A quantitative systems pharmacology model to explore combination efficacy of immuno-oncology compounds preclinically: Effects of CXCR2 and PD-1 inhibitions

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EXECUTIVE SUMMARY

- A mechanistic model describing interactions among host immune cells and tumor cells was developed;
- The proposed model was used to explore the effects of CXCR2 and PD-1 antibodies, and their combination, on tumor microenvironment and tumor growth dynamics in experimental murine models;
- Local sensitivity analysis of model parameters was used to identify determinants of response and of inter-individual variability, for the various treatments.

INTRODUCTION

Tumors can be recognized and attacked by the host immune system, yet may also evade immune response via modulation of their environment. Numerous cells, including myeloid derived stem cells (MDSC) and regulatory T cells (Treg), use various molecular effectors (*e.g.*, PD-1, CTLA-4) to suppress proliferation and cause anergy of cytotoxic T lymphocytes (Teff). Anergic Teff are then unable to mount an effective attack against tumor cells, which results in continued net tumor growth. Targeting the tumor microenvironment, therefore, may be a promising approach in the advancement of cancer treatments, as monotherapies or in combination with other agents. For example, the inhibition of CXCR2-dependent MDSC influx into tumors, with simultaneous blockade of PD-1, has shown efficacy in murine rhabdomyosarcoma (RMS), although single agents did not affect tumor growth [1].

OBJECTIVES

- The main objective of this study was to provide mechanistic hypotheses relative to the potentially synergistic effects of combined anti-CXCR2/anti-PD-1 treatment, using a quantitative systems pharmacology (QSP) modeling approach;
- A related goal was to identify system parameters which would drive inter-animal variability in the observed tumor dynamics responses.

METHODS

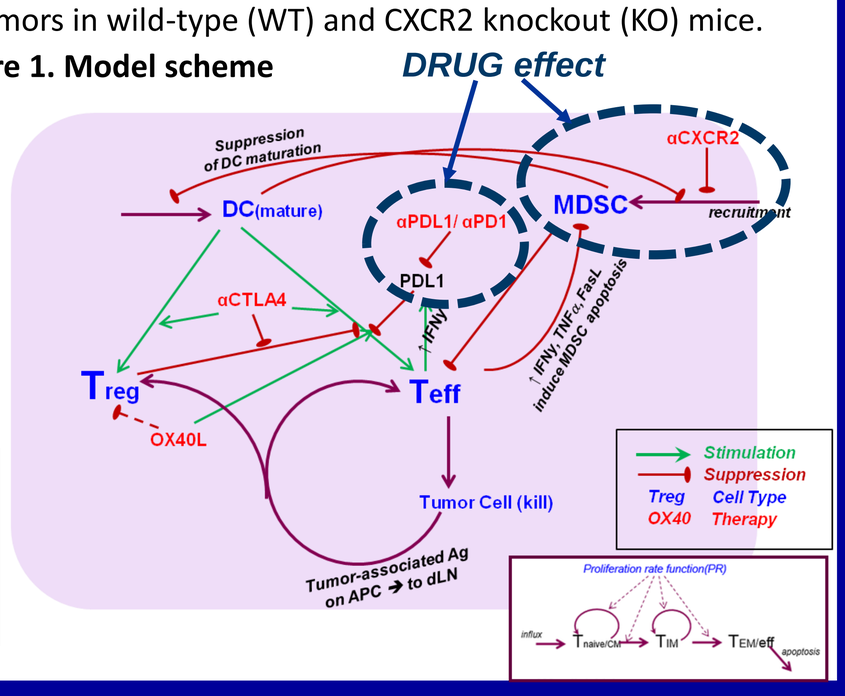
- The model is represented as a set of ordinary differential equations (ODEs), compiled in Matlab software;
- The model describes essential components of antitumor immune response (Table 1, Figure 1);
- The model is able to describe effects of various agents on immune response. These include: OX40 ligands; PD-1/PD-L1; CTLA-4; CXCR2.

Table 1. QSP model: Driving forces of anti-tumor immune response

Component	Suppression	Activation
Cells	MDSC, Treg	DC (other mature APC), Teff
Metabolites	CXCR2, Adenosine	
Checkpoints	PD-1, CTLA-4	OX40

The current example demonstrates effects of CXCR2 Ab, PD-1 Ab, their combination on the dynamics of RMS tumors in wild-type (WT) and CXCR2 knockout (KO) mice.

Figure 1. Model scheme



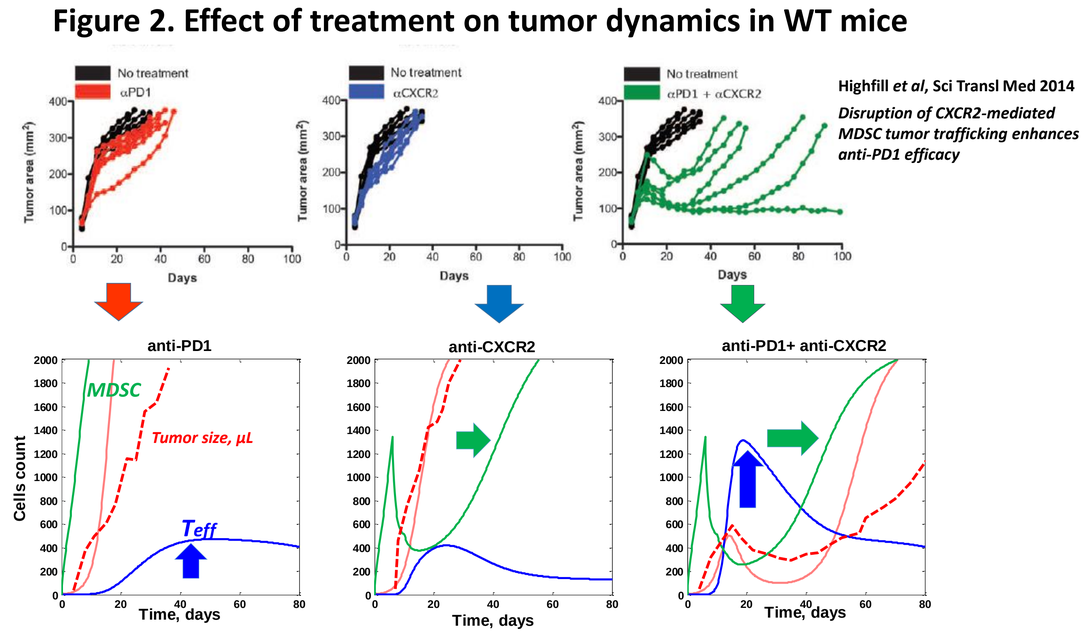
MDSC Myeloid Derived Suppressor Cells
DC Dendritic Cell
Ag Tumor antigen
Teff Effector T cell
Treg Regulatory T cell

Core model calibrated preclinically:
- OX40, PD-1, PD-L1
- CTLA-4
- Combination (OX40, PD-1, PD-L1)
- Combi. (Radiation + anti PD-L1)
- CXCR2

RESULTS

Quality of experimental data reproduction within the QSP model

Figure 2. Effect of treatment on tumor dynamics in WT mice



Highfill *et al*, Sci Transl Med 2014
Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy

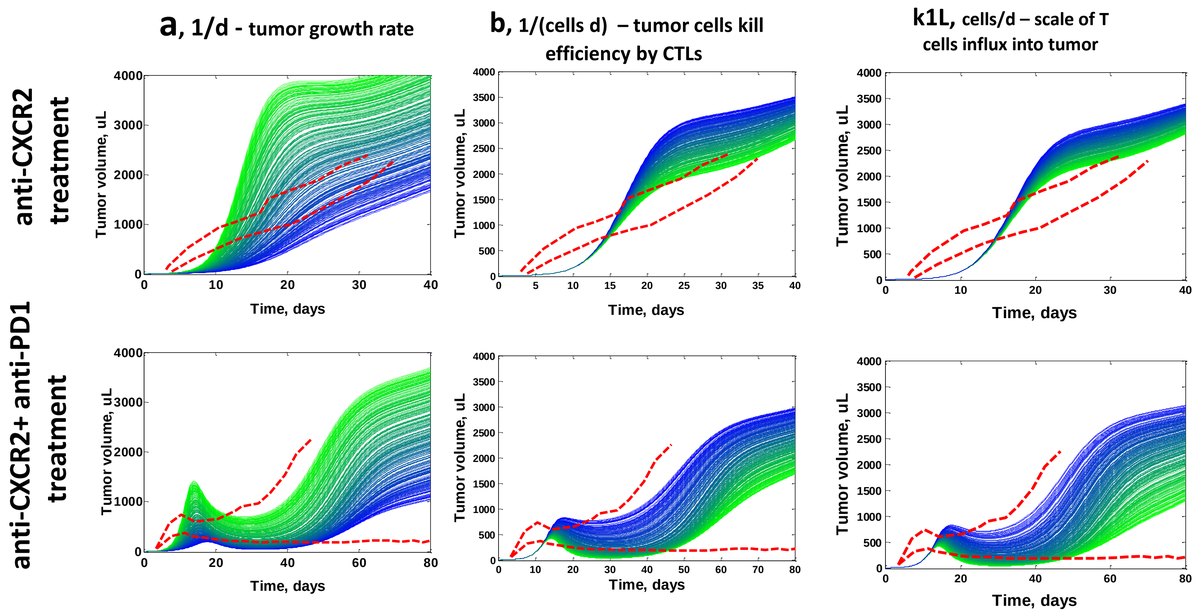
Solid lines: model predictions; Dashed lines: mean from individual experimental traces, top row

- The QSP model reproduces all experimental data adequately;
- Synergy is observed, when CXCR2 inhibition and PD-1 inhibition are combined;
- Significant variability in tumor response is observed, in the combination treatment setting: individuals can be responders, partial responders, or non-responders

Local sensitivity analysis (LSA)

1. For each parameter in model: parameter value was varied gradually, *e.g.*, ±60% around a median value, in 300 steps;
2. Model endpoint (tumor dynamics) was simulated at each step;
3. Sensitivity of endpoint to gradual change in parameter value was assessed.

Figure 3. LSA results



- Individual characteristics are important only when combination treatment is applied; **T cell influx into tumor tissue** is an important factor of treatment efficacy. This may be mapped to a positive correlation between tumor immunogenicity and immune drug efficacy;
- Functional status of T cells is crucial for treatment efficacy: anergic T cells are unable to cause tumor shrinkage.

CONCLUSIONS

- Blockade of a single immuno-suppressive mechanism is not sufficient to mount an effective anti-tumor immune response. Combination of anti-CXCR-2/anti-PD-1 is synergistic.
- This model captures the experimental data on tumor growth inhibition and immune cells both on average, and at the individual level.
- Individual response to treatment vary significantly and is driven by individual characteristics of the host immune system, *e.g.*, T cell influx into tumor tissue.

REFERENCES

Highfill *et al*.: Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD-1 efficacy***. Sci. Transl. Med.*** 2014 May 21;6(237):237ra67. doi: 10.1126/scitranslmed.3007974.

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