ABSTRACT FACE PAGE

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11. **Is this the research presented in this abstract supported by IMAG MSM-related U01 funding? Yes**
12. **If the Presenting Author is a trainee, who is the trainee's primary research advisor? Aleksander Popel**

TRAINEE POSTER AND ORAL PRESENTATION COMPETITONS:

New to the meeting this year, we are holding *both* a trainee poster competition and a trainee oral presentation competition! If the presenting author is a trainee (i.e., a student at any level or a post doctoral trainee), he/she may enter his/her abstract in the trainee poster competition, the trainee oral presentation competition, or both competitions. Trainees may also submit more than one abstract to the meeting and enter more than one abstract in these competitions. Prizes will be given to the presenters of the top-ranked trainee oral presentation and the top-ranked trainee poster (judged during the meeting by the Program Committee).

13. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Poster Competition*? Yes**

*Note: Trainees who enter the poster competition are expected to stand by their poster during the scheduled poster sessions and present them to the judges.

14. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Oral Presentation Competition**? Yes**

**Note: The Program Committee will select the top four abstracts from trainees who elect to enter their abstract into the trainee oral presentation competition, these four trainees will be notified by Feb. 17th, and they will deliver their oral presentations (which will be judged) on the second day of the meeting after lunch.

QSP-IO: A multiscale quantitative systems pharmacology model for immuno-oncology applications

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INTRODUCTION: Over the past decade, numerous therapeutics have been developed to enhance recognition and killing of cancer cells through distinct mechanisms, such as immune checkpoint inhibitors, T cell engagers, and epigenetic modulators, and have been widely investigated in clinical trials. The survival rate of patients with cancer has been improved by immunotherapies and their combination with other types of therapies. However, the general response rates of the current clinical trials are highly variable. Since only a small subset of patients respond favorably even in biomarker-selected cohorts, it is of significant translational value to build an integrative mechanistic understanding of cancer biology, inter-individual variability, and drug-target interactions using state-of-the-art, quantitative systems-level models to answer critical questions in immuno-oncology (IO) studies.

METHODS: A modularized quantitative systems pharmacology (QSP) model platform is developed using the SimBiology Toolbox in MATLAB (MathWorks, Natick, MA) to conduct simulations of patient outcomes in response to different immune- and combination therapies. The QSP-IO platform consists of seven modules: a cancer module, an antigen presentation module, an antigen module, a T cell module, a checkpoint module, a myeloid-derived suppressor cell model, and a pharmacokinetics module. The cancer and T cell modules can be called multiple times to simulate different clones of cancer/T cells. Similarly, the antigen module can be called multiple times to simulate different antigens (including competing self-peptides). Additionally, the pharmacokinetics module can be called for each drug. Due to the modular nature of QSP-IO, additional modules can be added by following the structure of the existing modules. The model considers a whole patient, with mechanistic description of molecular and cellular interactions in tumor, lymph nodes, blood, and peripheral compartments, thus multiple scales.

RESULTS: The proposed QSP model is used to conduct *in silico* clinical trials of virtual patients with various cancer types, such as breast cancer, colorectal cancer, and hepatocellular carcinoma. We make predictions of anti-tumor response to various types of therapies using one or more of anti-PD-1, anti-CTLA-4 antibodies, an epigenetic modulator, and a bispecific T cell engager. As shown in Figure 1, according to model-based simulations, tumor-mutational burden, effector T cell and regulatory T cell density and their ratio are significantly higher in responders in triple combination therapy using anti-PD-1, anti-CTLA-4 antibodies and an epigenetic modulator in breast cancer, which could be potential biomarkers to consider in future studies.

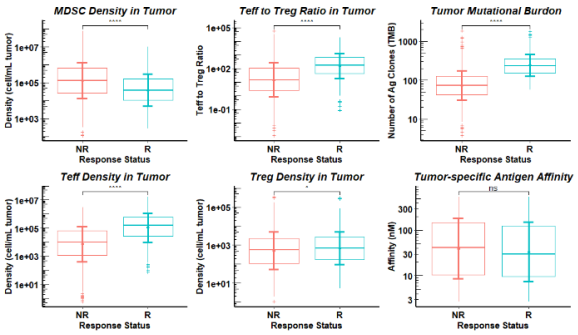

Figure 1: Distributions of Potential Biomarkers in Responders and Non-responders.

CONCLUSIONS: Overall, we present a readily reproducible modular model platform to conduct *in silico* virtual clinical trials on patient cohorts of interest, which is a step toward personalized medicine in cancer immunotherapy. Importantly, ongoing clinical trials may provide insights on the effect of therapeutics on the immune system and resistance mechanism in tumor development, which would allow us to make step-by-step modifications to the model, improve its predictive power, and thereby guide drug development and clinical trial design.

REFERENCES:

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