CD8 T cell epitope vaccines: composition, not size it's what matters

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Is there any future for cancer vaccines?

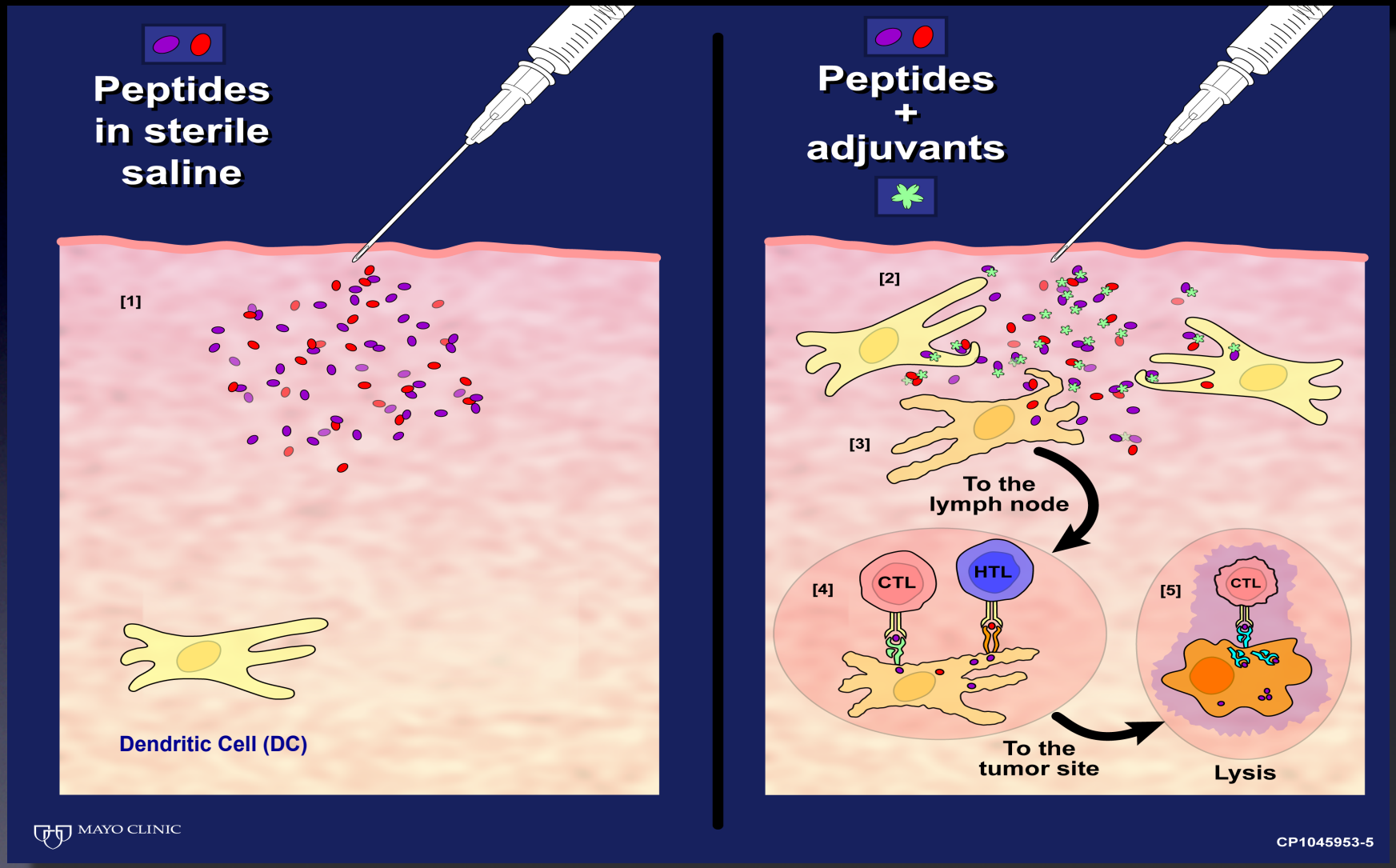
- Vaccines that induce T cell responses
  - Promising results but no real homeruns
  - Suboptimal immune responses (quantity and quality of T cells)
  - Short minimal peptide epitopes induce tolerance
- Adoptive cell therapy (ACT)
  - Some homeruns and many good hits
  - Achieves huge numbers of tumor-reactive T cells
  - Technically challenging, toxic and not cost effective

Working Hypothesis

It is possible to design a simple, cost-effective vaccine that achieves what ACT does by mimicking a systemic acute infection

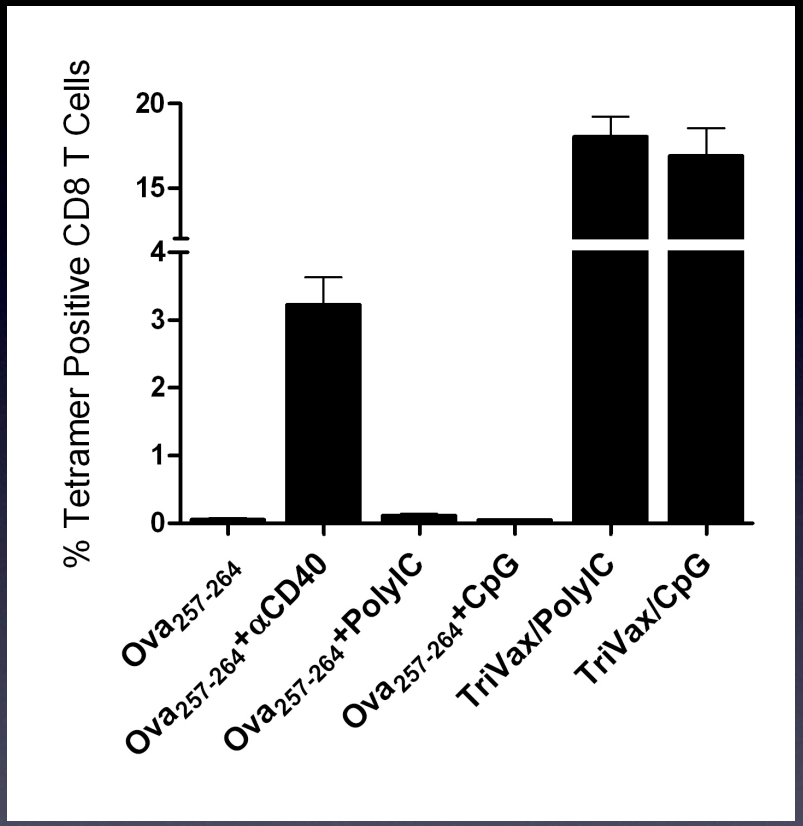
- Magnitude of response : > 10% of all T cells
- Duration of response: until disease is eradicated and more (memory CD8 T cells)

Peptides are in general poor immunogens



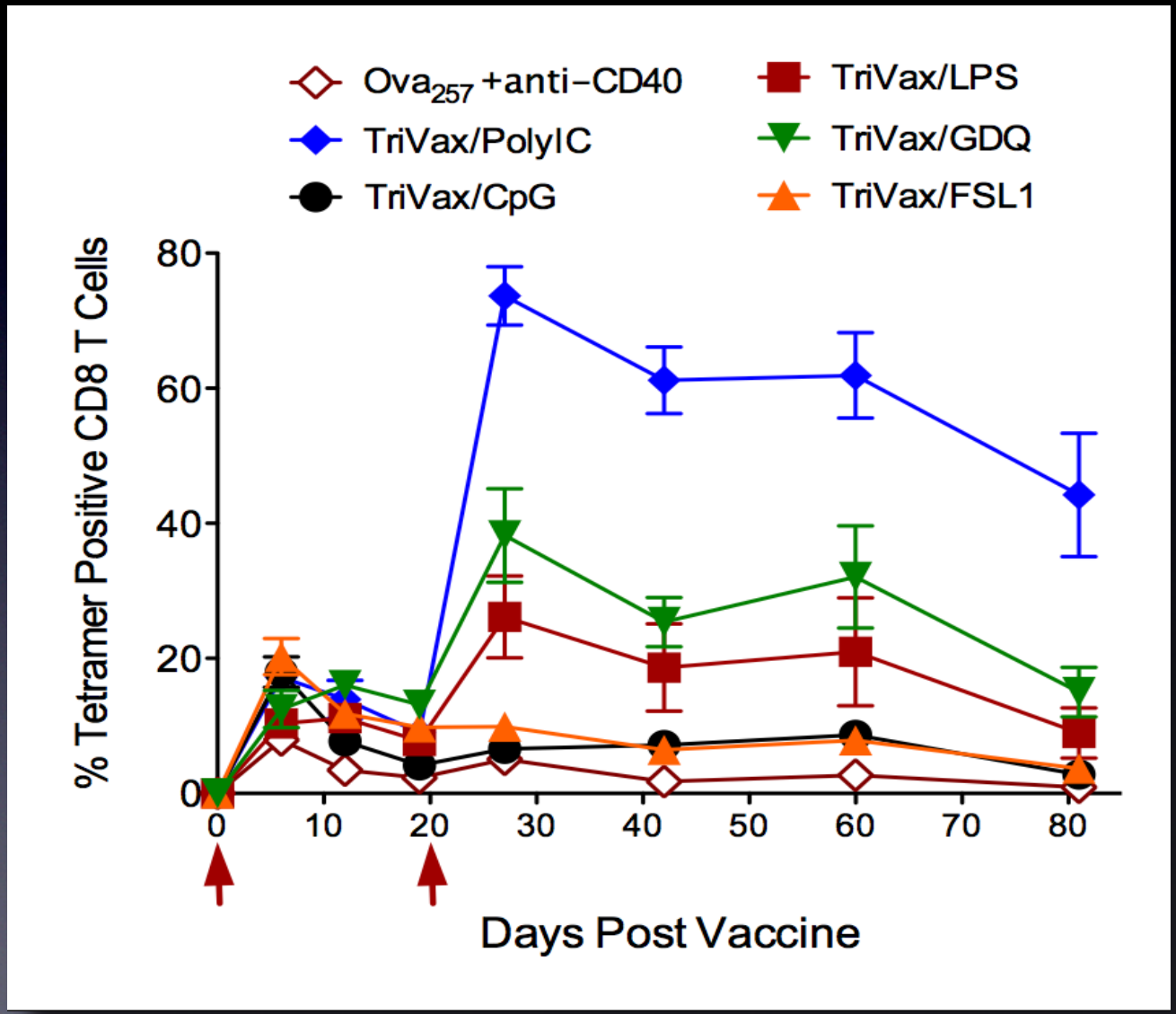
Buteau C, Markovic SN, and Celis E, *Mayo Clin. Proc.*, 77:339-349; 2002

Soluble peptides are highy immunogenic when administered systemically with potent adjuvants

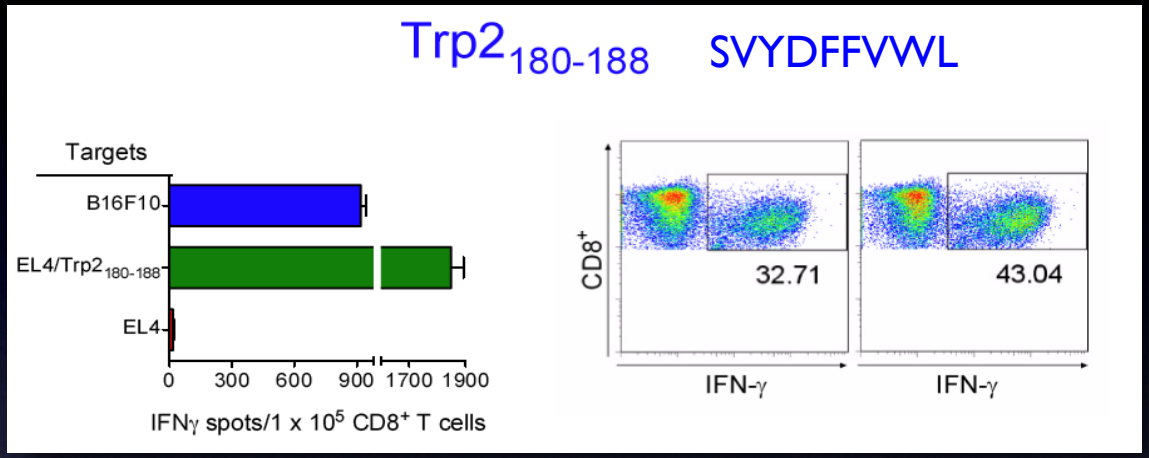


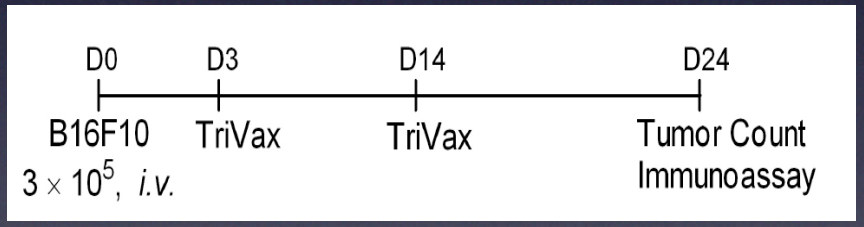
- One single *i.v.* injection of Ova_{257} (SIINFEKL) in PBS
- TriVax: peptide + TLR-L + αCD40 mAb
- Responses measured in blood 6 days post-vaccination

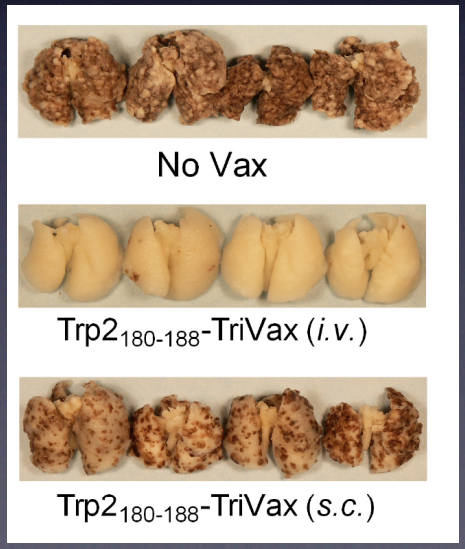
Differences in boosting responses

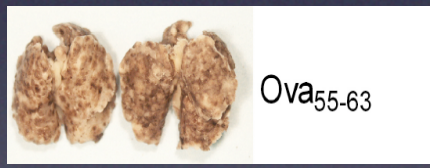


TriVax against B16 melanoma antigens









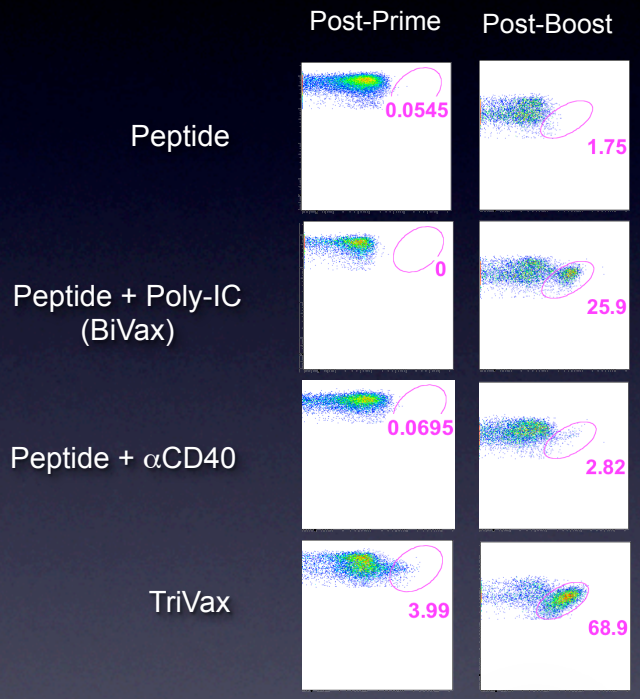
Cho and Celis, Cancer Research 69:9012; 2009

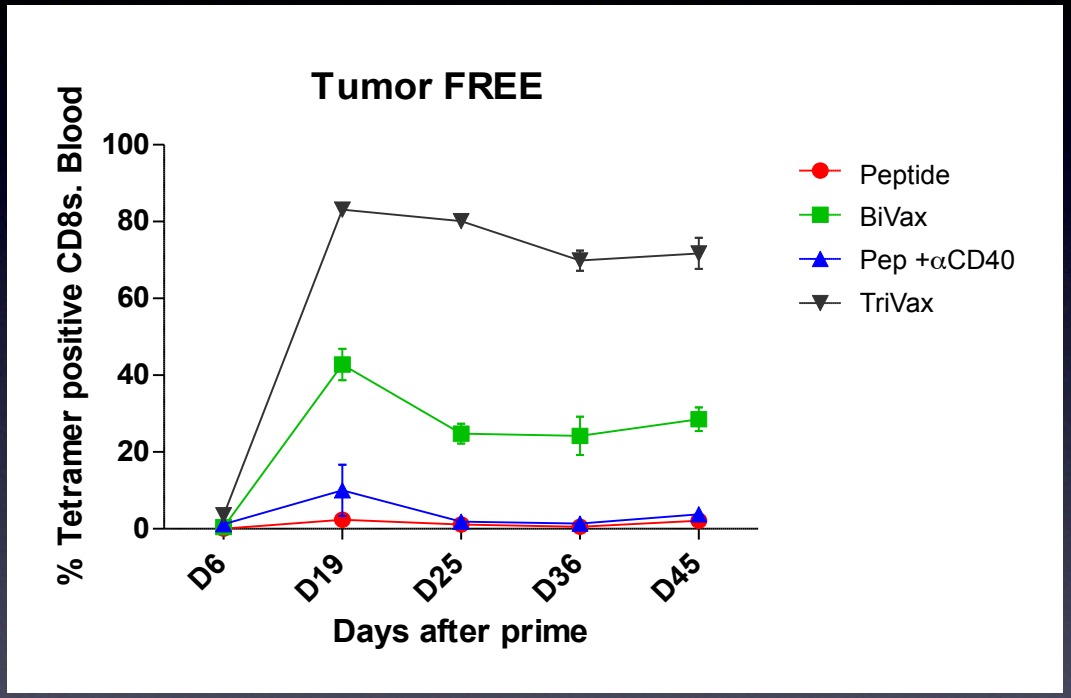
Reassessing the use αCD40 mAb

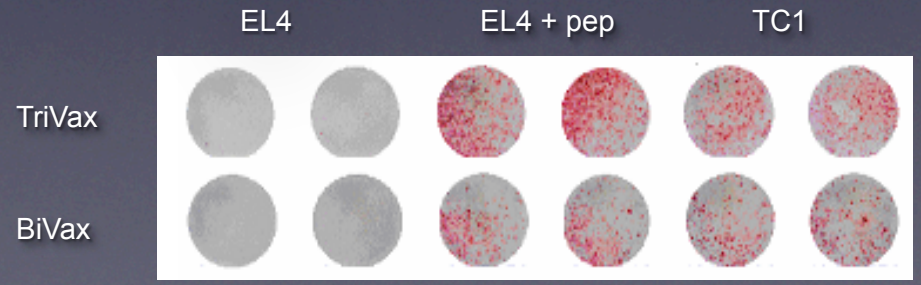
- αCD40 mAbs may contribute to toxicity
- Clinical development of agonistic human αCD40 mAbs has been suspended by Pfizer
- Can peptide plus poly-IC (BiVax) provide sufficient immune responses to control tumor growth?

HPV mouse tumor model

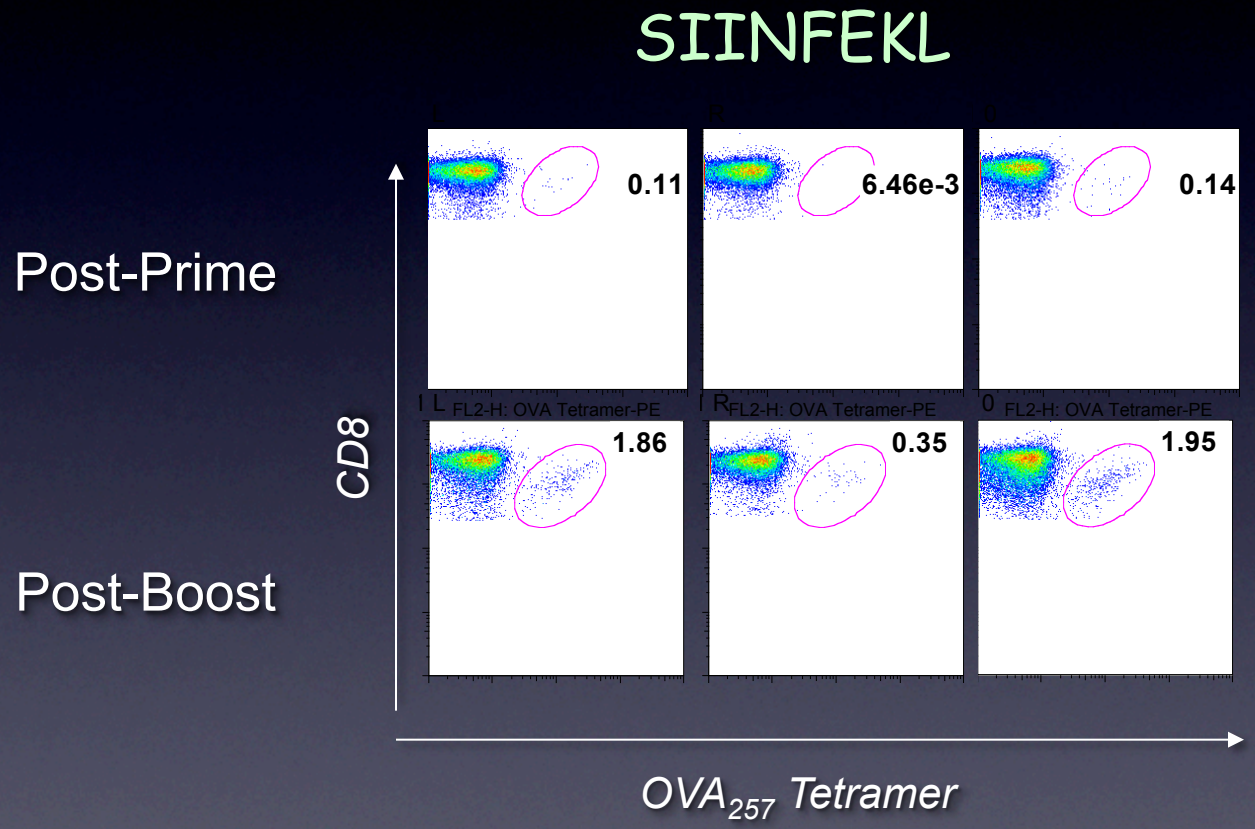
Experiments using HPV16-$E7_{49}$ (RAHYNIVTF) H-$2D^b$ epitope





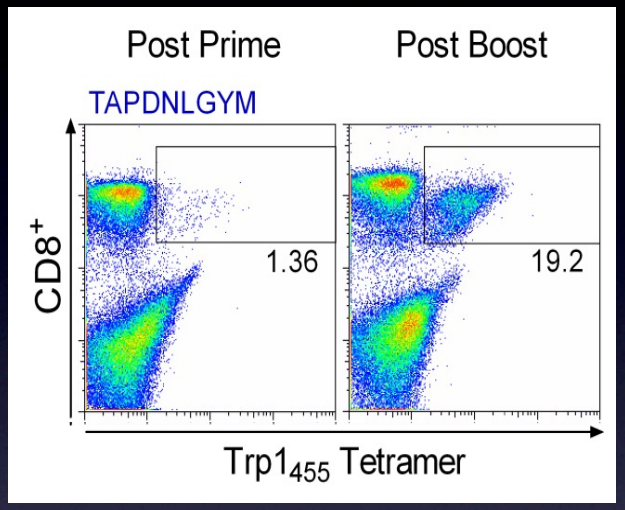


Ova_{257} BiVax fails to induce substantial T cell responses

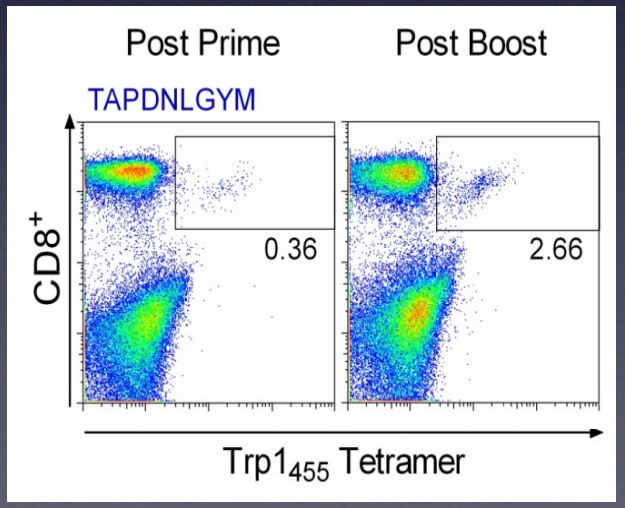


T cell responses to $Trp1_{455\text{-}463/9M}$

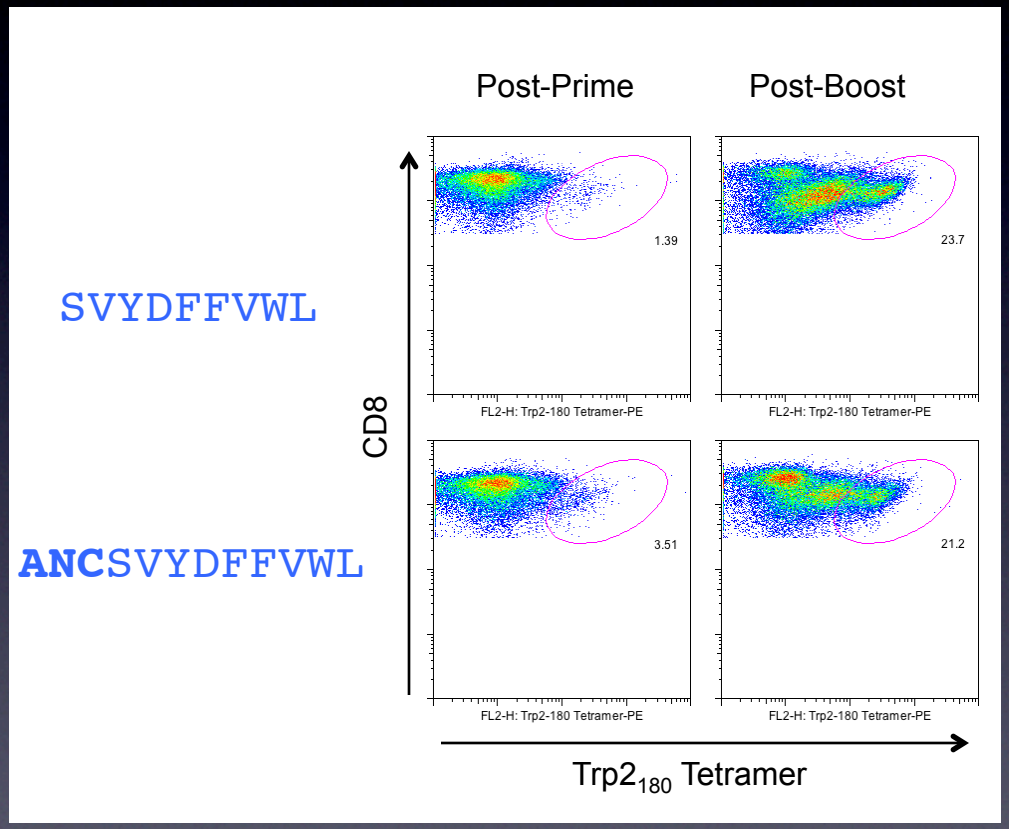
TriVax

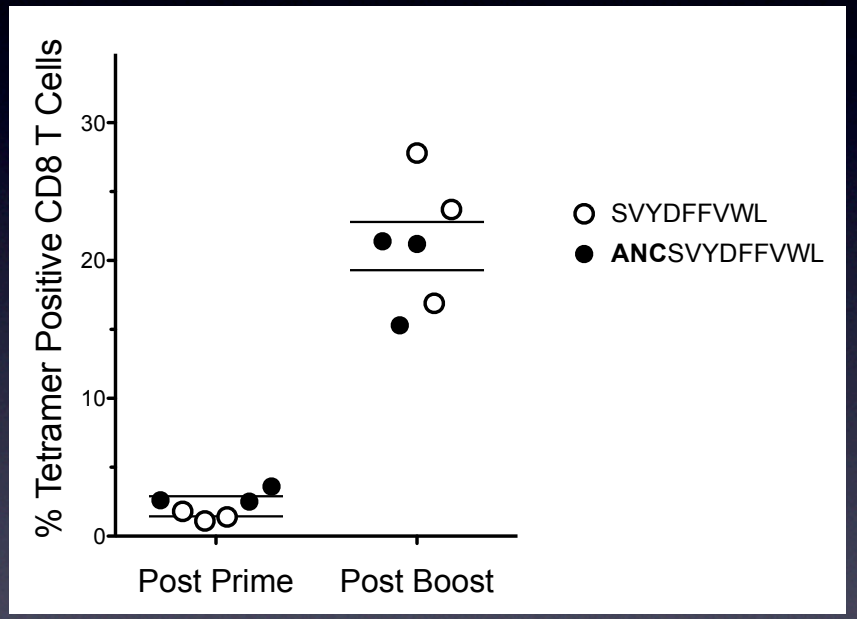


BiVax



T cell responses to $Trp2_{180\text{-}188}$ with BiVax immunization





Peptide composition may affect immunogenicity in BiVax

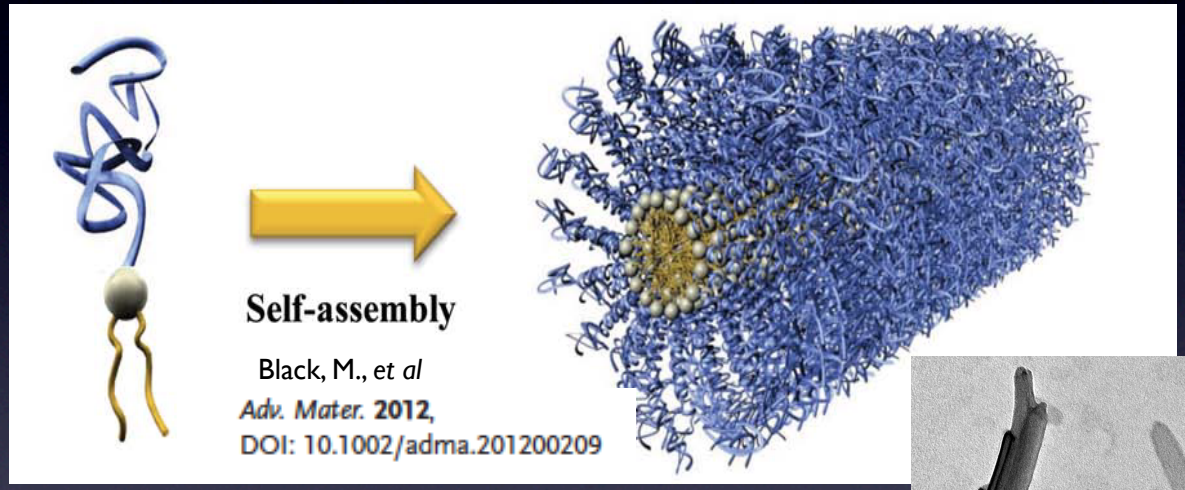
Amino Acid Hydrophobicity

Residue Type	kdHydrophobicity[a]
Ile	4.5
Val	4.2
Leu	3.8
Phe	2.8
Cys	2.5
Met	1.9
Ala	1.8
Gly	-0.4
Thr	-0.7
Ser	-0.8
Trp	-0.9
Tyr	-1.3
Pro	-1.6
His	-3.2
Glu	-3.5
Gln	-3.5
Asp	-3.5
Asn	-3.5
Lys	-3.9
Arg	-4.5

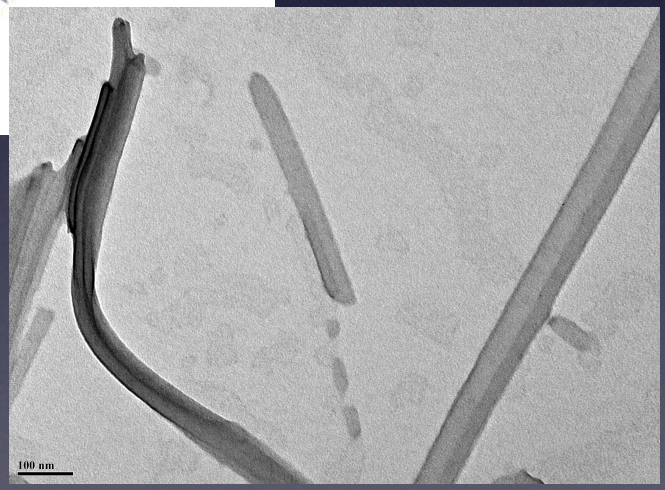
[a] A simple method for displaying the hydropathic character of a protein. Kyte J, Doolittle RF. *J Mol Biol*. 1982 May 5;157(1):105-32.

Sequence	*kd Hydrophobicity*
RAHYNIVTF	-0.1
SIINFEKL	+3.9
TAPDNLGYM	-3.5
SVYDFFVWL	+11.3
ANCSVYDFFVWL	+12.1

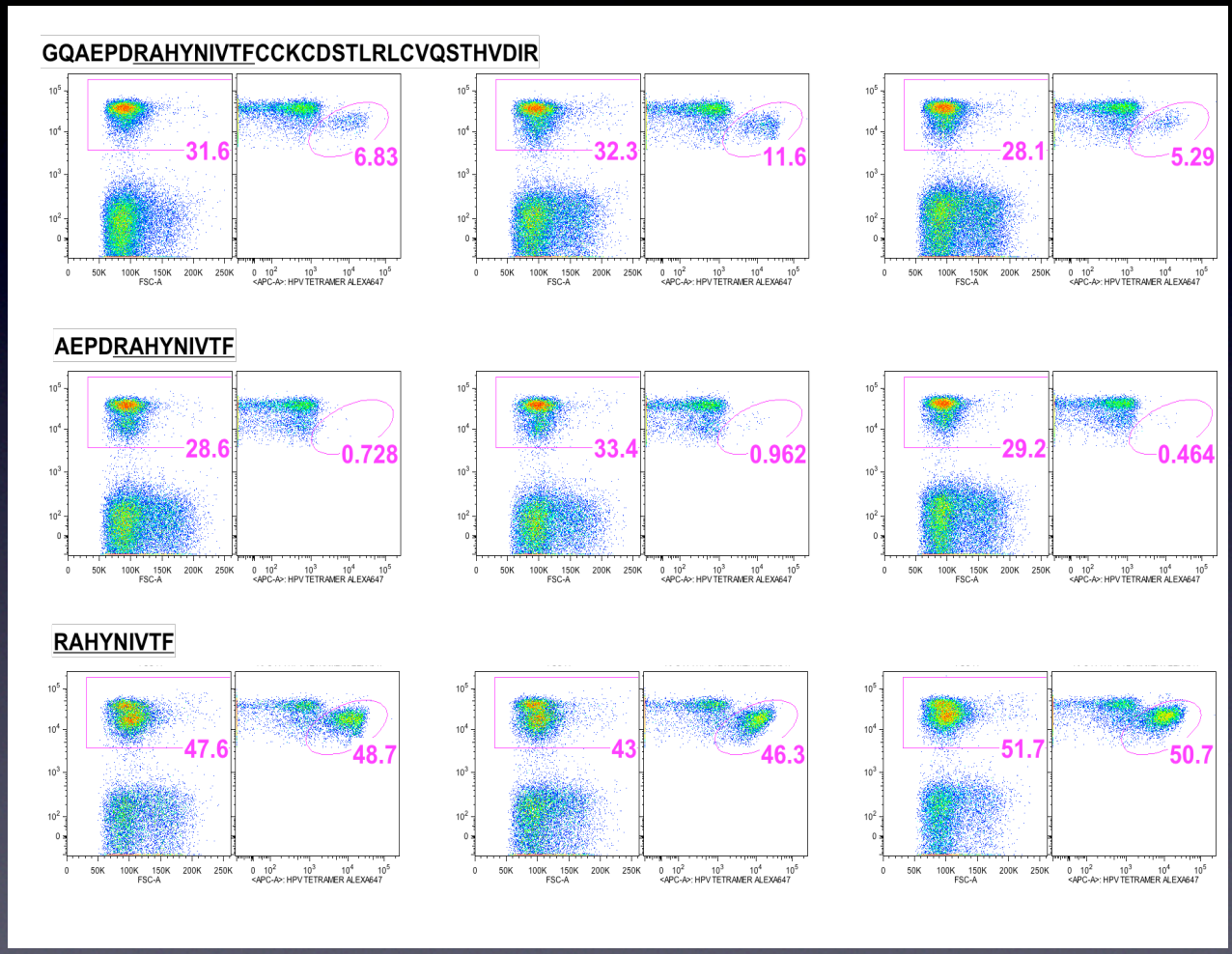
Peptides amphiphiles can assemble into tubular micelle structures



RAHYNIVTF

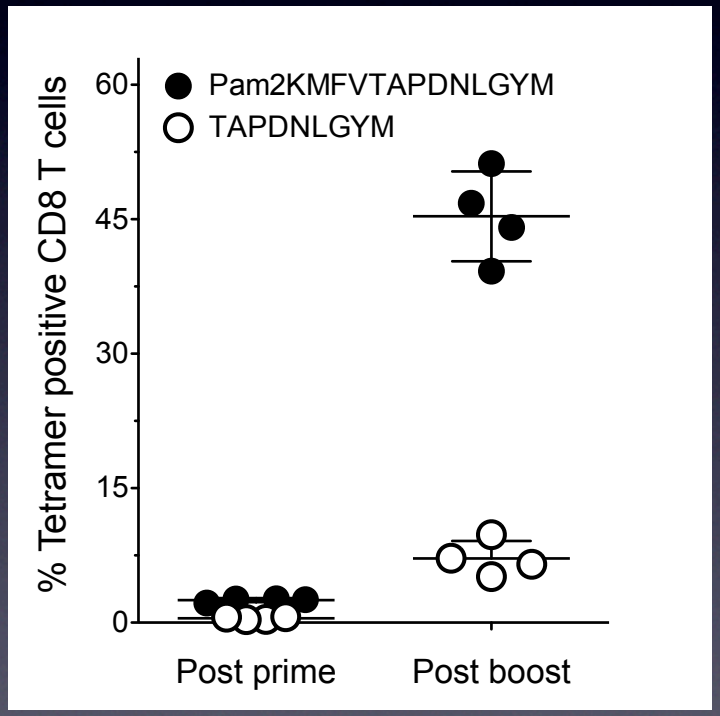


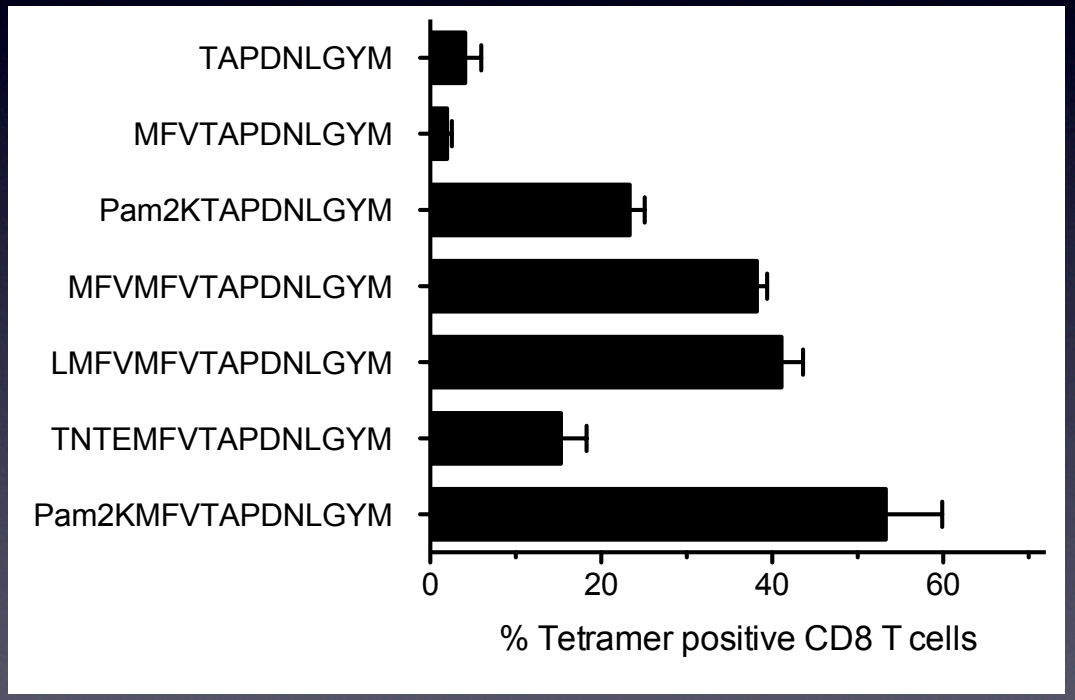
Simple peptide elongation does not increase immunogenicity



Immune responses in blood 6 days after BiVax boost

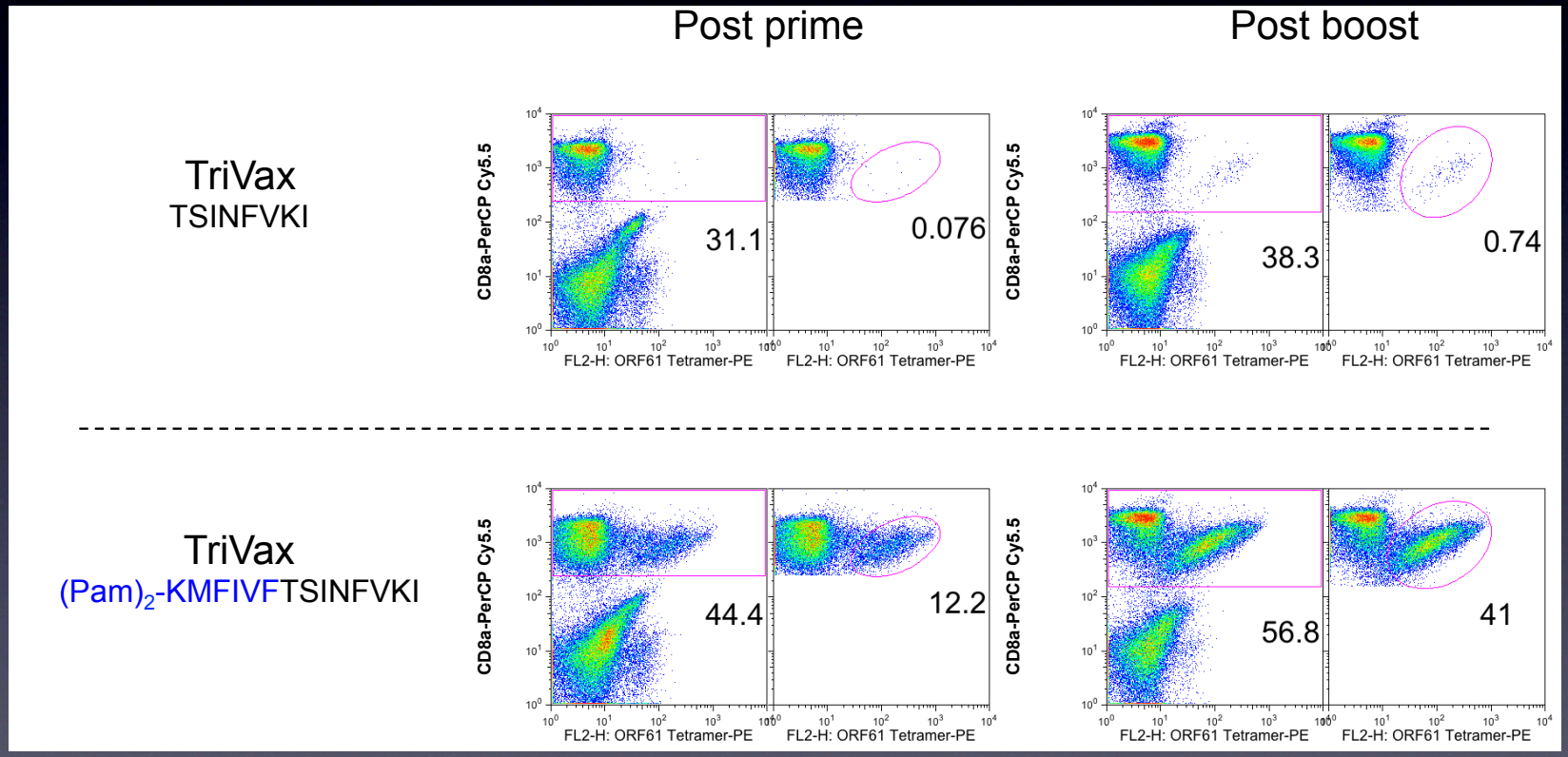
Increasing amphipathicity enhances BiVax efficacy





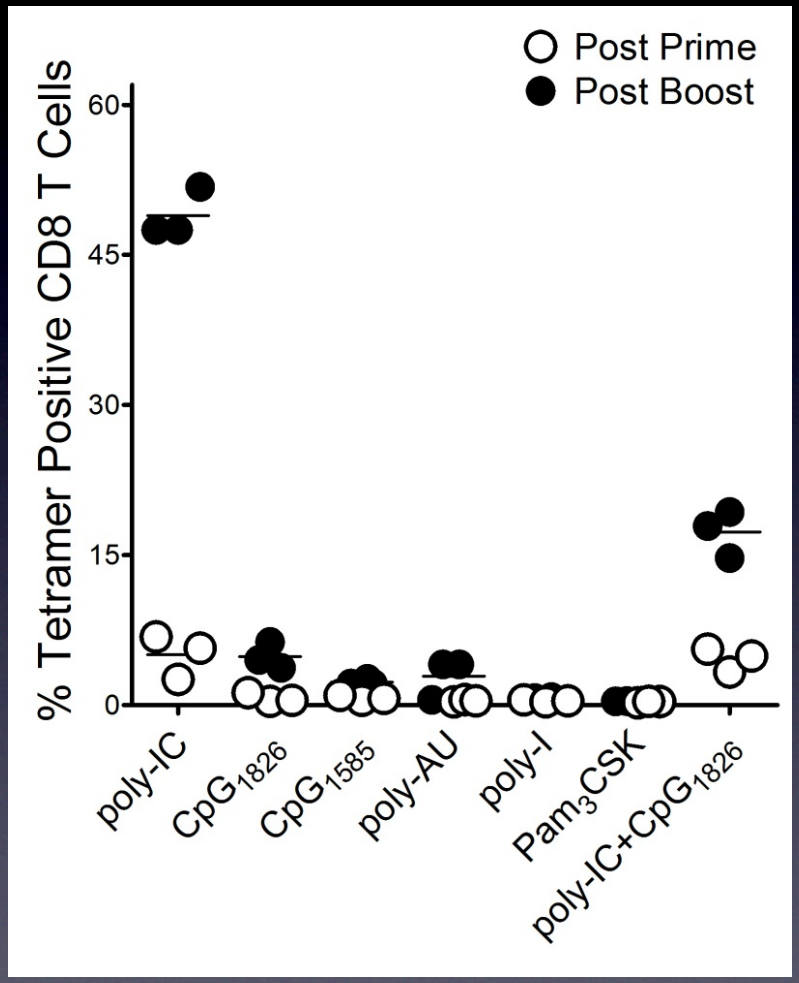
TAPDNLGYM (TRP1) H-2D^{b} T cell epitope

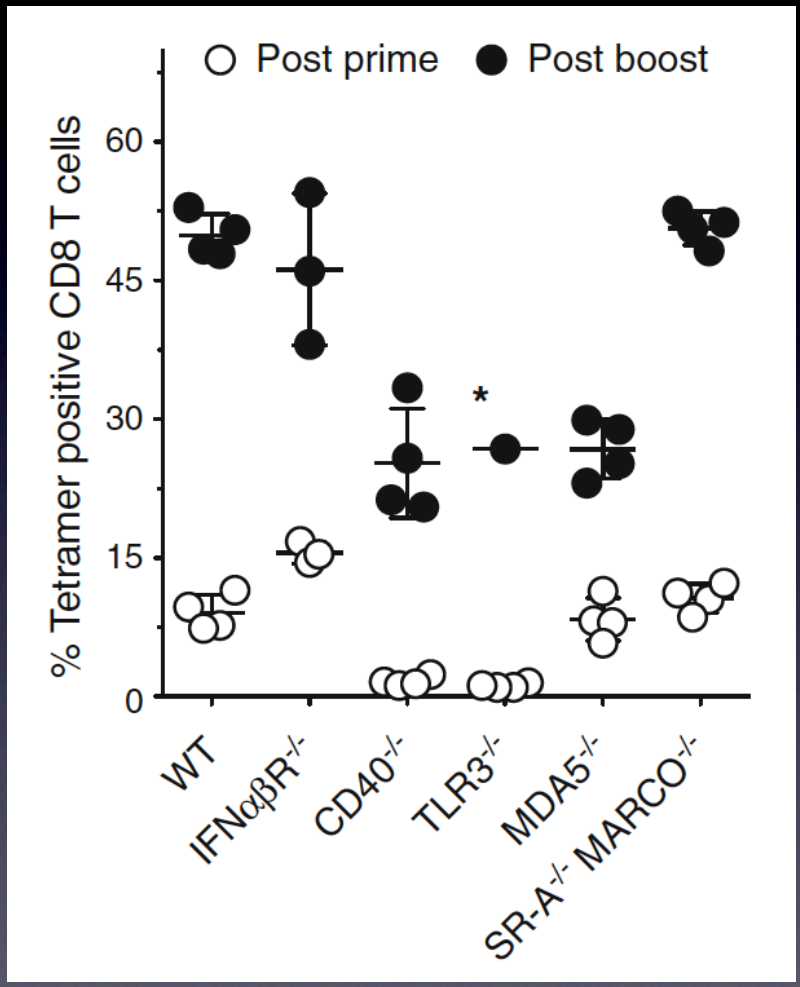
Increasing amphipathicity enhances TriVax efficacy



TSINFVKI (kdH = -6.4) Murine Gammaherpesvirus (MHV)-68 H-2K^b

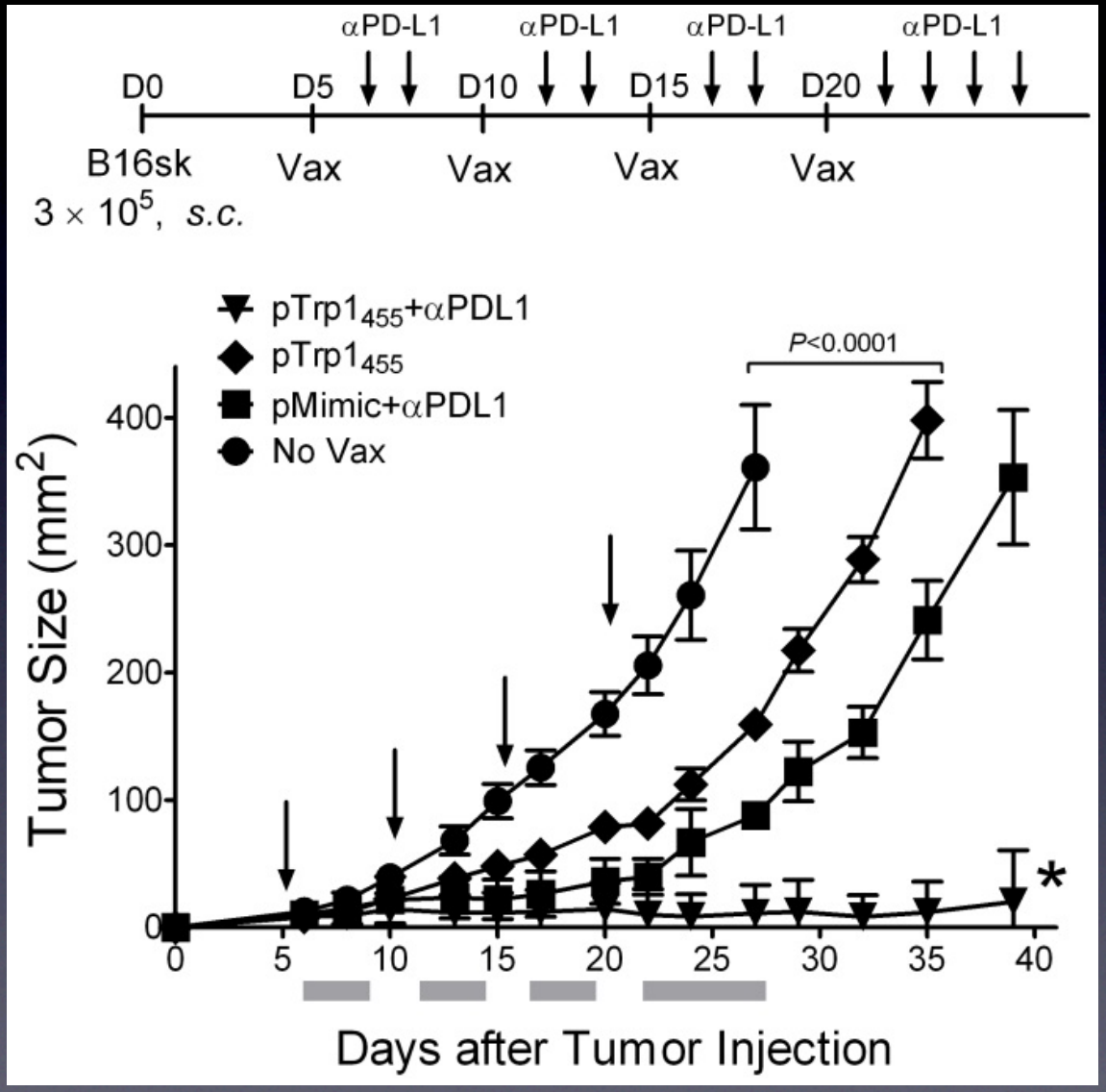
Mechanisms involved in immunogenicity





$(Pam)_2$KMFV**TAPDNLGYM** (TRP1) T cell epitope

Anti-tumor effects of BiVax



* 4/5 rejected their tumors

Summary

- Optimized peptide vaccines (TriVax and BiVax) generate strong CD8 T cell responses with remarkable anti-tumor effects
- Poly-IC is the most effective TLR-L
- Vaccine efficacy is influenced by peptide characteristics (i.e., amphiphilic peptides) and not simply by peptide size/length
- Peptide characteristic may impact antigen capture by APCs
- Vaccine efficacy is influenced by route of administration
  - *i.v.* > *i.m.* >> *s.c.*
- BiVax priming and boosting (expansion) appear to be 2 independent events
  - Priming requires relies on TLR3 and CD40 (pAPCs?)
  - Boosting relies on type-I IFN/MDA-5 (npAPCs?)

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