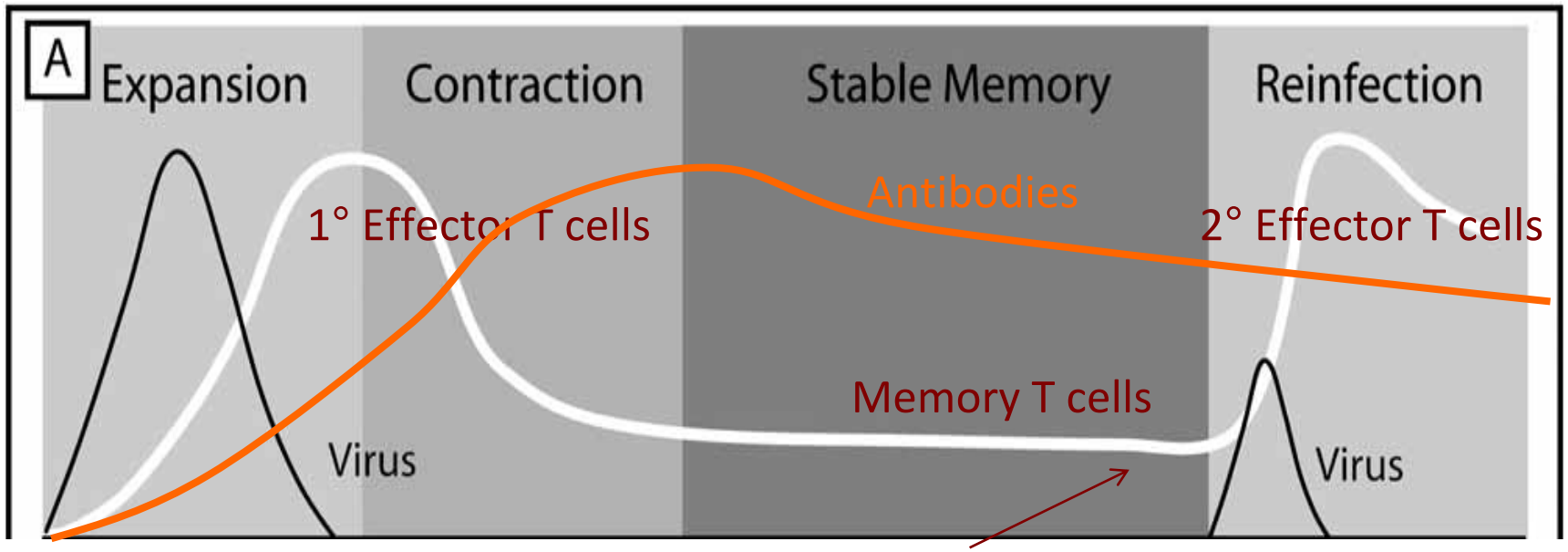
Disclosures

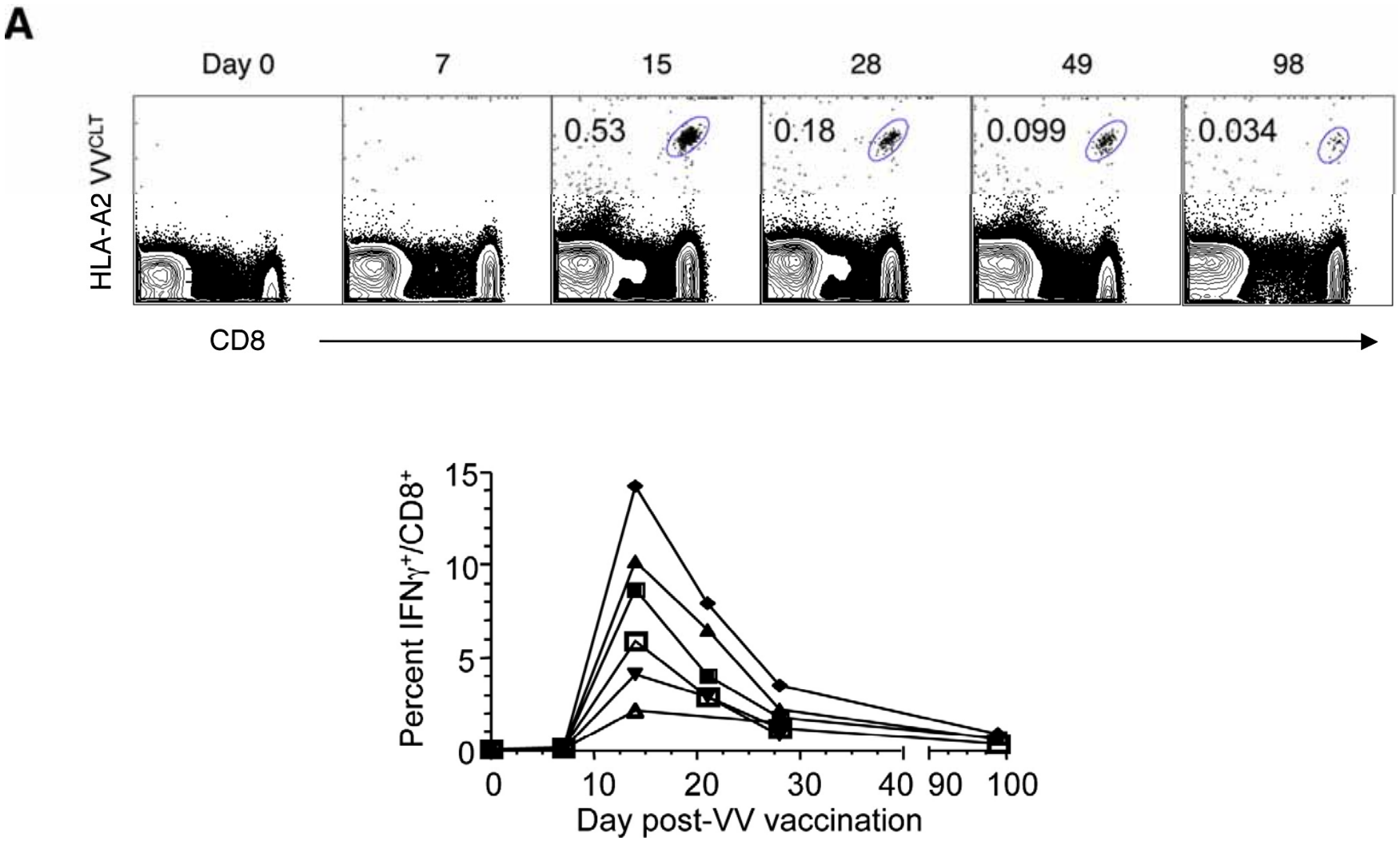
…I have none

Phases of adaptive immune responses



Memory = Increased Numbers of Responding Cells

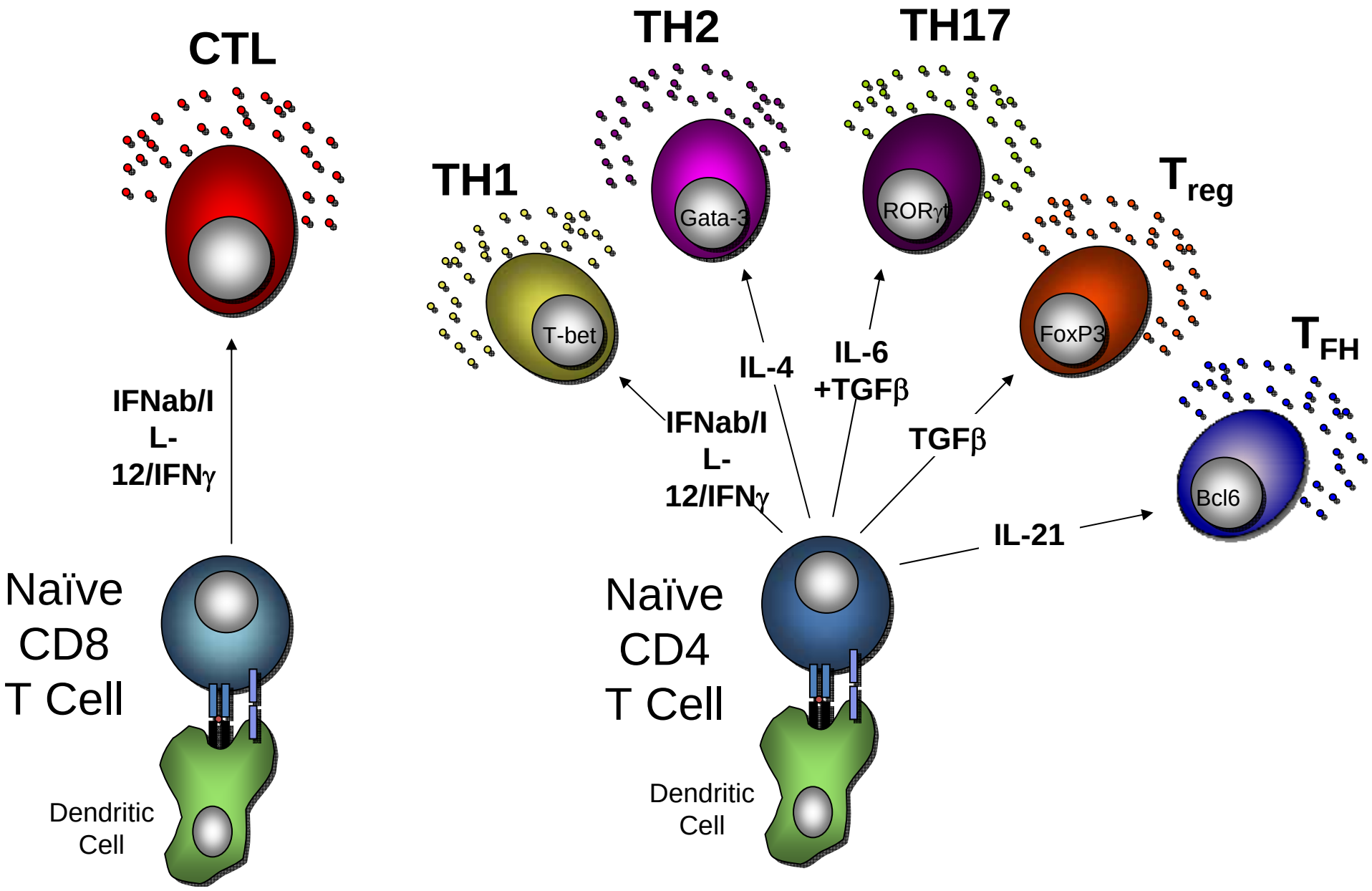
Kaech and Wherry (2007) Heterogeneity and cell-fate decisions in effector and memory CD8+ T cell differentiation during viral infection. Immunity. 27:393-405.



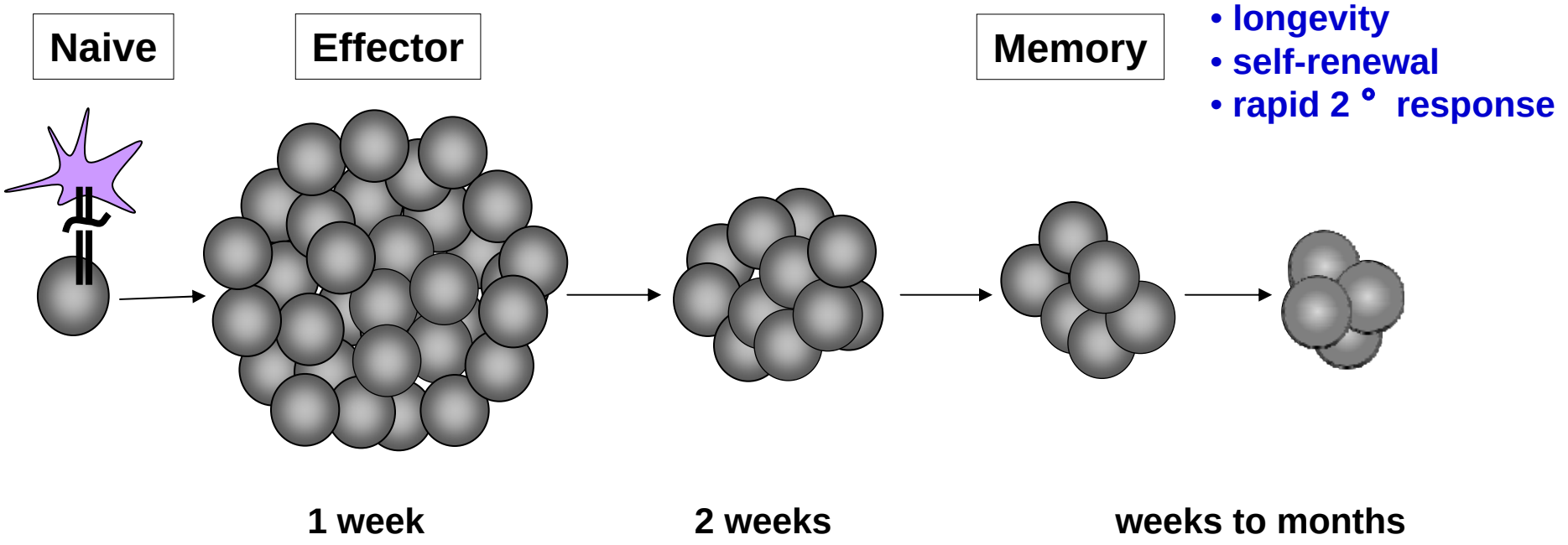
Can also detect tumor-specific CTLs in a few cases too.

Miller et al., *Immunity* 2009
(Ahmed's lab)

If EFFECTOR T cell fates are specified by the TYPE of '3rd Signal'…



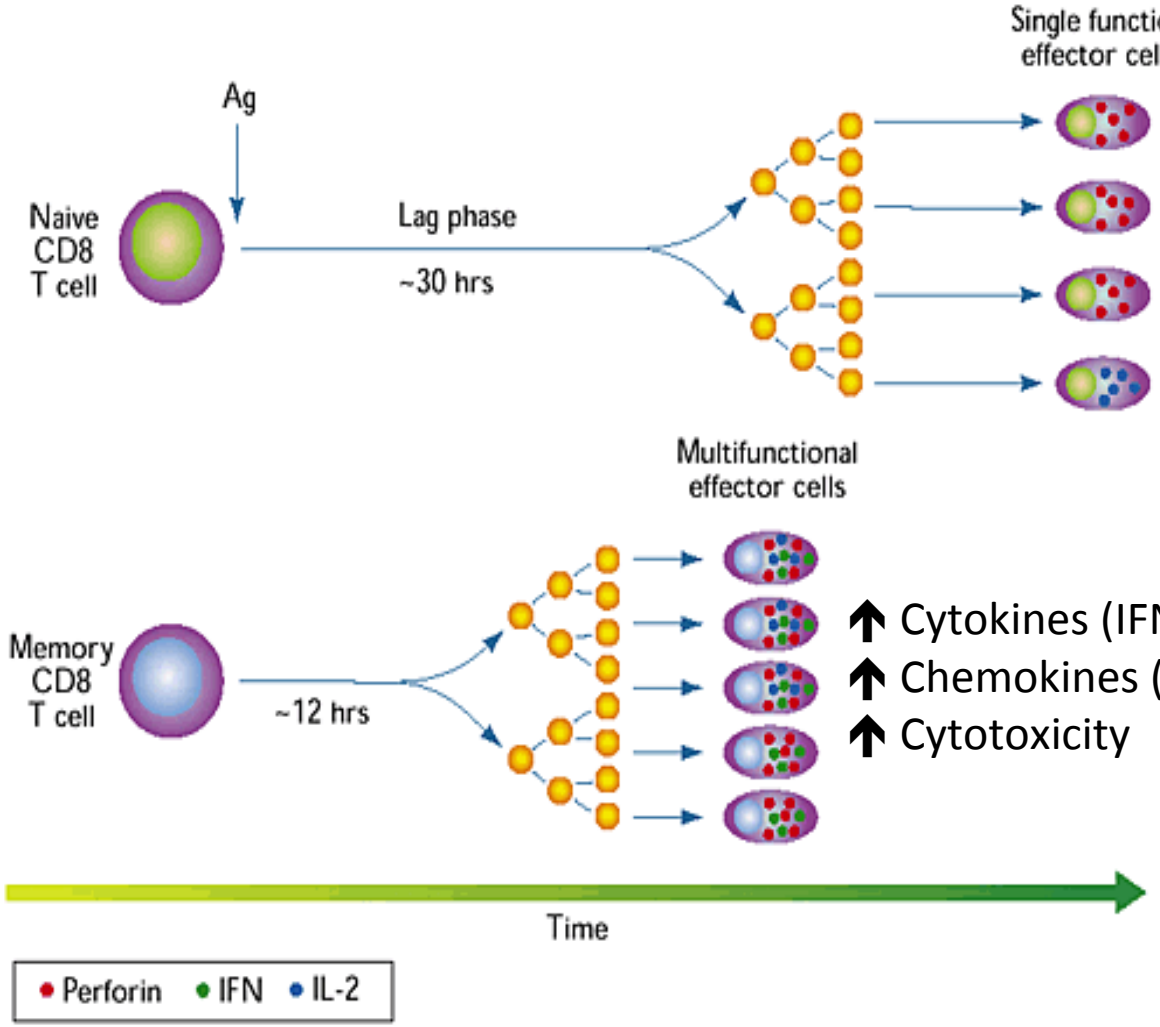
Effector T cells mature into memory T cells



1. How do memory T cells protect against re-infection?
2. What are the different types of memory T cells?
3. What determines the 5-10% of the cells that survive to become memory?
4. What effects do chronic infection/antigen persistence have on memory development?

Enhanced Function

Memory cells aren't simply naïve cells at a high frequency. T cells show enhanced functional responses, such as rapid induction of proliferation and effector responses, when they reencounter antigen



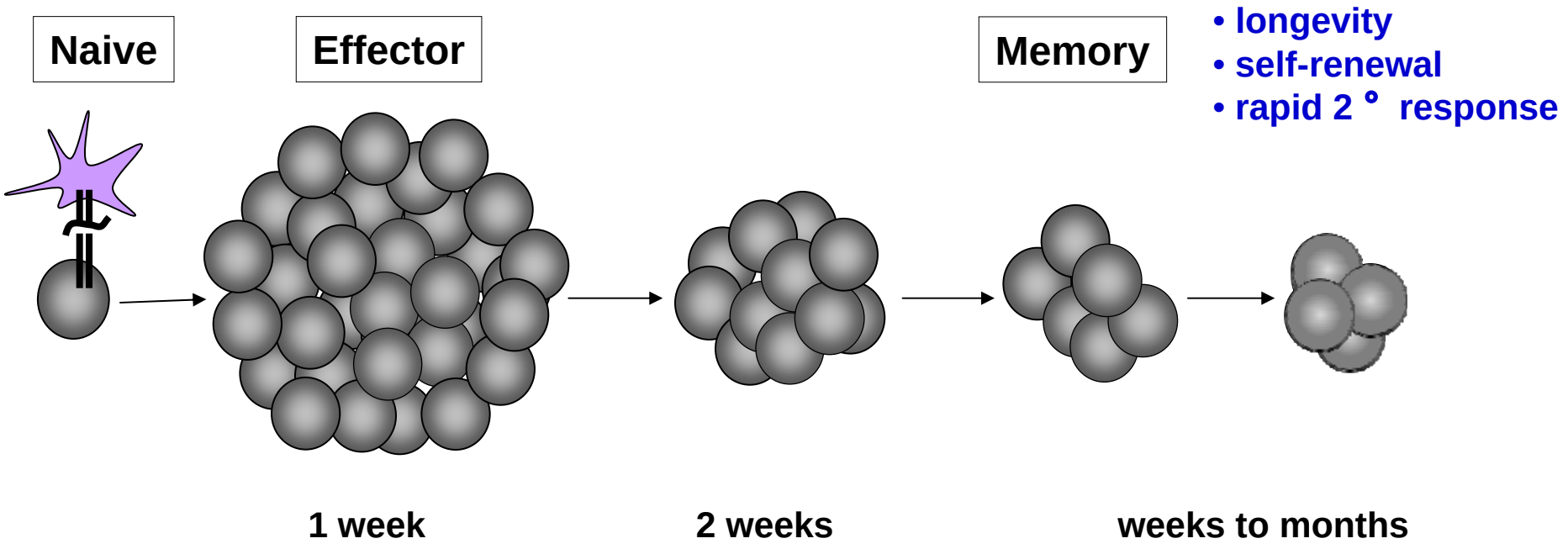
- ↑ Cytokines (IFNg, TNFa, IL-17)
- ↑ Chemokines (recruit other leukocytes
- ↑ Cytotoxicity

Gray
Nature Immunology **1**: 11 - 12 (2000)

Why are memory T cells more responsive to antigen than naïve T cells?

- Structural changes (avidity of TCR/ signalosomes)
- Gene expression changes (chromatin remodeling)
- Location

Effector T cells mature into memory T cells



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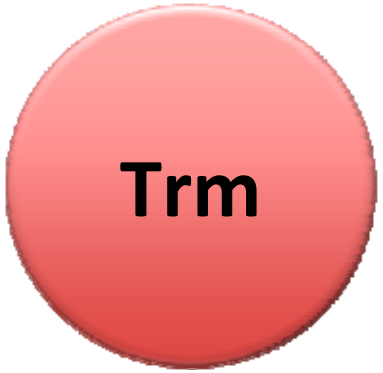
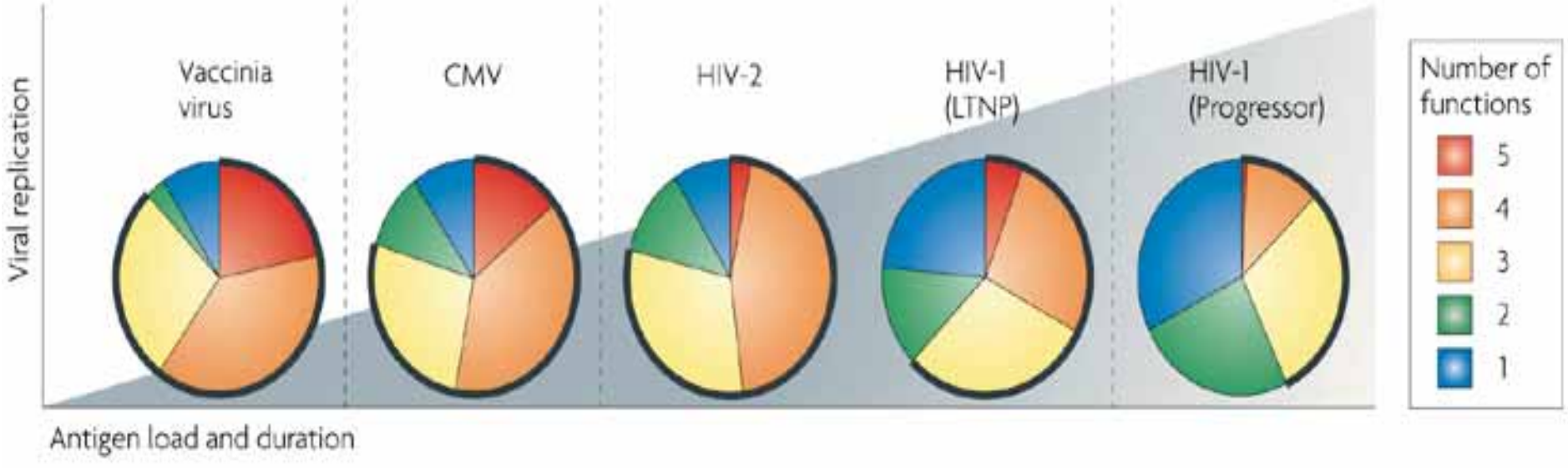
Subsets of memory T cells:

Different types of memory T cells

Central Memory	Effector Memory	Resident Memory
		
Tcm	Tem	Trm
Lymph node homing CCR7+ CD62L+ Circulating	Peripheral tissues Inflammatory chemokine receptor Circulating	Mucosal Tissues (skin, gut) Long-lived, but not circulating
Effector Functions +/- IL-2+	↑Effector Functions ↑Cytotoxicity	↑Effector Functions ↑Cytotoxicity
Higher proliferative capacity	Lower proliferative capacity	Lower proliferative capacity

Stability of differentiation states unclear

Assessing quality of memory



Assessment of memory (or effector) T cell "quality" by poly-functionality, not simple numbers. "Functions" in this example (from human CD8 T cells) were the ability to make IFN-γ, TNF-α, IL-2, CCL4 and to degranulate (CD107 assay) in response to TCR stimulation.

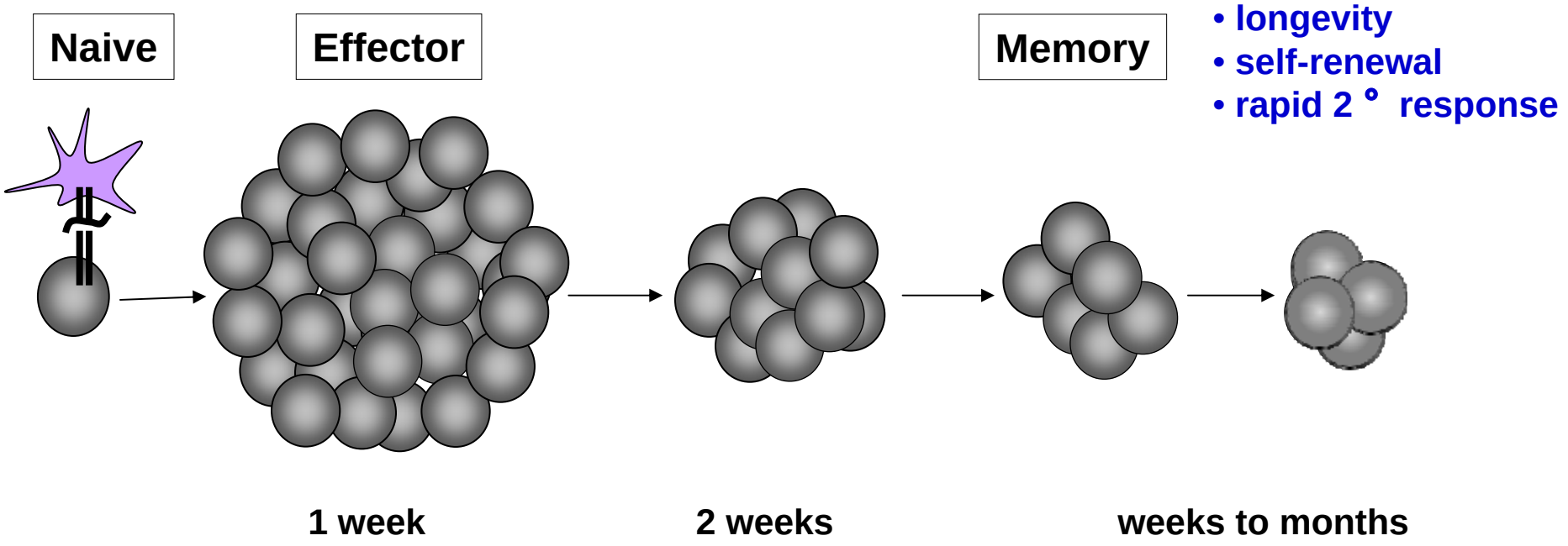
Seder et al. 2008 Nat. Rev. Immunol. 8:247-58

What are the roles of these different types of memory T cells in protection against infectious disease?

How do they collaborate?

What types of T cells are most protective against cancer?

Effector T cells mature into memory T cells



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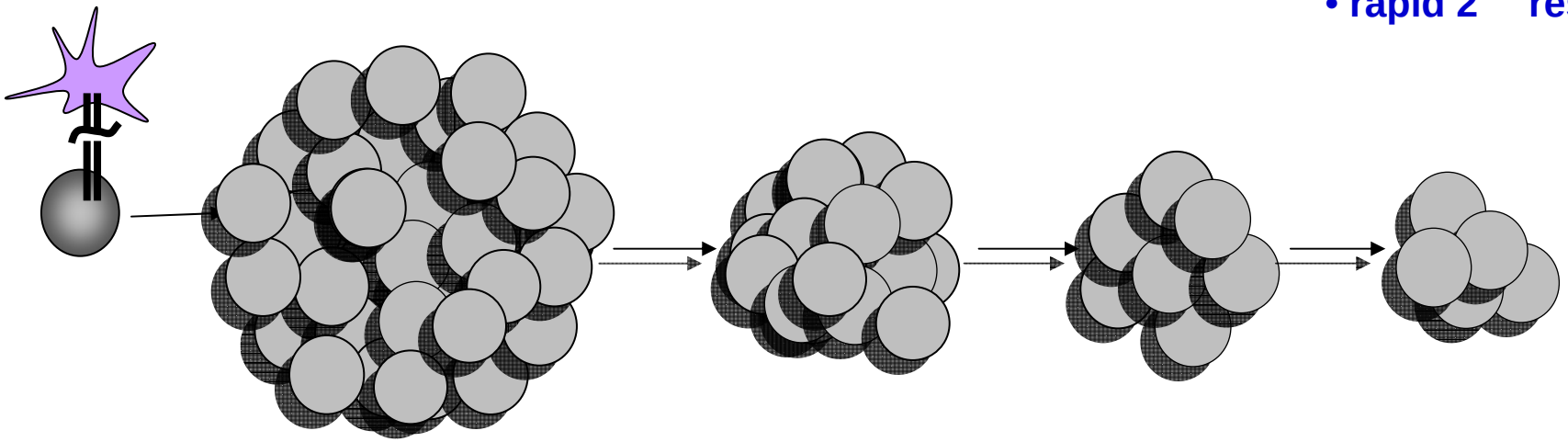
Effector T cells mature into memory T cells

Naive

Effector

Memory

- longevity
- self-renewal
- rapid 2 ° response



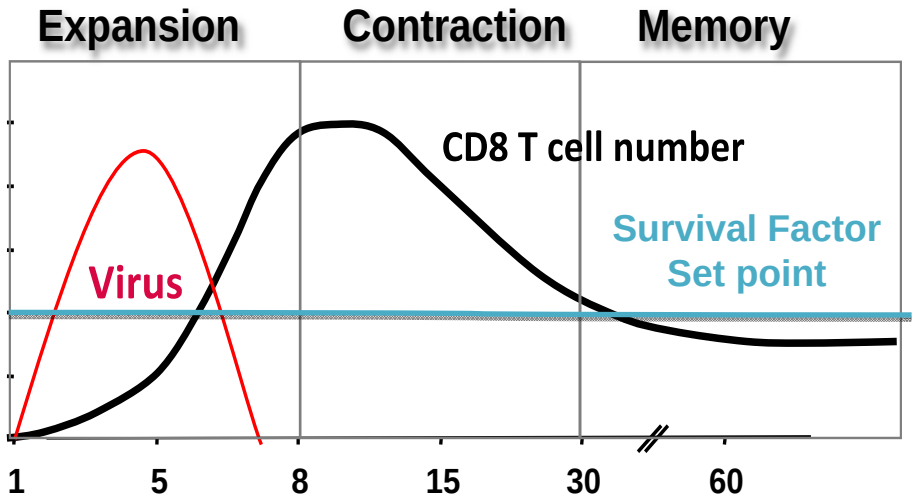
1 week

2 weeks

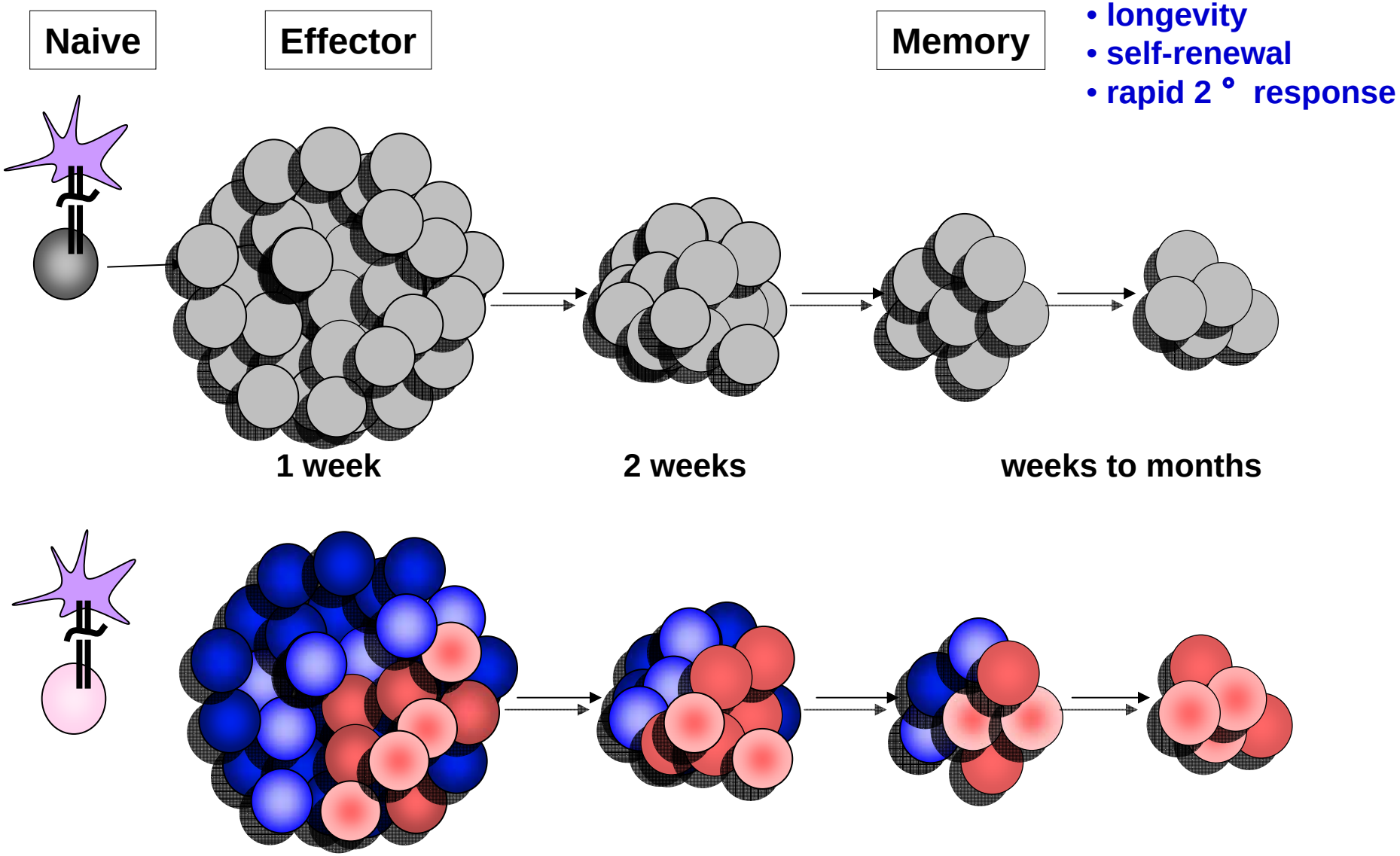
weeks to months

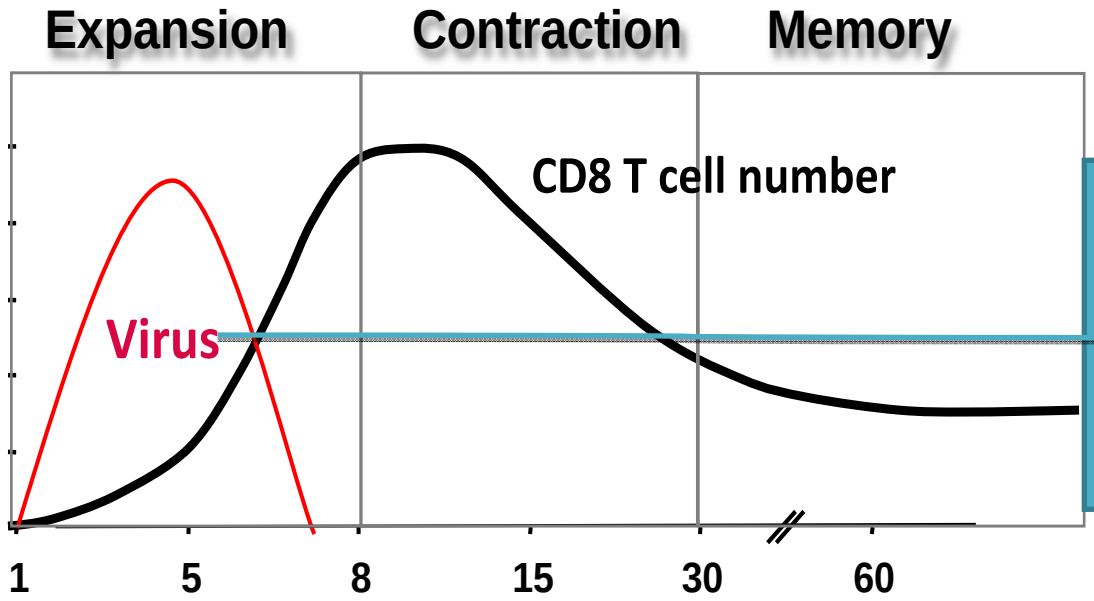
a.

Stochastic Model- competition for survival factors



Effector T cells mature into memory T cells





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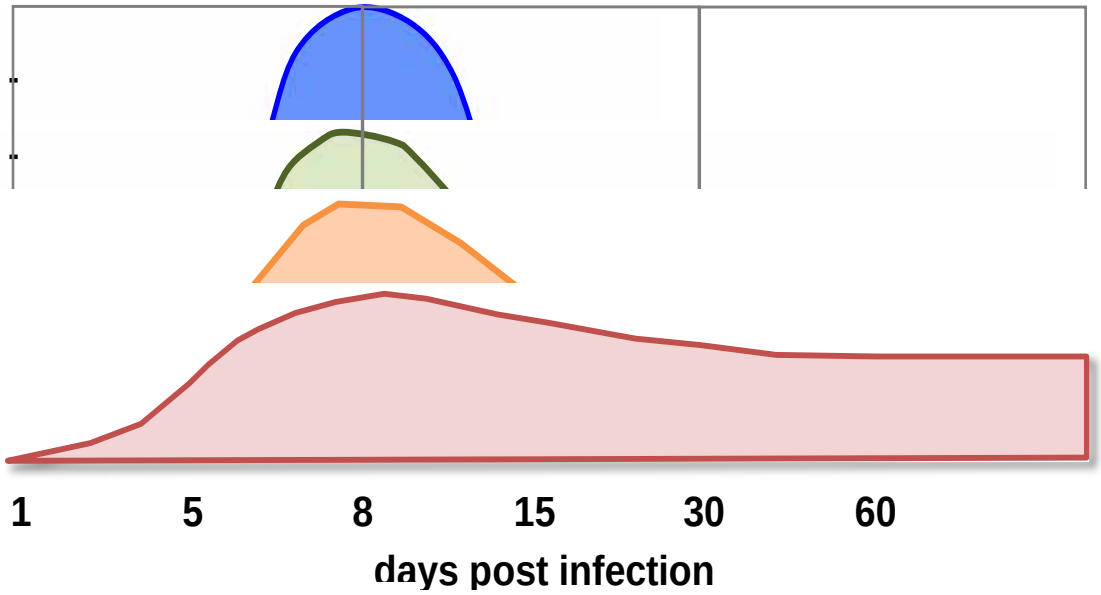
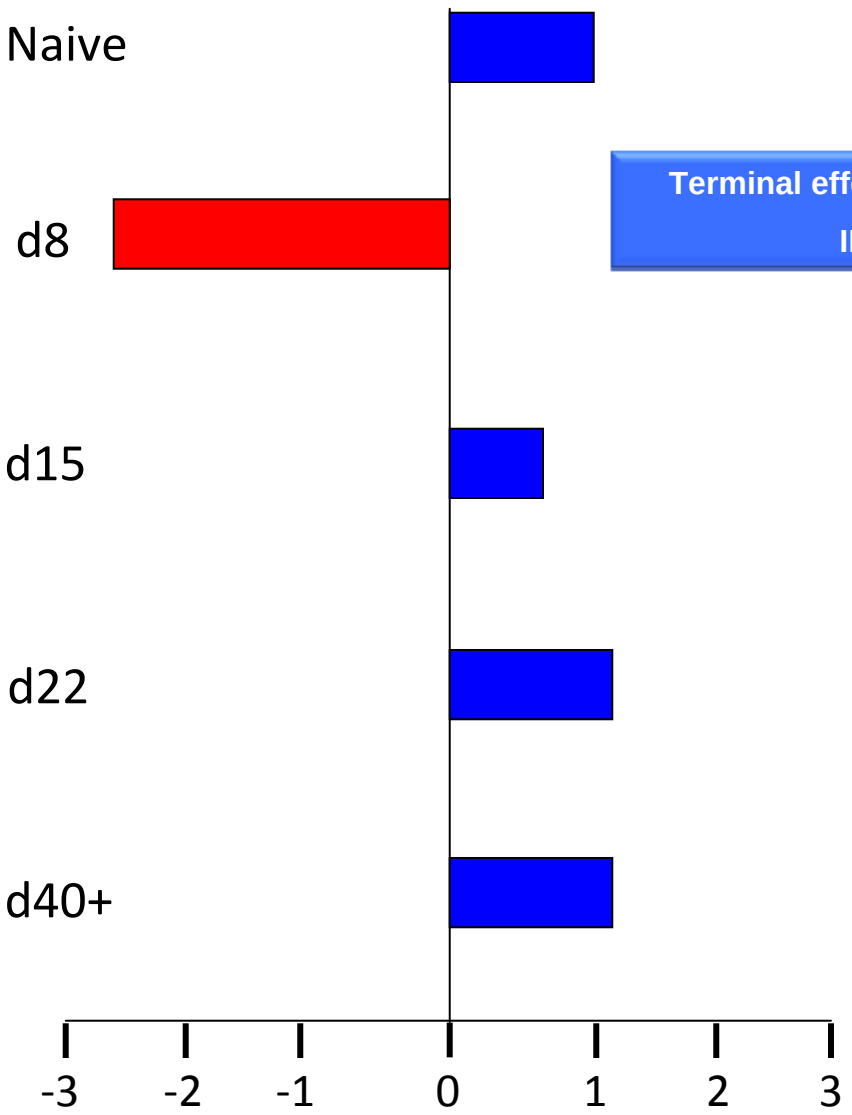


Cell intrinsic- fate Model

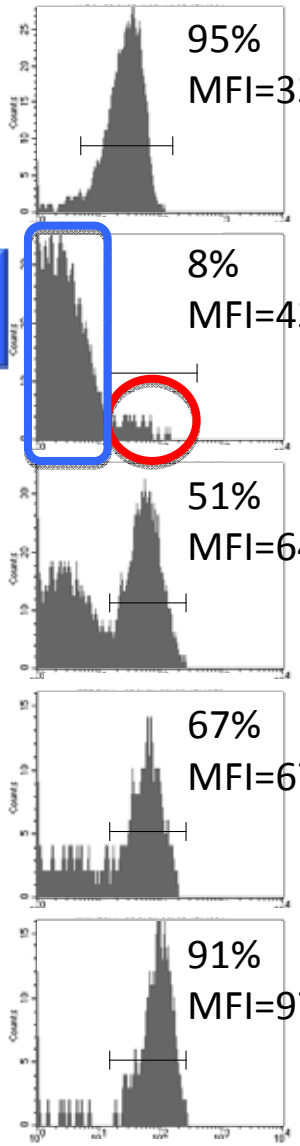
IL-7Rα chain expression



Relative mRNA levels
(compared to Naïve)

Terminal effector CD8 T cells
IL-7R^{lo}

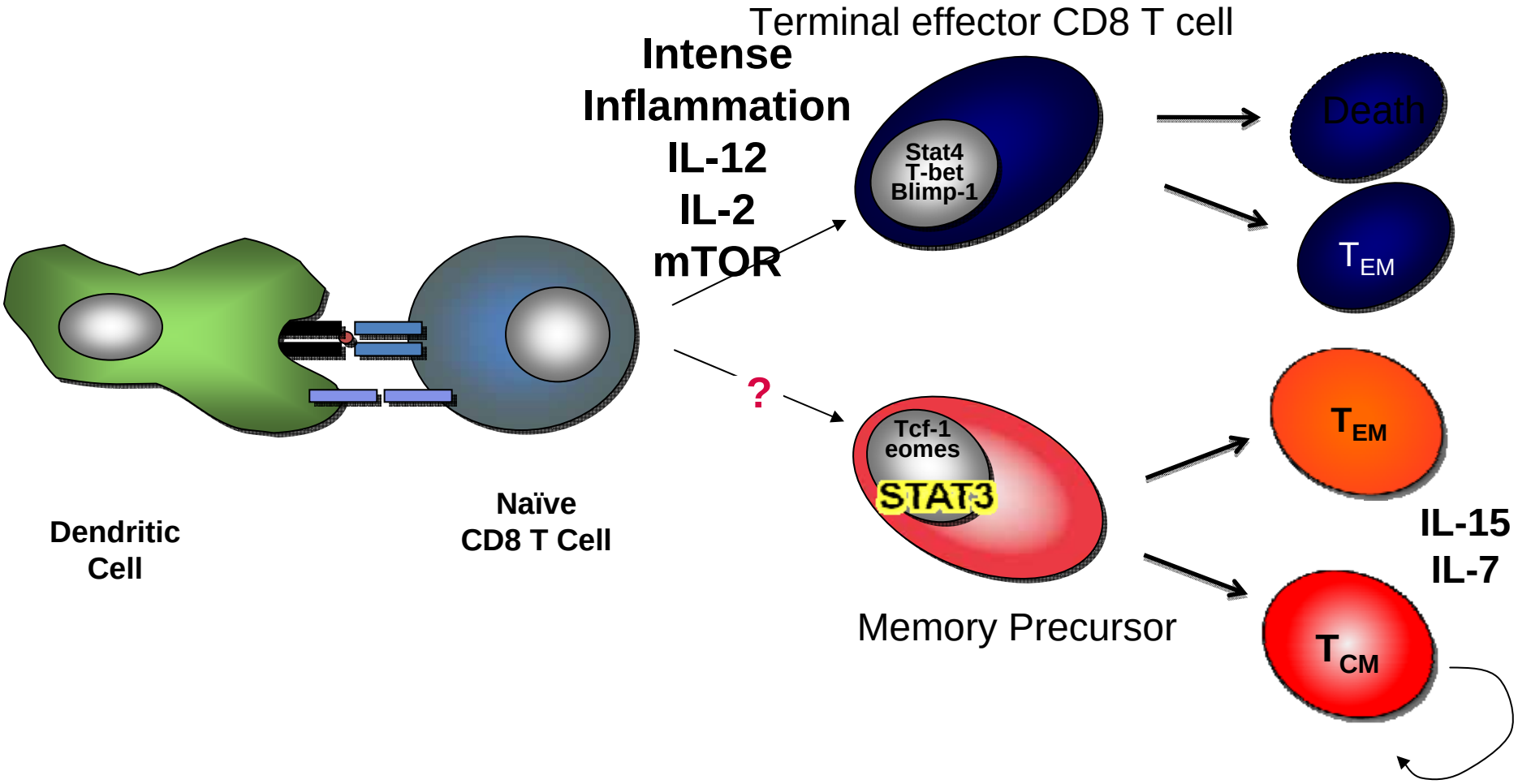
Memory precursor effector CD8 T cells
IL-7R^{hi}



CD127 (IL-7Rα)

Surface protein levels

What are the signals that determine this cell fate decision?



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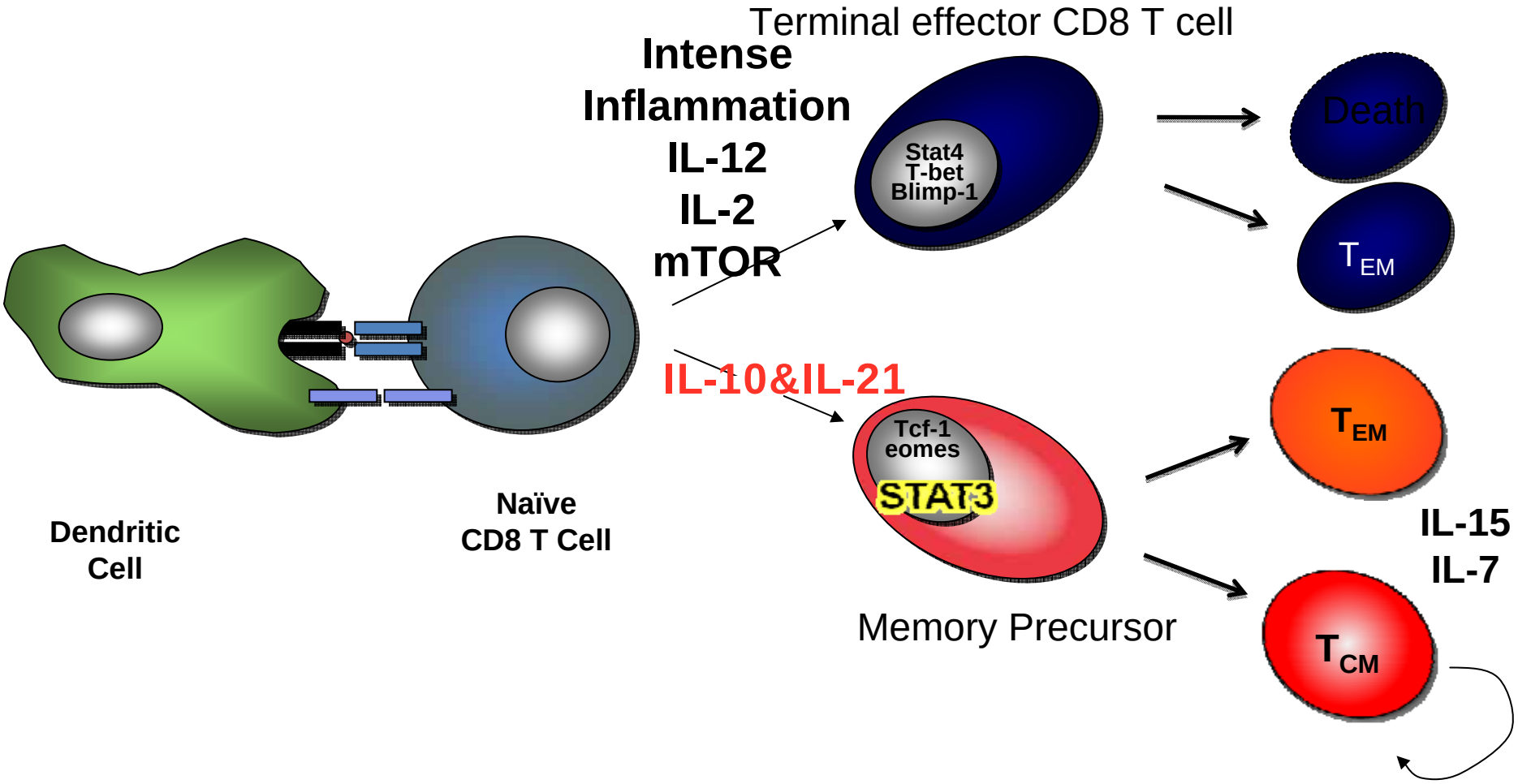
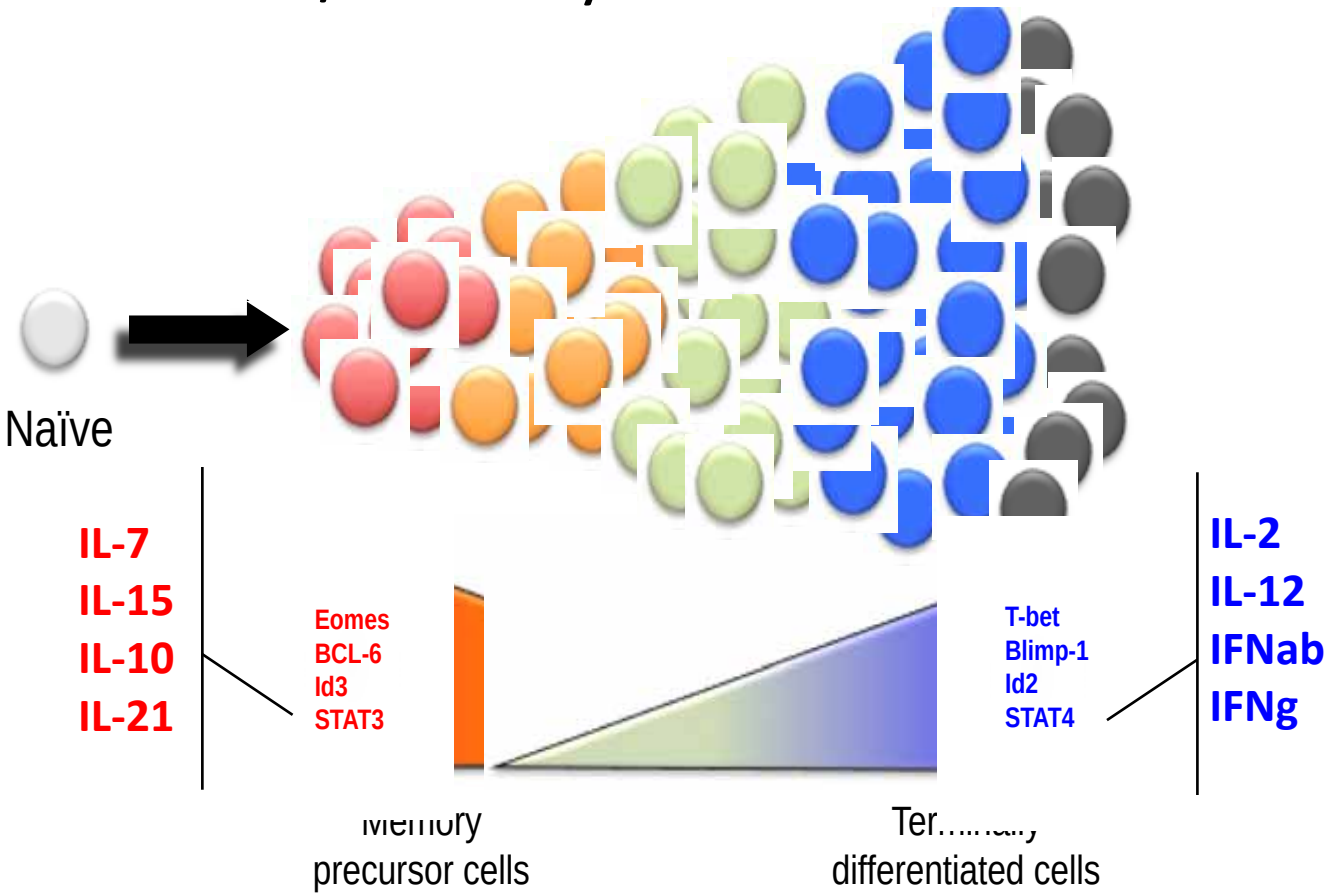
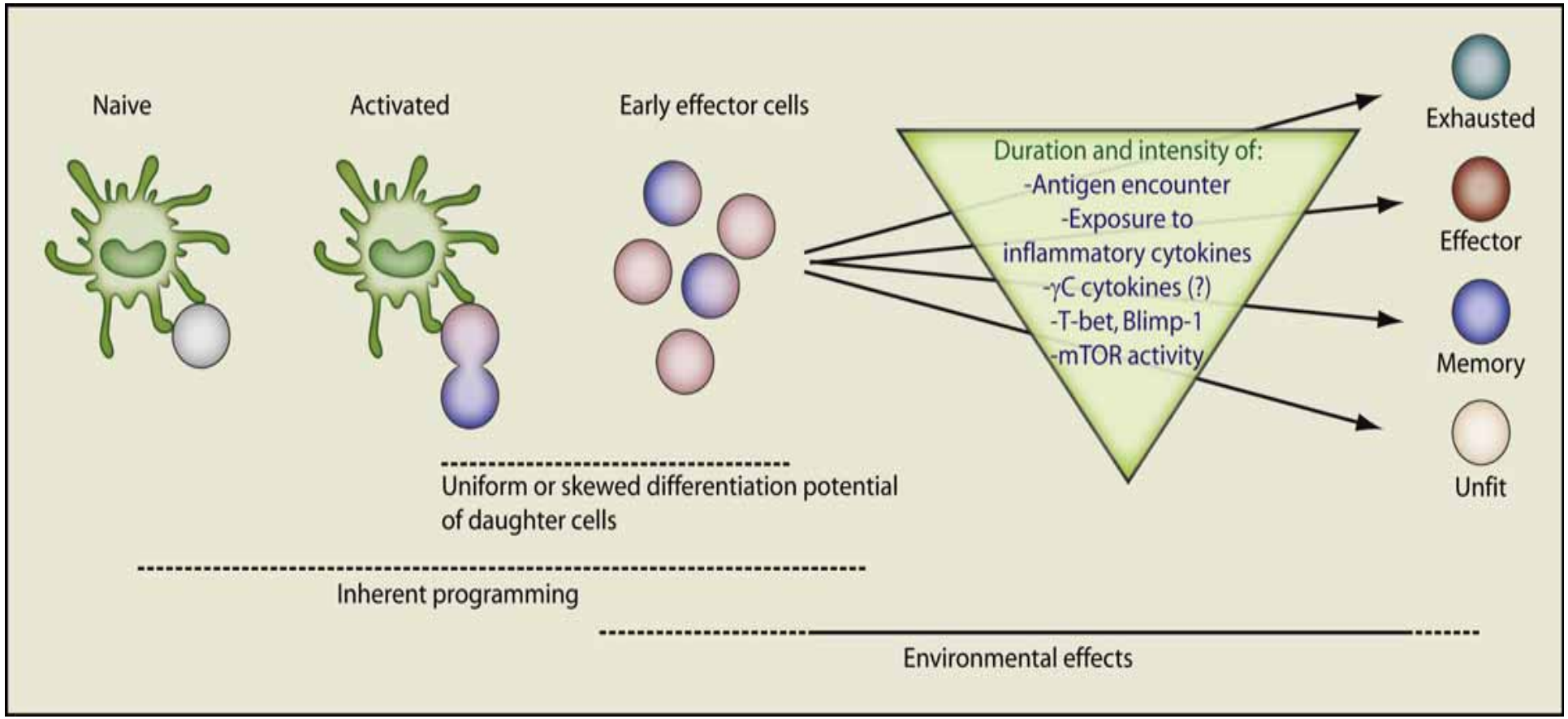


Opposing Transcriptional Programs Regulating Effector/Memory Fates in CD8 T cells



Balancing act: A goldilocks view of making memory T cells



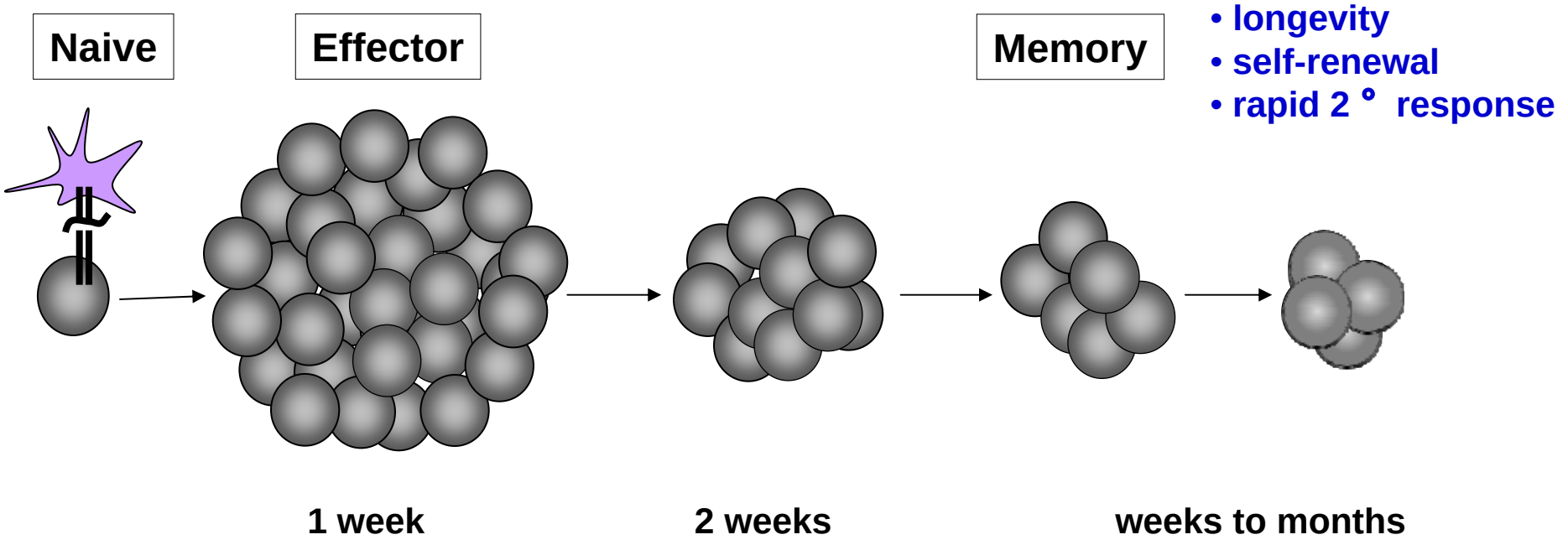
Masopust and Jameson (2009) Immunity

Summary #1

Generation of memory T cells:

- Effector and memory T cells can derive from the same naïve cell.
- Markers such as KLRG-1 and CD127 (IL-7 receptor) have been useful for distinguishing cells likely to become short-lived effectors versus long lived memory CD8 T cells. It is not clear though whether these molecules can positively dictate the cell fate.
- Numerous factors can affect production of memory versus effector T cells, including exposure to inflammatory cytokines and IL-2.
- These signals regulate a gradient of transcription factors T-bet, Eomes, Blimp/Bcl-6, Id2/Id3, STAT3/STAT4 that cooperatively function to influence the memory/effector differentiation states.

Effector T cells mature into memory T cells



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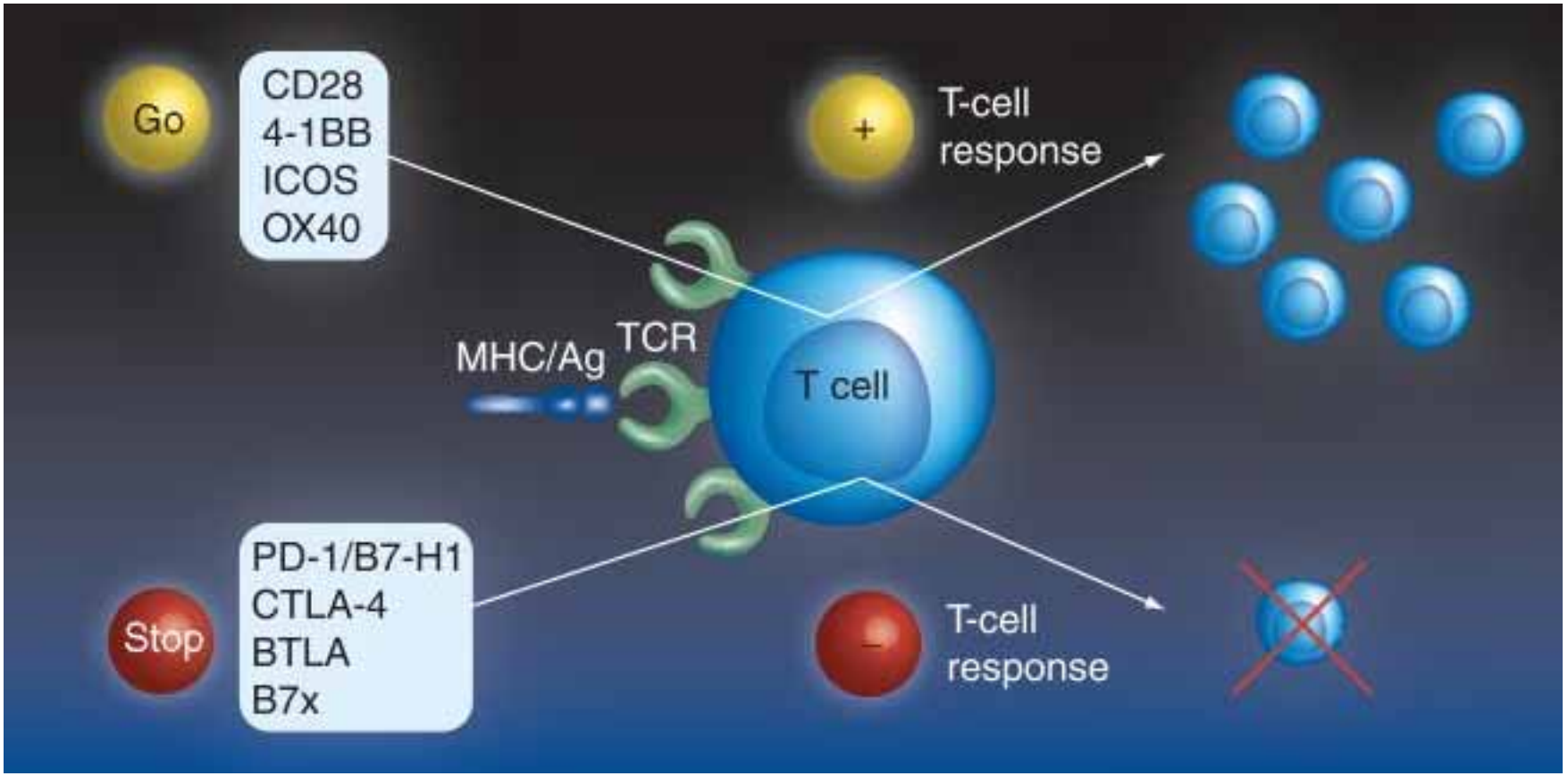
Negative regulation of adaptive T cell immunity: checks and balances



IL-10
TGF-b
Tregs
MDSC

T cell exhaustion is a common feature of chronic (viral) infections and cancer

- **Occurs in multiple animal models (e.g. LCMV, MHV, FLV, SIV, *L.major*) and in human infections (e.g. HIV, HCV, HBV, HTLV-I)**

- **Common feature of cancer and therapeutics targeting reversal of exhaustion in trials**

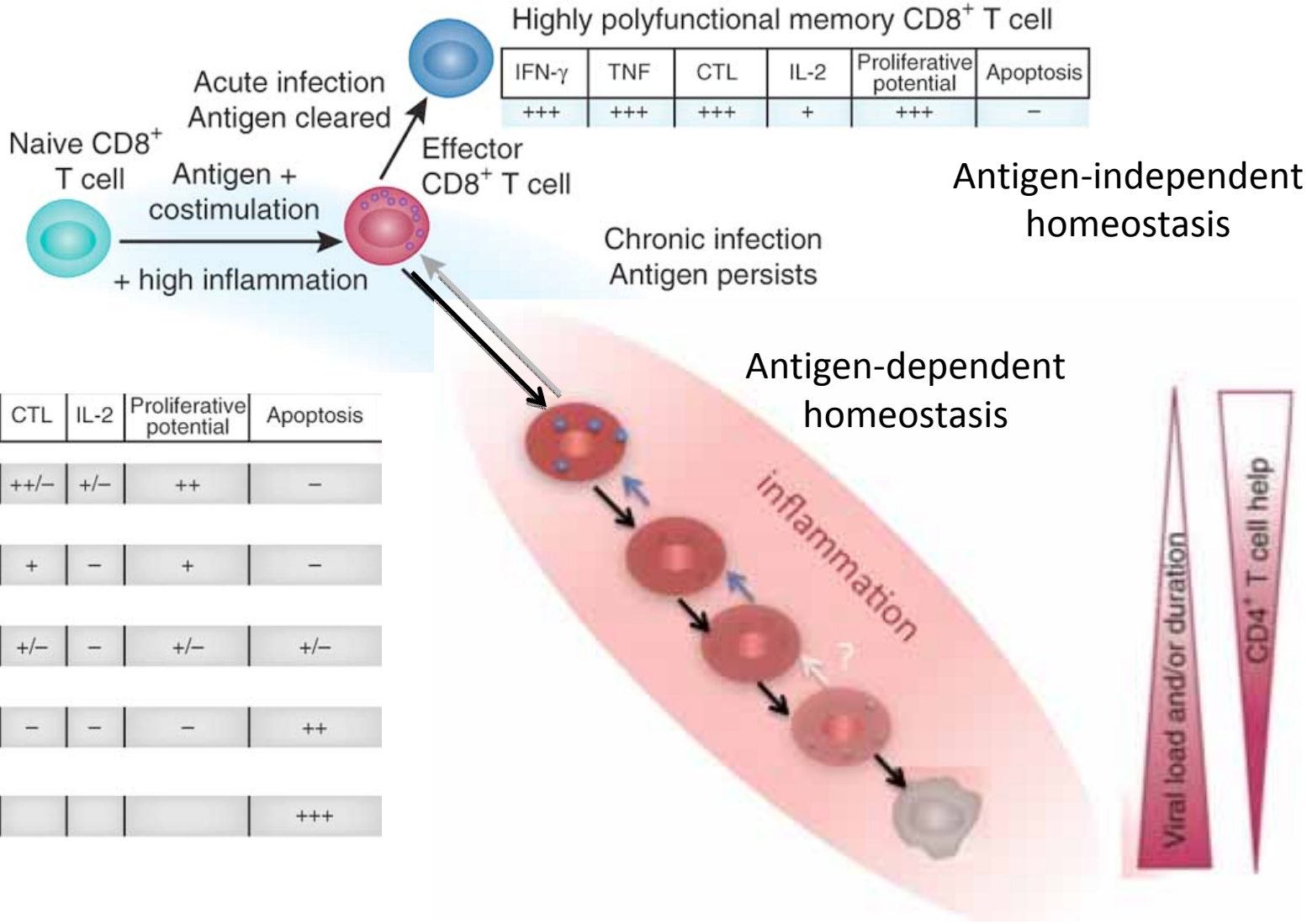
- **Dysfunction is hierarchical – Lose IL-2, Proliferation, Cytotoxicity, TNF, IFN-γ - eventually physical deletion**

- **Correlates with viral and/or antigen load, duration of infection, and low CD4 T cell help**

- **Major role for the inhibitory receptor PD-1 and co-expression of multiple other inhibitory receptors (LAG-3, 2B4, CD160, TIM3, EP2/4 etc)**

- **CD8 T cell exhaustion prevents optimal control of infection and tumors**

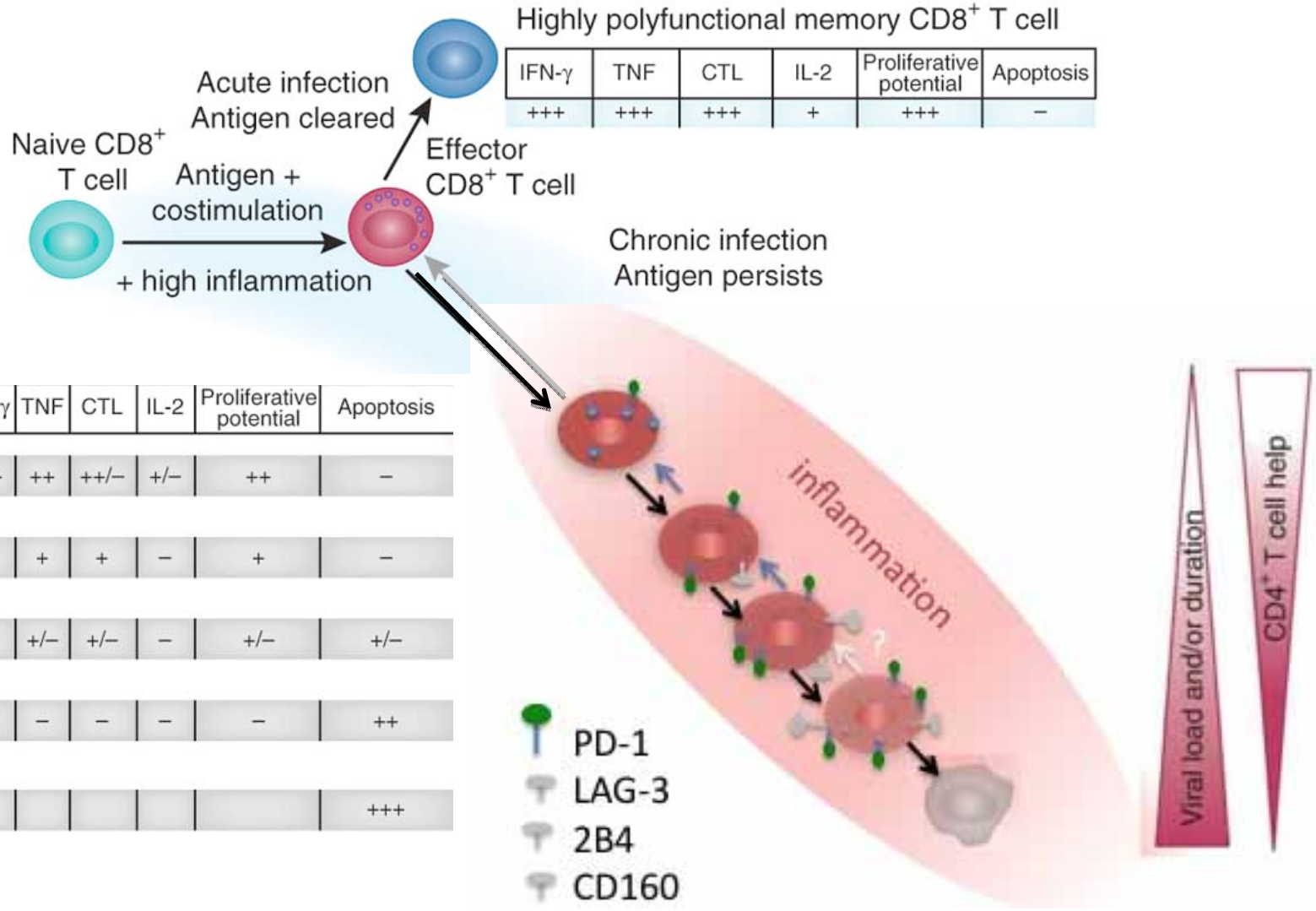
Model for hierarchical loss of T-cell function during chronic viral infection.



	IFN-γ	TNF	CTL	IL-2	Proliferative potential	Apoptosis
CMV	+++	++	++/–	+/–	++	–
	++	+	+	–	+	–
HIV	+/–	+/–	+/–	–	+/–	+/–
	+/–	–	–	–	–	++
						+++

Wherry et al. Nat. Imm.. 2011;77:4911-4927

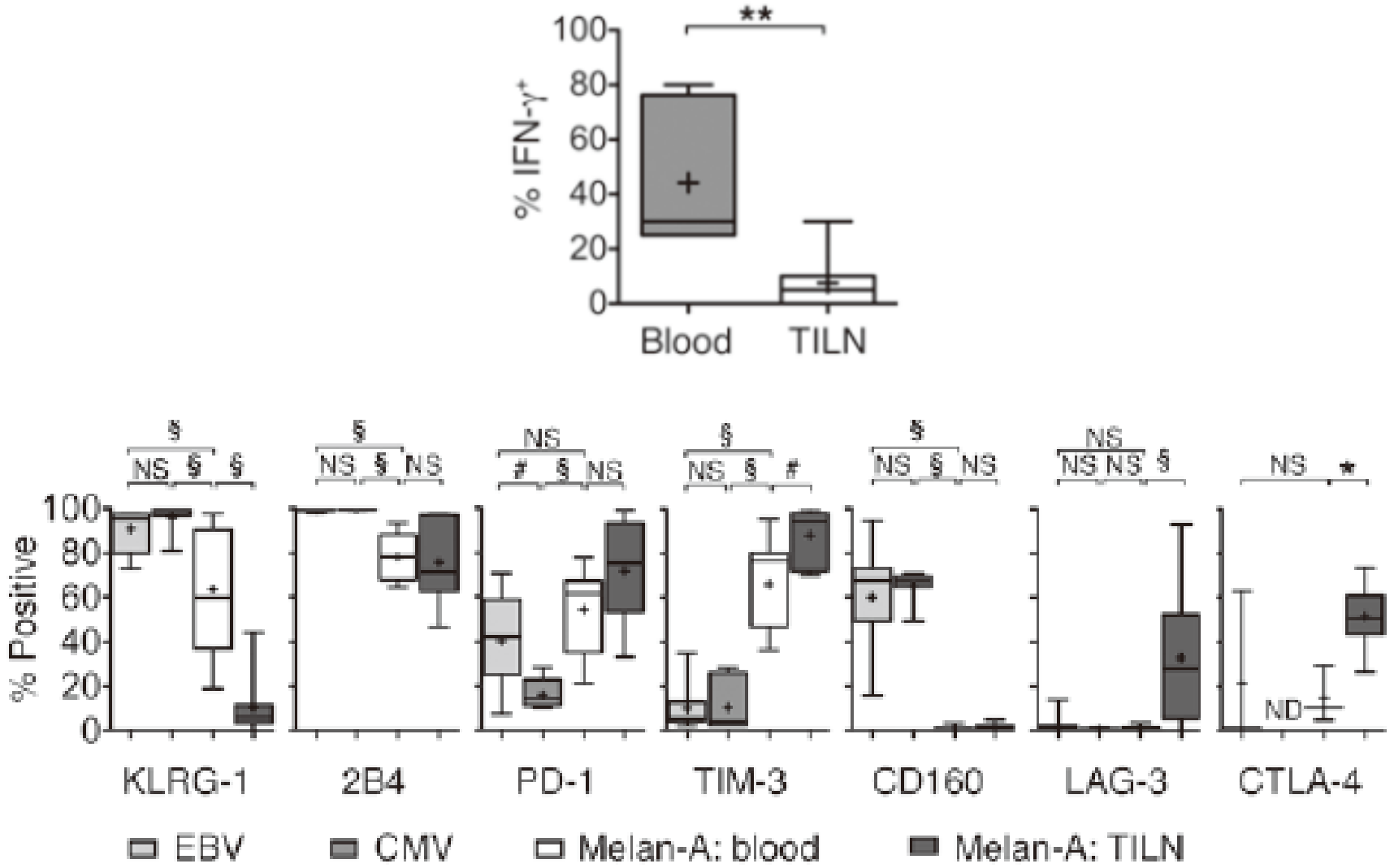
Model for hierarchical loss of T-cell function during chronic viral infection.



Wherry et al. Nat. Imm.. 2011;77:4911-4927

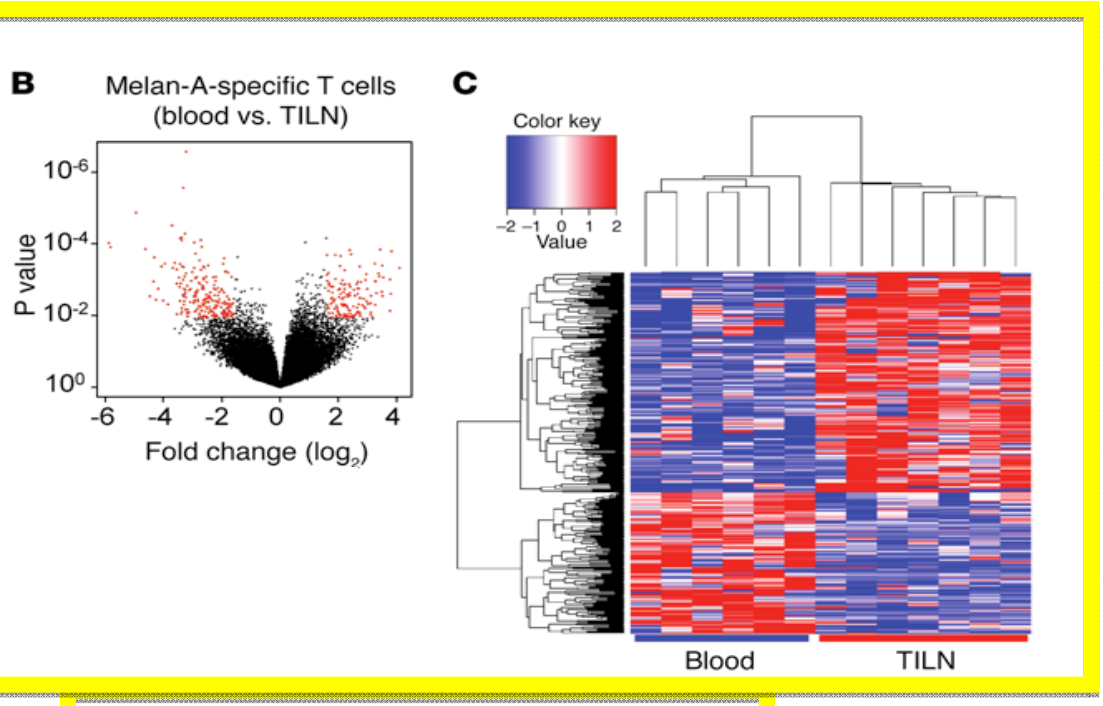
T cell exhaustion is a common feature of many chronic infections and cancer

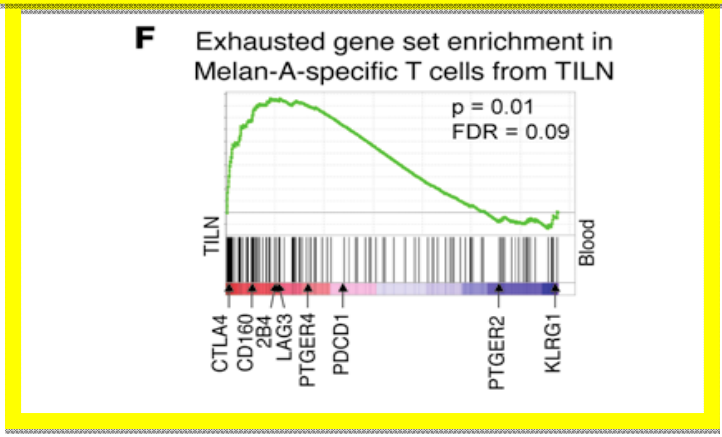
T cell exhaustion in melanoma



Lukas Baitsch, et al. J Clin Invest. 2011 June 1;121(6):2350-2360.

T cell exhaustion in melanoma





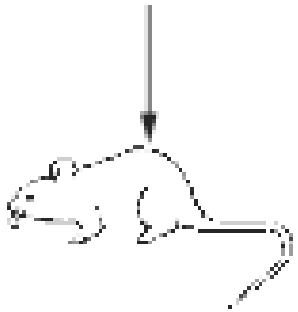
Lukas Baitsch, et al. J Clin Invest. 2011 June 1;121(6):2350-2360.

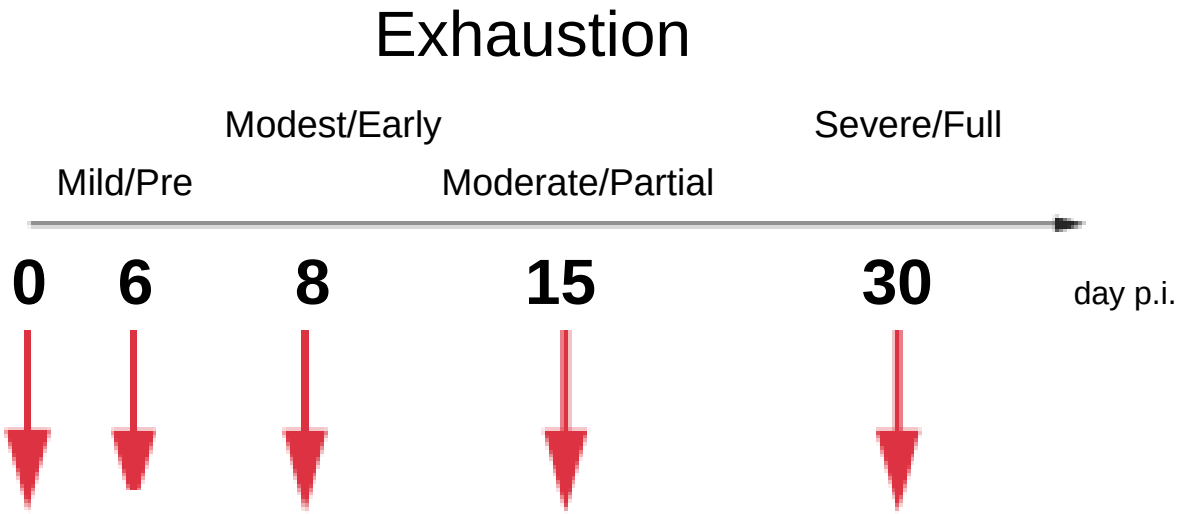
How is the process of T cell exhaustion regulated?

- Transcriptional regulation of exhaustion
- Subsets of exhausted T cells and therapeutic effects of anti-PDL1 mAb treatment

T cell Exhaustion is a Progressive Process

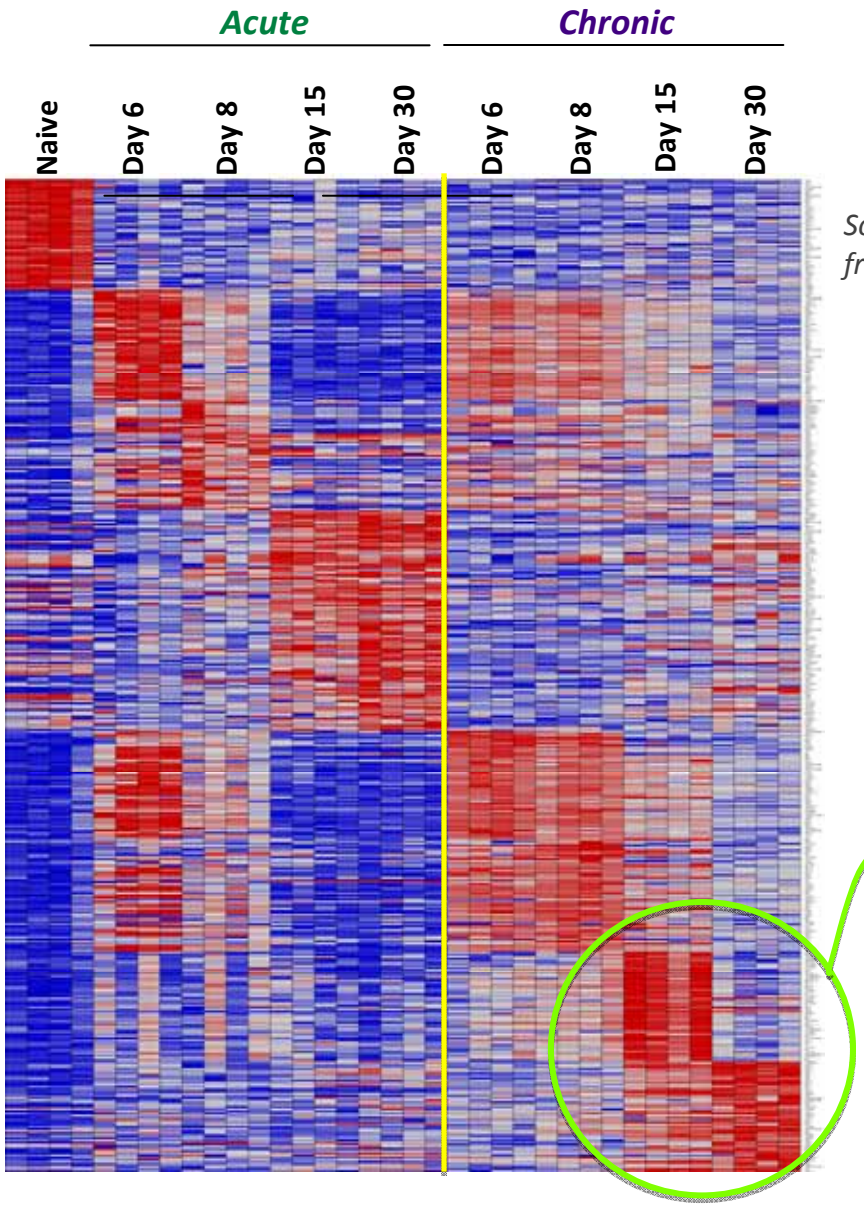
LCMV
Arm or clone 13





<u>Arrays</u>
acute LCMV: Transcriptional Profiling
chronic LCMV:

Unique Transcriptional Program of Exhausted CD8 T cells



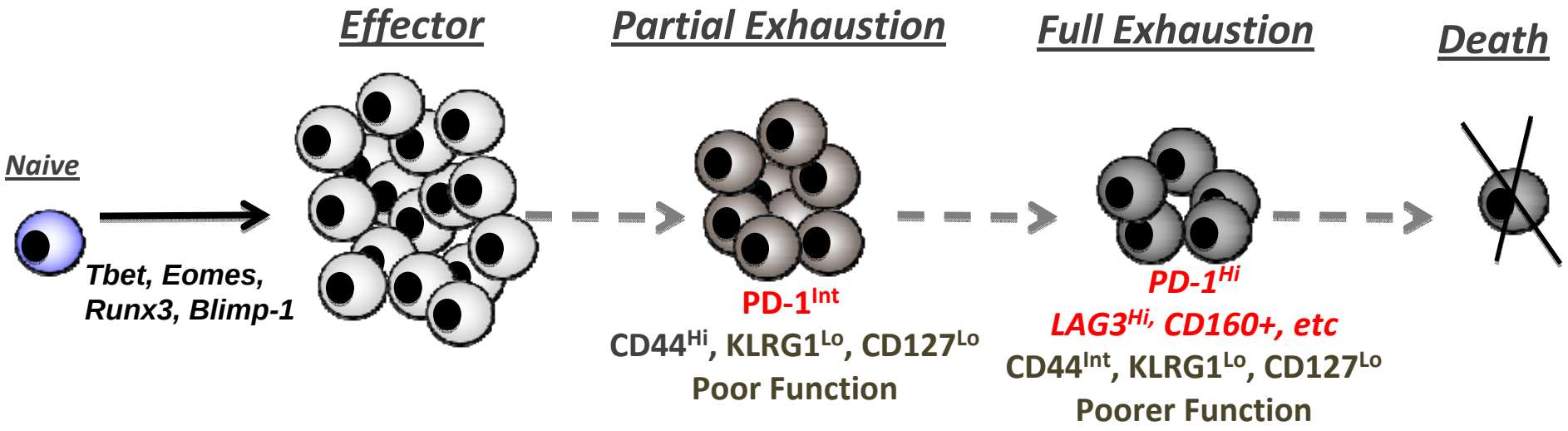
Sorted on DbGP33 tetramer+ CD8 T cells from LCMV Armstrong or clone 13 infection

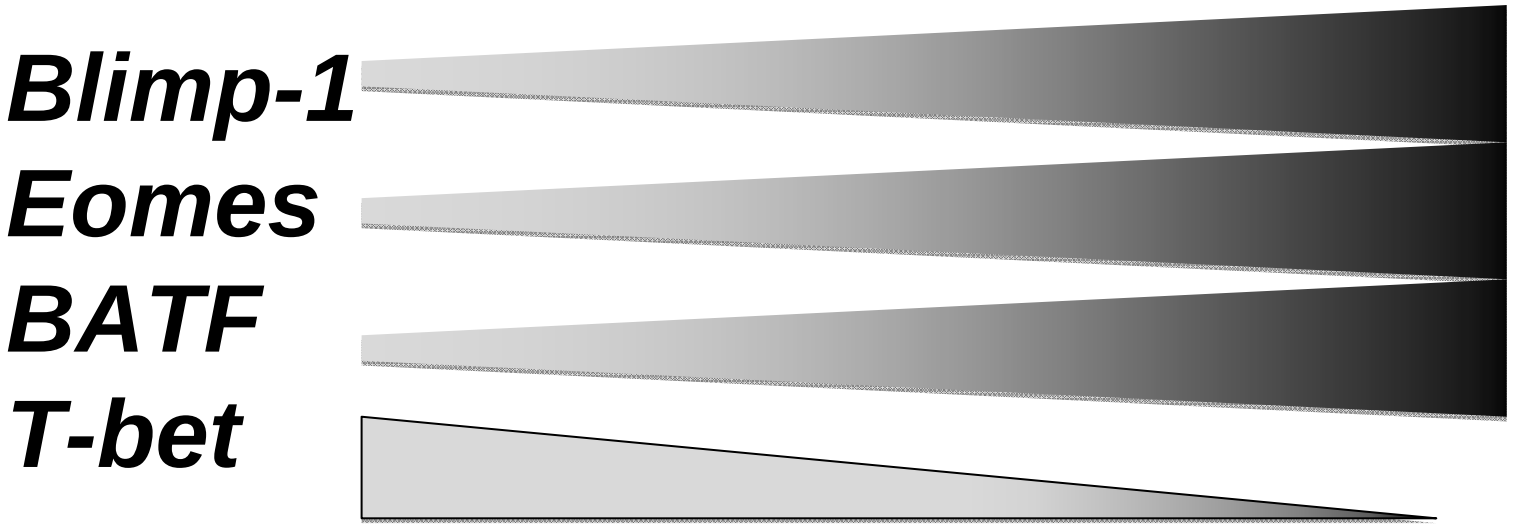
- **TCR and cytokine signaling**
- **Chemotaxis, Migration, etc**
- **Metabolism**
- **Transcription factors**
- **Inhibitory receptors**

Dr. John Wherry (UPENN), unpublished data

Jill Angelosanto and Alison Crawford

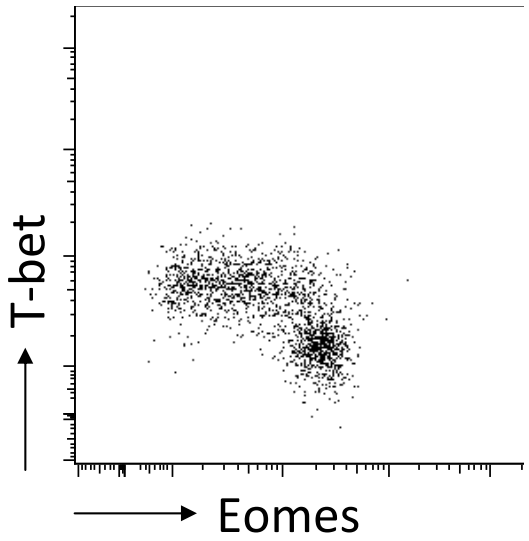
Differentiation, lineage and transcriptional control of CD8 T cell exhaustion





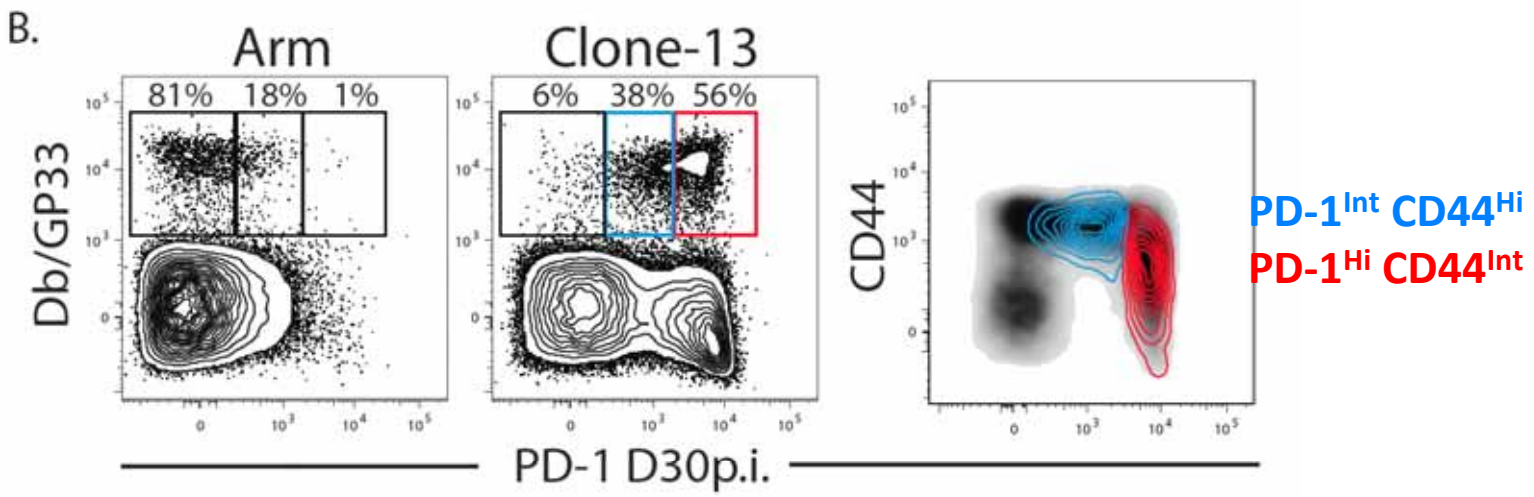
Expression of T-bet and Eomes inversely correlate in exhausted CD8 T cells

d60 (Chronic)



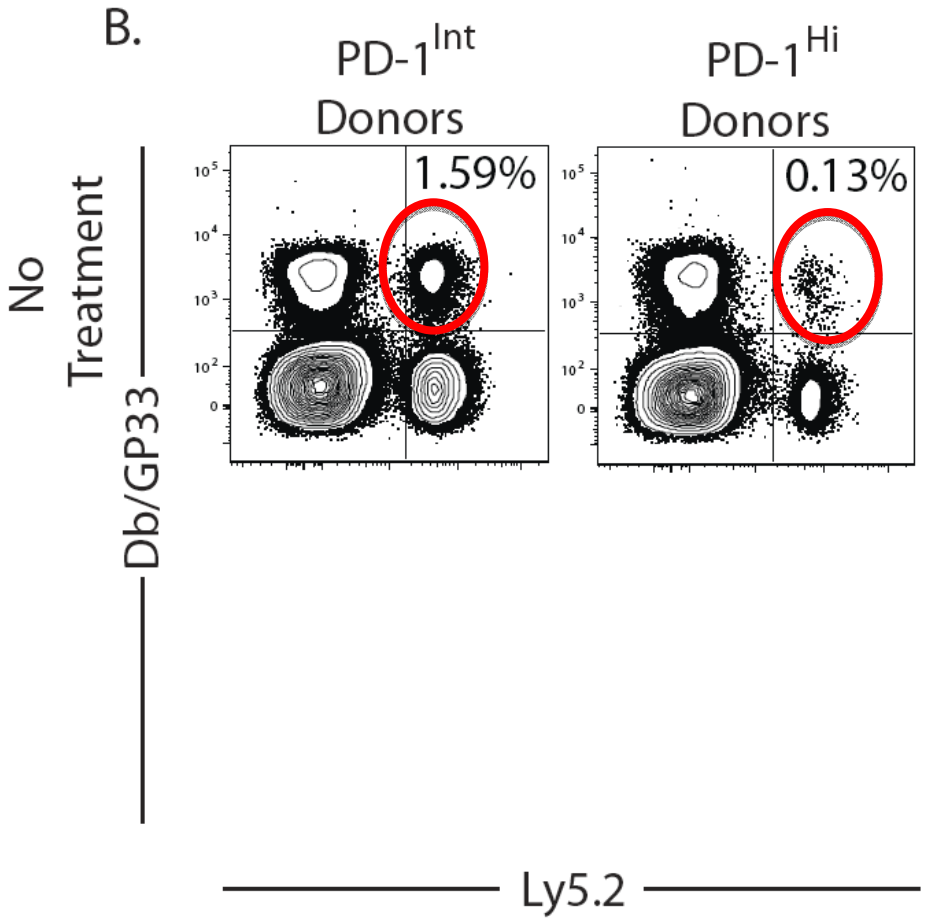
Paley and Wherry (UPENN), in press, Science

Subsets of exhausted CD8 T cells during chronic infection



Blackburn et al *PNAS* 2008

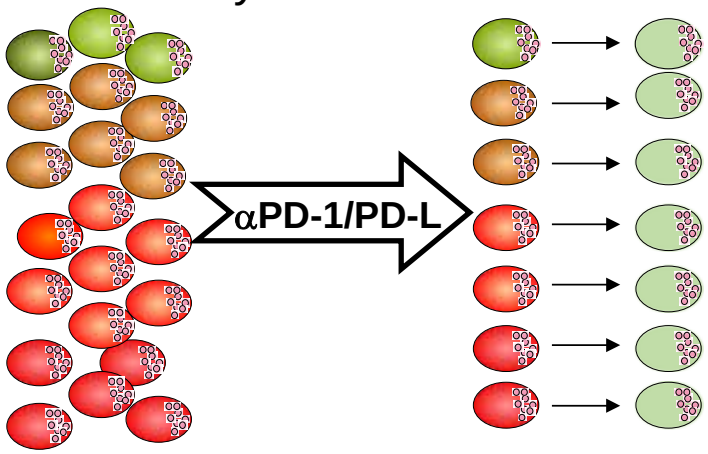
In vivo response of exhausted CD8 T cell subsets to PD-L1 blockade



PD-1^{Int} vs PD-1^{Hi} from spleen, clone 13 rechallenge d7.5

Re-invigoration of exhausted CD8 T cells by selective expansion

Model 1: Reversal of dysfunction in all exhausted T cells



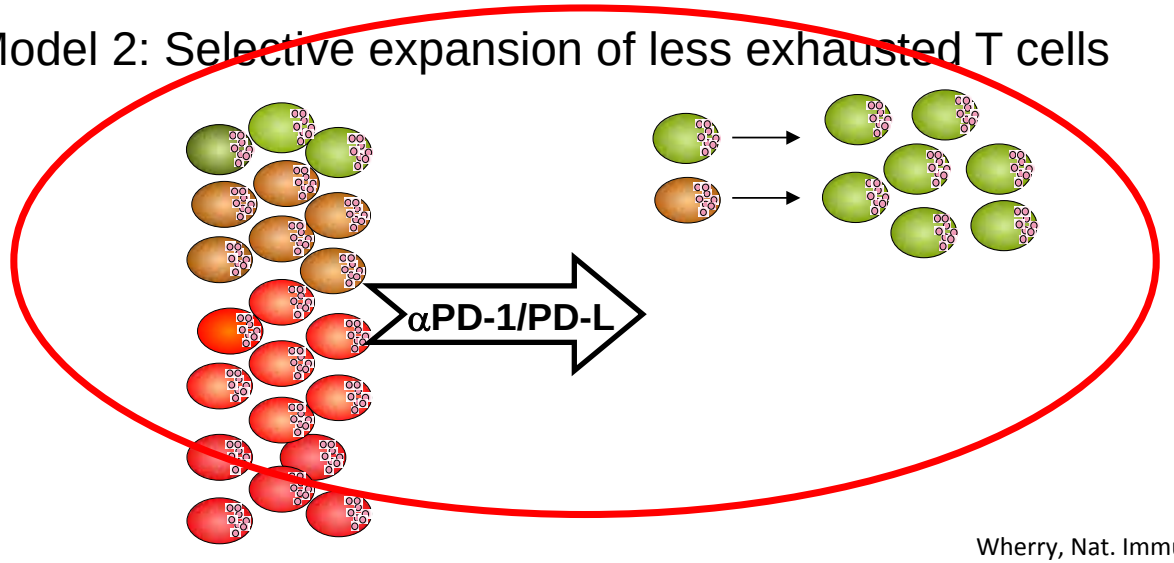
Exhaustion

High function
(Memory T cell)

Partial
Exhaustion

Full Exhaustion

Model 2: Selective expansion of less exhausted T cells



Wherry, Nat. Immunol 2011

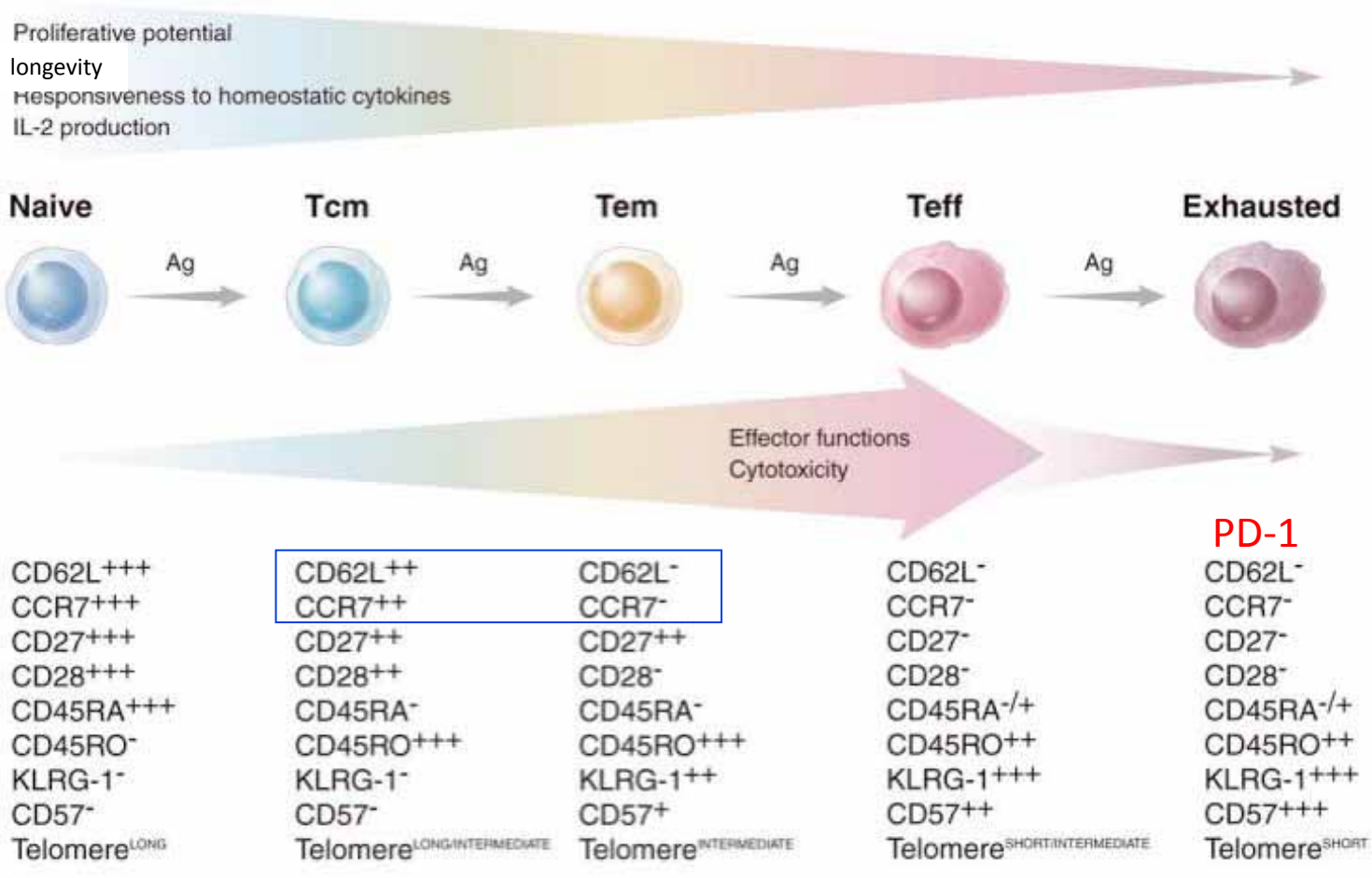
Summary #2

- CD8 T cell priming in the absence of CD4 T cells can lead to defective "helpless" memory CD8 T cells, which lose function and fail to survive long term.

- Exposure to persistent antigen, as occurs in chronic infection, leads to exhaustion, a progressive loss of CD8 T cell function and survival. This process involves PD-1 upregulation.

Thanks

- Kaech lab
- John Wherry (UPENN)
- Joe Craft (Yale)



Two major classes of memory T cells were first identified in humans, and were termed "Effector Memory" (Tem) and "Central Memory" (Tcm).

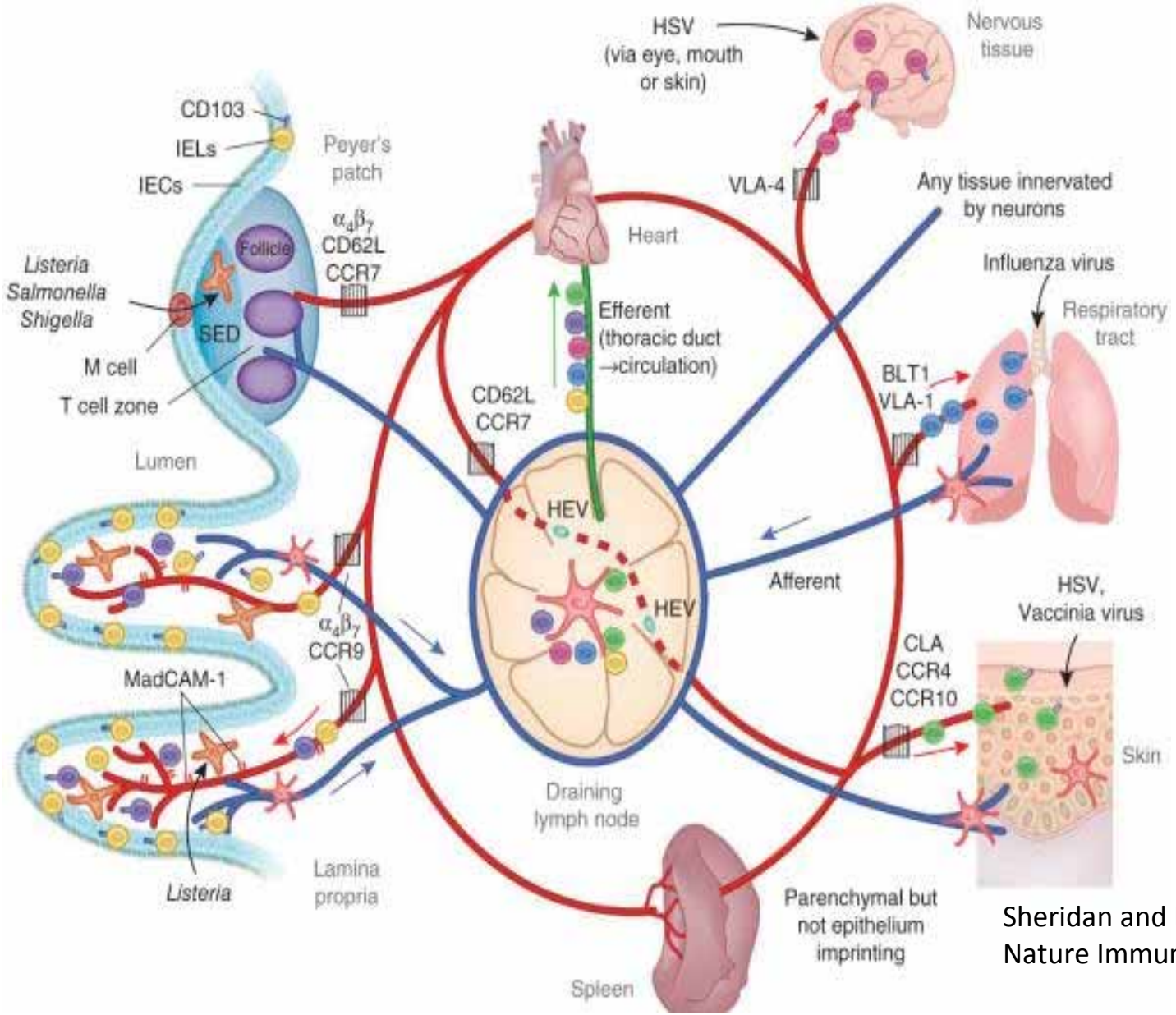
The distinction is mainly based on expression of **the trafficking molecules, CD62L (L-selectin) and CCR7**, which are expressed on Tcm but not Tem. This allows Tcm (but not Tem) to access secondary lymphoid tissues, similar to naïve T cells.

These features may differ for distinct memory T cell pools: e.g. human CD4 Tem and Tcm have more dramatic differences in effector functions than mouse CD8 cells (below).

Hinricks et al., 2006

Altered Trafficking

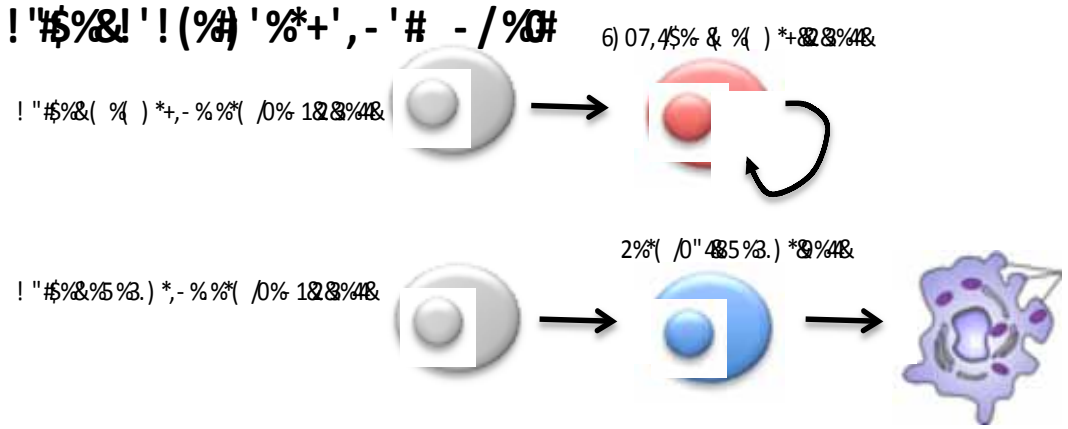
Memory cells are also altered in their distribution throughout the body -- having access to multiple non-lymphoid sites (unlike naïve T cells) allowing for improved surveillance.



Sheridan and Lefrancois 2011
Nature Immunology

Models for memory T cell generation: Distinct precursors?

Are the naïve precursors leading to effector versus memory the same or different?



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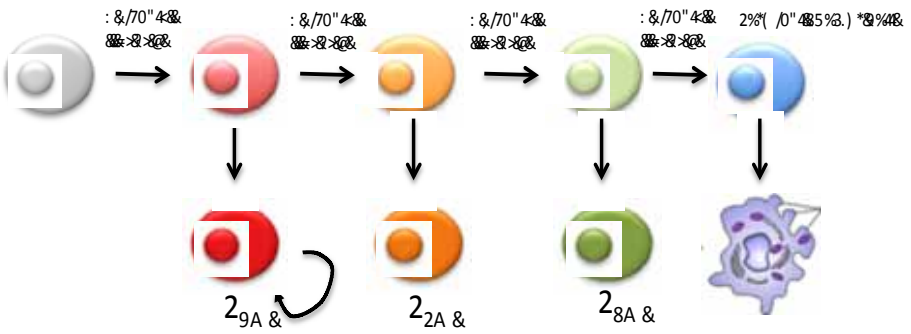

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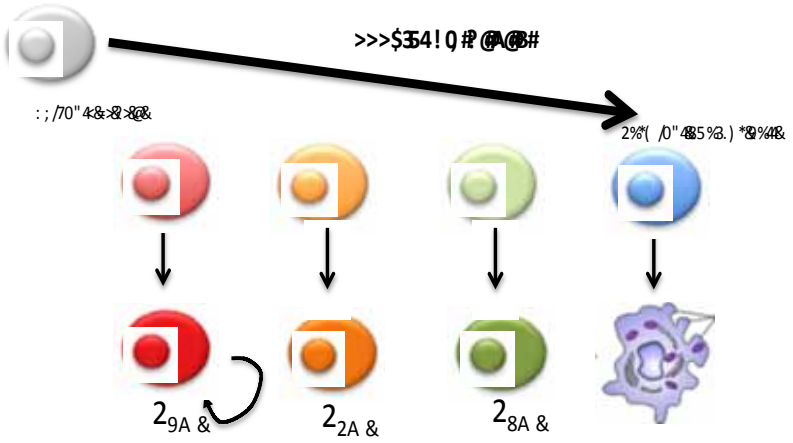
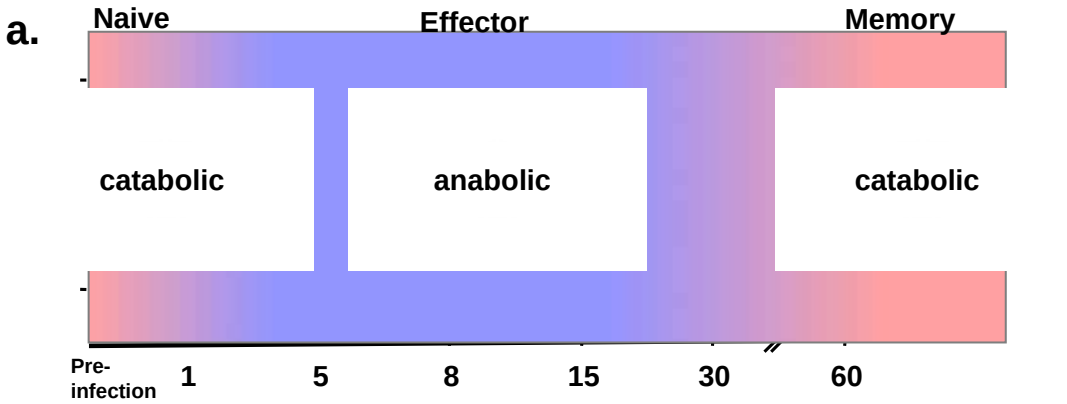


Metabolic coordination with effector and memory T cell differentiation


a.
Naive
Effector
Memory
catabolic
anabolic
catabolic
Pre-
infection
1
5
8
15
30
60

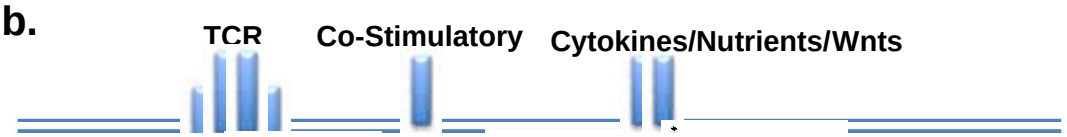
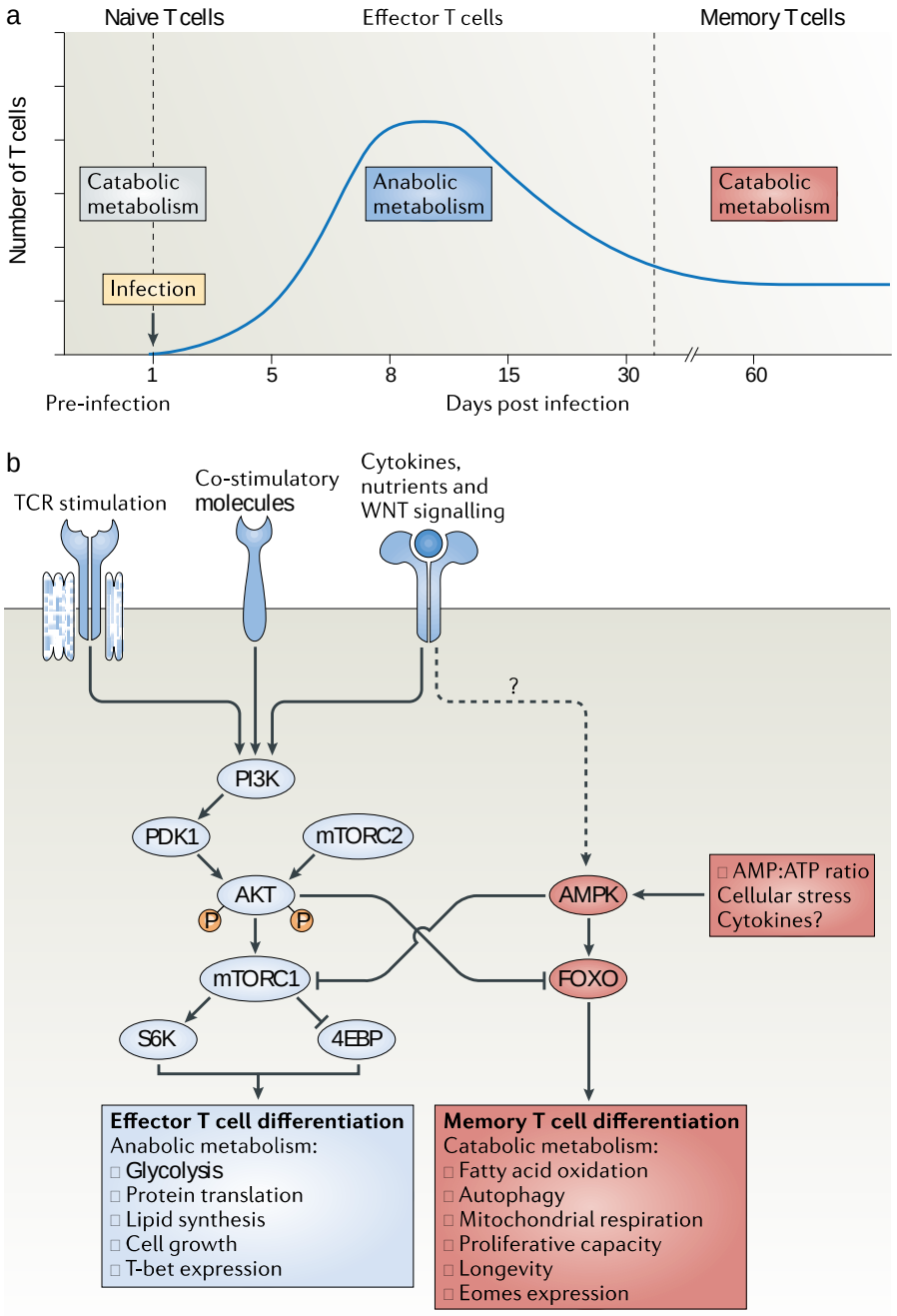
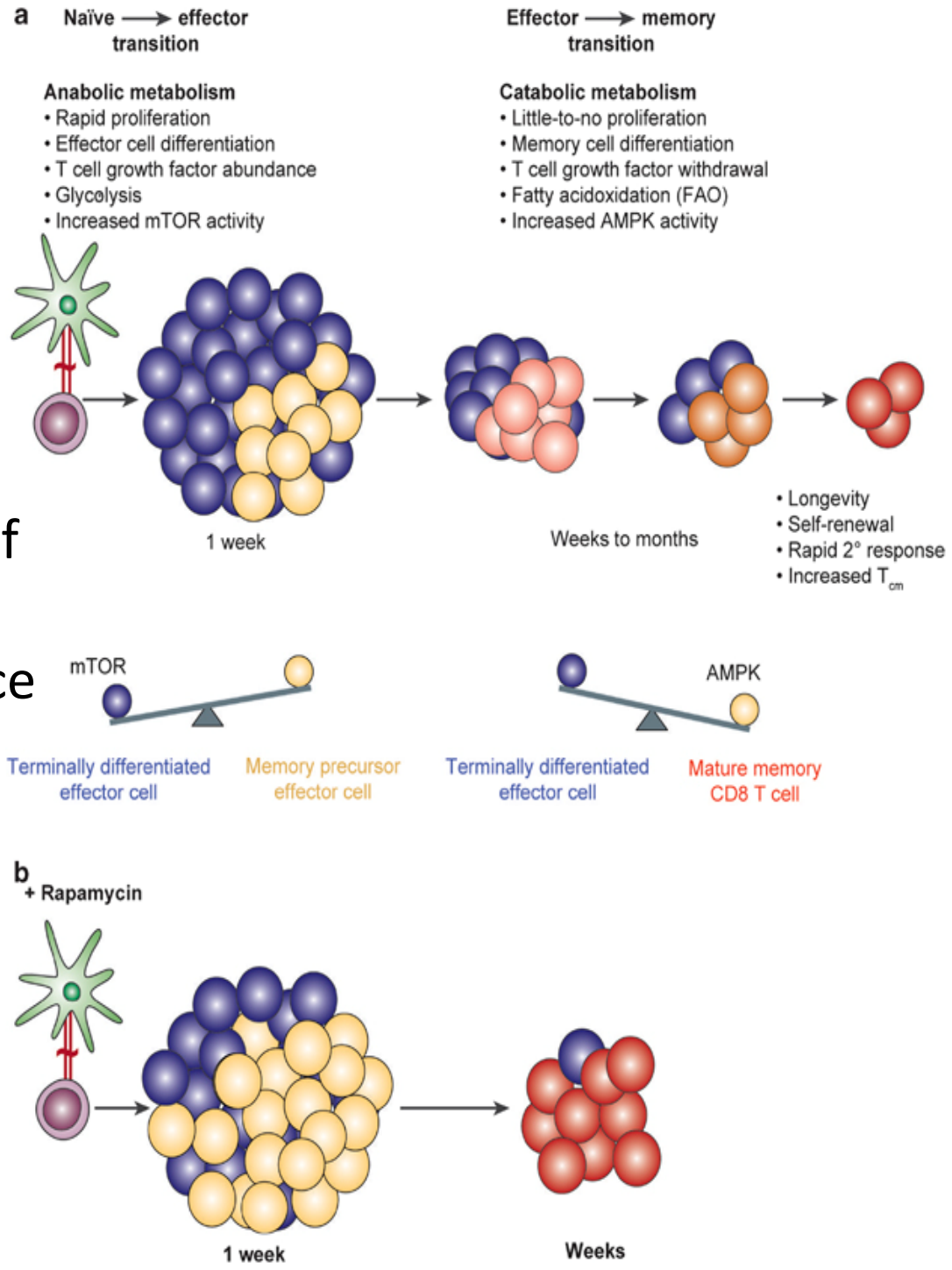

b.
TCR
Co-Stimulatory
Cytokines/Nutrients/Wnts

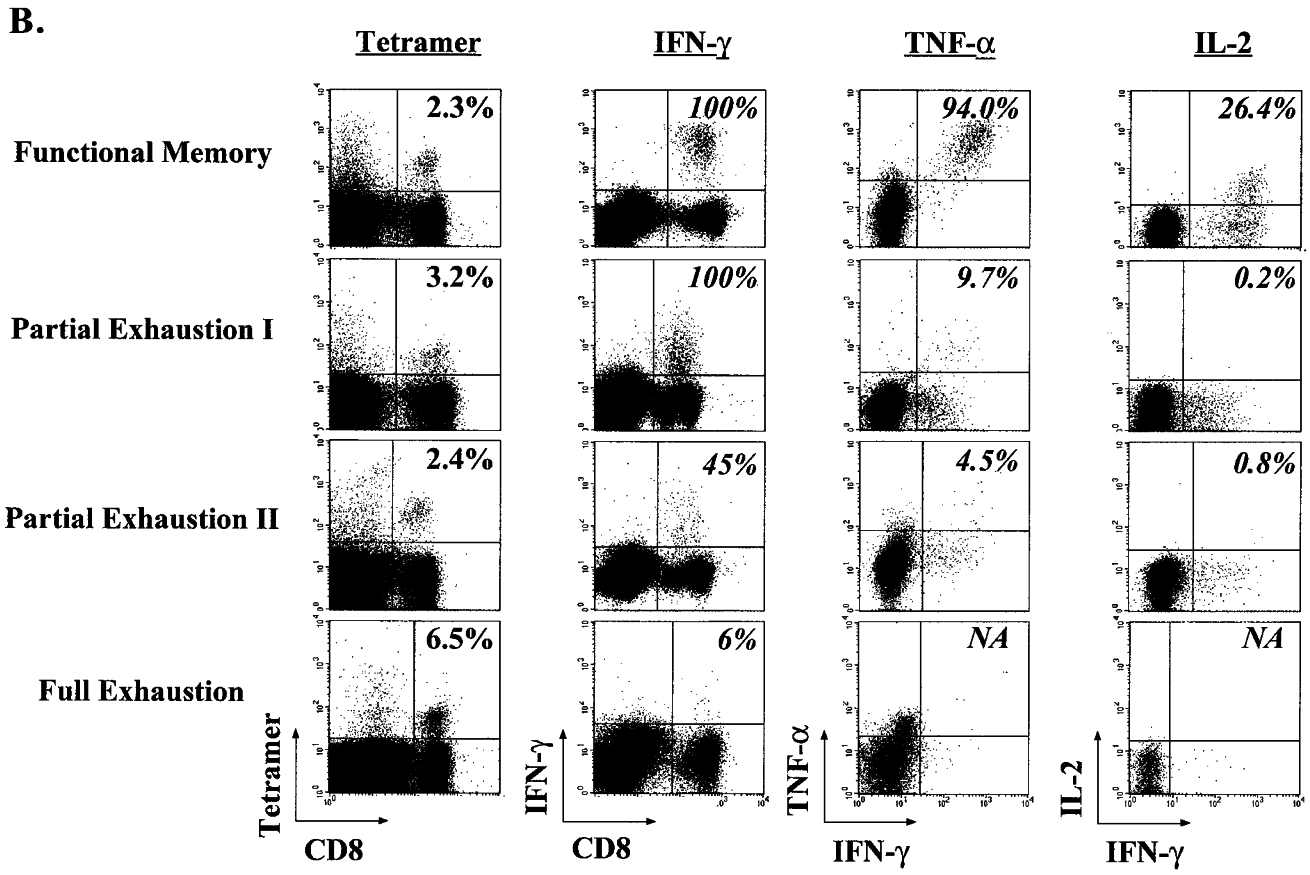
Figure 4

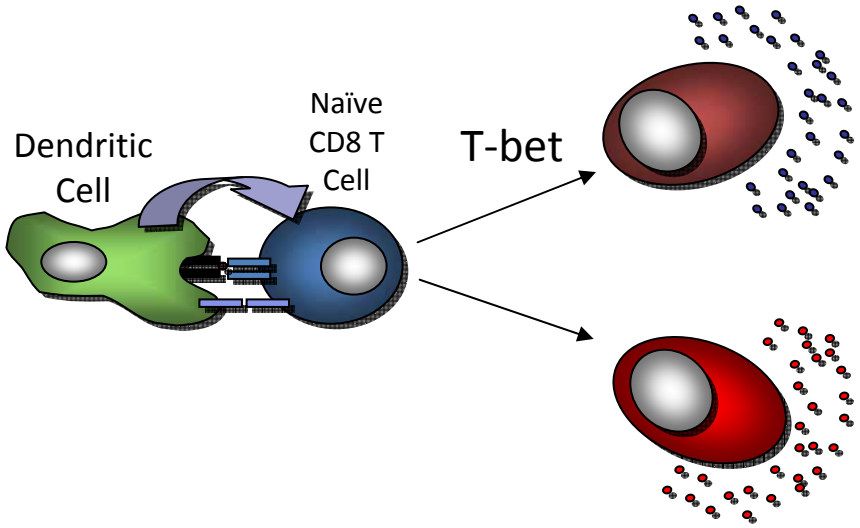

a
Naive T cells
Effector T cells
Memory T cells
Number of T cells
Catabolic metabolism
Anabolic metabolism
Catabolic metabolism
Infection
1
5
8
15
30
60
Pre-infection
Days post infection
b
TCR stimulation
Co-stimulatory molecules
Cytokines, nutrients and WNT signalling
?
PI3K
PDK1
mTORC2
AKT
P
P
mTORC1
S6K
4EBP
AMPK
FOXO
AMP:ATP ratio
Cellular stress
Cytokines?
Effector T cell differentiation
Anabolic metabolism:
Glycolysis
Protein translation
Lipid synthesis
Cell growth
T-bet expression
Memory T cell differentiation
Catabolic metabolism:
Fatty acid oxidation
Autophagy
Mitochondrial respiration
Proliferative capacity
Longevity
Eomes expression

Metabolic regulation of memory T cell generation/maintenance



Antigen-specific T cells that persist in dysfunctional states and….





SLECs

Hard-wired
Binary

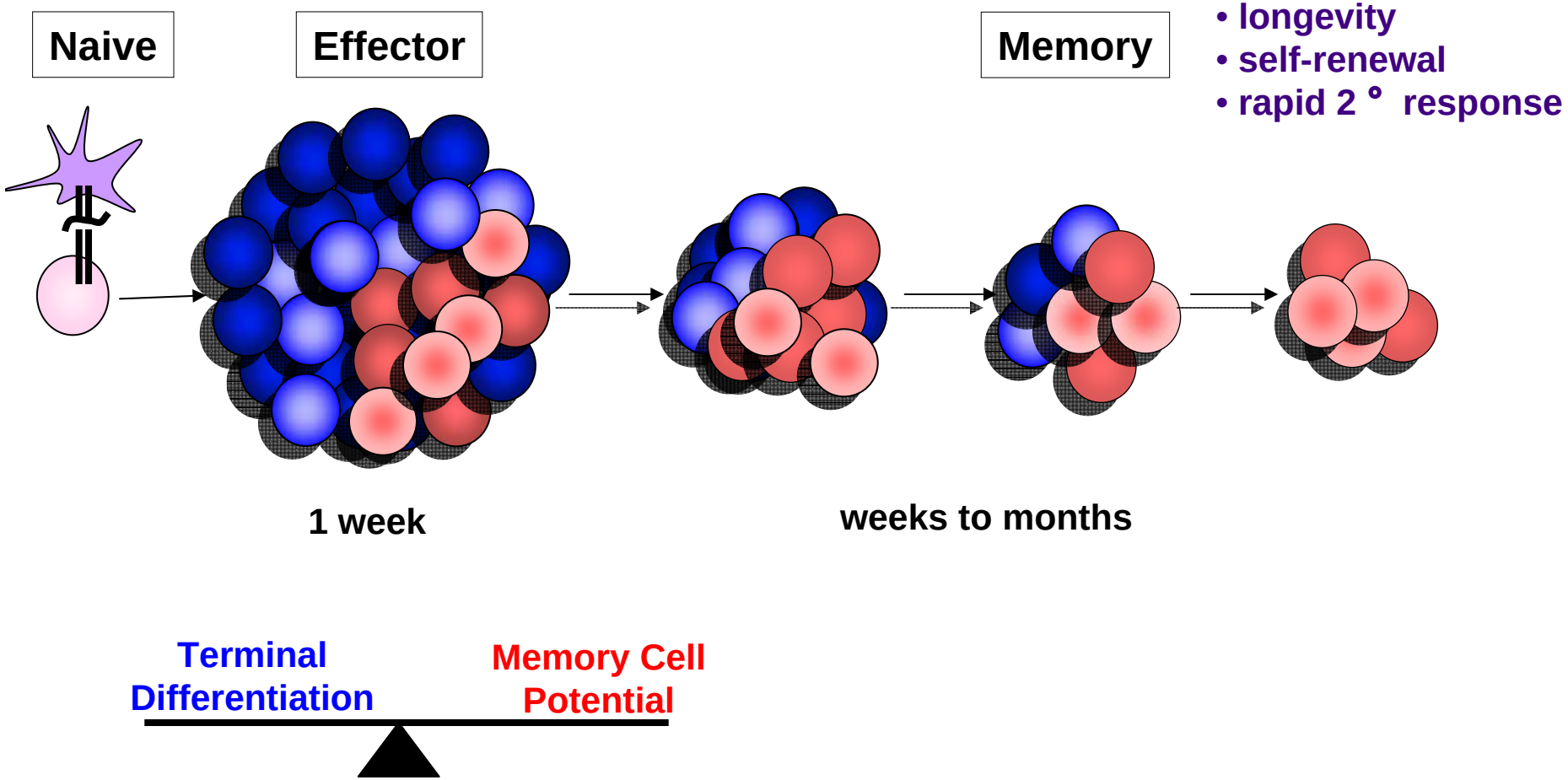
MPECs

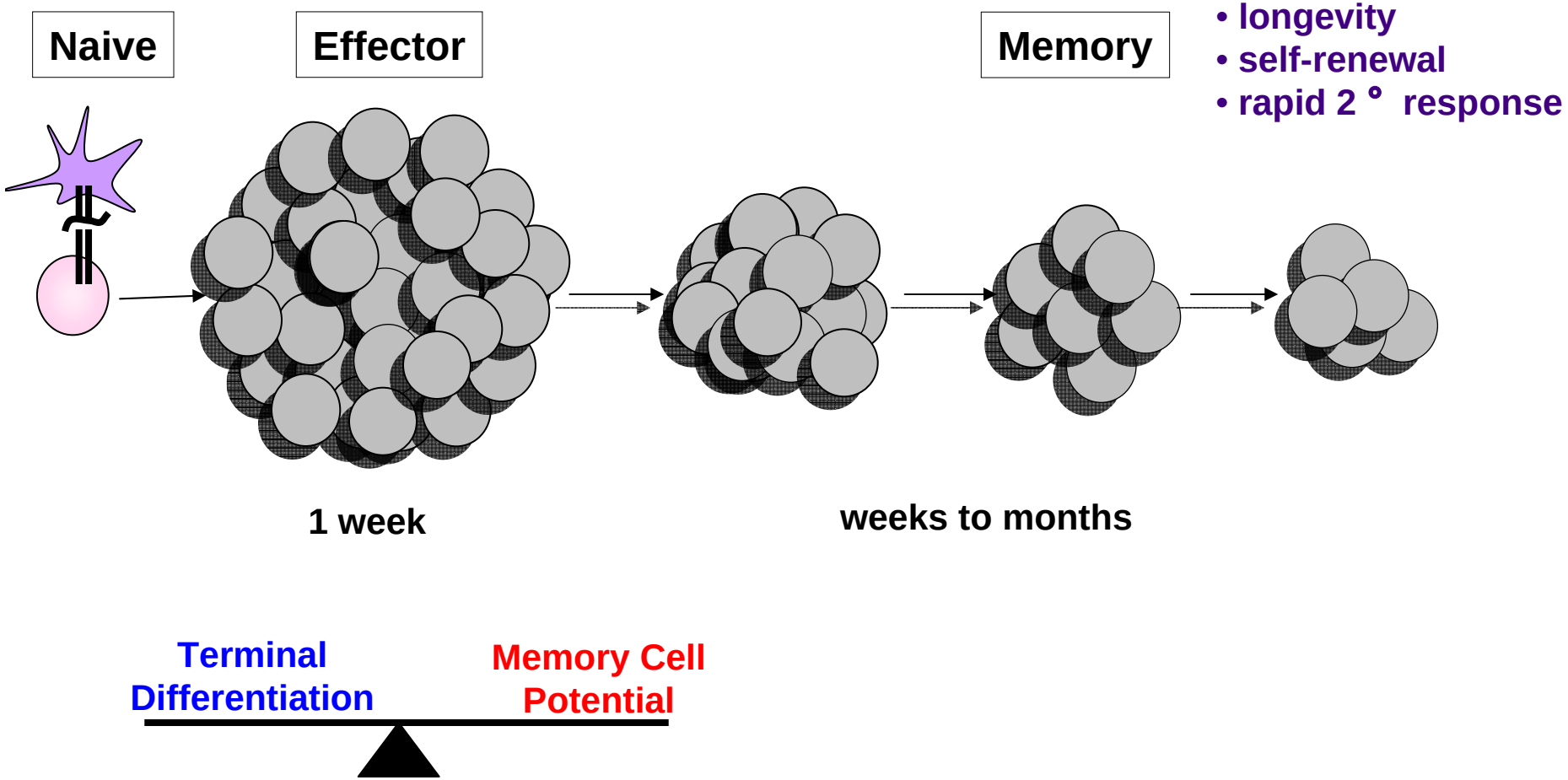
Memory T cells

Models for memory T cell generation

"A memory is what is left when something happens and does not completely unhappen."

Edward de Bono (1933-)


Naive
Effector
Memory
• longevity
• self-renewal
• rapid 2 ° response
1 week
weeks to months
Terminal Differentiation
Memory Cell Potential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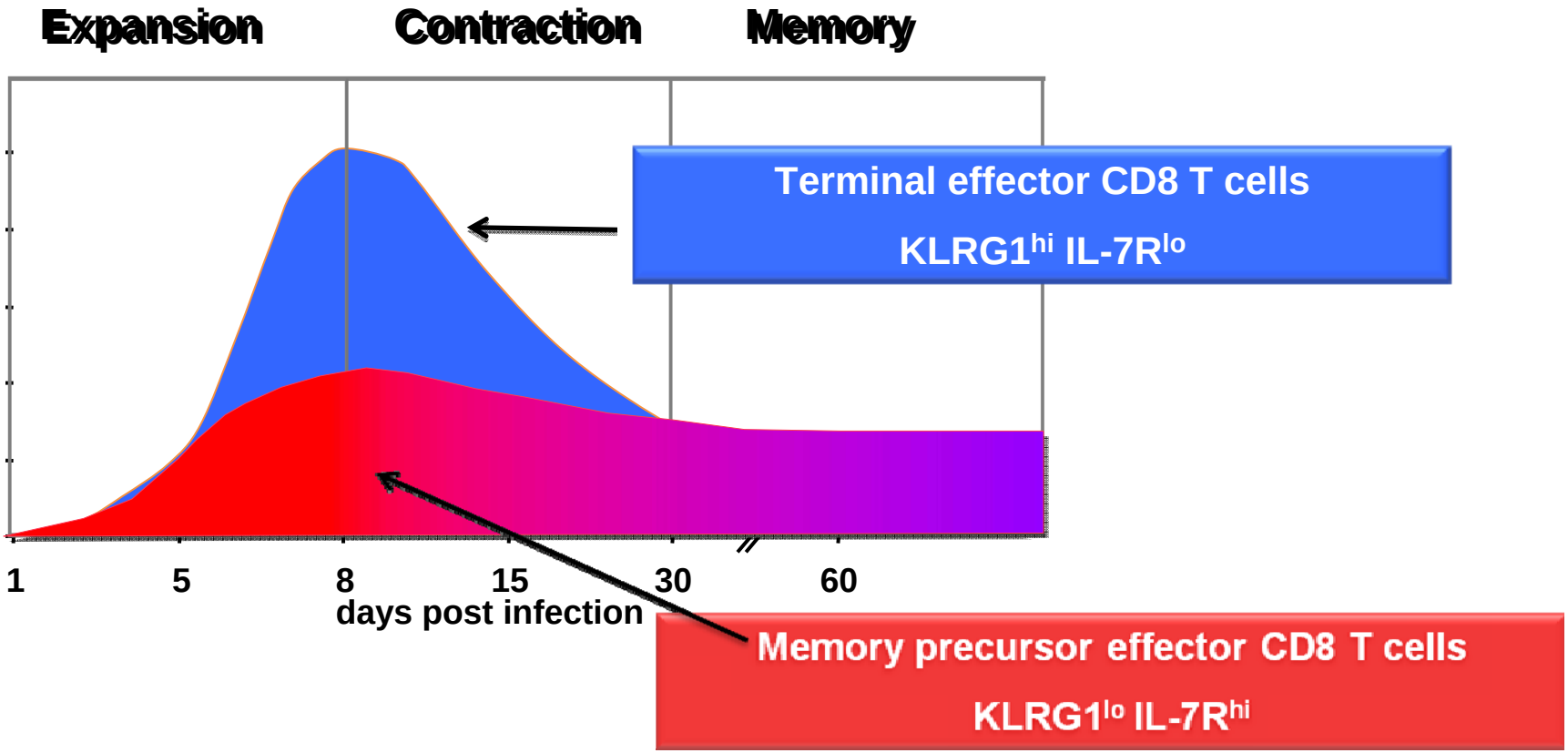
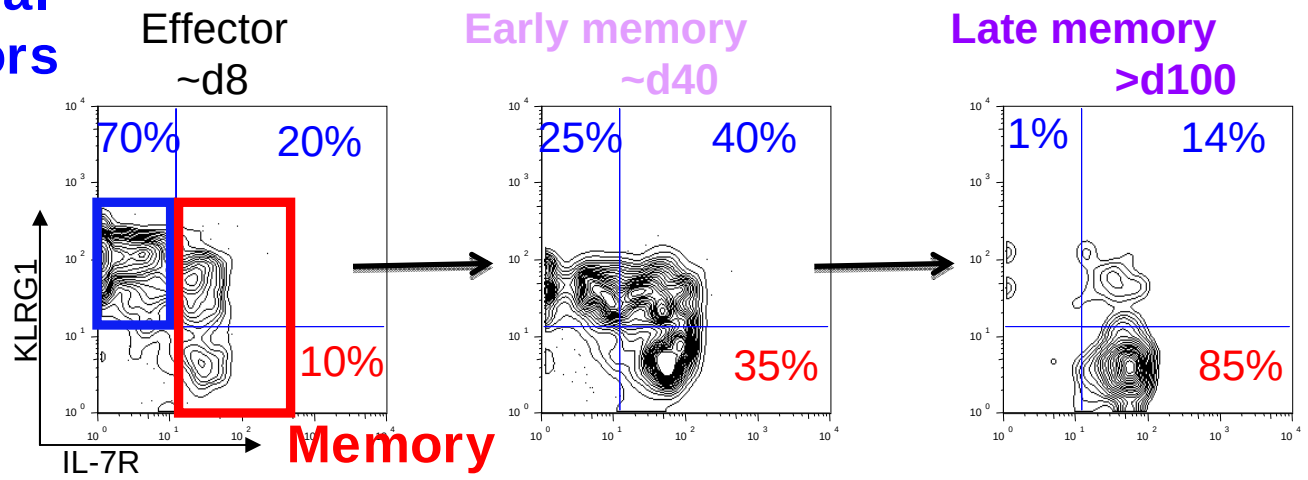
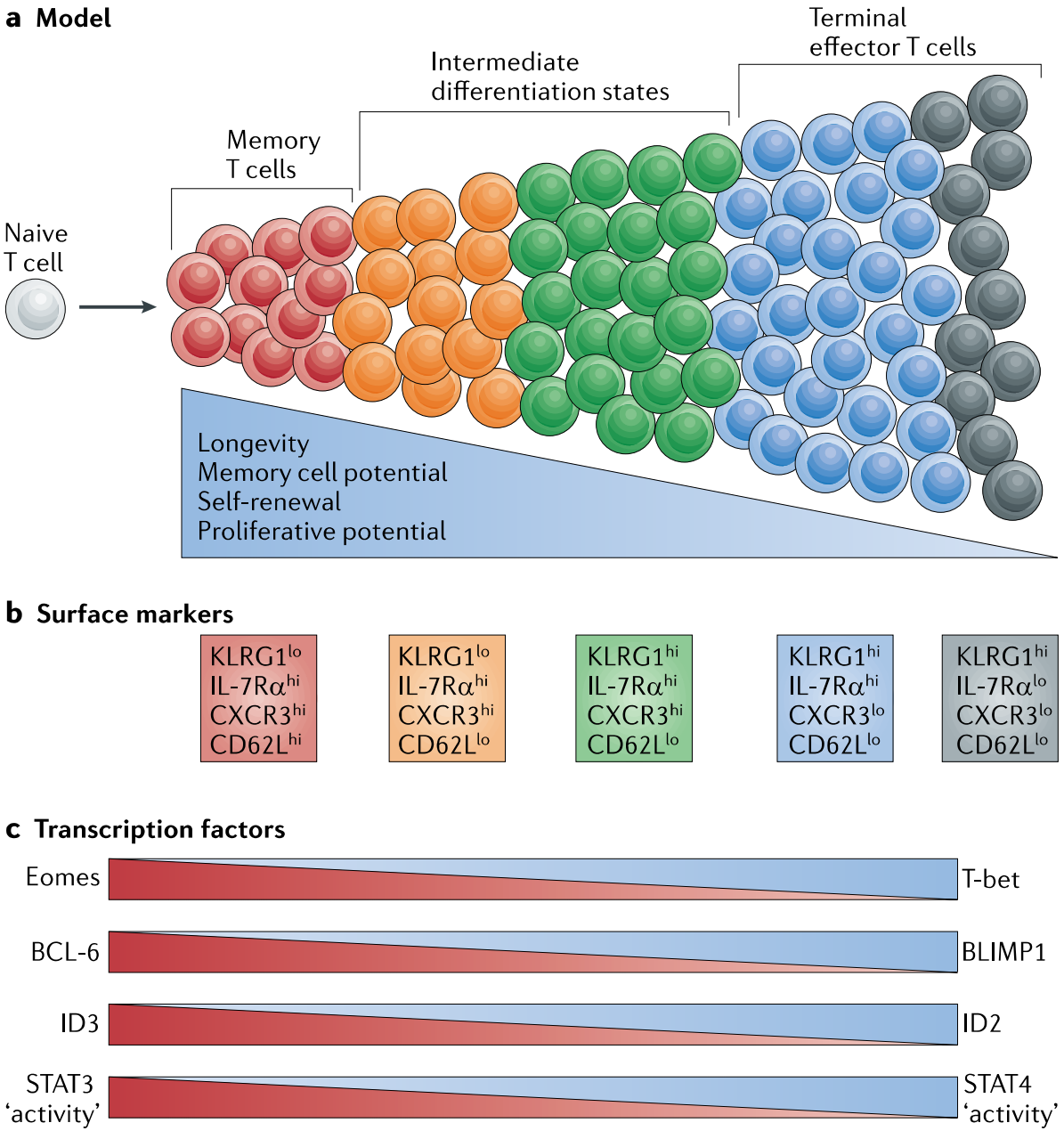


Terminal Effectors



Memory Precursors


a Model
Terminal effector T cells
Intermediate differentiation states
Memory T cells
Naive T cell
Longevity
Memory cell potential
Self-renewal
Proliferative potential
b Surface markers
KLRG1lo IL-7Rαhi CXCR3hi CD62Lhi
KLRG1lo IL-7Rαhi CXCR3hi CD62Llo
KLRG1hi IL-7Rαhi CXCR3hi CD62Llo
KLRG1hi IL-7Rαhi CXCR3lo CD62Llo
KLRG1hi IL-7Rαlo CXCR3lo CD62Llo
c Transcription factors
Eomes
T-bet
BCL-6
BLIMP1
ID3
ID2
STAT3 'activity'
STAT4 'activity'