National Cancer Institute

A promising candidate to enhance vaccine efficacy against cancer and HIV: IL-15

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National Cancer Advisory Board Meeting
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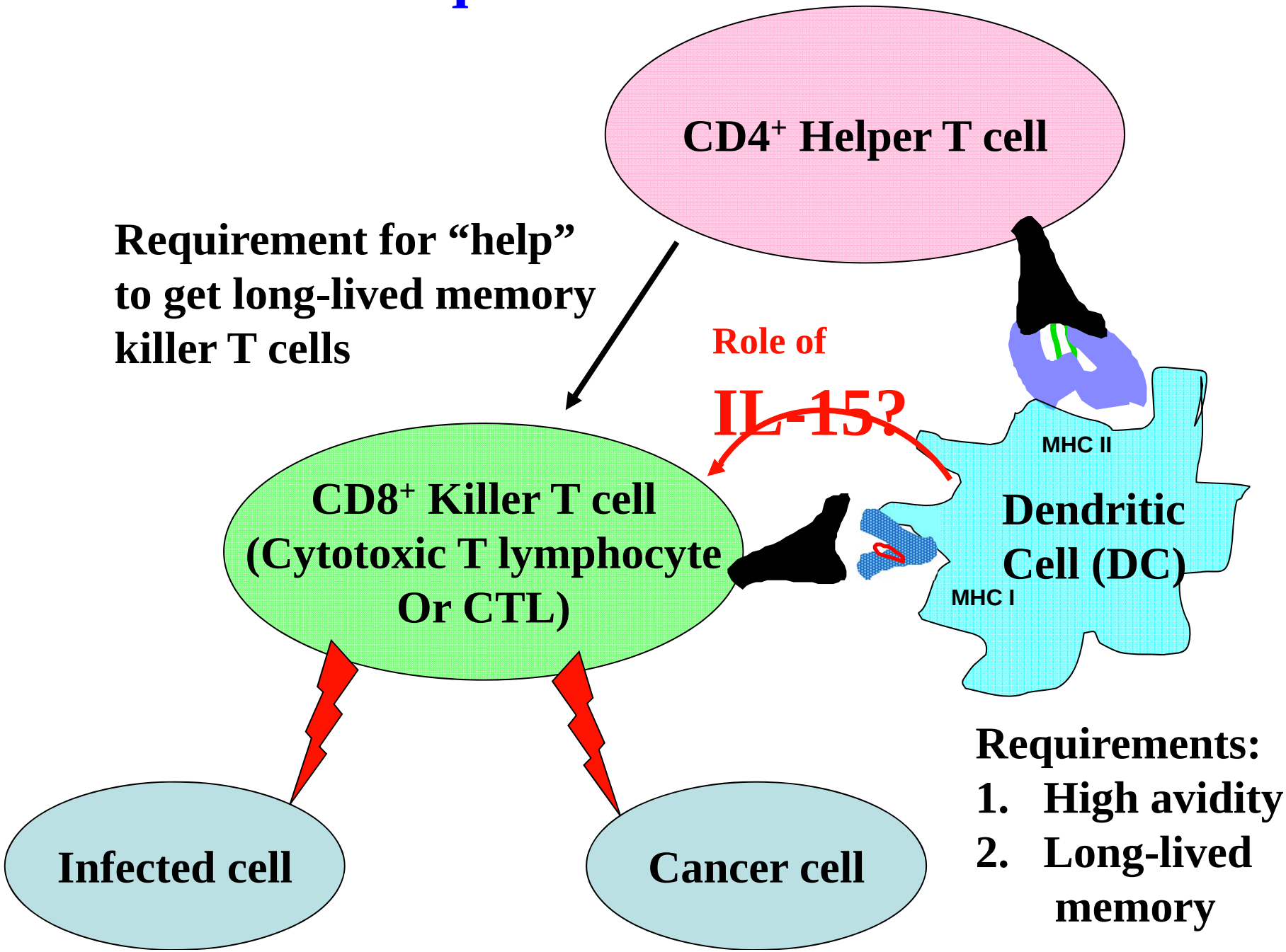
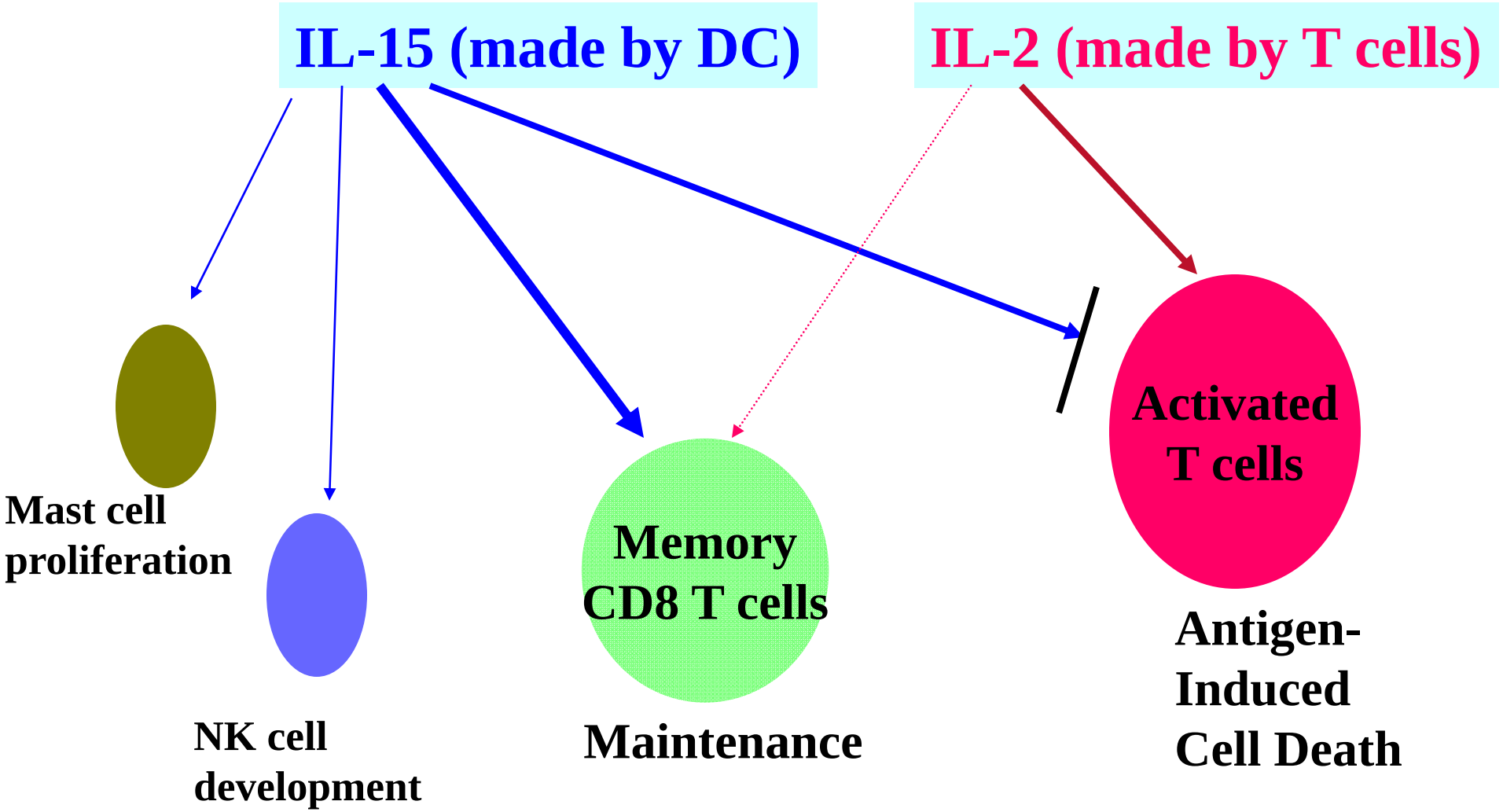
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

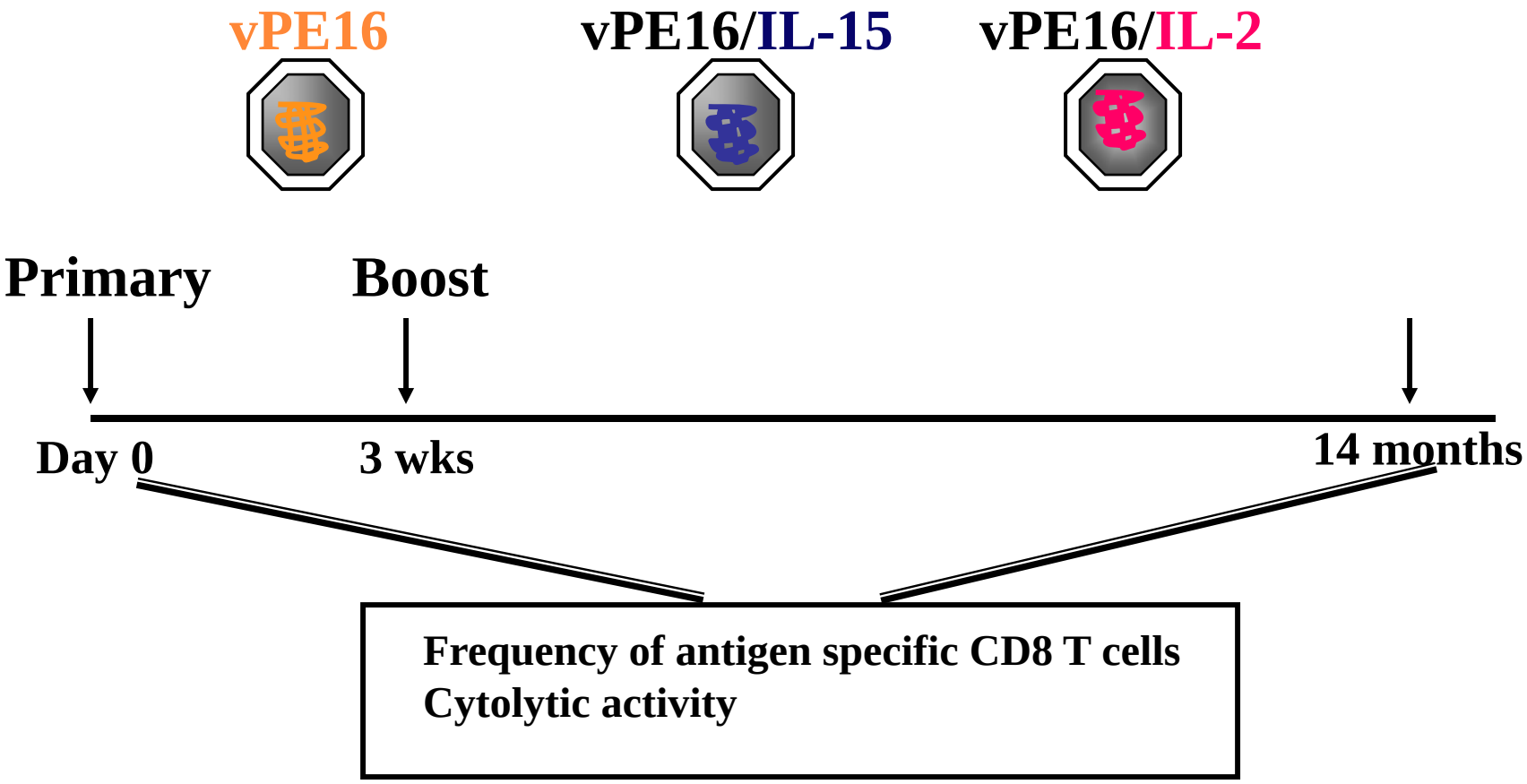
The cast and the questions



IL-2 & IL-15: DISTINCT SOURCE & FUNCTIONS

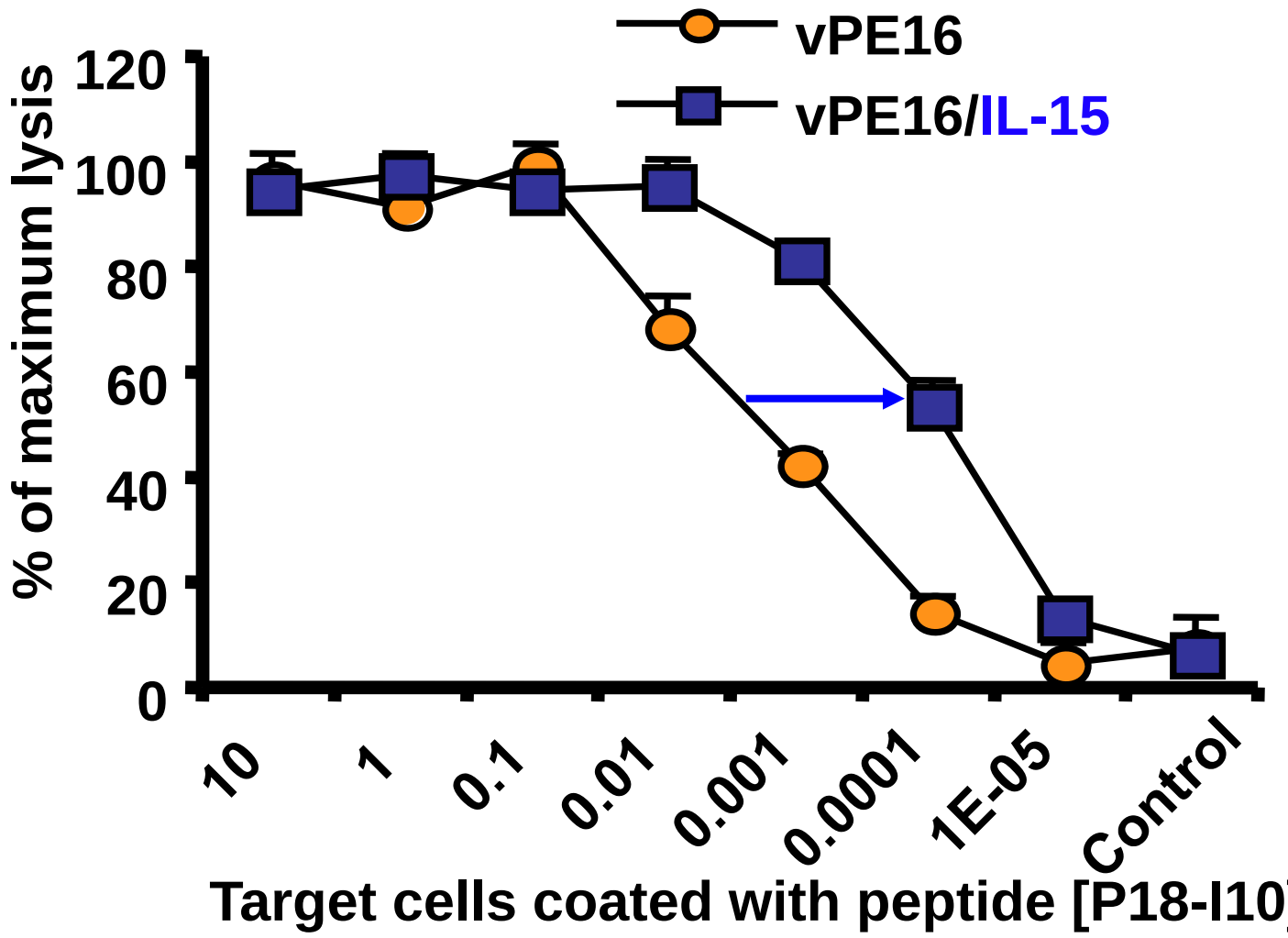


What is the role of IL-2 and IL-15 in the induction of immune response and the maintenance of immunity?



vPE16 is a recombinant vaccinia virus expressing HIVgp160

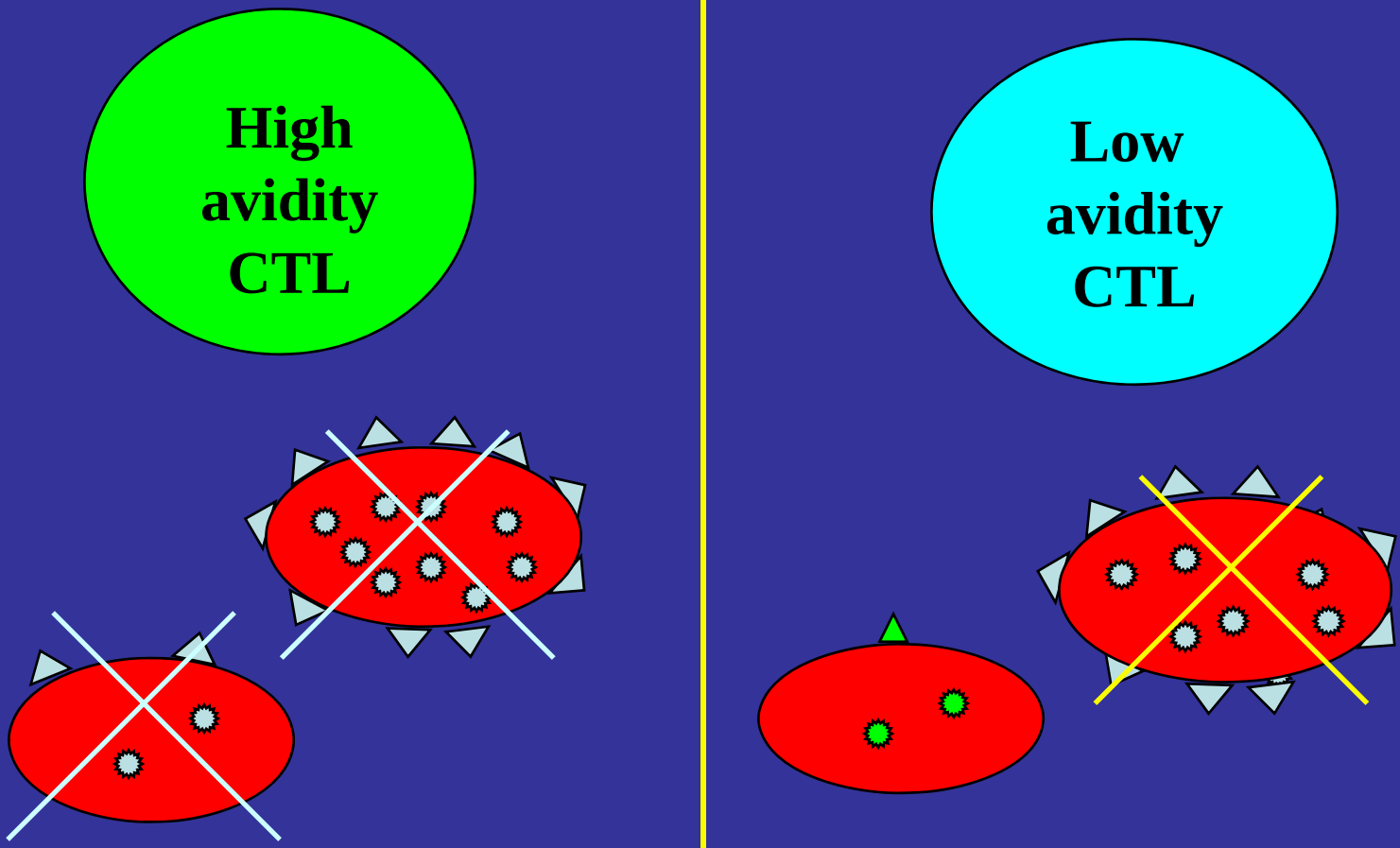
Immunization with antigen + IL-15 induces higher avidity memory CD8+ CTL



2 months after immunization

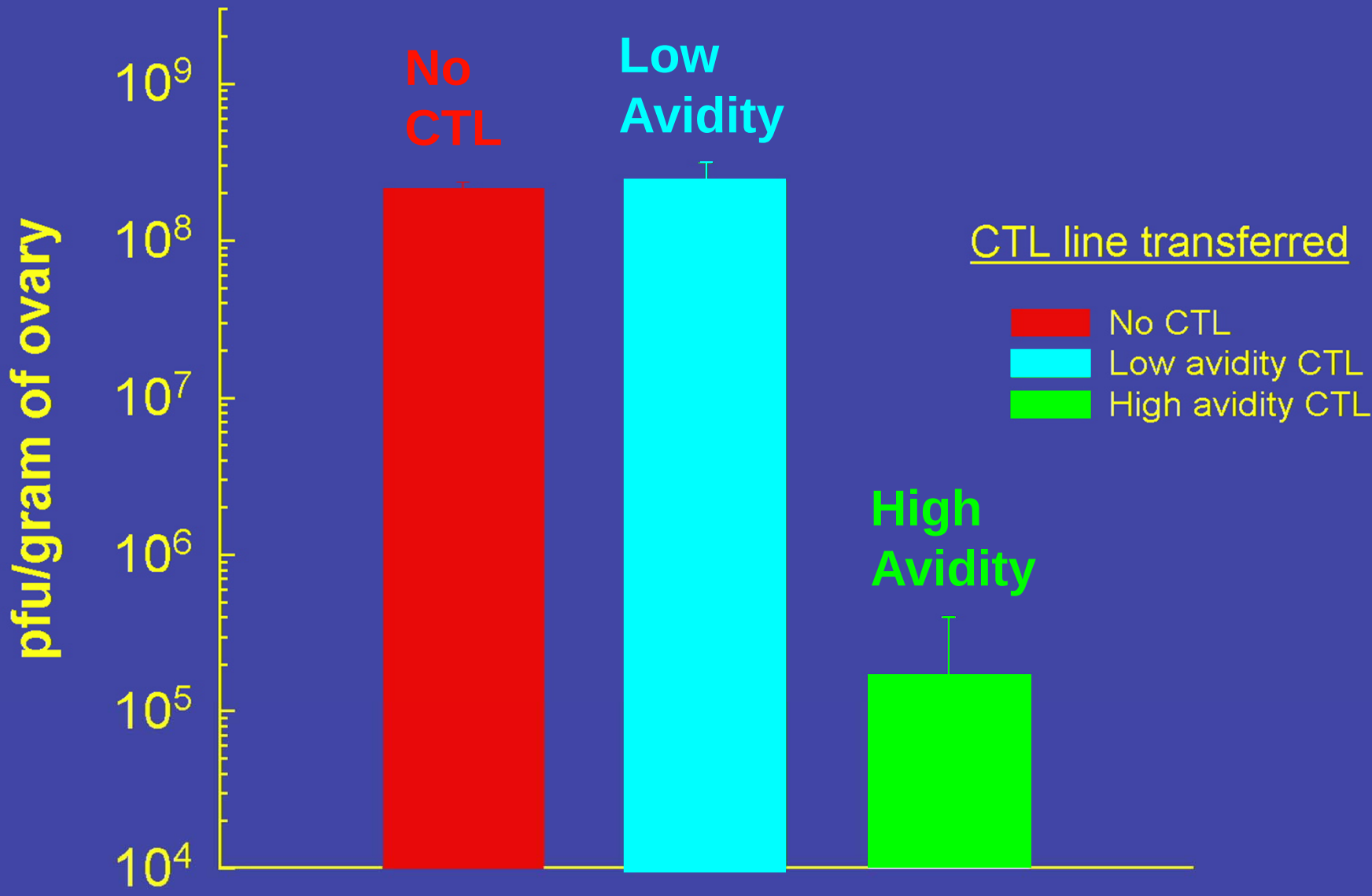
Oh et al., *PNAS* 2004

Hypothesis: are high avidity CTL more effective at viral clearance?



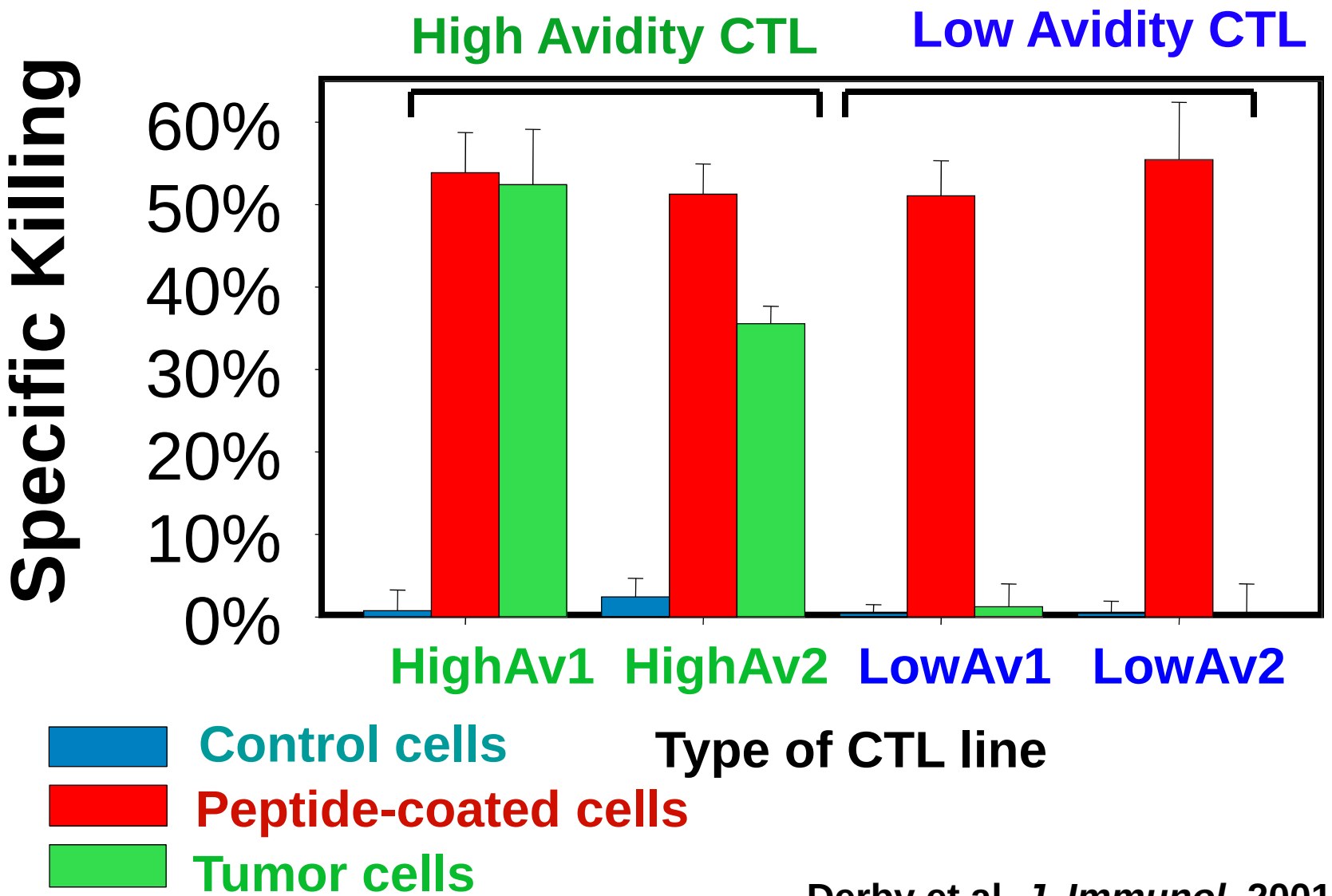
Alexander-Miller et al. *PNAS* 1996; Derby et al., *J. Immunol*. 2001; Belyakov et al, *Blood* 2006

High Avidity CTL Clear Virus Infection in SCID Mice More Effectively Than Low Avidity CTL



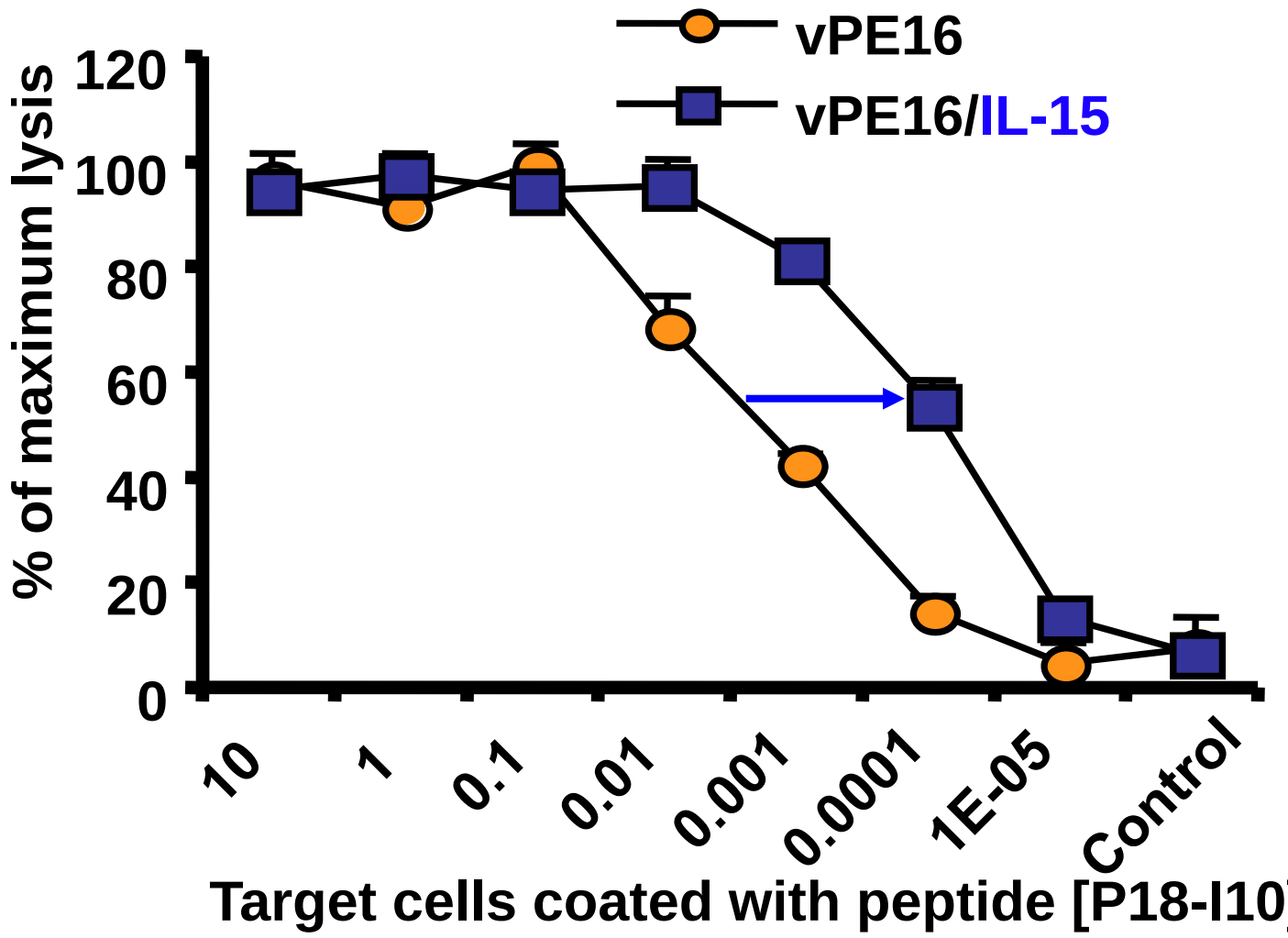
Alexander-Miller et al., PNAS 1996

Only HIGH AVIDITY CTL kill tumor cells



Derby et al, *J. Immunol.* 2001

Immunization with antigen + IL-15 induces higher avidity memory CD8+ CTL

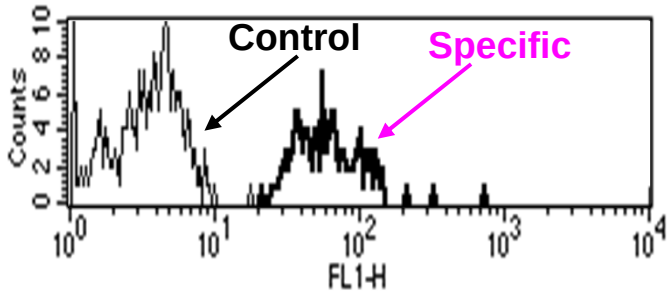


2 months after immunization

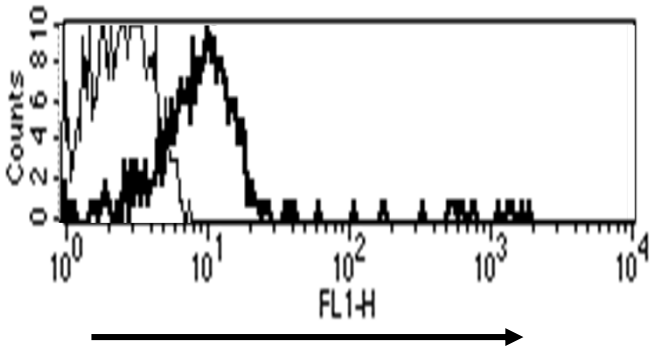
Oh et al., *PNAS* 2004

Higher avidity cells express more IL-15Rα, proliferate more in vivo, and persist longer

High



Low



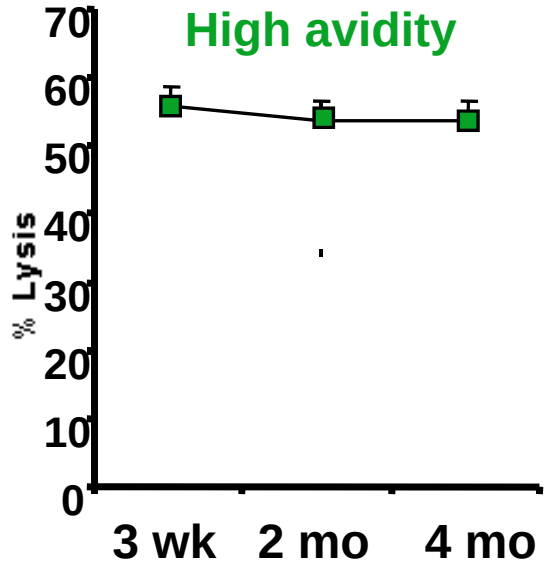
FITC anti-IL-15Rα
(Fluorescence, log scale)

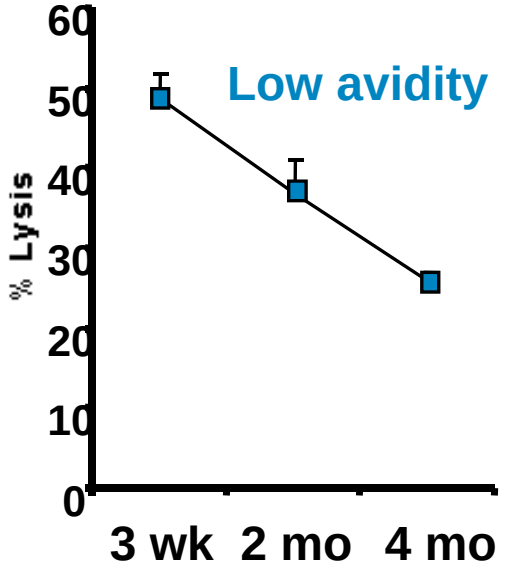
Proliferation
3 wk after adoptive Transfer to naïve Recipients.

87.2%

43.6%

Survival over time

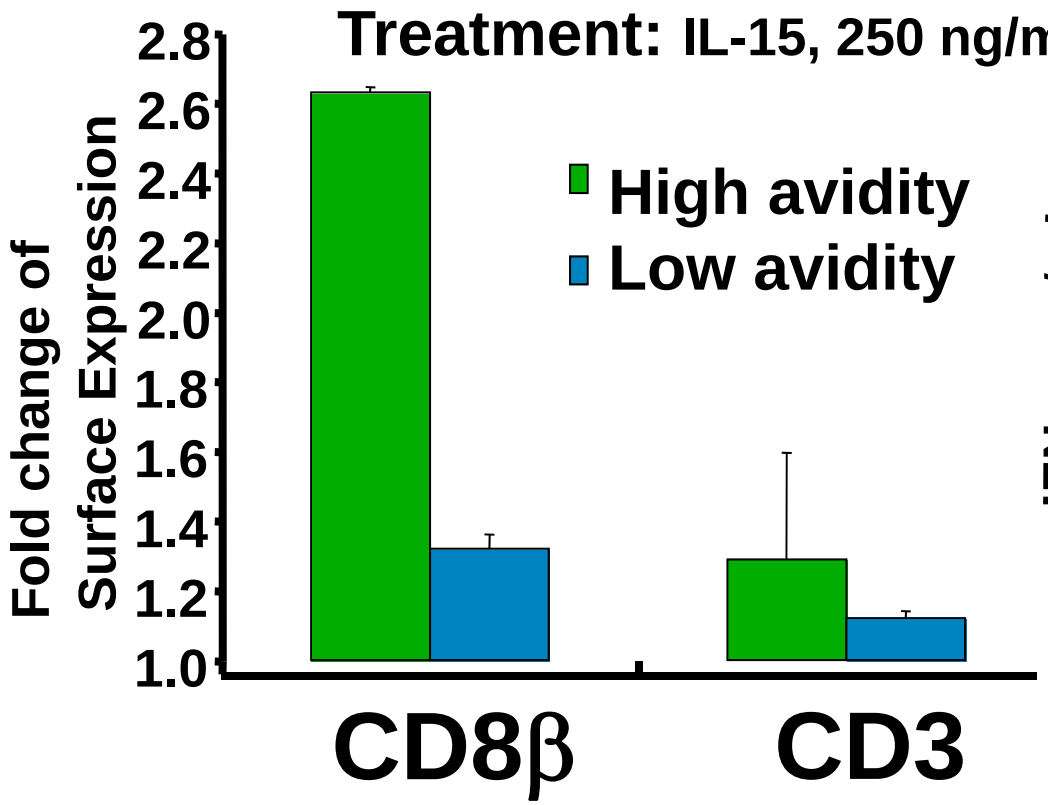


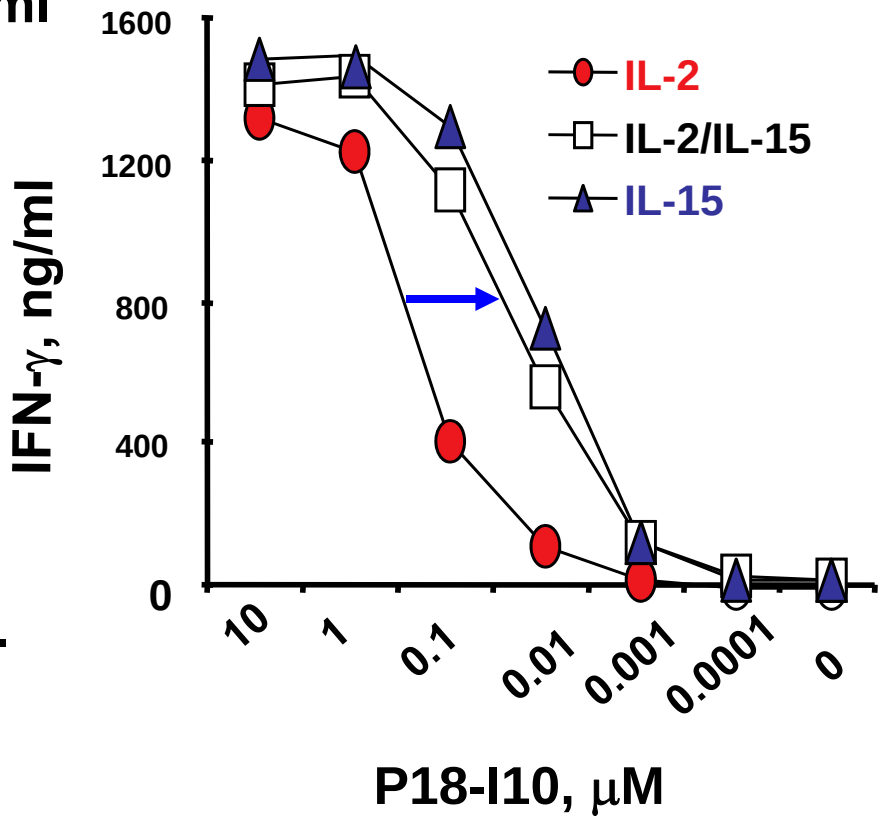


Time after boost

Oh et al., *PNAS* 2004

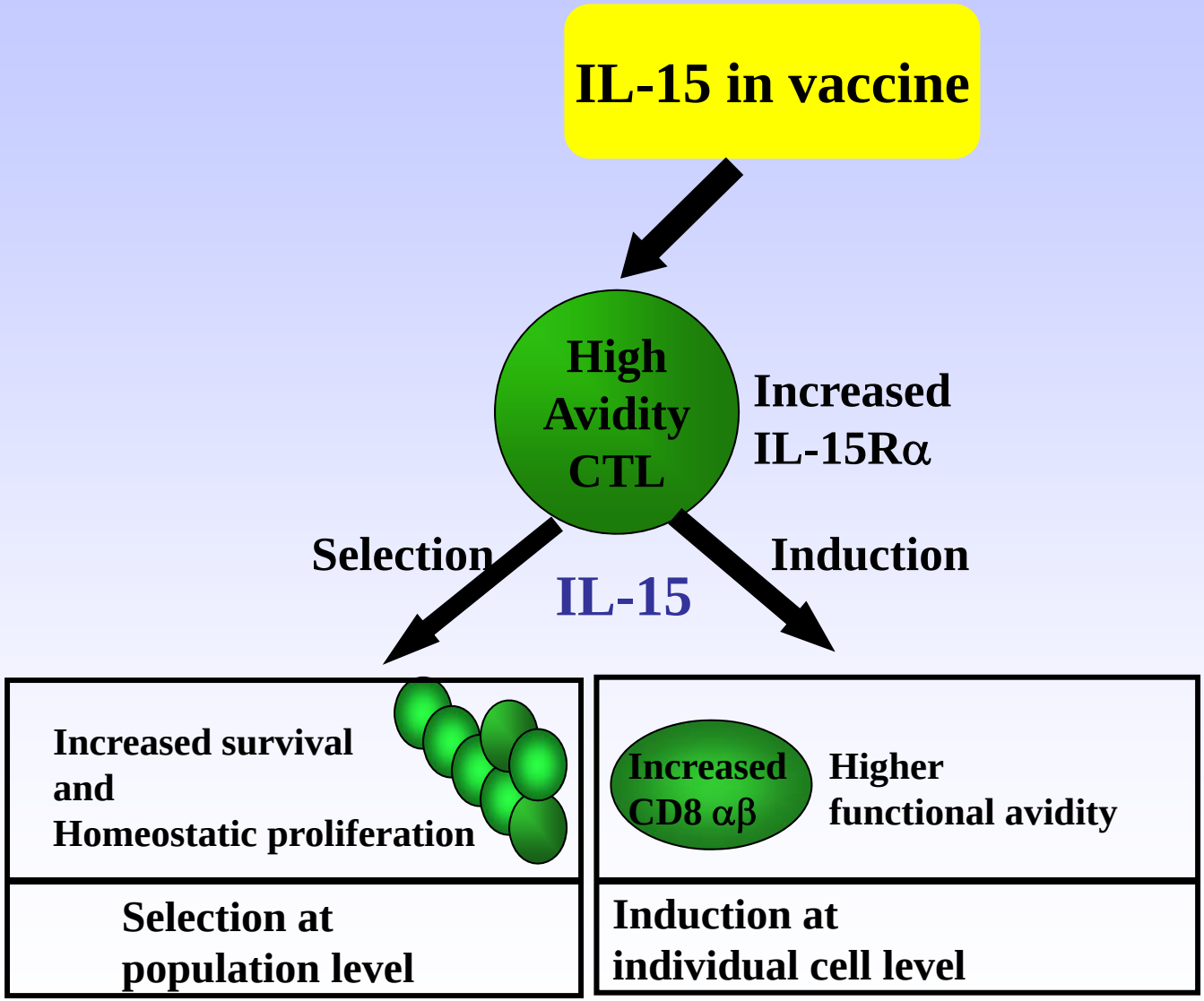
IL-15 increases the expression levels of CD8β in high avidity CD8+ CTL, and further increases their avidity





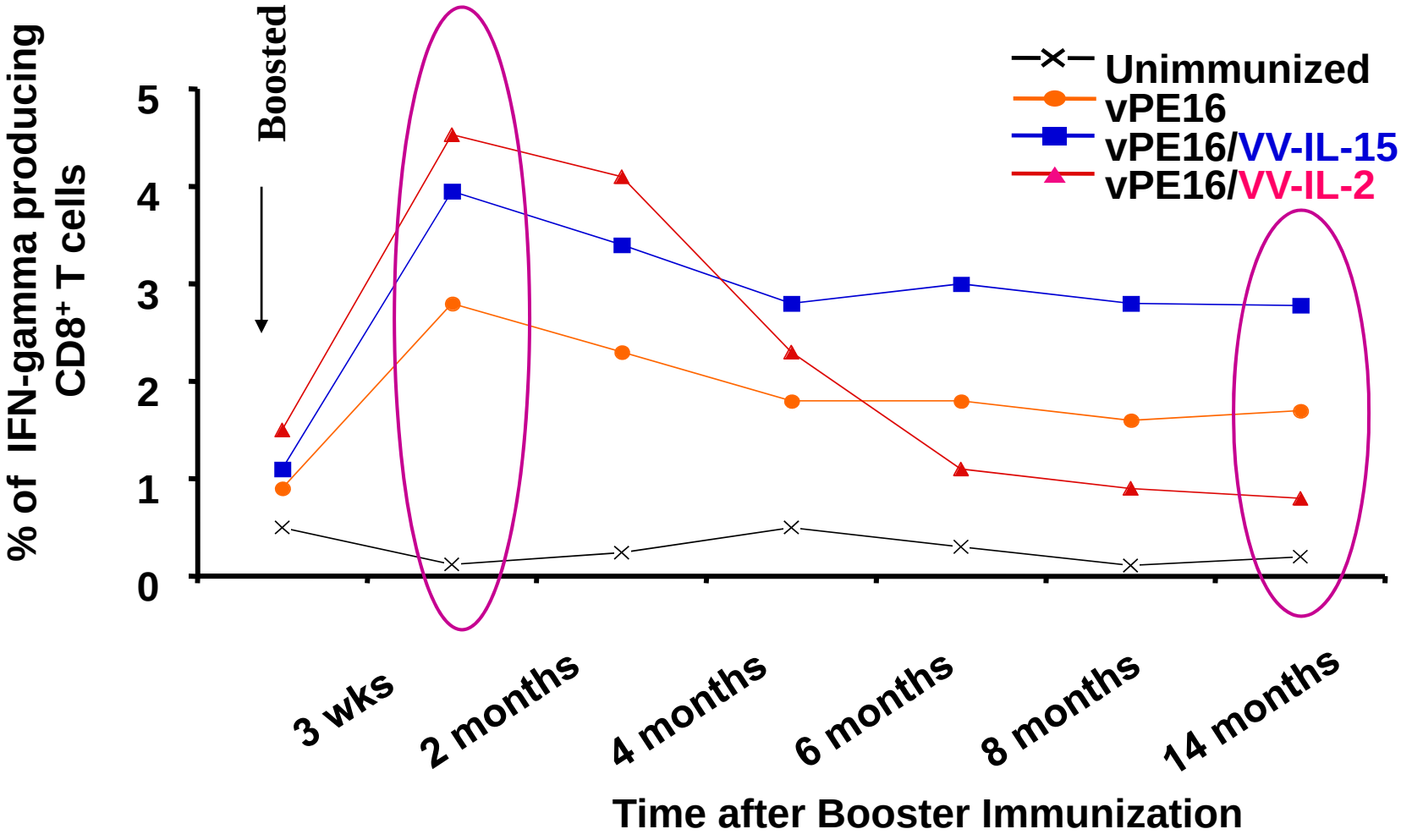
Oh et al., *PNAS* 2004

Role of IL-15 and costimulation in CTL Avidity Maturation



Oh et al. J. Immunol. , 2003; Oh et al. PNAS, 2003;Oh et al. PNAS, 2004

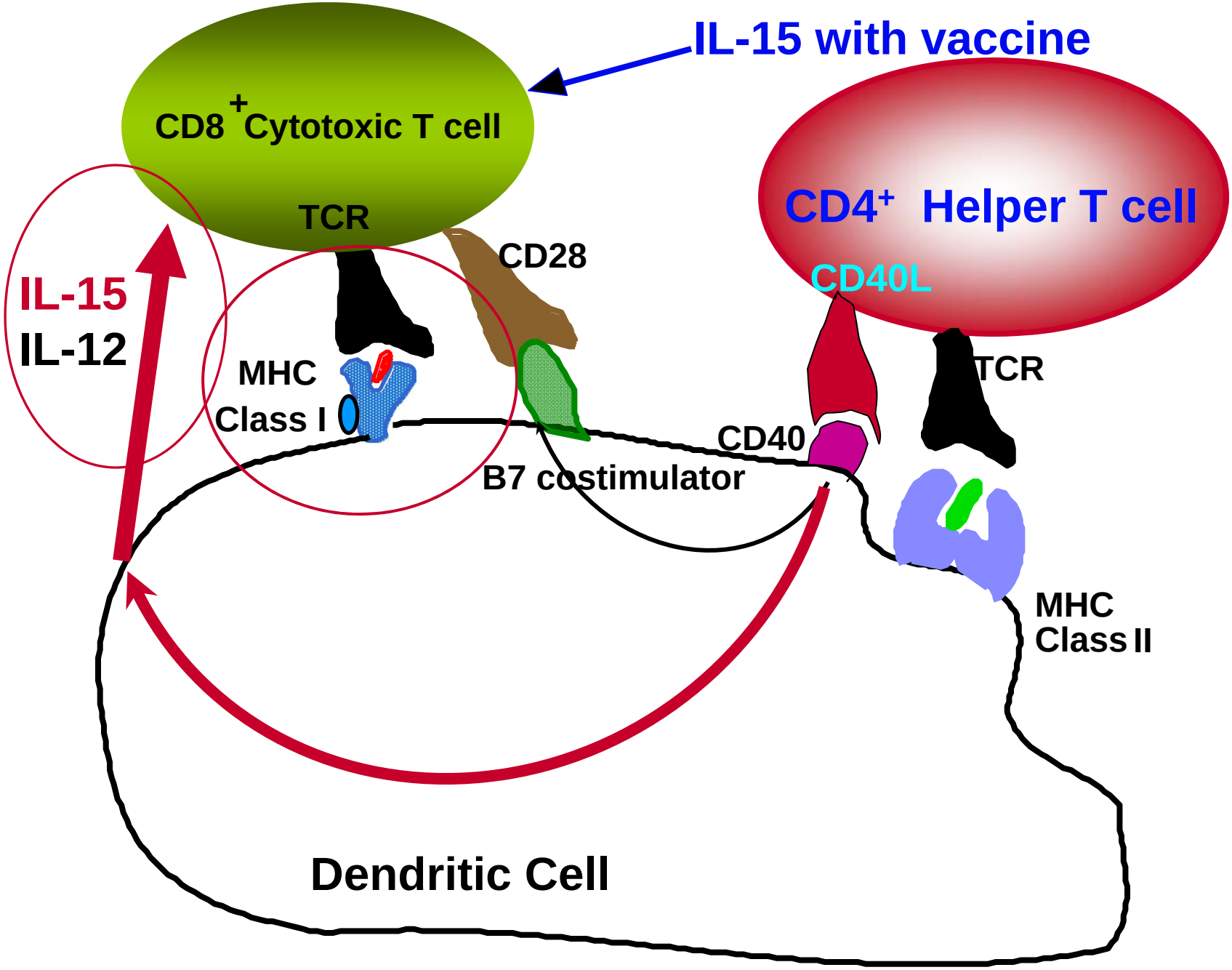
IL-15 expression by a vaccine vector induced longer-lived memory CD8+ CTL: IFN-gamma-producing cells



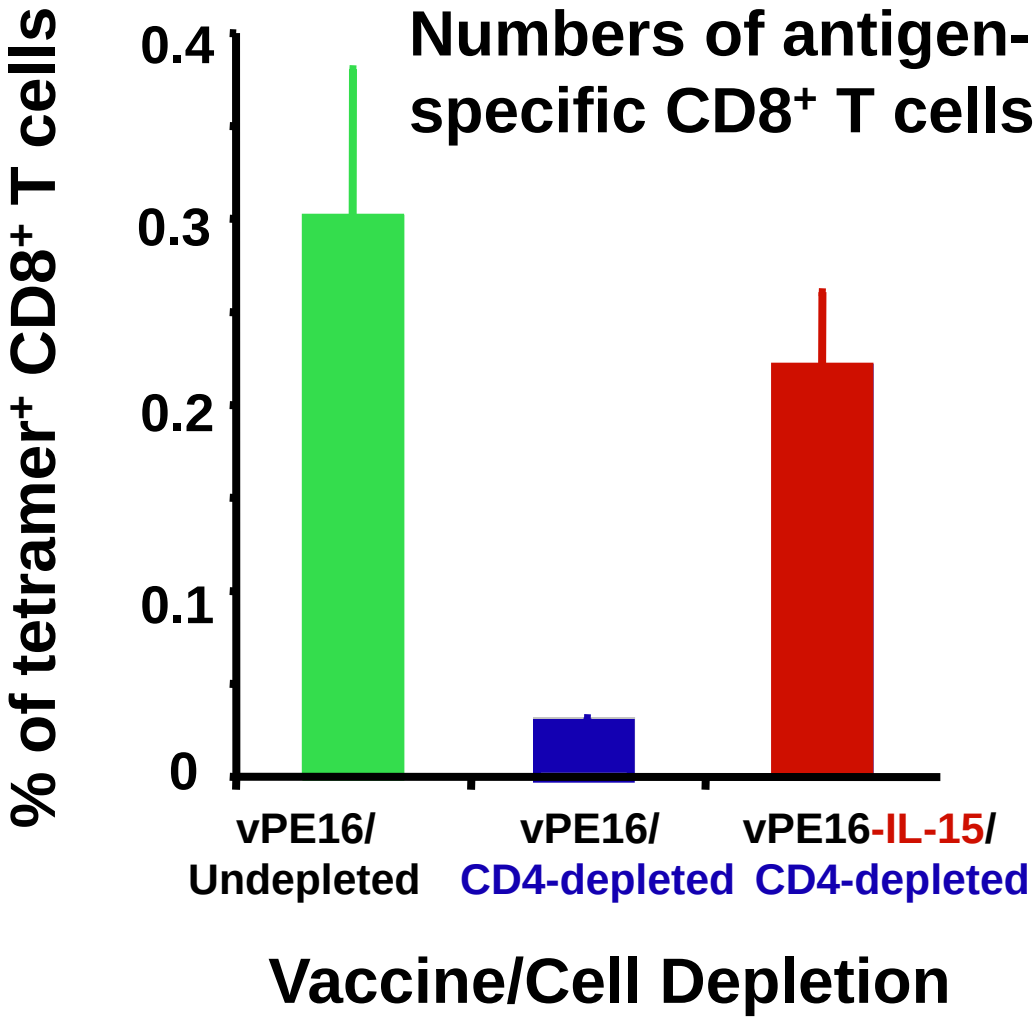
Explained by 1. Higher IL-15Rα expression
2. Greater homeostatic proliferation

Oh et al., *PNAS* 2003

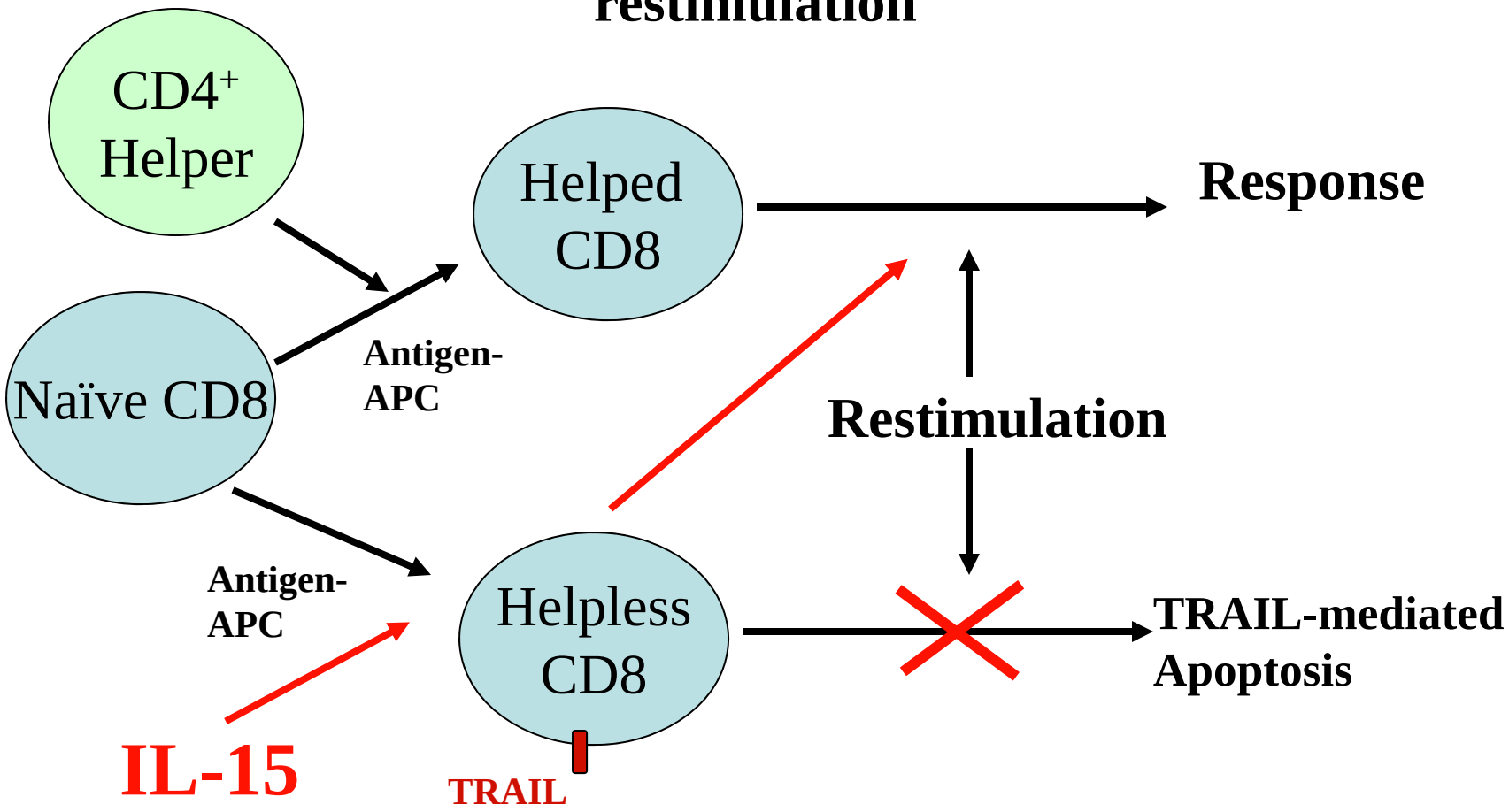
CD4+ T-cell Help for CD8+ CTL Mediated Through Activation of Dendritic Cell



IL-15 during immunization substitutes for CD4+ T cell help to induce long-lived memory CTL (One year after immunization)

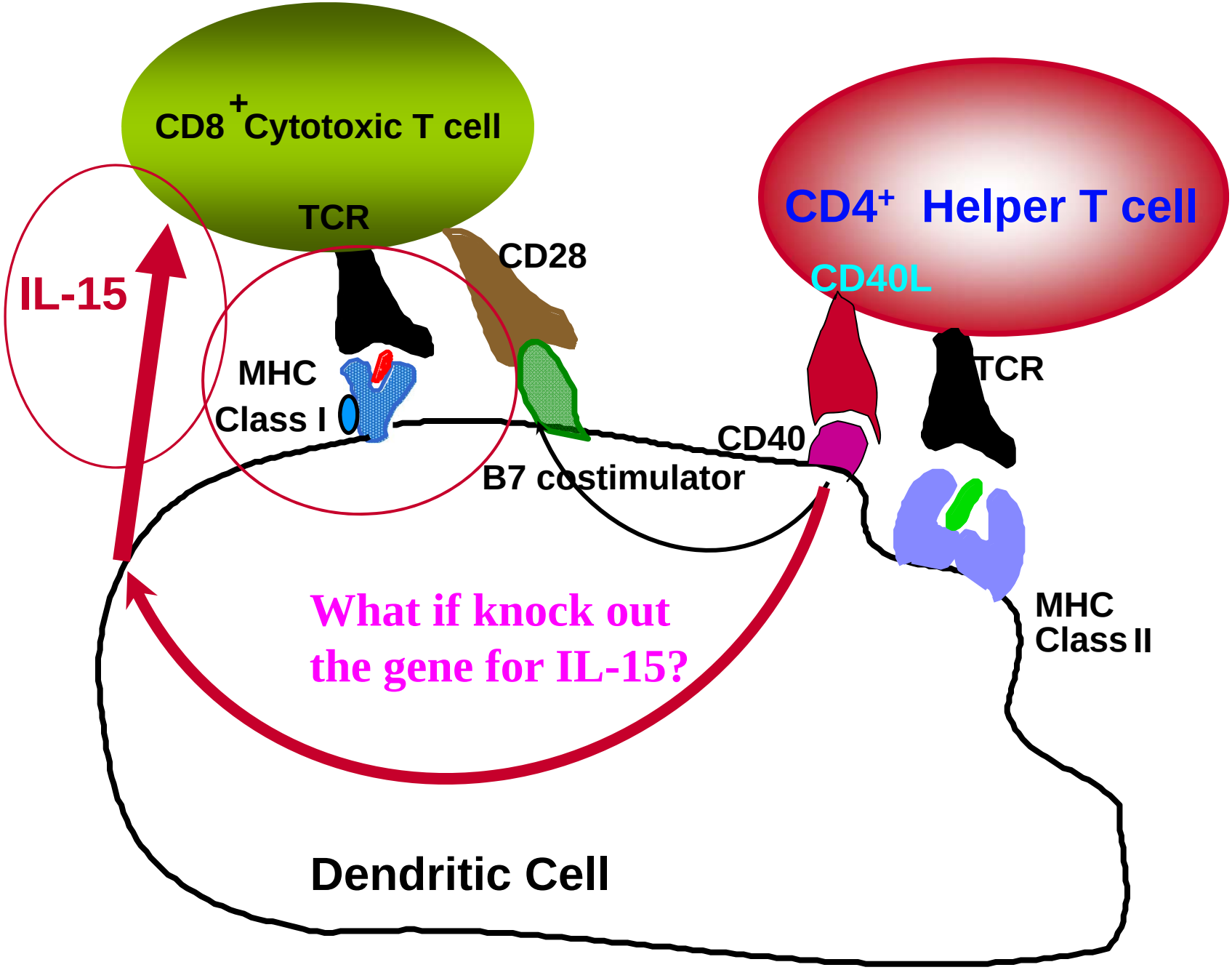


Helpless CD8 T cells upregulate TRAIL and undergo TRAIL-mediated apoptosis (programmed death) on restimulation

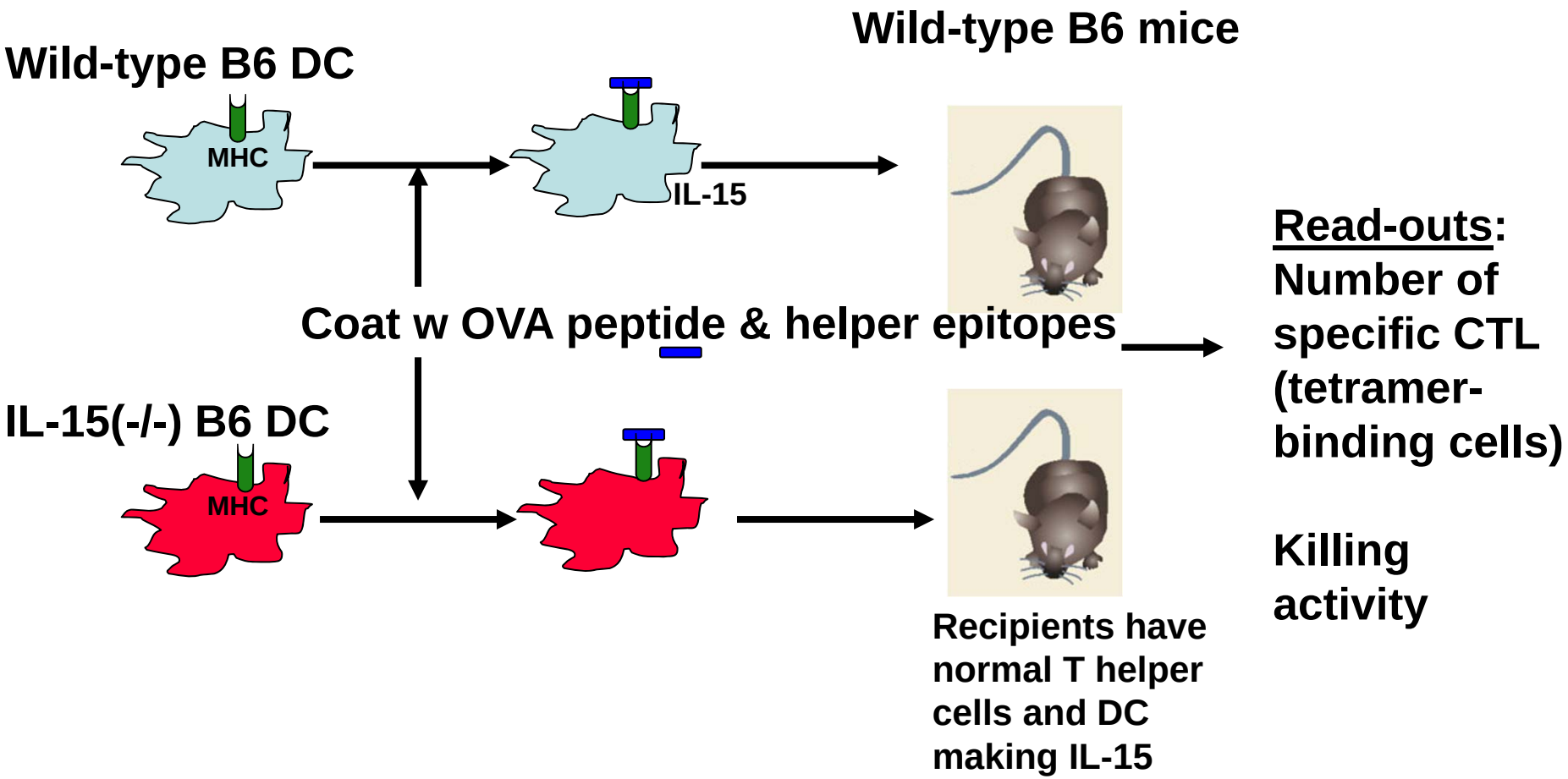


Janssen et al. Nature 434: 88, 2005

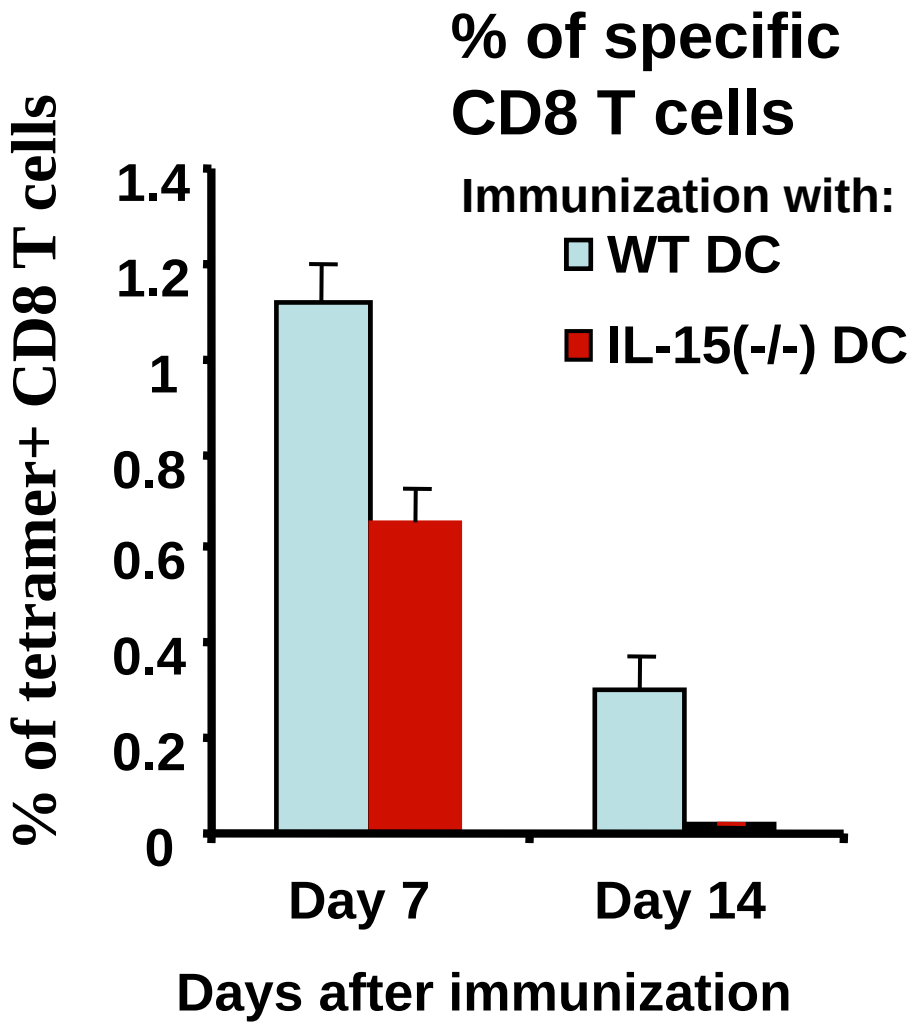
CD4+ T-cell Help for CD8+ CTL Mediated Through Activation of Dendritic Cell

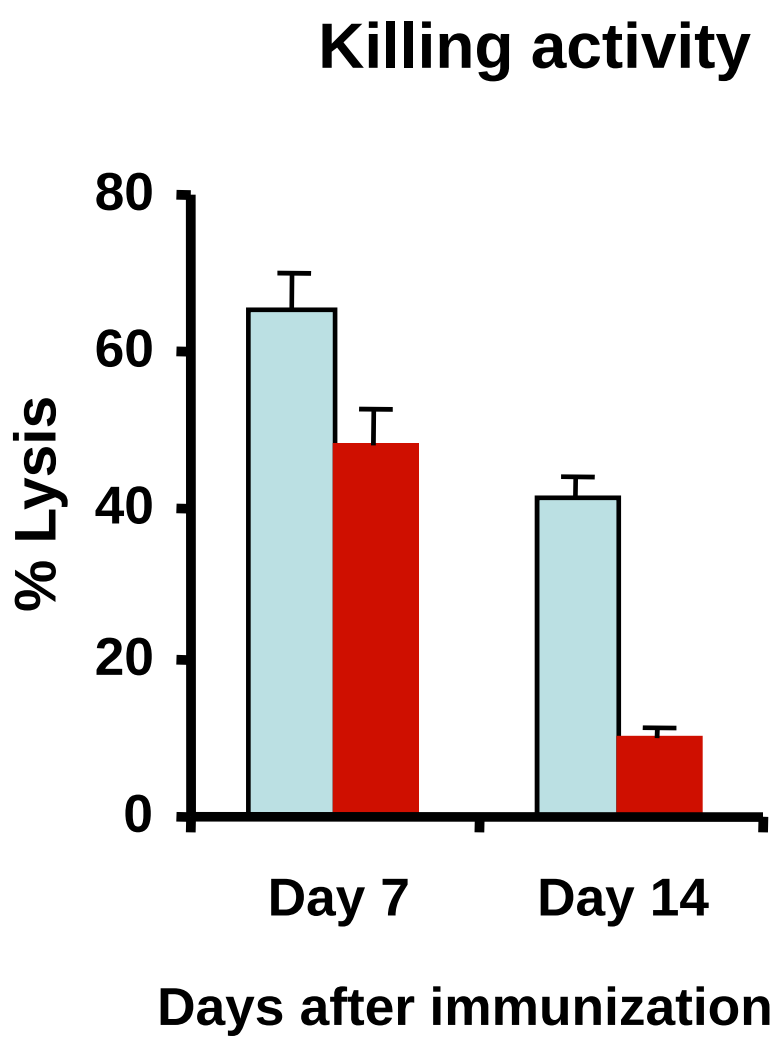


To test whether IL-15 is necessary for such help to be effective, we examined whether effective help required dendritic cells that could produce IL-15.



DC from IL-15-/- mice fail to induce memory Ova-specific CD8$^+$ T cells: Help requires induction of IL-15





Oh et al., unpublished

Conclusions

IL-15 in a vaccine:

- **Induces longer-lived memory CD8 CTL**
- **Induces higher avidity CD8 CTL**
- **Overcomes the need for CD4 T cell help to elicit prolonged CD8 T cell memory and prevent TRAIL-mediated apoptosis**
- **Is a critical natural mediator by which CD4 T help elicits long-lived CD8 memory T cells**

Responsiveness to IL-15 also accounts for CTL avidity maturation by

- **Selective survival of high avidity CTL**
- **Induction of expression of CD8 coreceptor**

Thus IL-15 is a most promising candidate to enhance the efficacy of vaccines for use in HIV-infected or cancer patients with a deficiency of CD4 T cell help (including therapeutic vaccines for AIDS or cancer).

Collaborators

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Jay A. Berzofsky[1]

NIAID Tetramer Facility, NIH

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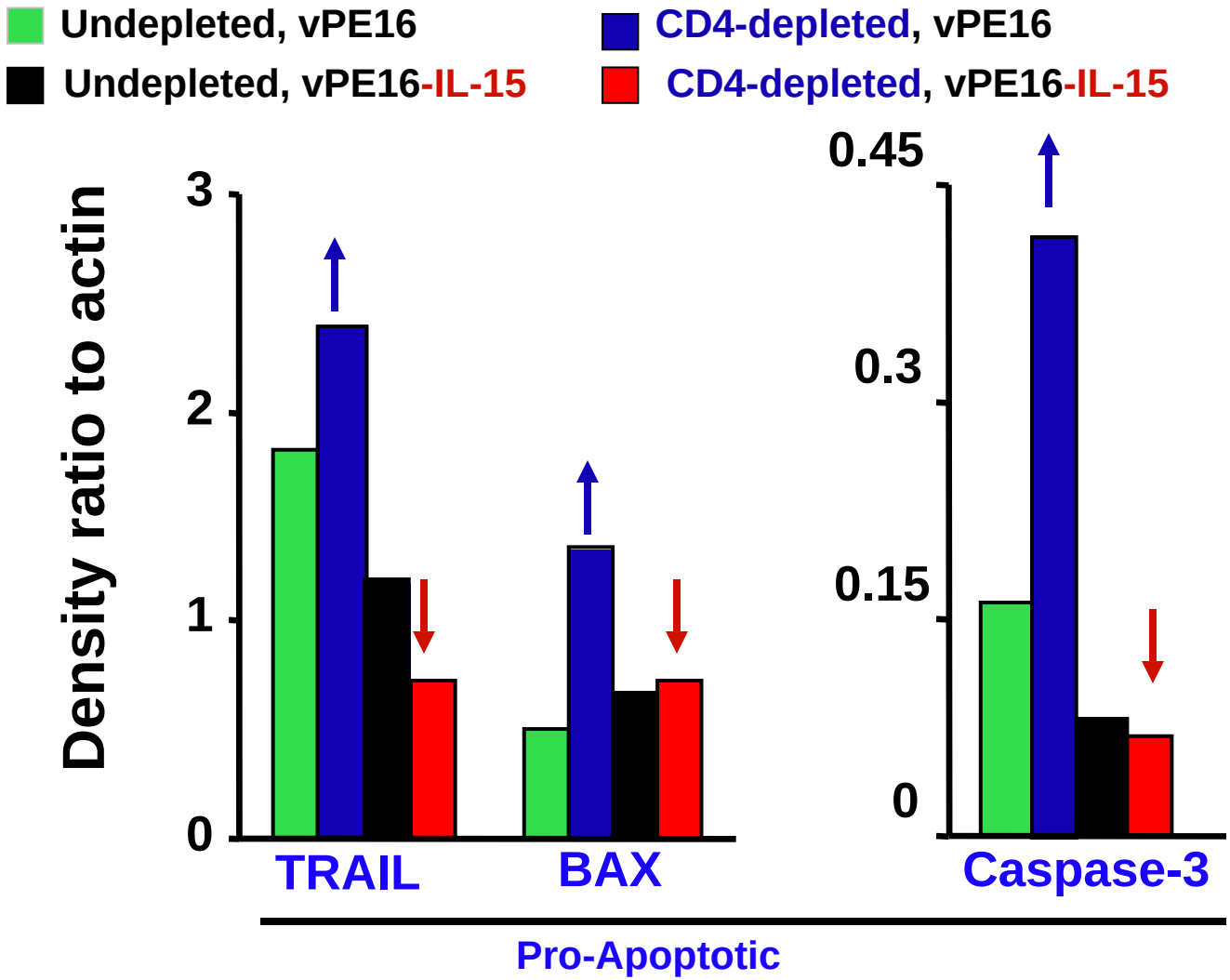
[3]Metabolism Branch, CCR, NCI, NIH

In vivo boosting of CD8 T cells primed without CD4 help upregulates TRAIL, Bax, and Caspase 3. IL-15 in vaccine reduces these and increases Bcl-XL, blocking apoptosis.

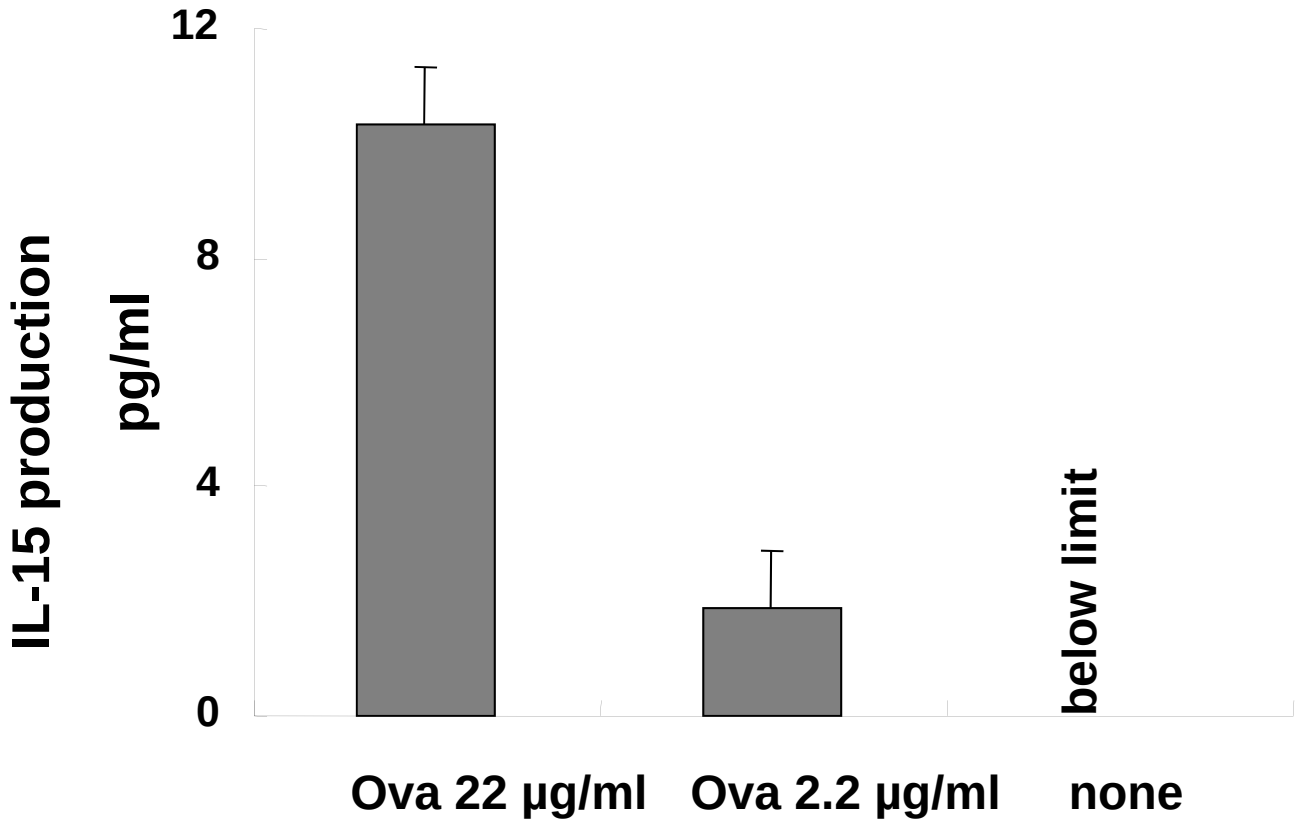


Western blot of bead-purified cells

Oh et al., unpublished

CD4+ T helper cells stimulating DC presenting cognate antigen to secrete IL-15

OTII OVA-Specific CD4 T cells + DC ± OVA --> Assay sup for IL-15



Antigen presented by APCs to OTII helper cells

IL-15 at priming selects for longer lived, higher avidity memory CTL and IL-15 responsiveness may account for CTL avidity maturation and replace CD4 help

Background:

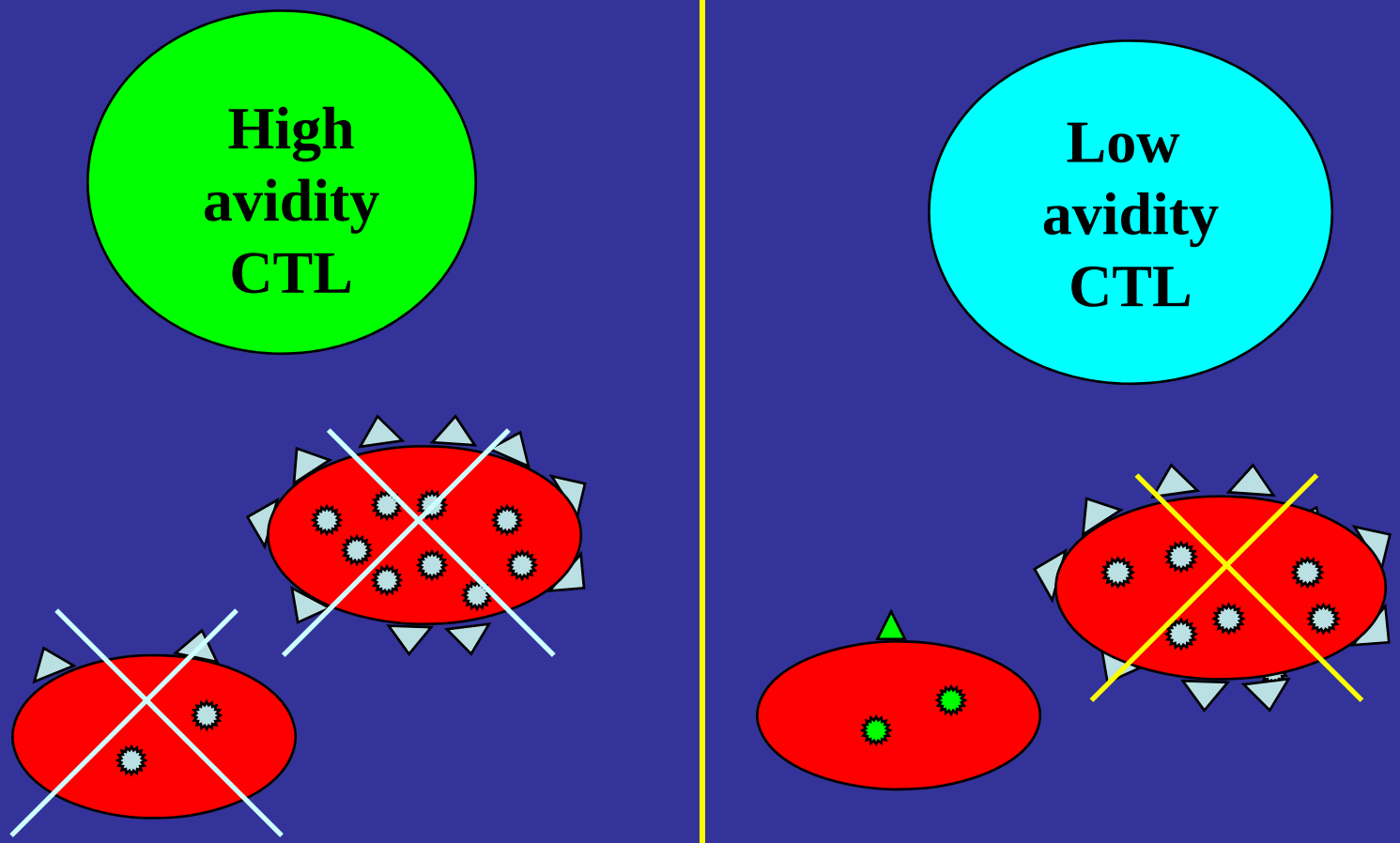
- **IL-15 is known to be required for maintenance of CTL, but we asked whether priming in the presence of IL-15 would affect the quality of the response long after the IL-15 was gone.**

- **We previously showed that high avidity CTL were more effective at clearing virus in vivo, but it was not known how to induce them preferentially with a vaccine.**

- **T cell avidity maturation has been a longstanding enigma, in that TCRs do not undergo somatic mutation, unlike antibodies.**

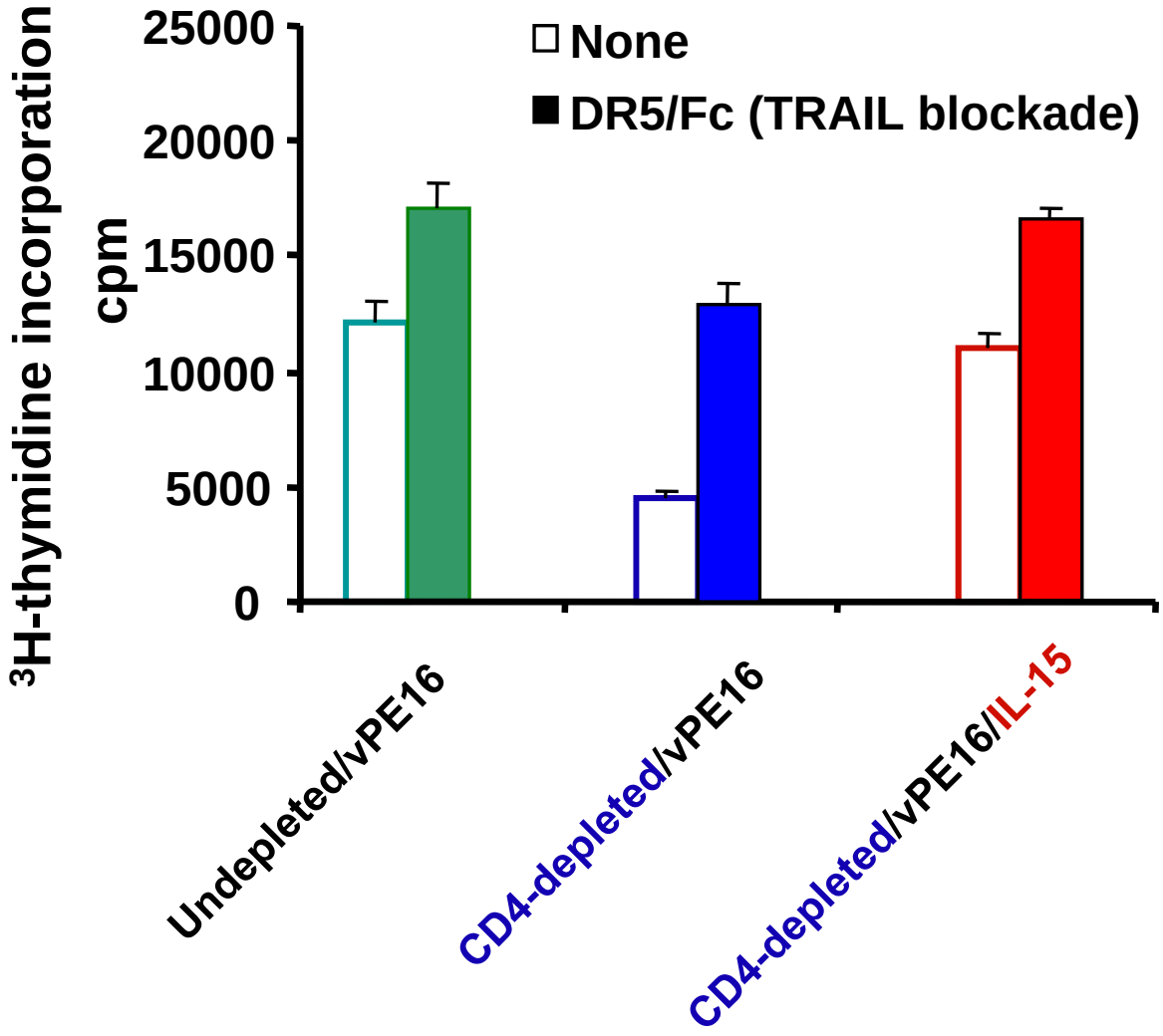
- **$CD4^+$ T cell help is necessary for induction of long-lived memory CTL, but the molecular mechanism of this help is unknown.**

Improved viral clearance by high avidity CTL



Alexander-Miller et al. *PNAS* 1996; Derby et al., *J. Immunol*. 2001; Belyakov et al, *Blood* 2006

IL-15 mimics CD4$^+$ T cell help to prevent TRAIL-mediated apoptosis on restimulation of T cells in vitro

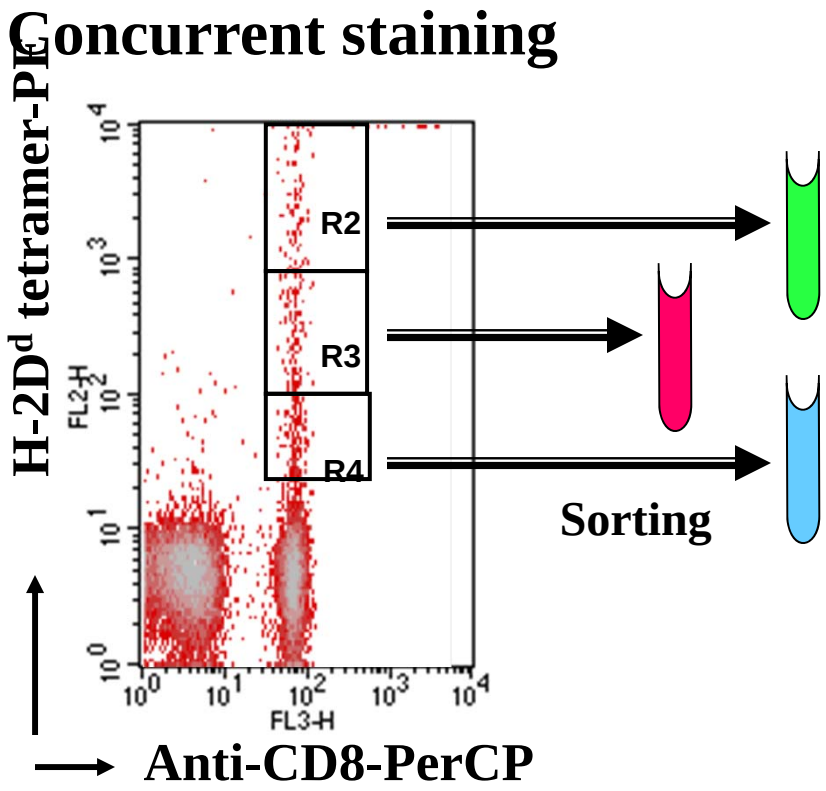


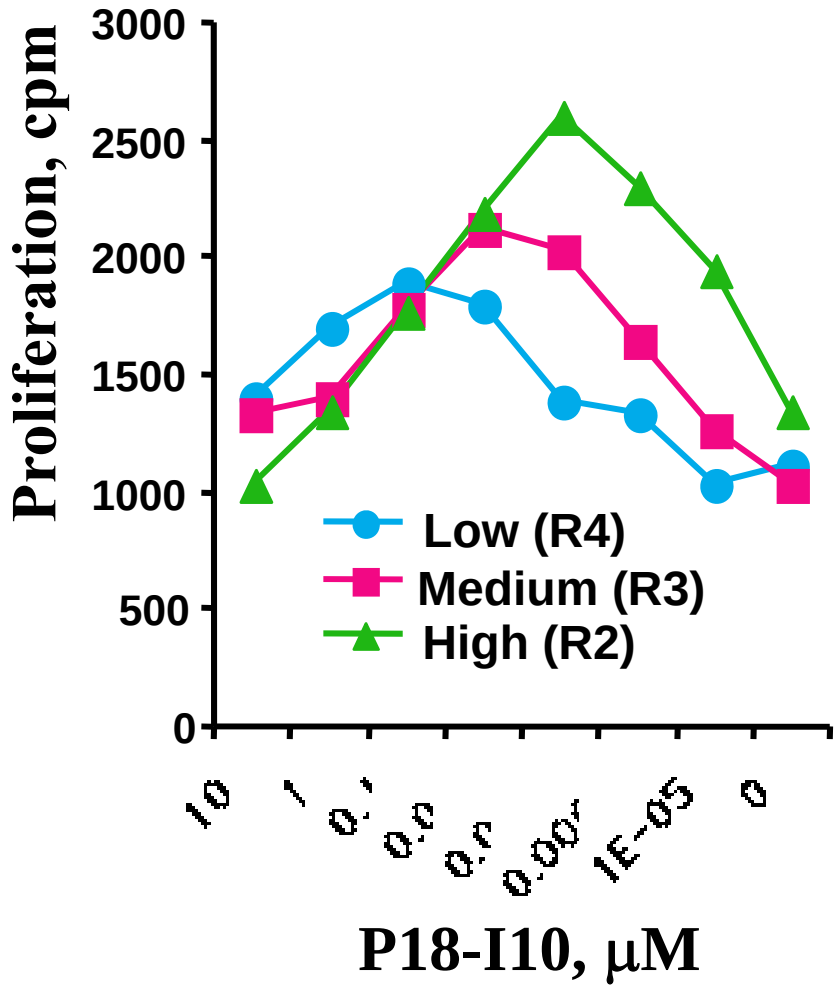
Oh et al., unpublished

Hypothesis :

These results may in part explain recent observation from Schoenberger lab (*Nature*, 2003) and the Shen and the Bevan labs (*Science*, 2003) that a major role of $CD4^+$ T-cell help in a $CD8^+$ T cell response is to induce long-lasting memory T cells.

Concurrent staining of CD8+ CTL with anti-CD8 and tetramer can separate CD8+ CTL bearing a broad range of avidity: *Proliferation assay of the sorted-cells*





Oh et al., *PNAS* 2004

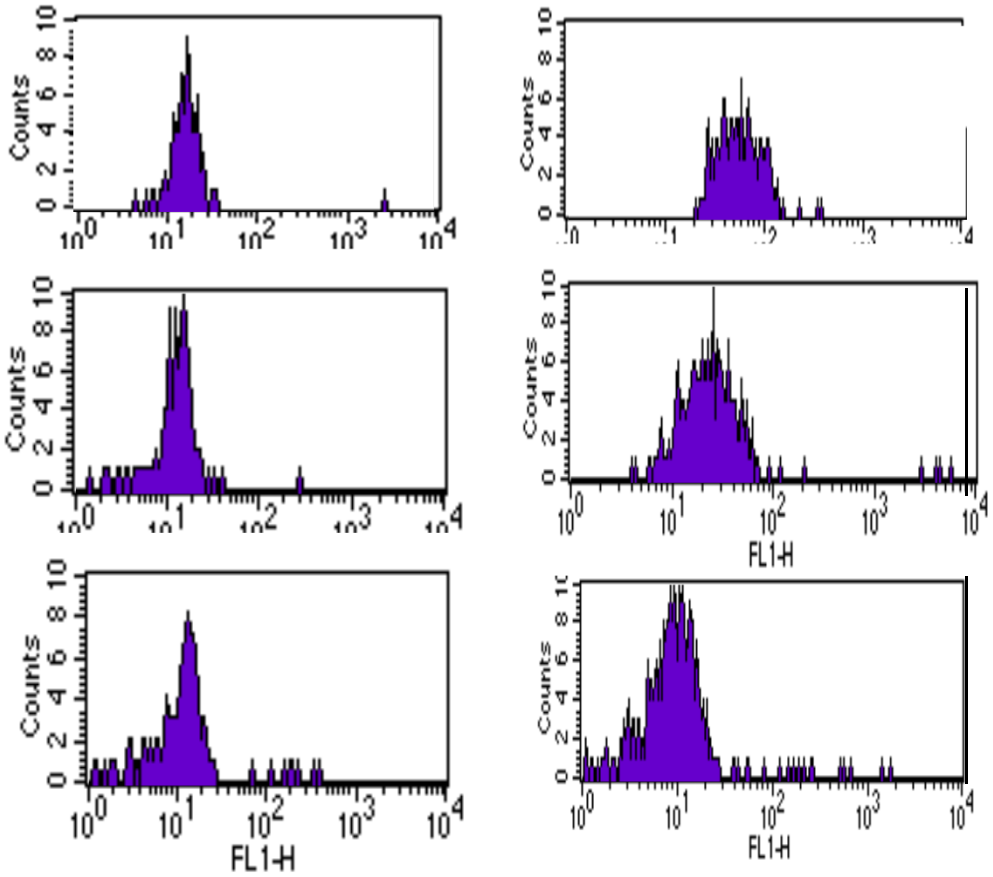
High avidity CD8+ CTL express higher levels of CD8β, but not TCRβ (2 months after boosting)

(Avidity by Concurrent staining)

High

Intermediate

Low



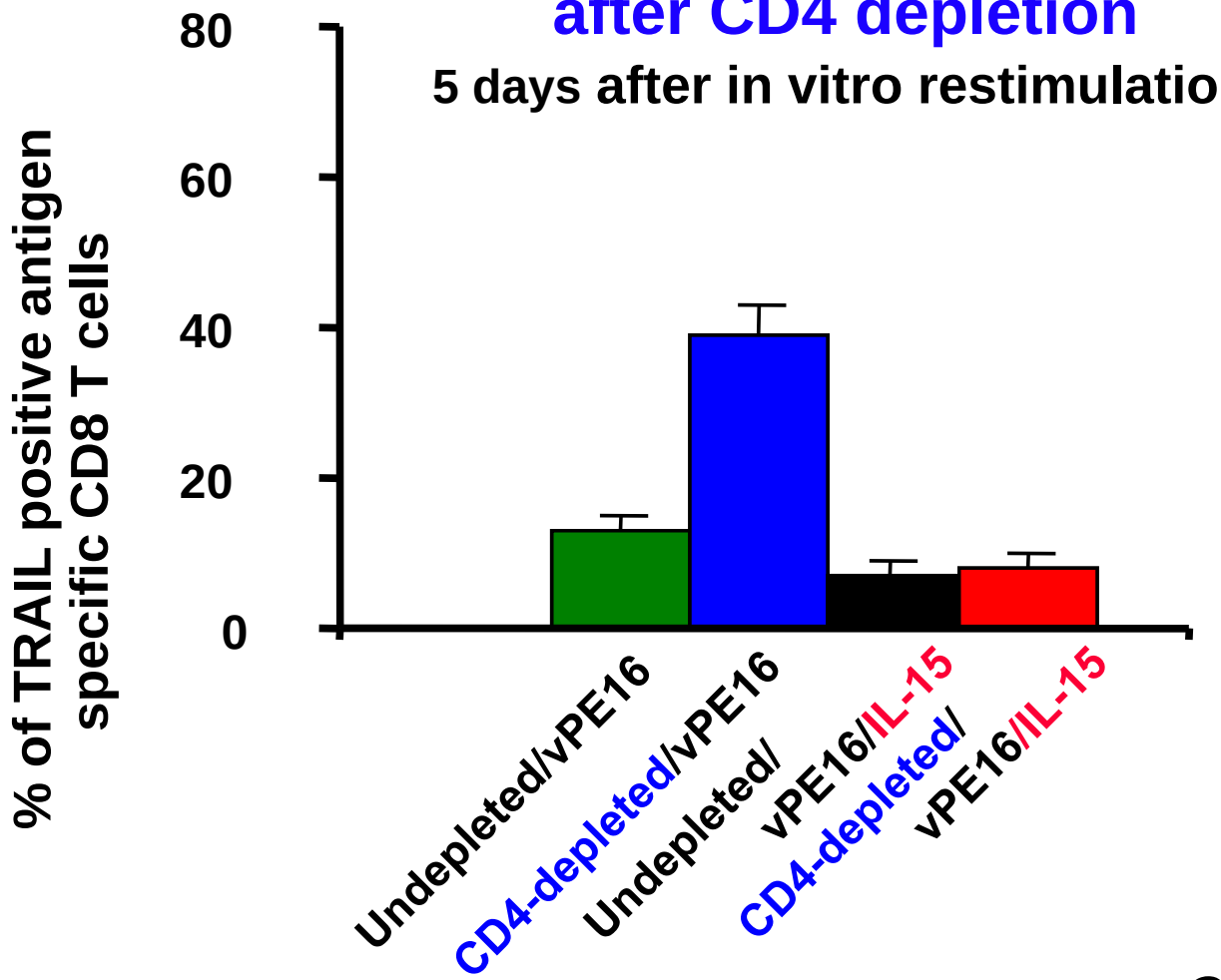
TCRβ ⟶

CD8β ⟶

Oh et al., *PNAS* 2004

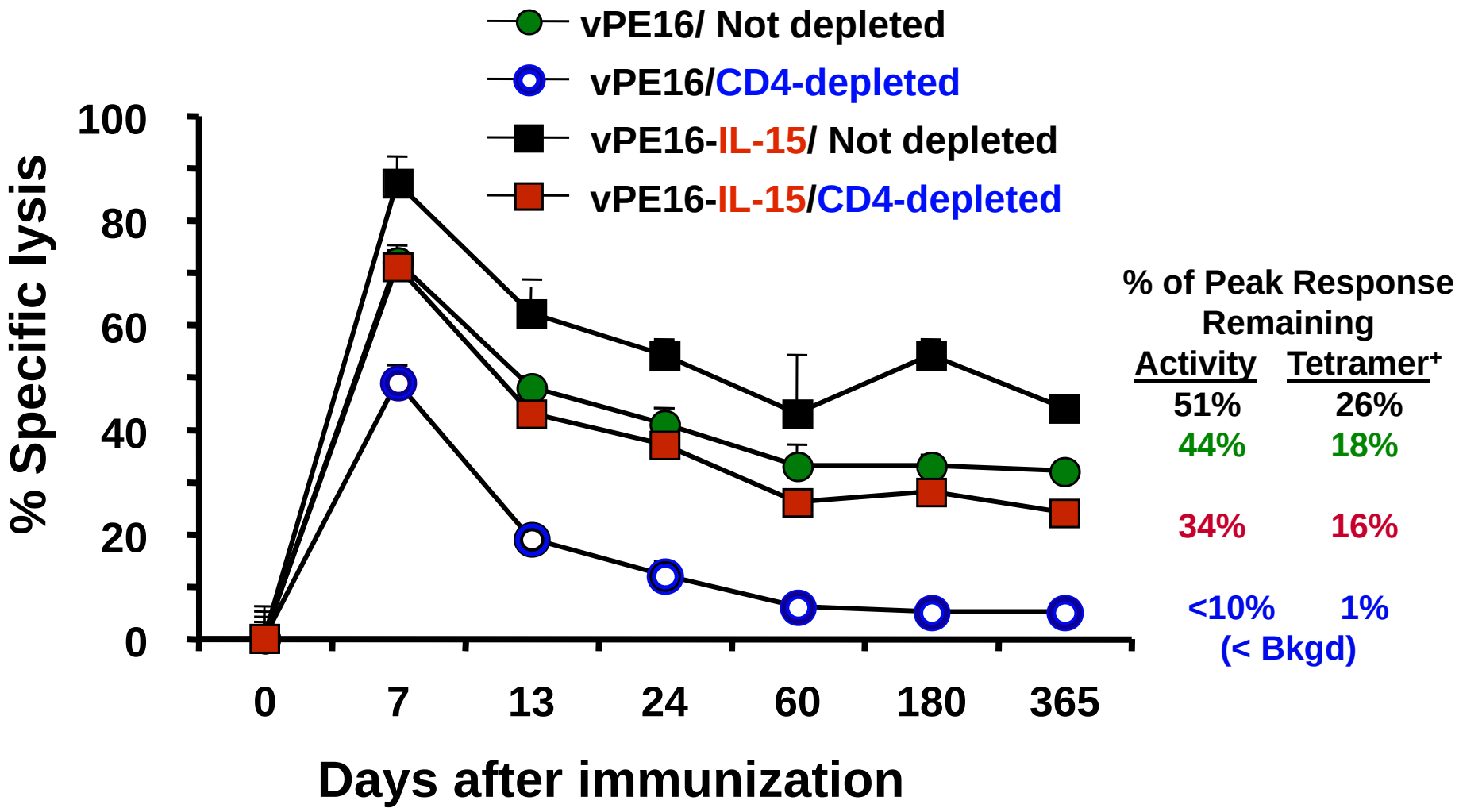
TRAIL expression on antigen-specific tetramer$^+$ CD8$^+$ T cells from immunized mice after restimulation with peptide and APC in vitro:

Higher TRAIL in cells from mice immunized without IL-15, after CD4 depletion



Oh et al., unpublished

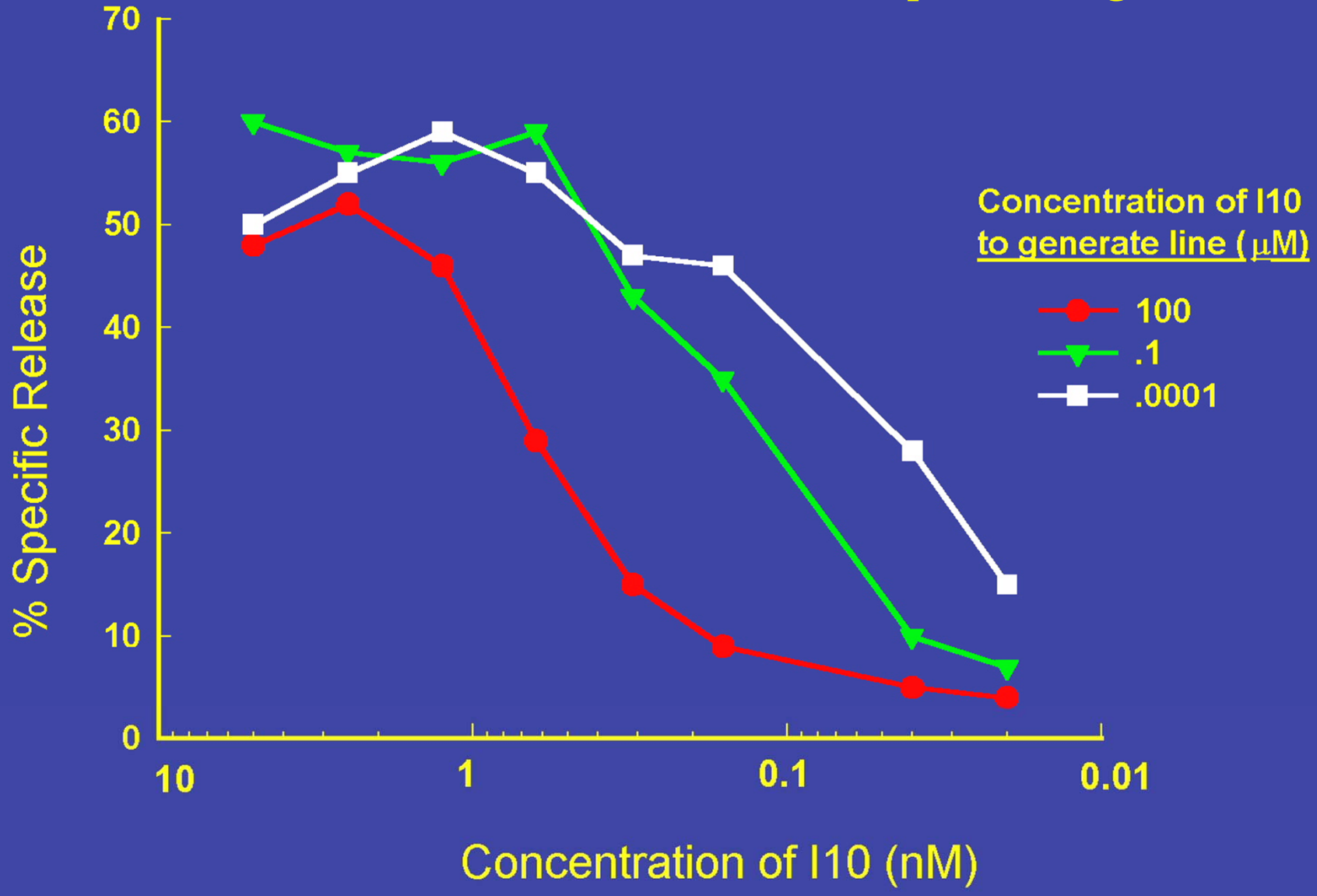
IL-15 substitutes for CD4+ T cell help to Induce long-lived memory CTL



E:T = 50:1

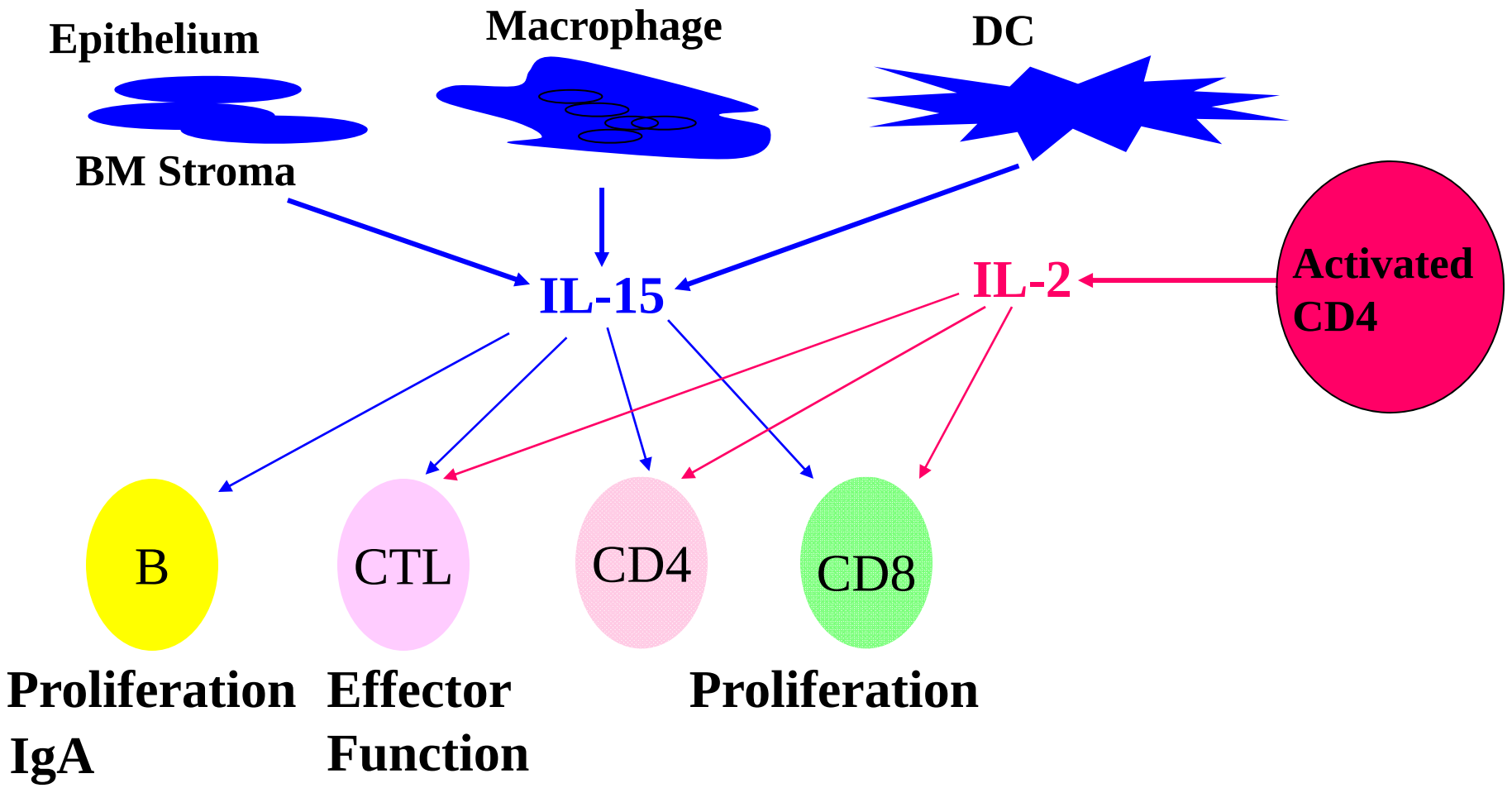
Oh et al., unpublished

High, Intermediate, and Low Avidity CTL Generated by Stimulation with Different Concentrations of Peptide Antigen

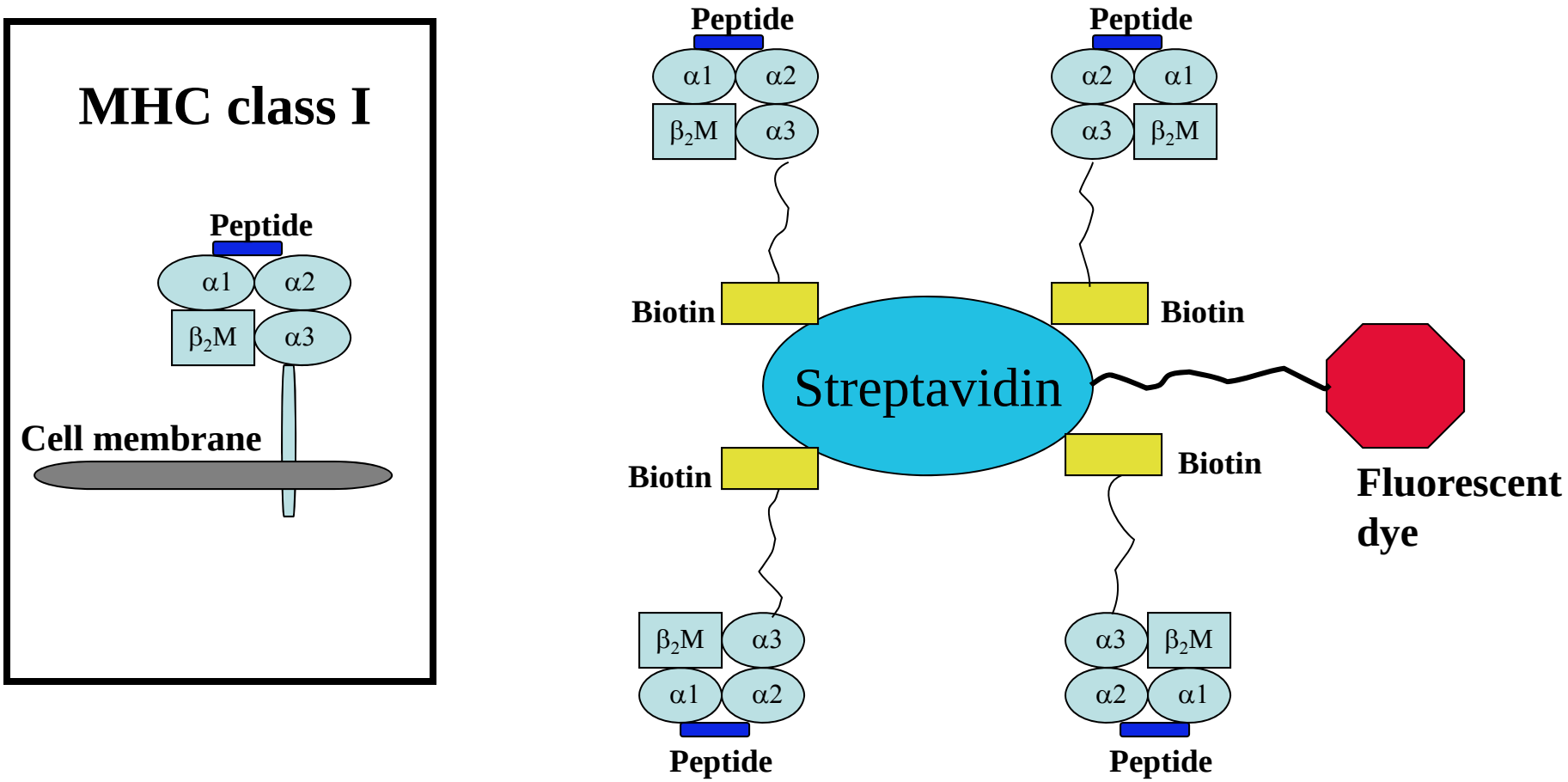


Alexander-Miller, Leggatt, & Berzofsky, *PNAS* 93: 4102, 1996

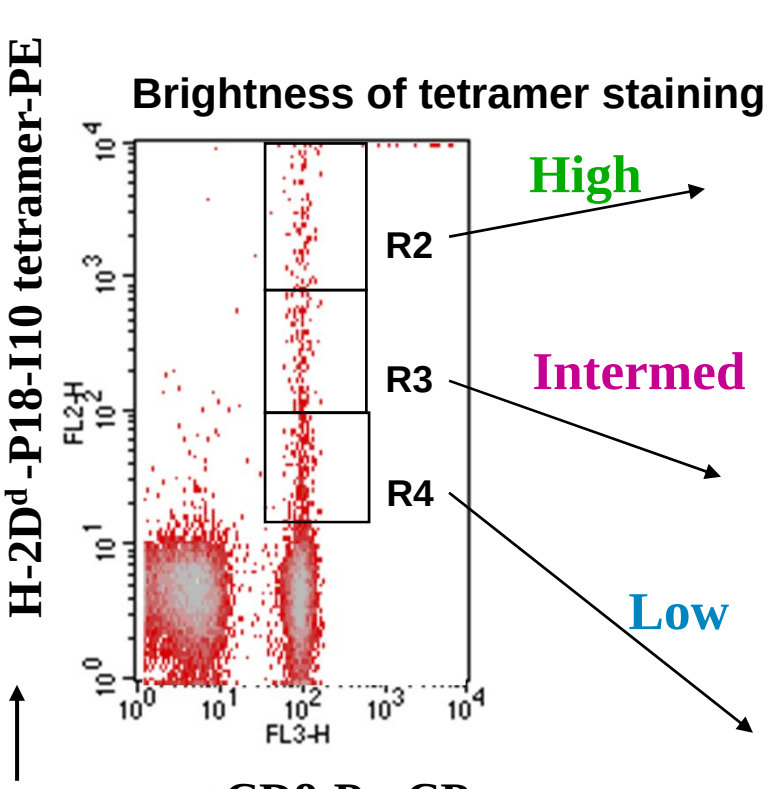
IL-2 & IL-15: SHARED FUNCTIONS IN IMMUNE SYSTEM (ADOPTIVE IMMUNITY)



MHC class I tetramer



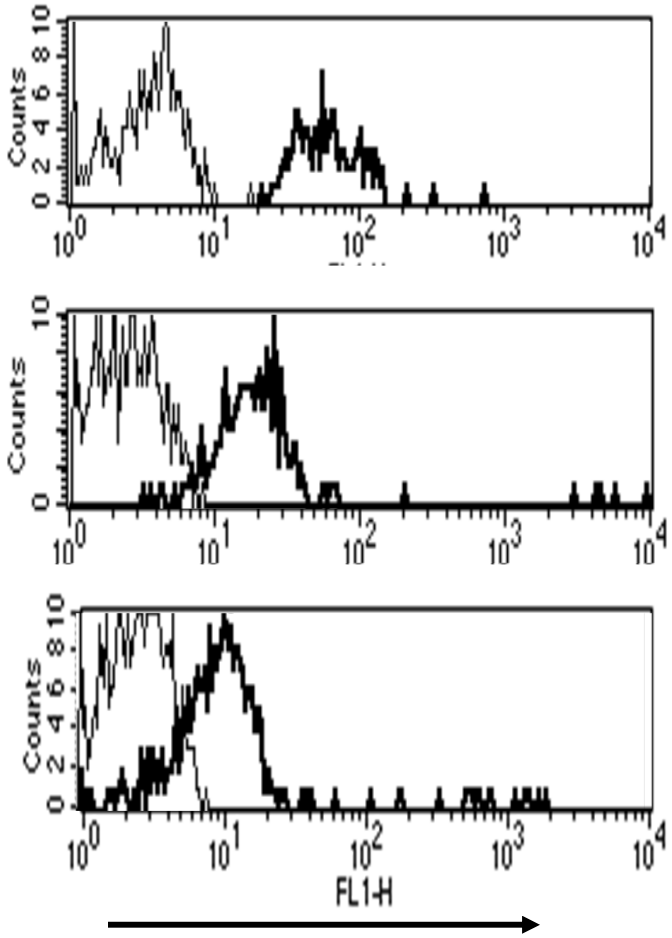
Higher avidity cells express higher levels of IL-15Rα and proliferate more in response to natural levels of IL-15 (homeostatic proliferation)



High

Intermed

Low



Homeostatic Proliferation 3 wk after adoptive Transfer to naïve Recipients.

87.2%

56.4%

43.6%

Oh et al., *PNAS* 2004