Anti-Tumor Vaccines Platforms

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Disclosure of conflict of interest

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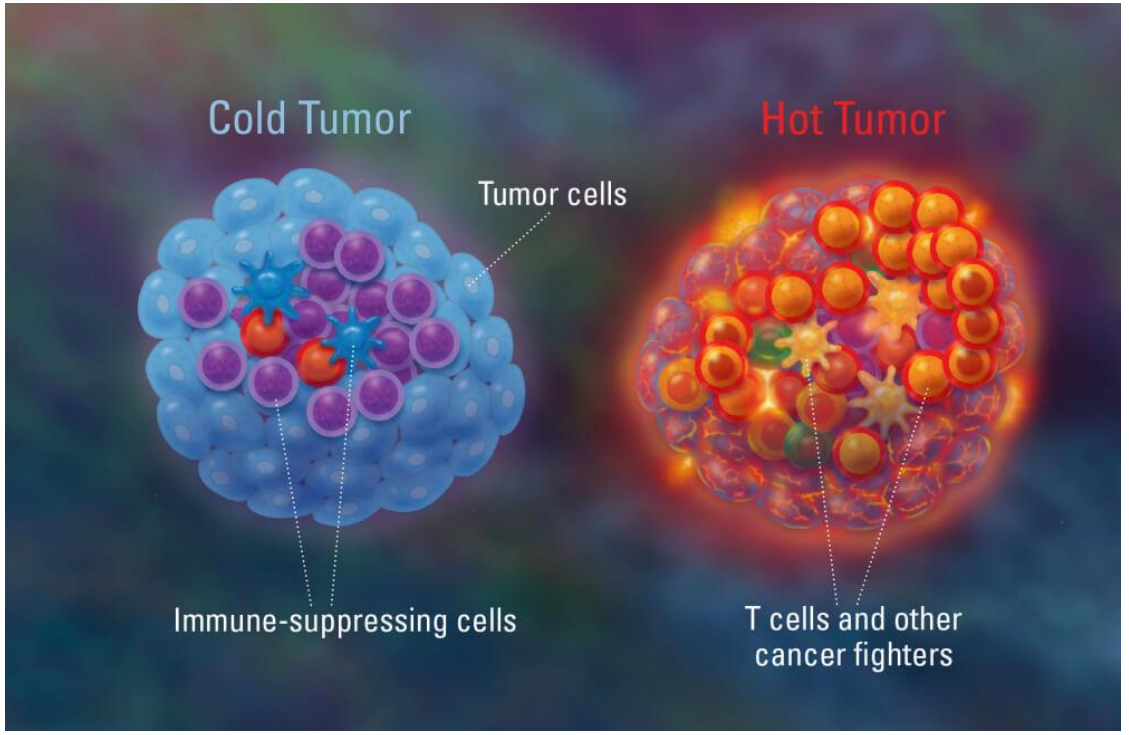
developer of Hiltonol™ (Poly-ICLC)

Why cancer vaccines?

- The most effective checkpoint blockade inhibitor (aPD1/aPD-L1) works in hot tumors (T cell infiltrated)
- Cold tumors may be the result of poorly immunogenic cancers that do not elicit endogenous T cell responses
- Cancer vaccines could turn cold into hot tumors and improve checkpoint blockade efficacy



Cancer vaccines classes
according to time of administration

- **Prophylactic**
  - Prior to cancer initiation
    - Healthy individuals (HPV, HBV vaccines)
    - For high risk patients (BRCA1/2+; HER2, EGFR, FR, MUC1 vaccines?
  - Presence of pre-malignant lesions (CIN, PIN, polyps)
  - Clinical “disease-free” patients (post conventional therapy)
- **Therapeutic**
  - Low tumor burden (most likely to respond, metastases prevention)
  - High tumor burden (immunocompromised patients?)

Goals of cancer vaccination

1. Elicit a **substantive** and **durable** immune response capable of recognizing tumor cells
   - Immune response: T cell mediated
   - Substantive: Similar to infectious disease vaccines or at least measurable w/o *in vitro* manipulations (e.g., peptide expansion culture)
   - Durable: Immune memory, capable of booster effects
   - Tumor recognition, not only immunogen recognition
2. Minimal or tolerable toxicity
   - Off-target toxicity (presence of Ag in normal tissues)
   - Exaggerated inflammatory responses (cytokine storm, adjuvant toxicity)

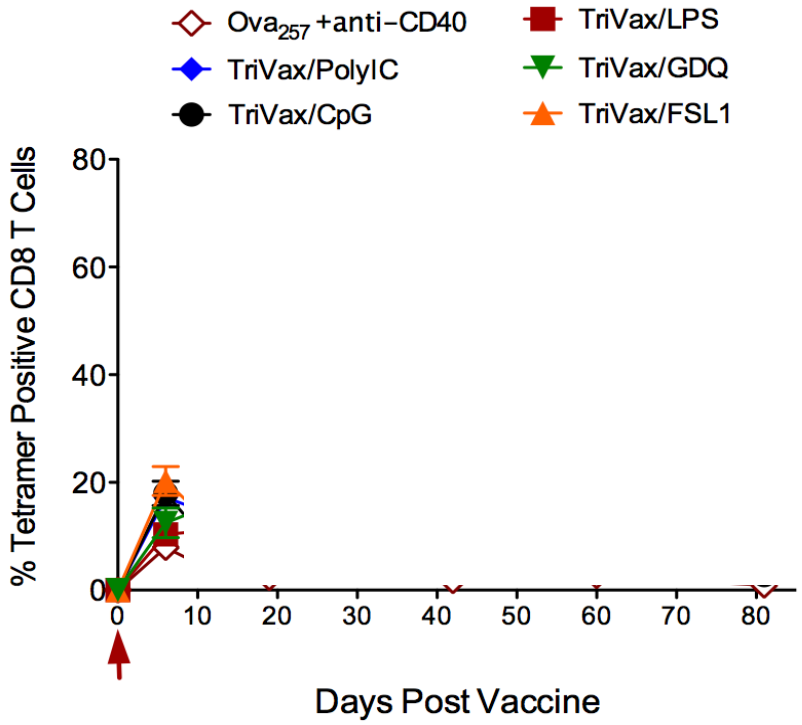
Tumor antigens used in vaccines

- Uncharacterized tumor-antigens
  - *In situ* tumor vaccination with adjuvant, oncolytic virus, beam irradiation
  - Whole self-tumor cell vaccines, tumor lysates
  - Tumor cell lines, sometimes genetically modified (CD80/86, IL-2, GMCSF)
- Characterized conventional/shared antigens
  - Viral antigens (HPV16-E6/E7)
  - Tissue differentiation antigens (MelanA, Trp1/2, PSMA)
  - Abnormally expressed products (HER2, CEA, MUC1)
- Products of genetic aberrations (mutations, translocations, etc.)
  - Neo T cell antigens: mutations within MHC-binding peptide regions

Characterized cancer vaccine components

- Antigen
  - Protein/peptides
  - DNA/RNA
- Adjuvant (e.g., TLR agonists)
- Delivery system
  - Saline/PBS
  - Oil:water emulsions, nanoparticles, ISCOMs, DCs
- Adjuncts
  - Costimulatory agents (antibodies, cytokines)
  - Checkpoint inhibitors

TriVax, a highly immunogenic peptide vaccine: comparison of several TLR adjuvants

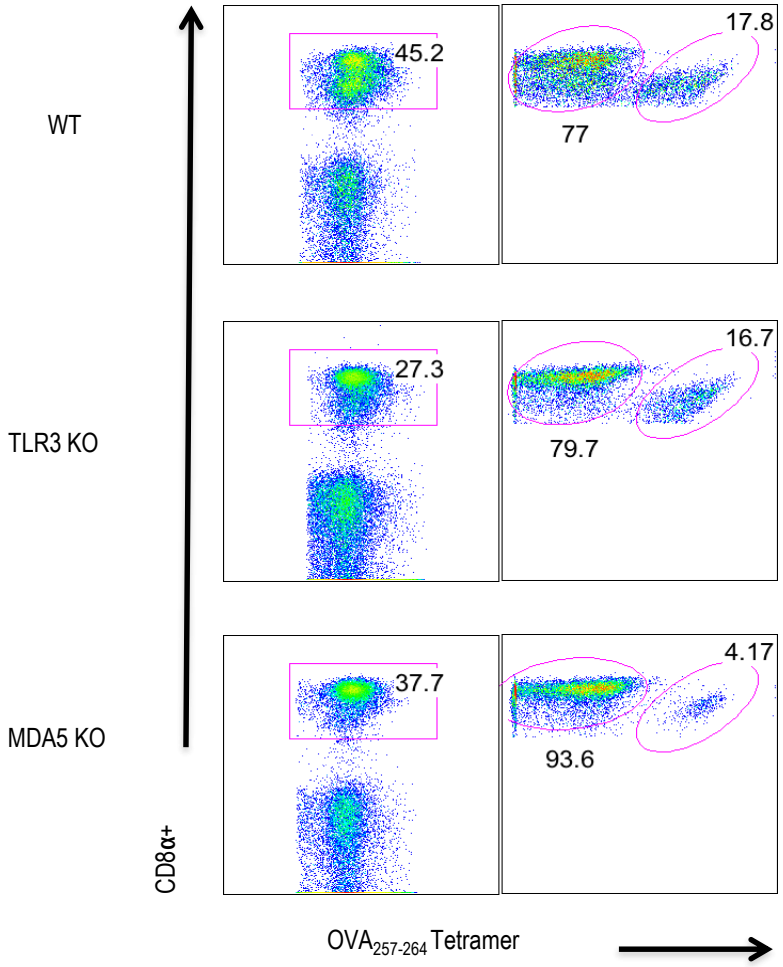


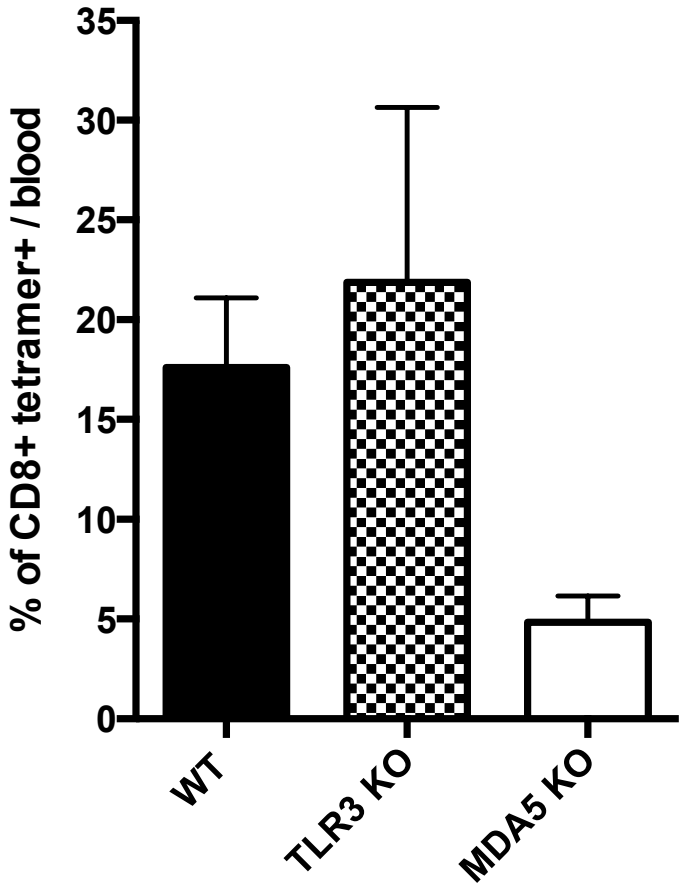
- One single *i.v.* injection of Ova_{257} (SIINFEKL) in PBS
- TriVax: peptide + TLR-L + aCD40 mAb
- Responses measured in blood 6 days post-vaccination

Q: So what is special about poly-IC?

A: Poly-IC stimulates TLR3 (endosomes) & MDA5, a RIG-I-like receptor (cytoplasmic)

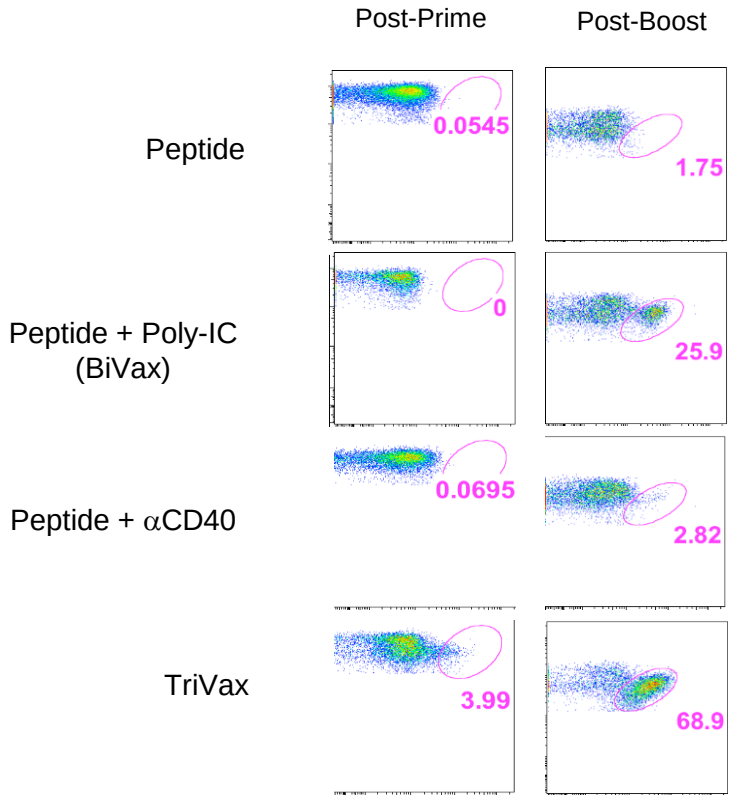
Role of TLR3 and MDA5 in vaccine responses

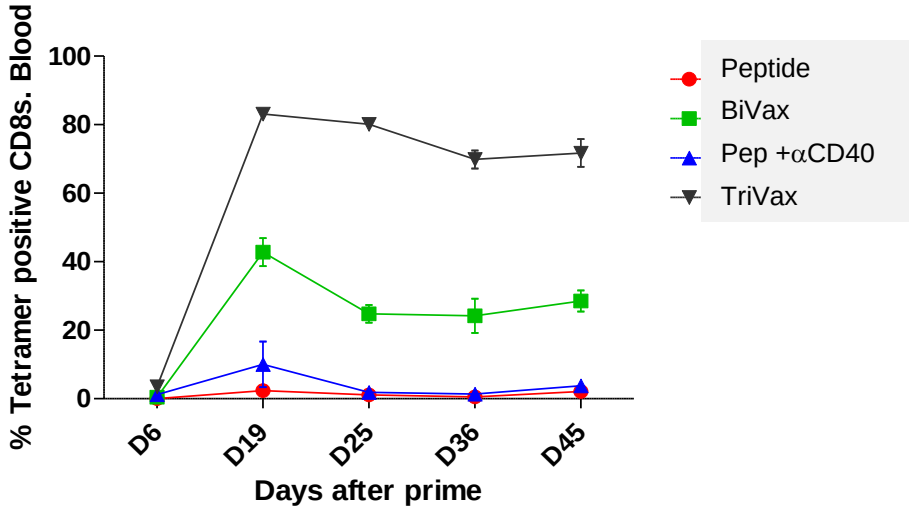


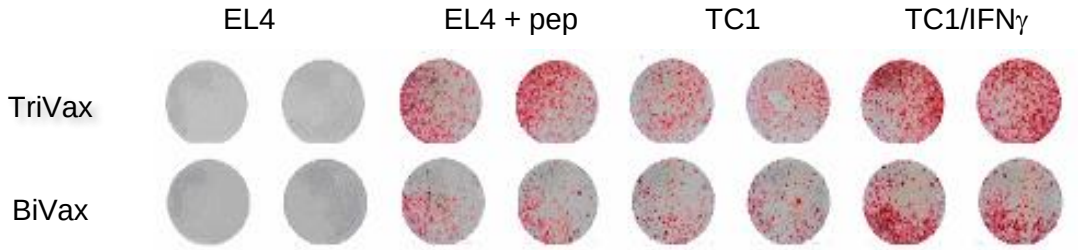


HPV mouse tumor model

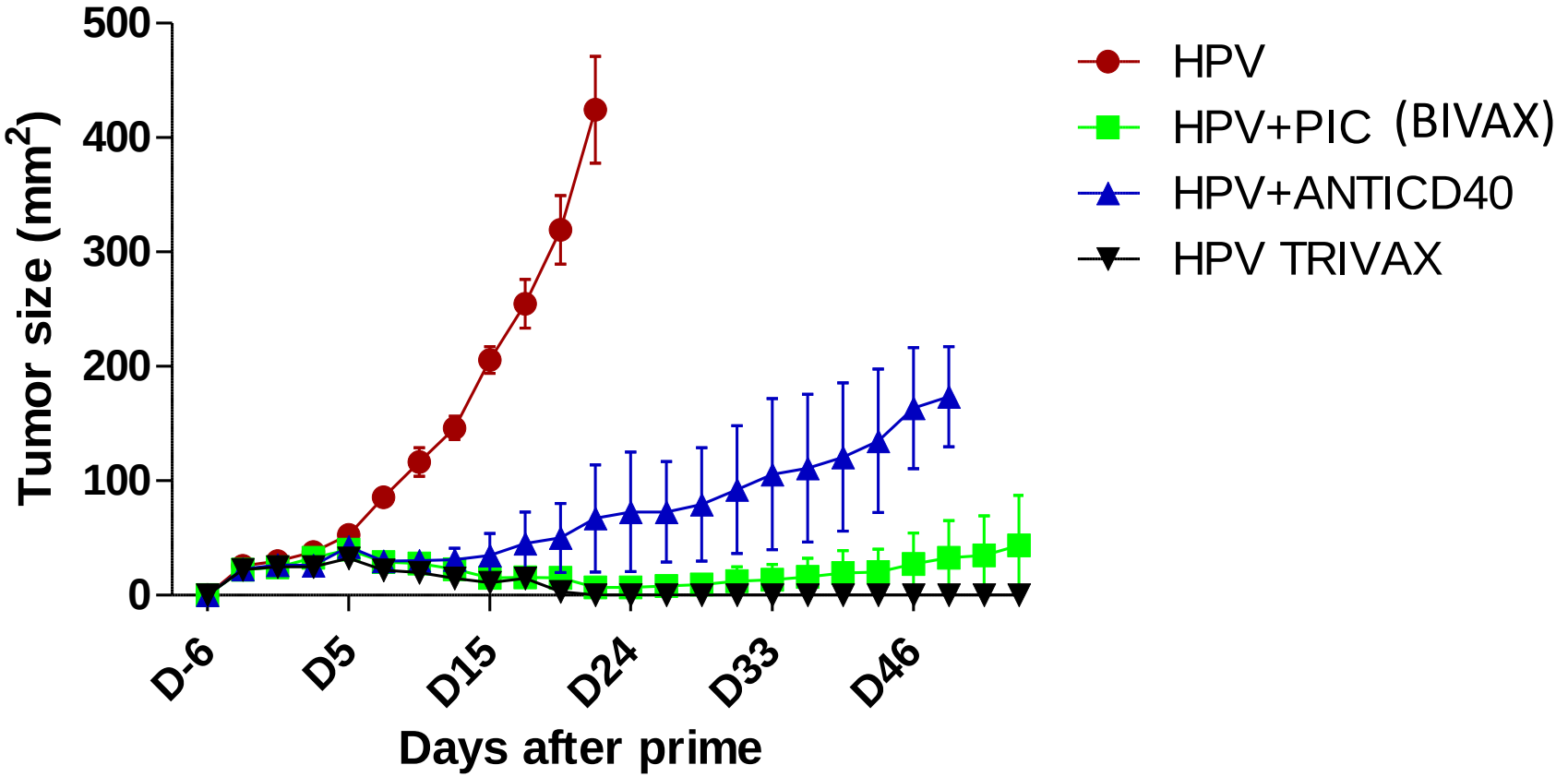
Experiments using HPV16-E7$_{49}$ (RAHYNIVTF) epitope





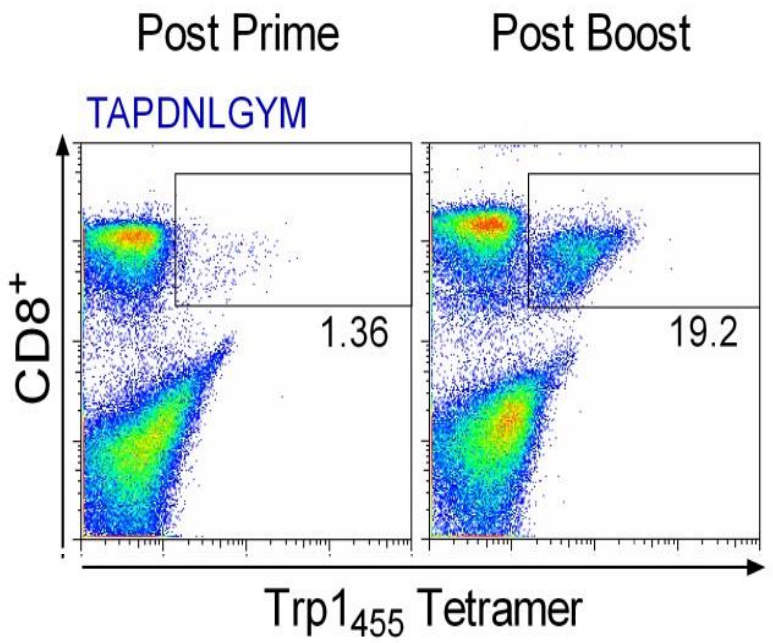


Therapeutic vaccine: anti-tumor efficacy

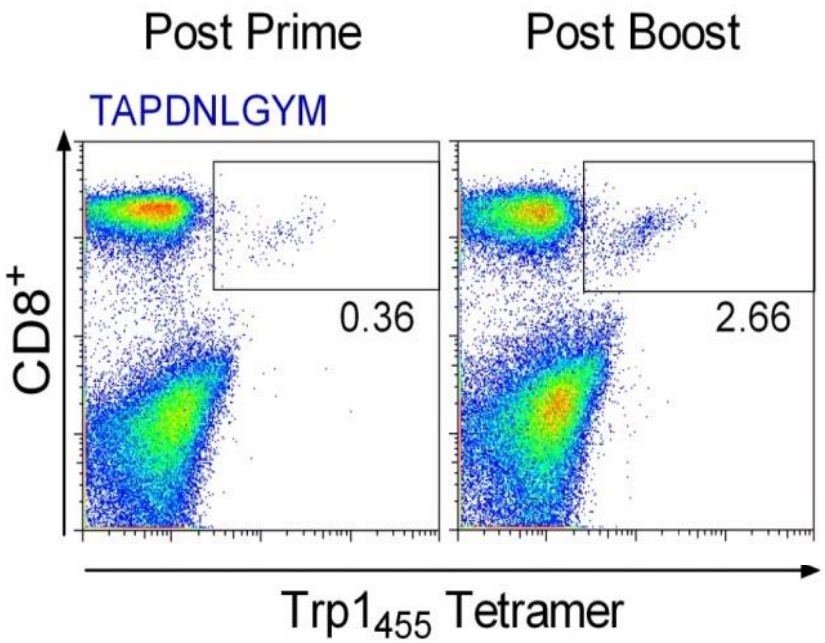


T cell responses to Trp1 melanoma antigen

TriVax



BiVax



Peptide composition affects immunogenicity

Amino Acid Hydrophobicity

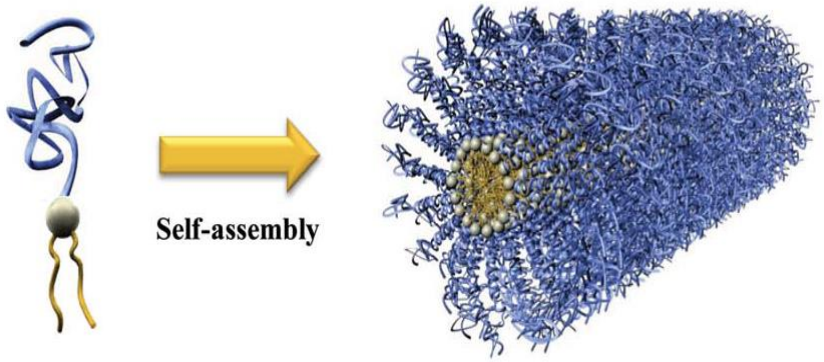
Residue Type	kdHydrophobicity[a]
Ile	4.5
Val	4.2
Leu	3.8
Phe	2.8
Cys	2.5
Met	1.9
Ala	1.8
Gly	-0.4
Thr	-0.7
Ser	-0.8
Trp	-0.9
Tyr	-1.3
Pro	-1.6
His	-3.2
Glu	-3.5
Gln	-3.5
Asp	-3.5
Asn	-3.5
Lys	-3.9
Arg	-4.5

[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.

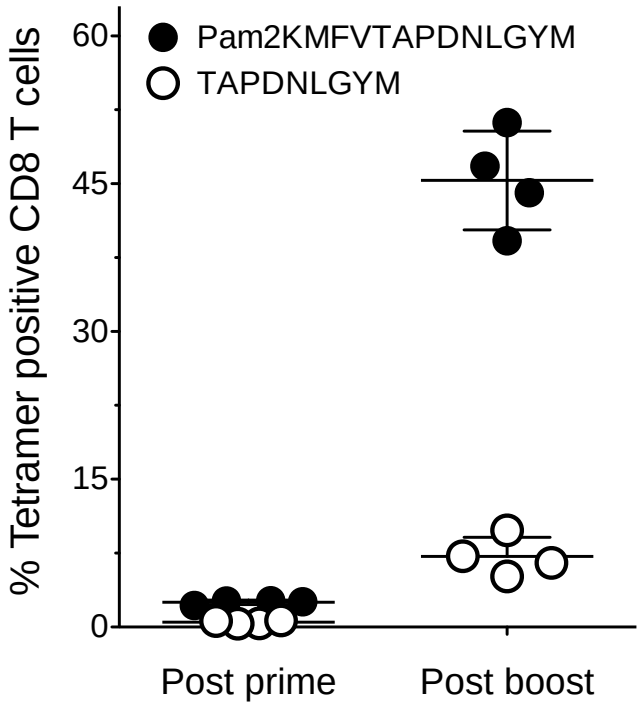
Sequence

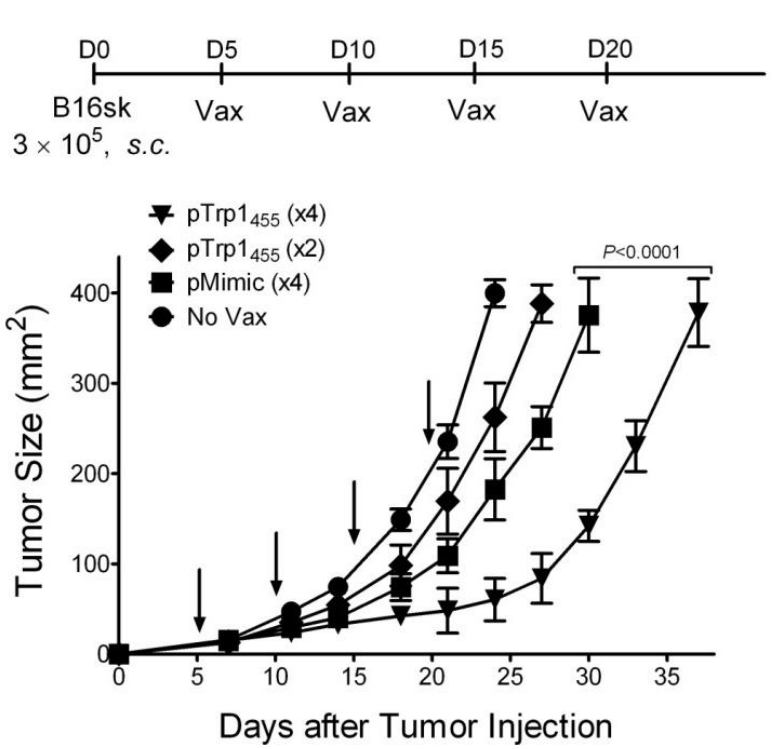
RAHYNIVTF (HPV)

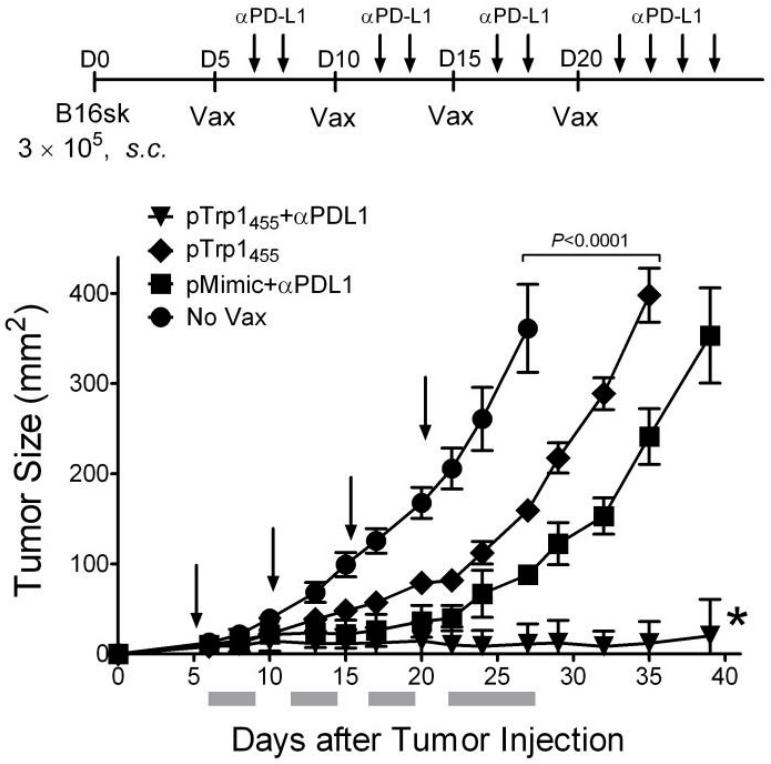
TAPDNLGYM (Trp1)



Enhanced vaccine potency by amphiphilic peptide



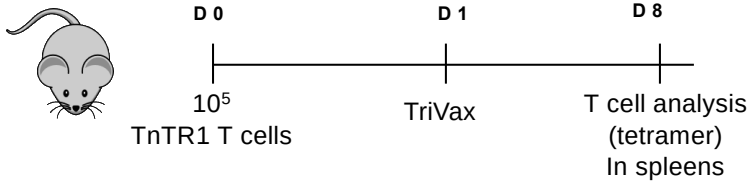


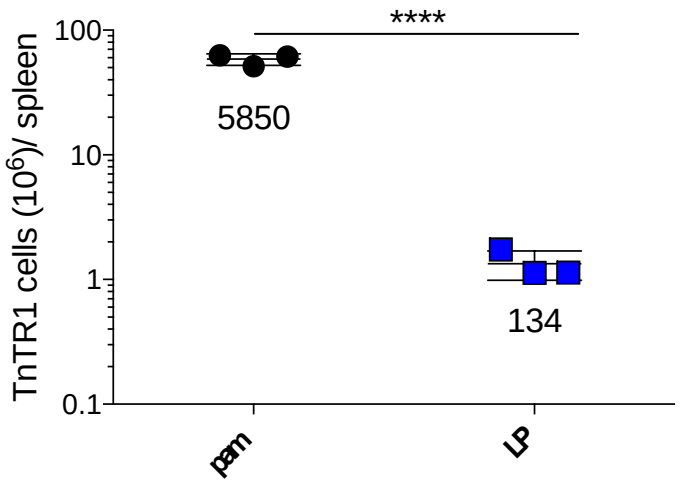


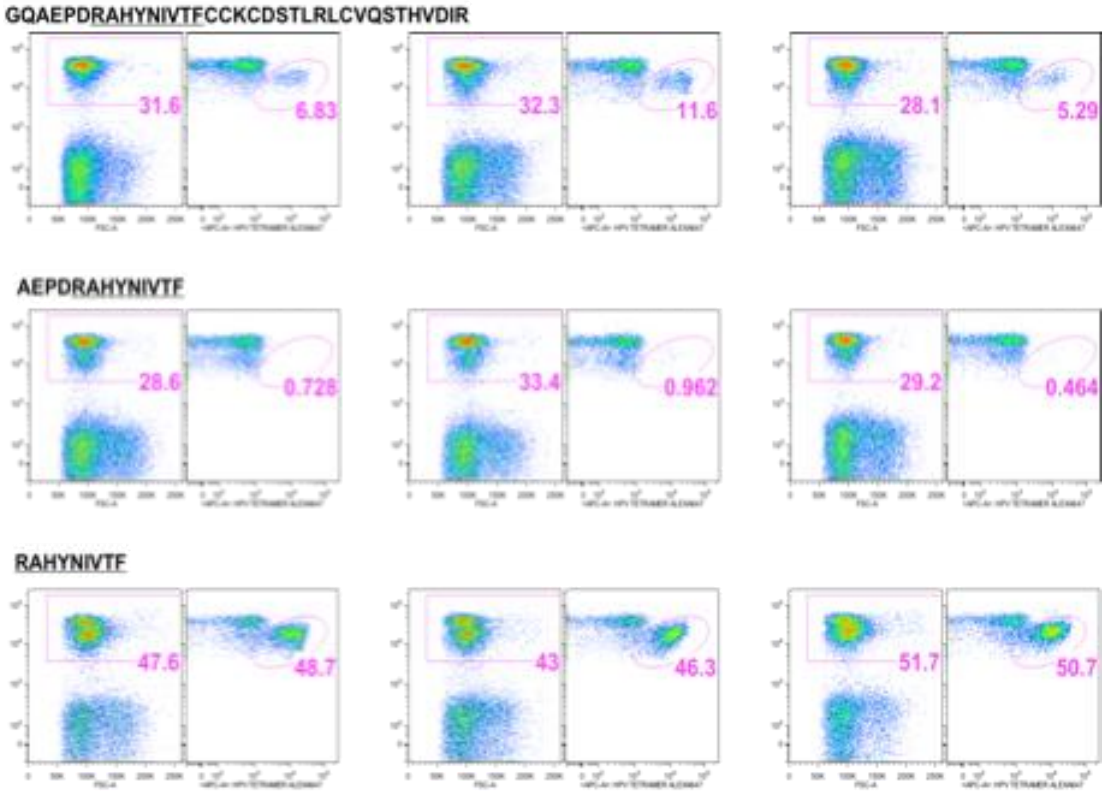
Long peptides Vs. amphi peptides

Antigen:

$(Pam)_2$-Trp1 or Long Trp1 (LP)







Vaccine route of administration

- Traditionally vaccines are injected via the s.c. route, to make antigen accessible to resident DCs, generating responses in draining lymph nodes
- Thus, s.c. vaccines do not disseminate Ag to distal lymphoid organs
- Other less common routes of vaccination:
  - intradermal
  - Intranodal
  - Intramuscular
  - Intravenous
  - intratumoral
- i.m. or i.v. vaccination may recruit more naïve T cells to the response by disseminating Ag throughout the immune system

Effect of vaccine route of administration

Antigen:

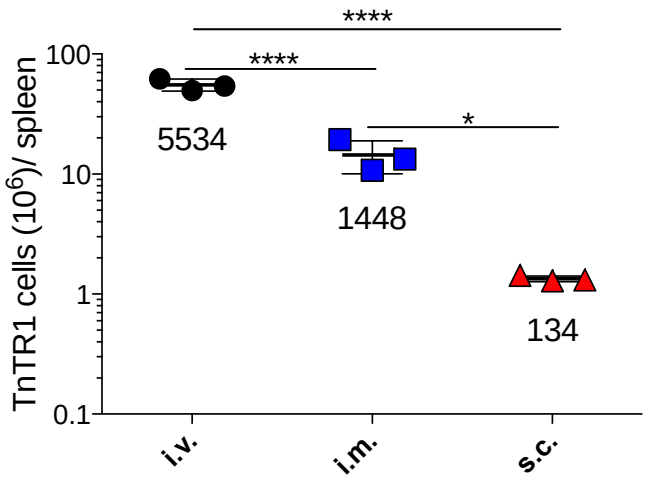
$(Pam)_2$-Trp1

ACT D 0 — Vaccine D 1 — D 8

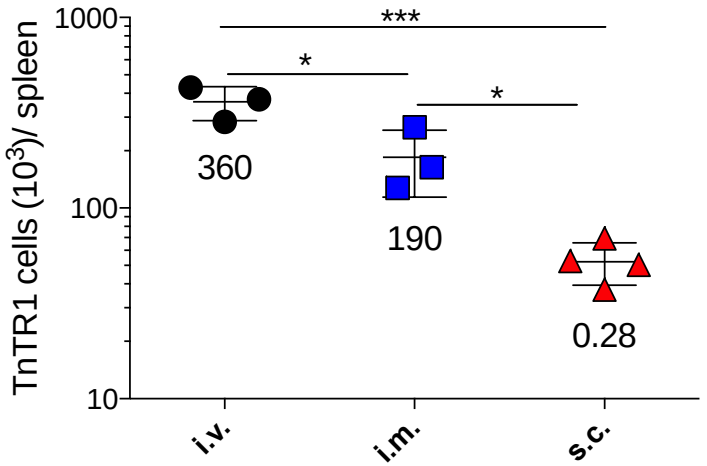
10^5 TnTR1 T cells

T cell analysis (tetramer) In spleens

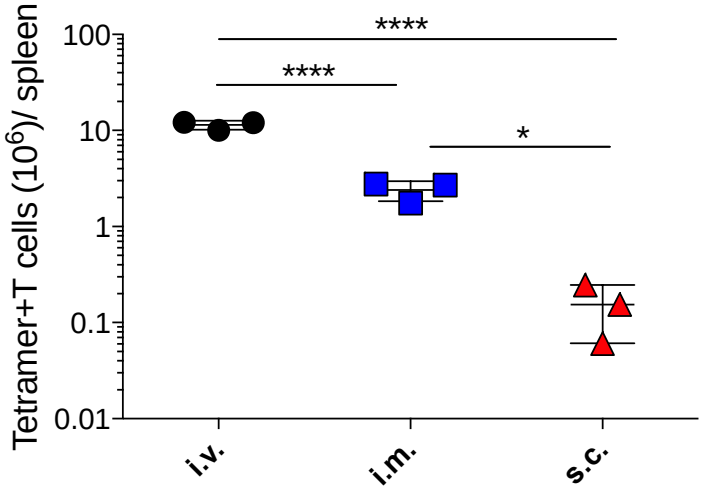
TriVax



BiVax



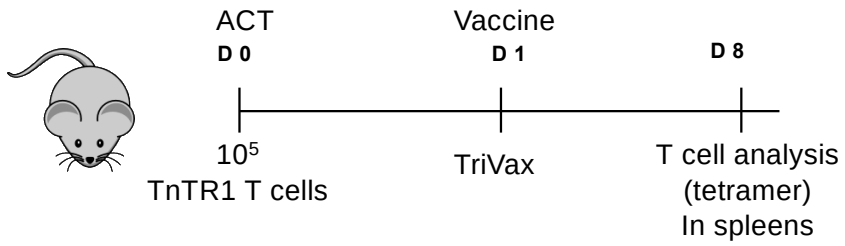
TriVax /No ACT

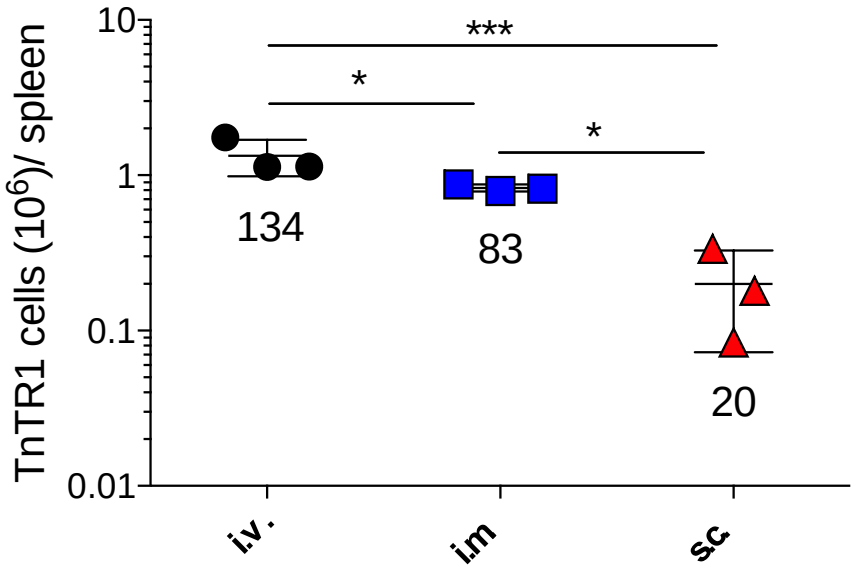


Effect of vaccine route of administration with long peptide

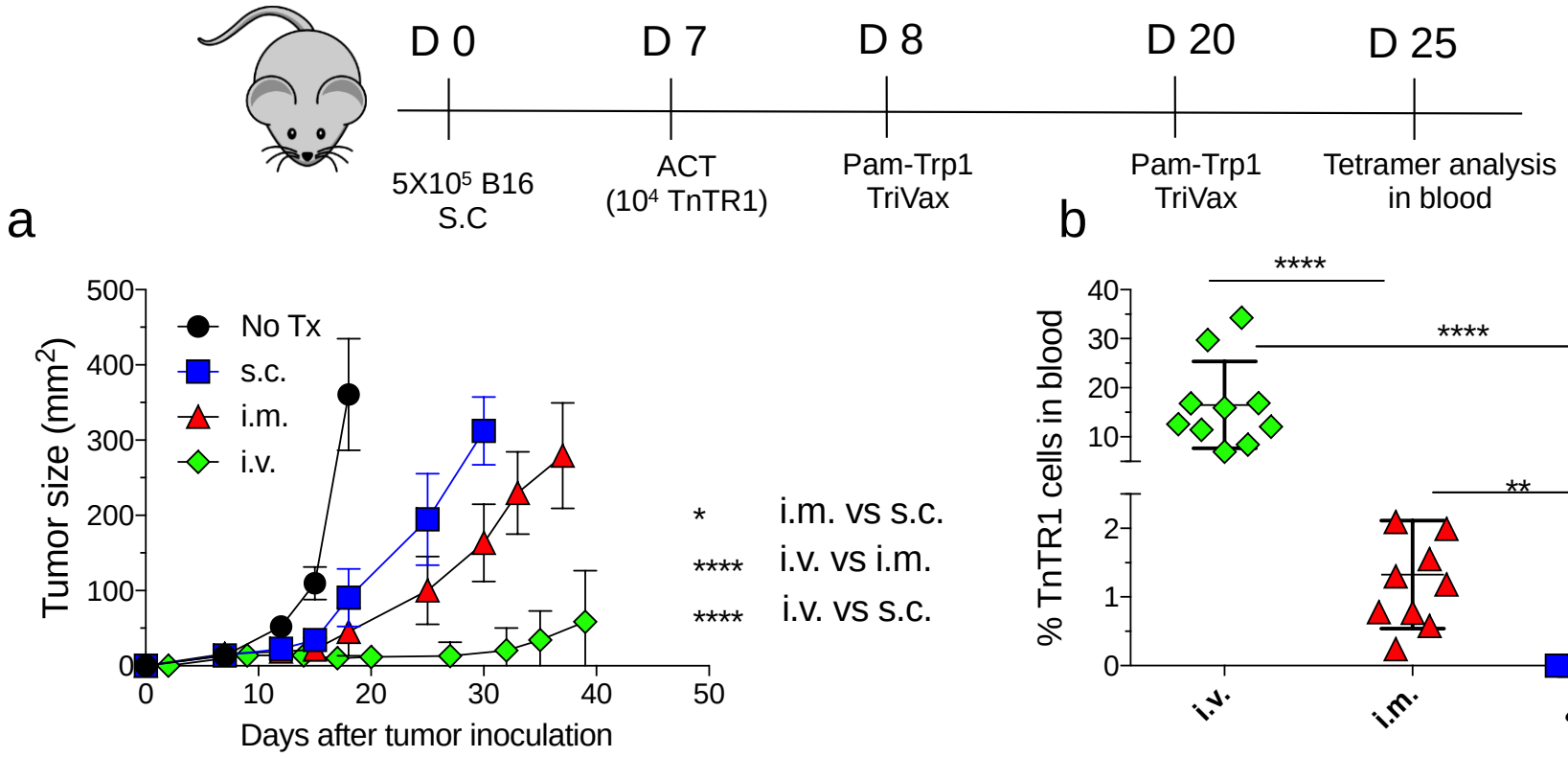
Antigen:

Long Trp1 (LP)





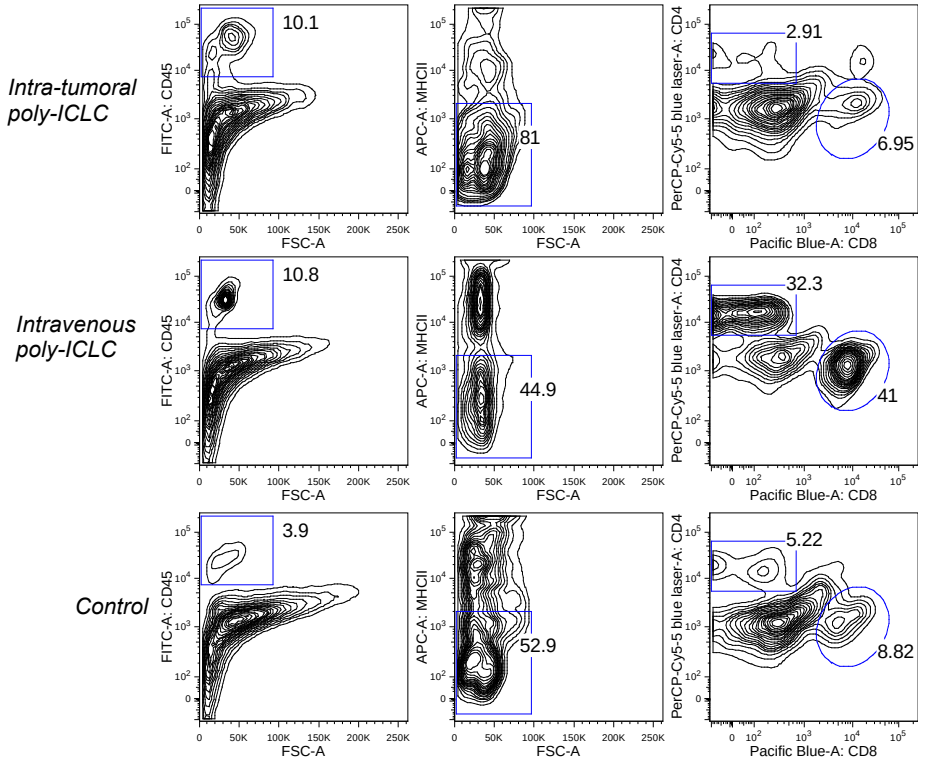
Vaccine route of administration: immunogenicity correlates with antitumor effects

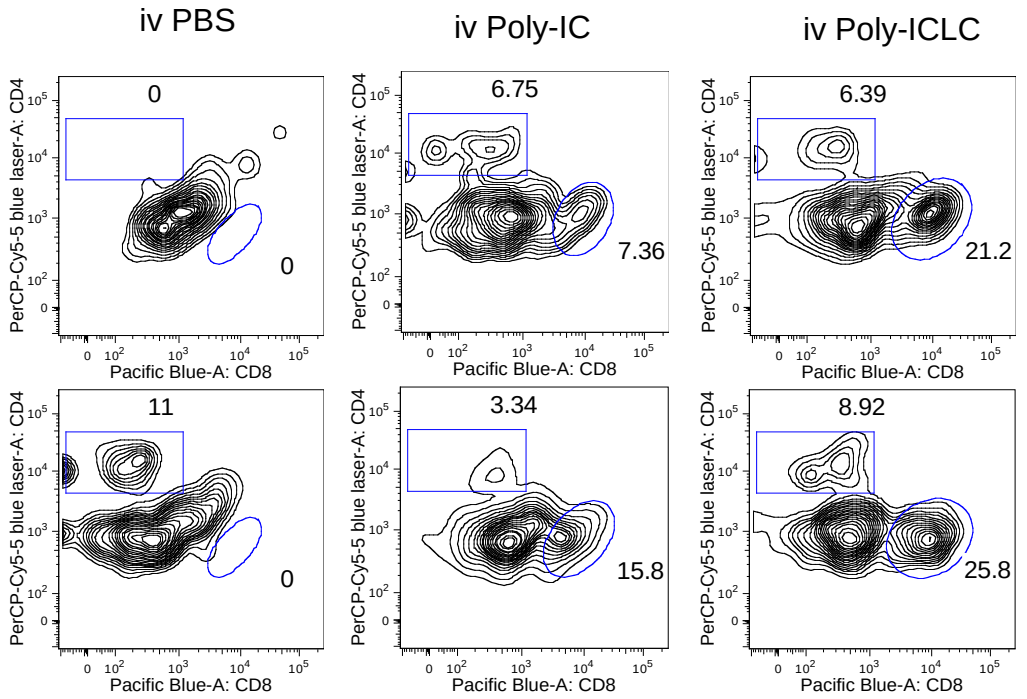


Ways to improve vaccine efficiency

- Costimulatory antibodies (aCD40, aCD27, aCD137/4-1BB, aCD134/OX40)
- Cytokines (IL-2, IL-15, IL-2/anti-IL-2 complexes)
- Checkpoint blockers (aCTLA4, aPD1), ARG IDO inhibitors
- Enhancing T cell infiltration to the tumor parenchyma

Enhancing T cell infiltration to the tumor

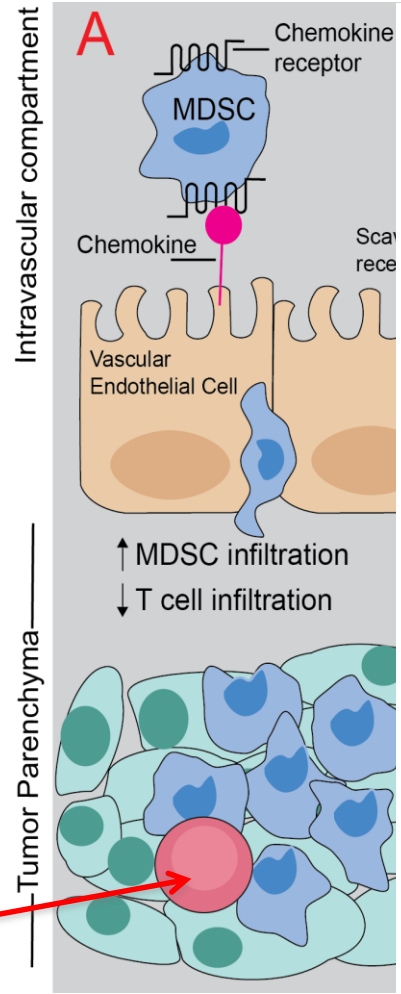




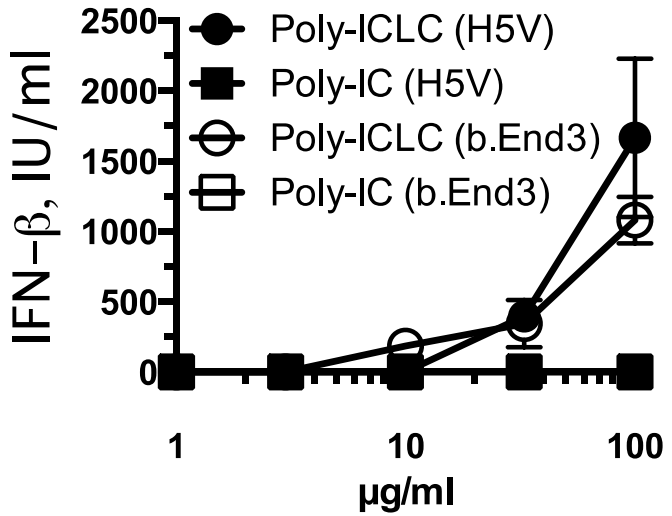
- Mice bearing sc B16 tumors were injected 2X (3 days apart) and tumors were harvested 2 days later and analyzed for CD4 and CD8 T cells
- Effects were absent in MDA5-KO and IFNabR-KO mice (not shown)

Model to explain how iv poly-IC augments tumor T cell infiltration

Cold tumor



Vascular endothelial cell lines make IFN-I when stimulated with Poly-ICLC



- Also chemokines (CXCL10)
- Enhanced VCAM-I expression

Conclusions

- Numerous and very diverse vaccine platforms are available to treat or prevent cancer
- Effective ones must elicit **strong** and durable responses capable of **tumor recognition**
- Both conventional Ag and neoantigen vaccines could be effective if administered sensibly with appropriate adjuvants and costimulation
- Improving T cell tumor infiltration and blocking immunosuppression by the tumor microenvironment will be necessary to achieve antitumor effects

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