Radiation and anti-PD-L1 treatment combinations: Immune cell responses and dose scheduling optimization using a joint experimental and systems modeling approach

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Modeling & Simulation Decisions

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Executive summary

• A semi-mechanistic ODE-based model describing interactions among host immune cells and tumor cells was developed;

• The proposed model was used to explore the effects of radiotherapy (RT) and anti-PD-L1 antibodies, including their combinations, on the tumor microenvironment and tumor growth dynamics in experimental murine models;

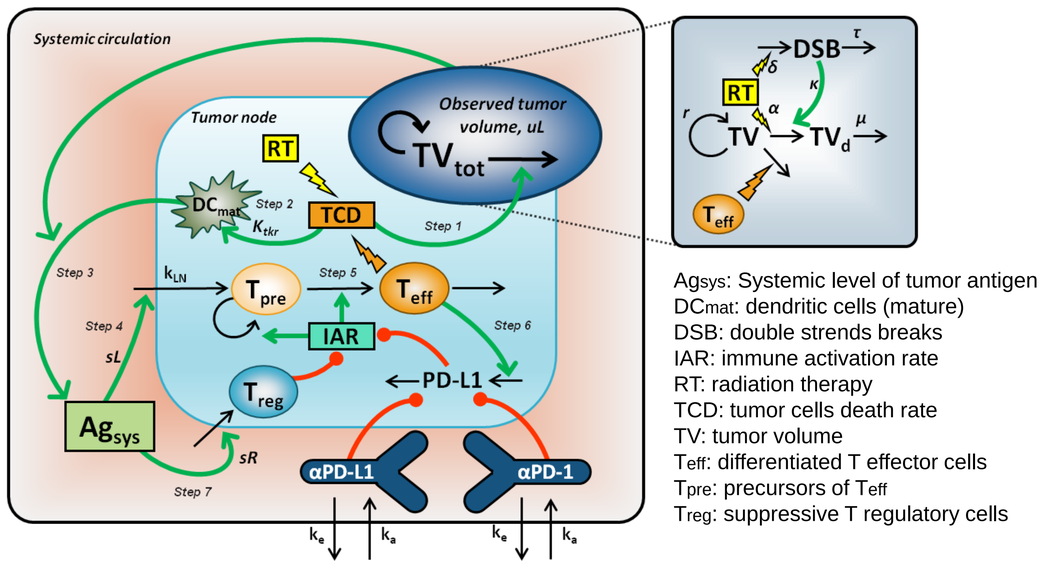
• A population approach was used to select the optimal model structure and identify determinants of anti-tumor responses and of inter-individual variability. The model was validated using independent data, and anti-tumor efficacy was predicted for a range of RT/anti-PD-L1 dosing schedules.

Introduction

Investigations into the interactions between radiotherapy (RT) and the host immune system have uncovered new mechanisms that can potentially be exploited to improve the efficacy of RT [1]. RT not only exerts direct cytotoxic effects on tumor cells, but may also modulate the tumor microenvironment to facilitate a significant anti-tumor immune response. Combination therapies of radiation and mAb blockade of the immuno-suppressive programmed death-ligand 1 (PD-L1) have indeed shown synergy in a number of preclinical studies [2, 3].

Methods

We developed a semi-mechanistic population model of anti-tumor T cell immune response development linked to CT26 tumor size dynamics in mice, under control, mono- and combination settings of RT and anti-PD-L1 treatments (Fig. 1). The model was implemented in MONOLIX, and the parameters was fitted to individual animal data from [2]. Variability in individual tumor size dynamics was taken into account using a mixed-effects model at the level of tumor infiltrating T cell influx.



Agsys: Systemic level of tumor antigen
DCmat: dendritic cells (mature)
DSB: double strends breaks
IAR: immune activation rate
RT: radiation therapy
TCD: tumor cells death rate
TV: tumor volume
Teff: differentiated T effector cells
Tpre: precursors of Teff
Treg: suppressive T regulatory cells

Fig. 1 Semi-mechanistic immune-oncology (IO)/RT model scheme

Model predictions for individual tumor size dynamics and median trends under all treatment conditions were examined (Fig. 2). Experimental tumor size data were then mapped onto prediction distributions; most of the data were captured within the 5% to 95% percentile intervals. In full agreement with [2], the model indicated that scheduling of an anti–PD-L1 mAb concomitantly with, but not following RT administration was required to maximize efficacy benefits.

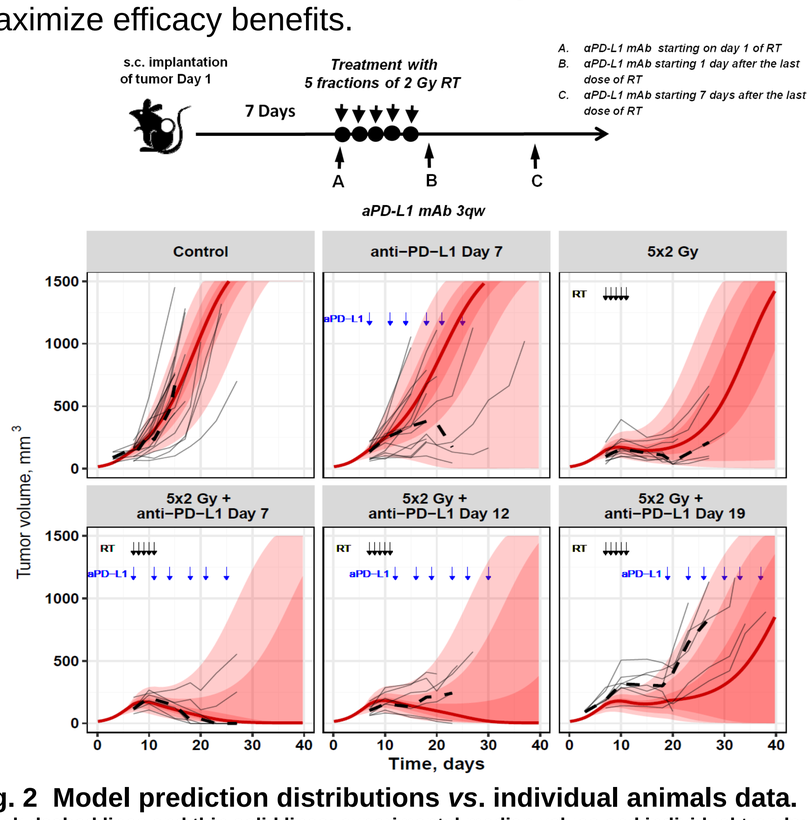


Fig. 2 Model prediction distributions *vs*. individual animals data.
Black dashed lines and thin solid lines: experimental median values and individual trends; red lines, solid: model-predicted median; graded (light to dark) red-shaded areas: respectively, 90%, 60% and 30% prediction intervals (PI).

Results

Model validation

To further assess the predictive power of the IO/RT semi-mechanistic model model, we used it in a 'forward-simulation' mode to independently reproduce additional experimental data from [4]. For example, the model adequately predicted independent CT26 tumor size data in response to novel RT/anti-PD-L1 combination dose regimens not used in model calibration (Fig.3)

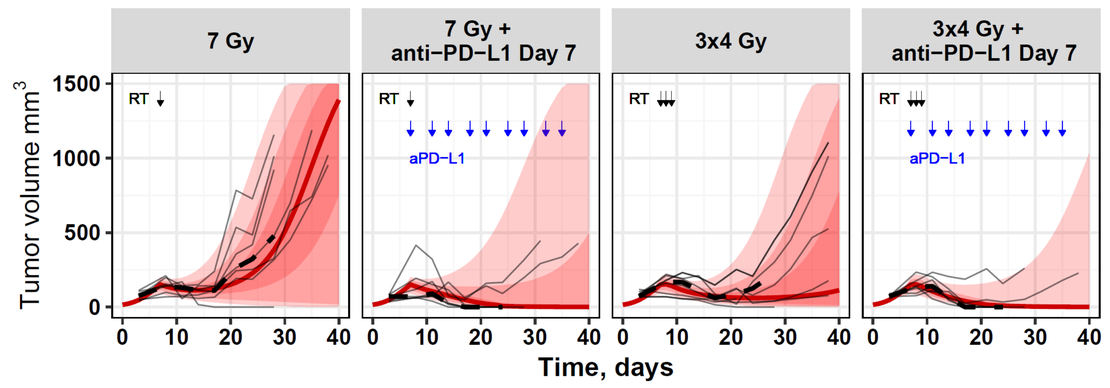


Fig. 3 Model predicted tumor size dynamics under additional RT/anti-PD-L1 combination treatment regimens. **Black dashed lines and thin solid lines: experimental median values and individual trends; red lines, solid: model-predicted median; graded (light to dark) red-shaded areas: respectively, 90%, 60% and 30% prediction intervals (PI).**

Model predictions

Using such a validated model, we gained a detailed quantitative understanding of the synergistic effects underlying immune cell interactions as linked to tumor size modulation, under RT and anti-PD-L1 treatments. The model indeed featured how RT may accelerate an immune response development by improving tumor antigen presentation, thereby inhibiting tumor growth and delaying the accumulation of immuno-suppressive regulatory T cells (T_{reg}) as a result. PD-L1 expression induction in tumor cells, which works as a negative feedback in the model, can be blocked by an anti-PD-L1 mAb. Thus, combinations of RT and anti-PD-L1 treatments may offset the immuno-suppressive impact of T_{reg} and PD-L1 over time, thereby inducing a sufficiently robust accumulation of cytotoxic T_{eff} cells with subsequent tumor shrinkage or rejection.

We further show the potential in using this model as an *in-silico* evaluation tool to explore, prospectively, different combination dosing regimens and sequencing, in order to achieve optimal anti-tumor responses (Fig.4). For example, a 10-Gy single-dose RT with either concurrent and preceding anti-PD-L1 (10 mg/kg 3qw) was found to be optimal in CT26 tumor-bearing mice.

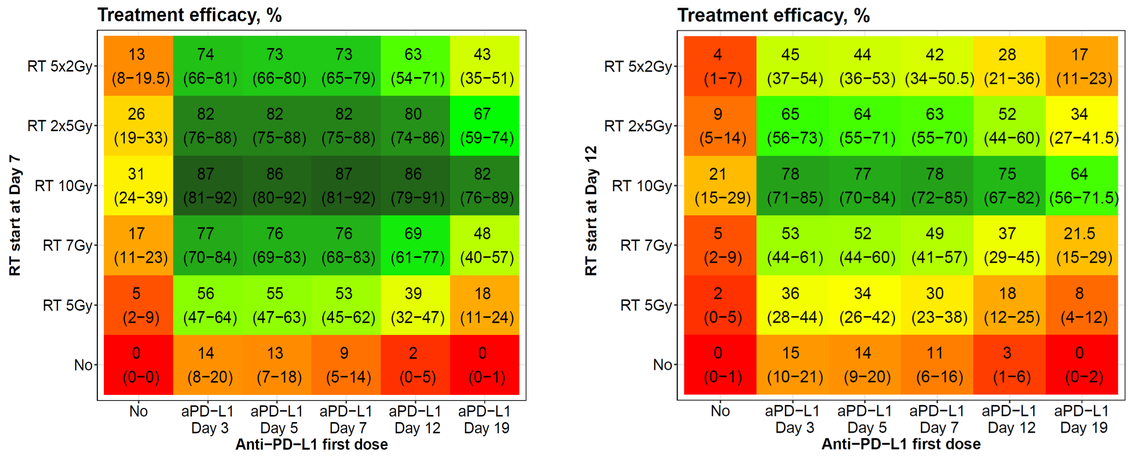


Fig. 4 Model predictions of efficacy for different mono- and combination dosing regimens and sequencing. **Efficacy was defined as the number of animals with complete tumor rejection in a virtual experiment of 100 mice per treatment group. Confidence intervals (CIs) treatment efficacy are shown in brackets.**

Conclusions

This modeling study provided quantitative mechanistic insights into the links between RT and anti-tumor immune responses, and described how appropriate combinations and schedules of immuno-modulation and radiation may tip the immune balance in favor of the host, robustly enough to lead to tumor shrinkage or rejection.

References

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