**A multiscale systems biology model to characterize antitumor immunity and evaluate biomarkers for immunotherapeutics**

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When the immune system responds to a developing tumor, spatial patterns emerge in terms of distribution of tumor infiltrating lymphocytes and focal expression of immune checkpoint molecules such as programmed cell death 1 ligand 1 (PDL1). This kind of pre-treatment tumor spatial heterogeneity bears information on the status of antitumor immunity, and could provide potential biomarkers for immune checkpoint modulators.

We developed a systems biology multi-scale, agent-based model to characterize the interactions between cancer and immune cells during tumor development and under immunotherapy. On a tissue-cellular scale, cancer and immune cells migrate on a three-dimensional lattice. Each cell reacts to its local microenvironment and carries out functions such as cell division, migration, apoptosis, cytotoxic killing, and switching between states each with different PDL1 expression levels. On a molecular scale, partial differential equations were employed to track the spatial-temporal dynamics of cytokines in the microenvironment. On an organ-system scale, we conceptualize immune response arising as a separate compartment connected to the tumor via lymphatic blood circulation; the modular design of our platform allows alternative sub-models of different levels of sophistication. Against this background, we analyzed the emergent behavior of tumor progression and responses to local and systemic factors.

Using this model, we are able to reproduce temporal dynamics of cytotoxic T cells and cancer cells during tumor development, as well as their three-dimensional spatial distribution change over time. Our simulations generate a spectrum of pre-treatment spatial patterns of PD1/PDL1 expression by varying the characteristics of the neoantigen profile of individual patients, such as mutational burden and immunogenicity. Those simulated patterns resemble immuno-architectures obtained via immunohistochemistry from patient biopsies. By correlating these spatial characteristics with in silico treatment data with immune checkpoint inhibitors, our simulation results suggest that the percentage of PDL1 positive cancer cells which are not in close proximity of the tumor boundary or vasculature is indicative of successful anti-PD1/anti-PDL1 treatment. The model provides a framework for predicting treatment/biomarker combinations in different cancer types based on cancer-specific experimental data.