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Kinetics of T cell responses to vaccination for HIV with heterologous DNA prime-rAd5 boost contrasted with homologous rAd5 prime-boost

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HVTN Protocol 068 Objectives

- An experimental trial using vaccines with known immunogenicity: VRC DNA (4 plasmid) and replication-defective adenovirus serotype 5 (Ad5)
- Designed to answer scientific questions and not necessarily to provide information affecting future clinical testing of this vaccine
  - Kinetics of T cell immune responses
  - Cytokine and memory marker distribution of induced T cell responses
- Also compares two vaccine regimens:
  - Ad5 prime/Ad5 boost and
  - DNA prime/Ad5 boost

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HVTN Protocol 068 Design

Vaccine: developed by NIH Vaccine Research Center

- DNA (4 mg total) encoding:
  - Env clades A, B, C (in 3 plasmids)
  - Gag, Pol, Nef clade B (in 1 plasmid)
- Ad5 10^{10} PU encoding:
  - Env clades A, B, C
  - Gag and Pol clade B

Note that in current trials a new 6 plasmid DNA vaccine has replaced the 4 plasmid vaccine

Study Participants: n = 66

low Ad5 neutra[illegible]2)

Current trials prime with 3 doses of DNA

Study Design: n=33 in each g[illegible]oup, includes 3 placebo

- Group 1: Ad5 prime 0 m[illegible] and Ad5 boost 6 mo
- Group 2: DNA prime 0 and 1 mo; Ad5 boost 6 mo

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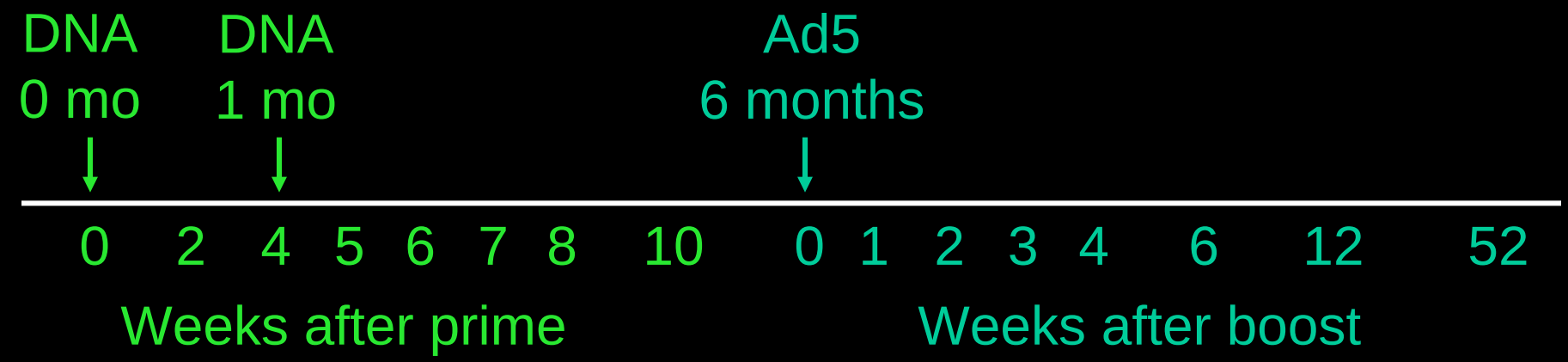
Frequent blood draws after each vaccination

Ad5/Ad5 Group

DNA/Ad5 Group



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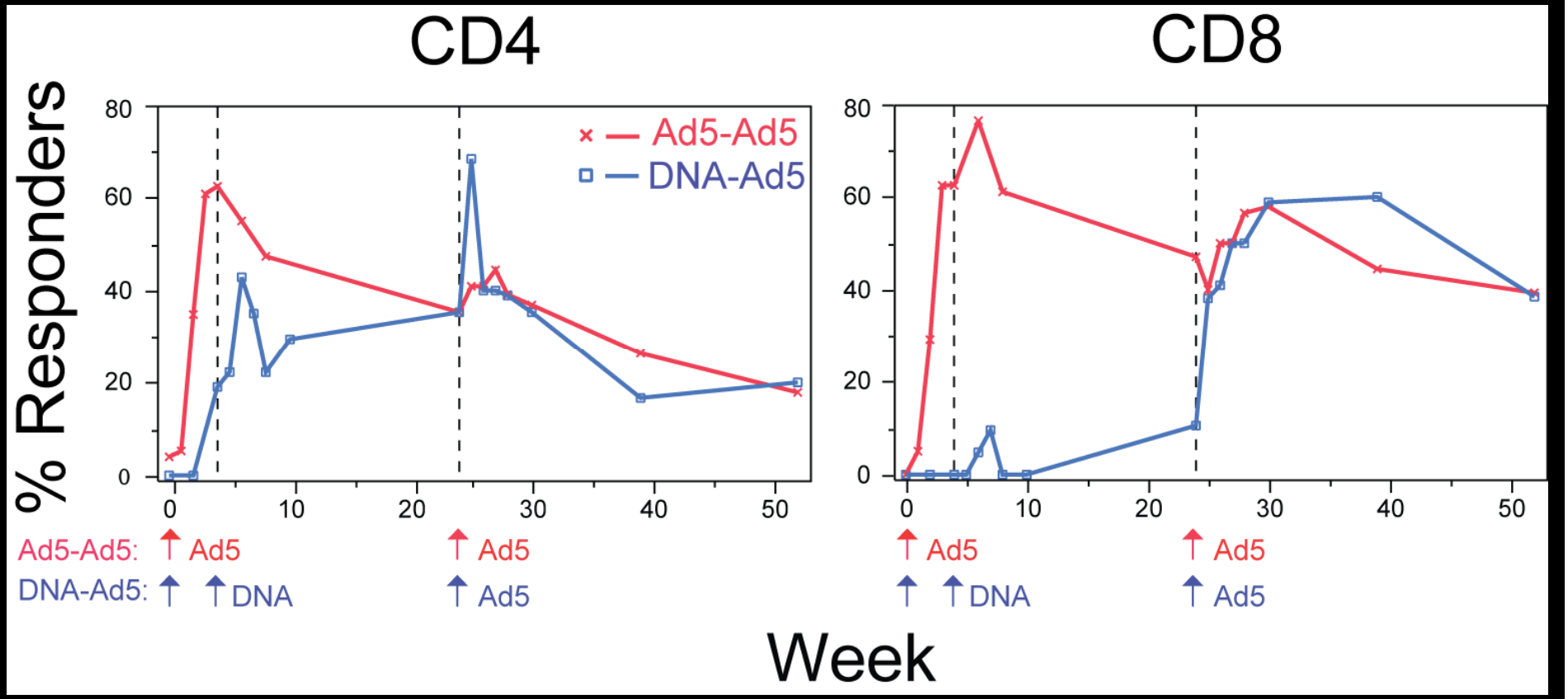
Intracellular cytokine staining (ICS) detects vaccine-specific T cells

- Global potential T cell epitope (PTE) peptide pools for Env, Gag, Pol and Nef used for *in vitro* stimulation
- IFN-γ, IL-2 and TNF-α examined in the primary validated assay
- CCR7, CD45RA, CD27 and CD57 examined in a second ICS assay

Percentage of individuals responding with both CD4 and CD8 T cells is high for both treatment groups



Individuals responding to Env, Gag, or Pol

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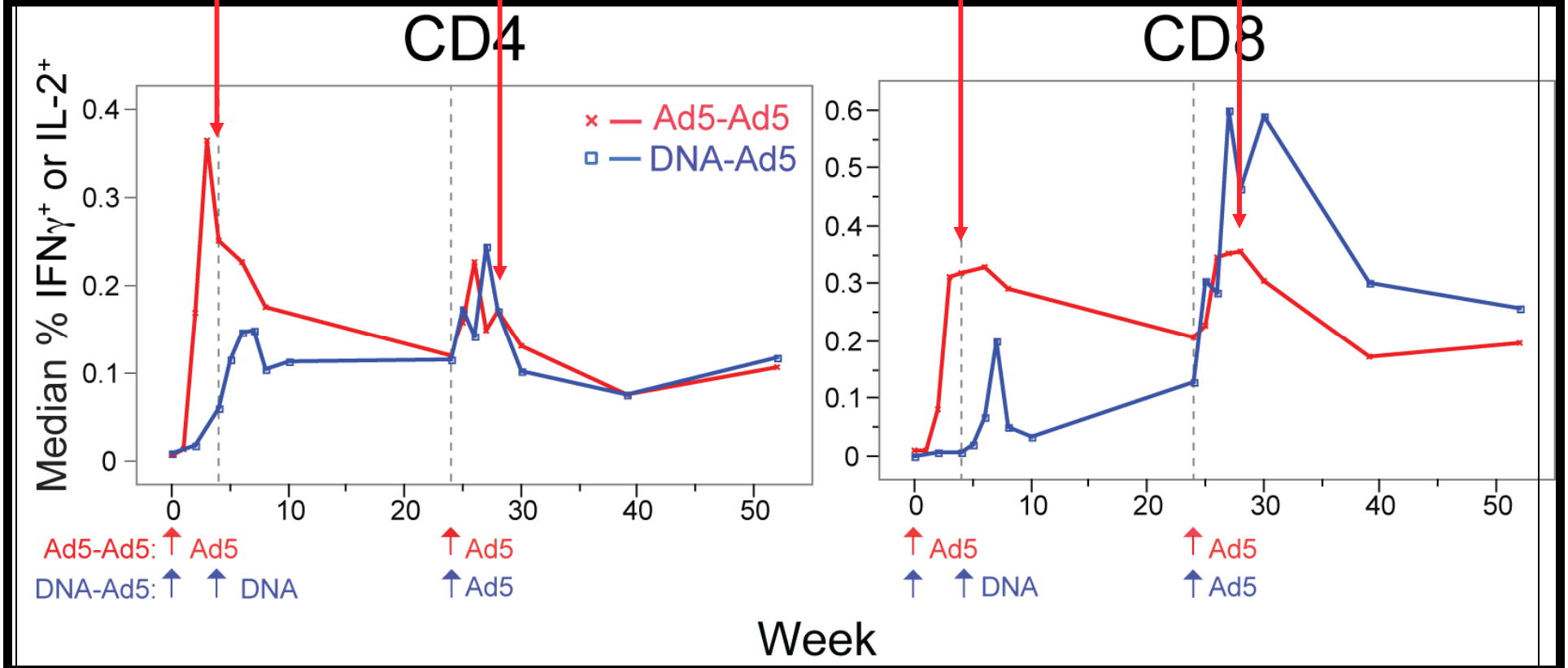
Ad5 boosts CD4 and CD8 T cell responses after DNA prime but not after Ad5 prime

Primary immunogenicity time points Ad5/Ad5



Sum of responses to Env, Gag, or Pol

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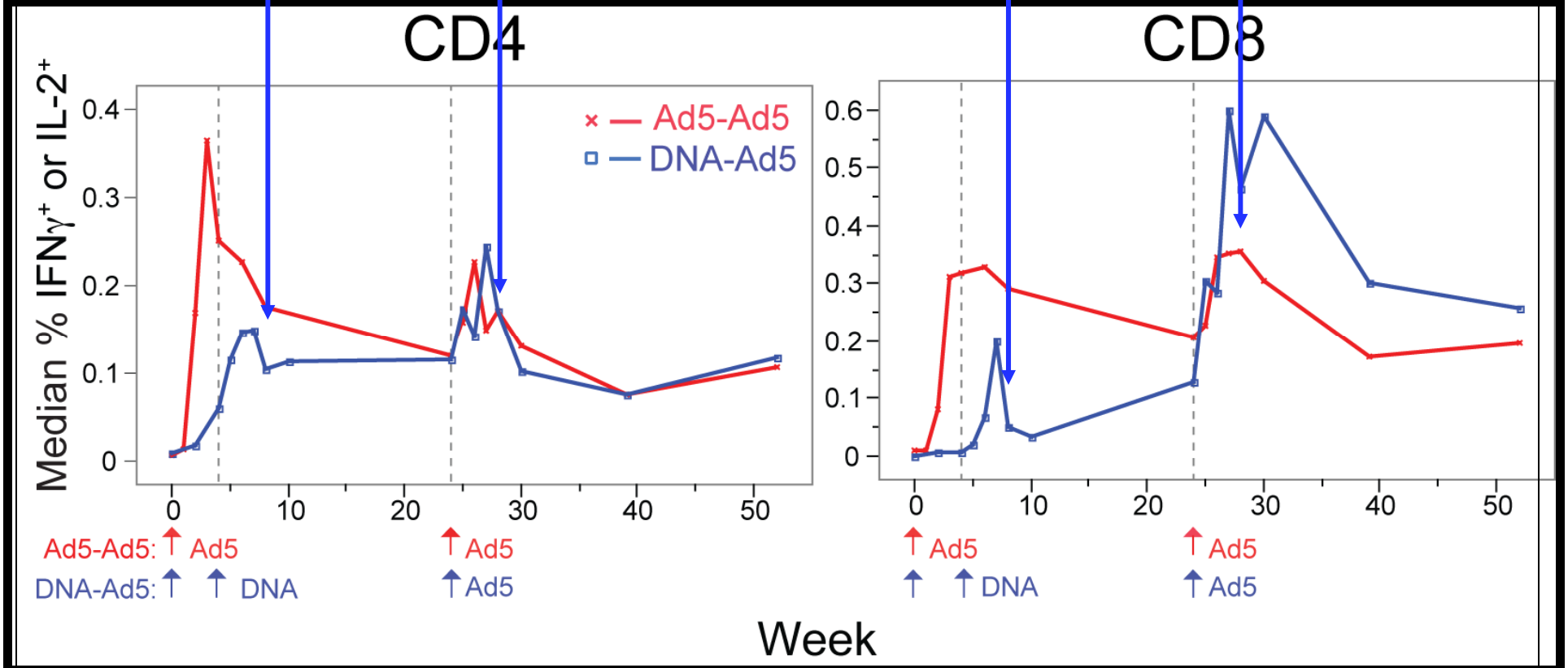
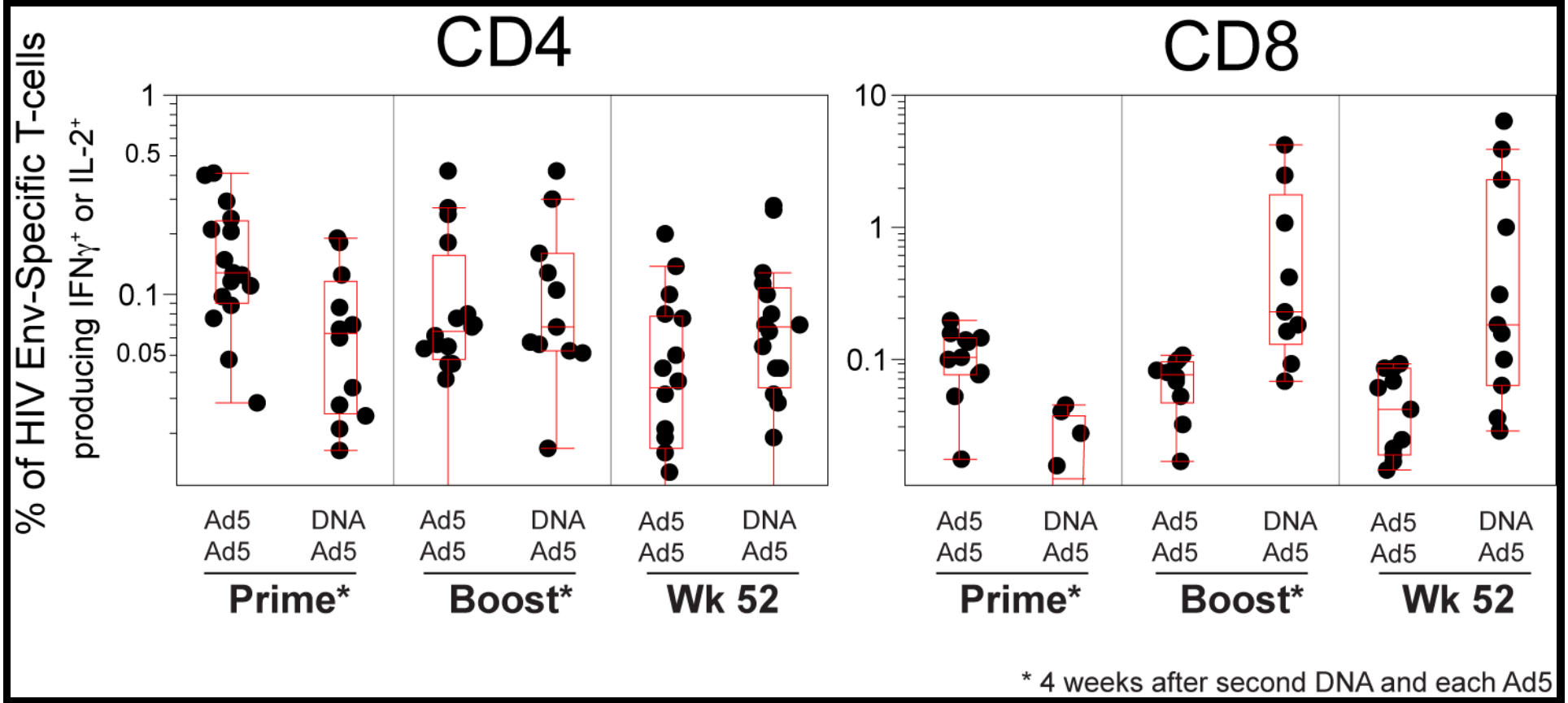
Ad5 boosts CD4 and CD8 T cell responses after DNA prime but not after Ad5 prime

Primary immunogenicity time points DNA/Ad5



Sum of responses to Env, Gag, or Pol

The frequency of Env-specific T cells is increased after Ad5 boost following DNA prime as compared with Ad5 prime



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Dual-producing CD4 T cells expressing both IFN-γ and IL-2 are more frequent following boosting of DNA prime

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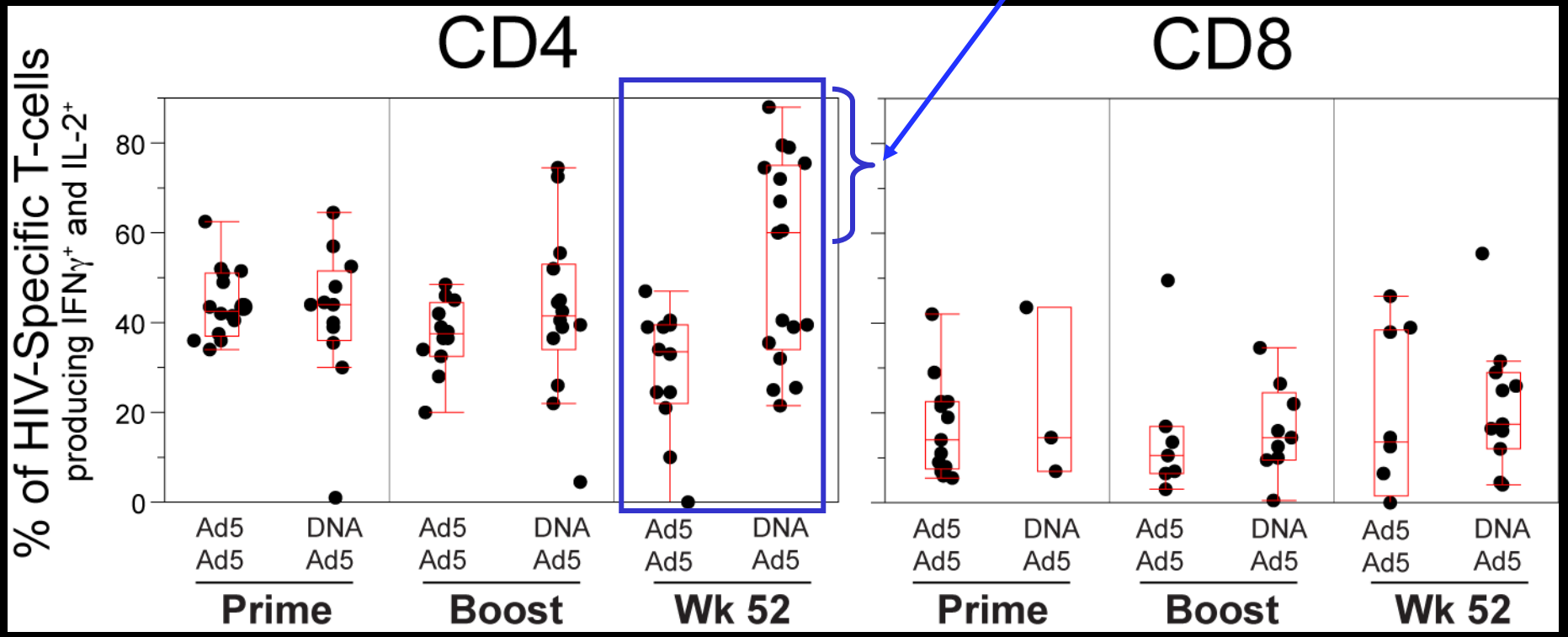
Some participants have high proportions of dual-producing CD4 cells



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Summary of T cell kinetics as determined by cytokine production

- Timing of peak responses is variable between individuals
- For Env-specific T cells, DNA priming of Ad5:
  - results in more dual cytokine-producing CD4 T cells
  - and a higher frequency of CD8 T cells 6 months after boost
- For Gag- and Pol-specific T cell responses after boosting:
  - Similar frequencies of CD4 and CD8 T cells in both groups,
  - Similar percentage of responding individuals for CD8 Gag
  - Lower percentage of responders for Pol after DNA priming
  - Note that 4-plasmid DNA vaccine includes a fusion construct for Gag/Pol/Nef

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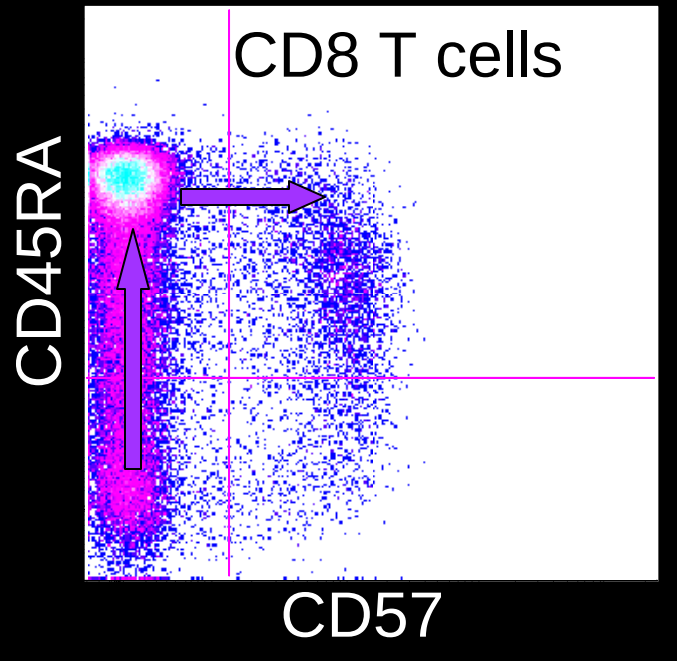
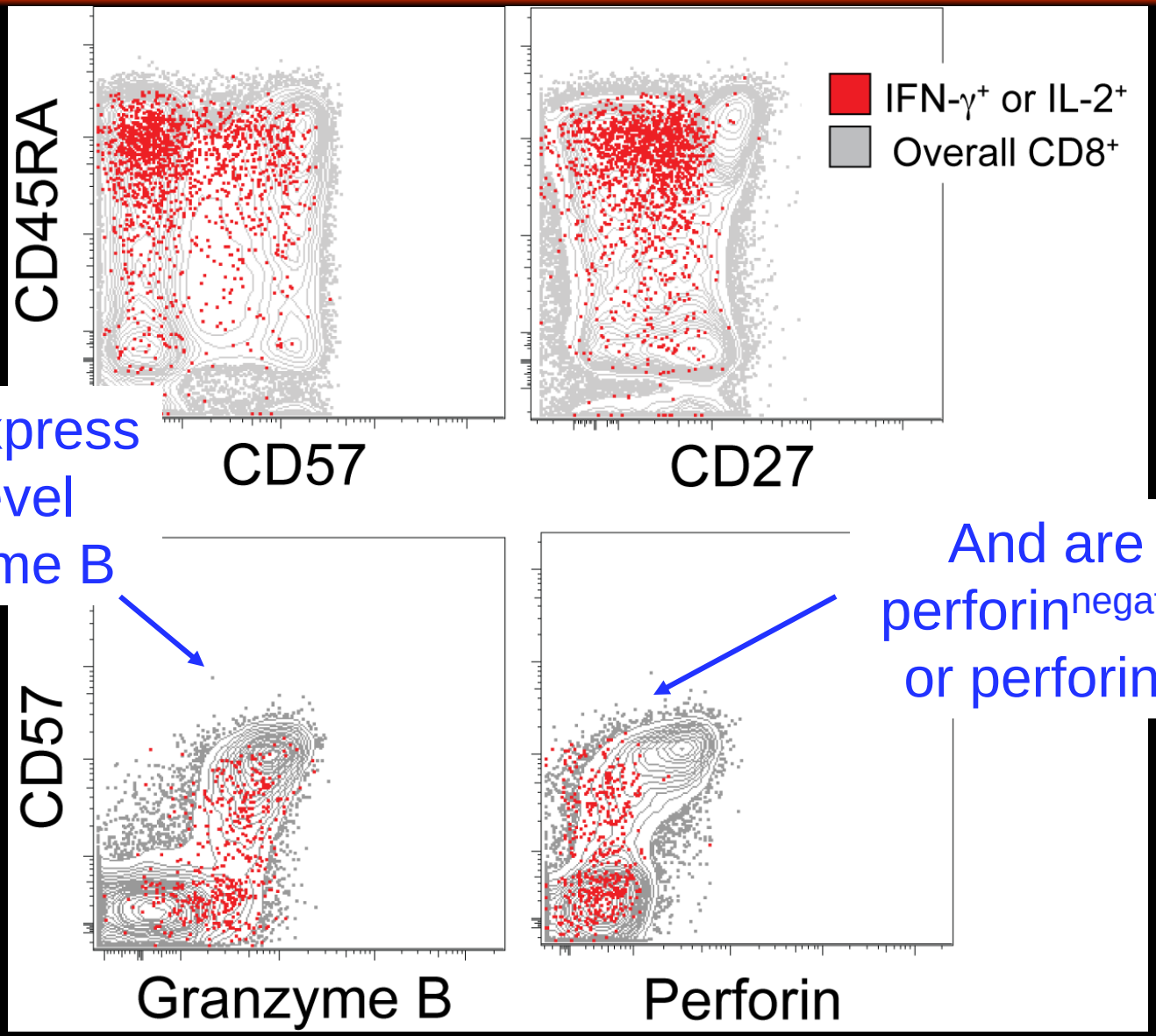
Type of vaccine-induced memory T cell identified by memory marker expression

- CCR7, CD45RA, CD57 and CD27 examined on vaccine-induced T cells (cell producing IFN-γ or IL-2)
- Initial analysis focuses on CD45RA and CD57
  - Lack of CD45RA expression identifies memory cells; "re-expression" of CD45RA identifies effector T cells
  - CD57 is a marker of unknown function; identifies terminally-differentiated effector cells; prior studies show association with perforin expression
- Likely order of differentiation for CD8 cells is shown by the arrows



At 6 months post boost, most vaccine-induced CD8 T cells express CD45RA and some express CD57



Many express low-level granzyme B

And are perforin^{negative} or perforin^{lo}

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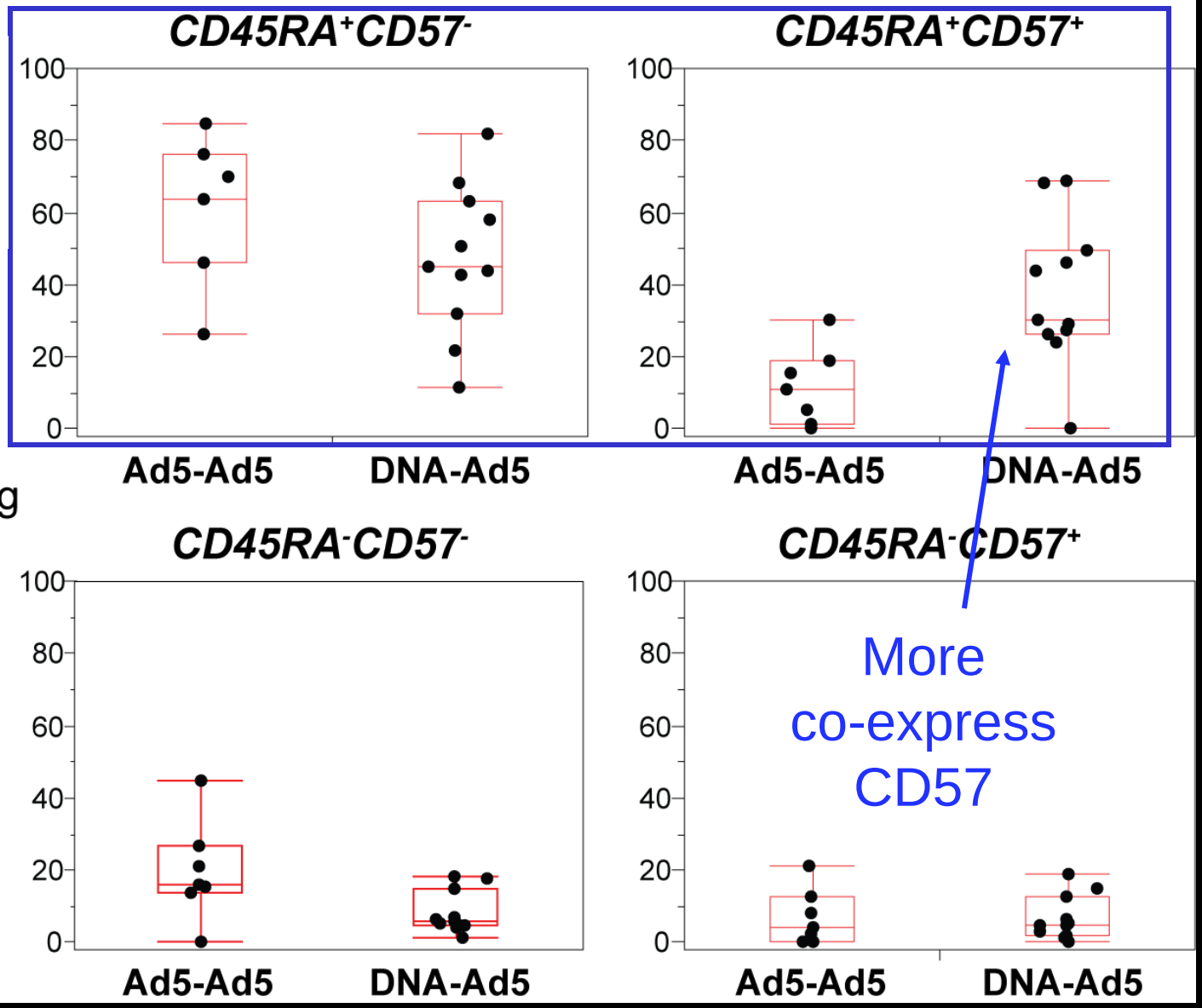
At 6 months post boost, DNA priming results in more vaccine-induced CD8 T cells expressing CD57

Most cells are CD45RA$^+$



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Memory marker summary

- Vaccine-induced CD8 T cells in both groups express CD45RA, a marker associated with fully-differentiated effector cells
- This has also been observed for memory cells following vaccinia and yellow fever vaccination, two vaccines known to induce long-term effective memory T cells
  - Precopio et al *JEM* 2008; Miller et al *Immunity* 2008
- Despite this differentiated phenotype, the $CD45RA^{+}$ cells proliferate and likely contribute to long-term memory

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Conclusions

- Ad5 alone is highly immunogenic; Ad5 boosting of Ad5 dampens responses
- Memory T cells at 6 months post boost differ between treatment groups. Following DNA prime:
  - More CD4 T cells co-express IFN-γ and IL-2
  - More CD8 T cells express CD57
- Cells expressing CD57 also express granzyme B, may be precursors to cytotoxic T cells, and may therefore be armed for quick response to viral challenge
- In sum, heterologous priming can influence the type of memory cell induced by the boost

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