Modeling & Simulation Decisions

Radiation and PD-(L)1 treatment combinations: immune response and dose optimization via a predictive systems model

Visual abstract

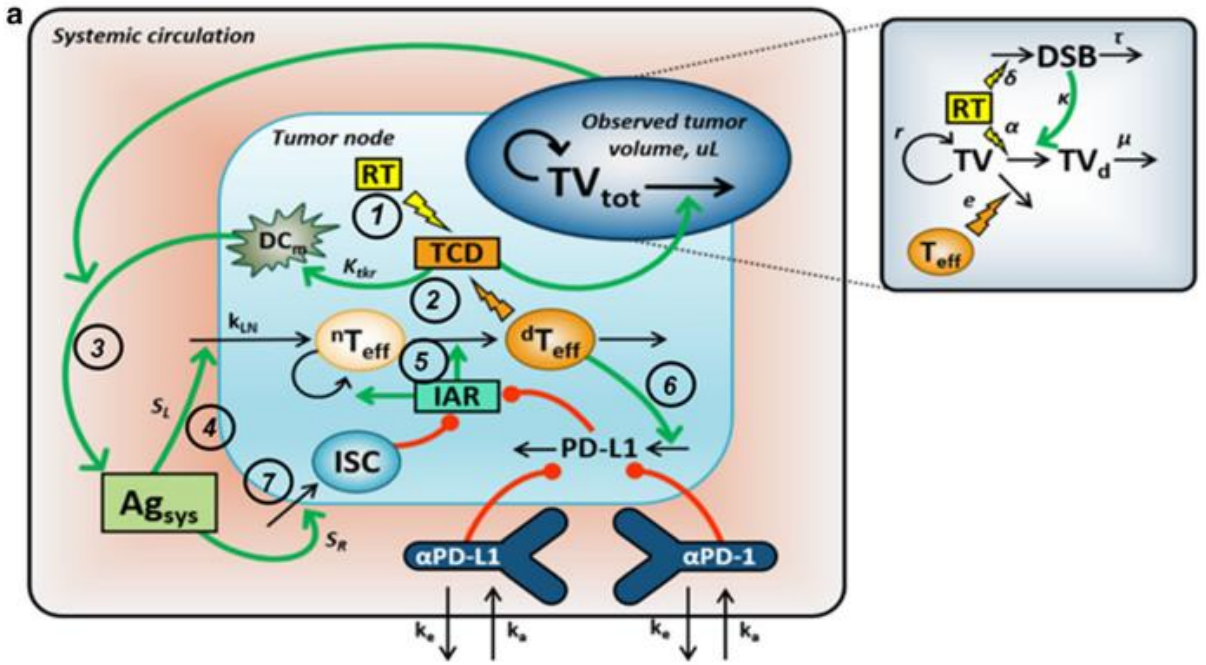
Radiation and PD-(L)1 treatment combinations: immune response and dose optimization via a predictive systems model

Yuri Kosinsky et al. J ImmunoTherapy of Cancer (2018) 6:17

- A quantitative systems pharmacology model, which includes key elements of the cancer immunity cycle, tumor growth and dose-exposure-target modulation features, was developed to reproduce experimental data of CT26 tumor size dynamics upon administration of RT and anti-PD-L1 agent.

- The model allowed for a detailed quantitative understanding of the synergistic kinetic effects underlying immune cell interactions as linked to tumor size modulation, under these treatments.

- This study provides quantitative mechanistic explanations of the links between RT and anti-tumor immune response and describes how optimized combinations and schedules of immunomodulation and radiation may tip the immune balance, sufficiently to lead to tumor shrinkage or rejection.



Modeling & Simulation Decisions

Compact work review

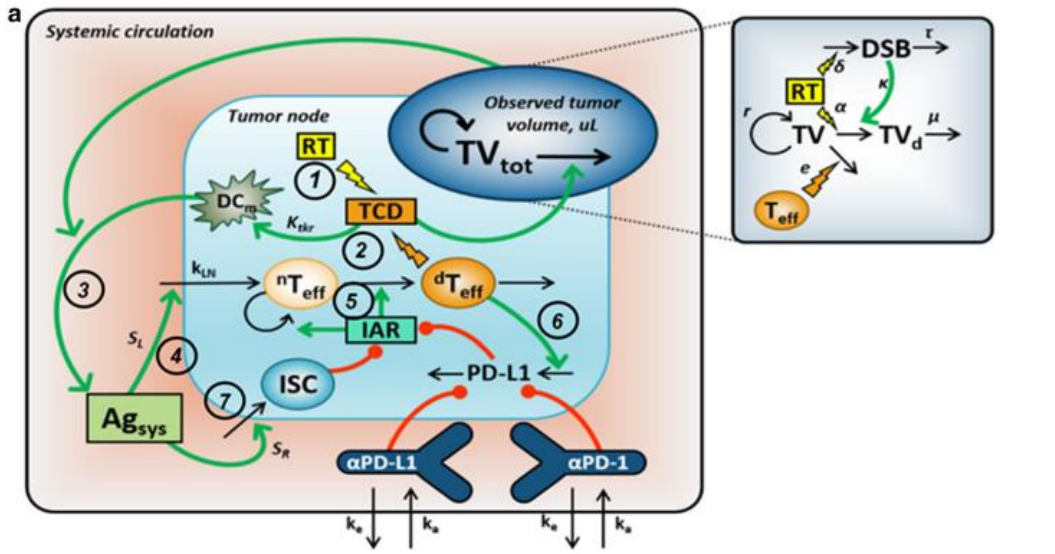
Radiation and PD-(L)1 treatment combinations: immune response and dose optimization via a predictive systems model

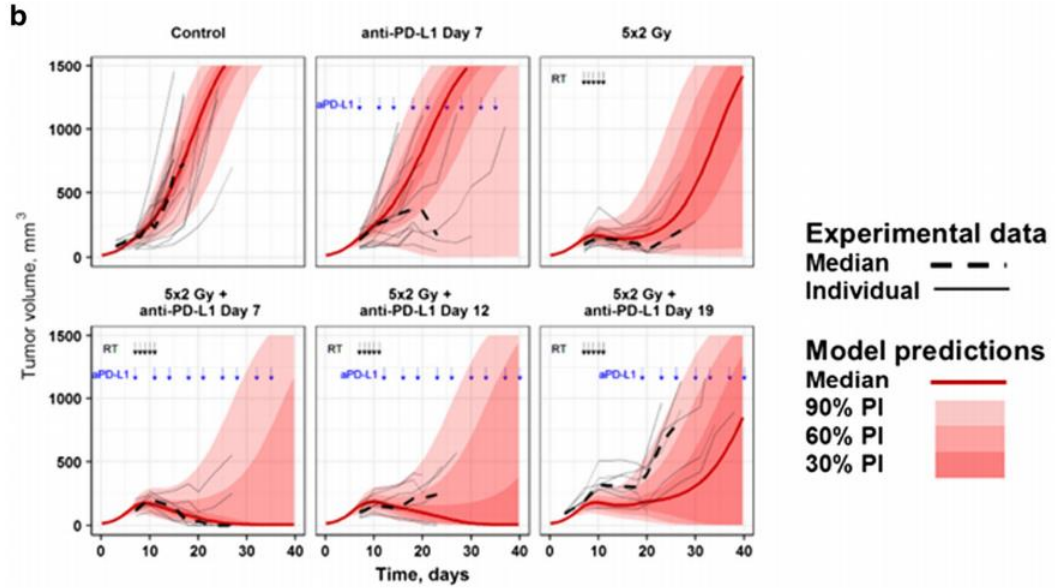
Objectives

Numerous oncology combination therapies involving modulators of the cancer immunity cycle are being developed, yet quantitative simulation models predictive of outcome are lacking.

The objective of the work was to develop the semi-mechanistic model of tumor size dynamics and immune markers, which integrates experimental data from multiple studies and provides a validated simulation framework predictive of biomarkers and anti-tumor response rates, for untested dosing sequences and schedules of combined radiation (RT) and anti PD-(L)1 therapies.

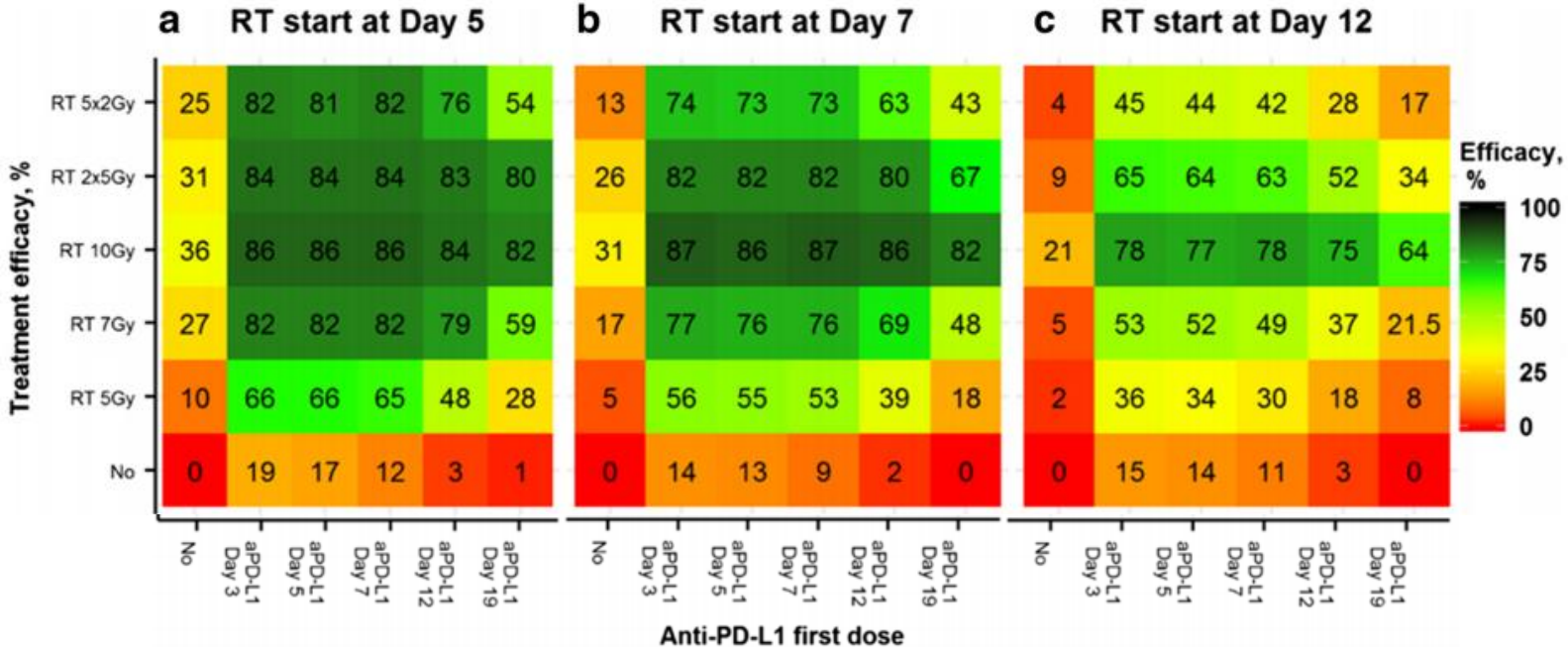
IO QSP model was developed to describe syngeneic tumor size dynamics in mice





- We developed the mathematics of the QSP model, which includes key elements of the cancer immunity cycle and the tumor microenvironment, tumor growth, as well as dose-exposure-target modulation features, to reproduce experimental data of CT26 tumor size dynamics upon administration of RT and/or a pharmacological IO treatment such as an anti-PD-L1 agent.
- Ordinary differential equations were implemented to describe and simulate intrinsic tumor growth, proliferation and differentiation of effector T cells, tumor cell kill processes, and PD-L1 expression dynamics.

IO QSP model was used to simulate a wide spectrum of realistic treatment scenarios.



- We used the QSP model to simulate a wide spectrum of realistic treatment scenarios. Different dosing times of anti-PD-L1 mAb administration in combination with several RT regimens.
- All simulation results were summarized as percentages of ‘responders’, which may be interpreted as a ‘complete response rate’.
- Sequential scheduling of anti-PD-L1 treatment administered after RT revealed decreased response rates which were progressively poorer with longer intervals between respective administrations.
- Simulations of combinations showed that response rates were significantly dependent upon times of treatment start following tumor implantation; a result which may be explained by the critical roles of initial tumor size and levels of TME immuno-suppression at baseline.

Conclusions

- The quantitative dynamic model described here characterizes the cancer immunity cycle and captures kinetic features of immune and tumor cell interactions in mouse CT26 tumors.

- More importantly, this model provides a basis for an in-silico evaluation tool to explore different RT and PD-L1 blockade combination regimens, suggesting that anti-PD-(L)1 treatment prior to, or concurrently with RT maximizes anti-tumor responses.