

Introduction

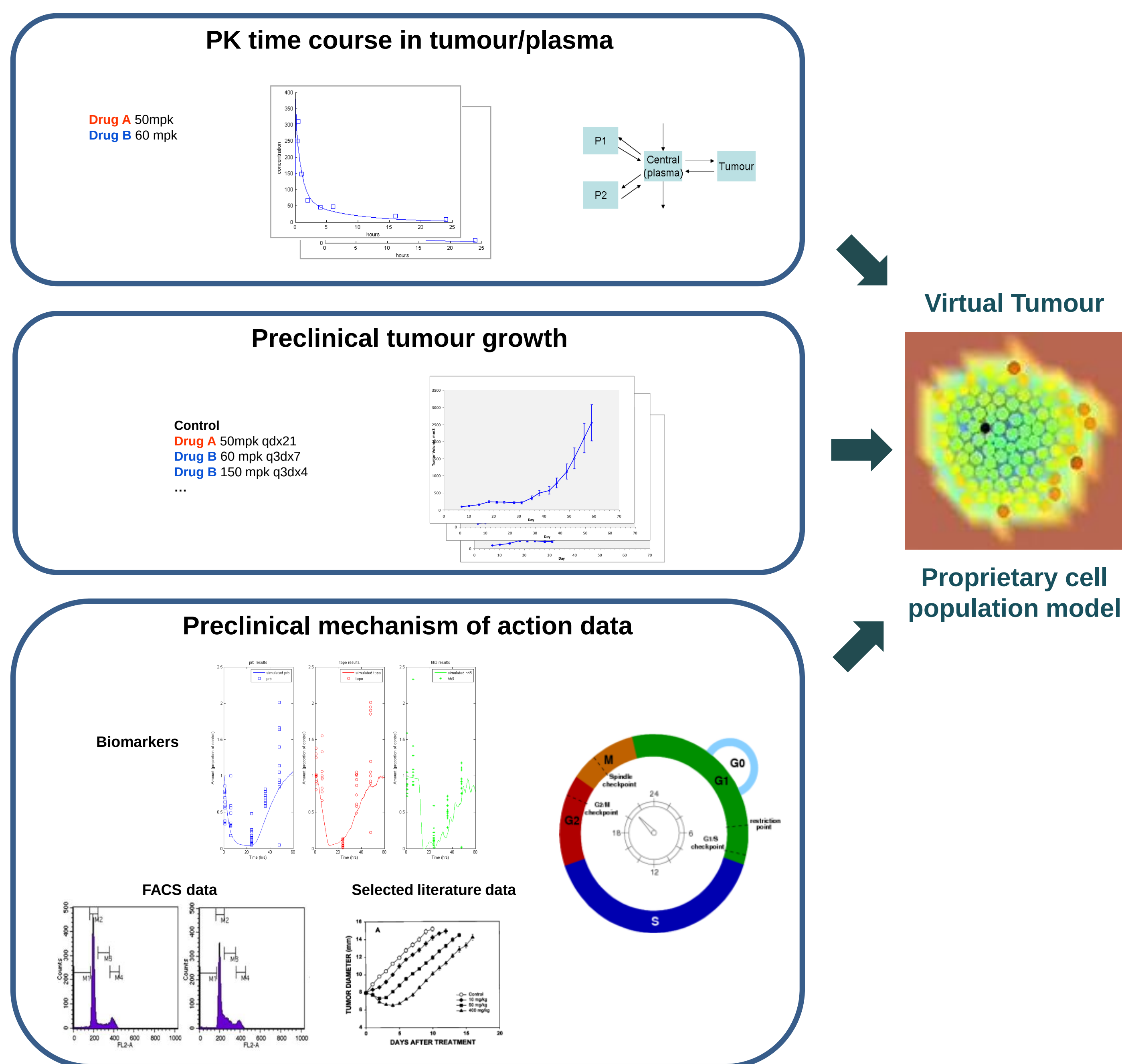
Immunotherapy has become a highly active area of anticancer drug development. The field is dominated by immune-checkpoint blockers, which counteract the suppression of the immune response that is often observed in cancer. While early results for monotherapies are promising, the real potential of immunotherapy 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 tumour 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 modelling not only tumour 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 modelling 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.

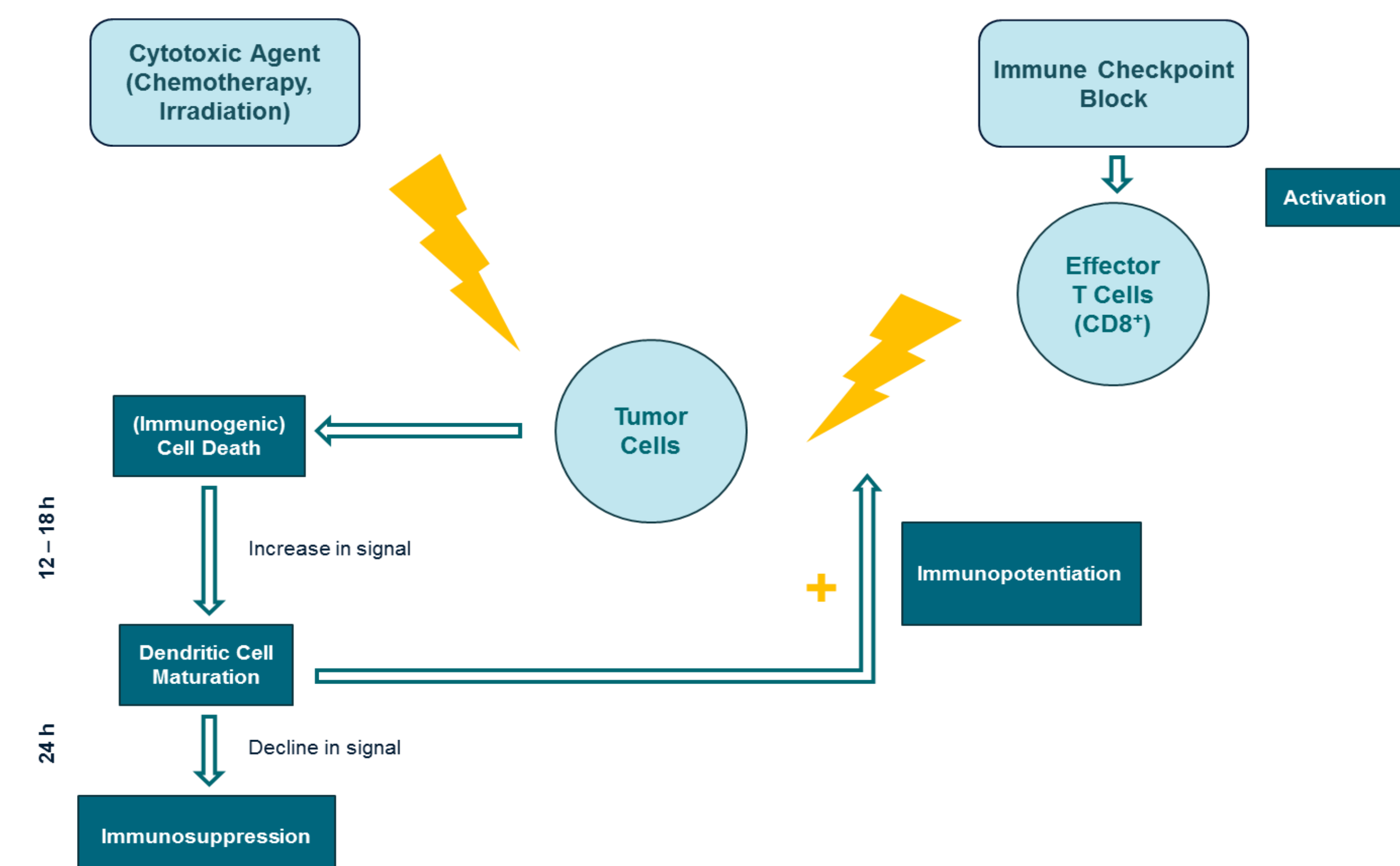
The Physiomics Virtual Tumour Technology

The Virtual Tumour takes as input the following data sets:



The Virtual Tumour simulations and predictions can be used to design and simulate new, rational experiments by ranking combinations and dosing schedules in specific tumours. This allows researchers to eliminate unnecessary and redundant experiments/clinical studies, thus reducing the amount of animal and human studies.

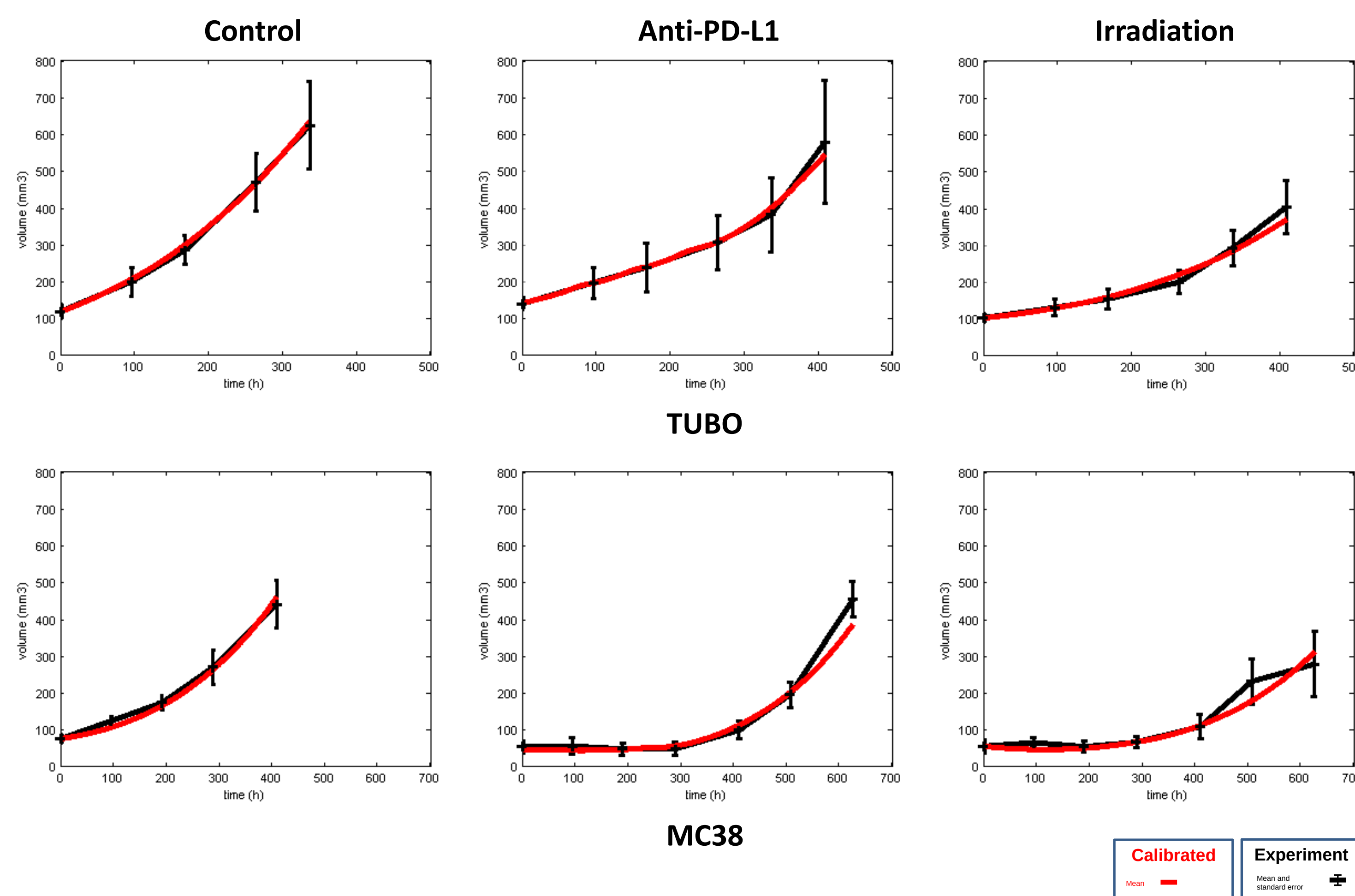
The Immunotherapy Module



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 tumour growth inhibition data for the monotherapies in two in vivo models (TUBO and MC38)^[7].

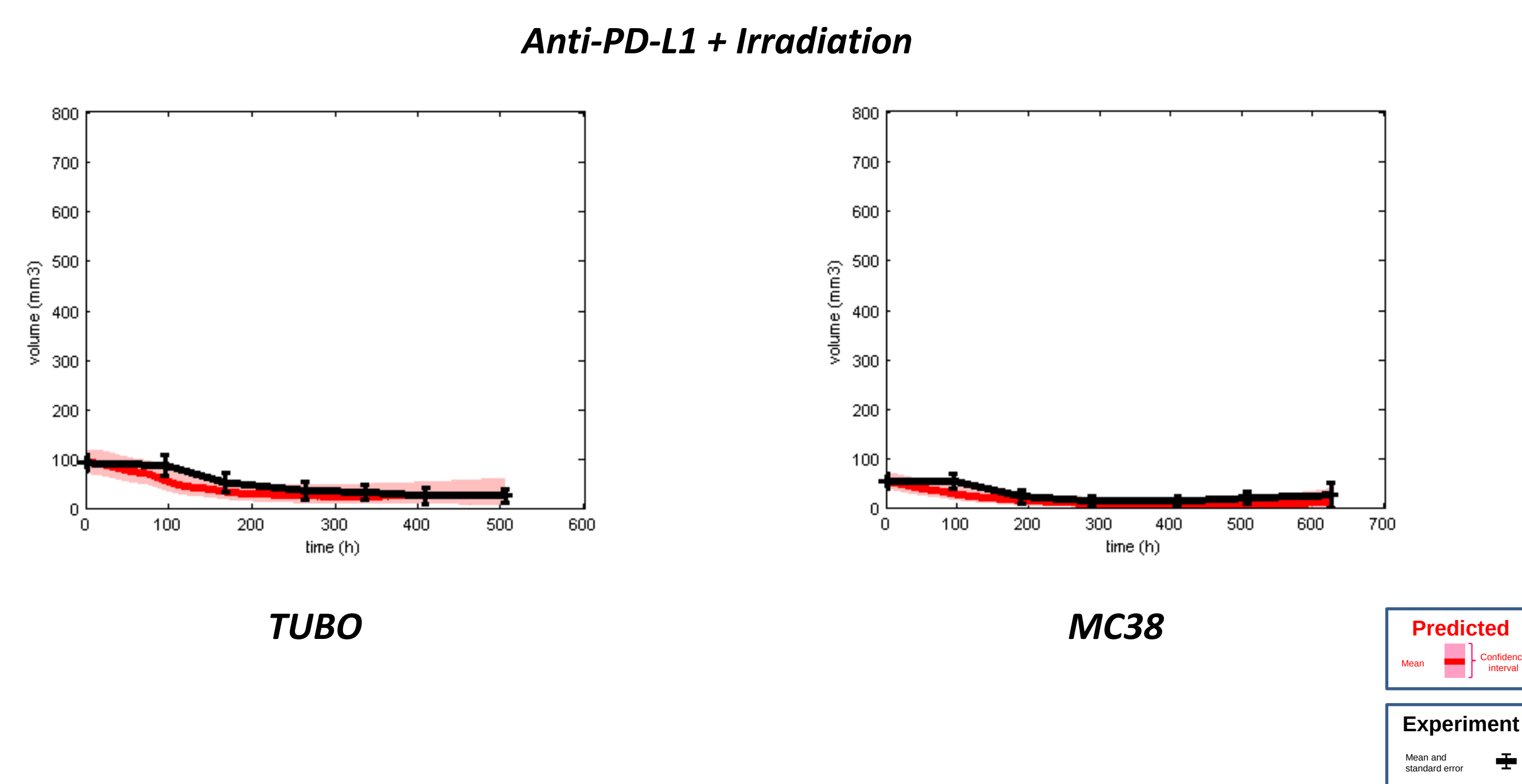


Model Predictions and Validation

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 immunopotentiality. 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 immunopotentiality 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 tumour 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 TumourTM 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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