Application of precision cancer immunotherapy design tools to bladder cancer: Non-self-like neo-epitopes as a prognostic biomarker

Guilhem Richard1, Randy F. Swies2, Leonard Moise1,3, Matthew Arndt1, William D. Martin1, Gad Berdugo4, Gary D. Steinberg2, Anne S. De Groot1,3
1EpiVax, Inc., Providence, RI, USA, 2University of Chicago, Chicago, IL, USA, 3University of Rhode Island, Providence, RI, USA, 4EpiVax Oncology, Inc., Providence, RI, USA

Abstract

Precision cancer immunotherapy targeting mutations expressed by cancer cells has proven to effectively control the tumor of patients in multiple clinical trials [1,2]. However, the selection of immunogenic Class I neo-epitopes remains challenging and many epitopes selected using traditional methodologies fail to induce effective T cell responses. Poor performance may be due to inclusion of mutated epitopes cross-reacted with self-epitopes recognized by regulatory (Treg), energy, or extinct T cells. Vaccination with self-epitopes can lead to weak effector responses, active immune suppression, and toxicity due to immune-mediated adverse events. Immunological studies focus on the selection of CD1 T cell neo-epitope candidates due to an apparent lack of robust and accurate CD4 T cell epitope prediction tools.

We have developed Ancer™, an integrated and streamlined neo-epitope selection pipeline, that accelerates the selection of both CD4 and CD8 T cell epitopes from NGS data. Ancer leverages EpiMatrix and JanusMatrix, predictive algorithms that have been extensively validated in prospective studies for infectious diseases [3,4]. Distinctive features of Ancer™ is its ability to accurately predict Class I HLA ligands, or CD4 epitopes, with EpiMatrix, and to identify tolerable or Treg epitopes with JanusMatrix. In addition, screening candidate sequences with JanusMatrix enables the removal of neo-epitopes that may induce Treg-mediated adverse events, which in some cases already halted the development of precision cancer therapies.

Ander was applied to NGS data derived from the BLCA bladder cancer cohort from the Cancer Genome Atlas (TCGA) database. On average, 88 out of 202 missense mutations in bladder cancer patients' tumors met Ancer’s quality control standards. This subset of high-quality missense variants was then screened using Ancer settings defined by the unique HLA of each patient to derive the best candidate epitope sequences encompassing these mutations. A median number of 122 candidate sequences were generated for a representative set of eleven patients. The time required to select sequences for all of the patients in this study was less than two days. The initial analysis of eleven BLCA bladder cancer cohort patients demonstrates the capacity of Ancer to define a sufficient number of candidate sequences for vaccinating bladder cancer patients in a precision immunotherapy setting. We also assessed Ancer’s ability to explain patients’ disease free survival (DFS) times. While BLCA patients with DFS greater than 3 months could not be distinguished by their tumor mutational burden (AUC = 0.65, p = 0.18), nor by their load of CD8 T cell neo-epitopes, Ancer defined Class II neo-epitope load will serve as a biomarker for prognosis and response to therapy in the BLCA cohort.

Our analysis of the BLCA cohort from the TCGA database showcases the value of Ancer in clinical settings. Ancer can be used to identify high-value candidate sequences for inclusion in personalized therapies while removing potentially tolerated or tolerogenic self-epitopes from consideration. Our next step will be to investigate whether Ancer-defined Class II neo-epitope load will serve as a biomarker for prognosis and response to therapy in the BLCA cohort.

Conclusions

- Analysis of the MHC- and TCR-facing residues of T cell epitopes by JanusMatrix™ enables prediction of epitope phenotype.
- EpiVax’s immunogenomic screening tools (EpiMatrix® and JanusMatrix™) are integrated into the Ancer™ platform for streamlined designs of personalized cancer vaccines.
- While only 28% of Class I alleles were available for TCGA bladder cancer patients, preliminary results reveal that Ancer™ may predict likelihood of disease-free survival. Follow-up analyses are planned where HLA Class II will be considered.
- Ancer™-derived vaccines are currently being evaluated in prospective studies using the CT26 and GL261 syngeneic mouse models.

References


Acknowledgments

This work was supported by the EpiVox Oncology, Inc. and the TCGA Research Network. Some images used in this paper were taken by Phoenix from www.Remark.com and are licensed to EpiVax Inc.