

Vaccine sites as sinks and graveyards for tumor-specific T cells

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~~Cancer~~ Center

Making Cancer History[®]

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The following relationships exist related to this presentation:

No Relationships to Disclose

gp100 peptide vaccine + IL-2 has activity in metastatic melanoma

Stage IV and locally advanced stage III melanoma patients

High-dose IL-2 +/- gp100 in IFA

	IL-2+gp100/IFA	IL-2	p-value
Overall response rate	22.1%	9.7%	0.022
Progression free survival	2.9 months	1.6 months	0.010
Median overall survival	17.6 months	12.8 months	0.096

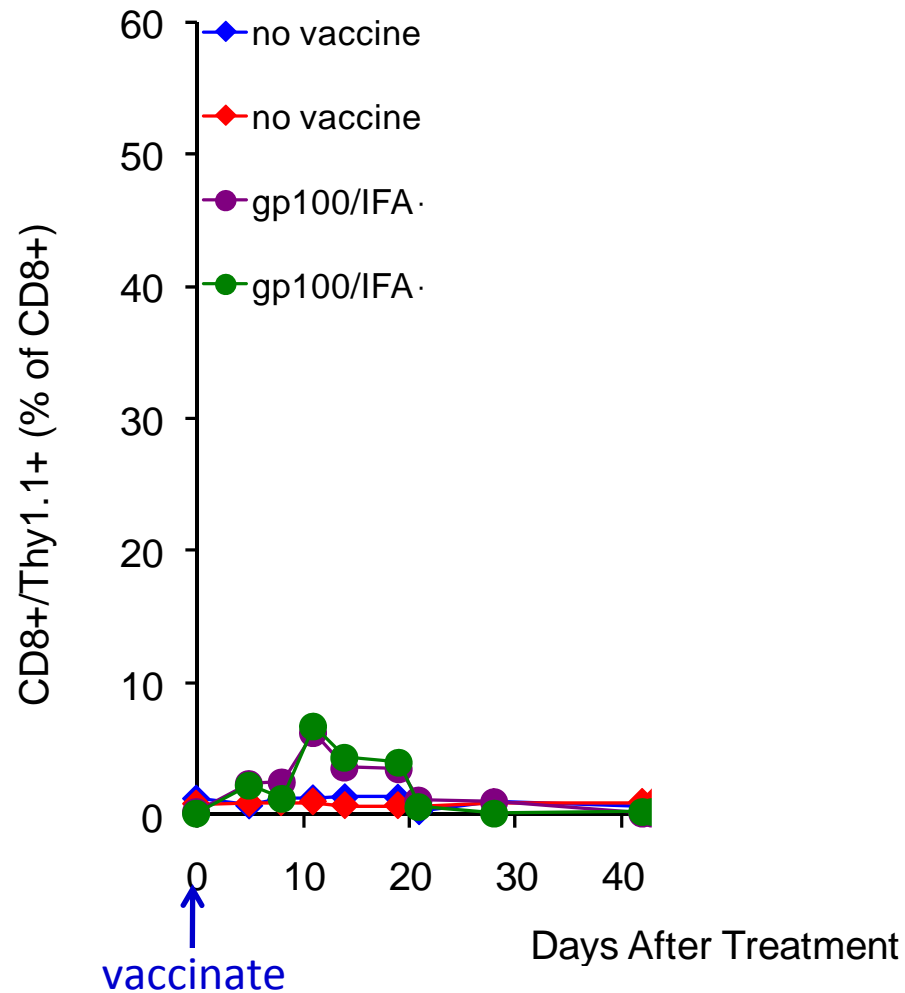
Reports on detrimental properties of vaccination with peptide/IFA

- Aichele *et al.*, JEM 1995: s.c. inj. → Immunity; i.p. inj. → Tolerance
- Toes *et al.*, PNAS 1996: Systemic peptide presentation → Tolerance
- Bijker *et al.*, EJI 2008: Ag presentation by non-prof. APC → Tolerance

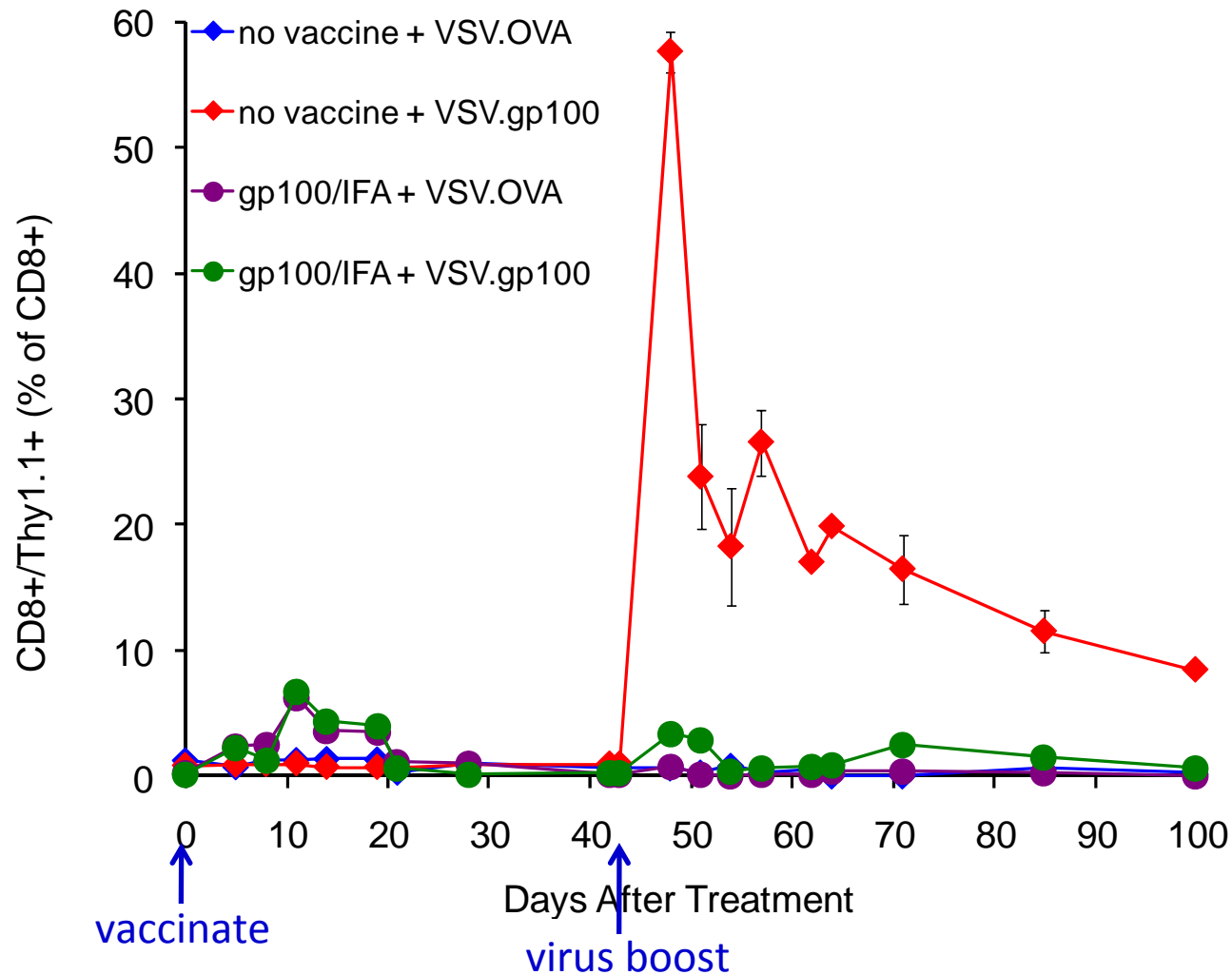
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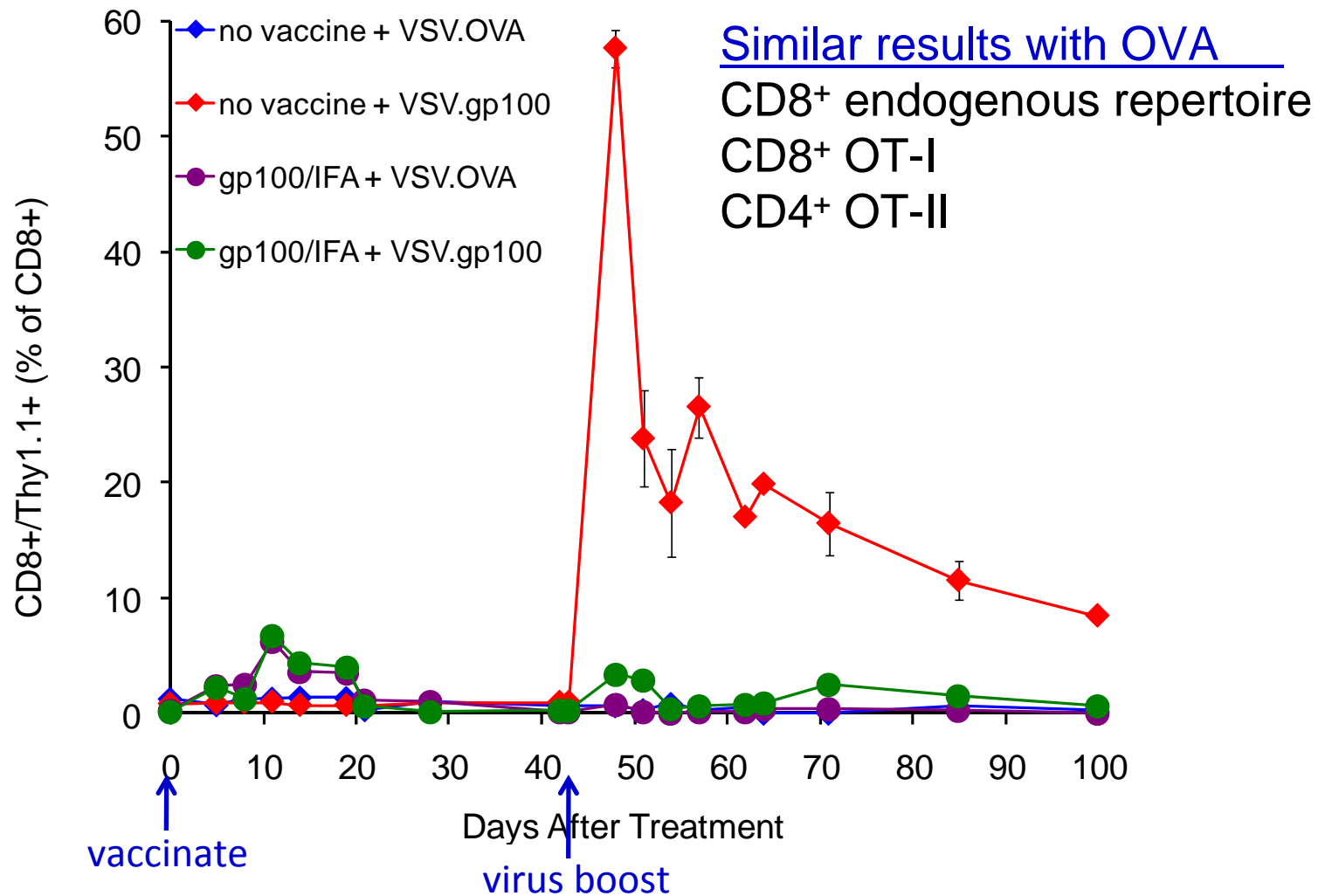
gp100 peptide/IFA primes T cells ...



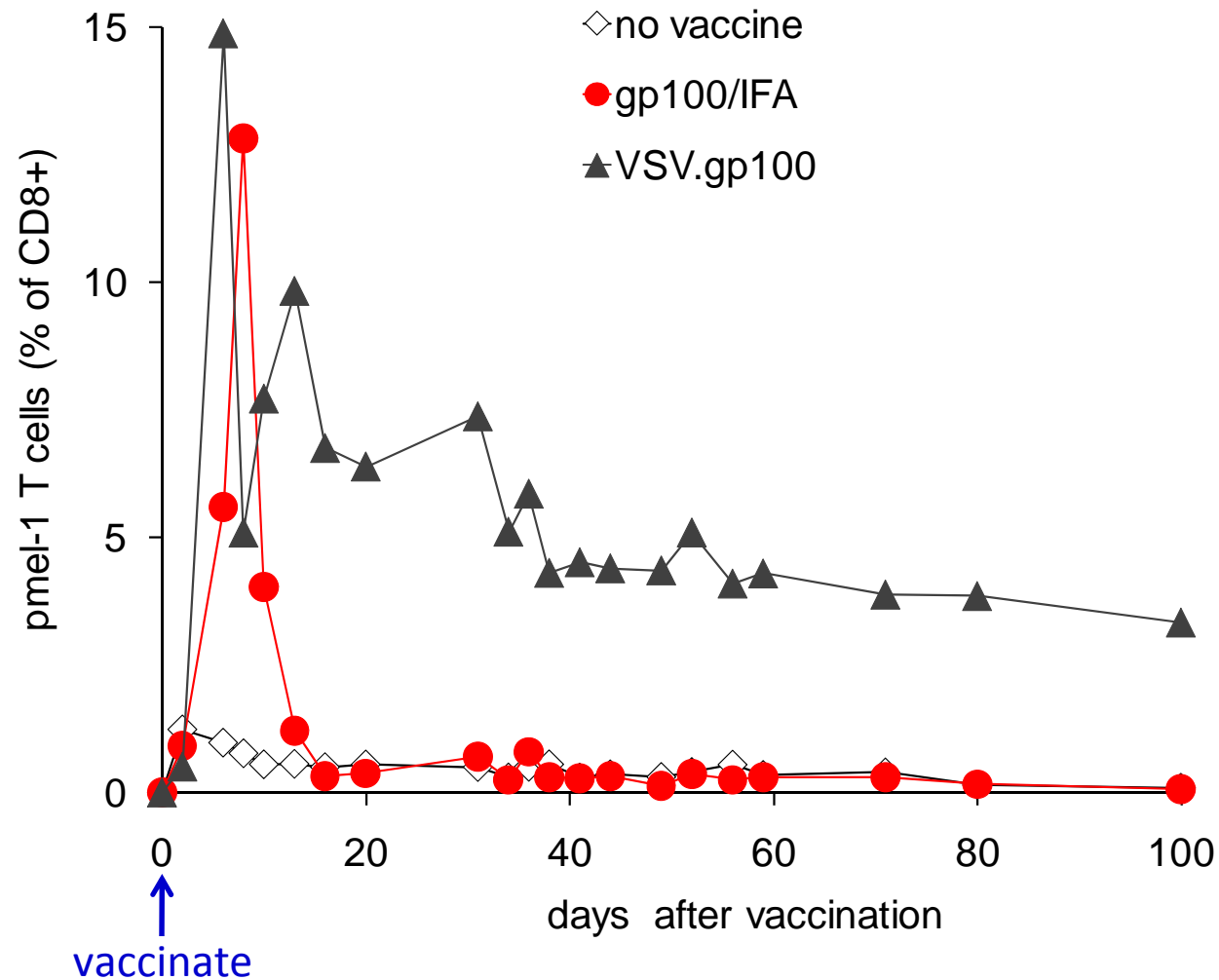
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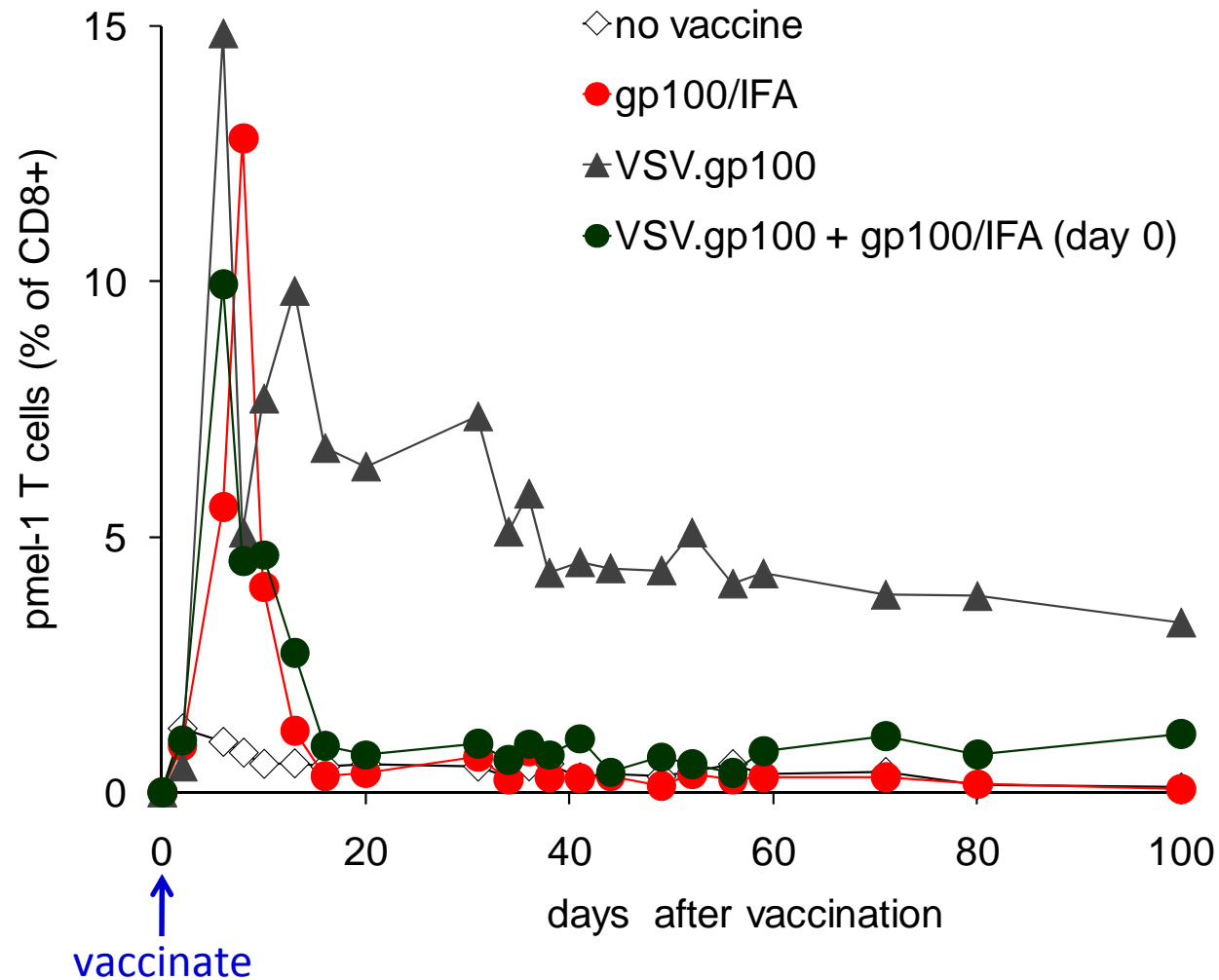
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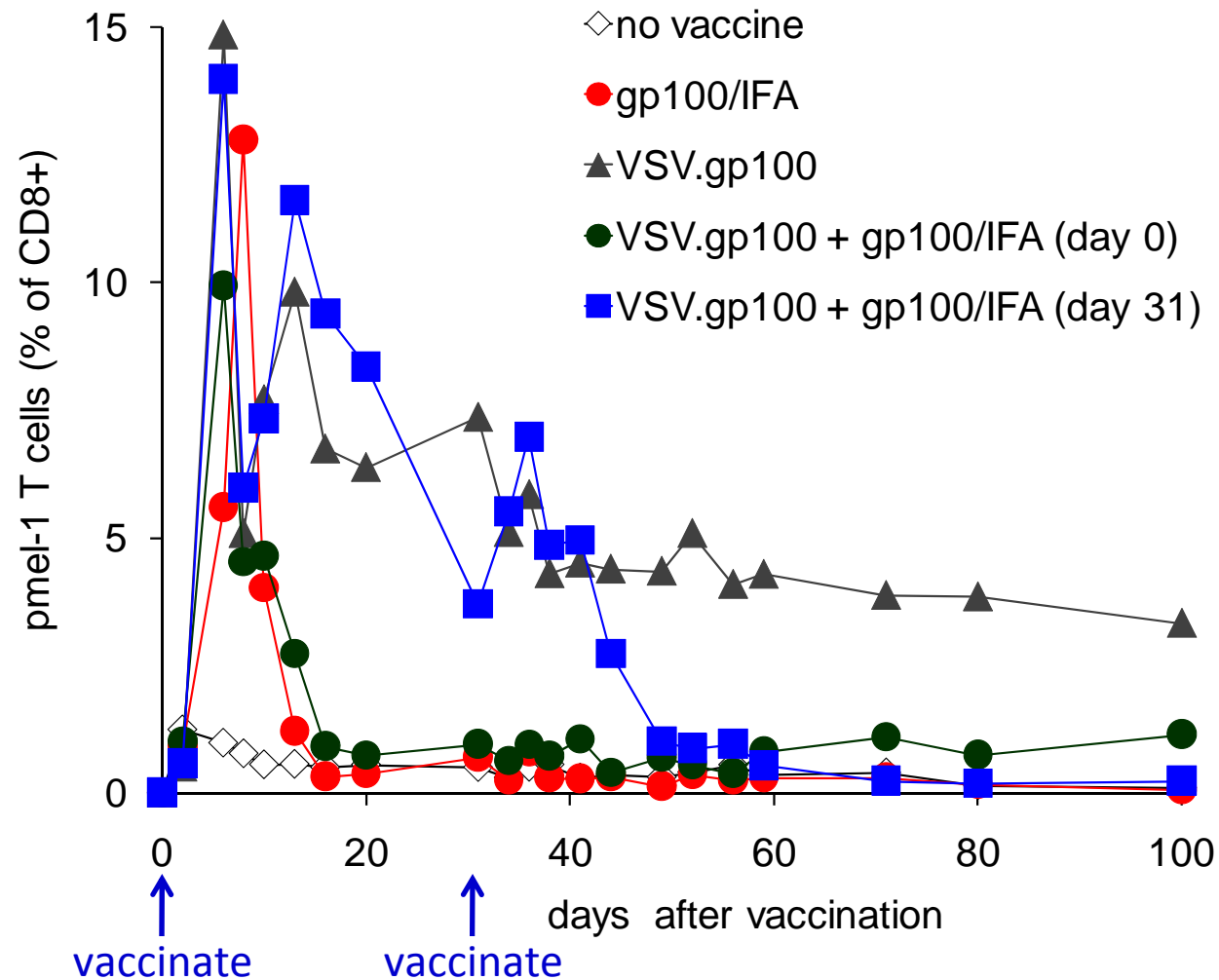
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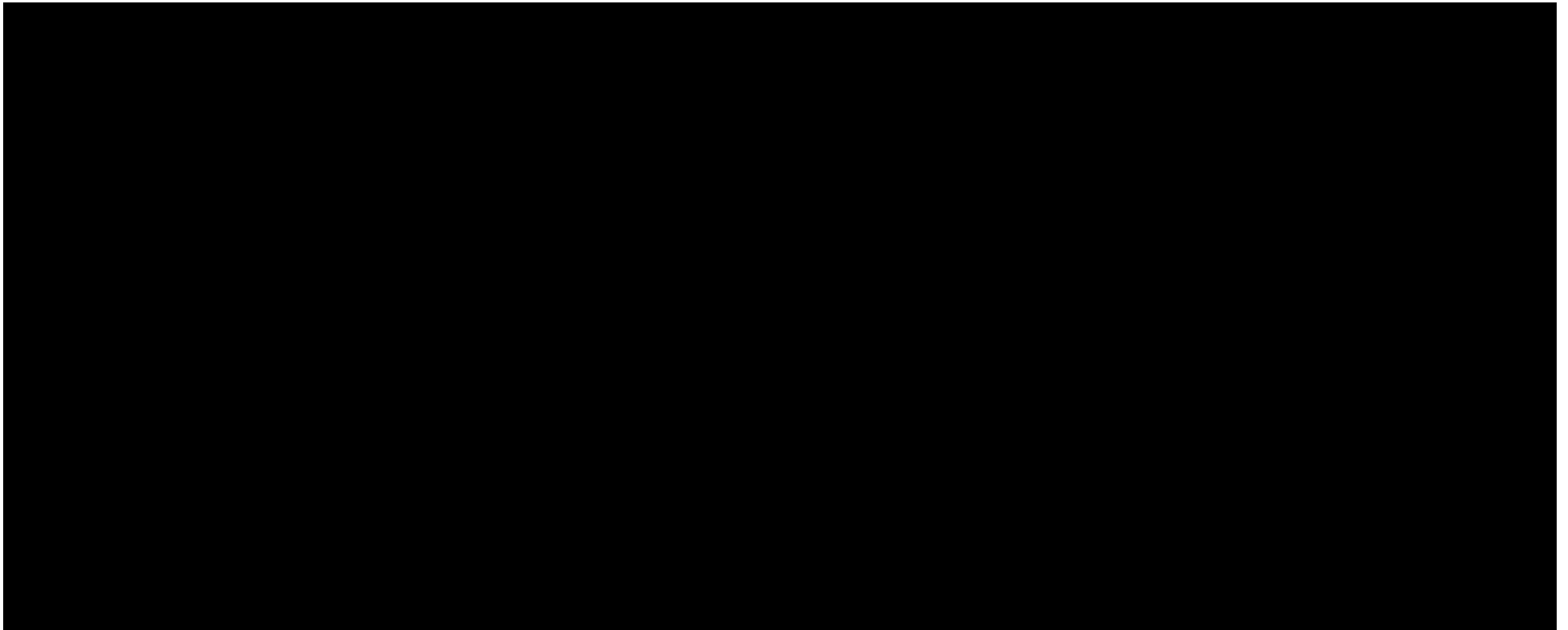
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Where are the T cells?

gp100/IFA s.c. + *eLuc*-transduced pmel-1 T cells i.v.

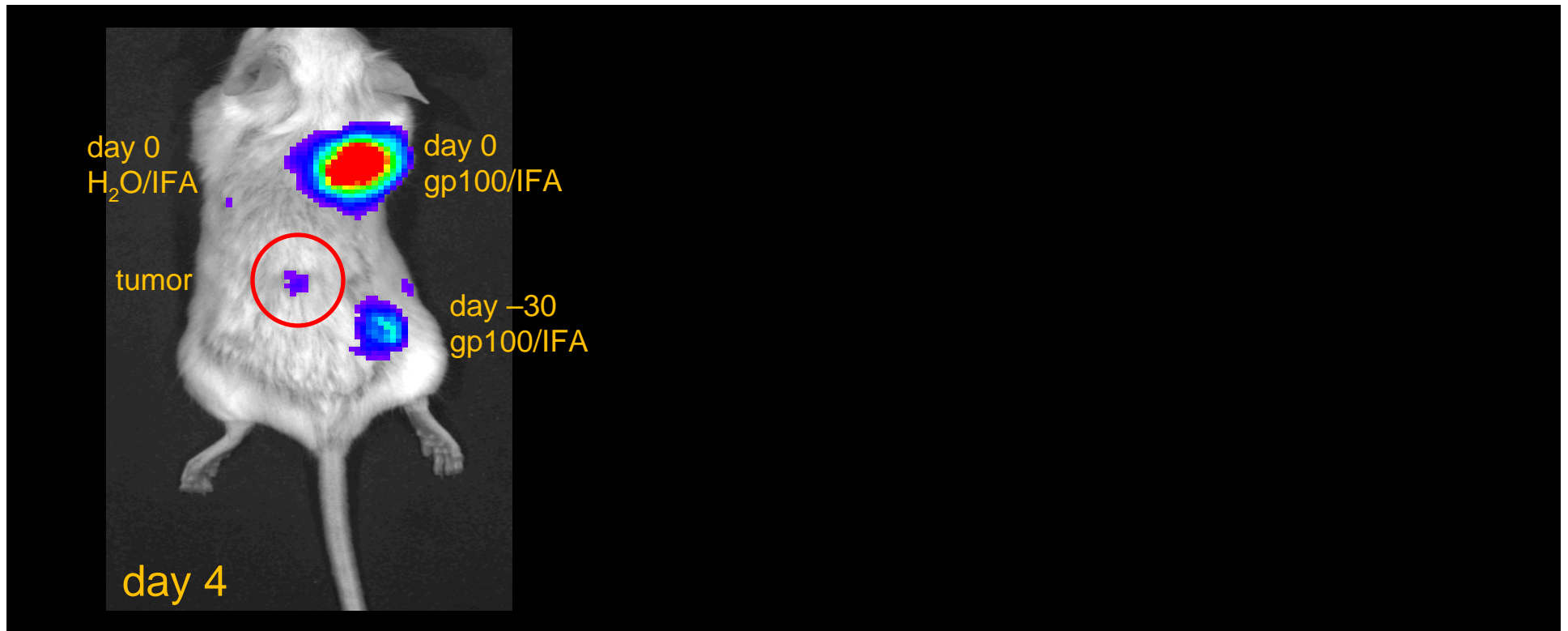
Rabinovich *et al.*, PNAS 2008



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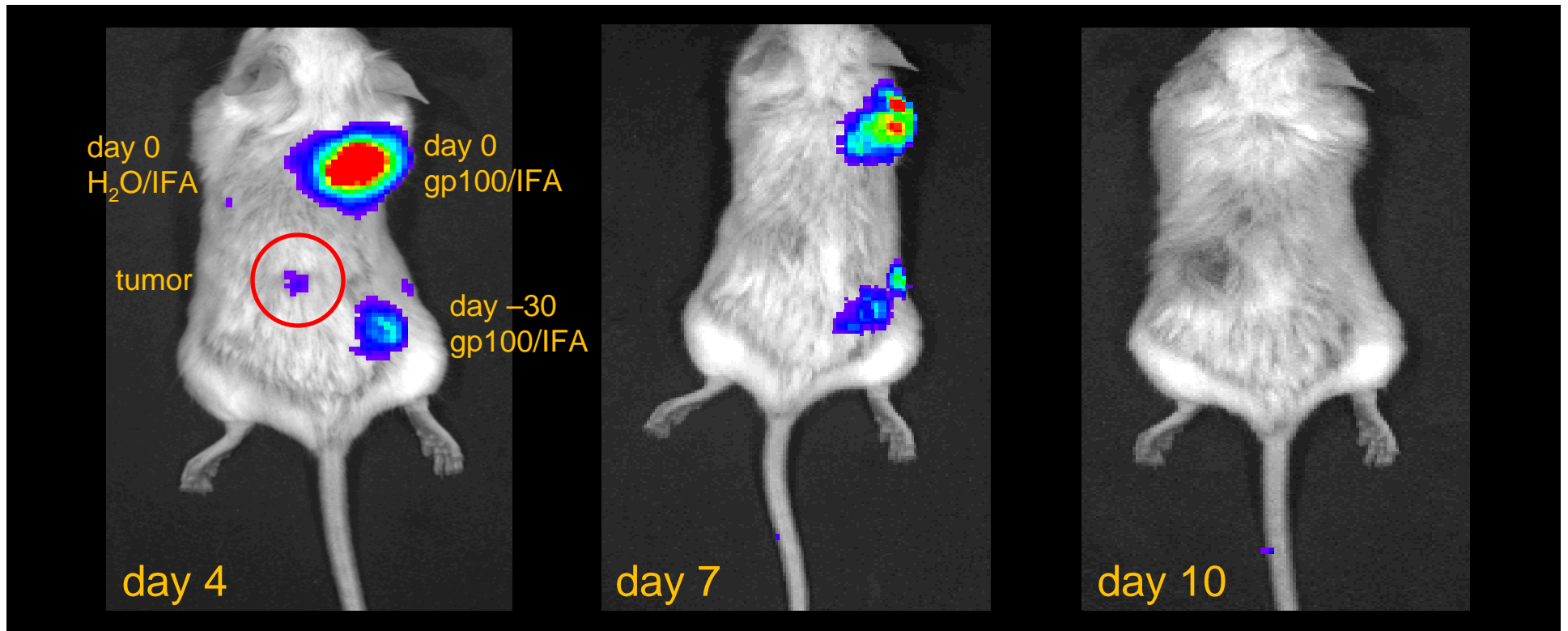
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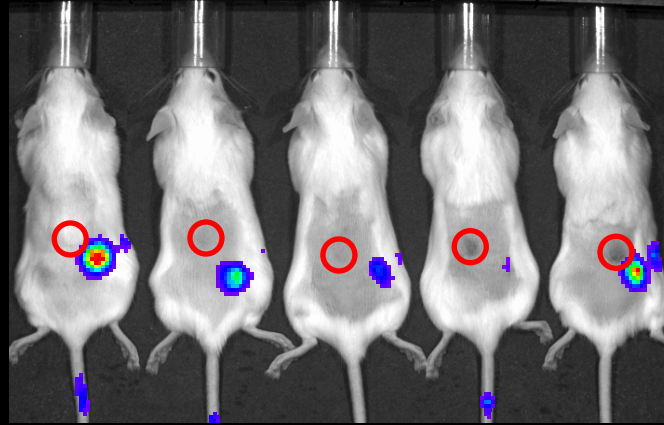
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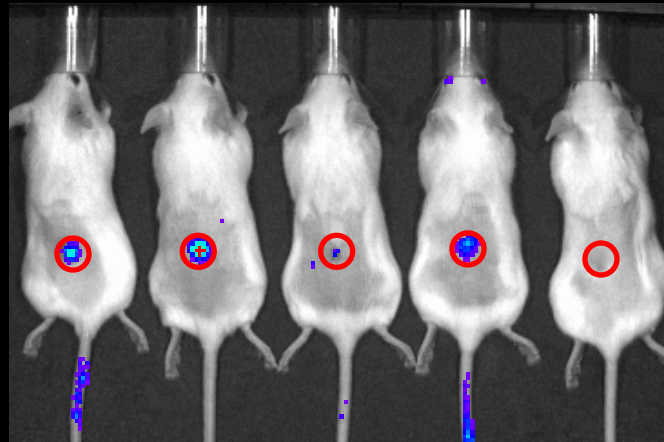
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Vaccinate site is a sink for T cells



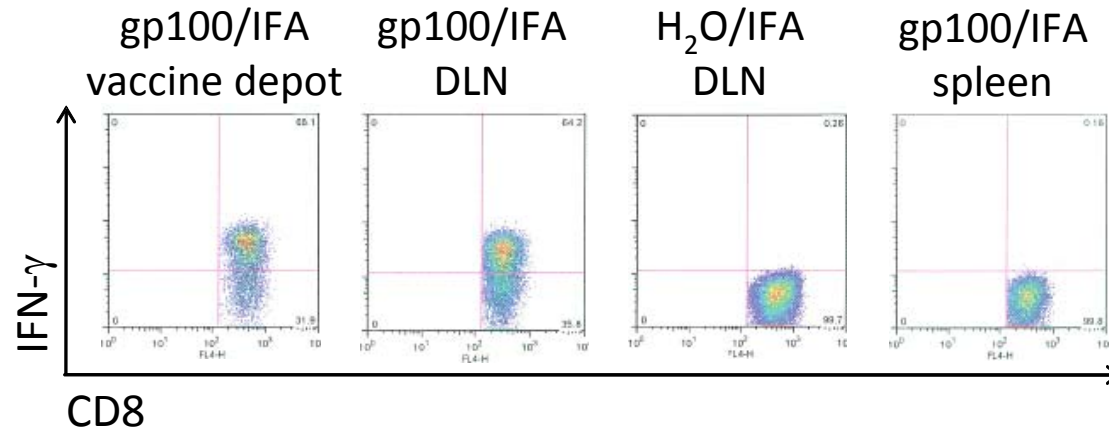
gp100/IFA
+ IL-2



H₂O/IFA
+ IL-2

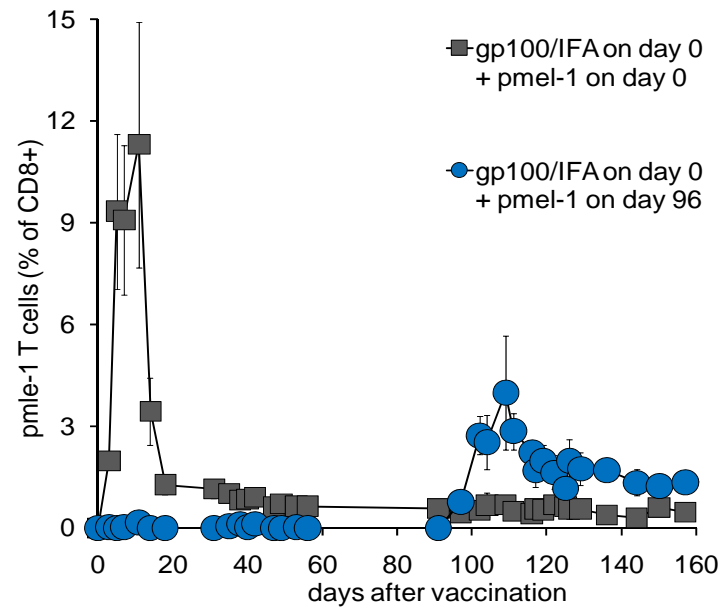
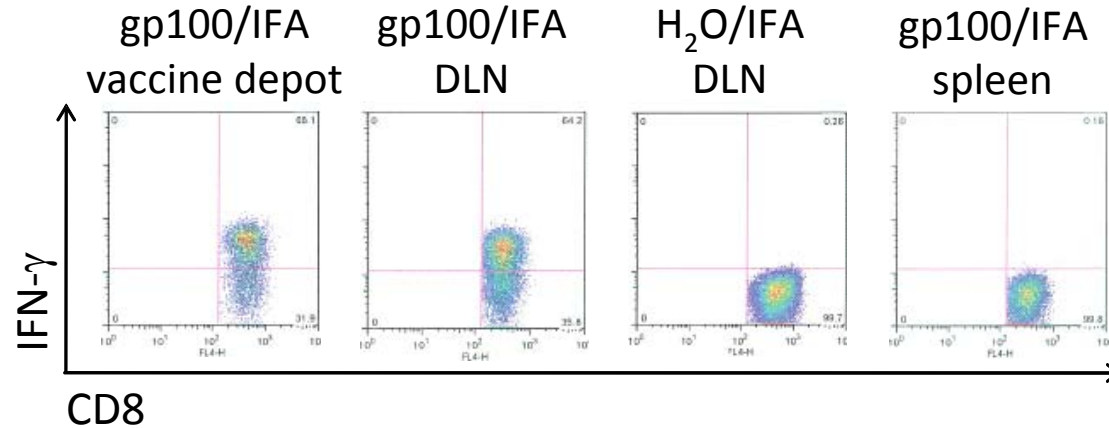
Antigen-rich vaccine depots persist

30 days post
vaccination

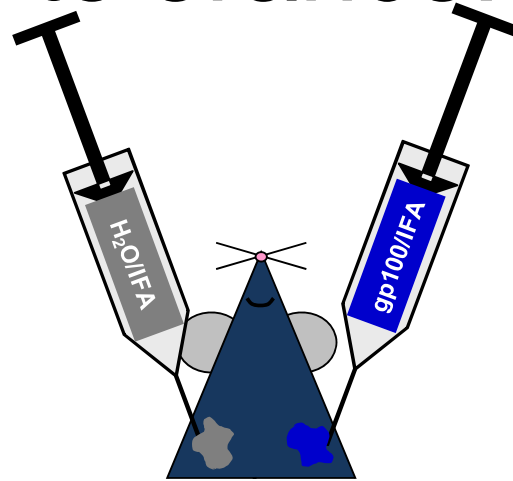


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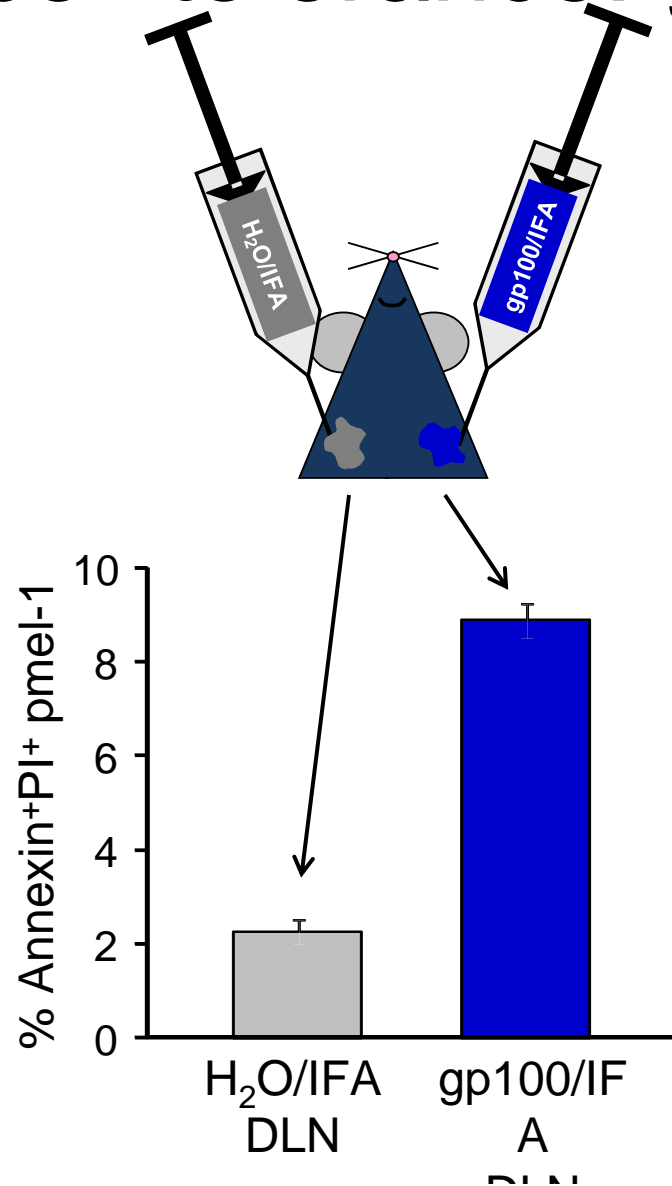
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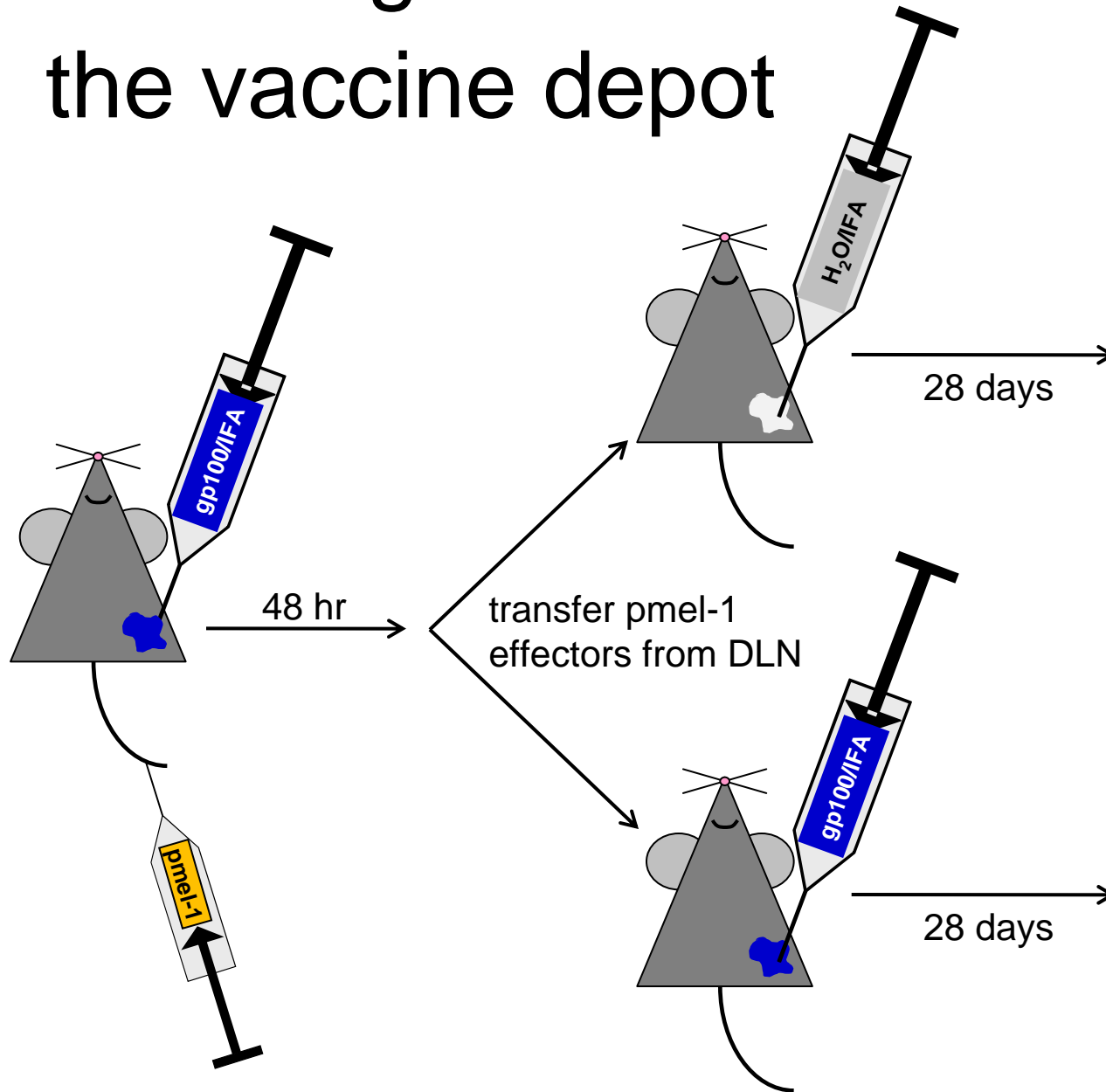
Persistent vaccine induces antigen-driven T cell tolerance: graveyard



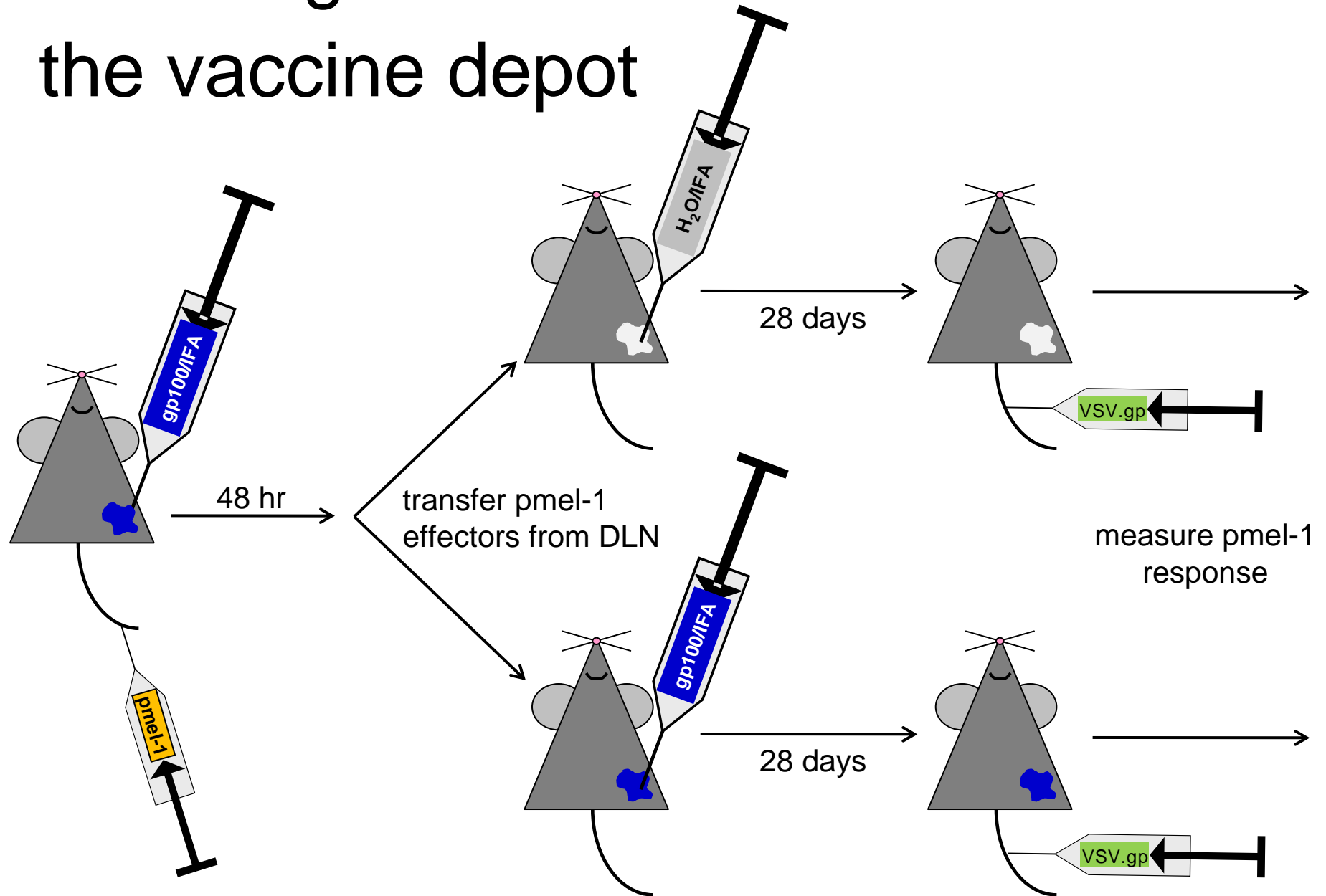
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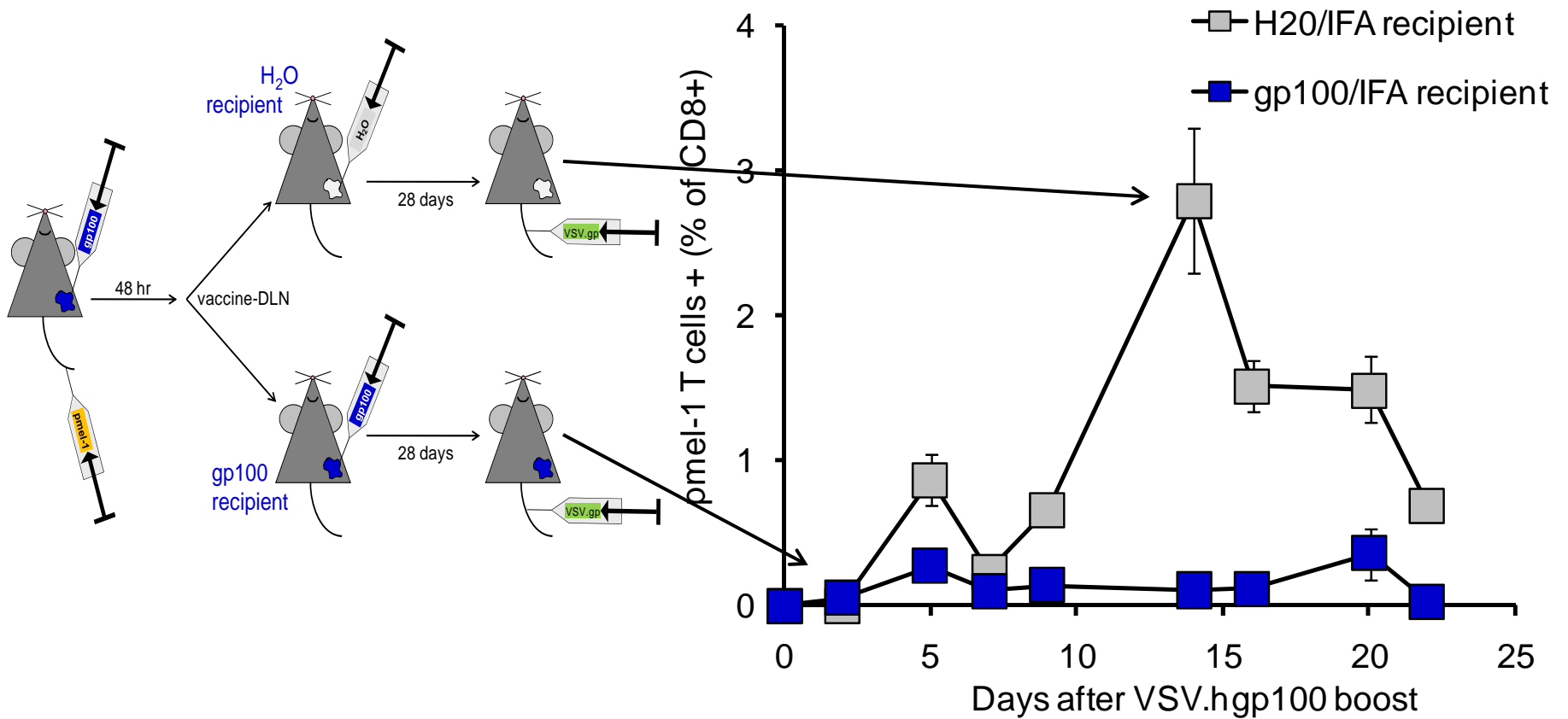
Limiting T cell interaction time with the vaccine depot



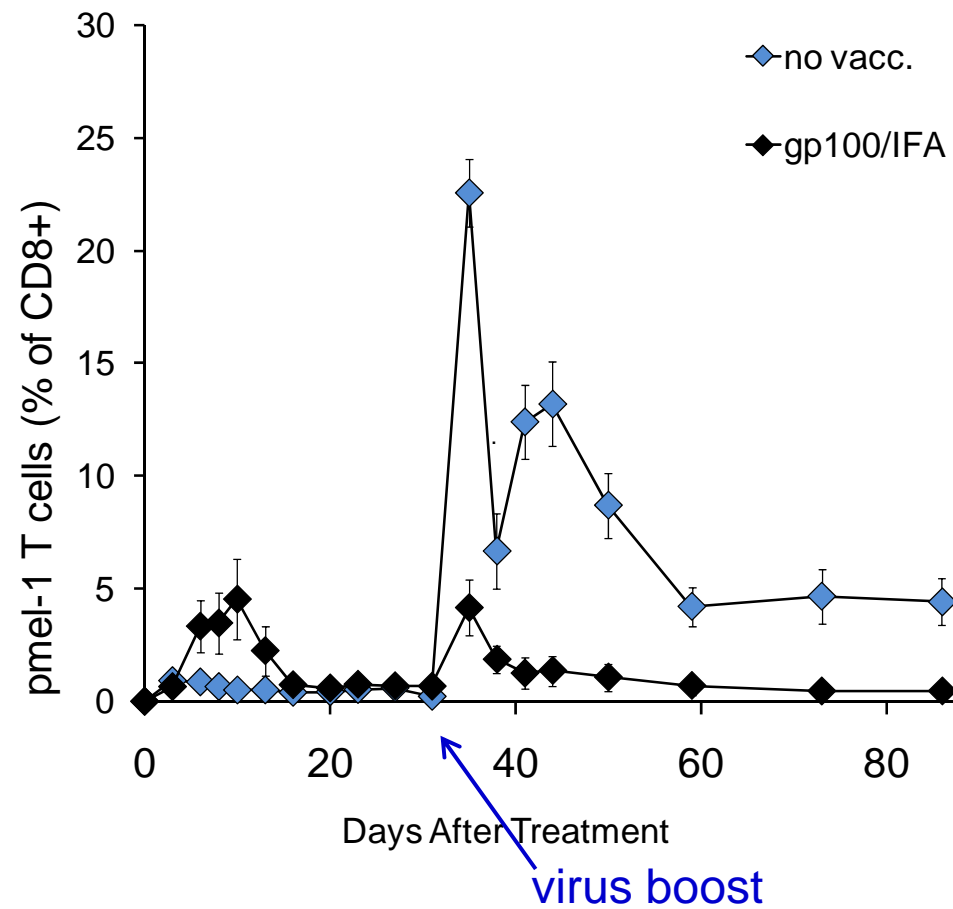
Limiting T cell interaction time with the vaccine depot



Limiting T cell interaction time with the vaccine depot prevents tolerance

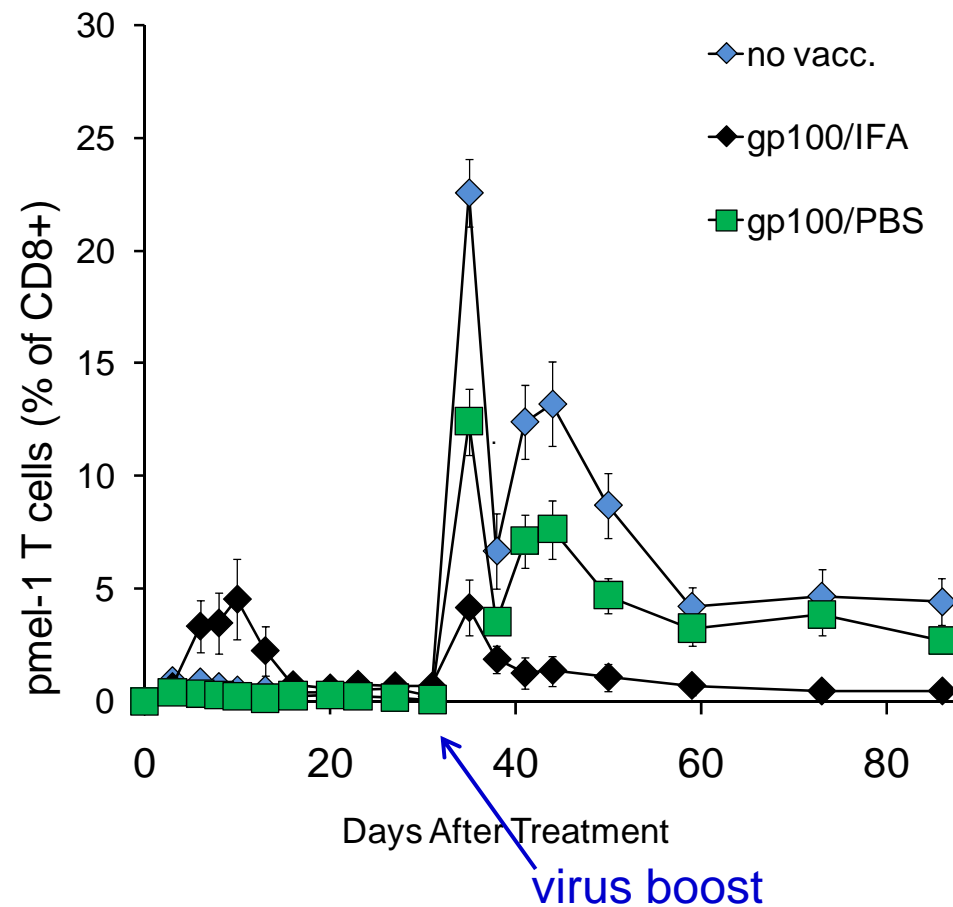


Vaccinating without IFA



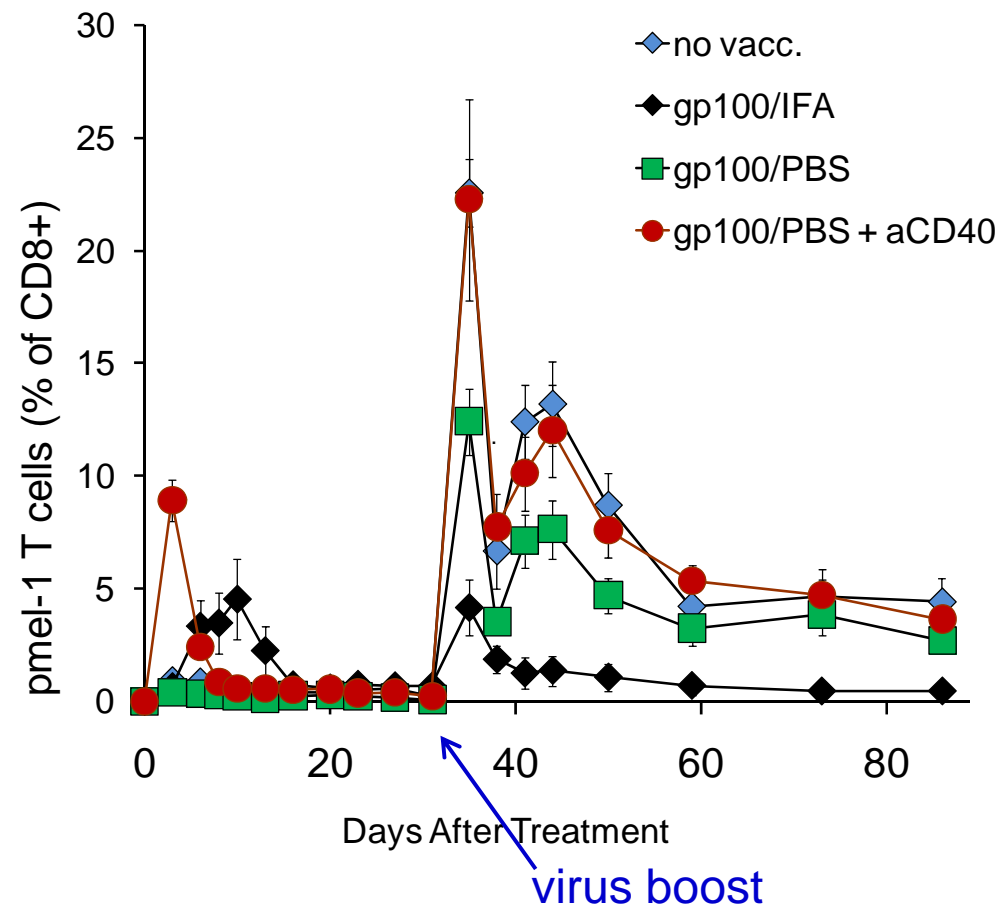
Vaccinating without IFA

No priming, some tolerance



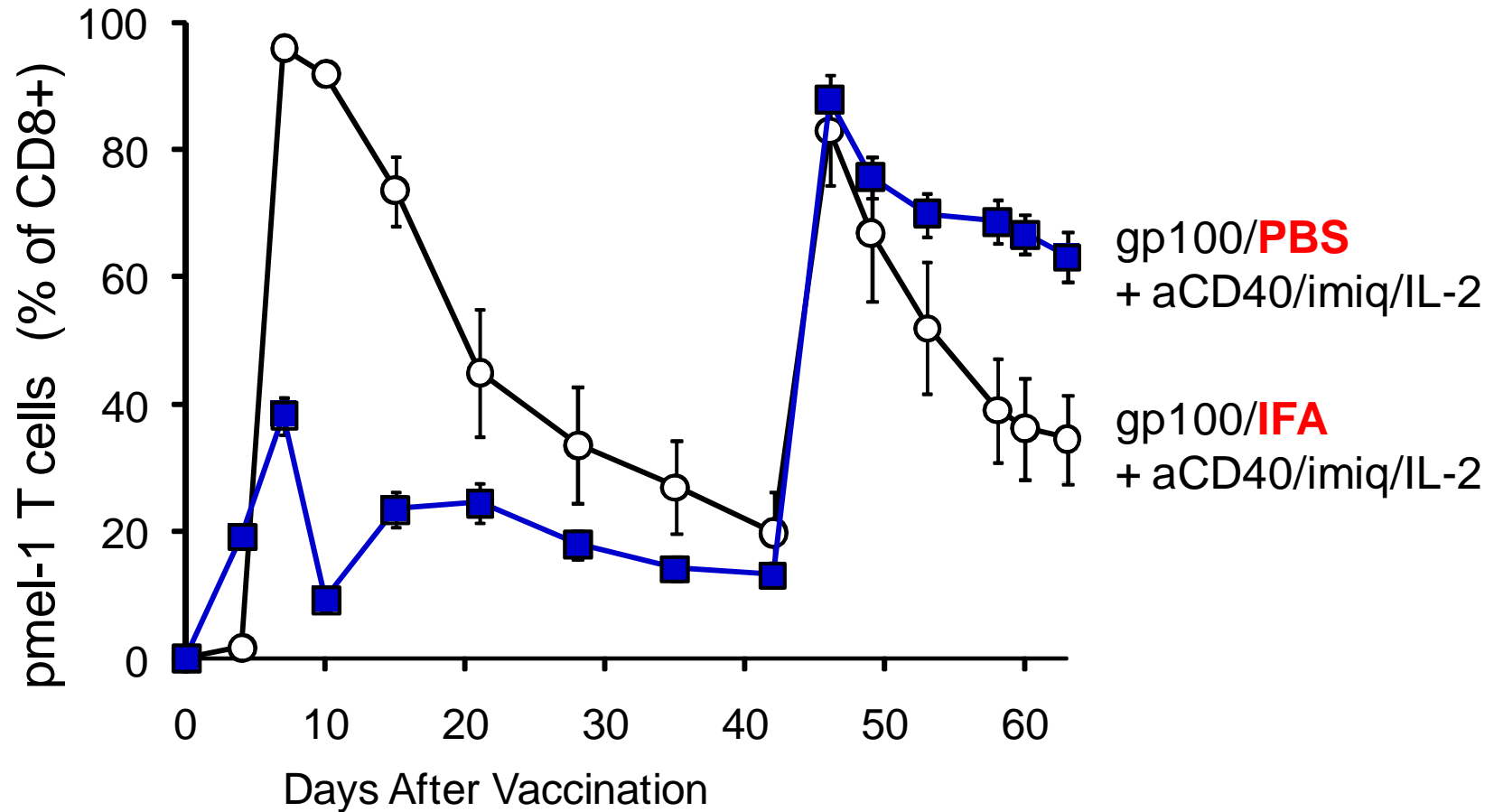
Vaccinating without IFA

Water-based vaccines require an adjuvant

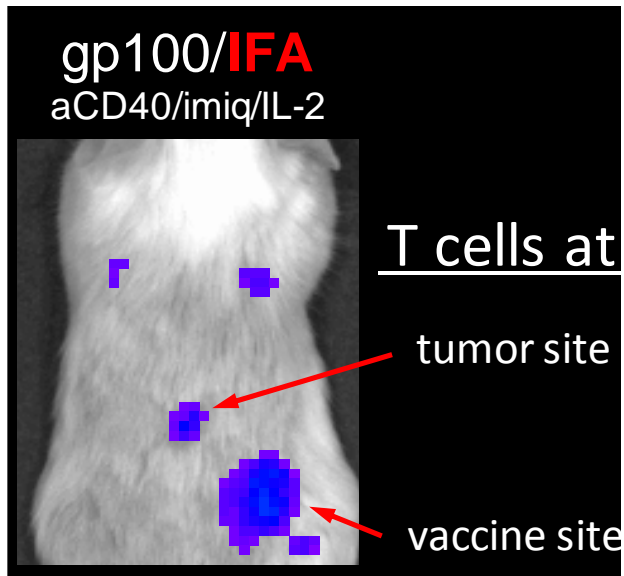


Melief *et al.*
Schoenberger *et al.*
Noelle *et al.*
Kedl *et al.*
and many others

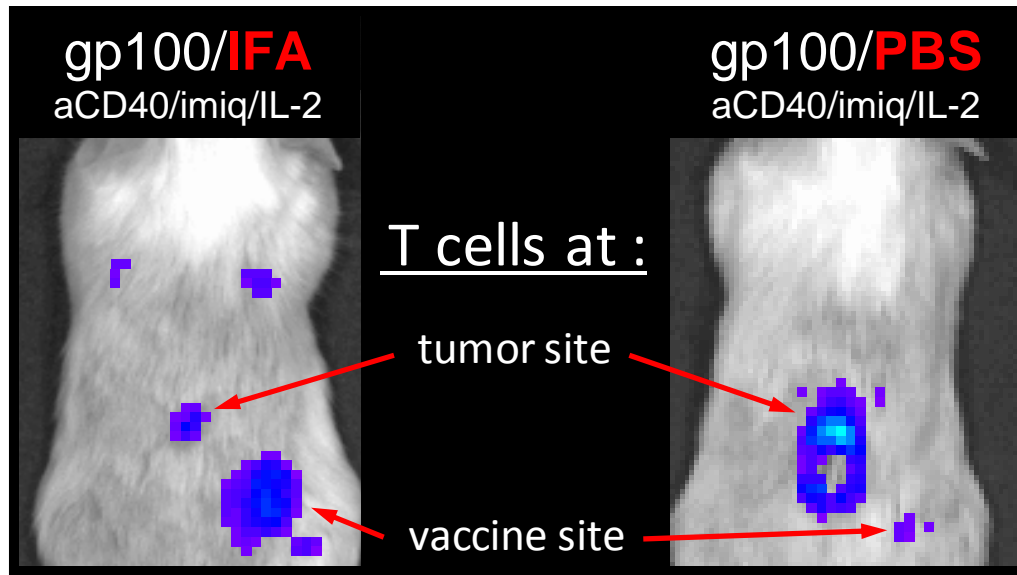
aCD40/imiq/IL-2 combo overcomes tolerance



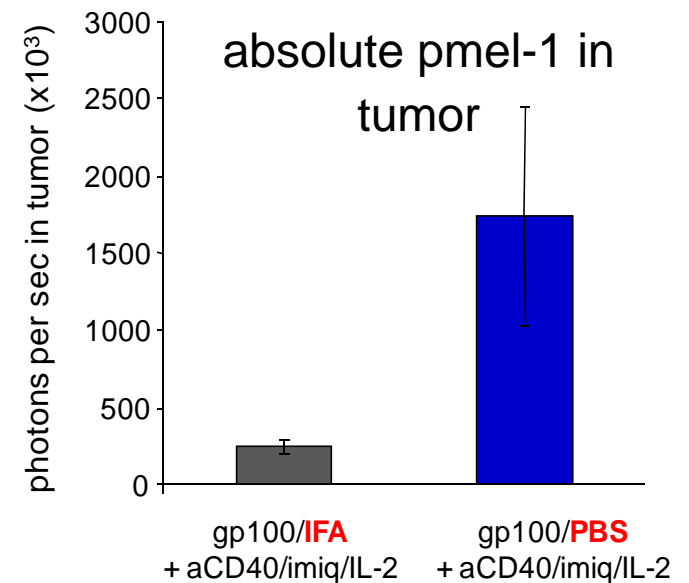
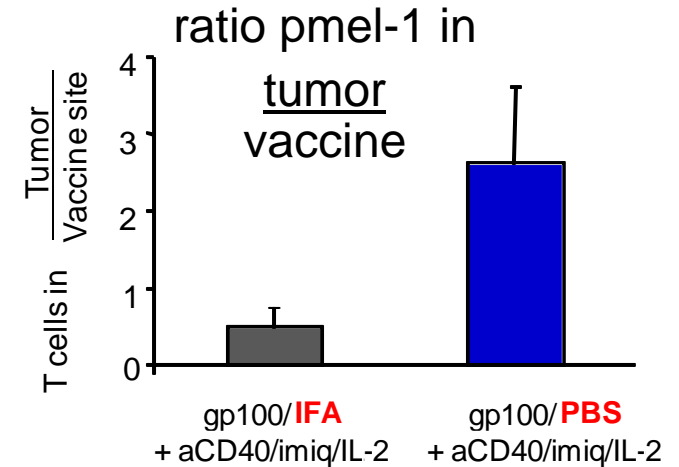
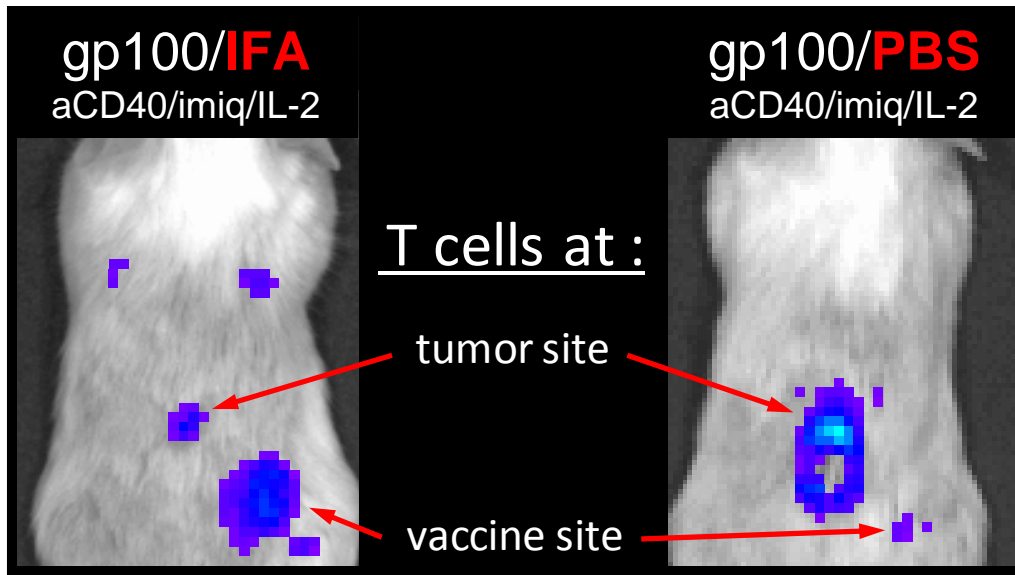
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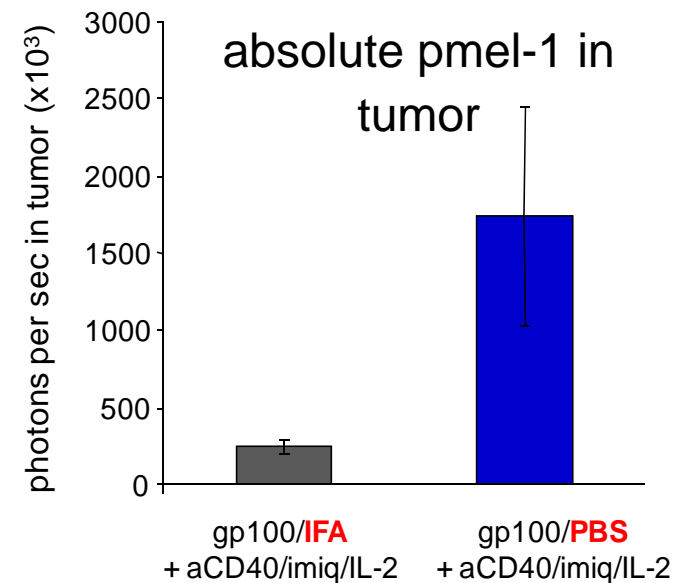
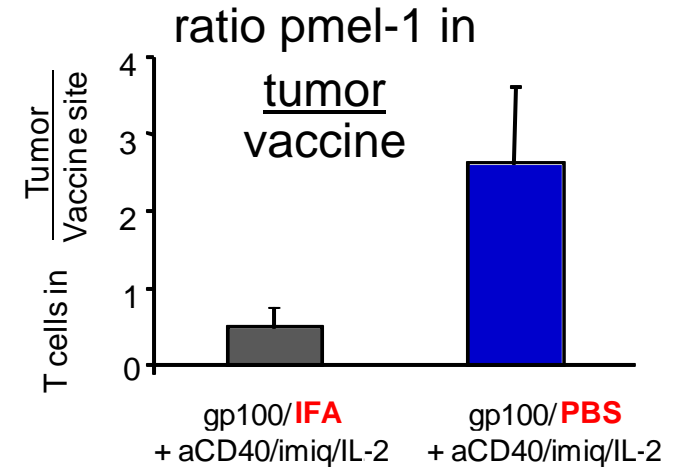
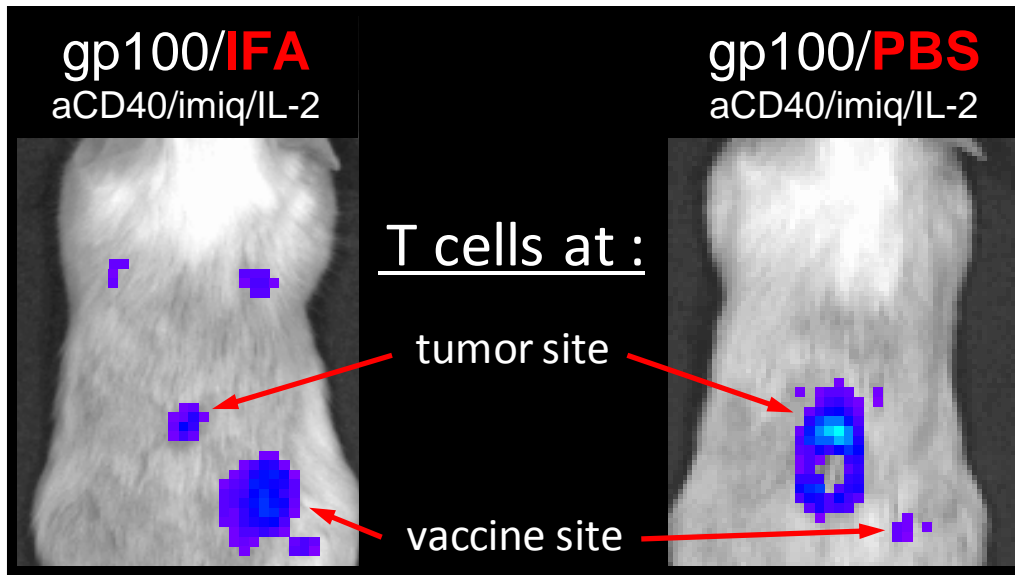
Water-based vaccines permit T cell accumulation in tumor



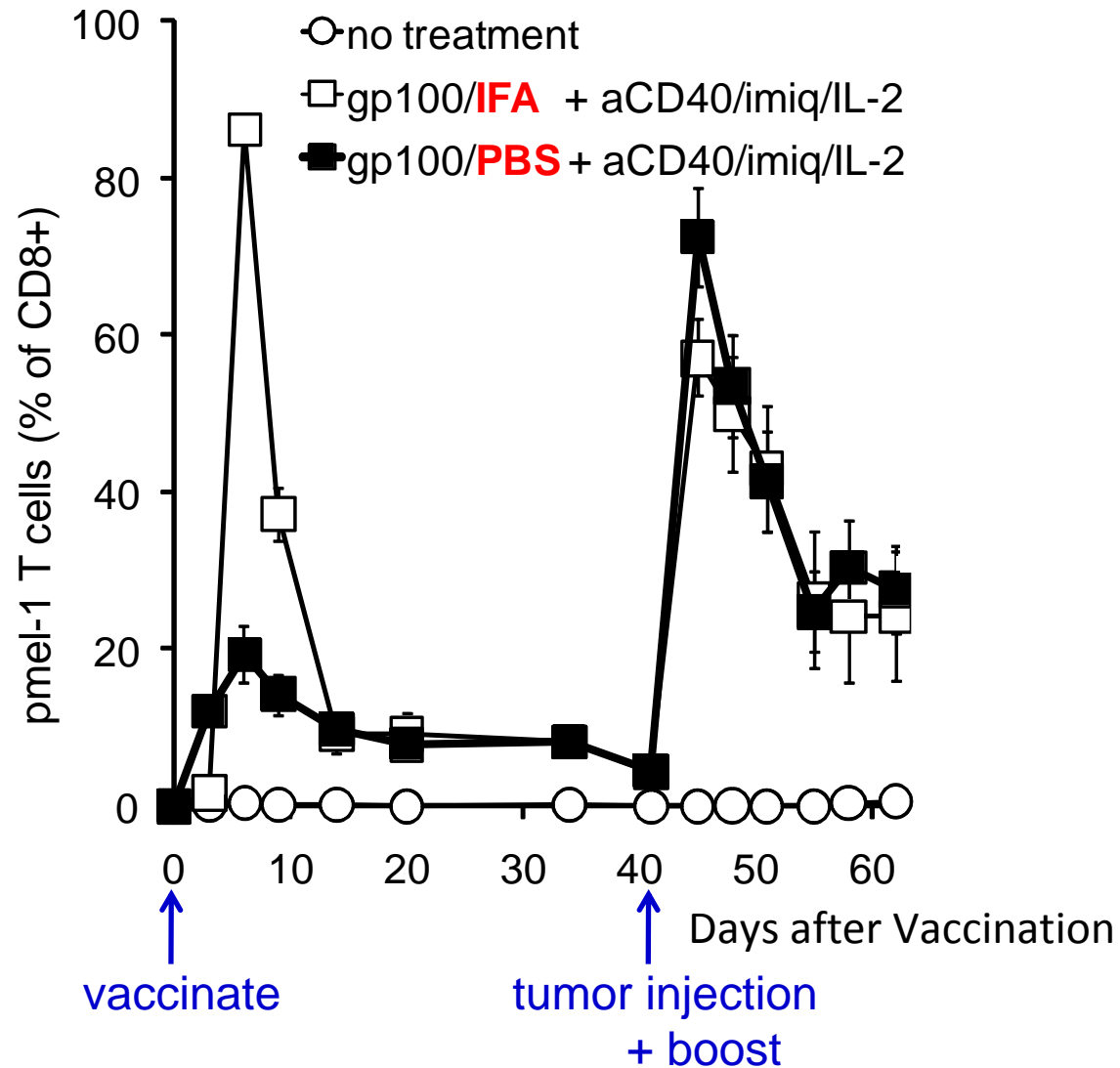
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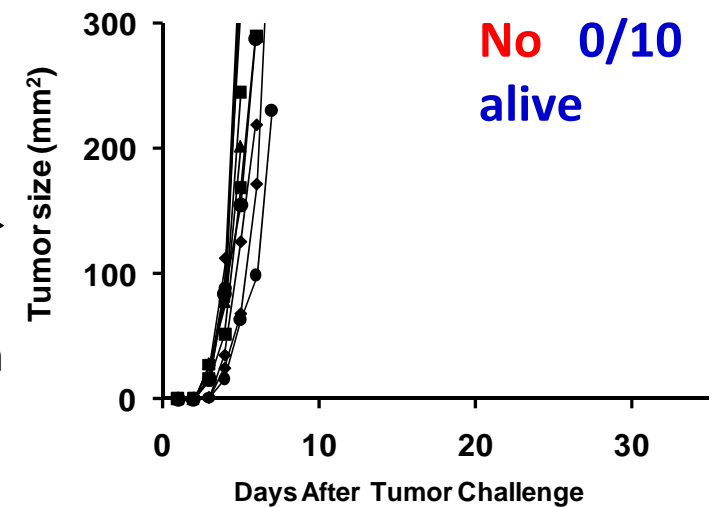
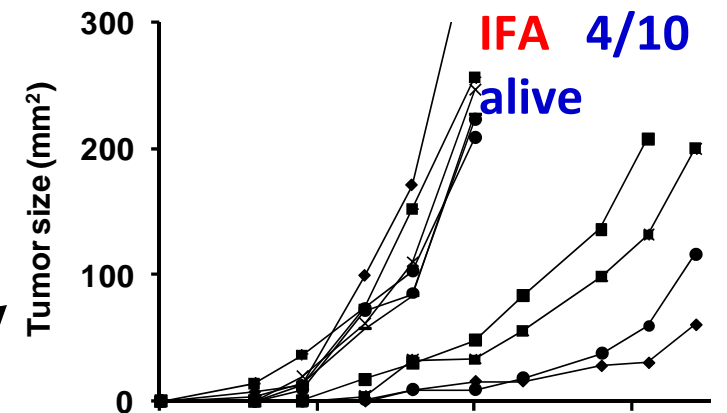
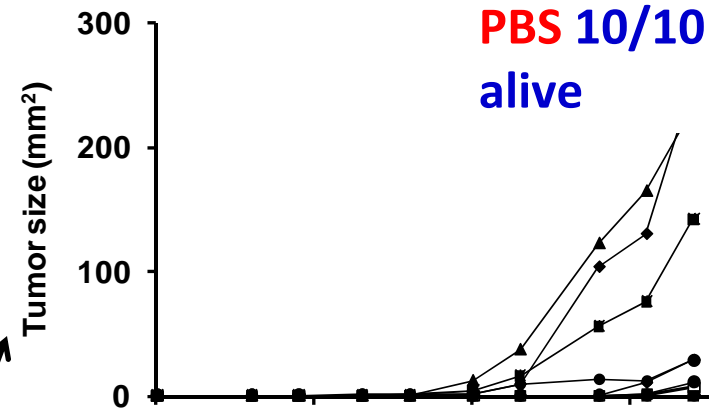
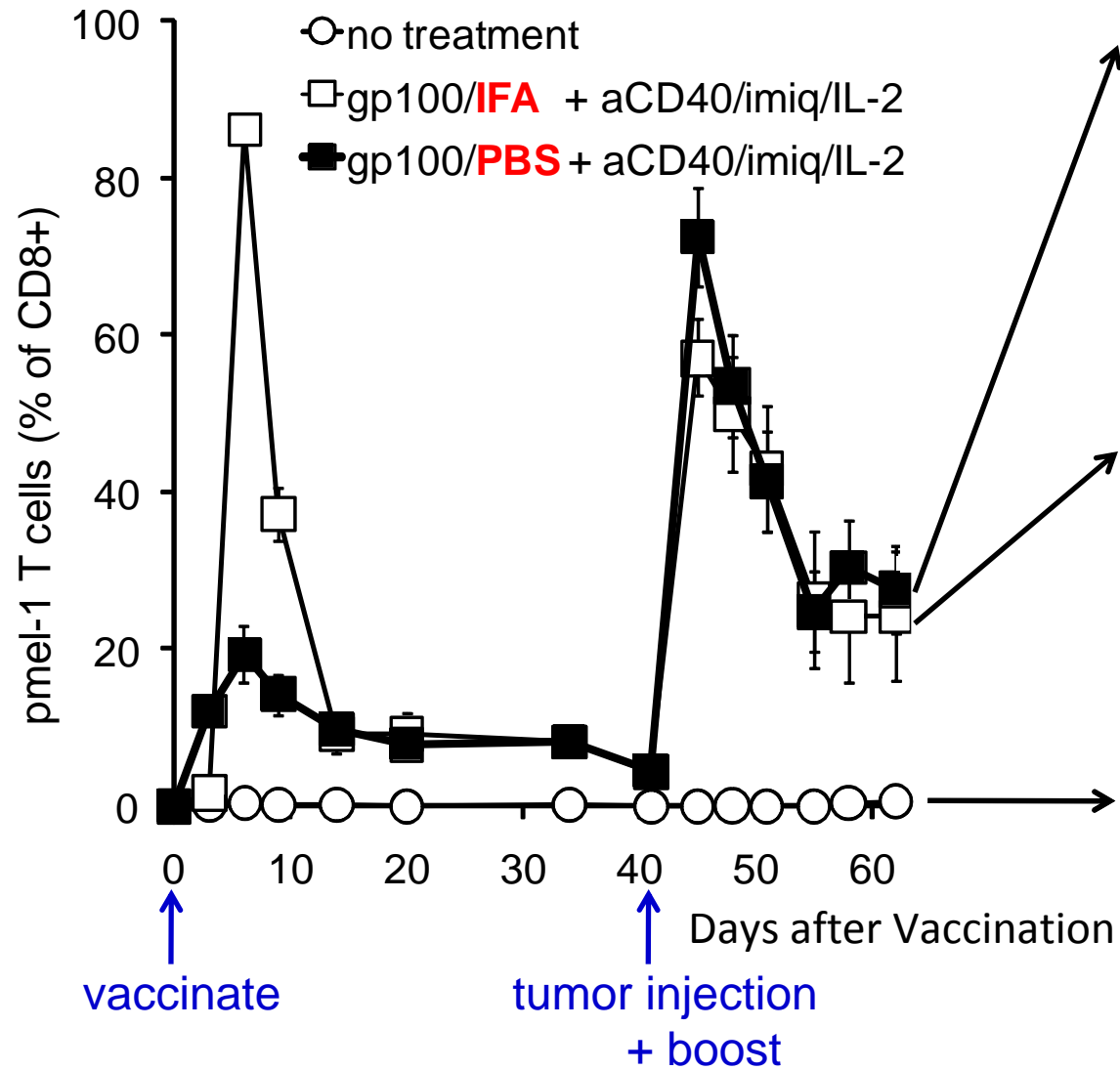
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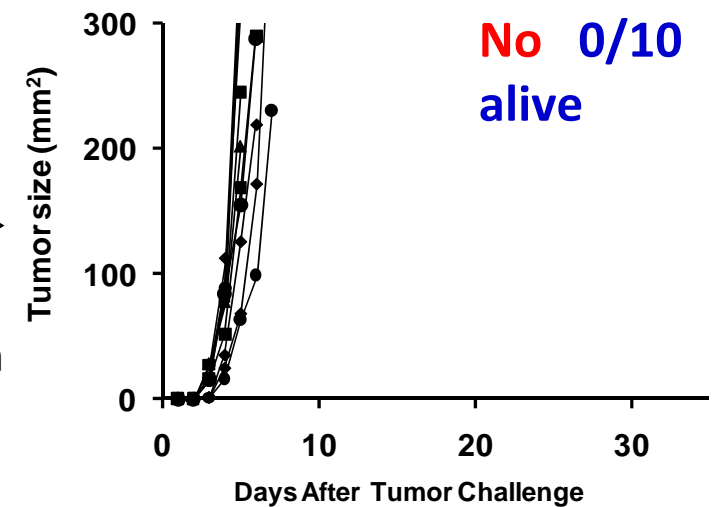
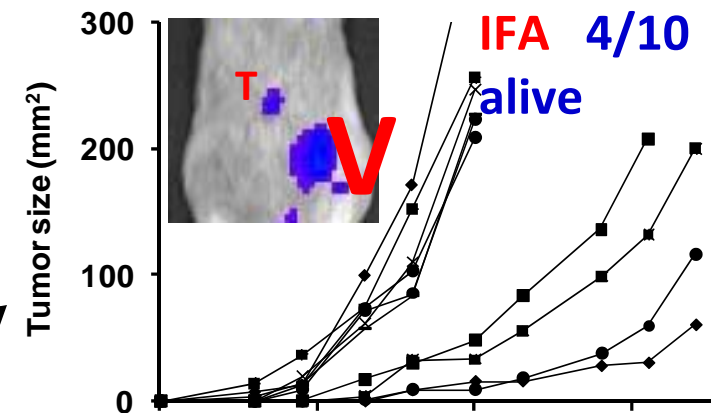
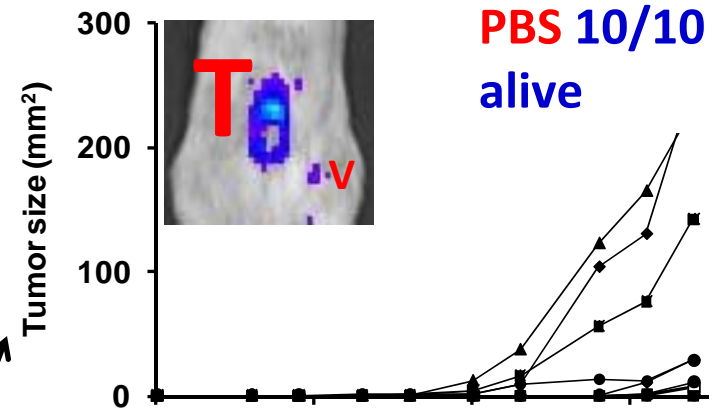
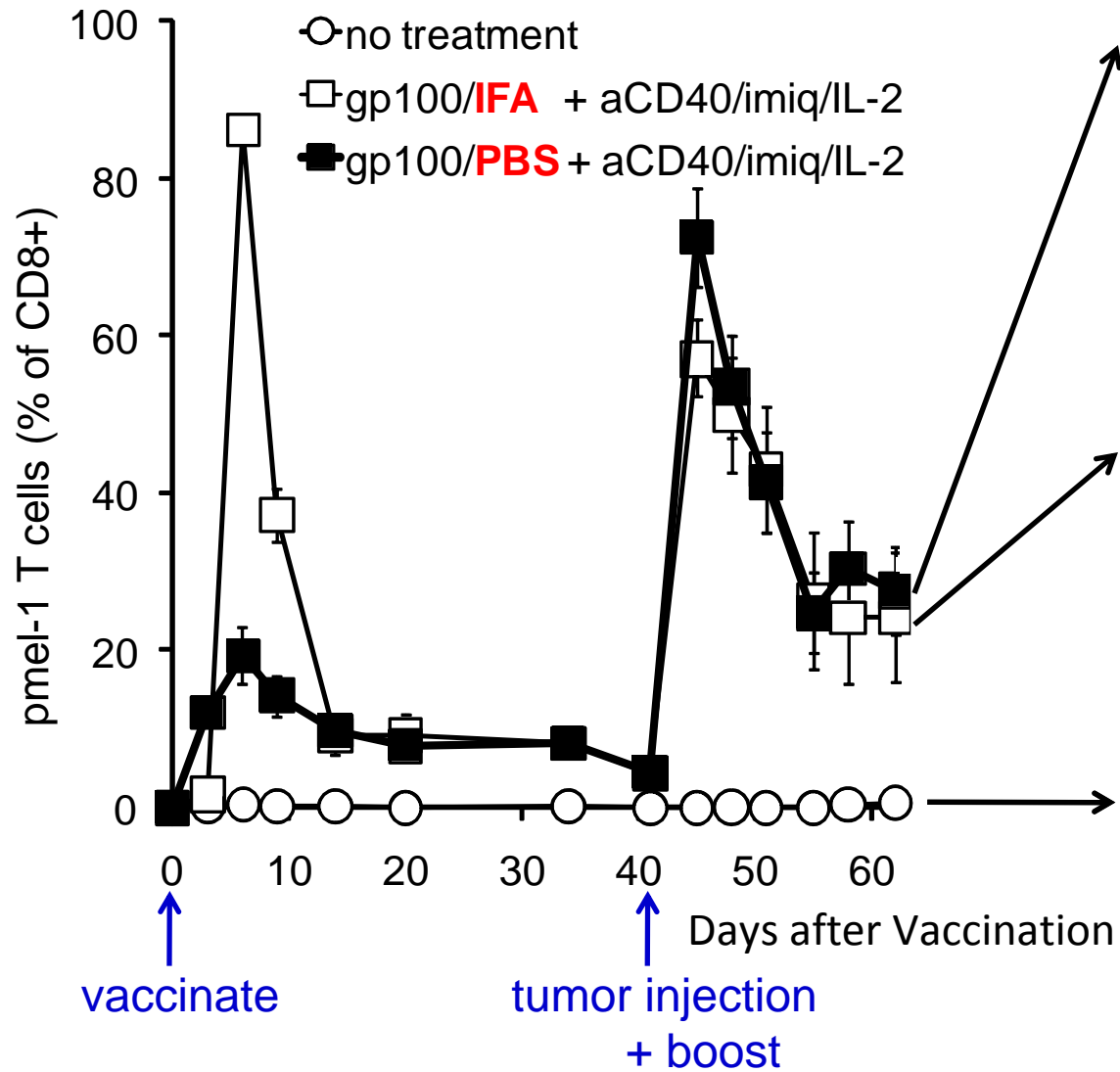
Therapy with long-lived vs. short-lived vaccine



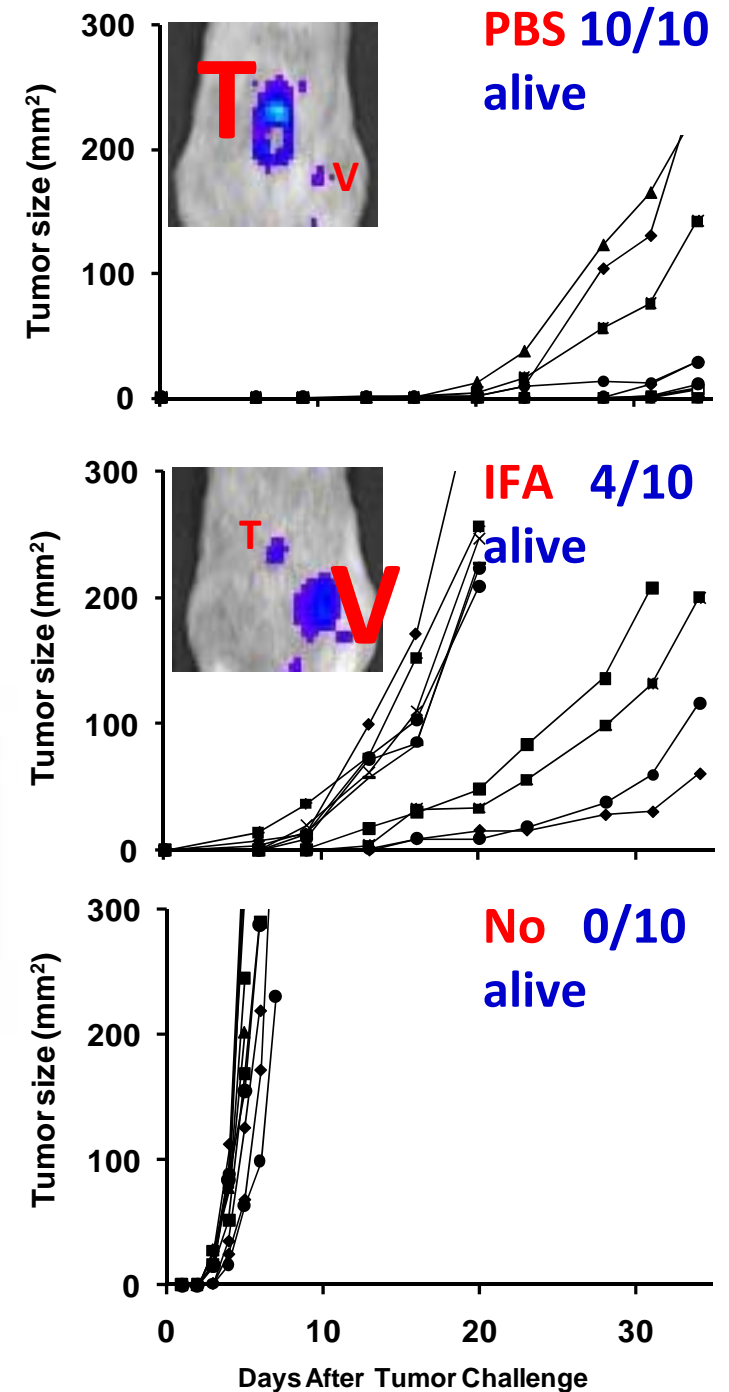
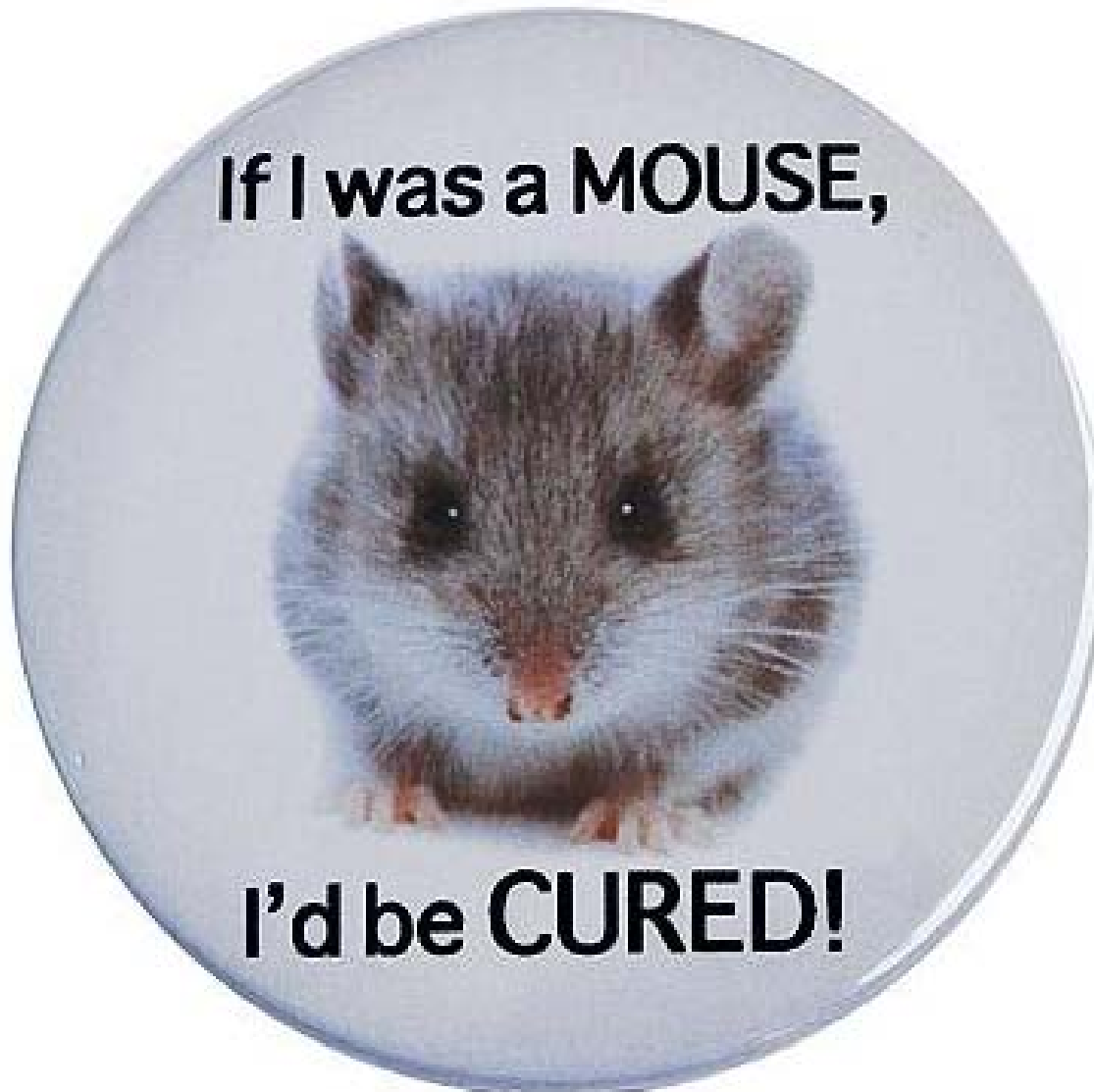
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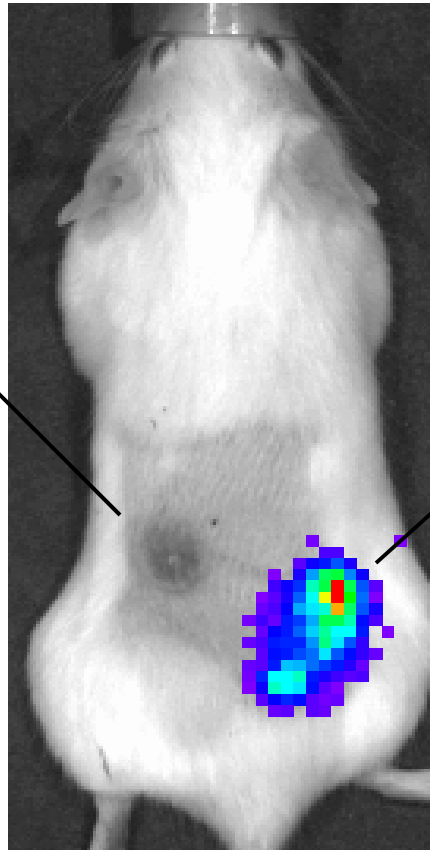
Therapy with long-lived vs. short-lived vaccine



Working Model

Tumor

Low [antigen]
Low MHC-I
Abnormal endothelium
Stromal Barrier
Immunosuppression



Vaccine site

High [antigen]
Normal MHC-I
Normal endothelium
No stromal Barrier
No Immunosuppression?

brief: priming

chronic: priming →
tolerance + sink

Conclusions

- Oil-based/long-lived vaccine formulations:
 - activate T cells, eventually tolerize
 - tolerance can be overcome by additional adjuvants
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Long-lived vaccines can induce sub-optimal anti-tumor immunity

Short-lived peptide vaccine formulations deserve consideration



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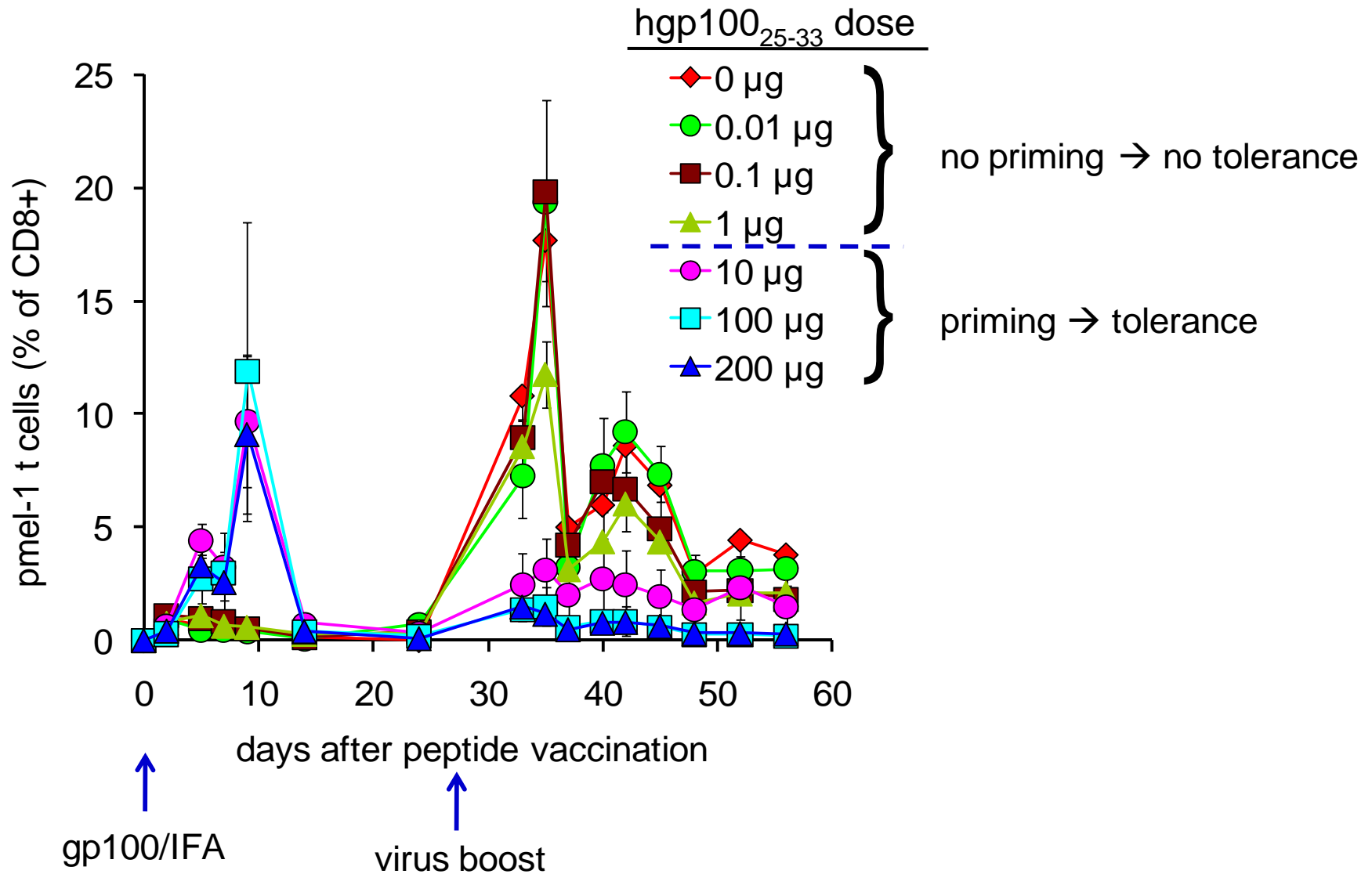
This work was partially funded by:

NIH/NCI: 1R01-CA143077-01A1

NIH/NCI: 1P01 CA128913-01A1

Melanoma Research Alliance

Not high-zone tolerance



gp100 peptide/IFA vaccine: uncertainty about impact of IFA variants

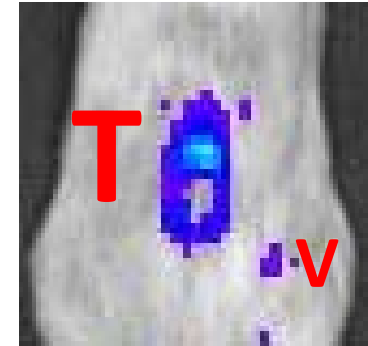
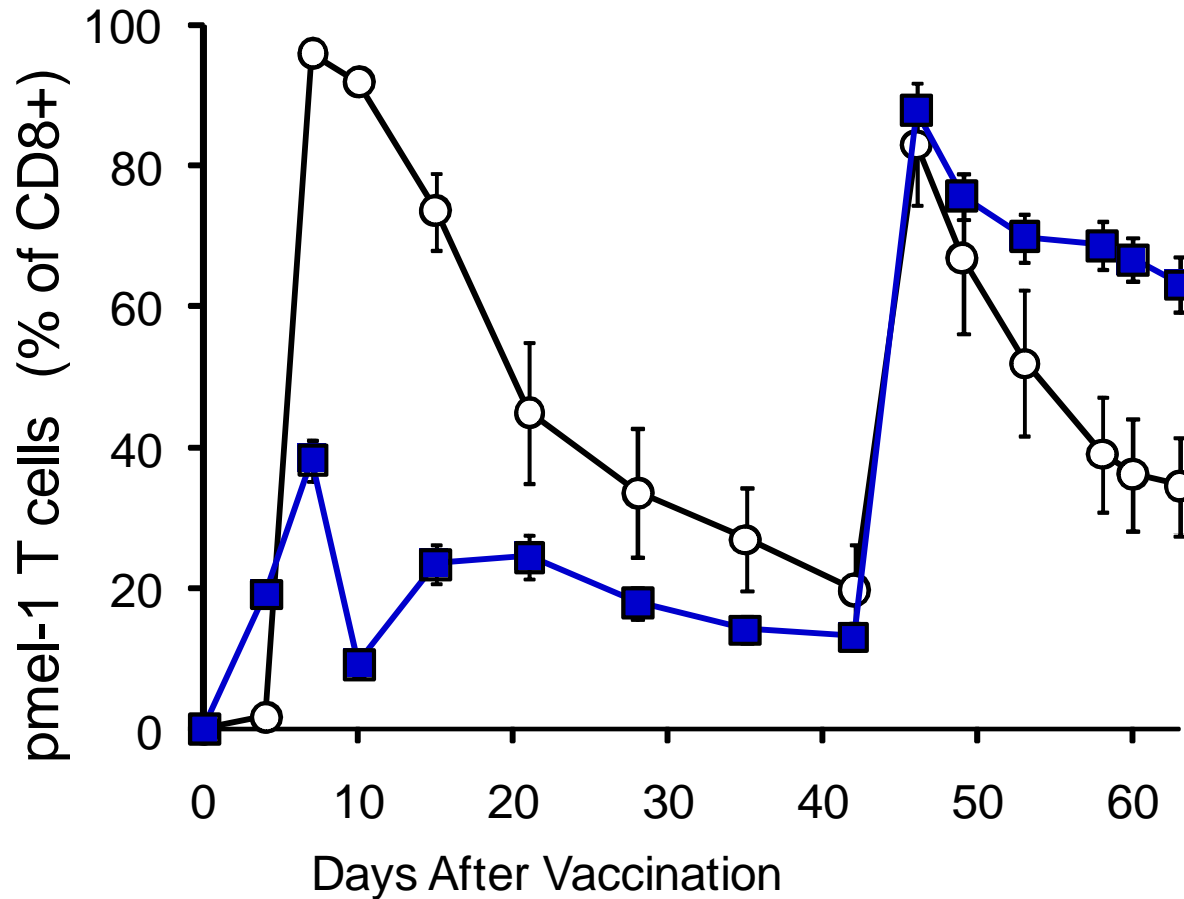
Different Adjuvanticity of Incomplete Freund's Adjuvant Derived From Beef or Vegetable Components in Melanoma Patients Immunized With a Peptide Vaccine

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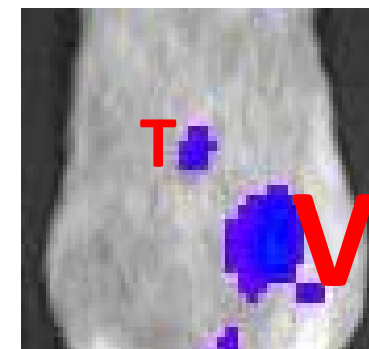
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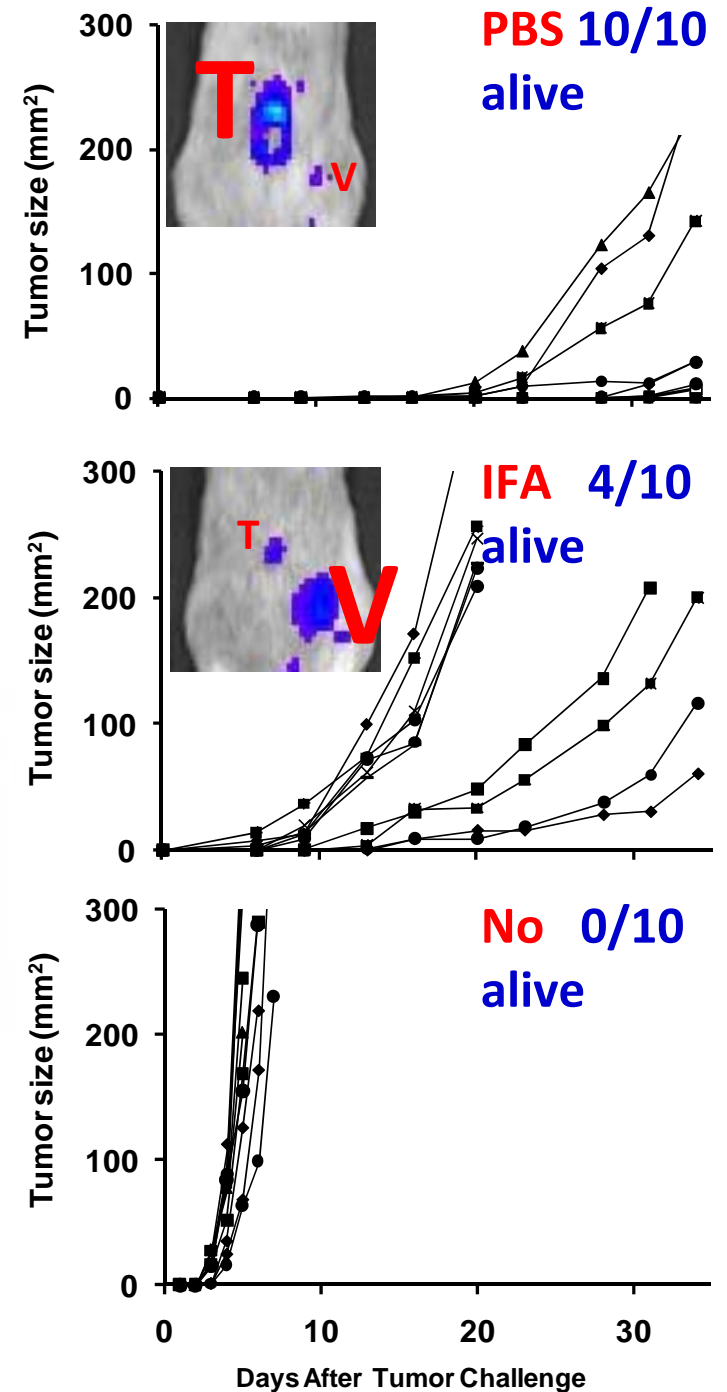
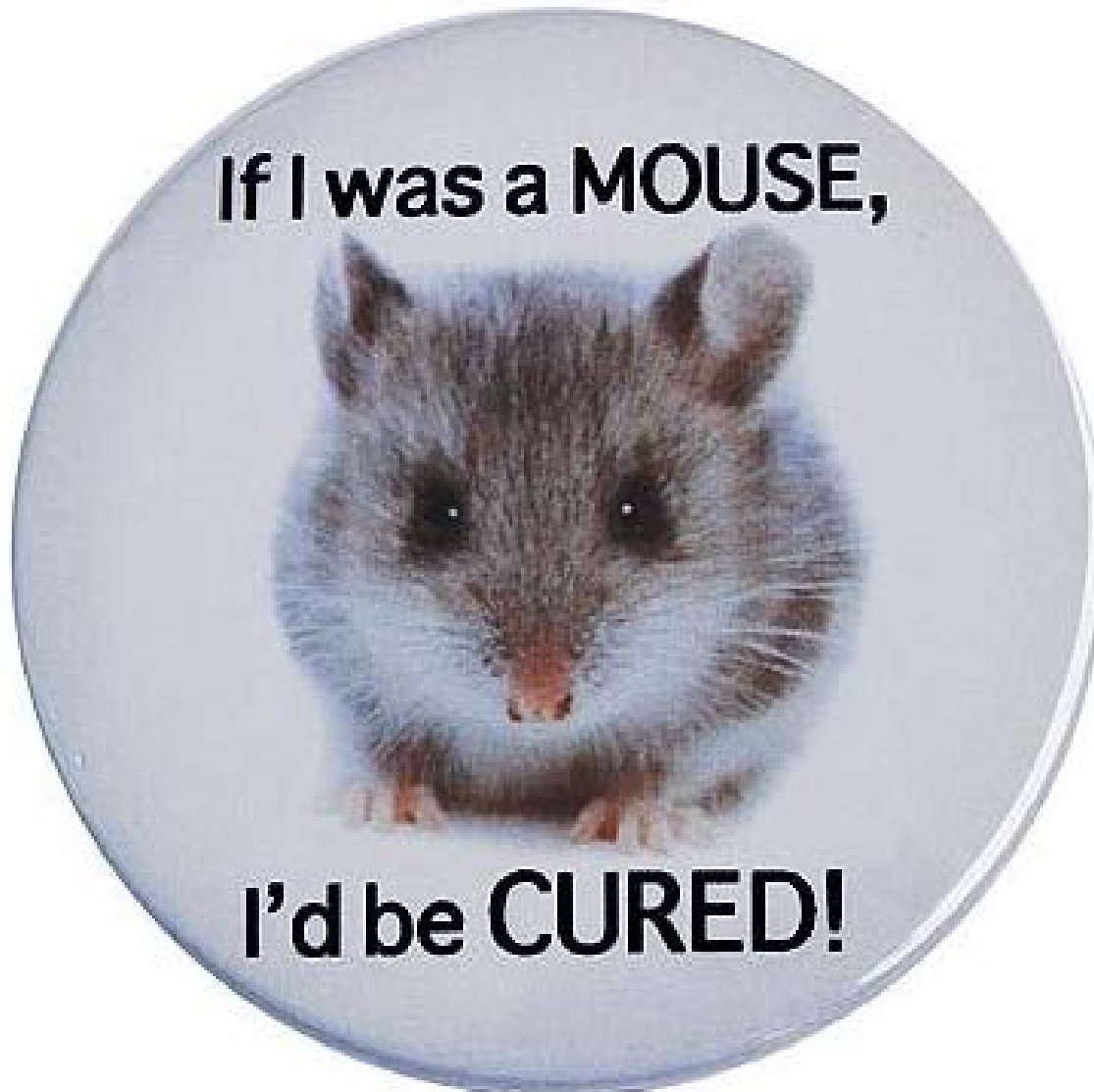


gp100/**PBS**
+ aCD40/imiq/IL-2

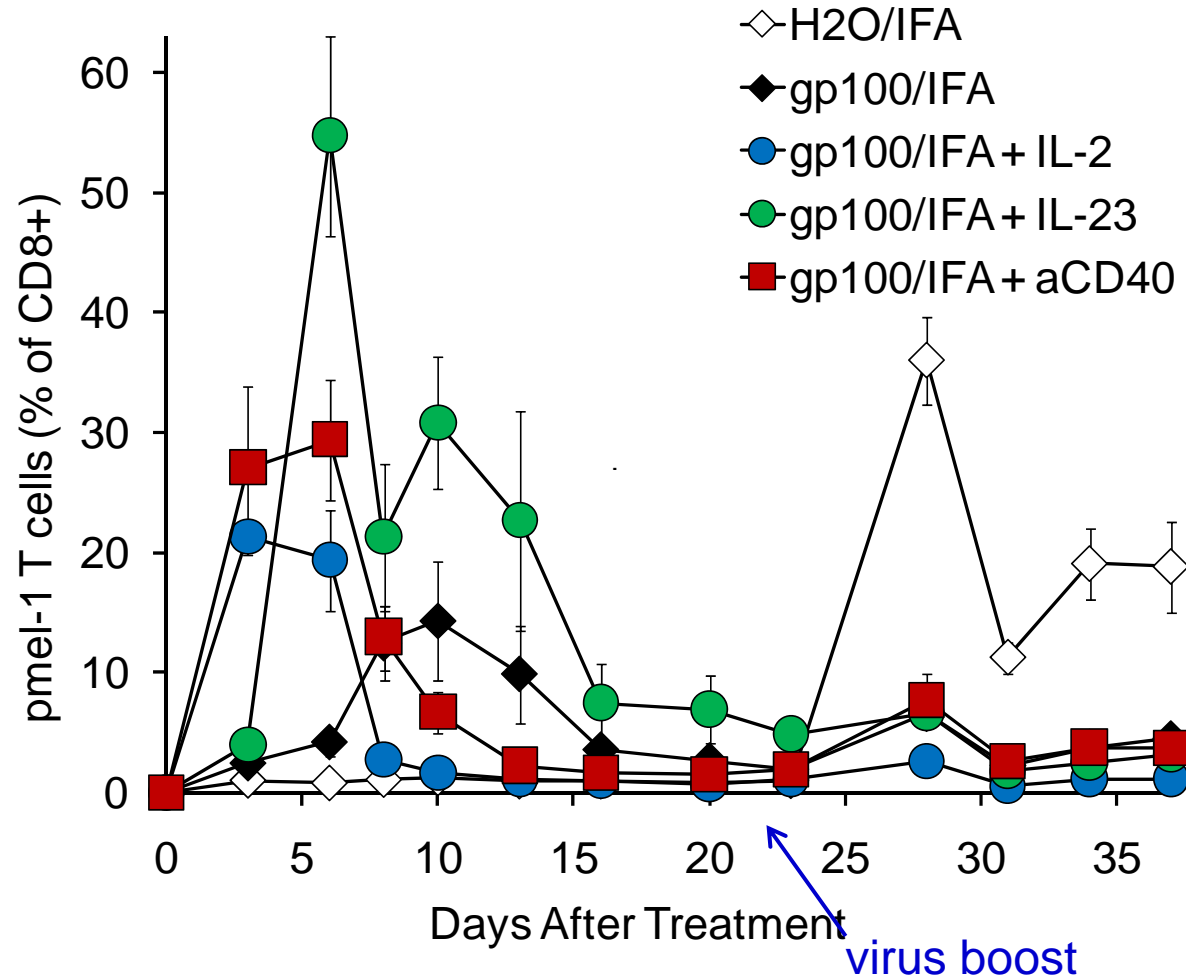
gp100/**IFA**
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Therapy with long-lived vs. short-lived vaccine



Adjuvants do not prevent tolerance



Persistent vaccine induces antigen-driven T cell tolerance

