A combination of antigen presentation and T-cell recognition features improves neoantigen immunogenicity predictions

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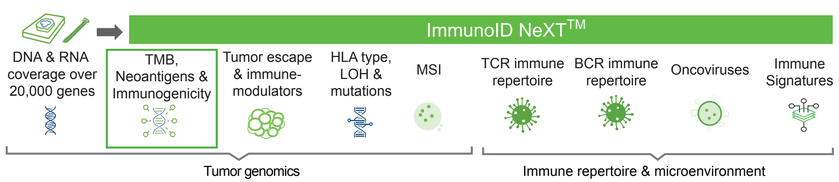
I. Background

Tumor neoantigen burden outperforms tumor mutational burden (TMB) in prediction of patient response to immune checkpoint blockade (ICB) therapy by better capturing the biological mechanism underlying response [1]. However, immune recognition of neoantigens by T-cells requires more than antigen presentation, which has been the focus of tumor neoantigen burden thus far. To address this need, we extend the existing SHERPA™ MHC-presentation framework [2] to predict neoantigen immunogenicity.

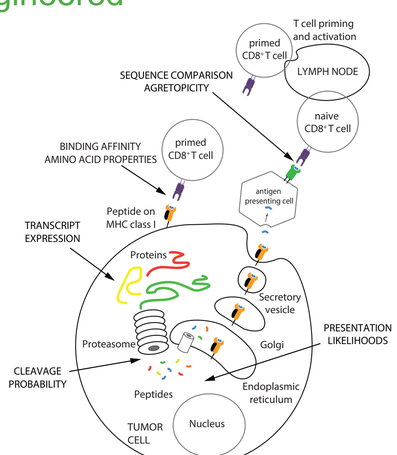
II. Augmented exome capture with ImmunoID NeXT™

The ImmunoID NeXT Platform™ provides joint tumor genomics and immune profiling from a single tumor/normal sample. In depth interrogation of tumor and normal samples and identification of tumor-specific genomic events allows us to comprehensively profile the landscape of potentially immunogenic neoantigens, a critical aspect of precision neoantigen discovery.



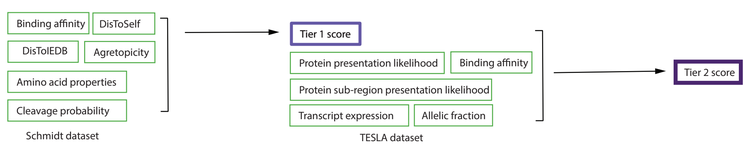
III. Immunogenic features engineered

Previous studies have shown that immunogenic features are associated with antigen availability, processing, MHC binding and T-cell recognition. To capture antigen availability in our model, we measured gene expression level and variant allele fraction. We built a cleavage probability predictor from immunopeptidomics data for antigen processing in addition to using immunopeptidomics-derived presentation likelihoods. SHERPA-Binding, trained with high quality mono-allelic immunopeptidomics data from 110 alleles, was used to quantify antigen binding. We represented T-cell recognition with antigen amino acid properties, agretopicity, and sequence comparison features, such as dissimilarity to self antigens and similarity to known foreign antigens.



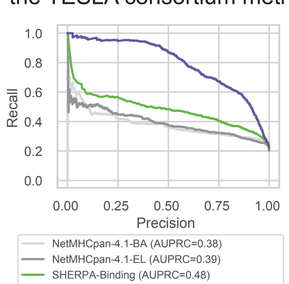
IV. Immunogenicity score models and development

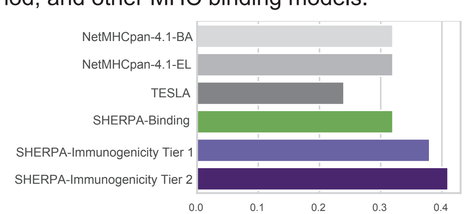
For training and validation, we utilized two datasets containing peptides experimentally validated for immunogenicity. The first dataset, curated by Schmidt et al. [3], aggregates experiments from 17 different sources and identifies 1282 immunogenic peptides across 67 MHC alleles. While the diversity of the dataset enables generalizability, a lack of associated sequencing data also limits the features that can be investigated. The second dataset, curated by the TESLA consortium, contains 37 immunogenic peptides across 13 MHC alleles with patient-specific exome and transcriptome sequencing data [4]. After evaluating the available feature landscape of both datasets (shown below), we developed a two-tiered model incorporating the features that demonstrated significant performance gains. Tier 1 integrates SHERPA-Binding, DisToSelf, DisToIEDB, and cleavage probability into a machine learning model. Due to the limited size of the TESLA dataset, Tier 2 employs a thresholding approach that combines the Tier 1 score, SHERPA-Binding and transcript expression to avoid overfitting.



V. SHERPA-Immunogenicity outperforms TESLA method and MHC binding prediction algorithms

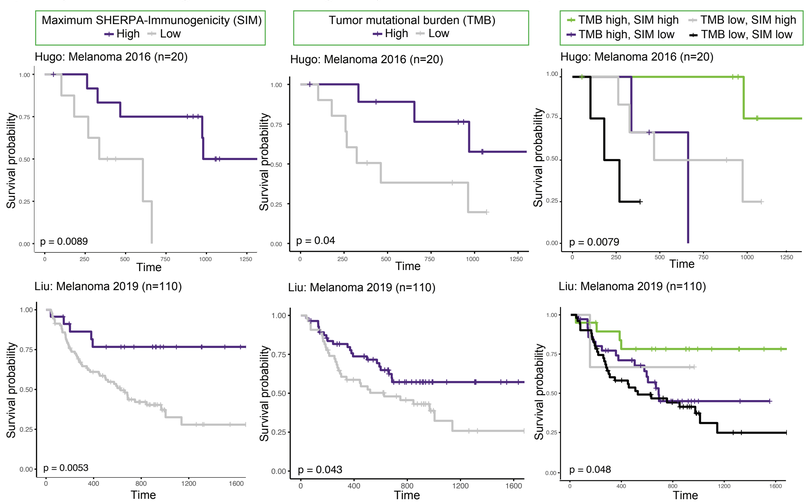
After cross validation on the Schmidt dataset, the Tier 1 SHERPA-Immunogenicity score distinguished immunogenic peptides with an area under the precision recall curve (AUPRC) of 0.80, far greater than SHERPA-Binding or NetMHCpan-4.1 alone (0.48 and 0.39 respectively). On the TESLA dataset, the Tier 2 SHERPA-Immunogenicity score yielded a positive predictive value (PPV) of 0.41, an improvement over the Tier 1 score, the TESLA consortium method, and other MHC binding models.





VI. Evaluation on clinical cohorts

To understand the clinical applicability of SHERPA-Immunogenicity, we evaluated it alongside TMB as a biomarker in two melanoma cohorts treated with ICB therapy [5, 6]. Individual pMHC SHERPA-Immunogenicity (SI) scores were aggregated into a maximum patient score (SIM), as even one highly immunogenic neoantigen can drive an immune response [7, 8]. In both cohorts, patients with either high SIM or high TMB had significantly increased survival. Patients with both high SIM and high TMB had increased survival compared to patients with either low SIM or low TMB, suggesting that both quantity and quality of neoantigens are biologically relevant to response.



VII. Conclusion

We combined antigen presentation and T-cell recognition features in a two-tiered model to better predict immunogenic neoantigens. SHERPA-Immunogenicity has the potential to improve neoantigen-based biomarkers of checkpoint inhibitor efficacy and optimize personalized cancer vaccine target selections. Future work will involve further development of SHERPA-Immunogenicity and integration of SIM with other biomarkers such as NEOPS™ for checkpoint inhibitors.

VIII. References

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