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Personalized adaptive therapies for metastatic melanoma: A phase I approach

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Despite the impressive responses of patients with melanoma to targeted therapies, most patients ultimately fail therapy. Underlying reasons for failure involve intratumor heterogeneity. Adaptive therapy is an evolution-based treatment strategy that exploits the heterogeneity and costs being resistant for resistant cells, for example, molecular synthesis needed to survive treatment. For resistant cells, benefits exceed costs during therapy. In the absence of therapy, however, the costs make resistant cells less fit than their sensitive counterparts. Thus, withdrawal of therapy can make sensitive cells outcompete resistant cells, which can extend the length of responses without the need to add additional therapies. At Moffitt, adaptive therapy clinical trials in metastatic prostate cancer using abiraterone have already been shown to be more effective than continuous therapy. We will present mathematical model driven adaptive therapies in real animals and virtual melanoma patients.

We apply a previously developed virtual clinical trial framework (named phase i trials) with a goal of i) integrating the heterogeneity of actual patient responses and preclinical studies; ii) predicting and optimizing treatment schedules for both pre-clinical animal models and cancer patients; iii) Applying model predicted schedules in animal models. The phase i trials framework consists of mathematical model development, virtual patient generation, and treatment optimization. To describe treatment response dynamics and to investigate the underlying mechanisms of resistance, we develop a suite of mathematical models including a simple growth model, a two-compartment model (sensitive and resistance), and more complex multi-compartment models that incorporate intra-tumor heterogeneity.

The model parameters are estimated differently in animals and patients. For patients, the plasma LDH and cfNDA level are surrogates of burden and we calibrate the model by minimizing the difference between predicted and actual LDH (and/or cfDNA) and from individual patients. This results in a suite of parameter sets that fit to the data equally well, defining a virtual cohort of patients. Using the virtual cohort, we predict responses to various intermittent and adaptive therapies for individual patients. In the animals, we can explicitly quantify the burden and calibrate the models ‘on the fly’ over time. This allows us to directly modulate treatments in individual animals based on model predictions. Critically this is a feedback process where each additional animal time point drives a recalibration of the model that predicts the next treatment decision.