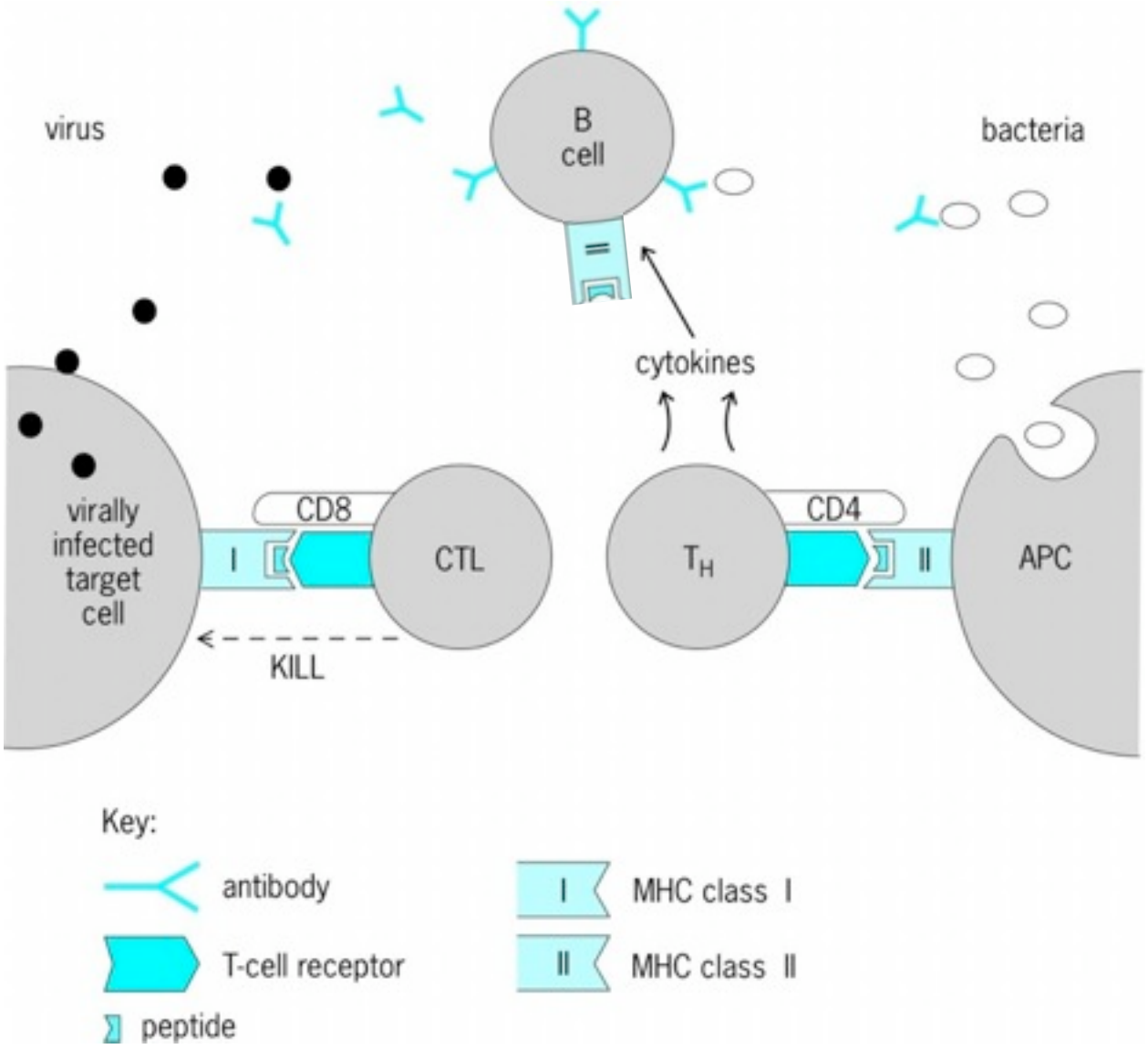
Tracking the effector cell progeny of single naive CD4$^+$ T cells

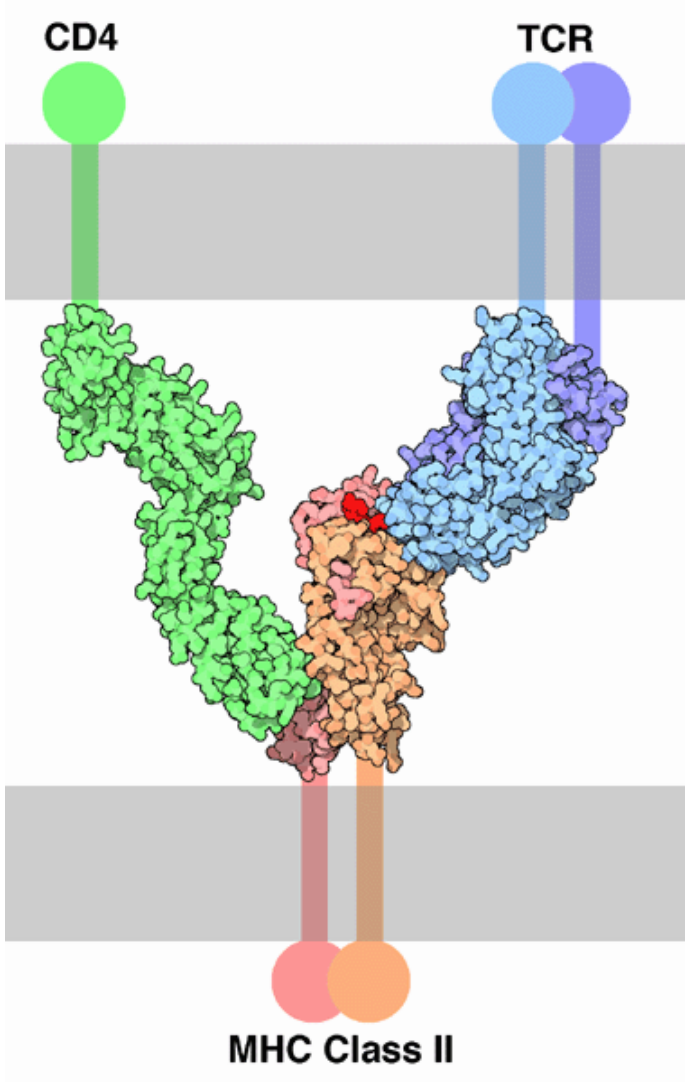
Marc K. Jenkins

UNIVERSITY OF MINNESOTA
CENTER for IMMUNOLOGY

Antigen recognition



p:MHCII recognition by CD4⁺ T cells



CD4⁺ T cell

dendritic cell
B cell
macrophage

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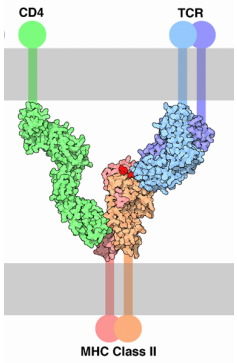

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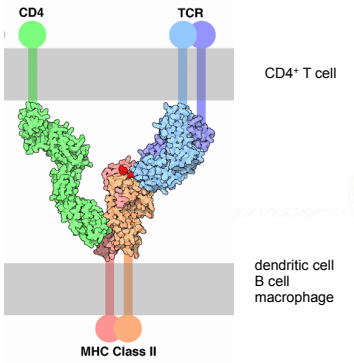

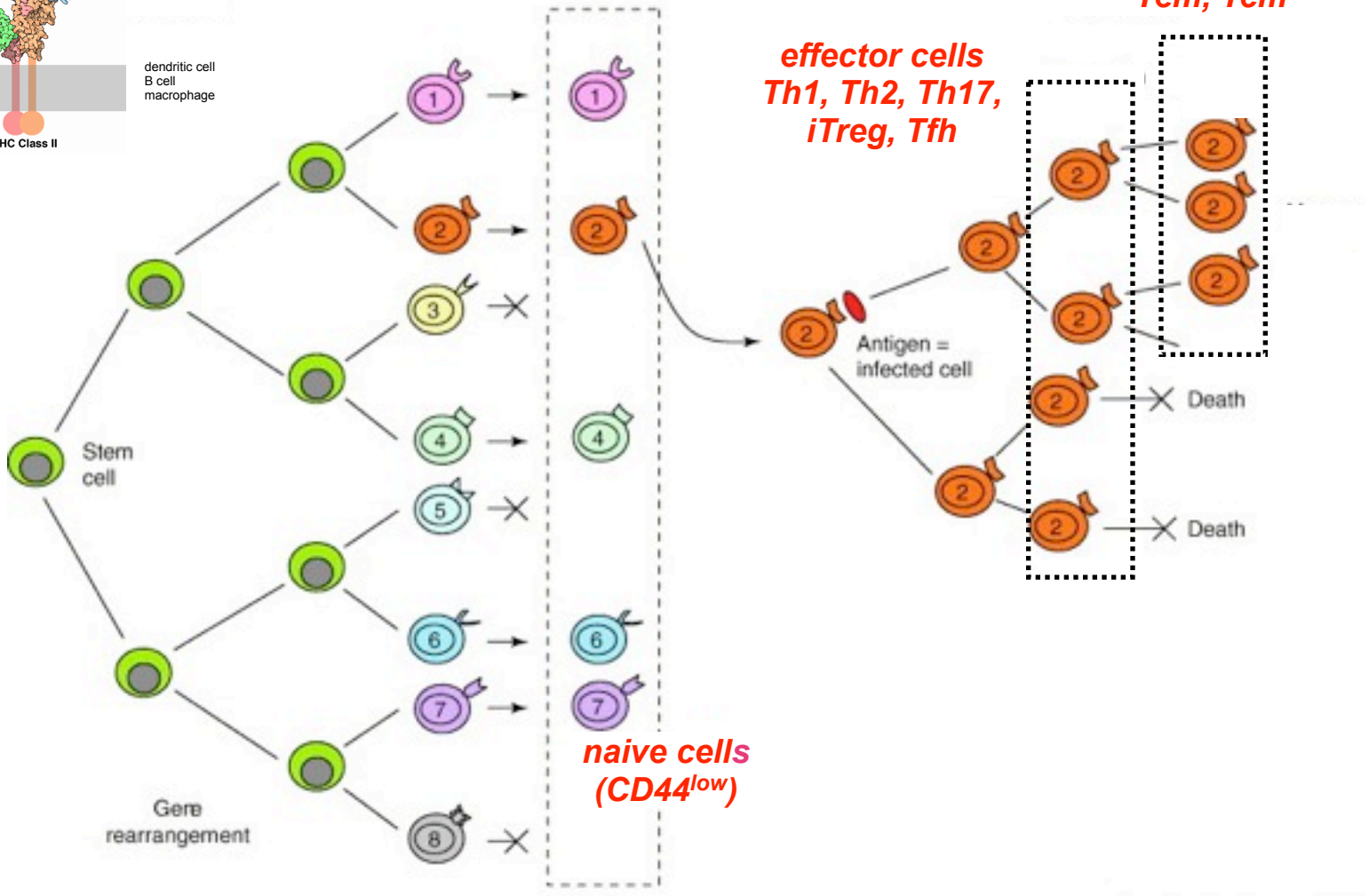

Bergstrom CT, Antia R. Trends Ecol Evol. 2006; 21:22-8.

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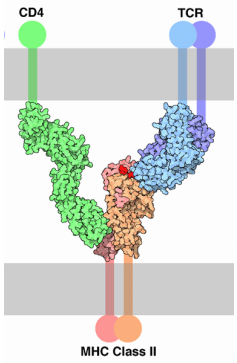
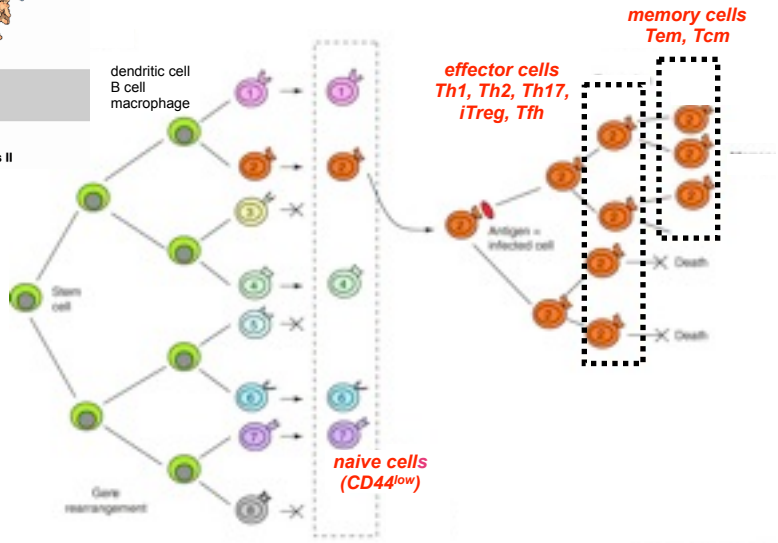


CD4⁺ T cell



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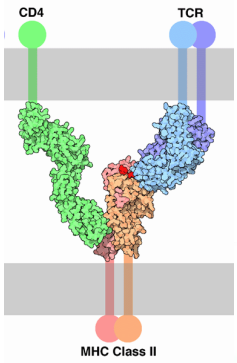

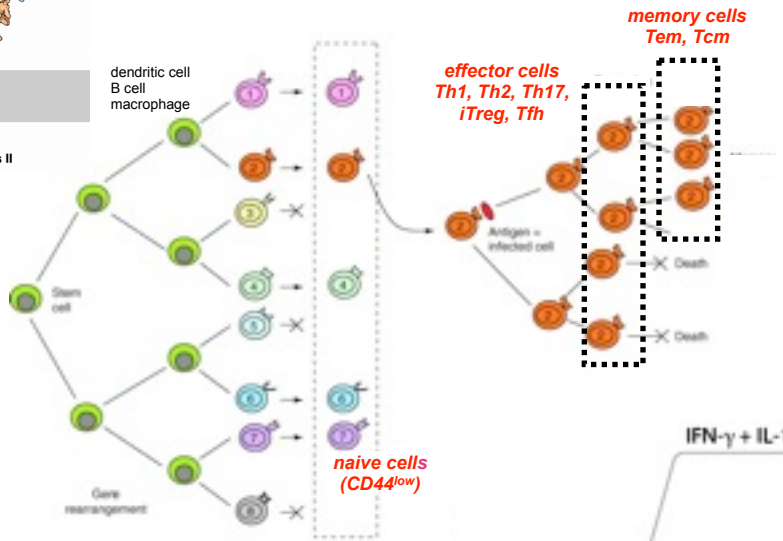

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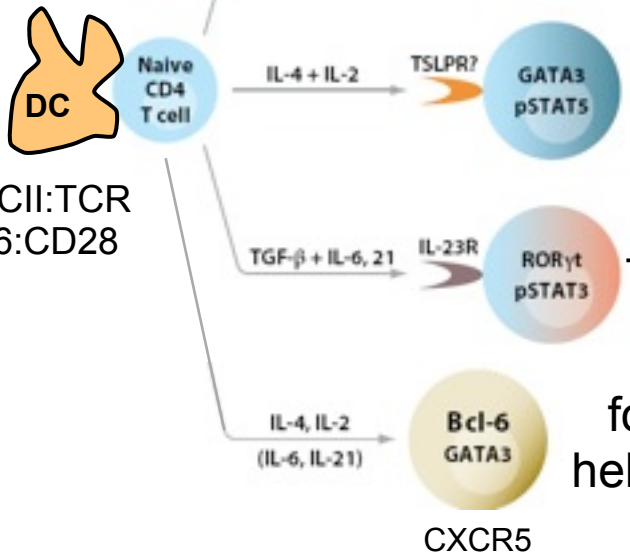
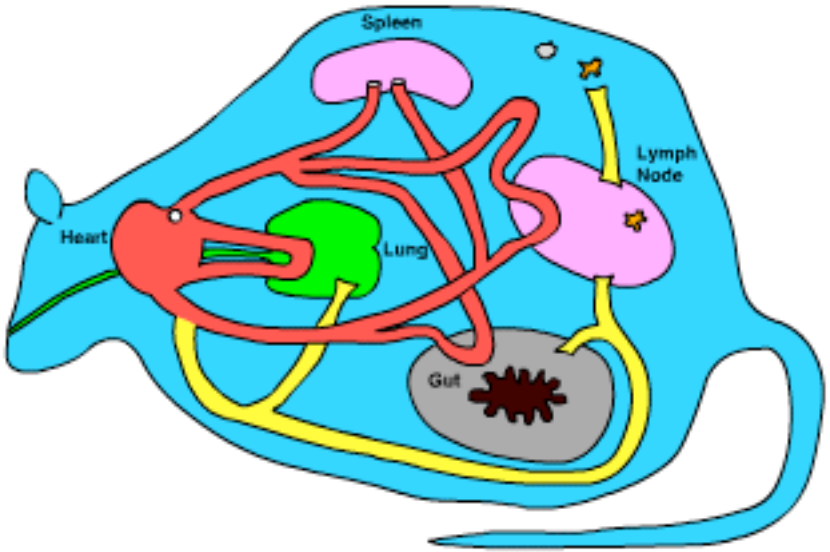
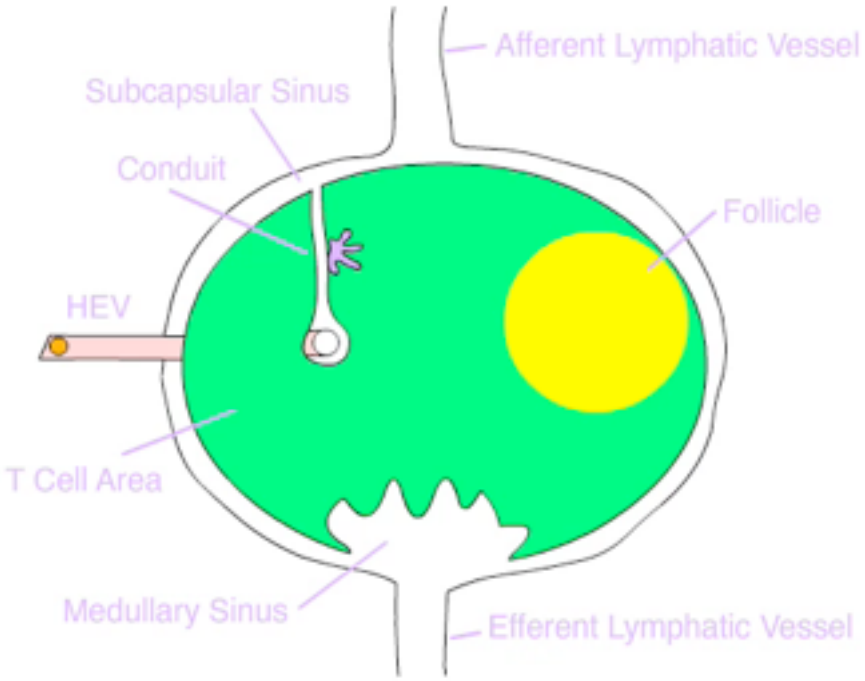


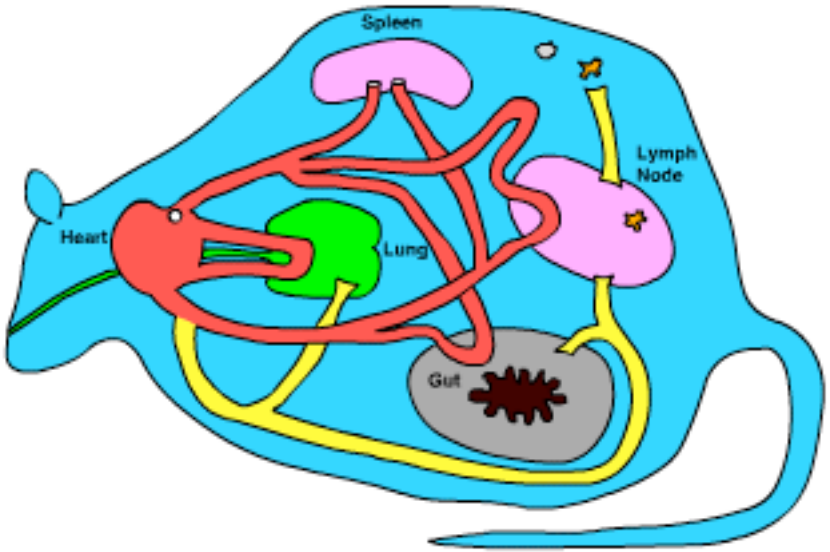
pMHCII:TCR
CD86:CD28

Canonical lymphokine	Cells helped
IFN-γ	macrophages CD8⁺ T cells
IL-4, IL-5, IL-13	B cells eosinophils
IL-17	neutrophils
IL-21	germinal center B cells

Zhu and Paul, Annu. Rev. Immunol. 2010


Spleen
Lymph Node
Heart
Lung
Gut


Afferent Lymphatic Vessel
Subcapsular Sinus
Conduit
Follicle
HEV
T Cell Area
Medullary Sinus
Efferent Lymphatic Vessel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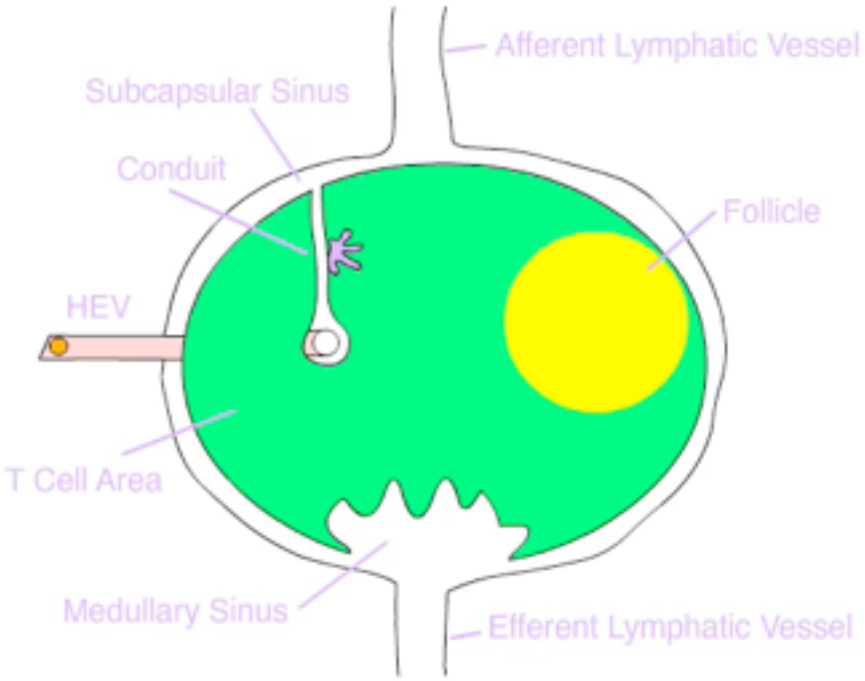
Afferent Lymphatic Vessel
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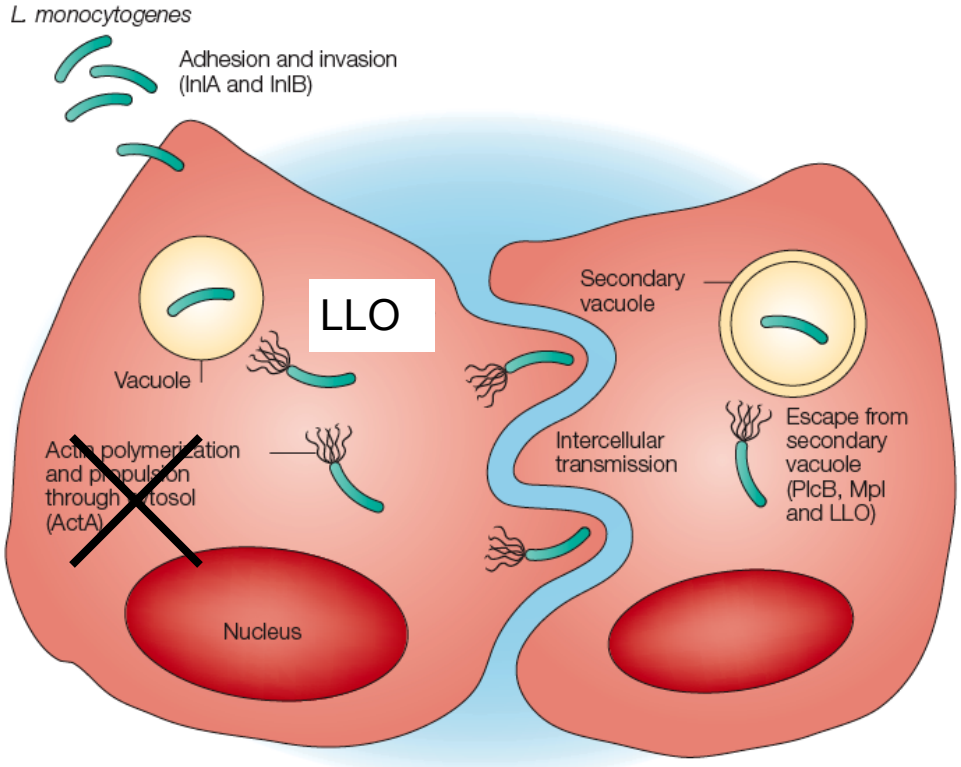
How are different effector and memory $CD4^+$ T cells formed from naive precursors?

ΔActA Listeria monocytogenes (Lm) infection



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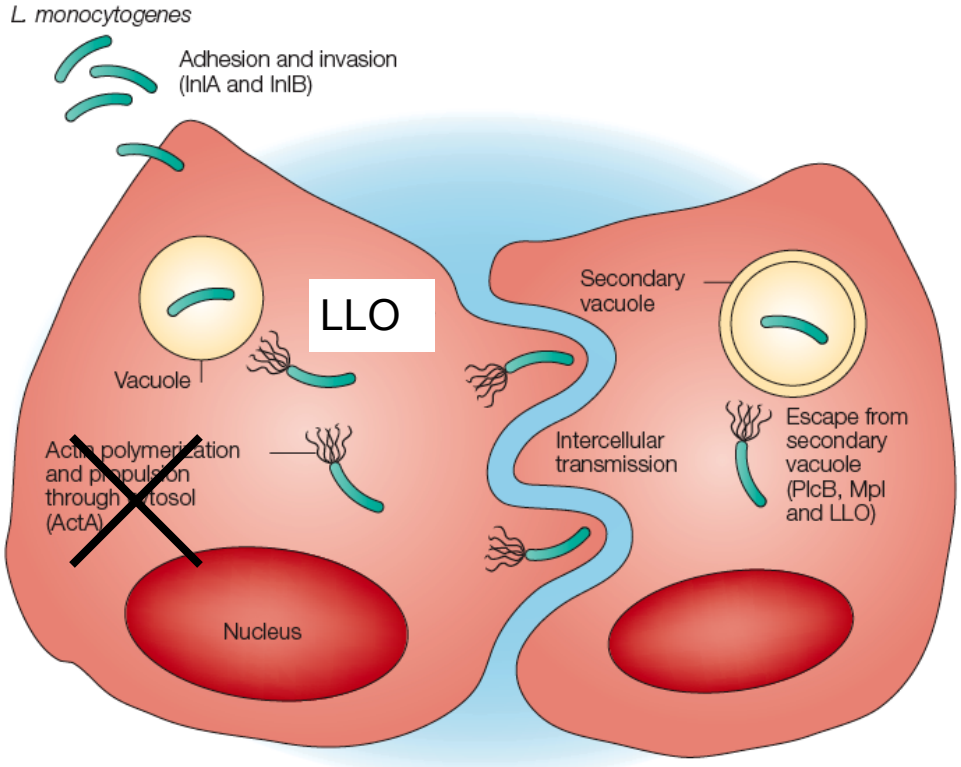

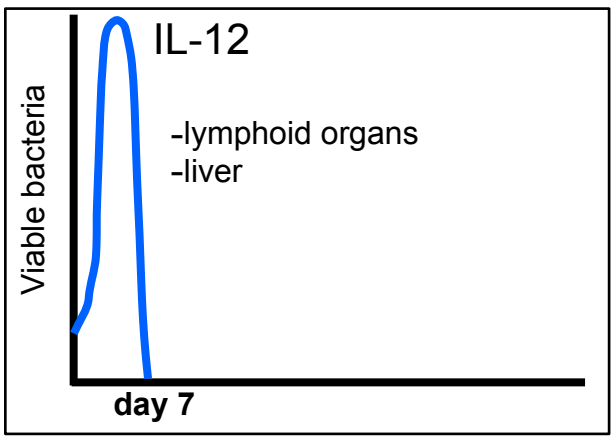

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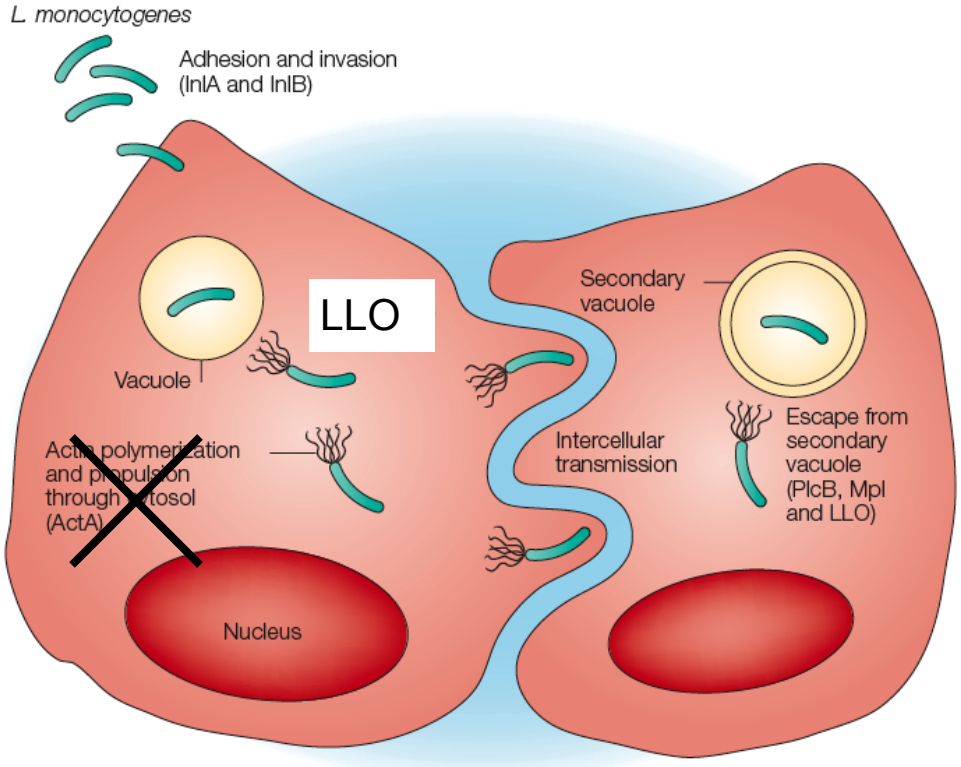
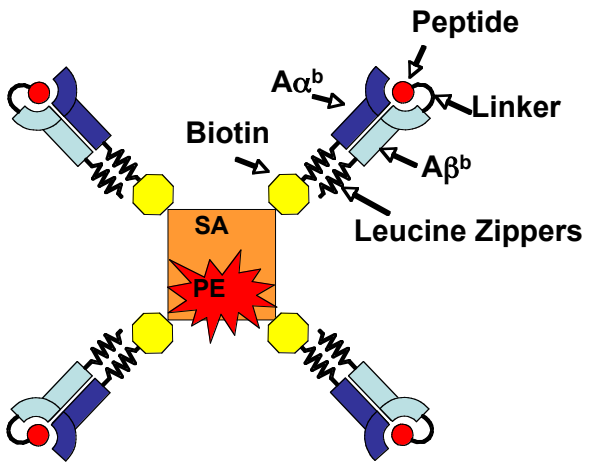
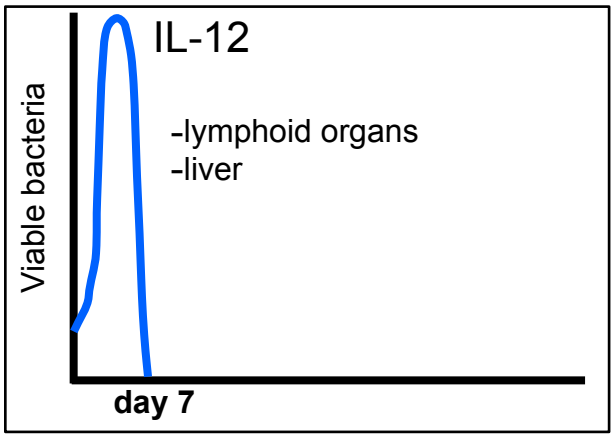
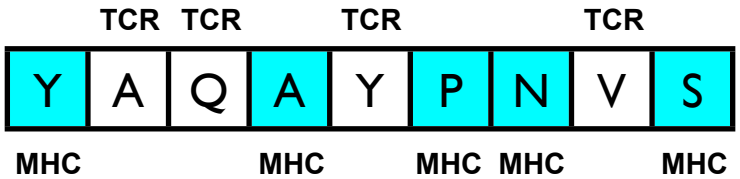


peptide:I-A^b tetramer

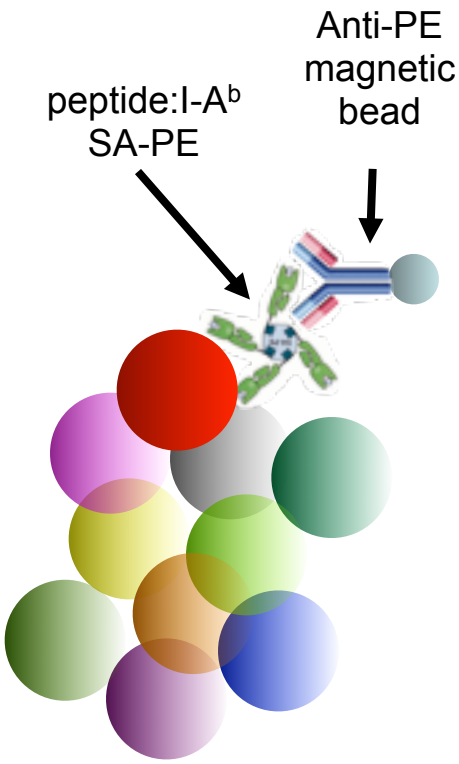






$LLO_{193\text{-}201}$

p:MHCII tetramer-based cell enrichment



Spleen and
lymph node cells
from 1 mouse
(~200x10^6 cells)

Kedl Jameson

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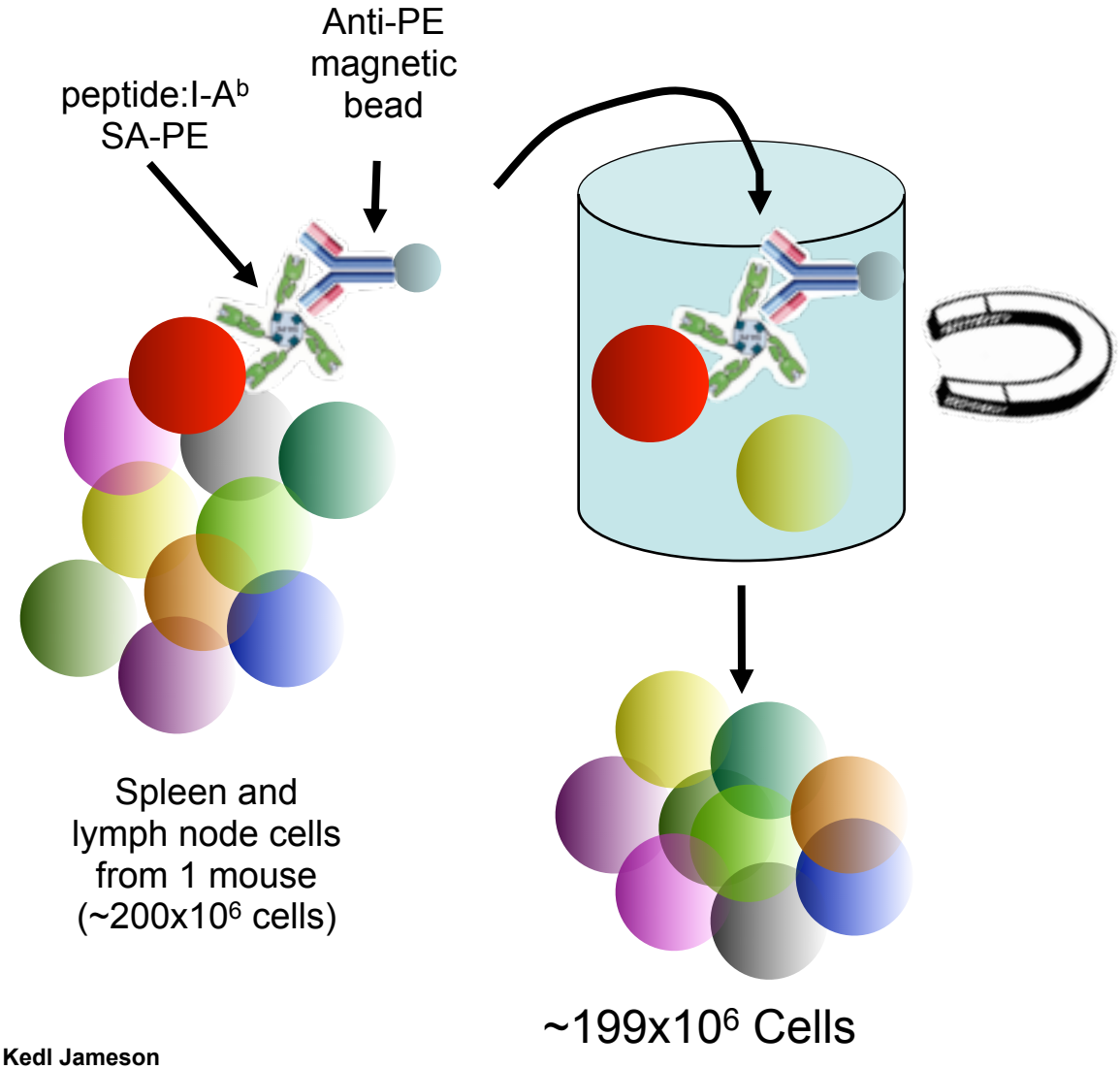

Kedl Jameson

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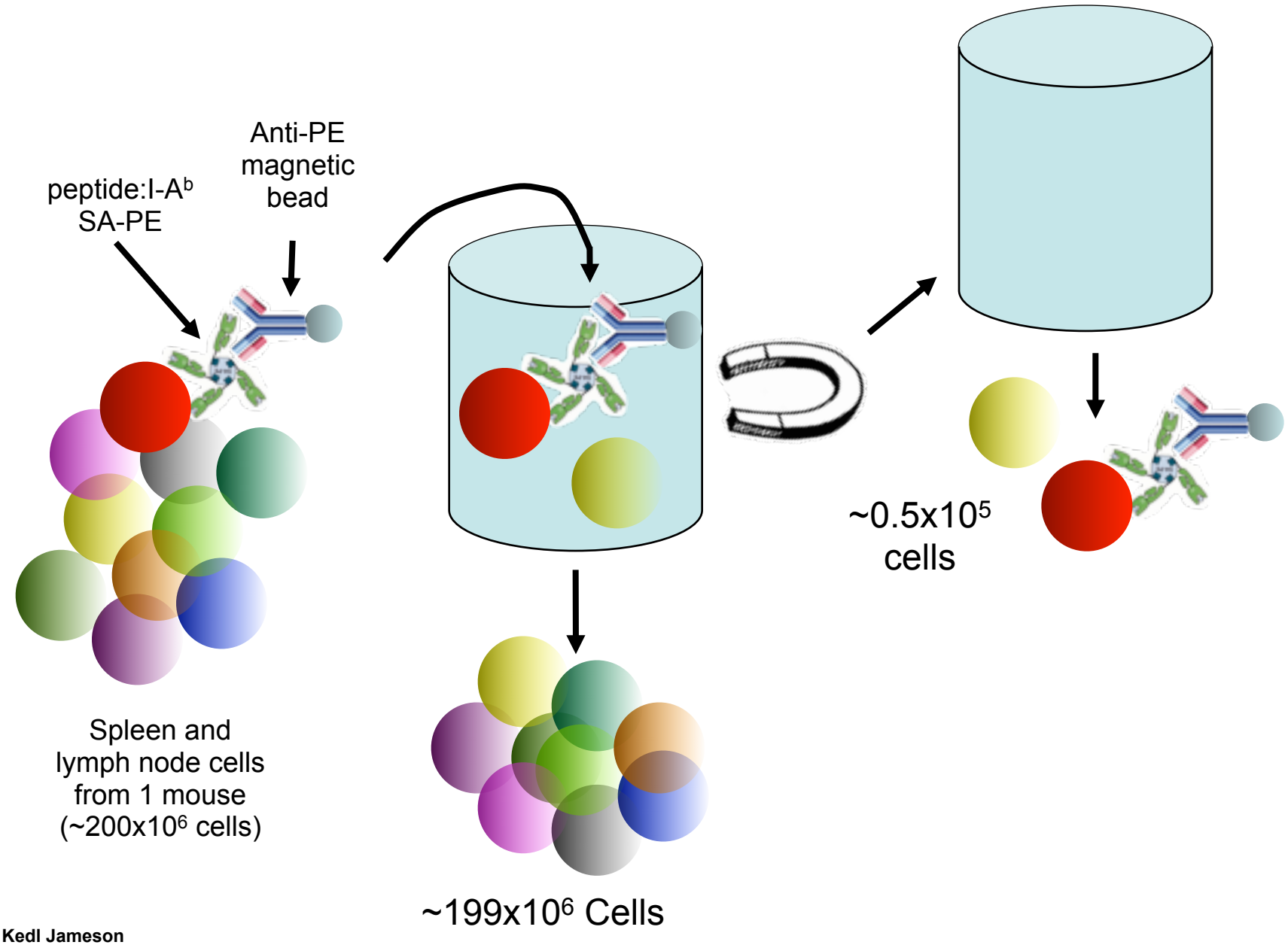

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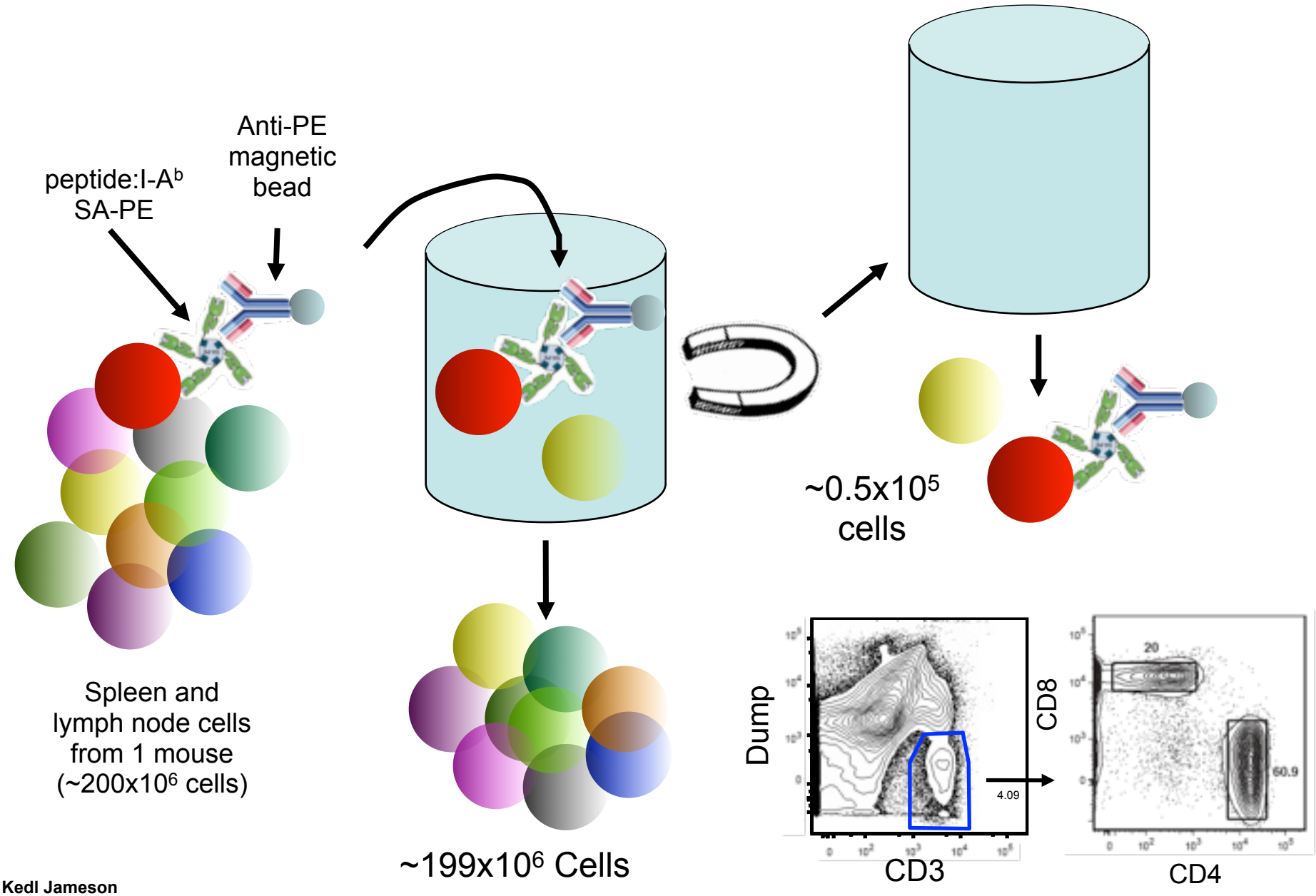
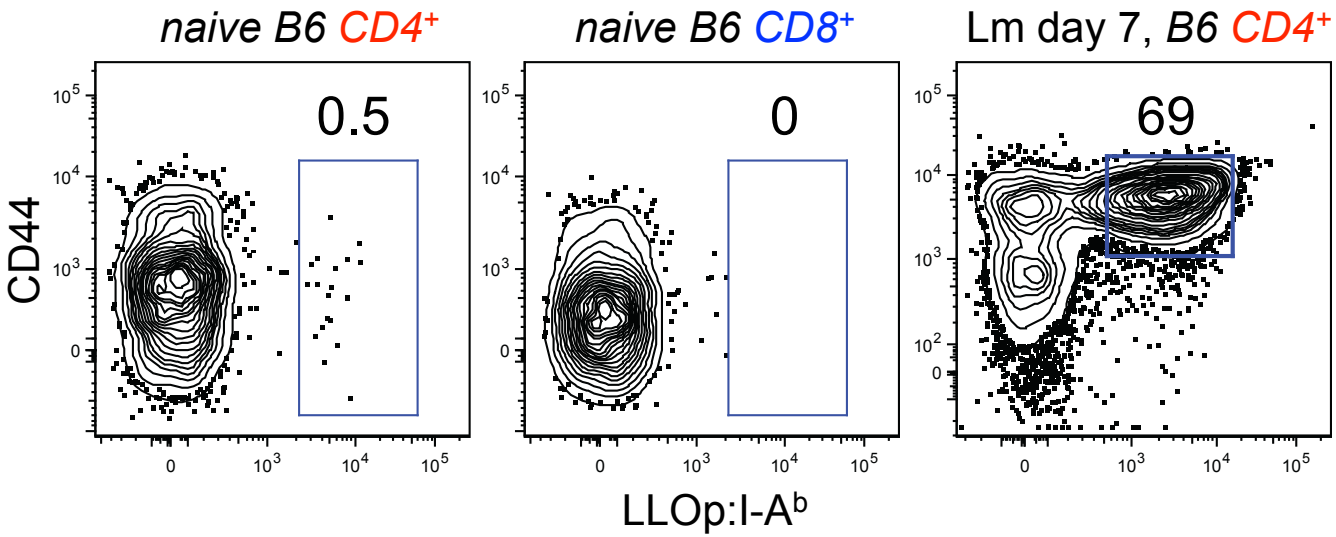


Kedl Jameson

Kinetics of the LLOp:I-A^b-specific T cell response



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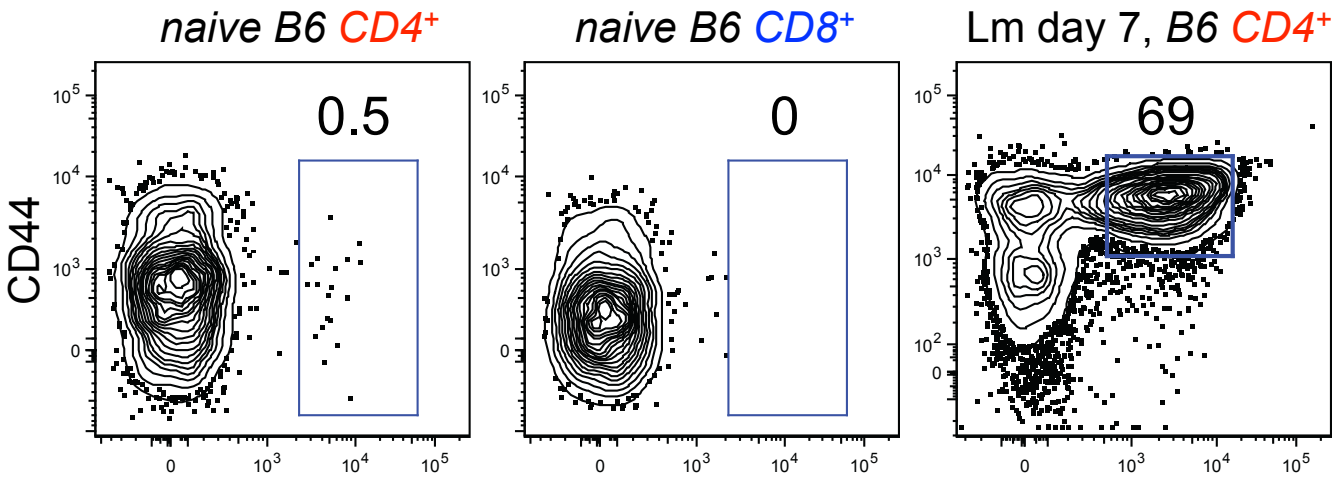
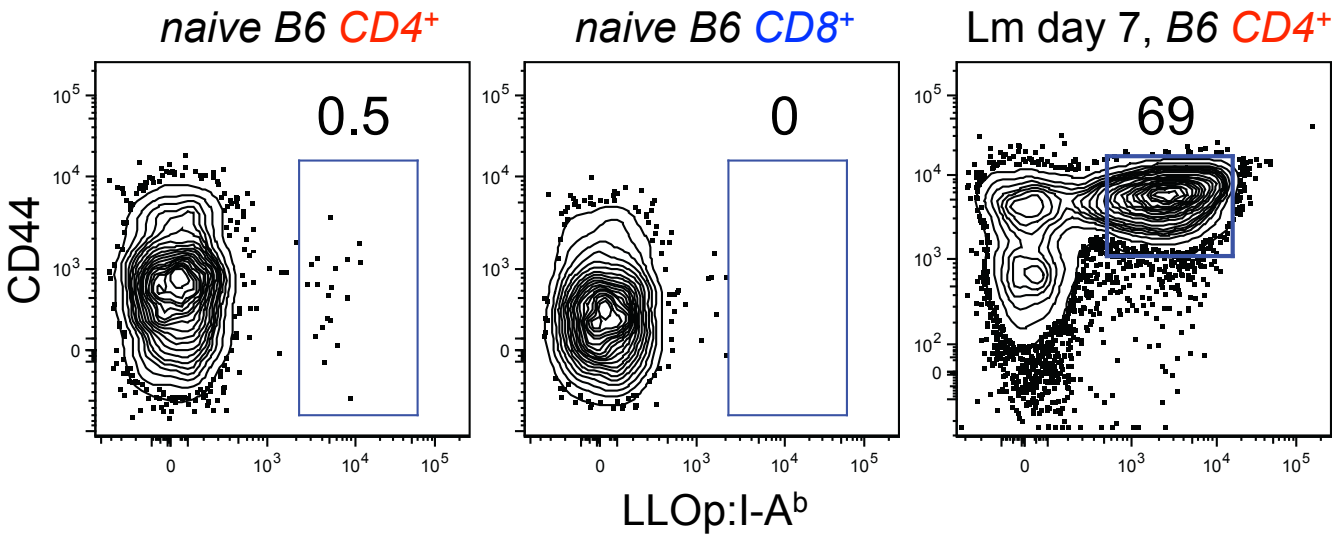
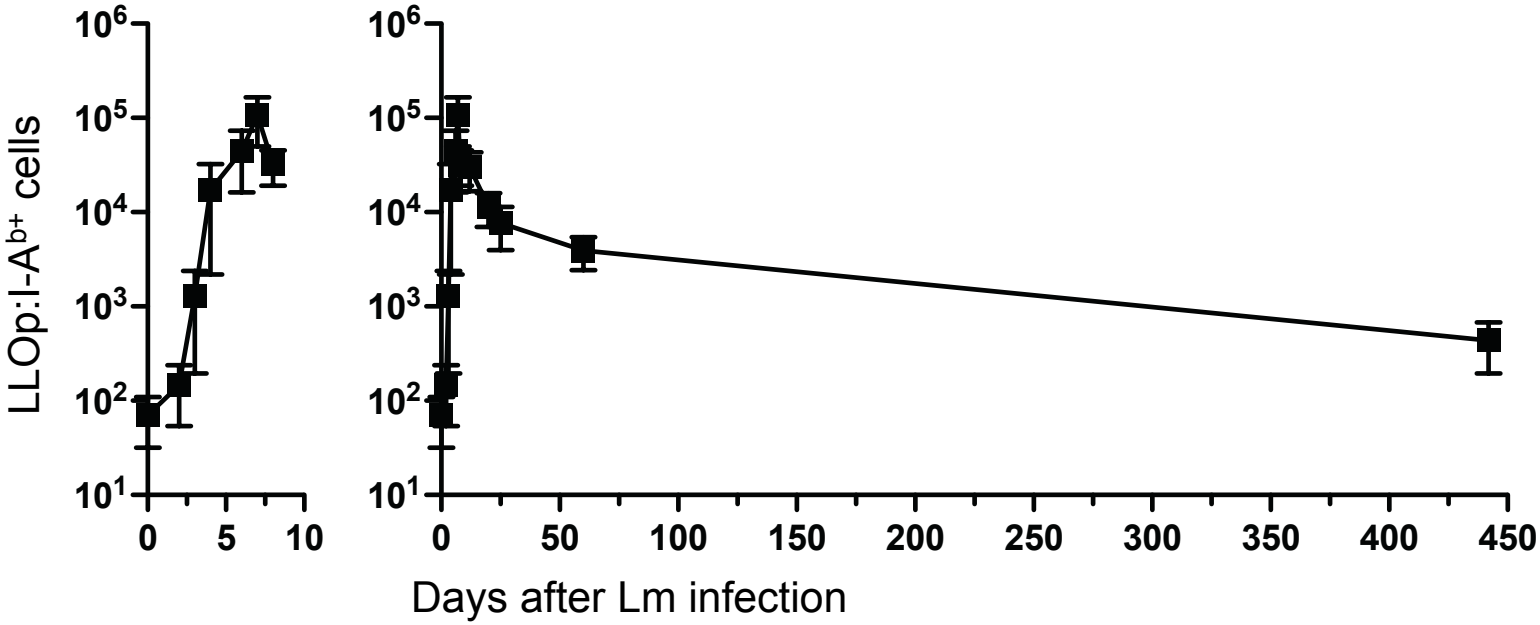


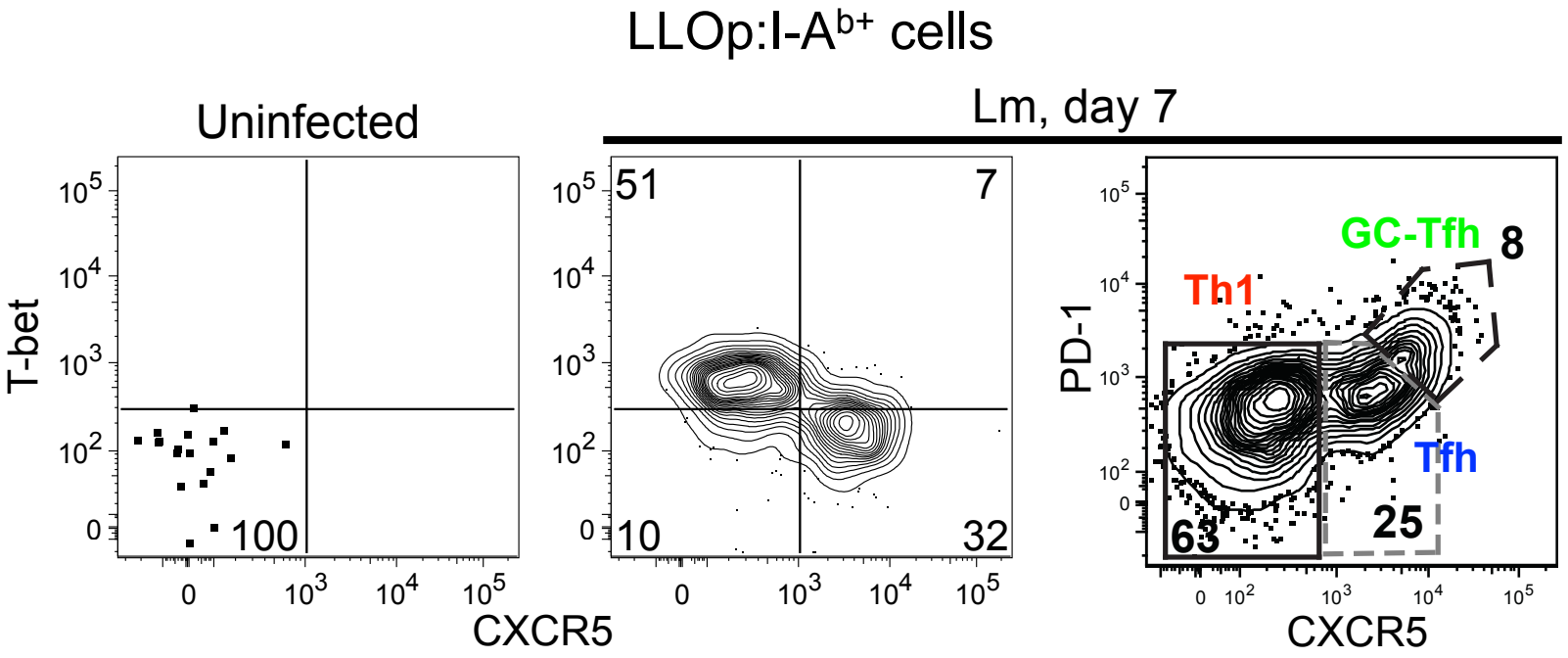
- ~5% Foxp3$^+$
- ~10% Vα2/Vβ13
- all unique CDR3β

Kinetics of the LLOp:I-A^b-specific T cell response





Lm infection induces functionally diverse effector cells



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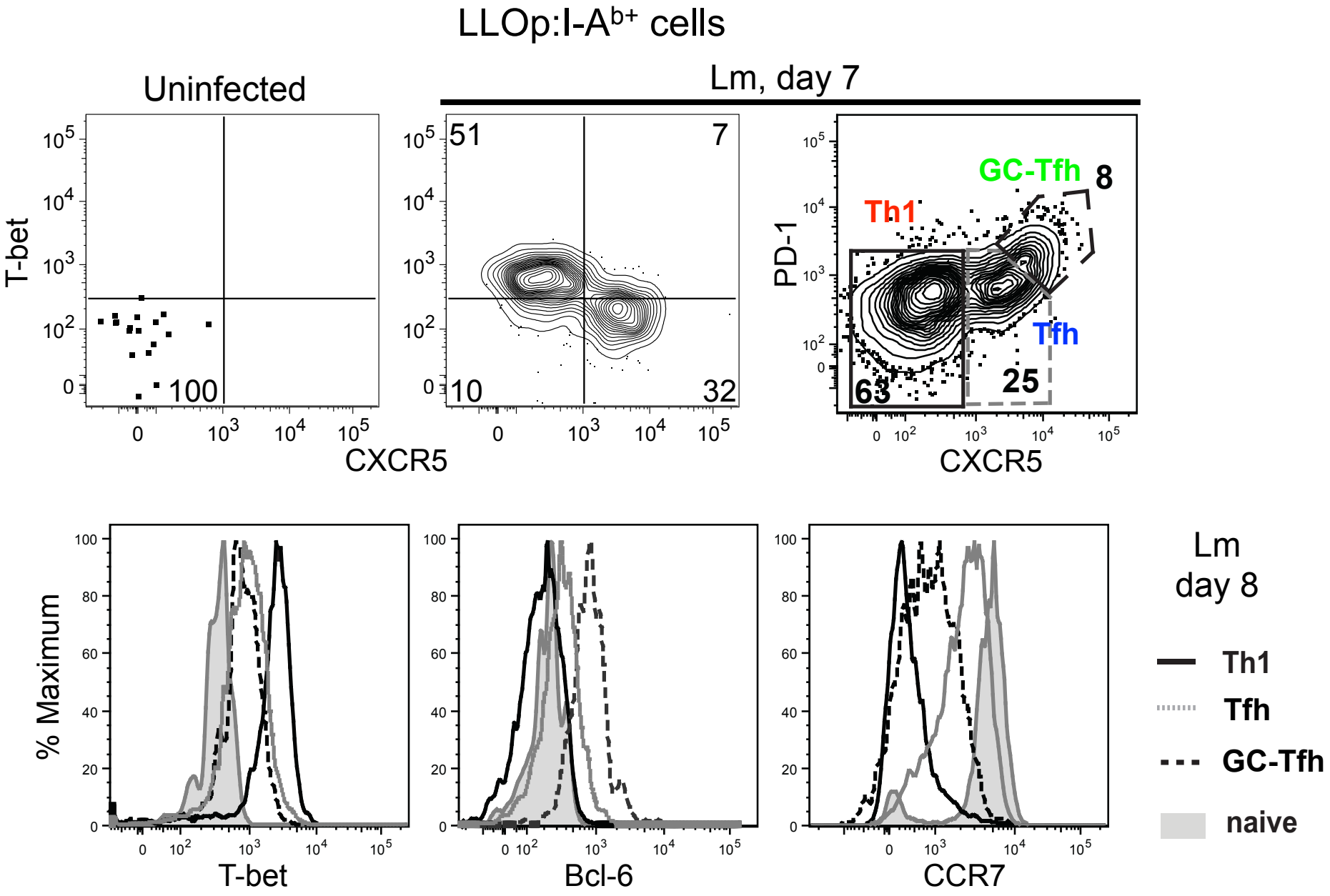
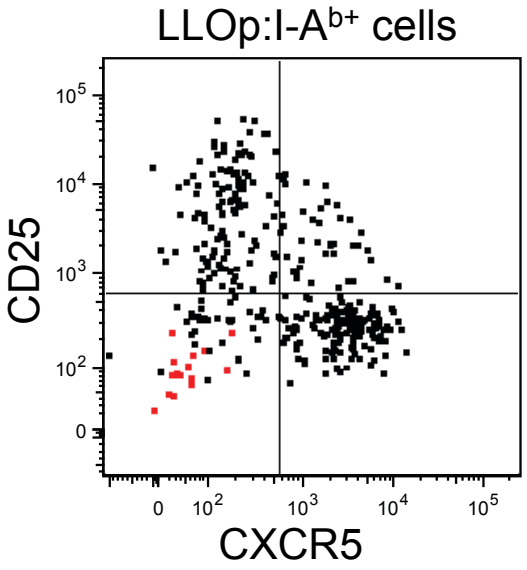
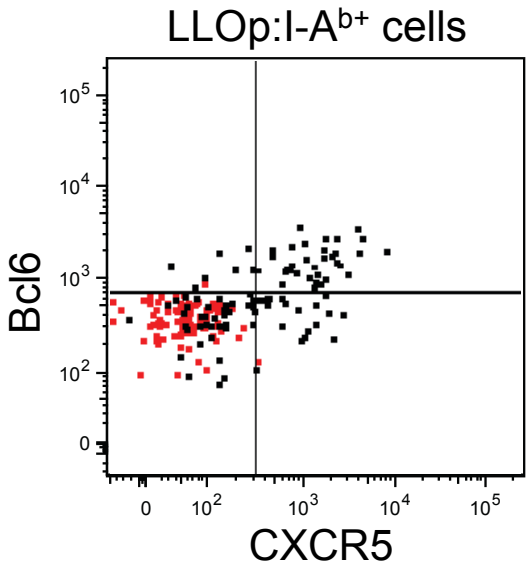


Th1 cells depend on CD25, Tfh and GC-Tfh cells depend on Bcl6



uninfected

Lm day 3



Lm day 3

wild-type

Bcl6$^{-/-}$

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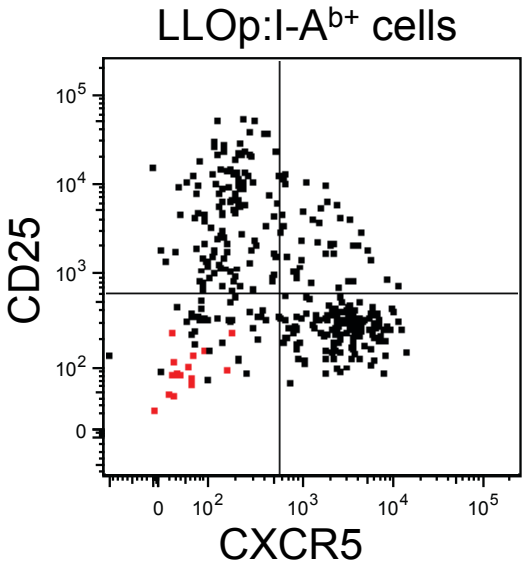
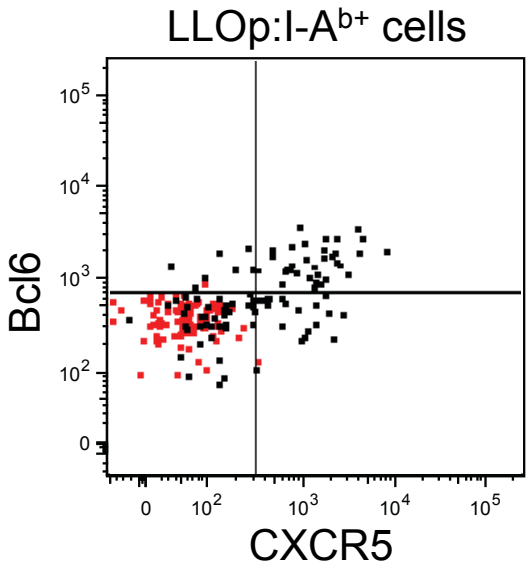


uninfected

Lm day 3

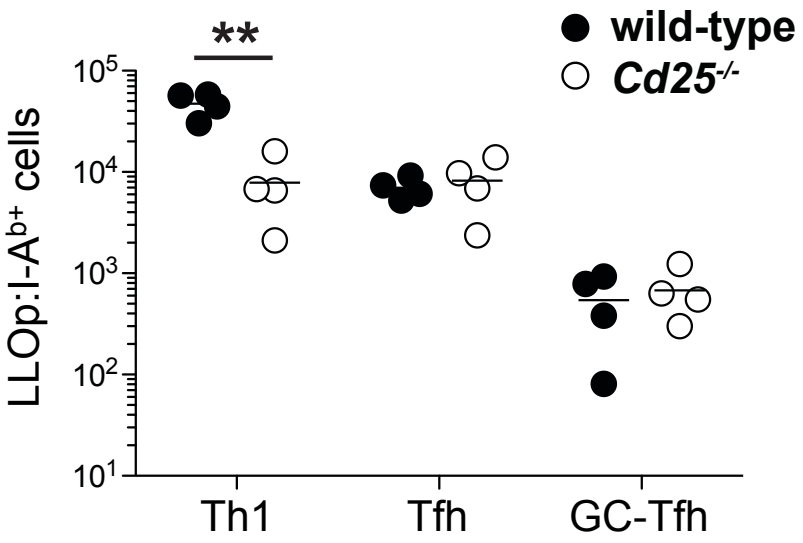


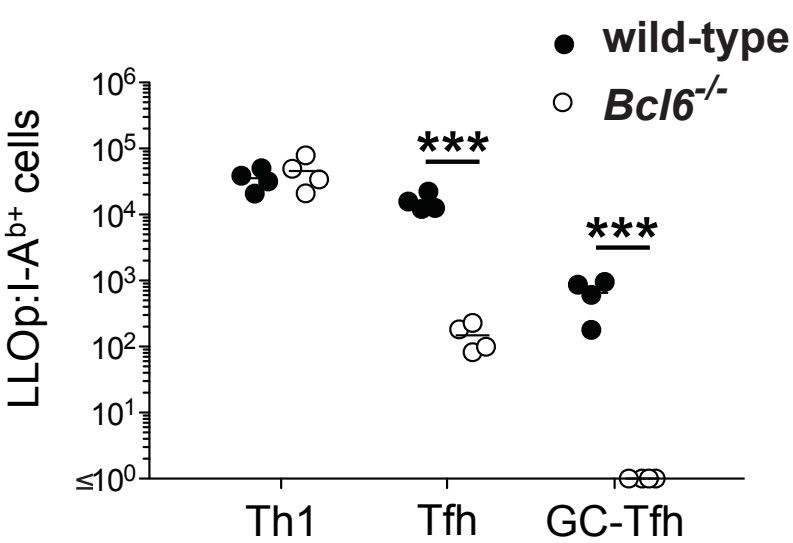
Lm day 3

wild-type

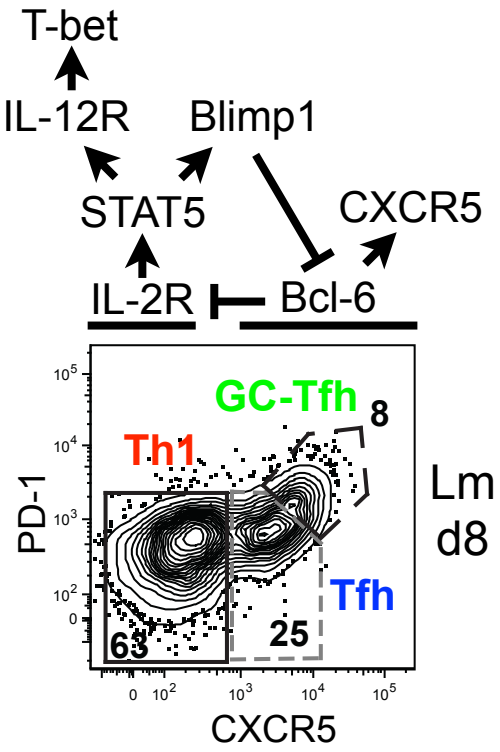
Bcl6$^{-/-}$

Lm, day 5-7





Lm infection induces functionally diverse effector and memory cells



LLOp:I-A^{b+} cells

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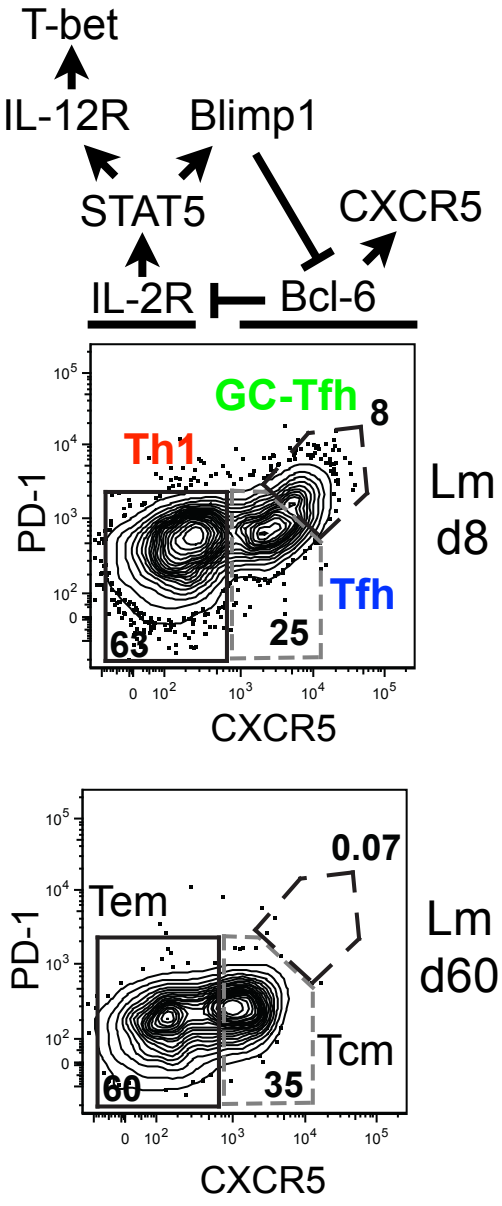

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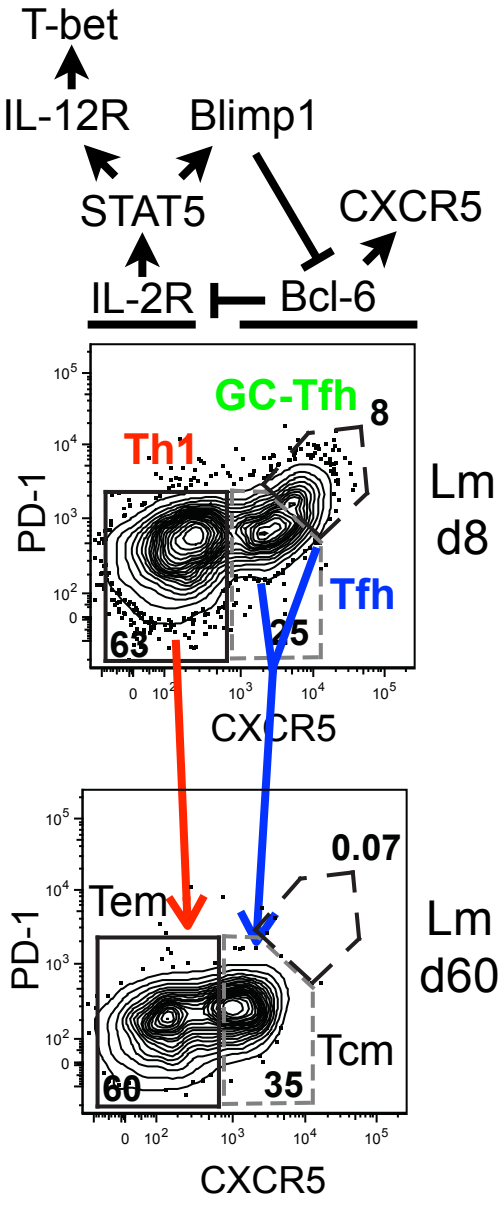

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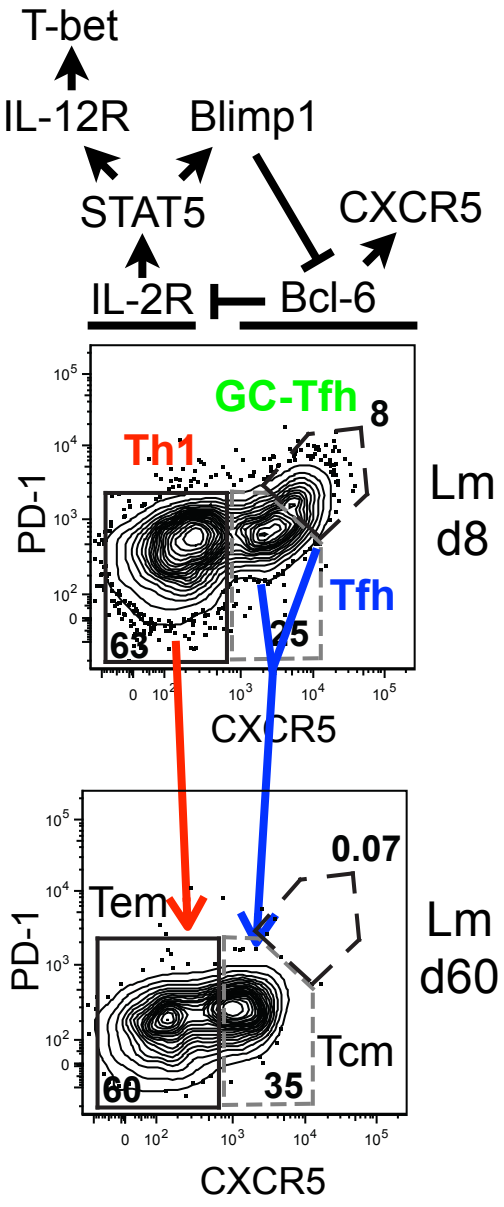
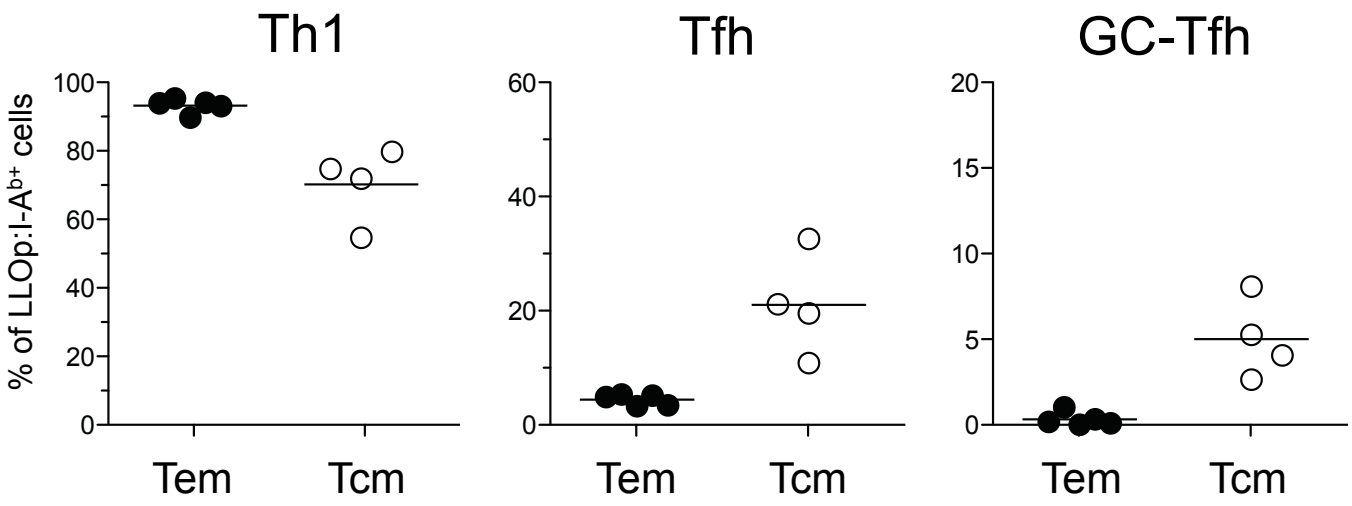


Effector cells produced from Tem or Tcm after Lm challenge



LLOp:I-A^{b+} cells

Why do some naive cells retain CD25 and become Th1 cells while others turn on Bcl-6 and become Tfh and GC-Tfh cells?

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Could individual naive cells vary in this regard?

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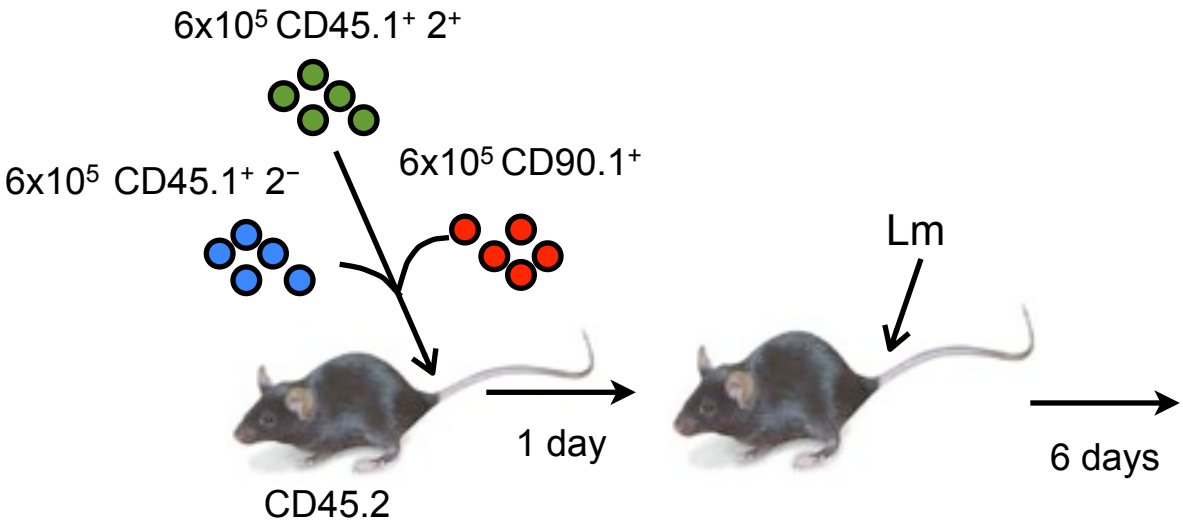
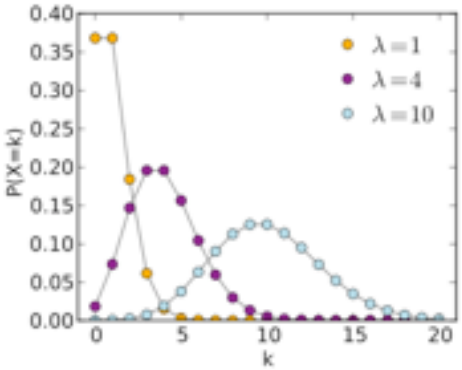
Could individual naive cells vary in this regard?

How to test this idea?

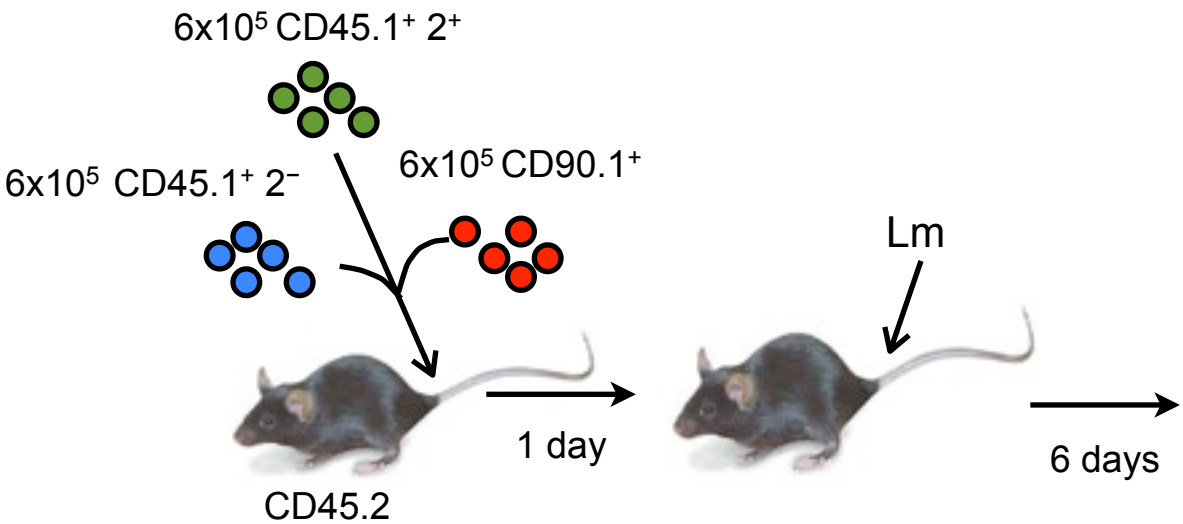
In vivo limiting dilution

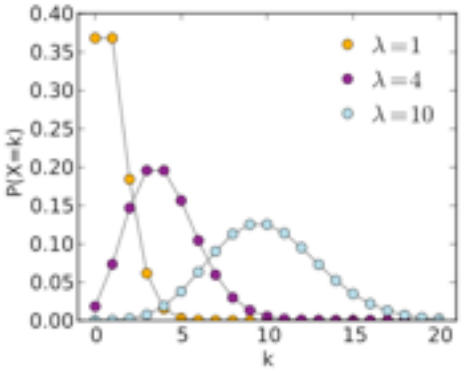


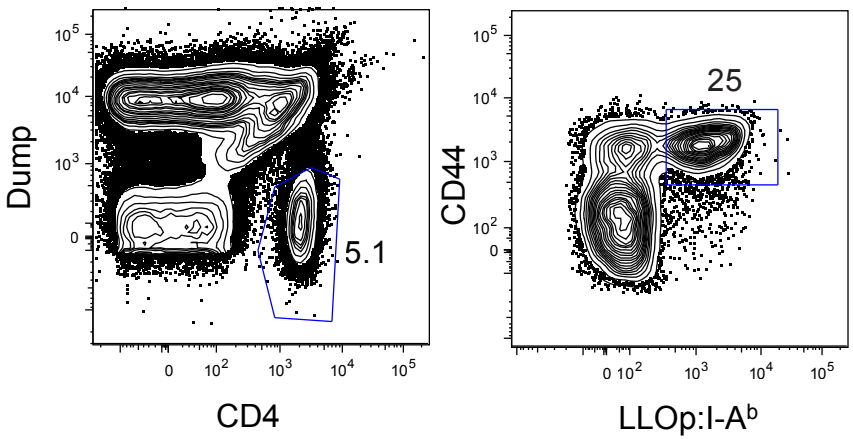


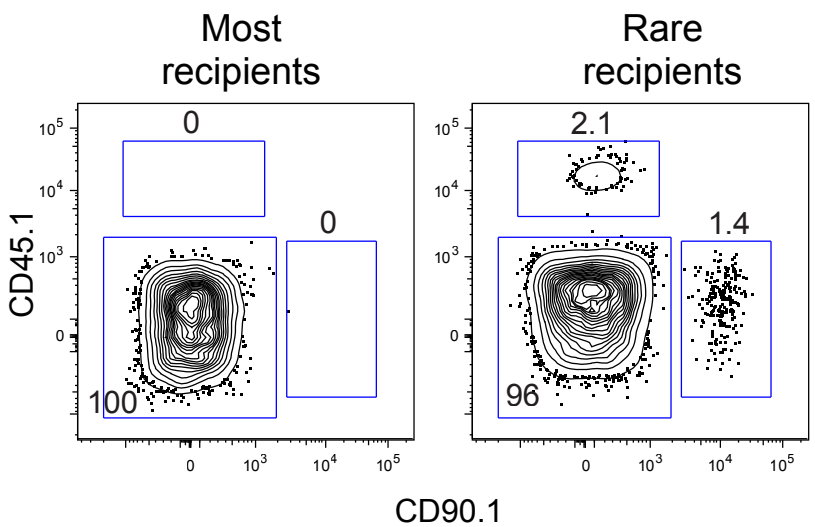
Assay LLOp:I-A^{b+} cells by tetramer enrichment

In vivo limiting dilution

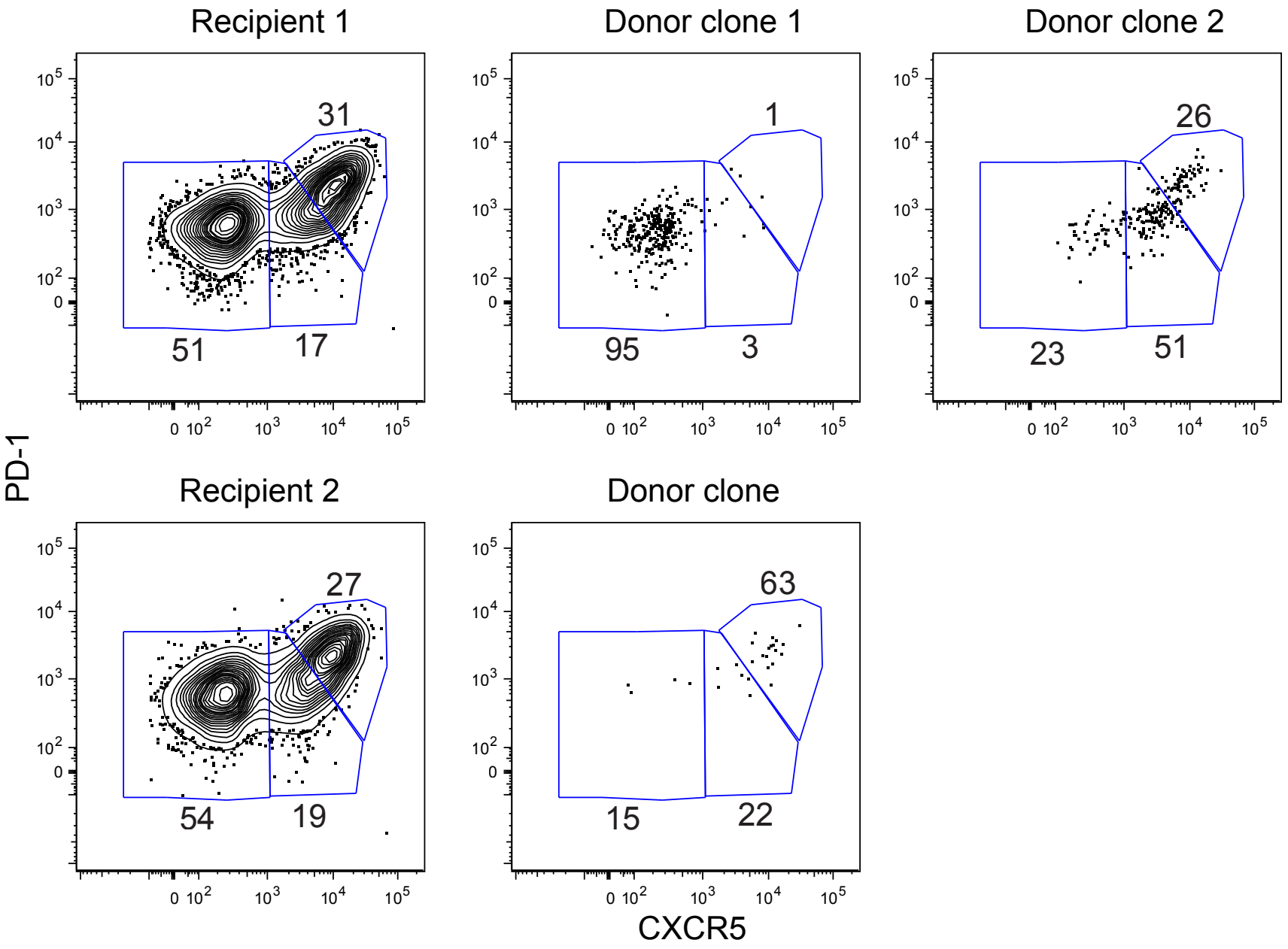




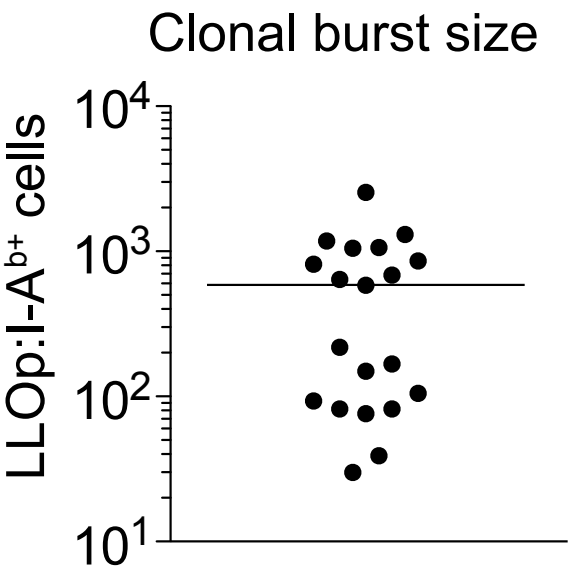


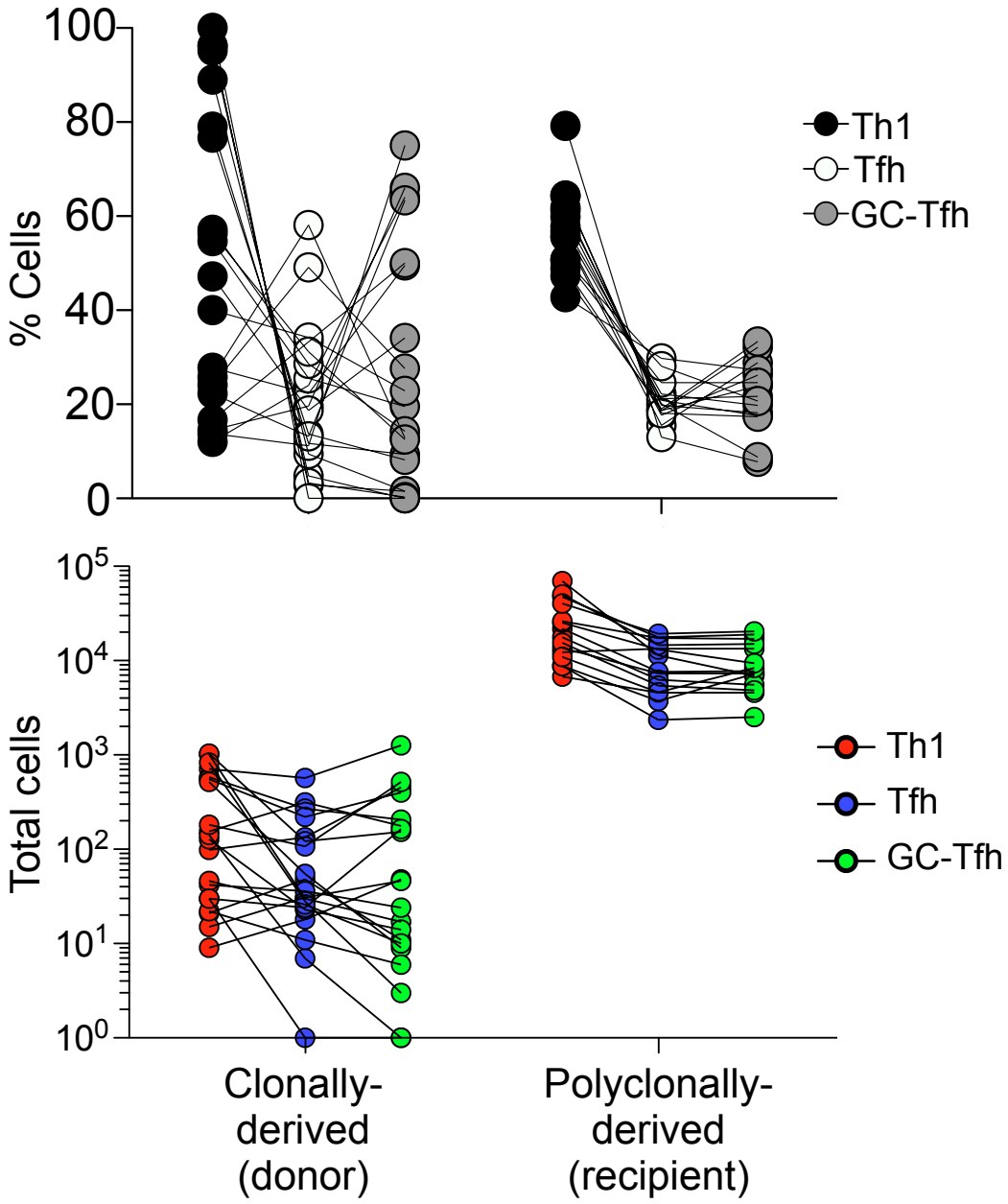


Individual naive LLOp:I-A^{b}-specific cells produce unique sets of effector cells



Individual naive cells produce unique sets of effector cells





Nature or Nurture?

- Each naive clone has a different intrinsic capacity to produce certain effector cells types, probably determined by the (nature) of its unique TCR.

Nature or Nurture?

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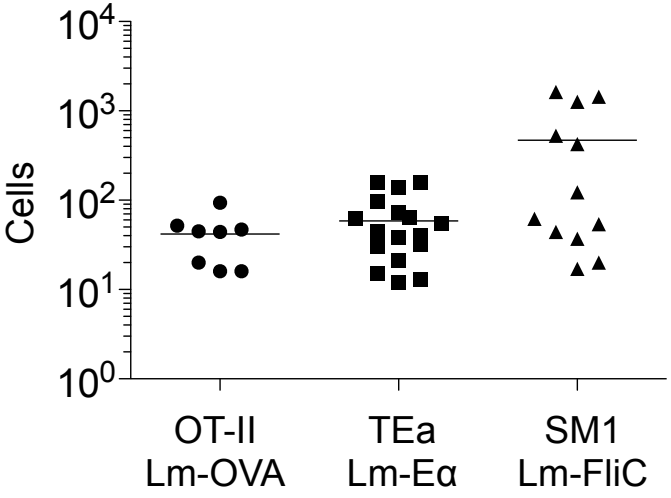
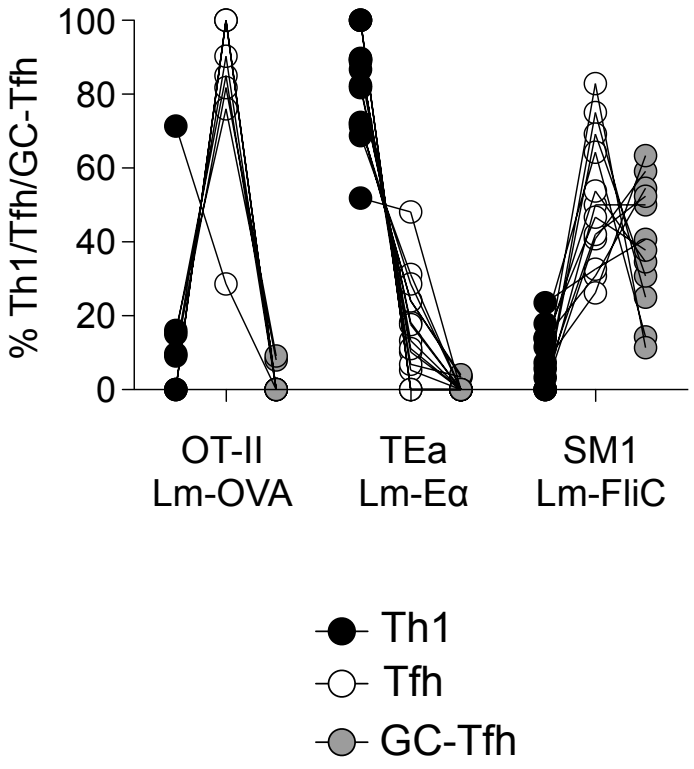
- Each naive clone has the same intrinsic capacity but can produce different effector cells types in response to extrinsic (nuture) factors, e.g., the amount of ICOS, cytokine p:MHCII.

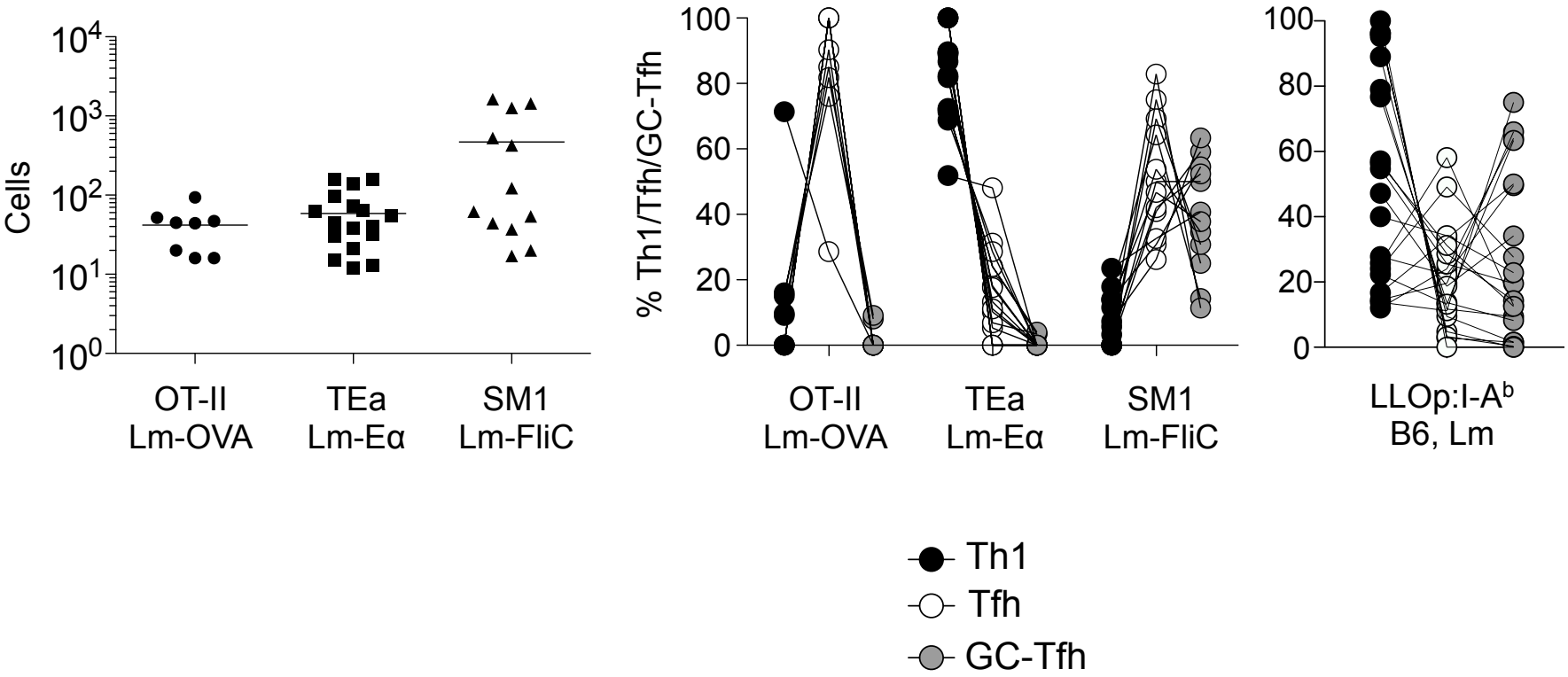
Transfer of single TCR Tg T cells provides evidence for lots of nature and a little nurture





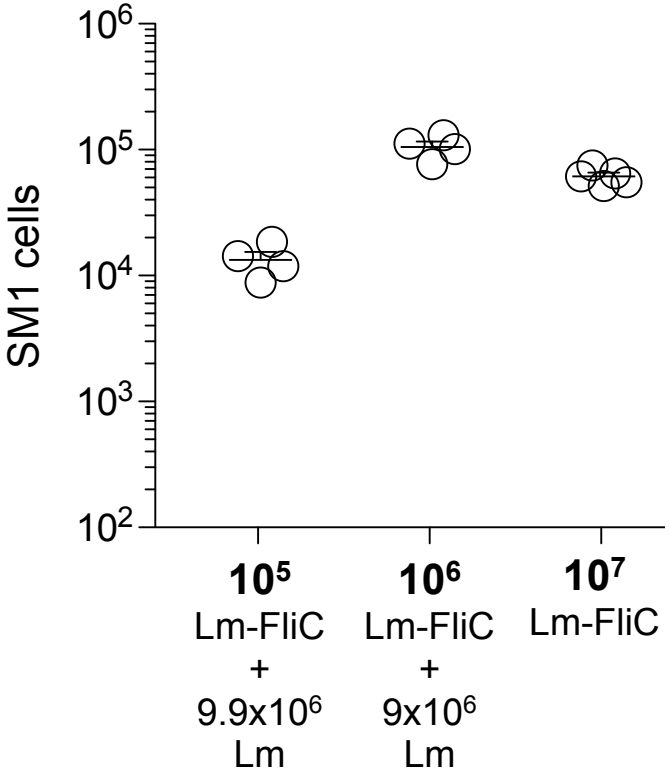
day 6-7 after infection

Transfer of single TCR Tg T cells provides evidence for lots of nature and a little nurture



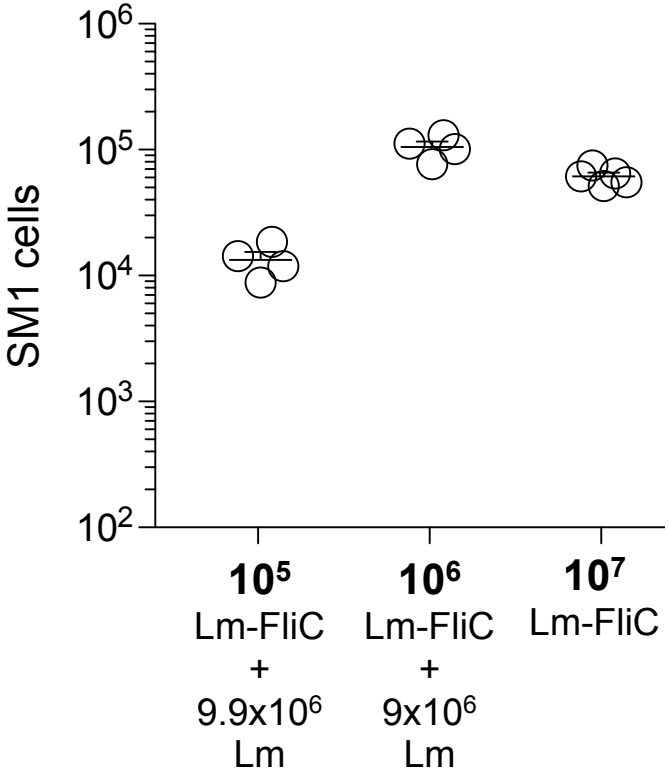
day 6-7 after infection

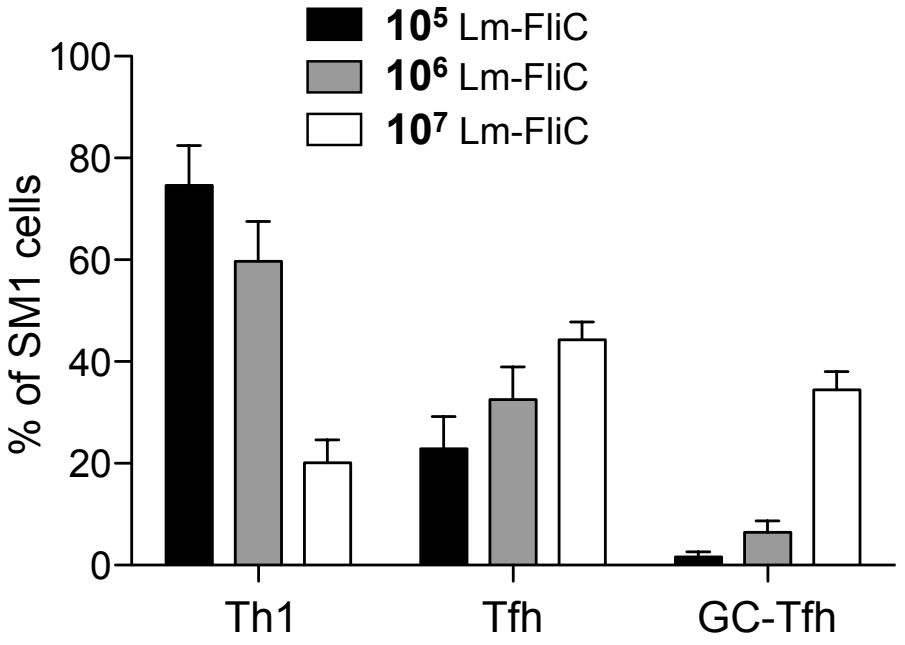
TCR signal strength influences the effector cell pattern produced by monoclonal T cells



100 SM1 cells, day 7 after infection

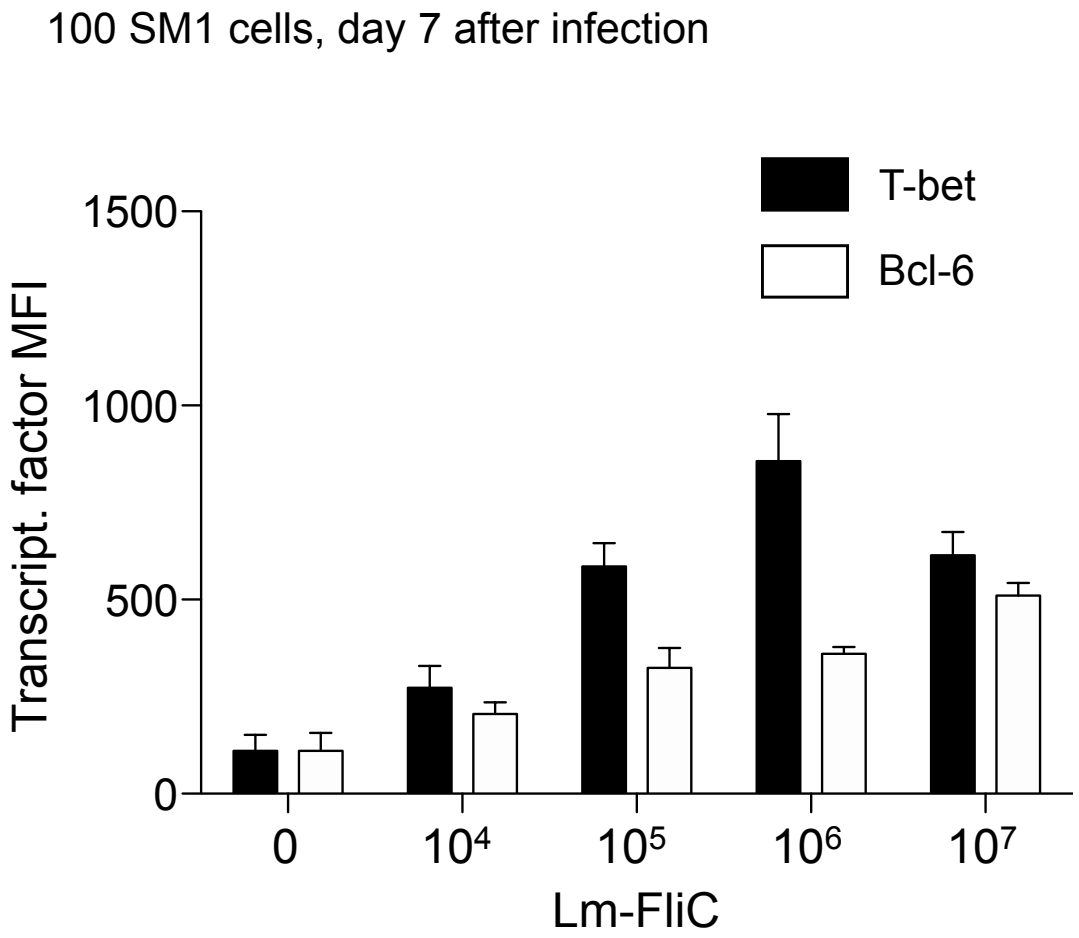
TCR signal strength influences the effector cell pattern produced by monoclonal T cells



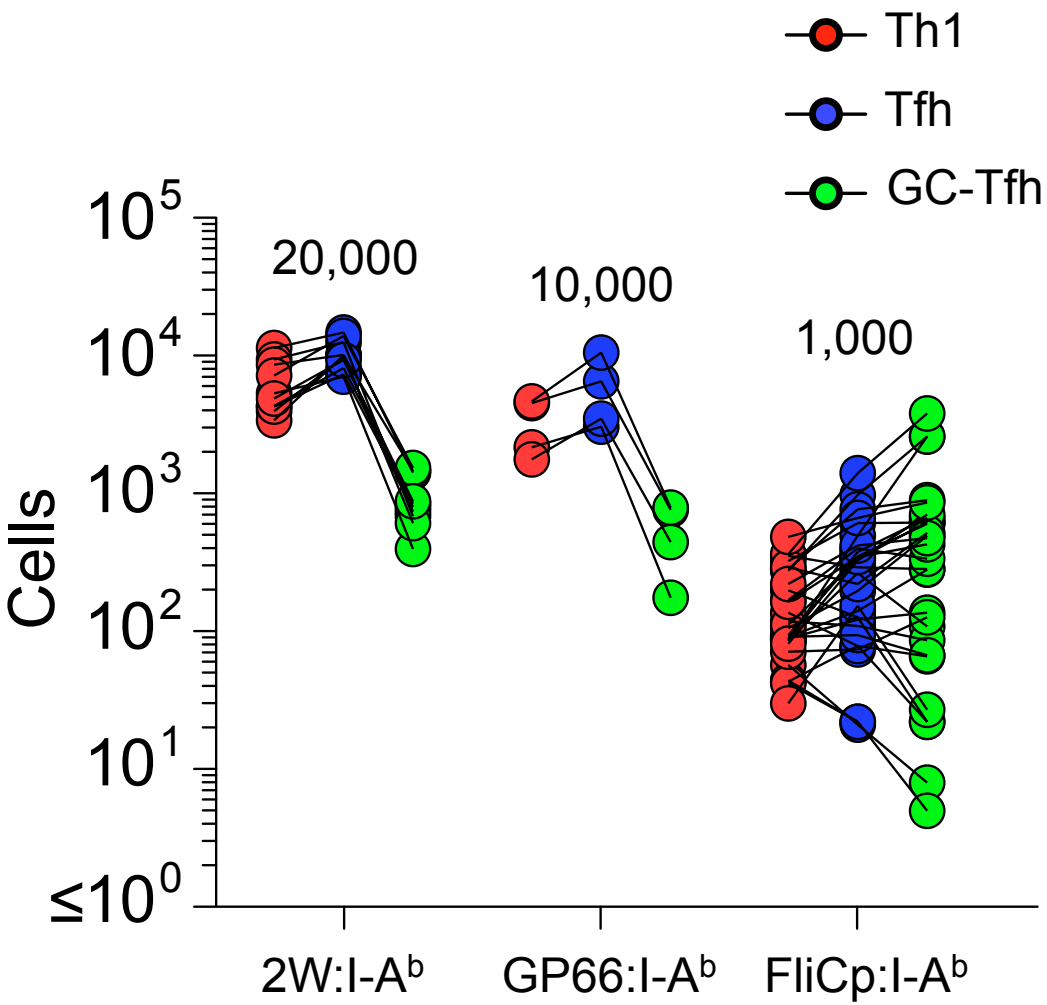


100 SM1 cells, day 7 after infection

TCR signal strength influences the T-bet/Bcl-6 ratio in monoclonal T cells



A small naive population produces variable effector cells in different individuals



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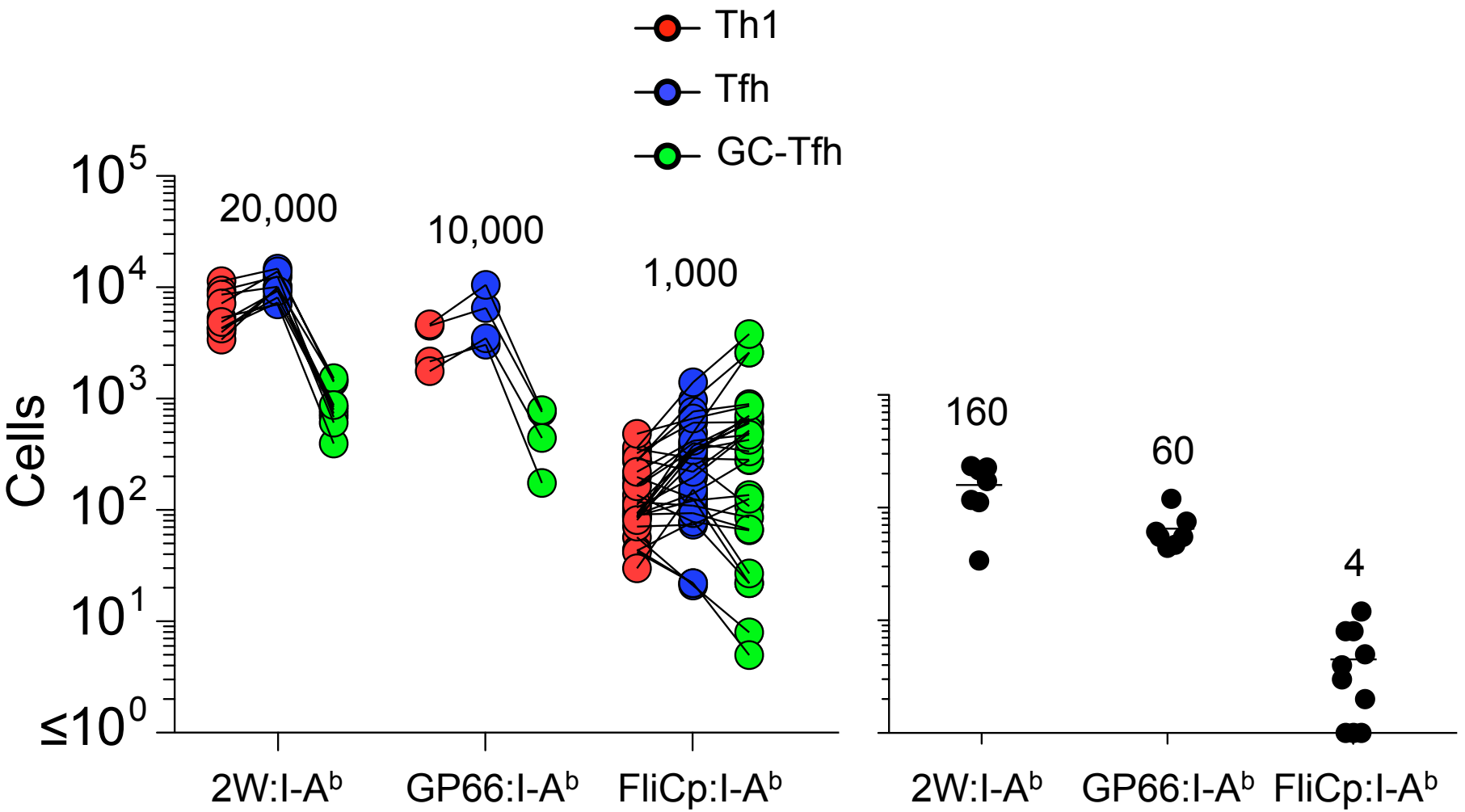

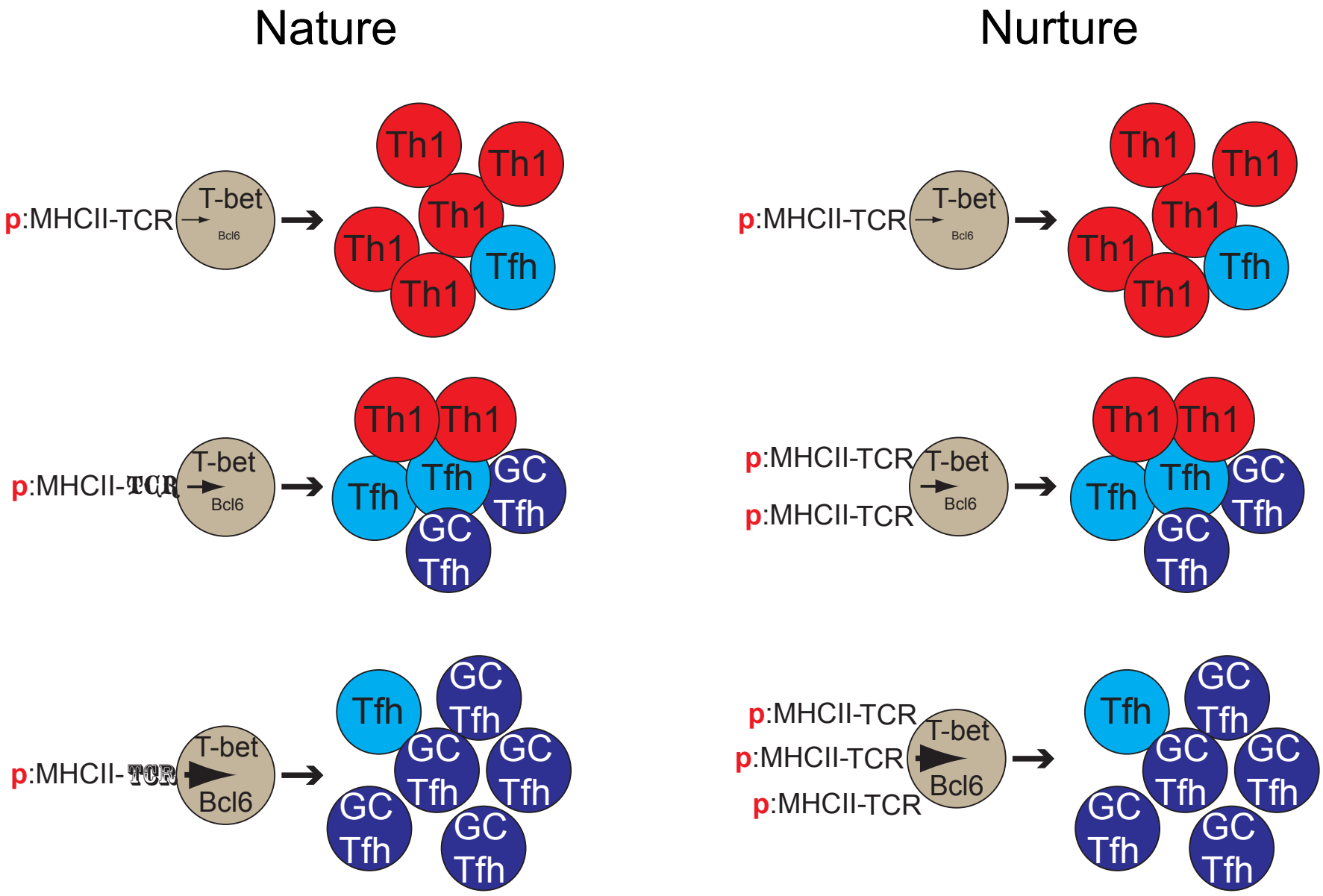
Nature
Nurture
p:MHCII-TCR
T-bet
Bcl6
Th1
Tfh
GC Tfh

Thanks to my colleagues, present and past

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(Postdoc,
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