Tumor homology with self as a biomarker for response to checkpoint inhibitor therapy

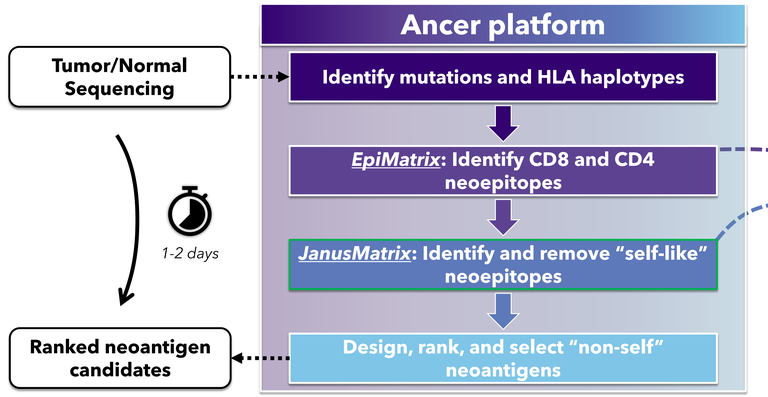
Guilhem Richard[1], Gary D. Steinberg[1,2], Nicole Ruggiero[1], William D. Martin[3], Anne S. De Groot[3,4]

[1]EpiVax Therapeutics, Inc., Providence, RI, USA, [2]NYU Langone Health, New York, NY, USA, [3]EpiVax, Inc., Providence, RI, USA, [4]University of Georgia, Athens, GA, USA

Overview

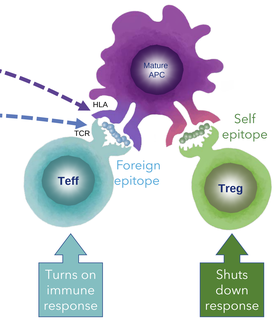
- **Hypothesis**: Tumor clones surviving checkpoint inhibition therapy harbor mutations more prone to immune avoidance.
- **Approach**: Tumors from melanoma patients collected **before and after** nivolumab immunotherapy (n=41) were analyzed with **Ancer, an advanced neoepitope screening platform** that combines proprietary machine learning-based **CD8 and CD4** epitope mapping tools with removal of **inhibitory Treg** epitopes [1,2].
- **Results**: **Mutations gained after nivolumab therapy are less immunogenic and more tolerogenic** compared to mutations found prior to therapy.
- **Response to therapy is associated with Ancer results.**
- **Summary**: Our Ancer analysis suggests that nivolumab therapy affects the immunogenicity and tolerance profiles of newly generated mutations in a manner that is **consistent with the concepts of immunoediting and immune camouflaging**.

Background – Mutanome-Directed Cancer Immunotherapy Based on 25 Years of Experience in Epitope Mapping

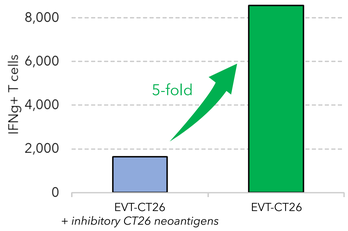


HLA binding predictions. ***EpiMatrix*** Class I an Class II predictions are respectively **95% and 74% accurate** [1].

Foreign vs self epitopes: ***JanusMatrix*** identifies **inhibitory (self-like) epitopes** *in silico*. Validation studies with pathogens [3, 4, 5] and cancer mutanomes [6].

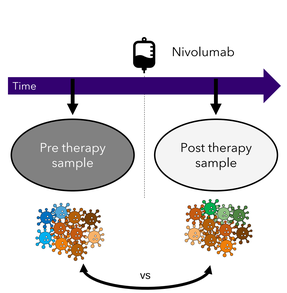


*CT26 self-like neoepitopes (**identified in silico with JanusMatrix**) suppress IFNg production to EVT-CT26 vaccine [6]*



Approach – Ancer analysis of melanoma samples

- Forty-one pairs of mutanomes collected before (*Pre*) and while on (*Post*) nivolumab therapy were retrieved from [7].
- Pre and Post mutanomes were compared to identify deleted, maintained, and newly acquired mutations.
- Immunogenic and tolerance potentials were calculated for all mutations with Ancer.

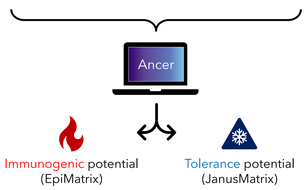


Simplification: one tumor cell clone = one mutation

Clones **sensitive** to checkpoint therapy

Clones **resistant** to checkpoint therapy

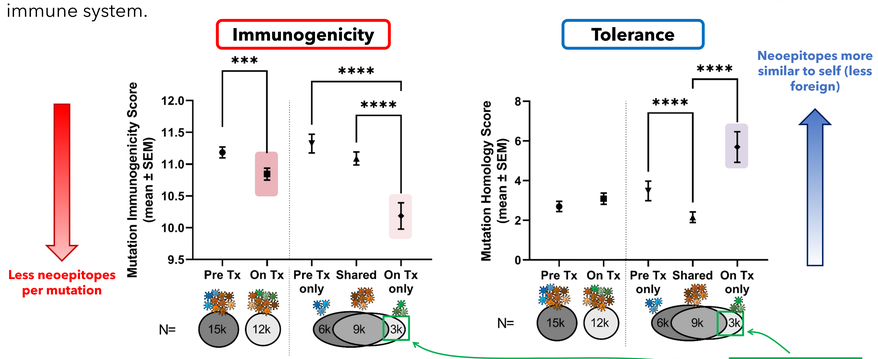
Clones **acquired** under checkpoint therapy



Results – Checkpoint therapy affects tumor immune profile

1. Mutations are less immunogenic (less neoepitopes) in tumors collected after nivolumab therapy
2. Mutations acquired after nivolumab therapy have low immunogenicity
3. Mutations acquired after nivolumab therapy are likely to be tolerated due to high homology with self antigens

→ Tumors respond to immunotherapy by reducing their immunogenicity and by avoiding the immune system.

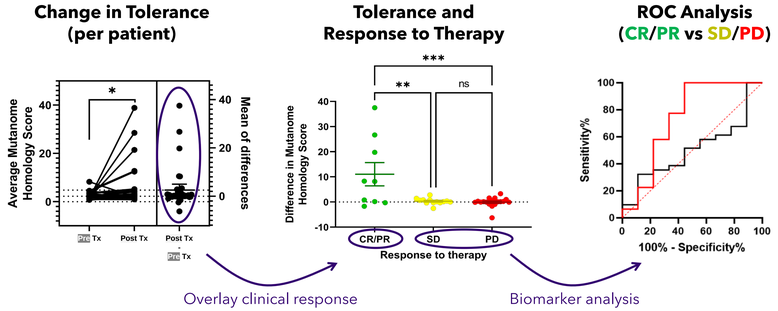


N = 41 paired Pre/On Tx samples. Mutations grouped across all patients.
Pre Tx vs On Tx: Mann-Whitney test. Pre Tx only vs Shared vs On Tx only: ANOVA (Krustal-Wallis, multiple comparisons)

Results – Ancer analysis is associated with response to therapy

- Tumors increase their tolerance potential (JanusMatrix homology scores) after nivolumab therapy.

→ Change in tolerance is associated with response to therapy.



Change in JanusMatrix (homology) scores correlates with responses to therapy

	AUC	p-value
Baseline TMB	0.50	0.96
JanusMatrix	**0.74**	**0.03**

N = 41 paired Pre/On Tx samples. Samples paired by patient.
Pre Tx vs Post Tx: paired t test. CR/PR vs SD vs PD: ANOVA (multiple comparisons)
CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease

Summary and Conclusions

- This study demonstrates **the utility of immunogenicity screening tools in the Ancer** platform for streamlined designs of personalized cancer vaccines.
- Our Ancer analysis suggests tumors reduce their immunogenicity (less neoepitopes) and increase their tolerance potentials (mutations more likely to be tolerated) in response to nivolumab therapy. **Mutations acquired after immunotherapy are more "stealth"** than mutations found prior to therapy.
- Ancer can be employed to **identify novel biomarkers** associated with clinical responses. Tumor neoepitopes become more similar to self in patients that respond to nivolumab therapy.
- These results highlight that **identifying relevant mutations for precision immunotherapy (e.g. personalized vaccines) will become more difficult** once patients are treated with a checkpoint inhibitor. Specialized tools, such as JanusMatrix are needed to correctly and quickly identify immunogenic mutations.

References

1. De Groot. et al., Front Immunol. 2020; 11: 442
2. Richard G. et al., Expert Rev Vaccines. 2022 Feb;21(2):173-184
3. Liu R. et al., Hum Vaccin Immunother. 2015 11:9, 2241-2252
4. Wada Y. et al., Sci Rep. 2017 Apr 28;7(1):1283
5. Jang H. et al., Hum Vaccin Immunother 2020 Sep 1;16(9):2042-2050
6. Richard G. et al., Proceedings: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA
7. Riaz N. et al., Cell 2017; 171, 934–949