Optimising Dual Immuno-oncology Combinations with a Virtual Tumor

Physiomics

Fernando Ortega, Frances A. Brightman, and Christophe Chassagnole

Physiomics plc, The Oxford Science Park, Oxford, OX4 4GA, United Kingdom.

Tel. +44 (0)1865 784980. Email: fortega@physiomics.co.uk

Abstract No LB-392
AACR Virtual Annual Meeting II
June 22-24 2020

Introduction

The aim of this study was to investigate the application of the Virtual Tumor ('VT') computer platform to the dosing and scheduling of dual immuno-oncology combinations [1]. The tumor microenvironment and local immune response play a key role in cancer biology, and immune resistance is a feature of many cancers. Immune checkpoints suppress the ability of the immune system to destroy cancer cells, and are a clear therapeutic target. However, response rates for such therapies are generally low. While anti-tumor efficacy can be improved by combining agents that target immune checkpoints with selected conventional anti-cancer therapies [2], the potential of immune-checkpoint blockade could be further unlocked through combination instead with other immunotherapies [3]. Modelling can be used to deliver insights to help optimize such combination immunotherapies [4]. VT is an integrated PK/PD simulation platform that can be used to optimize drug dosing and scheduling, and to design new combination therapies. VT integrates PK/PD effects and models the way that individual cells behave within a tumor population. VT uses an agent and state-based approach that is particularly suitable for modeling not only tumor cells, but also other cell populations such as those involved in the immune response. It provides insight into the interaction between these cell over time. Here we describe our recent development and application of the VT technology for modeling preclinical efficacy of novel immuno-oncology combinations, i.e. a myeloid-derived suppressor cell (MDSC) modulator (C5a inhibitor) combined with an anti-PD-1 agent.

Virtual Tumour immuno-oncology model was extended to include consideration of MDSCs

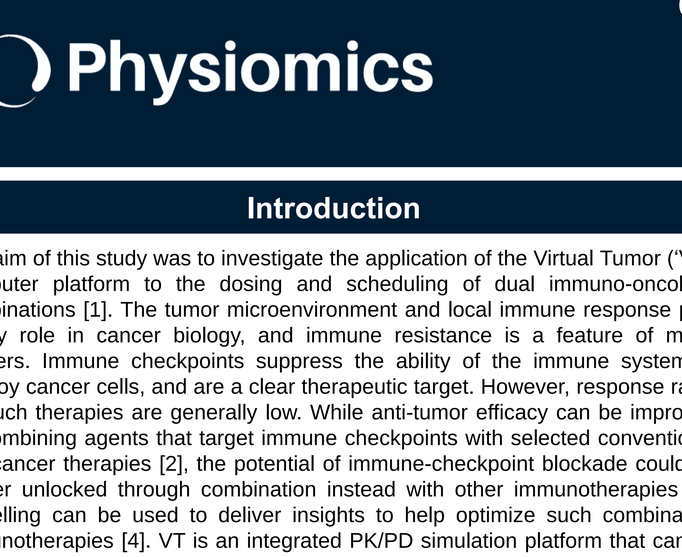

Figure 1. Three separate but interdependent effects are modelled:

- Stimulatory effect of anti-PD-(L)1 on T-cell activation levels, leading to tumor cell death
- Potentiation by certain cytotoxic agents via induction of immunogenic cell death and recruitment/maturation of dendritic cells
- Inhibitory effect of MDSCs on T-cell activity (allowing consideration of drugs that act on this cell type)

Each species in the immune system component of the model is tracked as a single variable that determines its effect on other species.

Details of the regulations involved in the Virtual Tumor model for the immune-system component

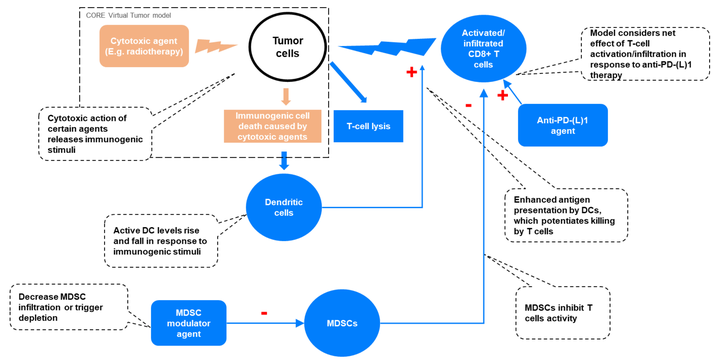

Figure 2. Schematic of the interaction between the Virtual Tumor and immune cells

Modelling the effect of more than one immunomodulatory pathway on tumor growth

We evaluated the capability of VT to model the efficacy of a C5a inhibitor in syngeneic mice engrafted with B16F10 cells, by modulating MDSC activity. We modelled this intervention alone and in combination with an anti-PD-1 antibody, through a preclinical case study derived from the literature [5].

The VT model was first calibrated for the control and the monotherapy arms using published PK data for the anti-PD-1 [5], C5a inhibitor [6] and the tumor growth data from a B16F10 *in vivo* model [5]; then the calibrated model was used to predict the combination efficacy.

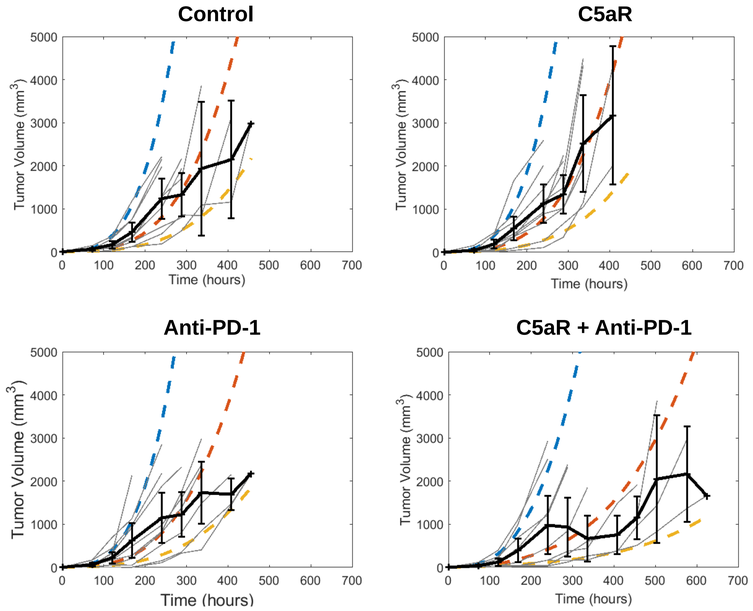

Figure 3. Simulation of the tumour growth over time. Experimental data were taken from [6], black lines correspond to experimental mean and SE, grey lines are the individual animal time courses, and orange lines shows the mean simulation of the VT model. Blue and yellow lines show the simulation of the extremes of tumor growth dynamics.

Model outputs – simulation of additional species

In addition to tumor volume, the model also enables tracking of other species (molecular and cellular), with a regulatory function such as activated T-cells and MDSCs, in order to the better understand the processes that lead to cellular death and tumor growth inhibition.

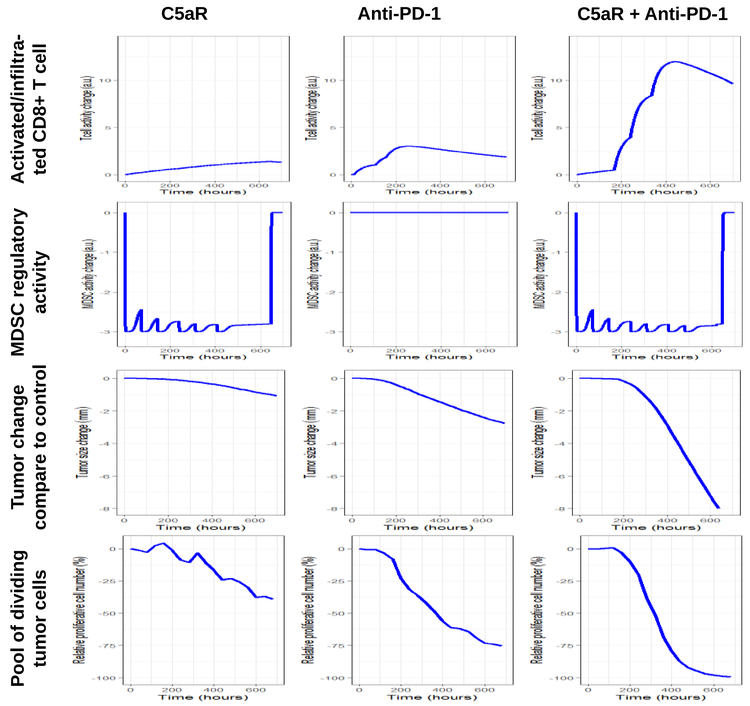

Figure 4. Examples of model output simulations.

Conclusions

Building upon the previous addition to the VT platform of a module that captured the synergistic interaction of PD(L)-1 blockade with conventional anticancer therapies [4], we have further extended the model to allow simulation of immune-checkpoint blockers with other immunotherapies. This extension captures the mechanisms by which immunotherapies activate the innate antitumor immune response, either through immune-checkpoint block or by targeting immunosuppression by MDSCs within the tumor microenvironment. Through a preclinical case study derived from the literature and additional data available in the public domain [5-6], we demonstrate that the extended VT can be used to simulate and predict the efficacy of PD-1 blockade combined with an anti-C5a agent, and that the combination treatment delays tumor progression. Furthermore, we modeled several scheduling strategies (not shown) showing that greater tumor shrinkage can be only achieved by increasing the dose. This enhanced capability of VT represents an important step in the development of a strategic tool to predict dosing and scheduling of immuno-oncology combinations.

References:
[1] Fernandez, *et al.* (2011) Modeling the sequence-sensitive gemcitabine-docetaxel combination using the Virtual Tumour. AACR 102nd Annual Meeting, Orlando, FL, April 2-6, 2011. **[2] Ott, PA *et al.***, *Journal for ImmunoTherapy of Cancer* **5**, 16 (2017). **[3] Galon, J. & Bruni, D.** *Nature Reviews Drug Discovery* (2019). **[4] Brightman, FA *et al.***, Abstract 4866. *Cancer Res* **75**, 4866-4866 (2015). **[5] De Maria et al** Characterization of anti-C5aR antibodies for specific targeting of myeloid cells and neutrophils in the TME. Third CRI-CIMT-EATI-AACR Inter. Cancer Immunotheraphy Conference . **[6] Ajona, D. *et al.*** *Cancer Discov* **7**, 694-703 (2017).