Modeling Synergistic Anti-PD-1/PD-L1 Immunotherapy Combinations with the Virtual Tumour™

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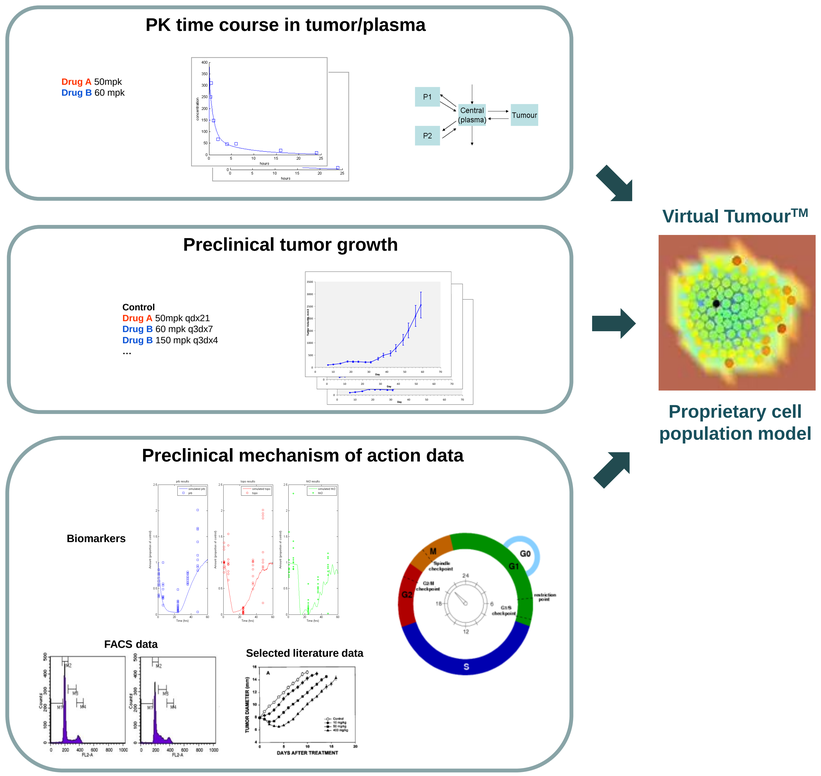
Introduction

Immunotherapy has become a highly active area of anticancer drug development. The field is dominated by immune-checkpoint blockers, which counteract the suppression of the immune response that is often observed in cancer. While early results for monotherapies are promising, the real potential of immunotherapy agents could be in combining them together or with other anticancer treatments. However, there is currently no rational basis on which to select optimal dosing regimens or combination schedules, and a clear unmet need for predictive tools to aid this process[1,2].

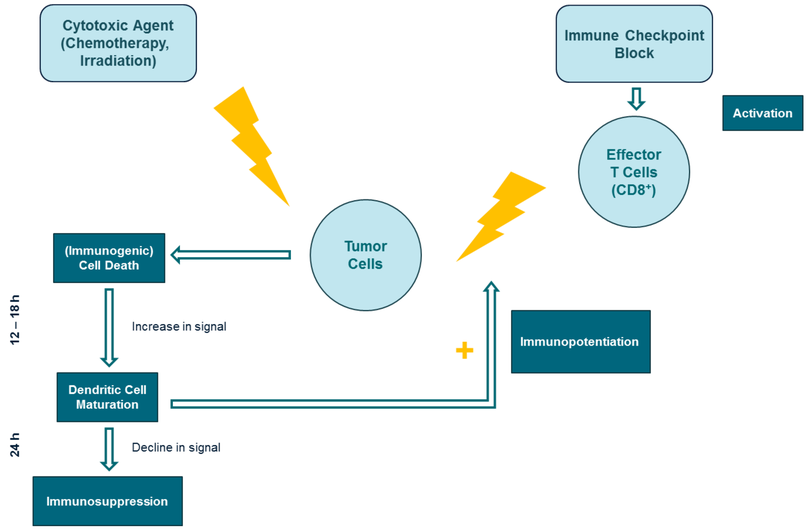
Physiomics has developed a preclinical and a clinical 'Virtual Tumour' ('VT') technology that can predict how a tumor will respond to drug exposure. The VT technology integrates PK and PD effects and models the way individual cells behave within a tumour population. These agent-based methods are particularly suitable for modeling not only tumor cells, but also those involved in the immune response, and interactions between cells.

Here we describe our development and application of the VT technology for modeling preclinical efficacy of immune-checkpoint blockers, with a focus on agents targeting the PD-1/PD-L1 axis. The VT platform has been extended by the addition of an immunotherapy module, which has been developed and calibrated using data from the literature[3,4,5]. This module captures the mechanisms by which immunotherapy activates the antitumor immune response and synergizes with conventional anticancer therapies.

The Physiomics Virtual Tumour™ Technology



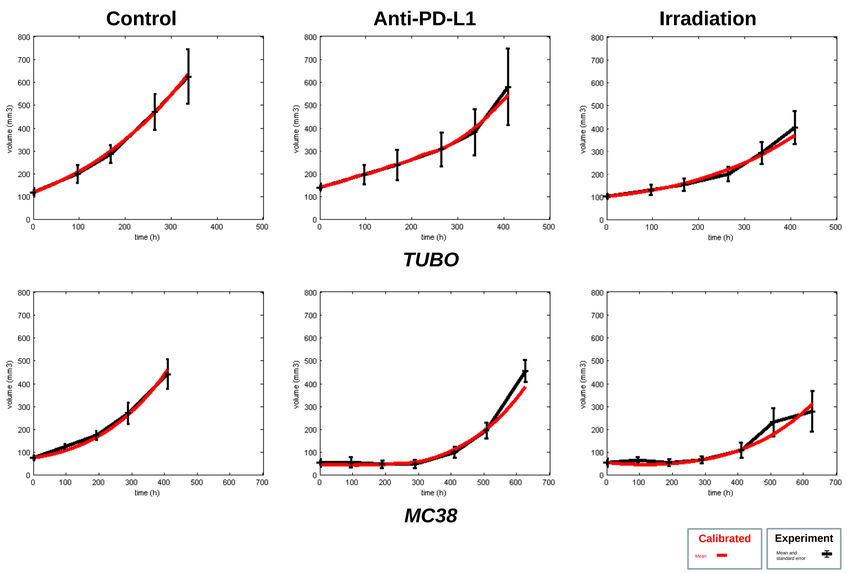
The Immunotherapy Module



Model Calibration

We evaluated the capability of the extended VT technology to model the efficacy of an anti-PD-L1 antibody in syngeneic mouse xenografts, both alone and in combination with irradiation, through a preclinical case study derived from the literature.

The VT model was calibrated for the separate monotherapies using published PK data for the antibody[6], and tumor growth inhibition data for the monotherapies in two *in vivo* models (TUBO and MC38)[7].

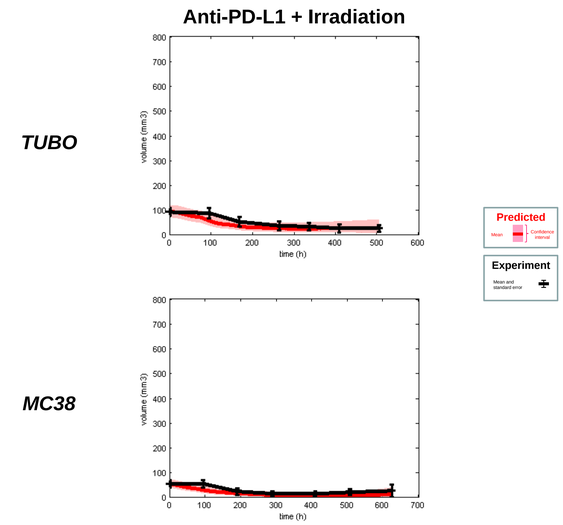


Model Predictions and Validation

As in a blind validation study, the calibrated model was used to predict the combination efficacies of the anti-PD-L1 antibody with irradiation in the same two *in vivo* models.

Within the model, synergy between an immune-checkpoint blocker and a cytotoxic agent arises through immunopotentiation. The level of synergy obtained is a function of the extent to which T-cell antitumor activity is enhanced by the cytotoxic agent. The degree of synergy to be expected from combining the anti-PD-L1 antibody with irradiation was estimated through a comprehensive, quantitative analysis of published combination studies with similar agents. Typically, such combinations are either additive, or up to three times more effective than the monotherapies, with many being around twice as effective. Based on this analysis, the immunopotentiation for irradiation was set to a level that approximately doubled the combination efficacy with the anti-PD-L1 antibody, which resulted in this case in tumor regression over the course of the experiment.

These predictions were validated against the published experimental data[7], and found to accurately reflect the reported efficacies of the combination treatment.



Conclusions

Through a preclinical case study derived from the literature, we have demonstrated that the extended Virtual Tumour™ technology can be applied to model and predict the synergy of an anti-PD-L1 antibody in combination with irradiation in syngeneic mouse xenografts.

Our enhanced VT capability represents the first step towards a ground-breaking tool for optimizing dosing and scheduling of immunotherapy, both alone and in combination with conventional anticancer therapies.

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