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Society for Immunotherapy of Cancer

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Clinical Response to Tumor Infiltrating Lymphocytes (TIL) in Stage 4 Non-small Cell Lung Cancer (NSCLC) Correlates with Neoantigen-Specificity: a Phase I Trial

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DISCLOSURES FOR SPEAKER CHAO WANG:
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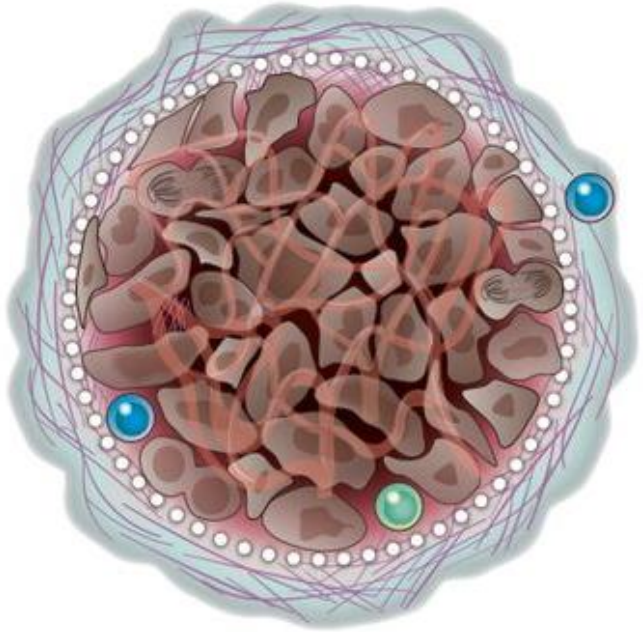
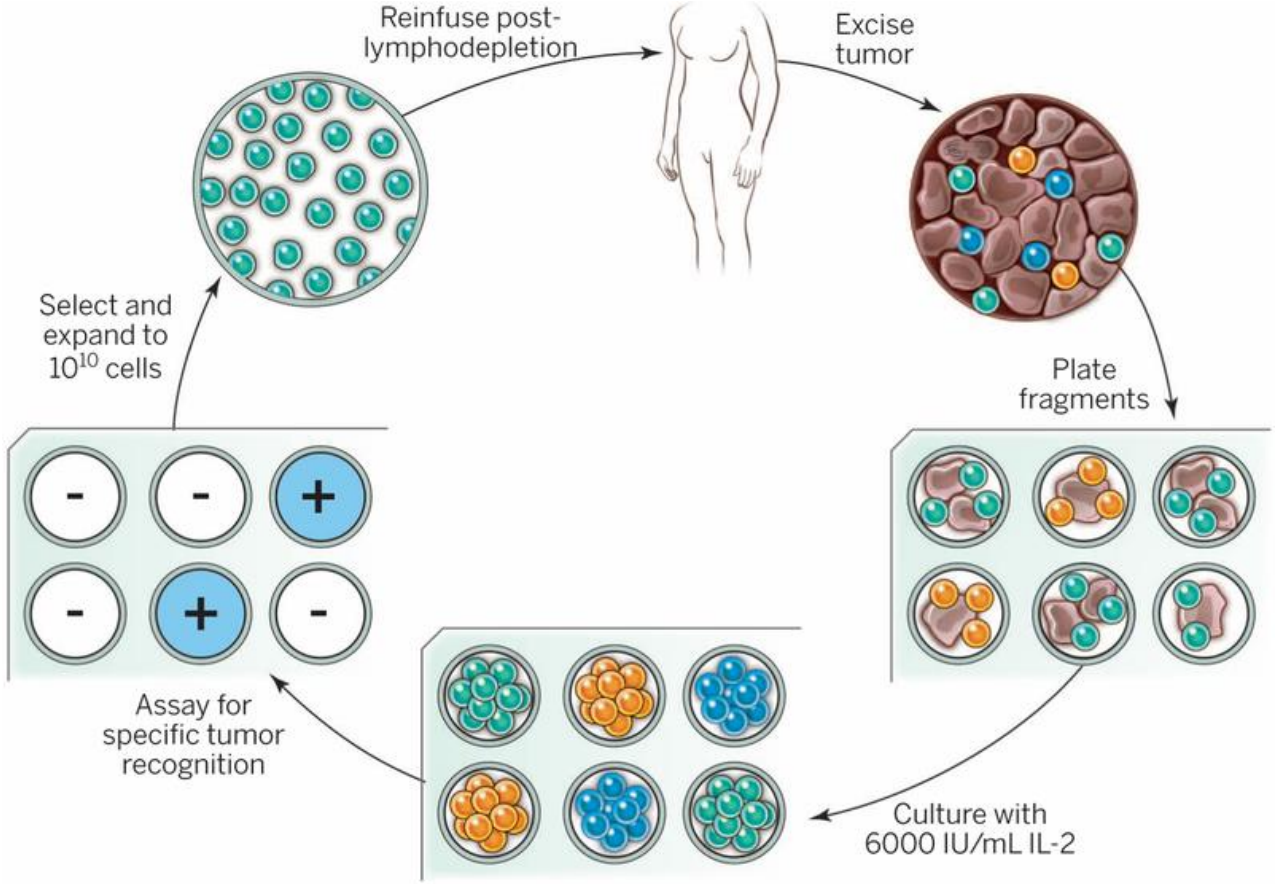
2. *Iovance Biotherapeutics*: Moffitt Cell Facility manufacturing costs
3. *Prometheus Laboratories Inc; Clinigen Group plc*: Aldesleukin drug supply
4. *Bristol-Myers Squibb*: Nivolumab drug supply
5. *Adaptive Biotechnologies*: Young Investigator Award 2018

Ex vivo expanded TILs can mediate tumor regression



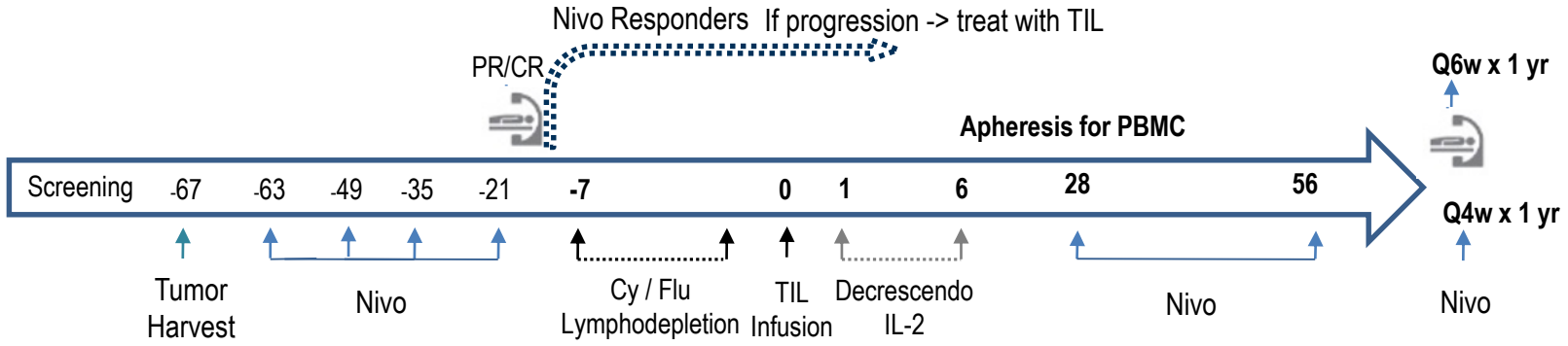
Insufficient lymphocyte infiltration

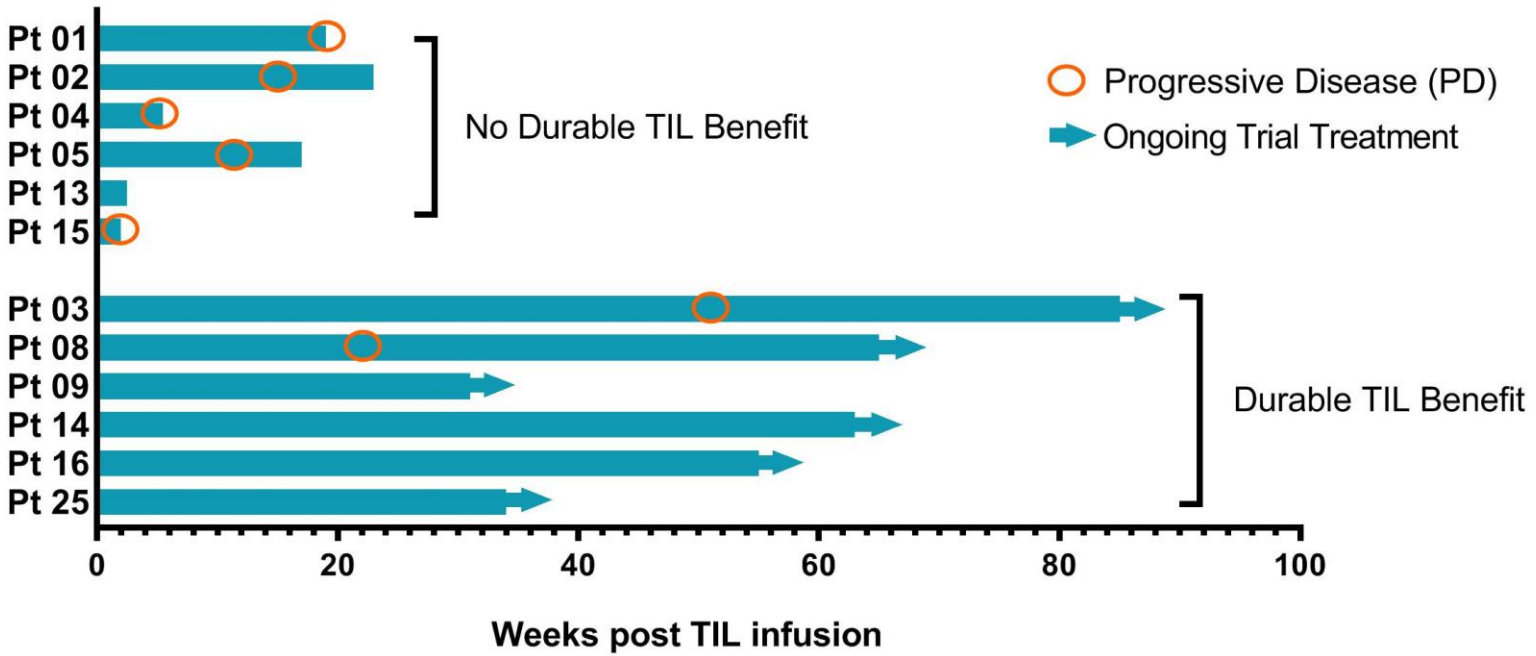
P Sharma et al. Science. 2015 Apr 3; 348(6230): 56–61



SA Rosenberg et al. Science. 2015 Apr 3; 348(6230): 62–68

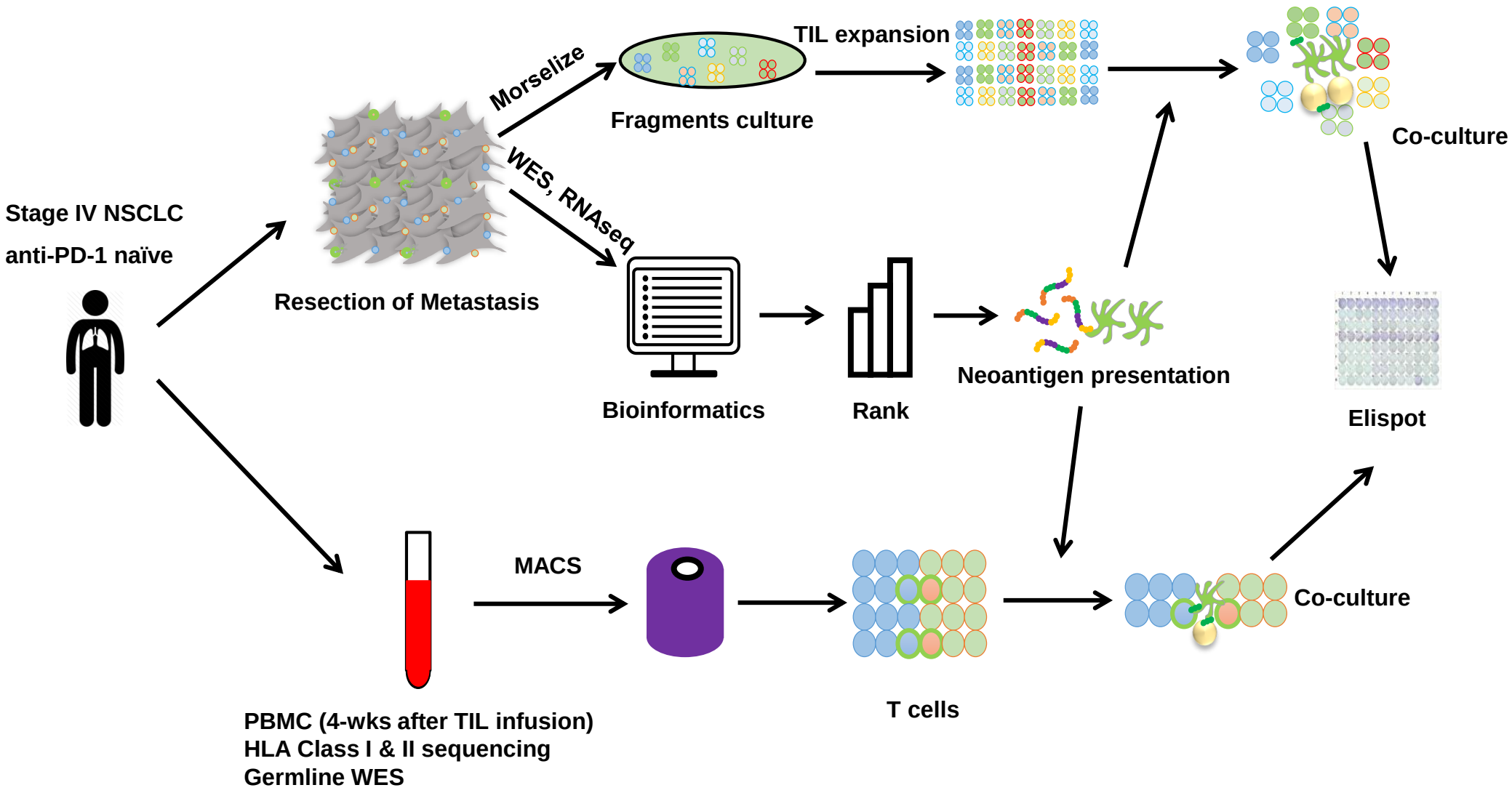
Lung Cancer TIL Trial Overview





Hypothesis: Neoantigens are the targets of TILs and mediate antitumor effects

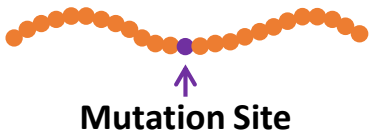
Neoantigen Identification Flowchart



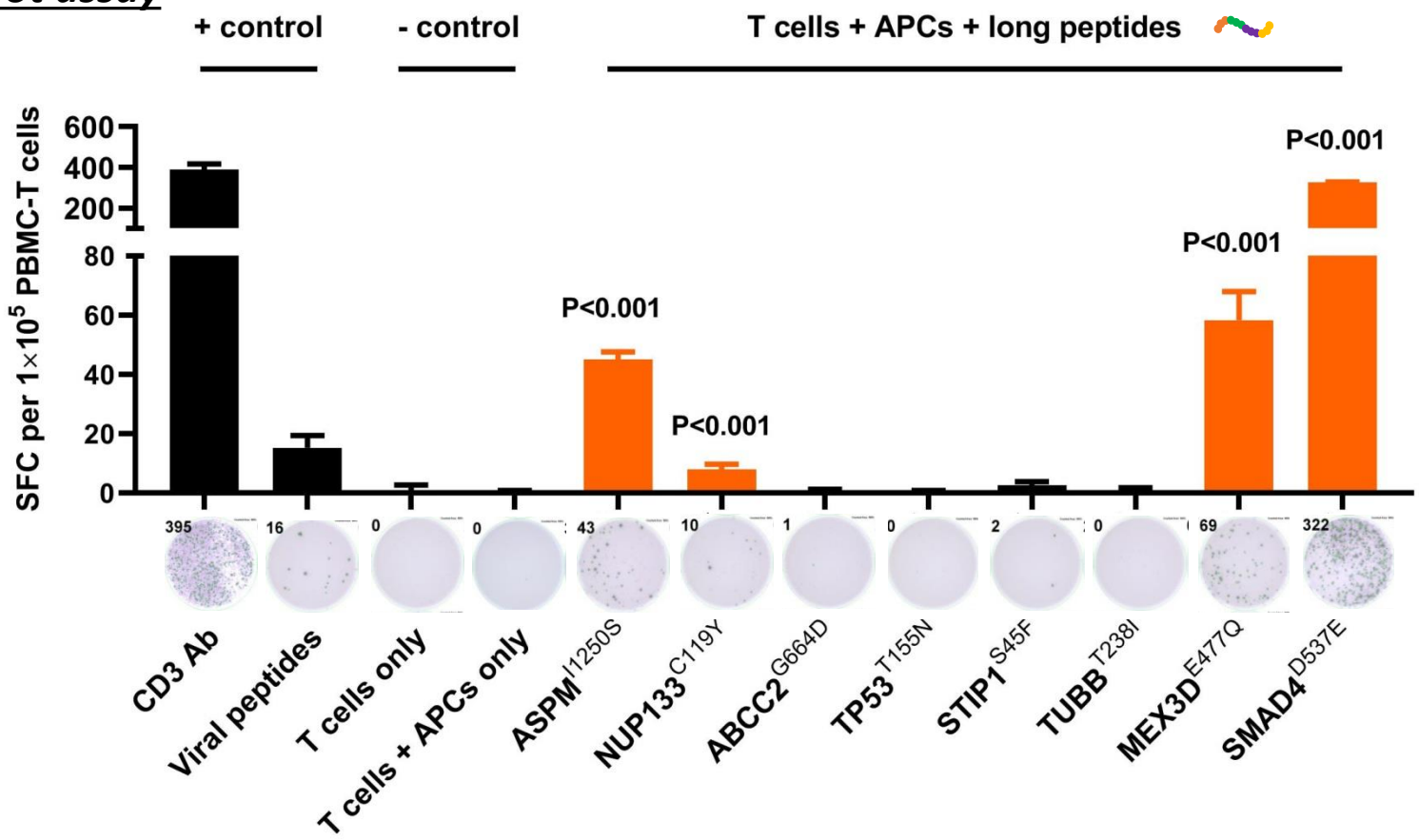
Neoantigen Identification for Pt 3

Long peptides:

- Contain genomic alterations unique to patient's tumor
- High MHC affinity (K_D <500 nM)
- High RNA expression (FPKM >0)
- Confirmed DNA/RNA coverage

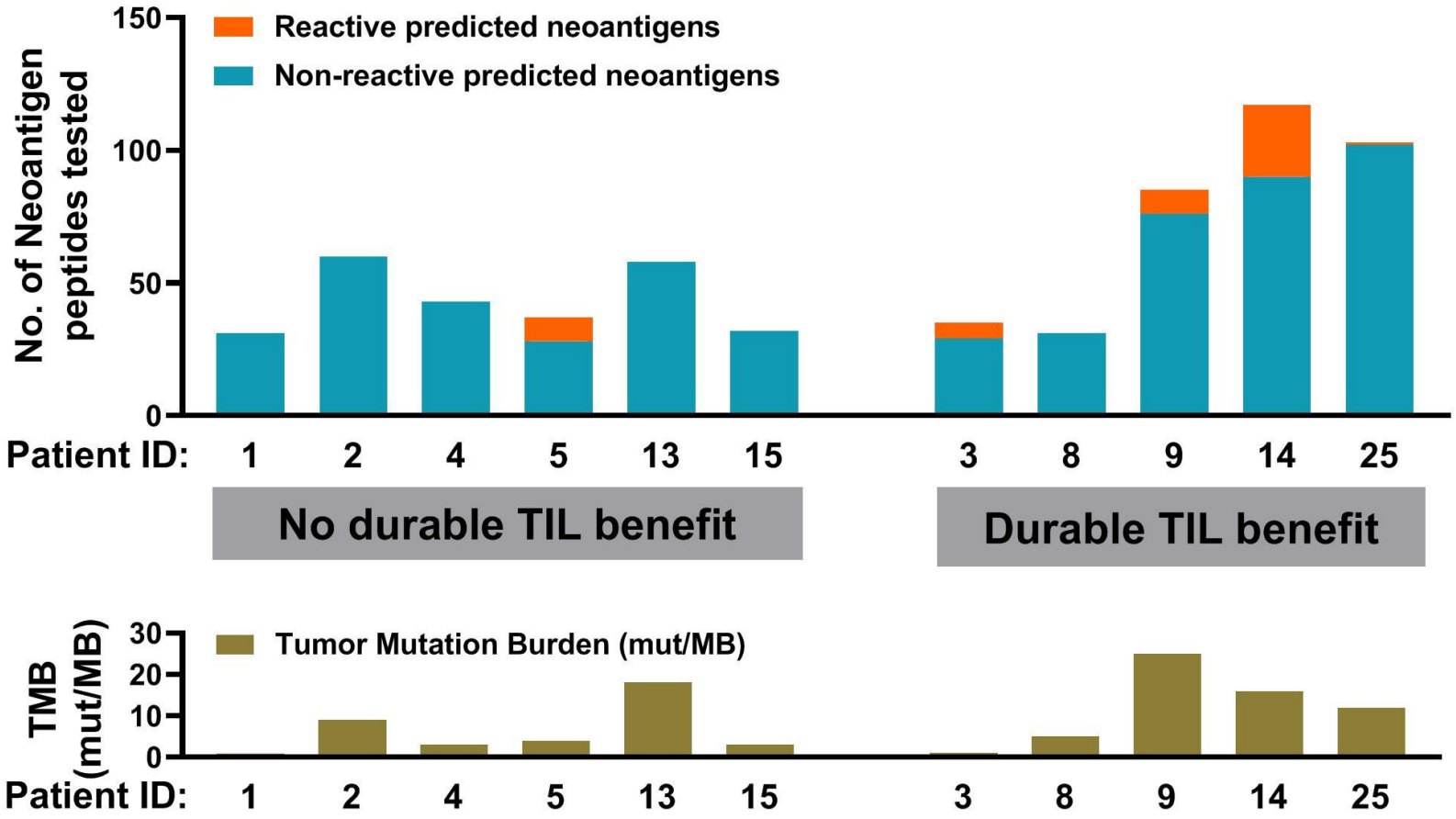


ELISpot assay



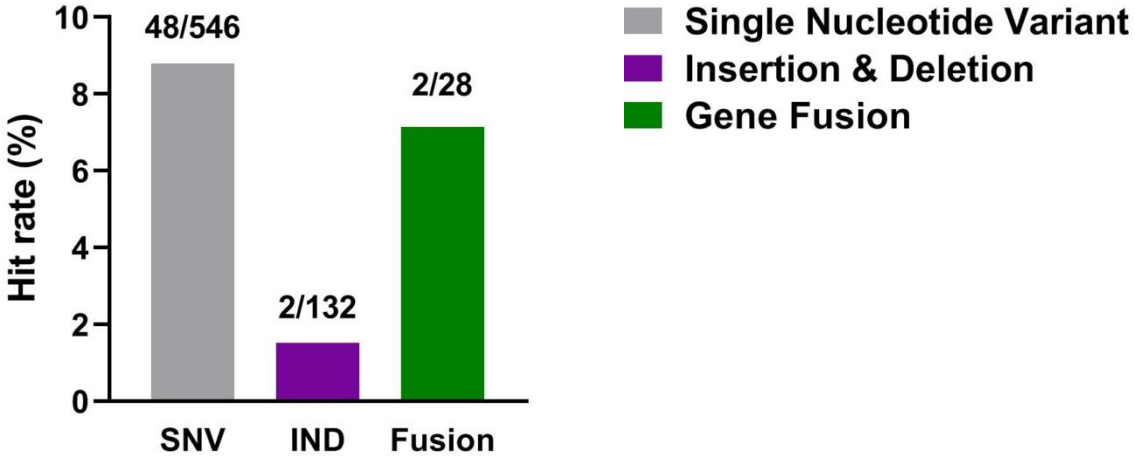
Bars indicate mean ± SD. Shown 2-sided *p*-value calculated by repeated measures ANOVA with Dunnett's multiple comparison test. n=3.

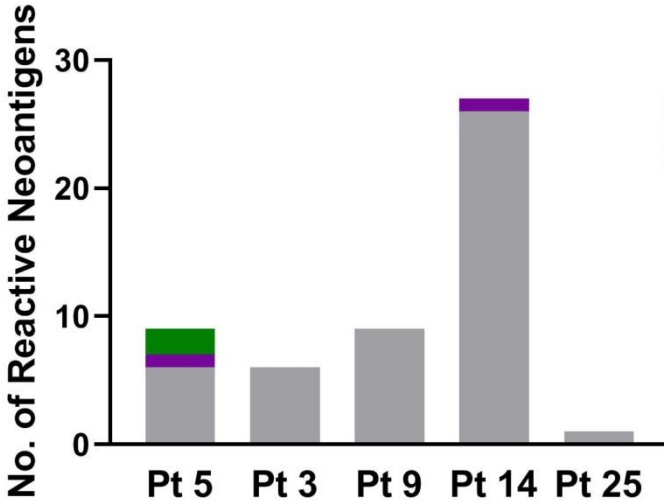
Presence of T cells which recognize neoantigens is associated with durable TIL benefit



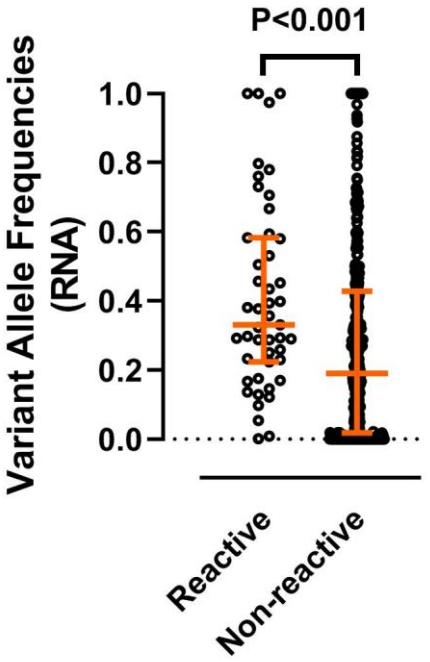
TMB: tumor mutation burden. T cells were derived from both Week 4 post-TIL PBMC & TIL pre-REP pool

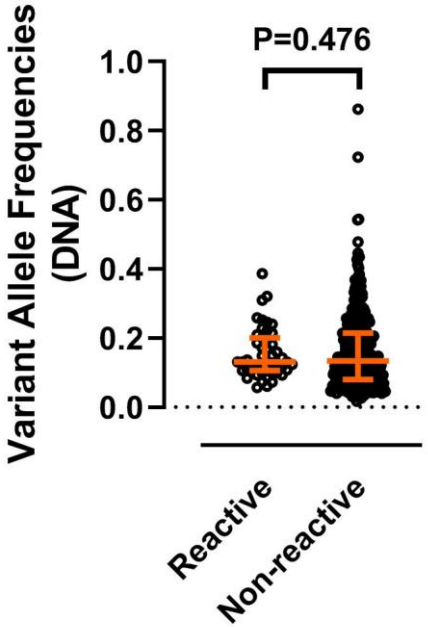
Various types of mutations can elicit T cell recognition

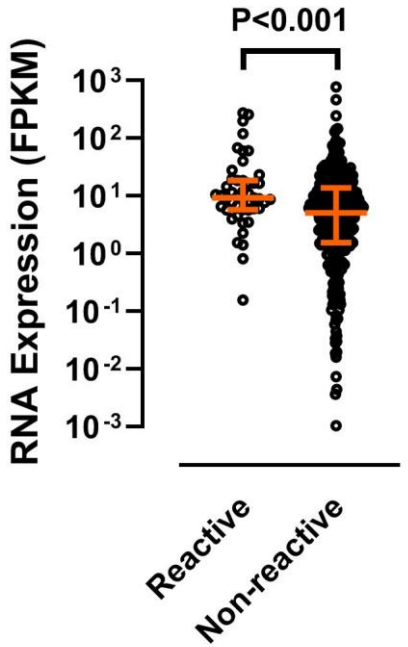




Mutations which elicit T cell recognition have higher RNA expression





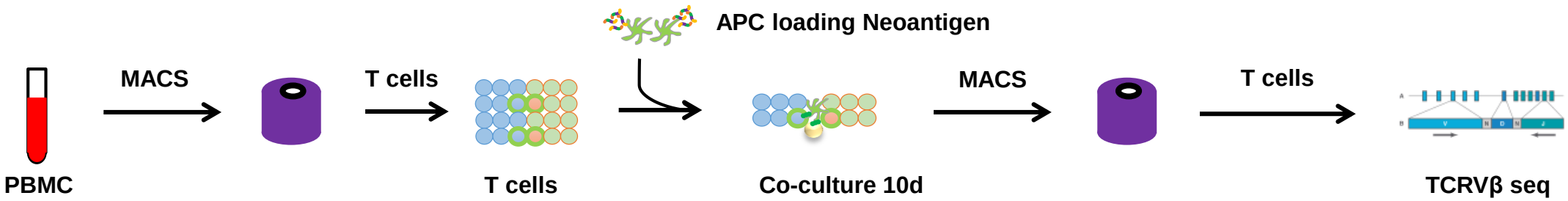


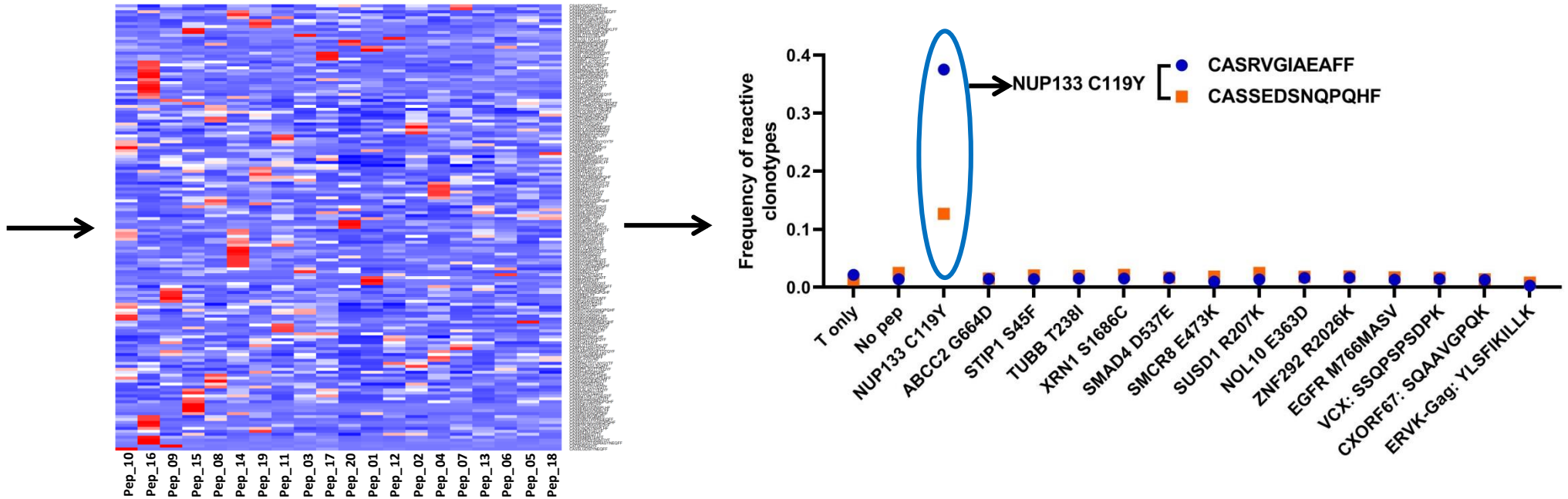
Reactive neoantigen: n=47

Nonreactive neoantigen: n=396

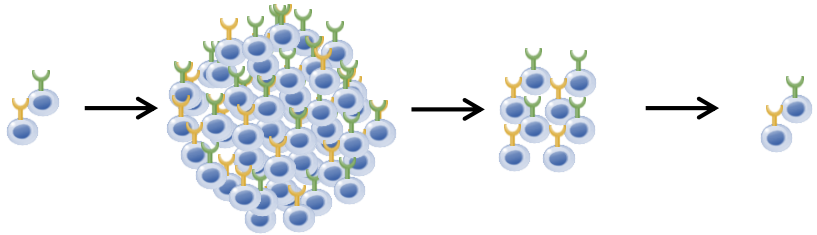
Mann-Whitney U test with 2-sided, 95% confidence

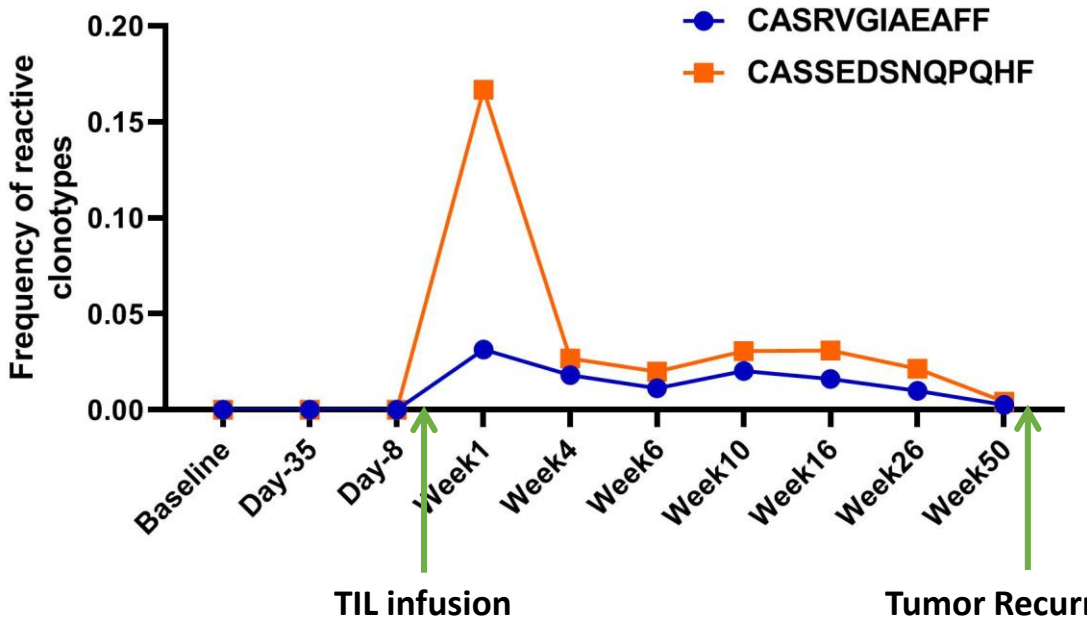
Neoantigen-specific clonotypes can be identified by TCR expansion

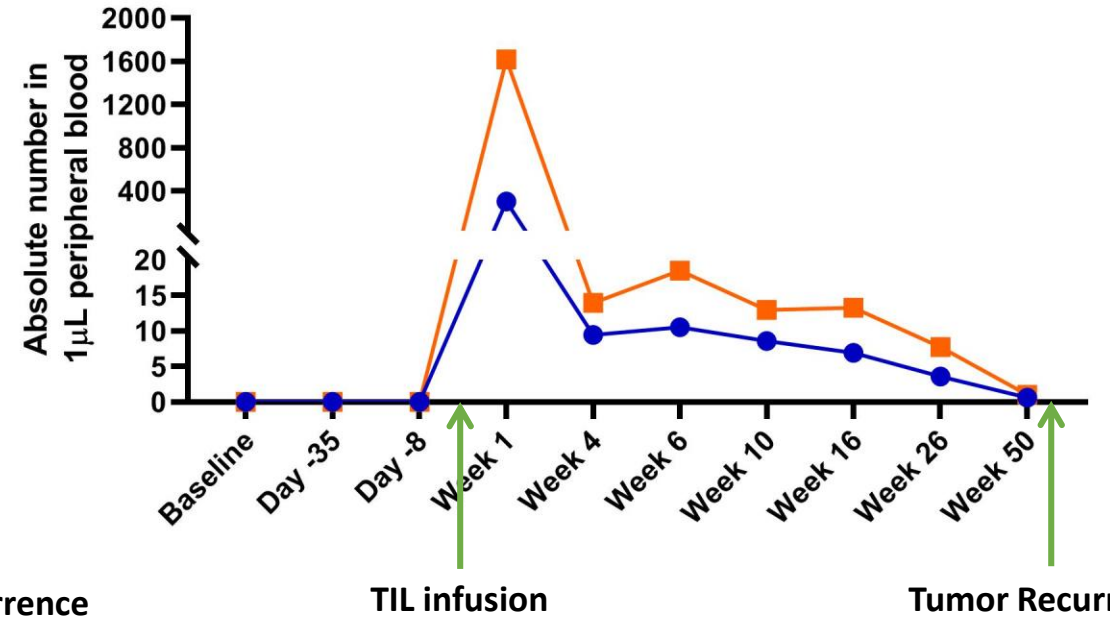




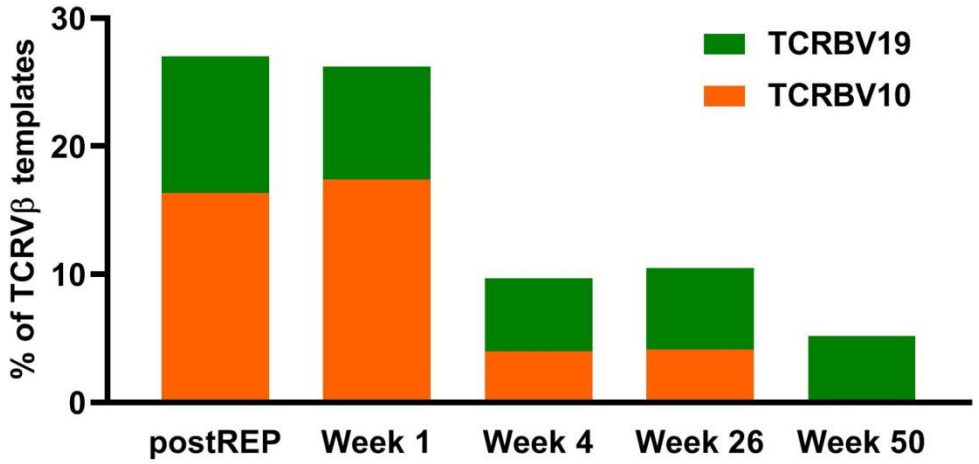
Decay of neoantigen-specific clonotypes over time

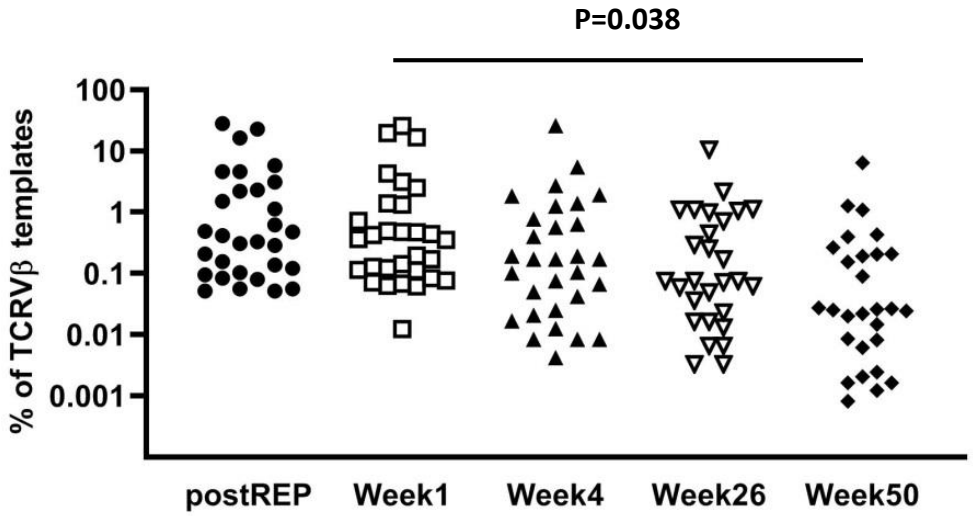






Decay of Neoantigen-specific TCRVβ Subtypes

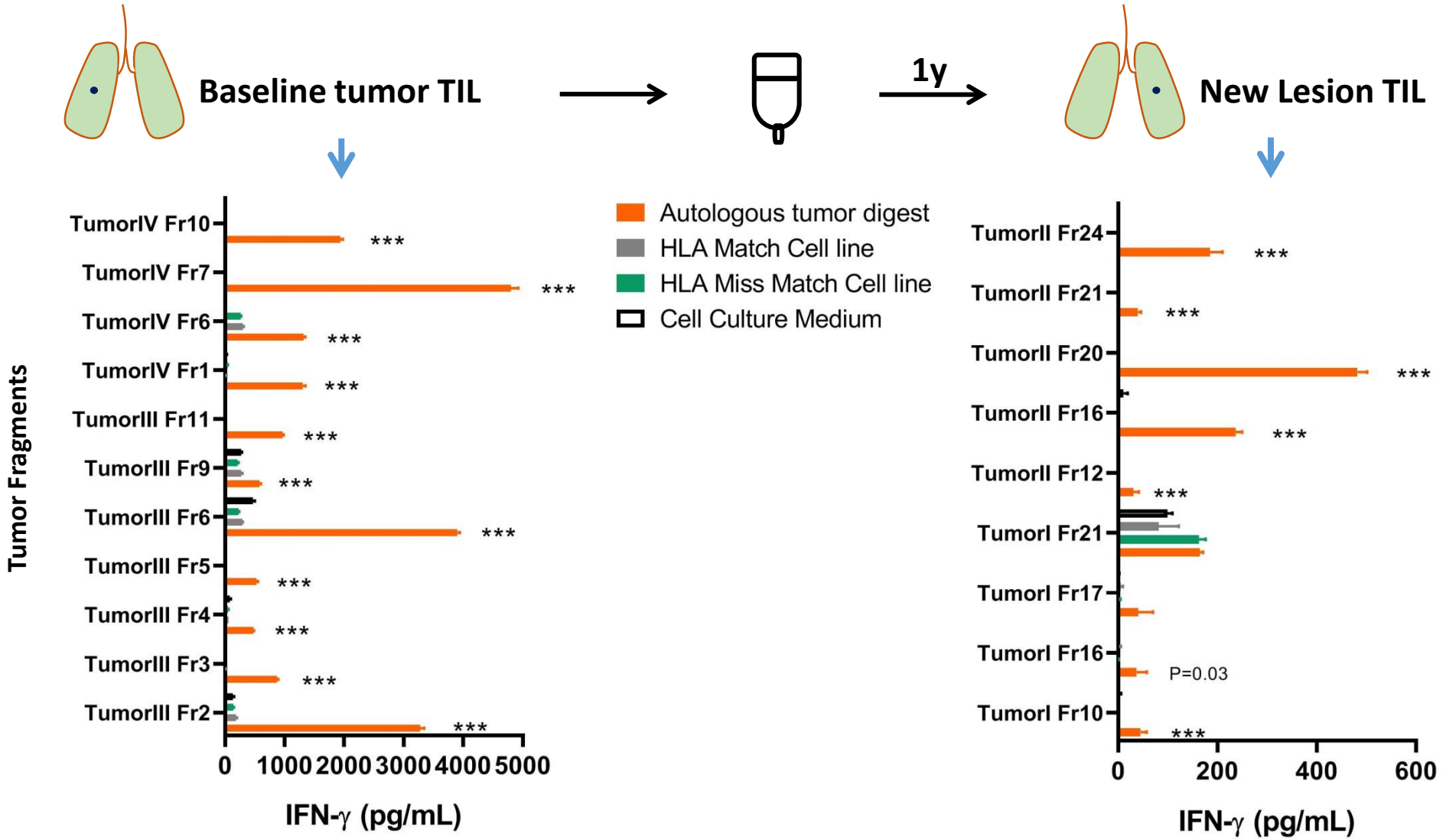




Top 30 TCRVb for TIL

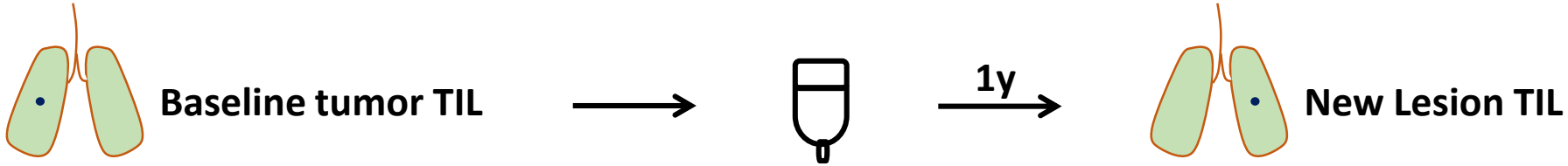
Paired t-test with 2-sided, 95% confidence

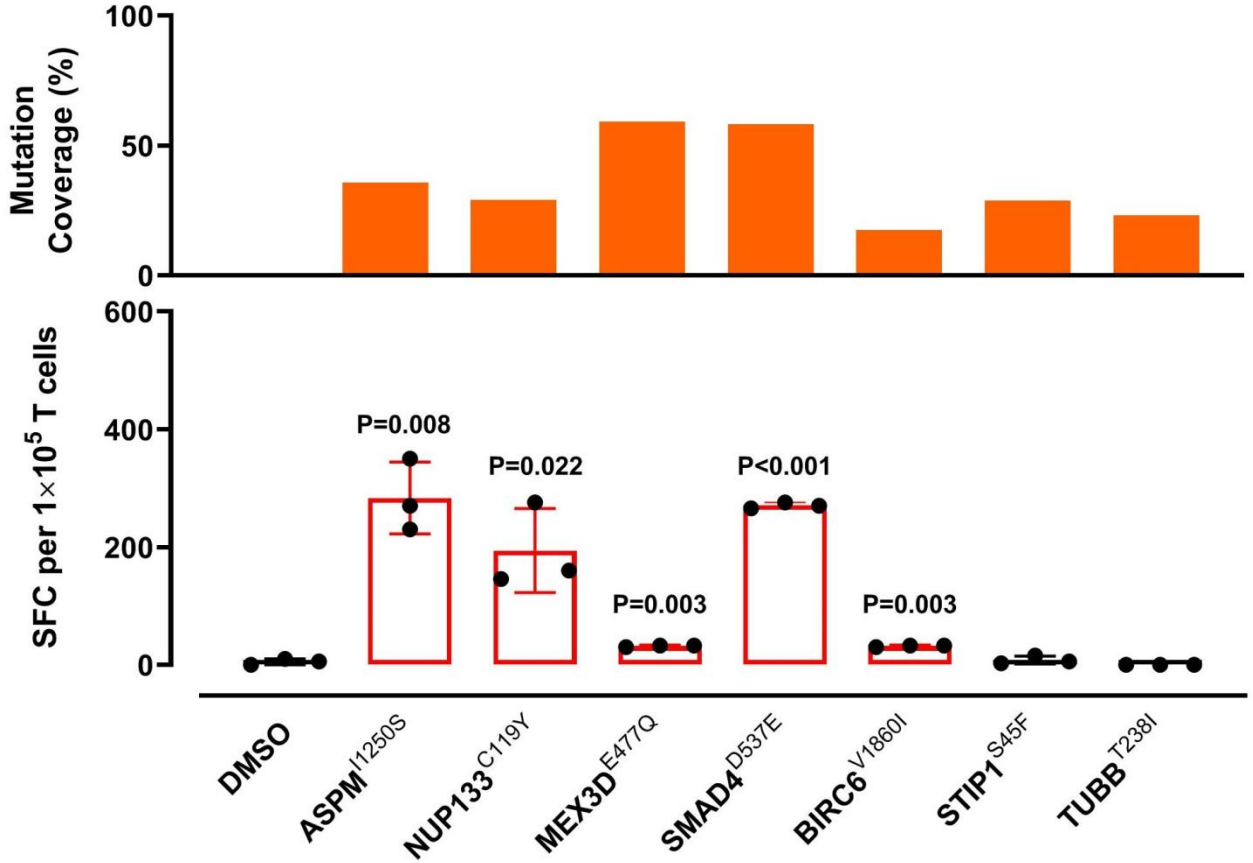
Reactivities of TIL Fragments in Pt 3's New Lesion

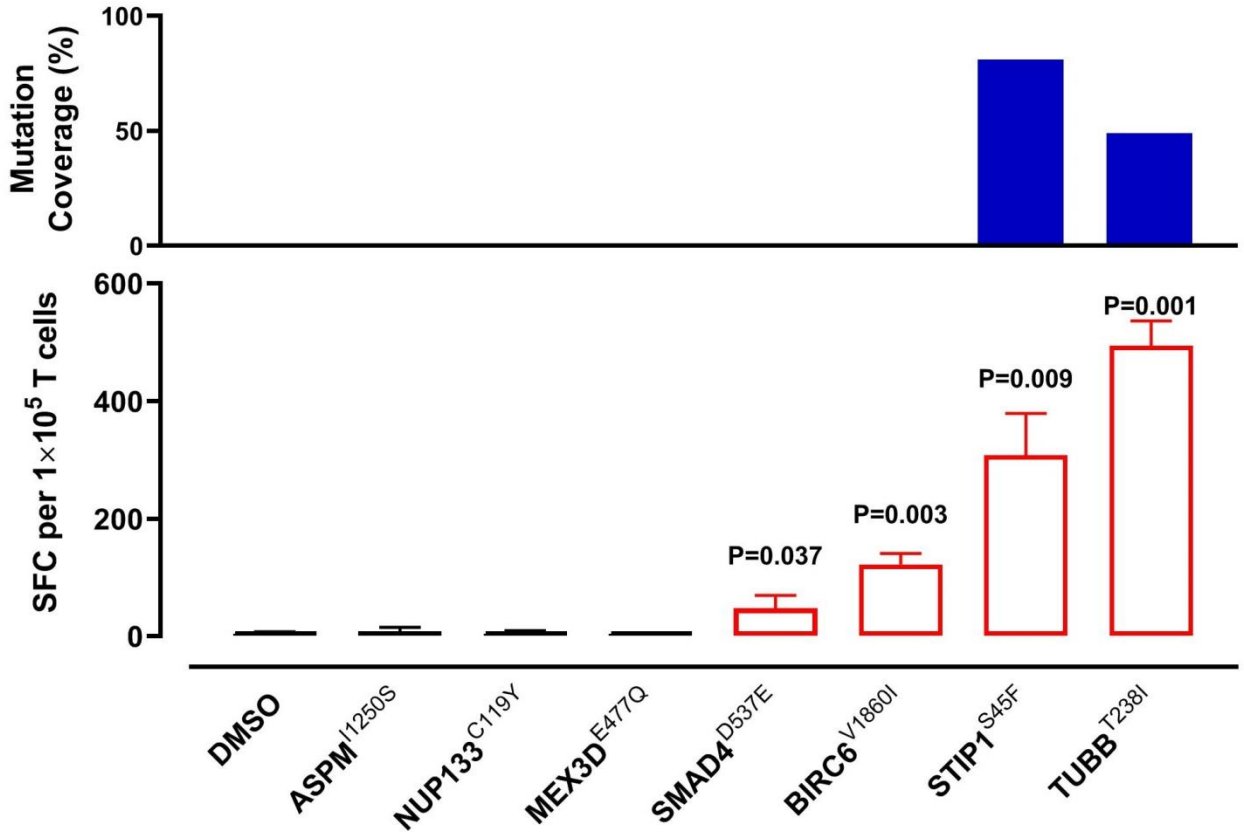


Bars indicate mean ± SD. Shown *p*-value calculated by repeated measures ANOVA with Dunnett's multiple comparison test. *** P<0.001

Neoantigen Editing Is A Possible TIL Resistance Mechanism







Summary

- Peptide-based neoantigen screening is feasible in lung cancer clinical trial samples
- Single-nucleotide variants, insertion/deletion and gene fusion may all function as effective neoantigens
- Recognition of neoantigens by T cells associates with TIL efficacy
- Decay of neoantigen-specific T cells and allelic editing in recurrent tumors may contribute to TIL resistance

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