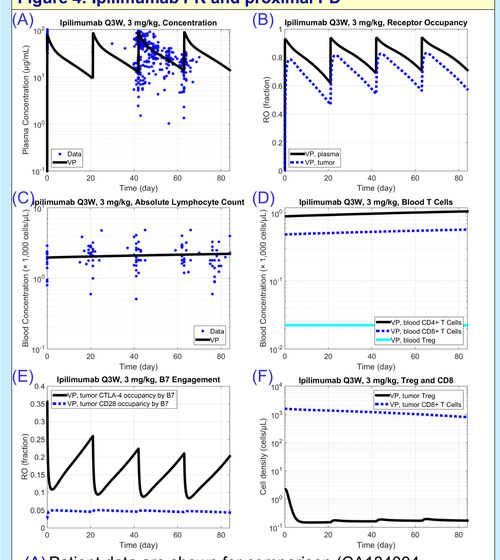


(A) Patient data are shown for comparison (CA209001, MDX1106-03, CA209005, CA209037, CA209063). Previously reported [10] pharmacokinetic parameters were used for the VP.

(B) PD-1 receptor occupancy by nivolumab, PD-L1, and PD-L2 are shown following nivolumab infusion. The simulations account for nivolumab PK and affinity as well as PD-1 expression. Results are reported after one hour on the log x-scale, a typical nivolumab infusion period.

METHODS: Ipilimumab implementation

Figure 4: Ipilimumab PK and proximal PD



(A) Patient data are shown for comparison (CA184004, CA184022). Previously reported [7] pharmacokinetic parameters were used for the VP.

(B) The simulations account for ipilimumab PK and affinity as well as CTLA-4 expression and internalization.

(C) Circulating absolute lymphocyte counts are of interest as they are pharmacodynamic markers and putative biomarkers of ipilimumab efficacy [8]. Changes were specified as 30 cells/μL/wk with ipilimumab (CA184004).

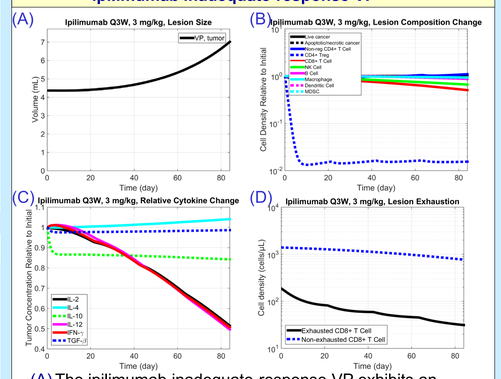
(D) Subfractions of circulating T cells were specified based on data from melanoma patients [9].

(E) Occupancy of CTLA-4 with B7 and CD28 with B7 in the VP's simulated lesion are shown.

(F) Antibody-dependent cell-mediated cytotoxicity is included. The simulated concentrations of Tregs and CD8+ T cells are shown.

RESULTS: Response to ipilimumab

Figure 5: Exploration of ipilimumab phenotype in an ipilimumab inadequate-response VP



(A) The ipilimumab inadequate-response VP exhibits an increase in lesion size with ipilimumab, although progression is less relative to untreated (Figure 7).

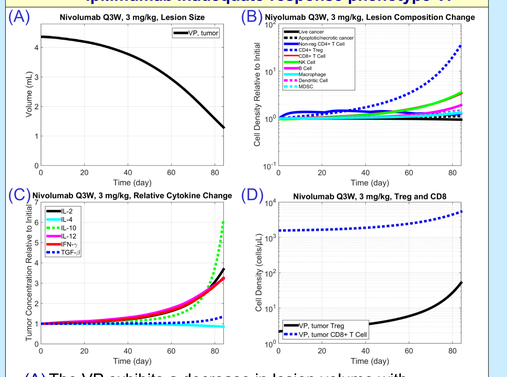
(B) The cellular composition of the simulated lesion changes with therapy. There is a decrease in Tregs, and other cell populations are impacted more modestly. Increases in CD8 transcripts have been reported in patients with clinical activity [11]. For this VP, the simulated lesion increases in volume over the 12-week treatment period, and a robust CD8 T cell response was not observed.

(C) Relative changes in cytokines are shown. There is an initial increase in IFN-γ concentration, but subsequently decreases. Interferon-stimulated genes have been observed to increase with clinical activity [11].

(D) Ipilimumab also results in changes in the active and exhausted CD8+ T cells in the VP.

RESULTS: Response to nivolumab

Figure 6: Exploration of nivolumab phenotype in the ipilimumab inadequate-response phenotype VP



(A) The VP exhibits a decrease in lesion volume with simulated nivolumab therapy.

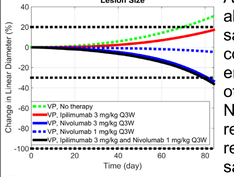
(B) The cellular composition of the simulated lesion changes with therapy. Increases are observed in NK, CD8+, and also Treg cells.

(C) Relative changes in simulated cytokines are shown. The increase of IFN-γ in the lesion is consistent with observations of IFN-γ gene expression changes in patients with renal cell carcinoma [12], study CA209009.

(D) The density of cells in the simulated, shrinking lesion is shown. Despite a large relative increase in the density of Treg cells, there remain 100-fold more CD8+ T cells.

RESULTS: Response to combination therapy

Figure 7: Exploration of combination response in the ipilimumab inadequate-response phenotype VP

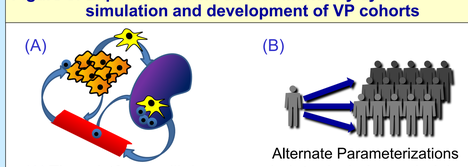


A comparison of the response to alternate dosing strategies in the same VP is shown. The combination strategy is that employed in a co-dosing stage of a concurrent regimen trial [2]. Note the simulated increased response for the combination relative to monotherapies at the same concentrations.

The black dashed lines are shown for reference only and are often used as cutoffs for progression, stable disease, partial response, and complete response based on the sum of longest diameters for multiple lesions [13].

NEXT STEPS

Figure 8: Expansion of the cancer-immunity cycle simulation and development of VP cohorts



(A) The platform will be expanded to include a draining lymph node and associated immune processes.

(B) VP cohorts will be established [14] to investigate the impact of variability in immuno-oncology pathways on treatment response.

CONCLUSIONS

- A QSP model was established for simulating the cancer-immunity cycle within a tumor lesion and the effects of immunotherapeutics.
- The development of an ipilimumab inadequate-response VP demonstrates agreement with published trends and serves as a mechanistic framework to start to explore biomarkers of response and to test combination therapy.
- The model serves as a starting point for a broader simulation of the cancer-immunity cycle and the development of new VP phenotypes in order to explore the response to immuno-oncology therapeutics, further elucidate their mechanism of action, and optimize therapeutic regimens.

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