Utilizing response in immune checkpoint inhibitor treated cohorts improves clinical applicability of neoantigen immunogenicity predictions

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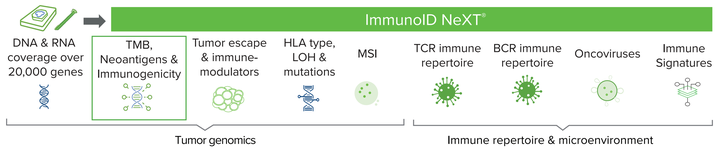
BACKGROUND

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 and demonstrate clinical relevance of the predictions.

AUGMENTED EXOME CAPTURE WITH ImmunoID NeXT

The SHERPA-Immunogenicity score was to augment the neoantigen predictions from 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.



SHERPA-IMMUNOGENICITY DEVELOPMENT AND VALIDATION

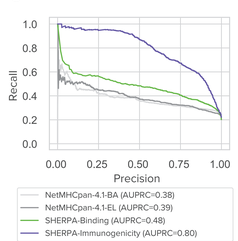
SHERPA-Immunogenicity development

For training, we utilized a dataset with peptides experiemental-ly validated for immunogenicity curated by Schmidt et al. [3]. This dataset aggregates experiments from 17 different sources and identifies 1282 immunogenic peptides across 67 MHC alleles. After evaluating the available feature landscape of the dataset, we developed a machine learning model incorporating features that demonstrated significant performance gains. These included SHERPA-Binding, cleavage probability, and two sequence comparison features: DisToSelf and DisToIEDB, which measure the dissimilarity of the epitope to the self proteome and IEDB antigens, respectively (**A**). Biological context for these features is shown in **B**. We calibrated the output probabilities of the model using percent rank values, with low ranks corresponding to higher immunogenic probabilities. After cross validation in the Schmidt dataset, the SHERPA-Immunogenicity rank 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) (**C**).

A

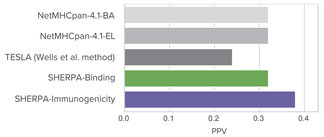
B

C



SHERPA-Immunogenicity validation

For validation, we utilized a dataset curated by the TESLA consortium, containing 37 immunogenic peptides across 13 MHC alleles [4]. The SHERPA-Immunogenicity rank yielded a positive predictive value (PPV) of 0.38, an improvement over the TESLA consortium method and other MHC binding models.



SHERPA-IMMUNOGENICITY EVALUATION

Description of clinical cohorts

We systematically re-processed publicly available DNA and RNA sequencing data from over 500 patients with a harmonized bioinformatics pipeline. The patients were treated with three classes of ICB therapies (anti-CTLA-4, anti-PD-1, and anti-PD-L1) and spanned 12 different cohorts across five cancer types. We chose to focus our analysis on melanoma initially to avoid cancer type-specific biases. We evaluated the performance of the SHERPA-Immunogenicity rank across the melanoma ICB training (N=5) [5,6,7,8,9] and validation (N=3) [1, 10, 11] cohorts using a meta-analysis framework.

Training cohorts

- Van Allen et al. 2015 (N=81)
- Sade-Feldman et al. 2018 (N=11)
- Liu et al. 2019 (N=115)
- Riaz et al. 2017 (N=63)
- Hugo et al. 2016 (N=21)

Validation cohorts

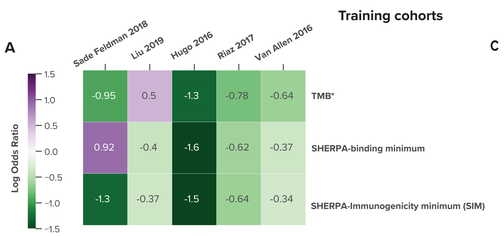
- Freeman et al. 2022 (N=18)
- Sade-Feldman et al. 2017 (N=9)
- Abbott et al. 2021 (N=24)

Impact of SHERPA-Immunogenicity on ICB response

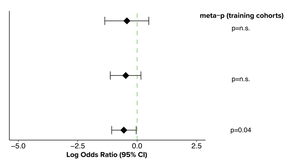
We aggregated the SHERPA-Immunogenicity pMHC predictions into patient-specific scores based on the most immunogenic peptide present, as even one highly immunogenic neoantigen can drive an immune response [12, 13]. This corresponded to peptides with the lowest immunogenic rank (SHERPA-Immunogenicity Minimum (SIM)). We evaluated SIM performance across the ICB training (N=5) **(A)** and validation (N=3) **(B)** cohorts. We observed that responders had lower SIM scores compared to non-reponders across the training (meta p = 0.04) **(C)** and validation cohorts (meta p= 0.005) **(D)**, suggesting that SIM has the potential to predict response to immunotherapy. Importantly, TMB and SHERPA alone were not significant (meta p > 0.05).

Training cohorts

A

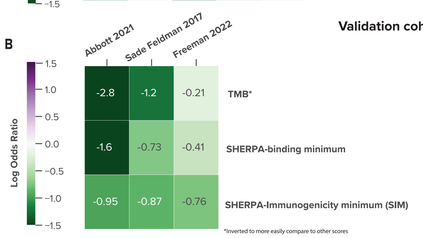


C



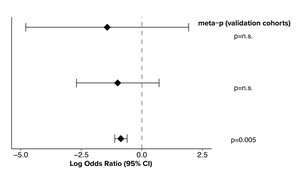
Validation cohorts

B



*Inverted to more easily compare to other scores

D

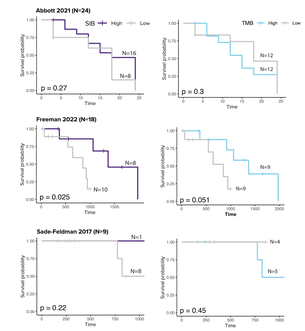


Impact of SHERPA-Immunogenicity on overall survival

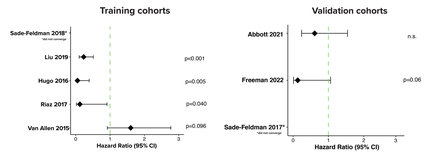
To further understand the clinical applicability of SHERPA-Immunogenicity, we evaluated it alongside TMB as a biomarker in the training and validation cohorts. Since overall survival is a long term outcome, individual pMHC SHERPA-Immunogenicity scores were aggregated into a patient score based on the overall burden of immunogenic neoantigens present (SIB). Patients with high SIB had significantly increased survival ($p<0.05$) in four of the training cohorts and one of the validation cohorts, whereas patients with high TMB had significantly increased survival in only two of the training cohorts and no validation cohorts **(A,B)**. We then ran a univariate and multivariate Cox proprtional hazards regression model (with low SIB/TMB as reference) on the training and validation cohorts. For the majority of the cohorts, high SIB and high TMB individaully had hazard ratios less than one, demonstrating that they are both associated with improved overall survival **(C)**. After, we ran ANOVA to determine if there was significant difference between the Cox multivariate regression model with both SIB and TMB compared to the model with TMB alone. The p-value was significant ($p<0.05$) in two training cohorts **(D)**, demonstrating the additional benefit of SIB. Taken together, the results suggest the SIB metric may provide novel and valuable clinical utility in predicting overall survival.

A **Training cohorts**

B **Validation cohorts**



C **SIB Cox regression hazard ratios**



D **ANOVA results with SIB + TMB Cox regression**

base model = overall survival ~ TMB, full model = overall survival ~ SIB + TMB

Training cohorts

Cohort	p-value*
Sade-Feldman 2018	NA
Liu 2019	0.06
Hugo 2016	0.004
Riaz 2017	0.13
Van Allen 2015	0.03

Validation cohorts

Cohort	p-value*
Abbott 2021	0.97
Freeman 2022	0.39
Sade-Feldman 2017	NA

*p-value measures significance between base and full model

CONCLUSION

We combined antigen presentation and T-cell recognition features in a 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/SIB with other biomarkers such as NEOPS™ for checkpoint inhibitors.

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