

# Immunological Ignorance to Tumor Neoantigens

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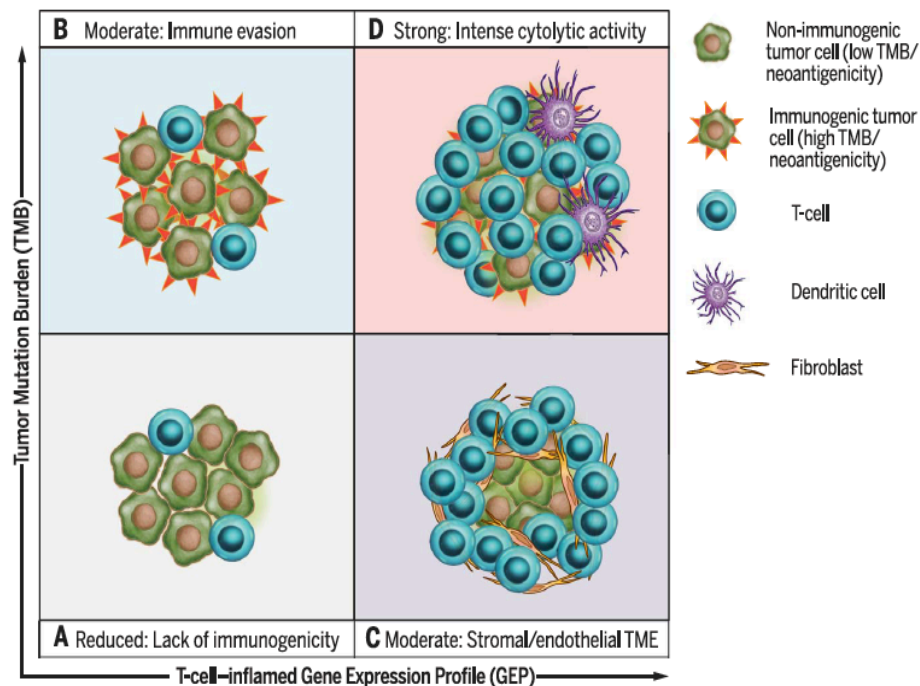
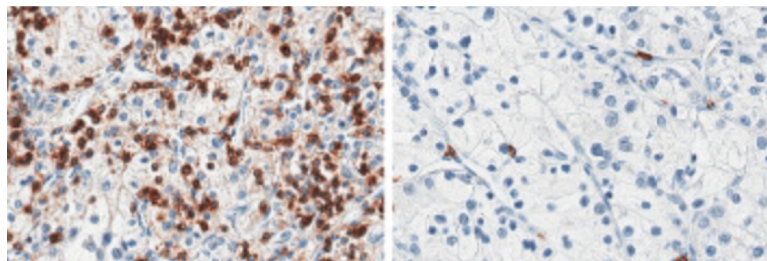
December 10, 2020



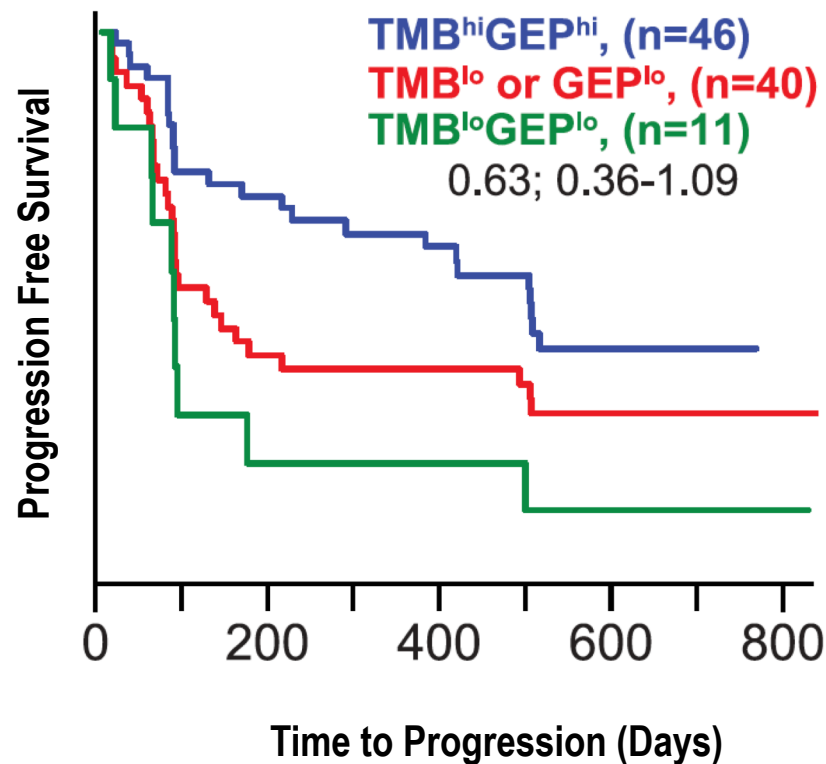
# Tumor Infiltrates and Anti-tumor T cell Immunity

Inflamed

non-Inflamed



Melanoma cohort



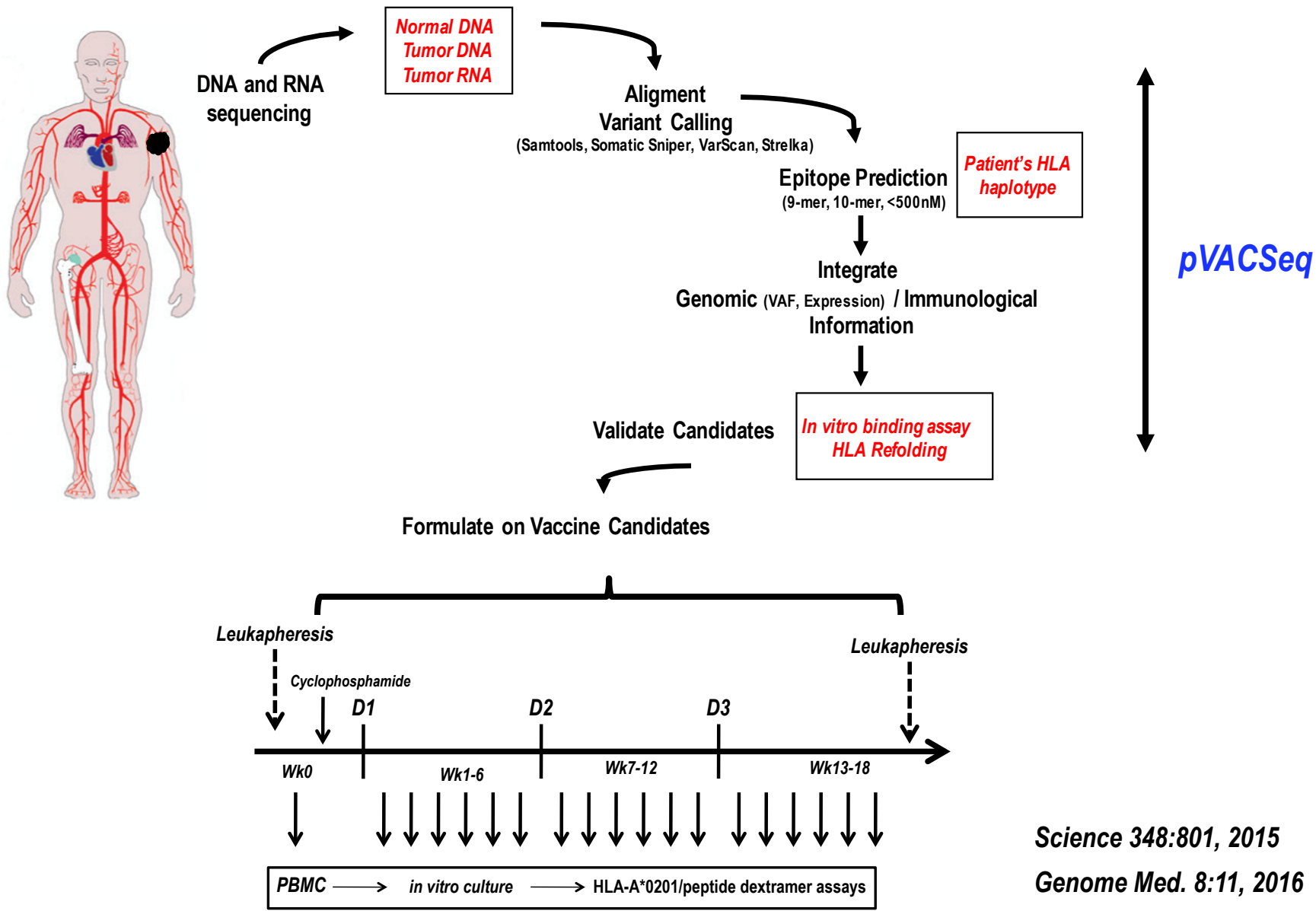
*Defining TIL neoantigen (p-MHC) specificity remains a challenge*

Science 362:197, 2018

# Melanoma Neoantigen Project

- Observation: Missense mutations can elicit T cell immunity in humans with cutaneous melanoma. (1995, 2 examples).
- Hypothesis: Missense mutations (single nucleotide variants) generate patient-specific (unique) tumor neoantigens and immunization will elicit T cell immunity.
  - Next-generation sequencing for mutations identification, pipeline
  - Does vaccination using missense mutation-containing peptides increase the breadth and diversity of the anti-tumor T cell response?
- **Develop a sensitive molecular assay to identify neoantigen-specific T cells within complex infiltrates.**

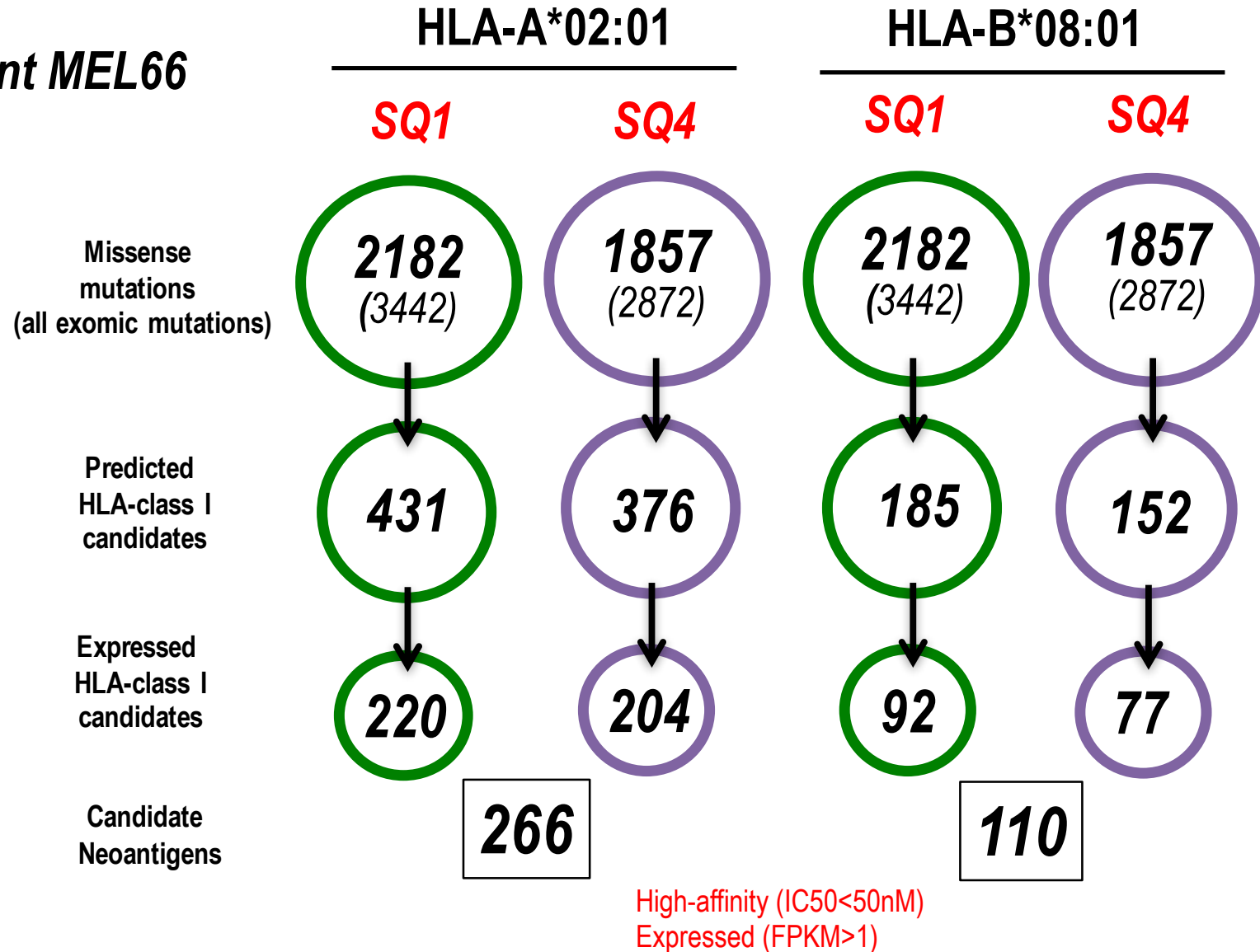
# Genomics Informs Neoantigen Discovery



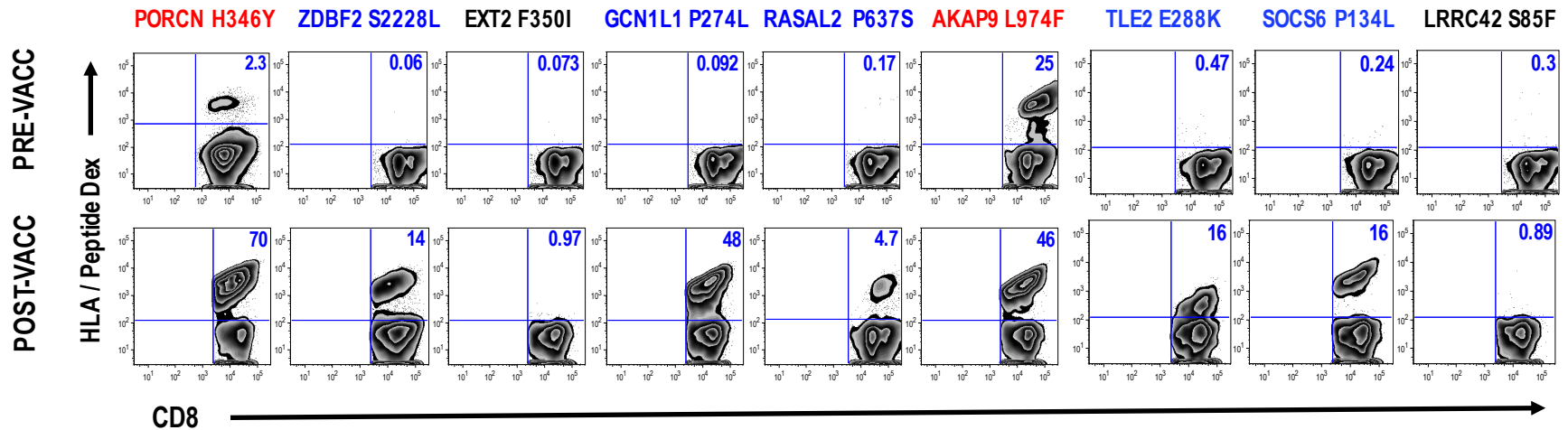
Science 348:801, 2015  
 Genome Med. 8:11, 2016

# Identification of missense mutations and vaccine candidates

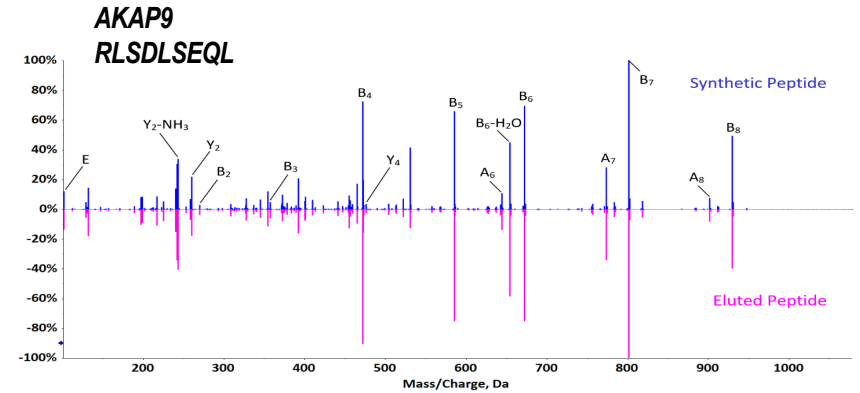
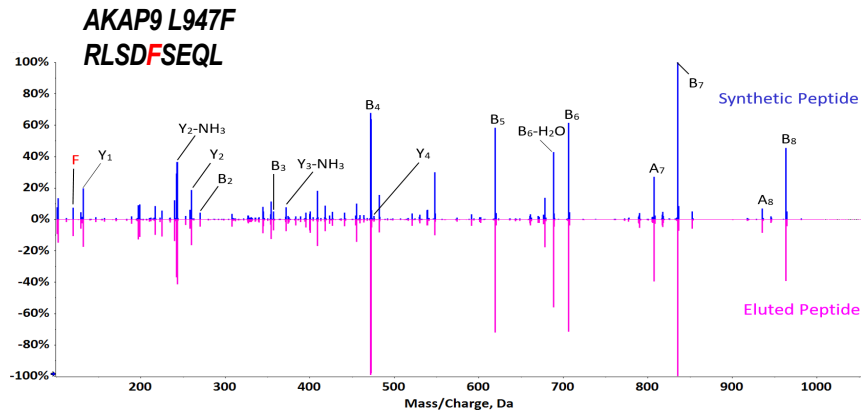
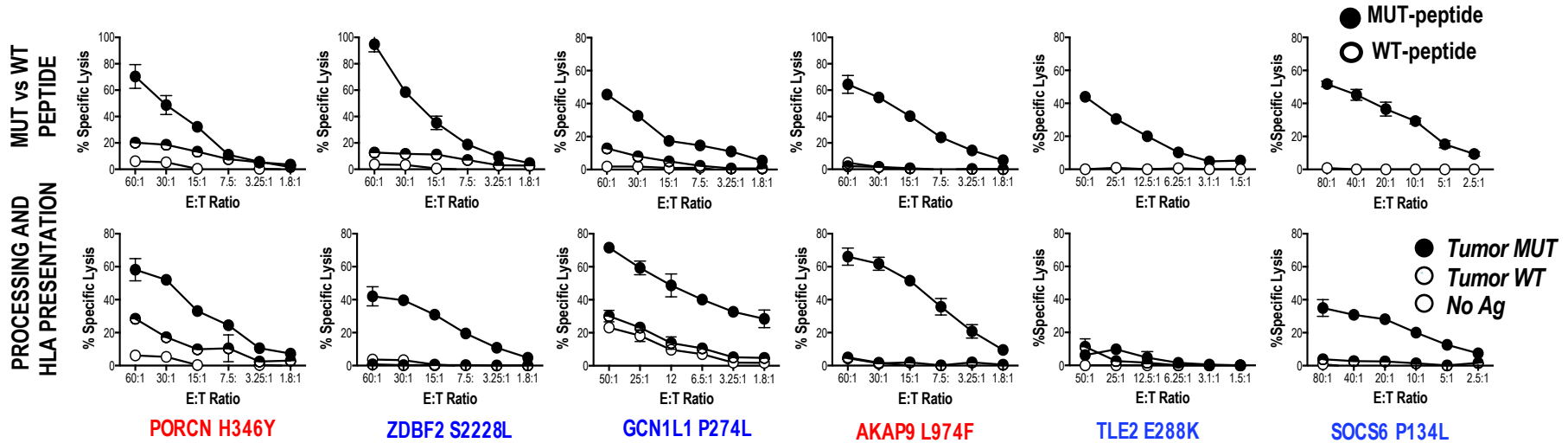
*Patient MEL66*



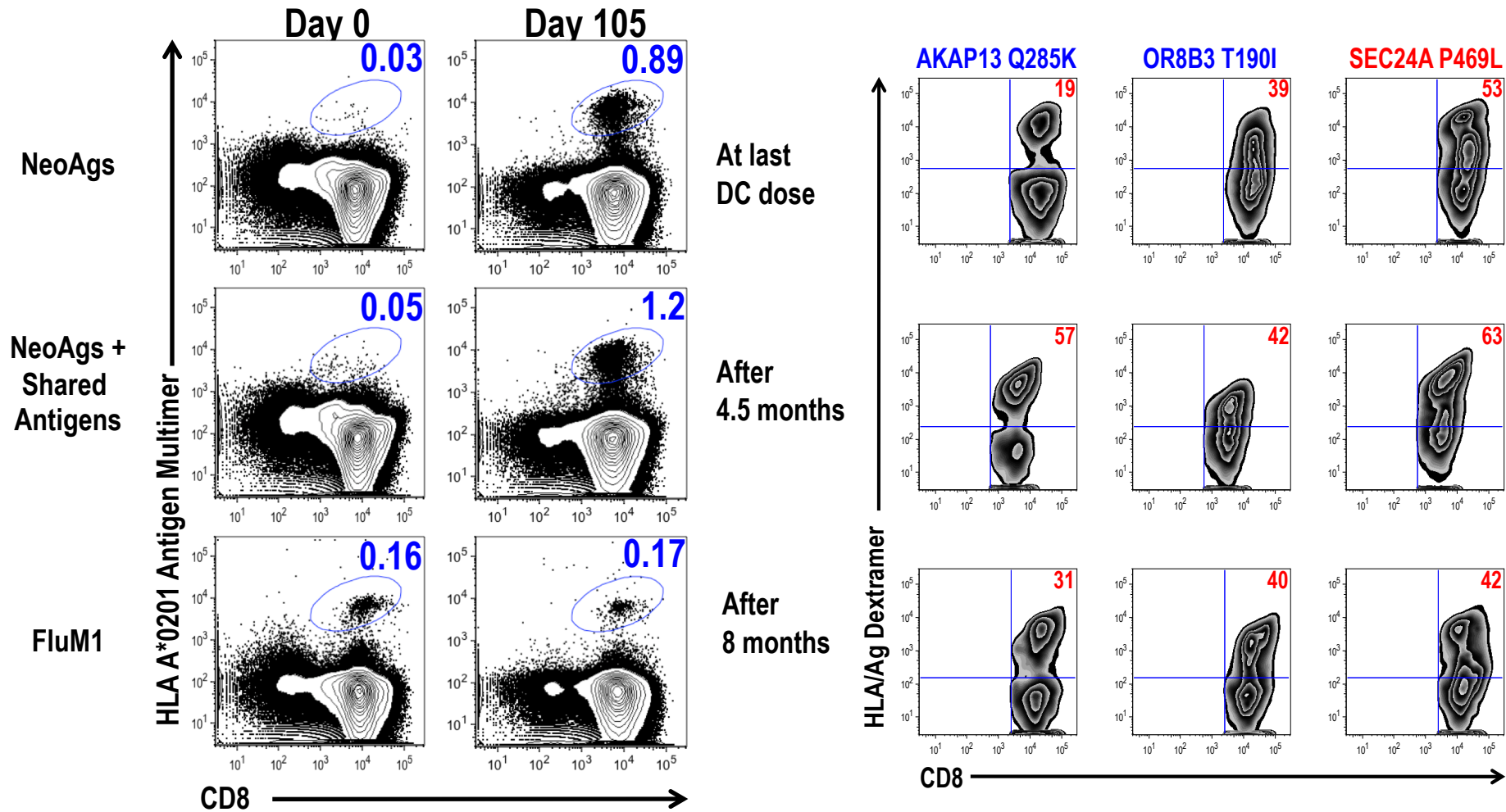
# Vaccination increases the antigenic breath of the neoantigen-specific T cell response



# Recognition of bona-fide neoantigens by vaccinated elicited -T cells



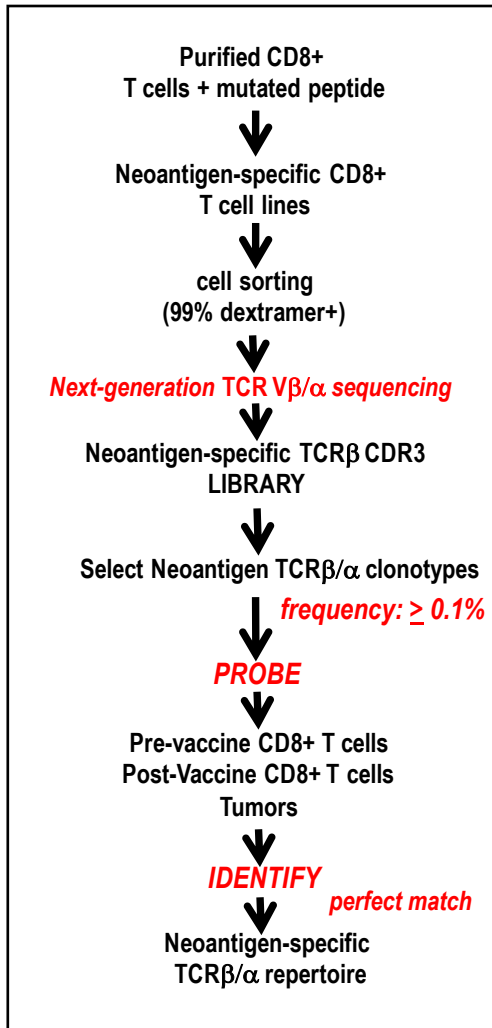
# Vaccine-elicited neoantigen-specific T cell responses can be detected directly in blood and are long-lasting





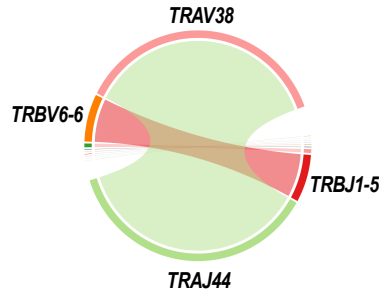
# What is the clonal diversity of neoantigen-specific T cells?

## Antigen-specific TCRVB Reference Libraries

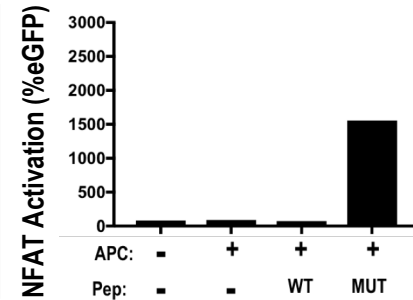
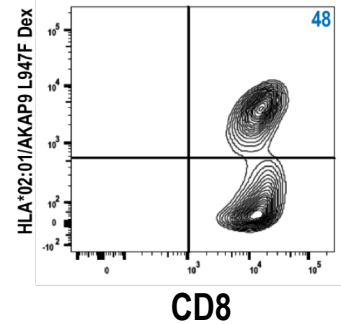


**TCRVB libraries:**  
*~100-500 clonotypes per neoantigen*

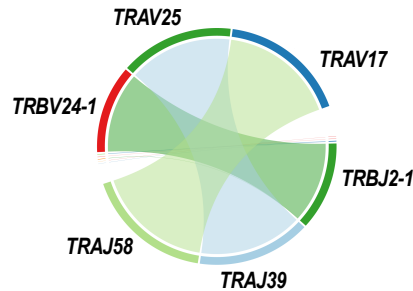
### AKAP9 L94F



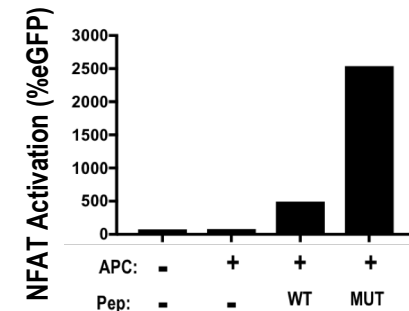
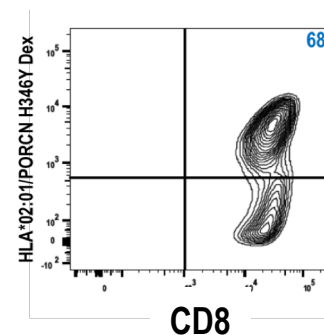
TRBV6-6/TRBJ1-5: **CASTPLSNQPQHF**  
 TRAV38/TRAJ44: **CAYGTGTASKLTF**



### PORCN H346Y

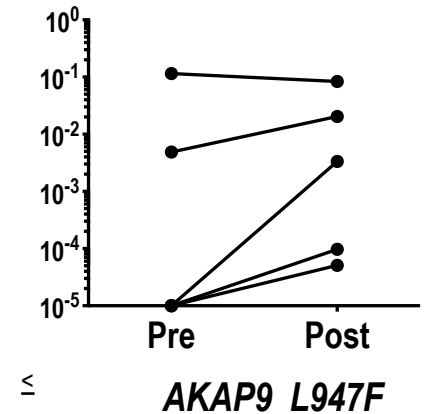
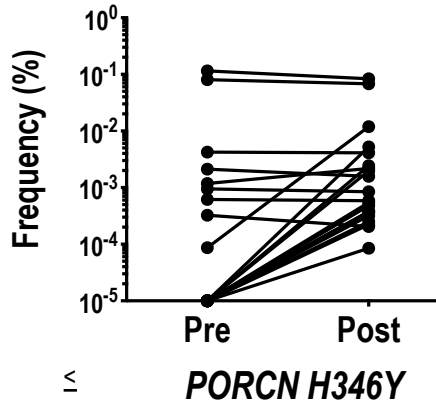
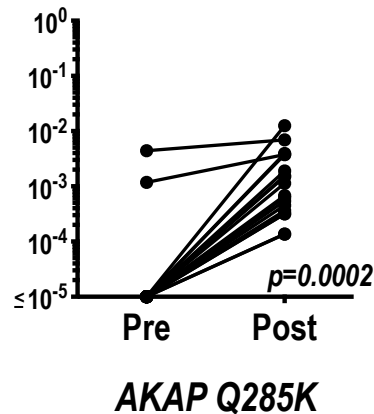
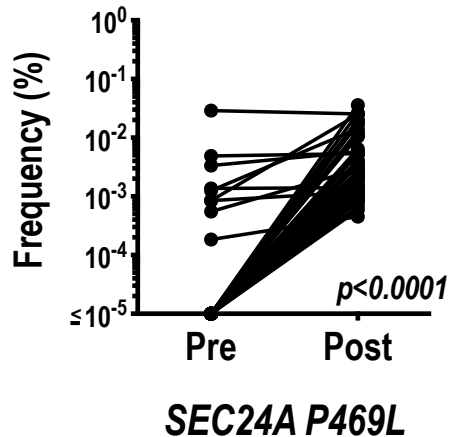
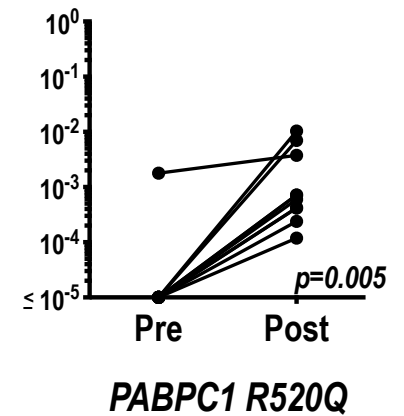
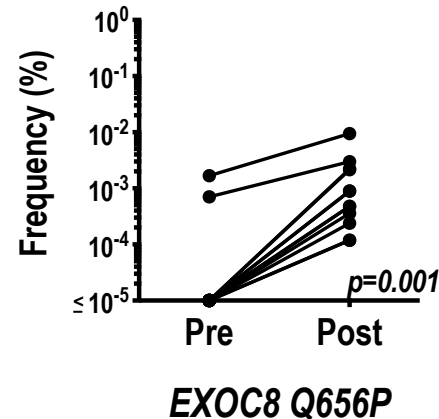
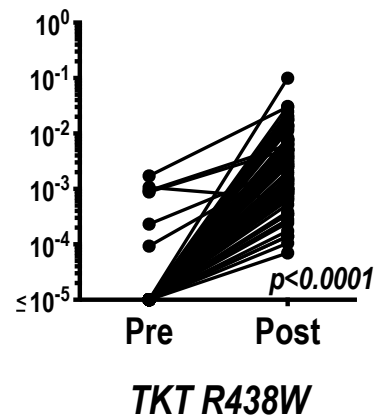
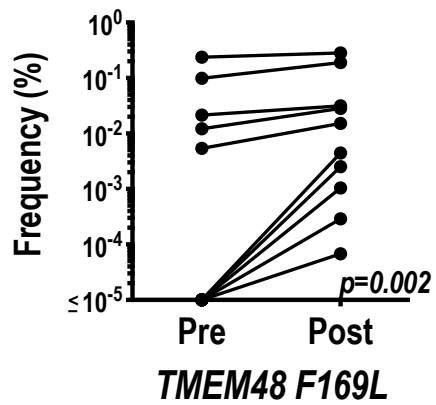


TRBV24-1/TRBJ2-1: **CATSTRDTGNEQFF**  
 TRAV17/TRAJ58: **CATEPTYSGSRLTF**



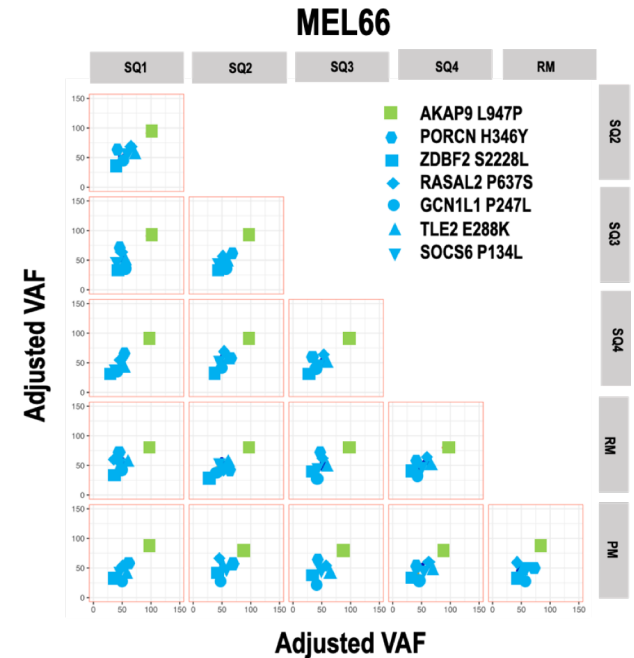
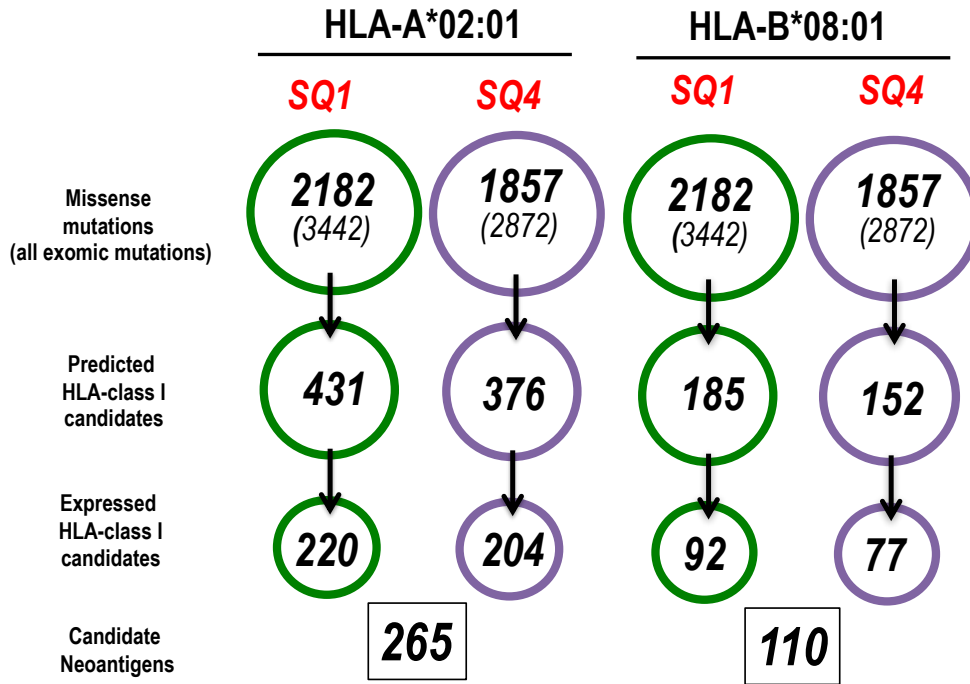
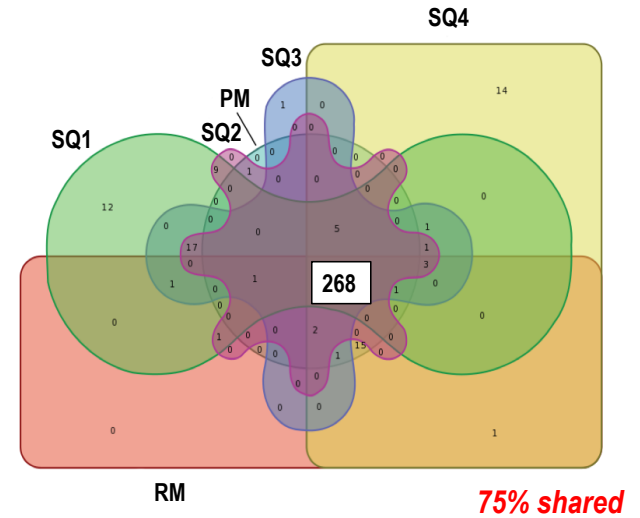
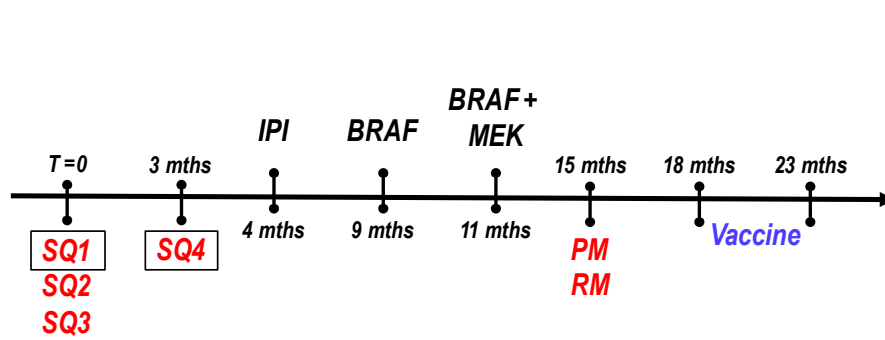
# What is the clonal diversity of neoantigen-specific T cells?

## Peripheral Lymphocytes – Pre- and Post-vaccine



● Unique TCR clonotype

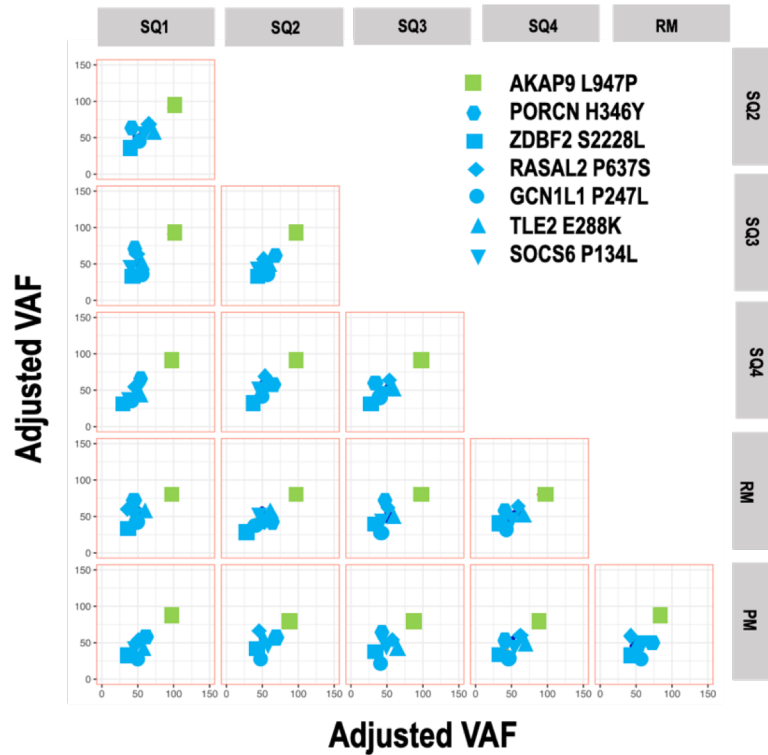
# Tumor Neoantigen Landscape



# Neoantigen-specific T cell clonal diversity in tumors

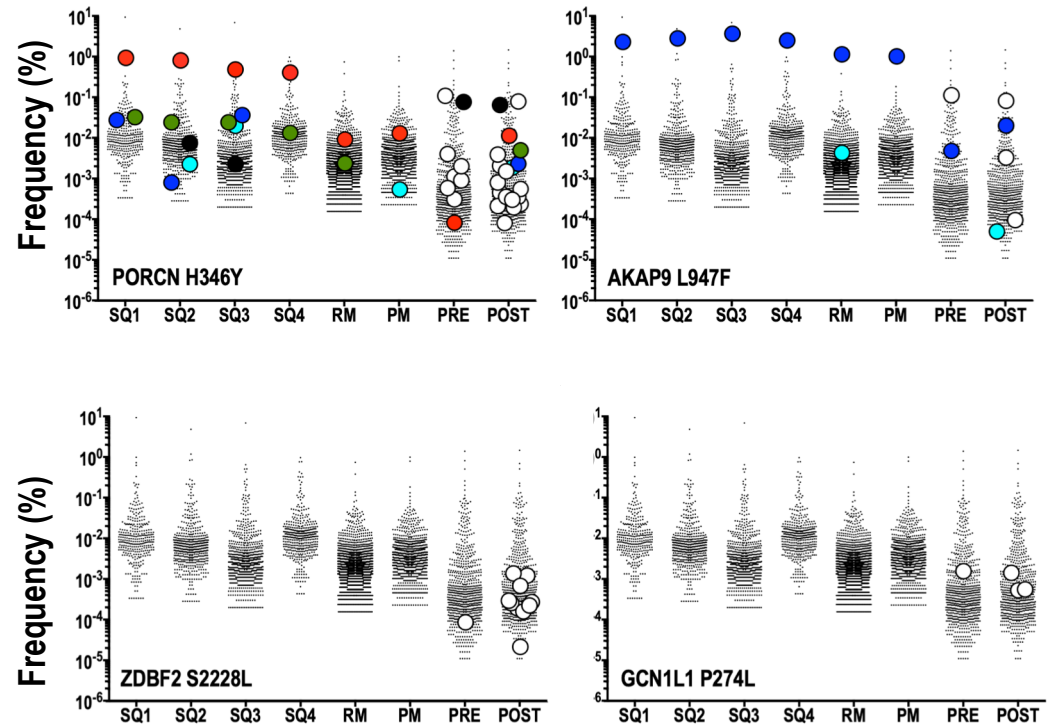
MEL66

Distribution of neoantigens in tumors



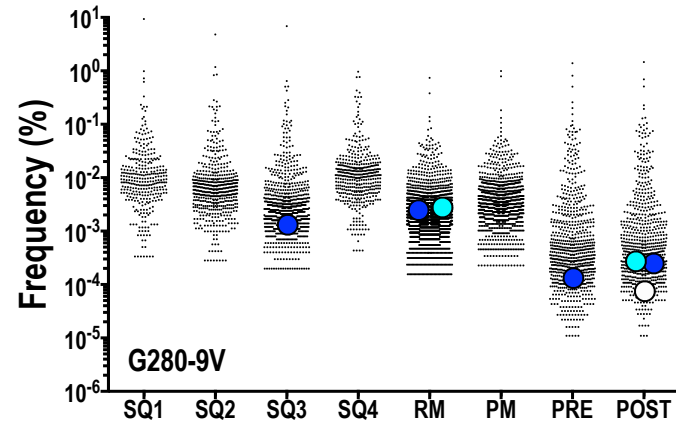
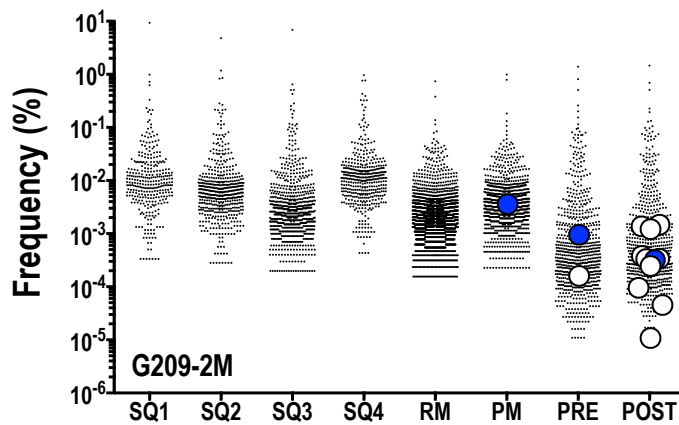
*Immunogenic neoantigens are clonal*

Distribution of neoantigen-specific T cells in tumors

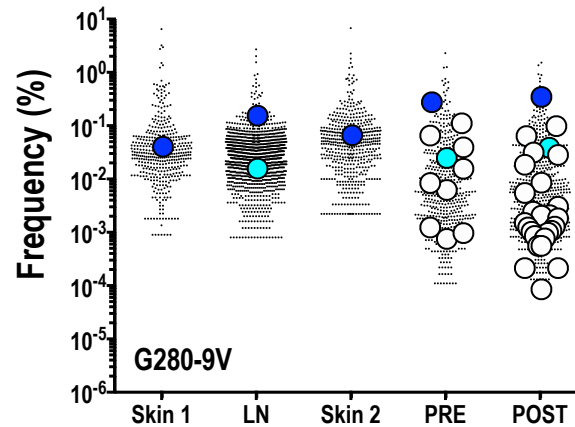
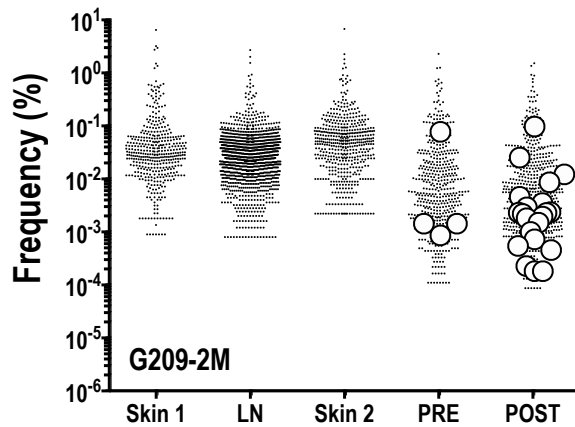


# gp100-specific T cell clonal diversity in tumors

MEL66



MEL21

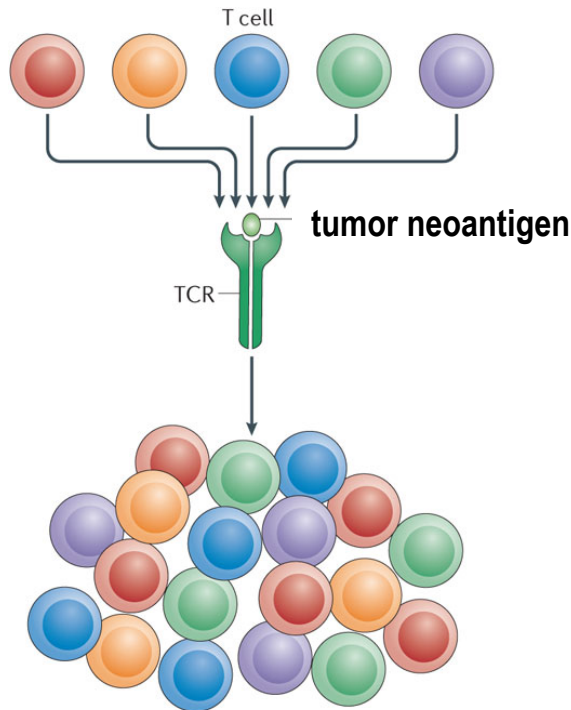


# Lessons learned: 9 patients treated with Neoantigen DC vaccine

- **Immunogenicity** (n=80 short peptides):
  - > 90% immunogenic peptides are high-affinity
  - No positional bias - AA substitutions mutations at either anchor or TCR contact residues
- **Vaccination increases the antigenic breath of the anti-tumor T cell response by promoting *de-novo* responses**
  - Antigenic diversity may address tumor heterogeneity
- **Immunological Ignorance – Antigen and Clonotype**
  - Ubiquitous sharing of clonal tumor neoantigens but neo-Ag CD8+ T cells are rare and monoclonal

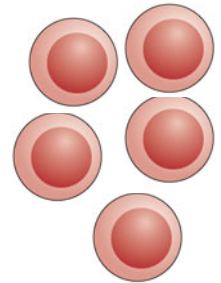
# Working model of neoantigen-specific T cell immunity (2020)

## Peripheral naïve T cell repertoire



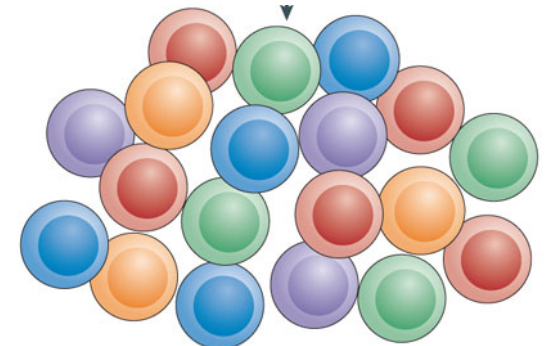
## Spontaneous immunity to neoantigen

- limited repertoire (ignorance)
- low frequency



## Vaccine-induced immunity to neoantigen

- broad repertoire (multiple clonotypes to many neoantigens)
- high frequency



***Therapeutic vaccination, as an adjunct to checkpoint inhibitor treatment, should be considered to increase the breadth and diversity of neoantigen-specific CD8+ T cells.***

# Acknowledgements

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