Computational prediction of MHC anchor locations guide neoantigen identification and prioritization

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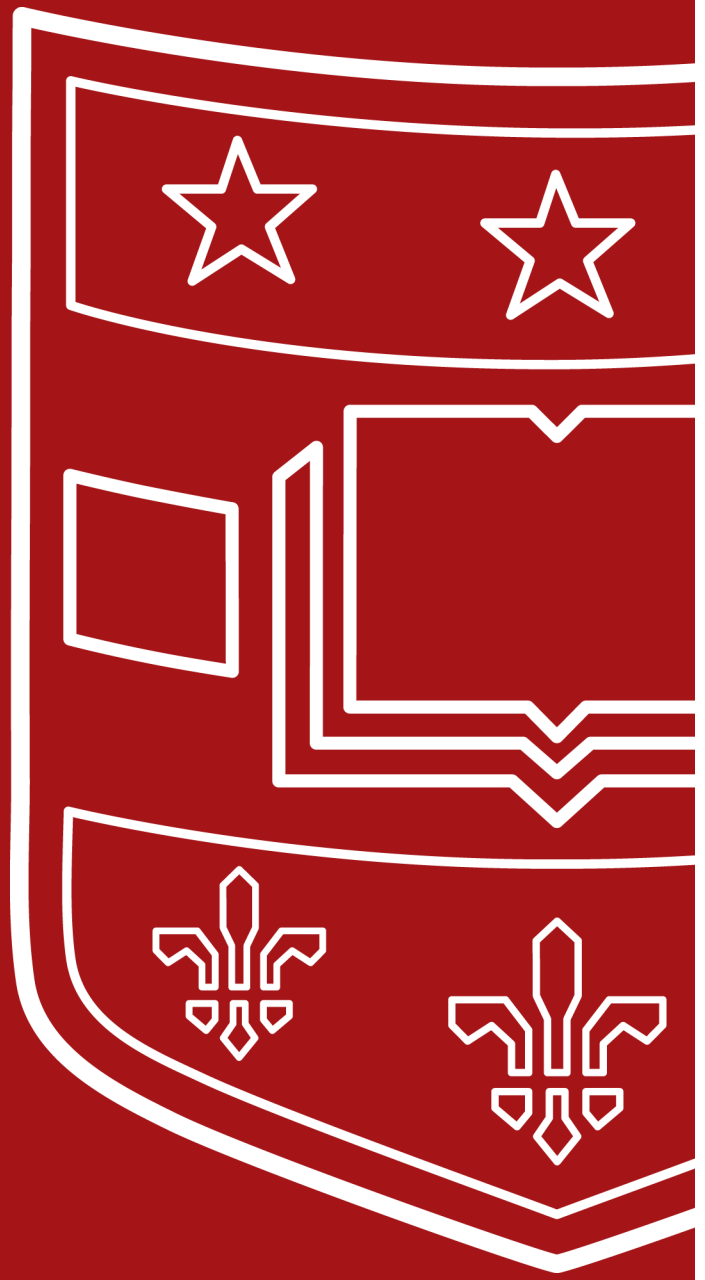
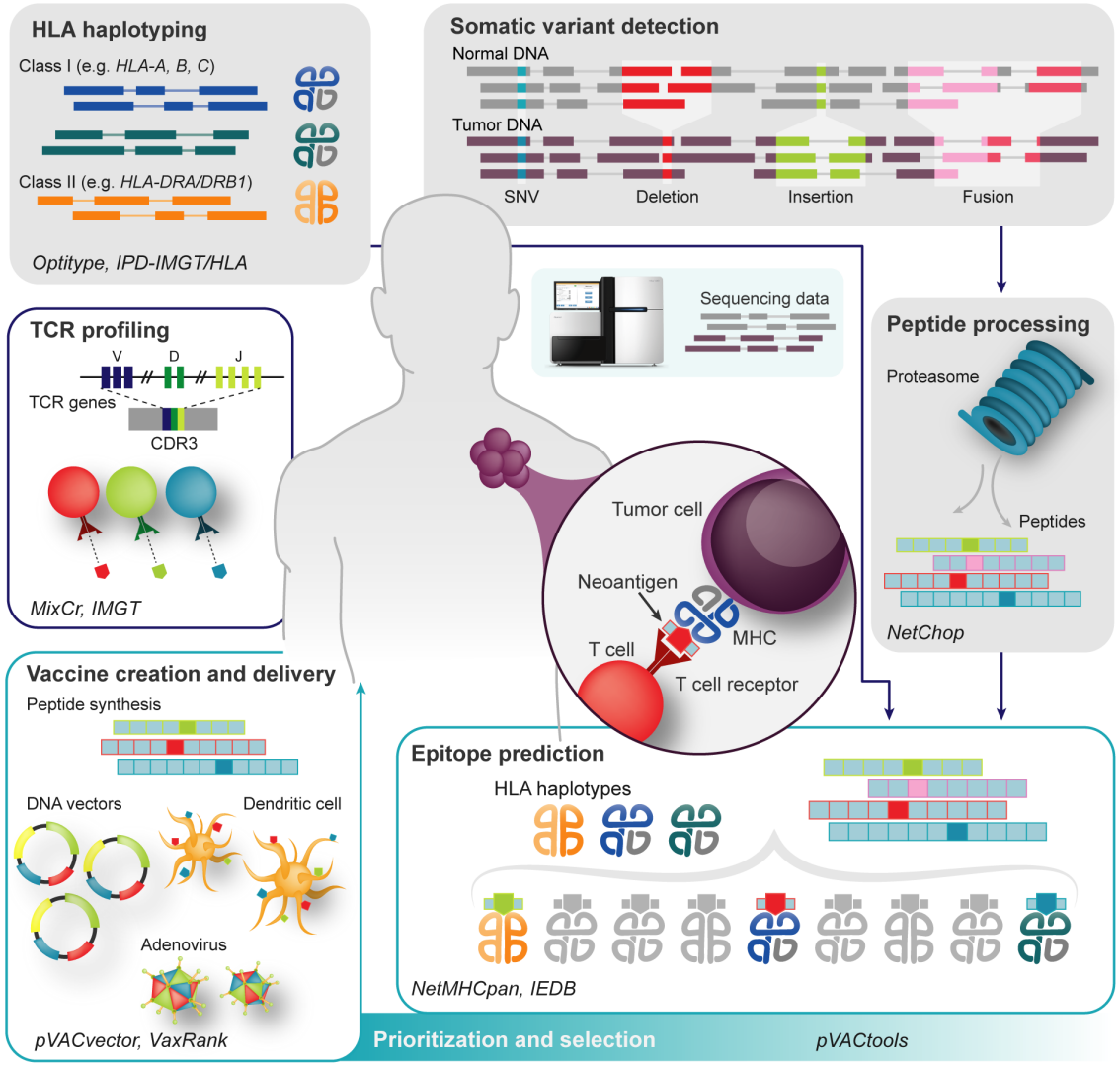


Washington University School of Medicine in St. Louis

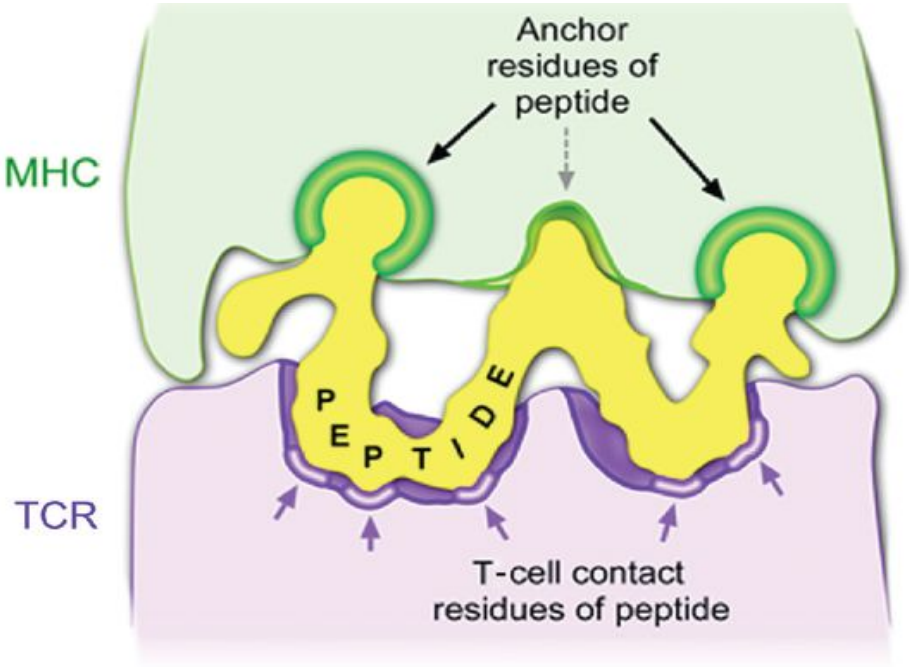
Neoantigens and their clinical utility



- Short peptide sequences resulting from somatic mutations in tumors
- Potential of binding and being presented by MHC class I or II molecules to allow recognition by cytotoxic T cells
- Activate a T-cell mediated cell death response for tumor cells
- Thus if given the ability to accurately predict neoantigens, the results can not only be used to design personalized vaccines for cancer patients but can also be exploited for predicting response to immune checkpoint blockade therapy.

Richters, Xia et al. *Genome Medicine* (2019)

Anchor vs Mutation Position in Neoantigen Prediction



- The effectiveness of a neoantigen-based vaccine relies in part on whether the sequence presented to T cells has previously been exposed to the immune system.
  - susceptibility to central tolerance
  - Auto-immunity
- Many pipelines and past neoantigen studies consider simple filtering strategies regarding WT vs MT peptides
  - MT IC50 < 500nM
  - Agretopicity > 1
- Only a subset of peptide positions are potentially presented to the T cell receptor for recognition while other positions are responsible for anchoring to the MHC

Fritsch, Edward F., et al. *Cancer immunology research* (2014)

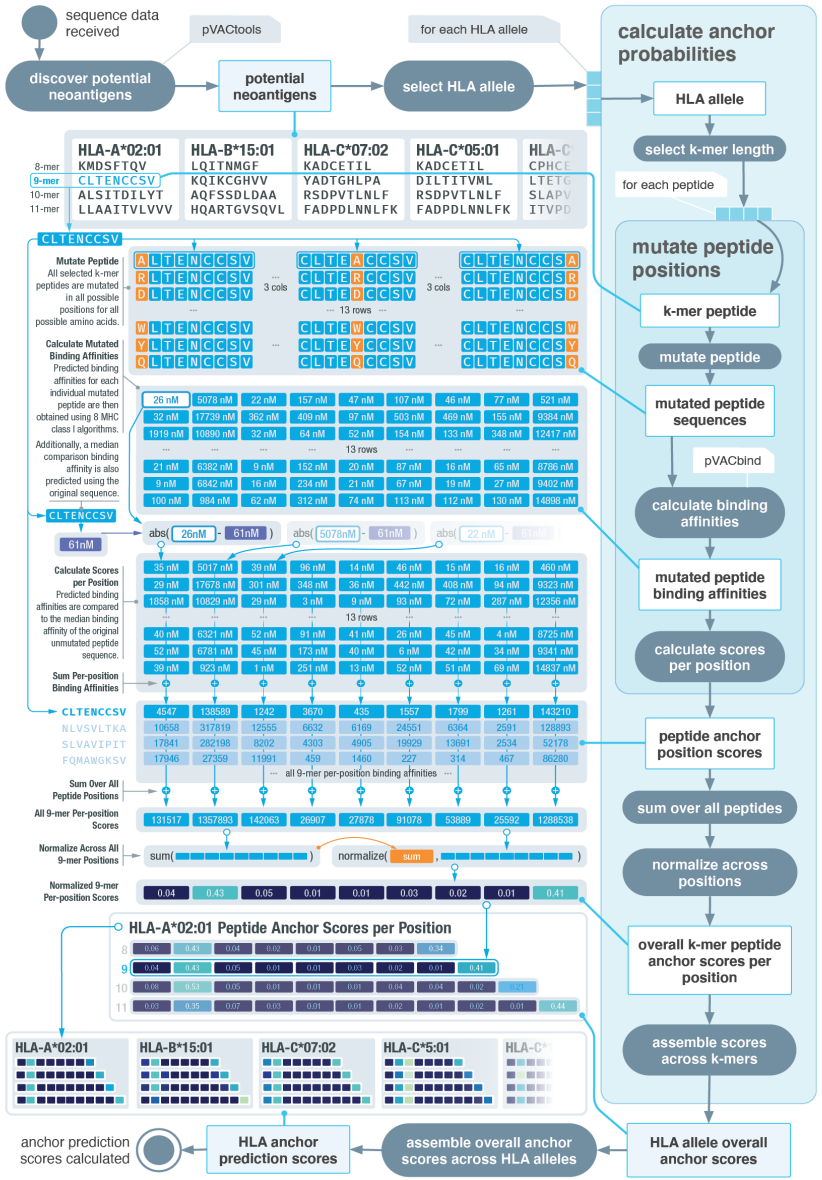
Computational and quantitative prediction of HLA-specific anchor positions

General Idea:

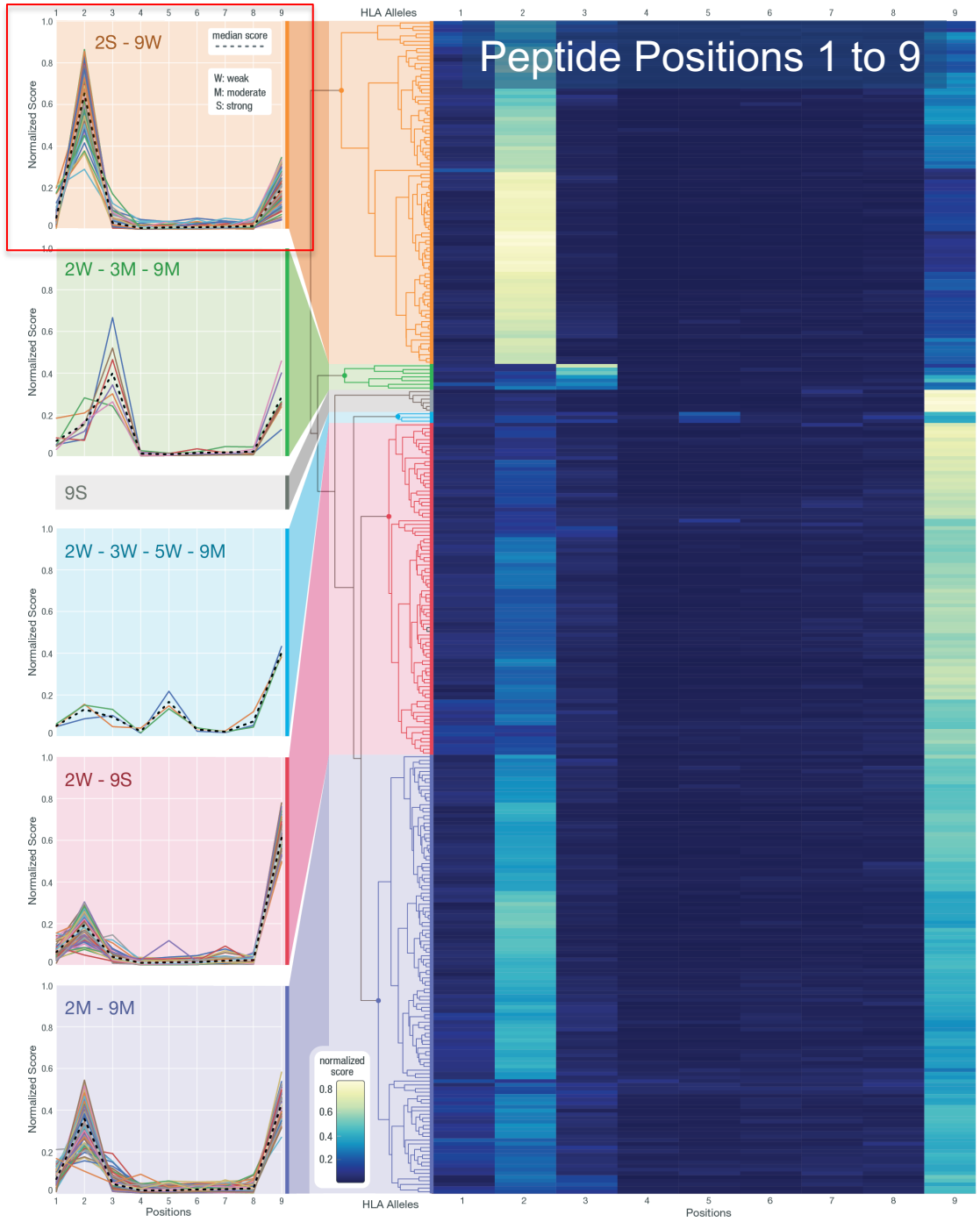
To evaluate how mutations occurring at each individual position change the predicted binding interaction between the strong binding peptide and the MHC molecule

Significant change observed at a particular location indicates a higher probability of the amino acid at the position acting as an anchor

Little to no change in binding affinities when a position is mutated would indicate a lower probability of the position acting as an anchor

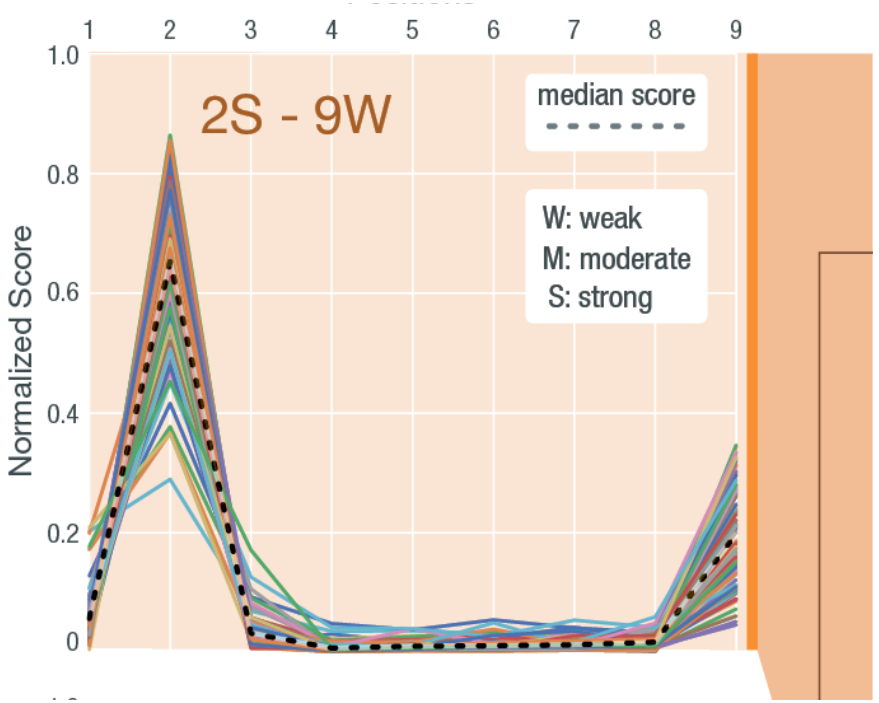


Prediction results show distinct patterns of HLA anchor locations



Heatmap showing anchor probabilities for 318 HLA alleles and 9-mer peptides

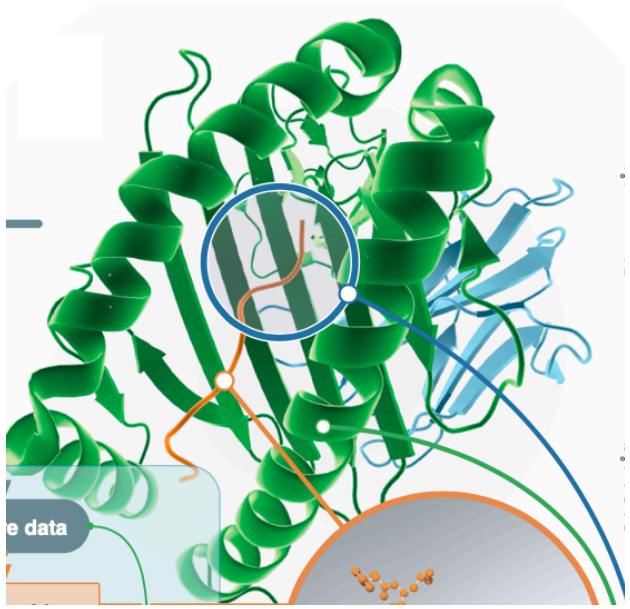
Six clusters showing different anchor patterns

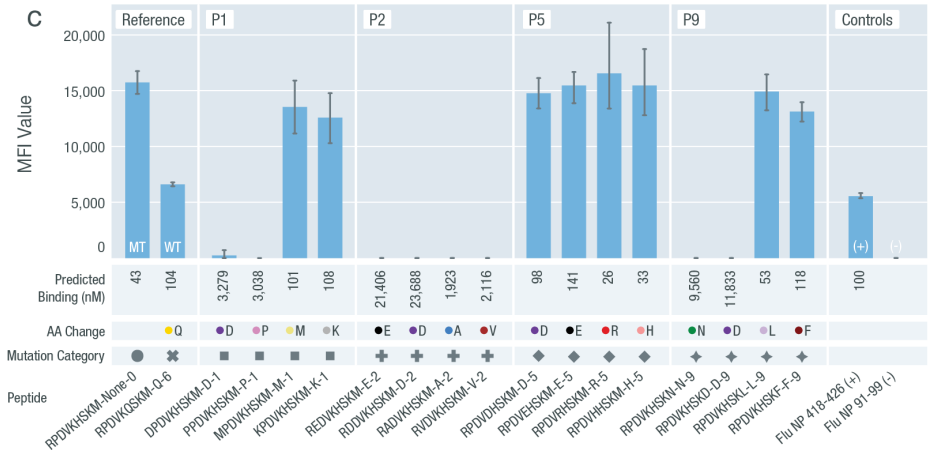


Validation Process and Results

1. Structural analysis with crystallography structures
   - 166 protein structures collected corresponding to 33 HLA alleles
   - Measured both distance between HLA and peptides as well as solvent accessible surface area
   - Spearman correlation used to compare our anchor predictions to the measured metrics

2. IC50 binding assays and cell-based stabilization assays
   - Mutated peptides at both anchor and non-anchor locations and performed cell-based stabilization assays and IC50 binding assays to assess their influence on peptide-MHC binding
   - Experimental results confirmed the varying strengths of individual positions acting as anchors for different MHC alleles





Conclusions

- Developed a computational workflow for predicting probabilities of anchor positions for a wide range of HLA alleles
- Prediction results show that anchor positions can vary substantially between different HLA alleles
- We further experimentally validated a subset of HLA allele anchor patterns using binding assays and cell-based stabilization assays
- The underlying quantitative scores from our anchor prediction workflow are available for incorporation into neoantigen prediction workflows (e.g. pVACtools) and we believe this will improve their performance in predicting immunogenic tumor specific peptides
- Additional work is needed to expand to a larger range of HLA alleles (including Class II) and further experimental validation measuring T-cell responses would be ideal

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Poster #15

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