827 STREAMLINING DESIGN OF SAFE AND EFFECTIVE TCR THERAPIES WITH AI

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Background Adoptive cell therapies with T lymphocytes expressing engineered T cell receptors (TCRs) are one of the most promising approaches to cancer therapy.[1] However, the experimentally driven development of novel TCR therapies is limited by the enormous biological variability of peptide: Human Leukocyte Antigen:TCR (pHLA:TCR) complexes. The in silico methods hold the promise to streamline the discovery of novel TCR therapies by reducing costs and time of laboratory research. In particular, the prediction of TCR binding to a target antigen, as well as the prediction of TCR off-target toxicity[2] can provide useful insights supporting the development of safe therapies. We aimed at the development of an experimentally validated AI model of pHLA:TCR binding that will help to prioritize and reduce the number of in vitro assays necessary to discover novel TCRs for cancer therapies.

Methods The limiting factor of successful pHLA:TCR binding modeling is data availability and completeness of TCR characterization. To address this issue, we are building an oncological pHLA:TCR database with paired alpha and beta chain TCR sequences. We are collecting and sequencing tumor and normal samples from 100 cancer patients, as part of an observational clinical trial. Those data are then screened with the Ardigen's ArdImmune Vax platform[3] [4] to select immunogenic epitopes. T cells that bind those epitopes are subsequently sorted and used to generate TCR sequencing data at single-cell resolution. We use data-driven and simulation-based models to extract insights about the dynamics of a pHLA:TCR system to predict the binding probability and explain the inference made by the model.

Results We optimized our data collection pipeline for the cost-efficient acquisition of a large oncological pHLA:TCR dataset. These data will enable us to build efficient models to streamline the development of TCR therapies against cancer.We benchmarked our modeling approach for pHLA:TCR binding against existing solutions[5–7] on publicly available data. We also show how focus on model explainability facilitates the detection of model inconsistency of uncertain predictions by expert inspection. Our toxicity assessment solution[2] extends the applicability of our system to the prediction of TCR safety profile.

Conclusions The presented work shows perspectives and limitations of AI-aided TCR therapy development. We present results for our pHLA:TCR binding model, a TCR-toxicity-screening solution, and the study design of our observational clinical trial. Our growing database of pHLA:TCR interactions will enable us to develop highly predictive pHLA:TCR binding models, in particular for oncological targets.

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