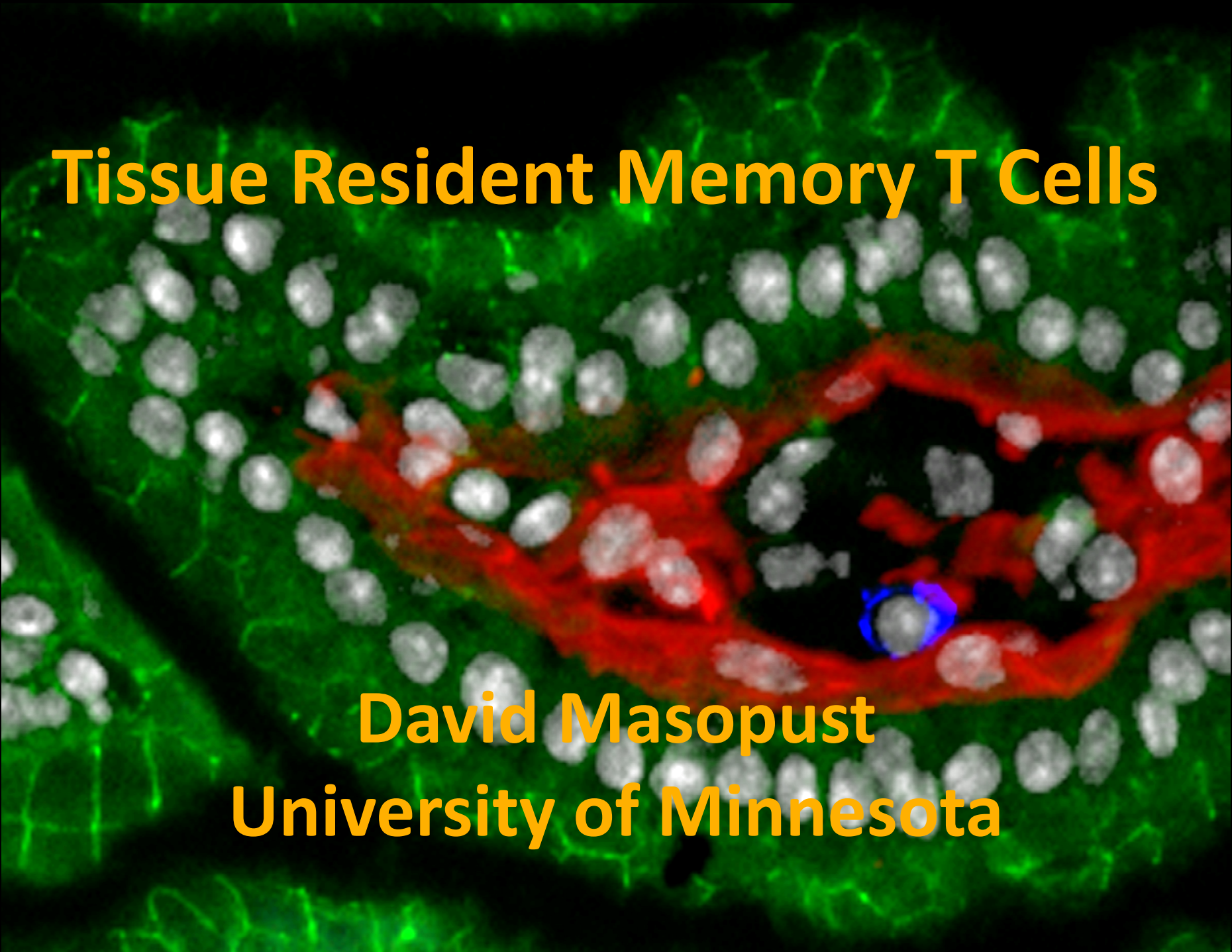


Tissue Resident Memory T Cells

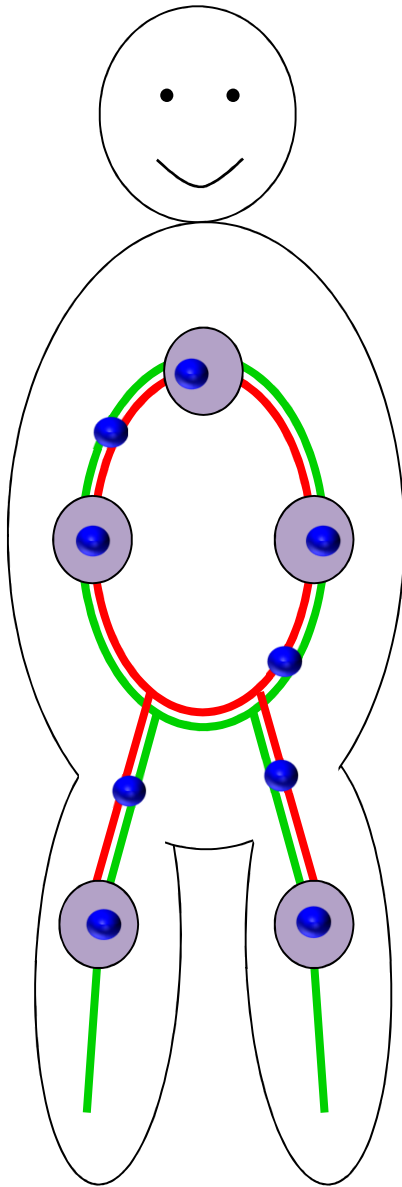
A fluorescence microscopy image showing a dense population of cells. The background is green, indicating a specific tissue component or cell type. A prominent red structure, possibly a blood vessel or a cluster of cells, runs diagonally across the center. Numerous bright white spots are scattered throughout the green field, representing individual cells or specific markers. A single cell is highlighted with a blue circle in the lower right quadrant of the red structure.

David Masopust
University of Minnesota

Presenter disclosure information

David Masopust

No relationships to disclose



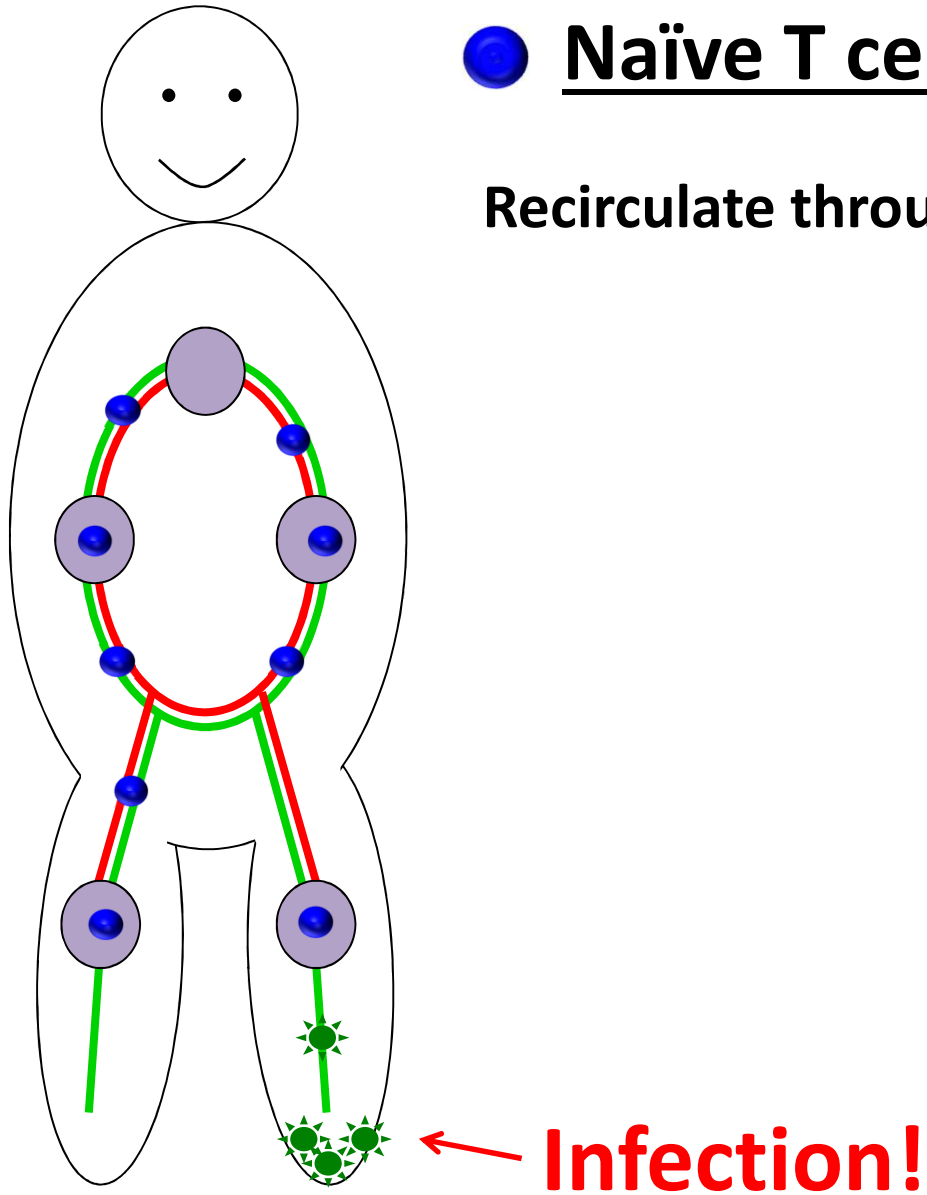
● Naïve T cell migration

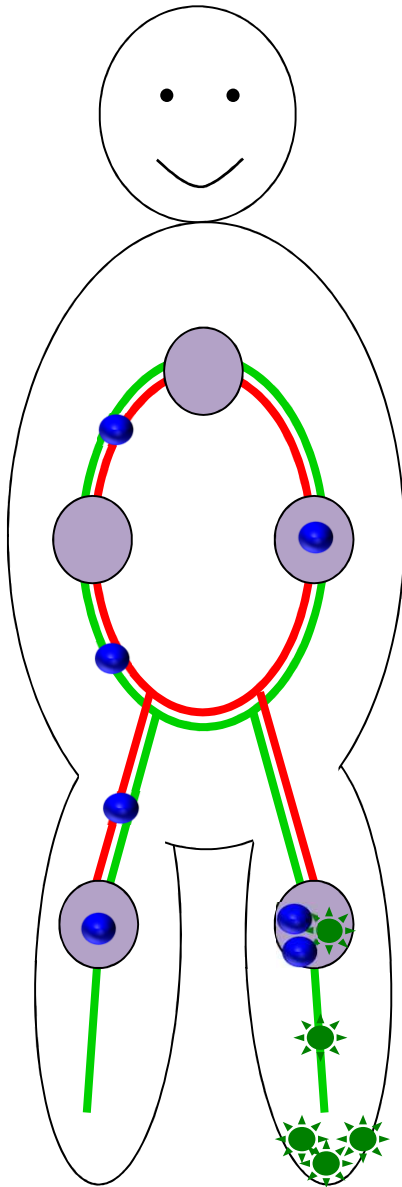
Recirculate through lymph nodes ●

-Use blood and lymph as a conduit

● Naïve T cell migration

Recirculate through lymph nodes

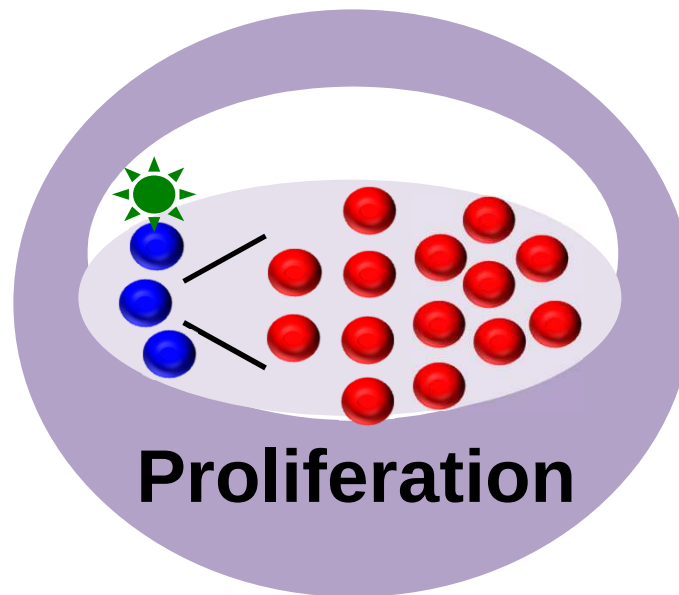




CD8 T cell priming

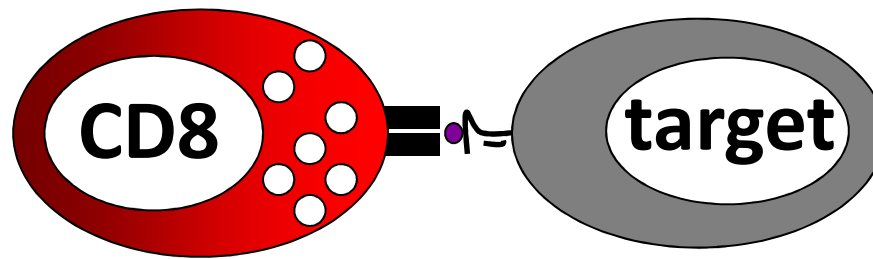
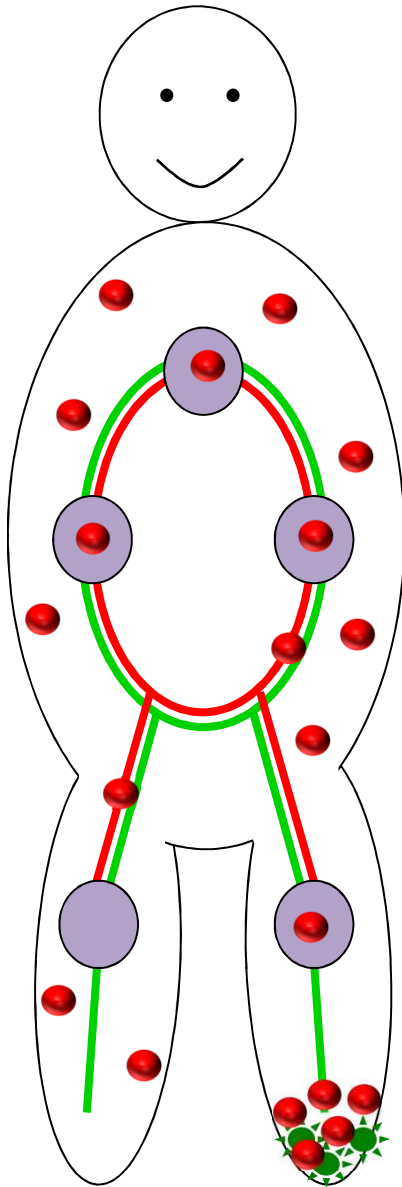
Occurs in lymph nodes

- Naïve T cells differentiate into effectors ●
- Proliferate



Recently activated effectors

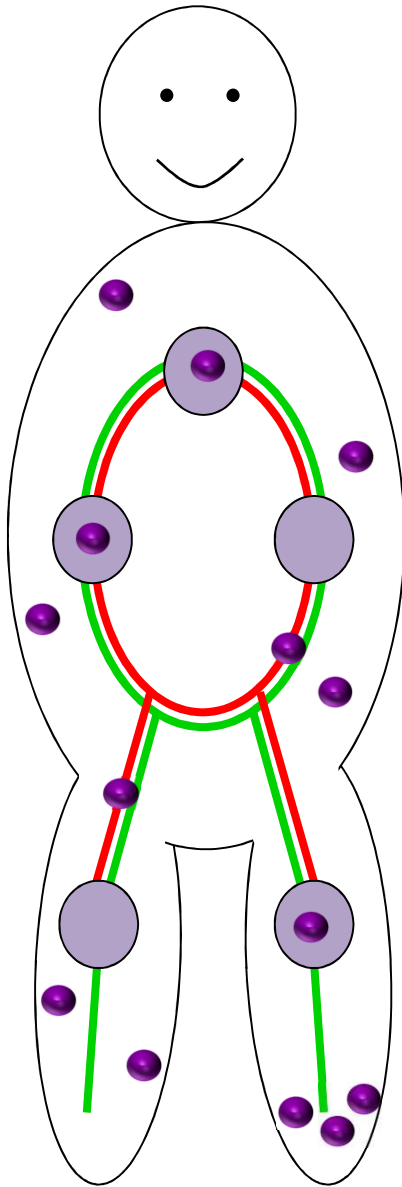
Distribute throughout body



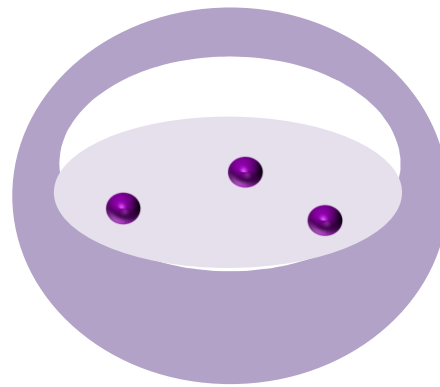
T cell memory

Host retains resting memory T cells

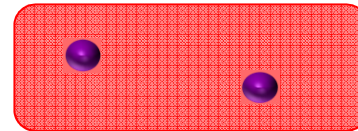
Remain broadly distributed



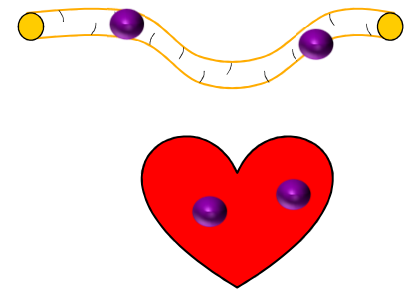
Lymph
Node



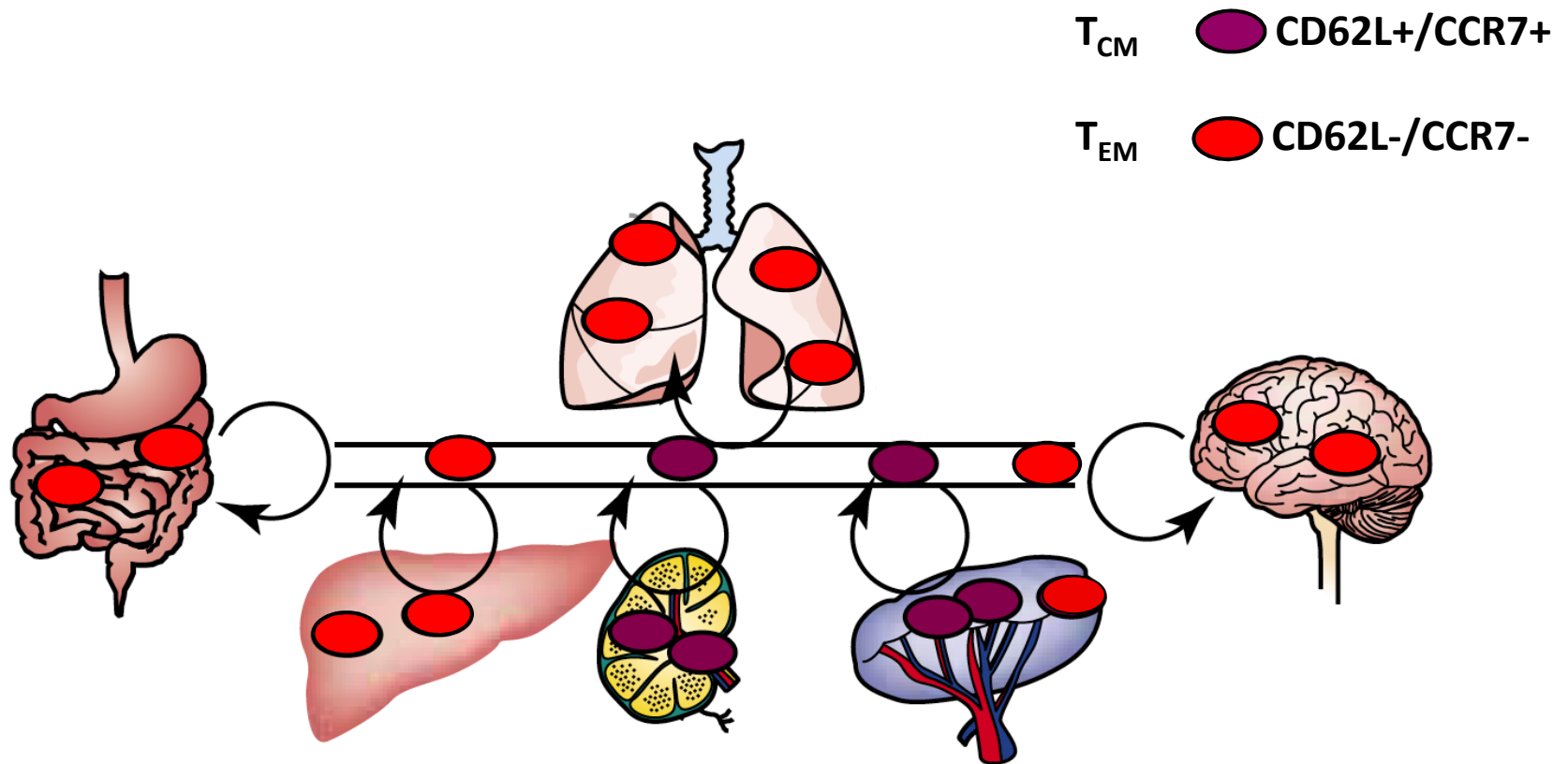
Blood



Nonlymphoid
Tissues



Hypothesis: memory T cells re-circulate through non-lymphoid tissues



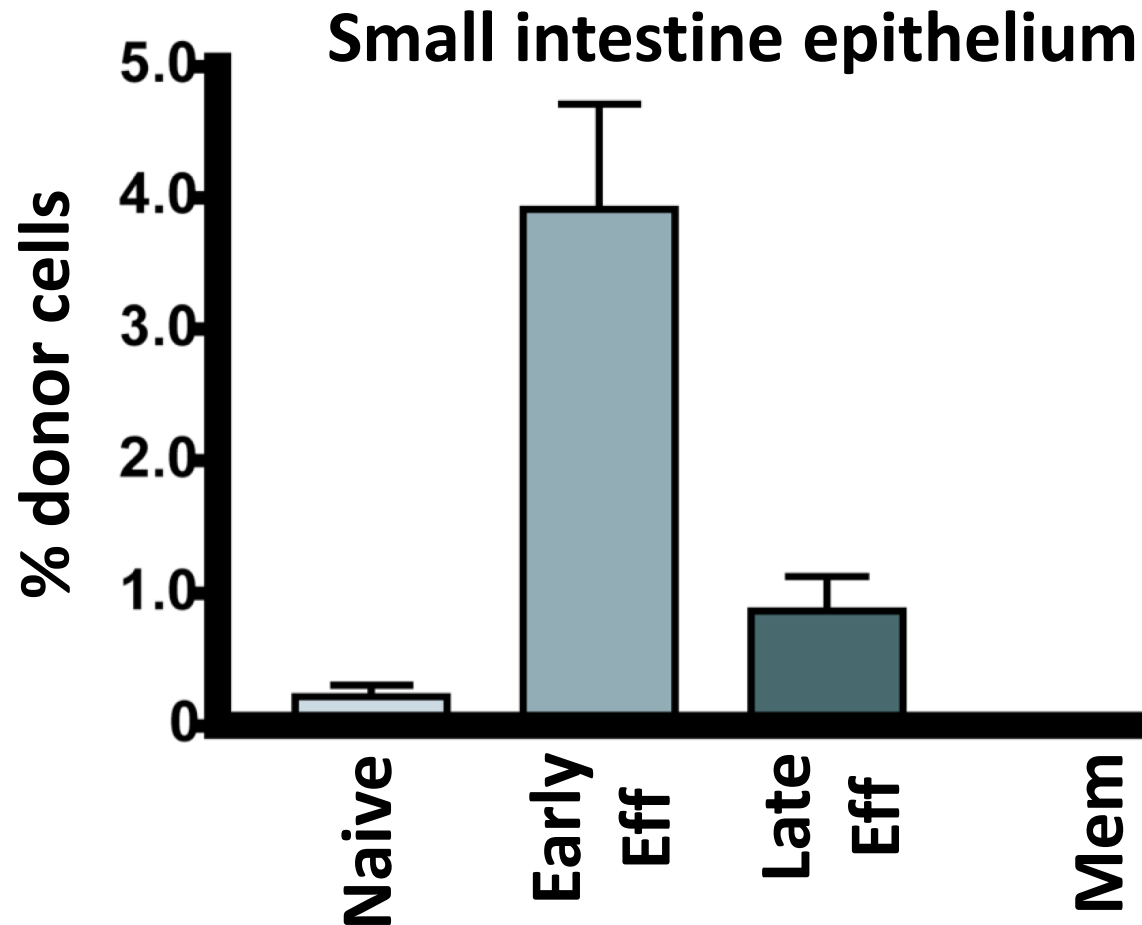
Migration depends on CD8 T cell differentiation state

Adoptive transfer CD8 T cells i.v.

Naïve, early effector,
late effector, memory

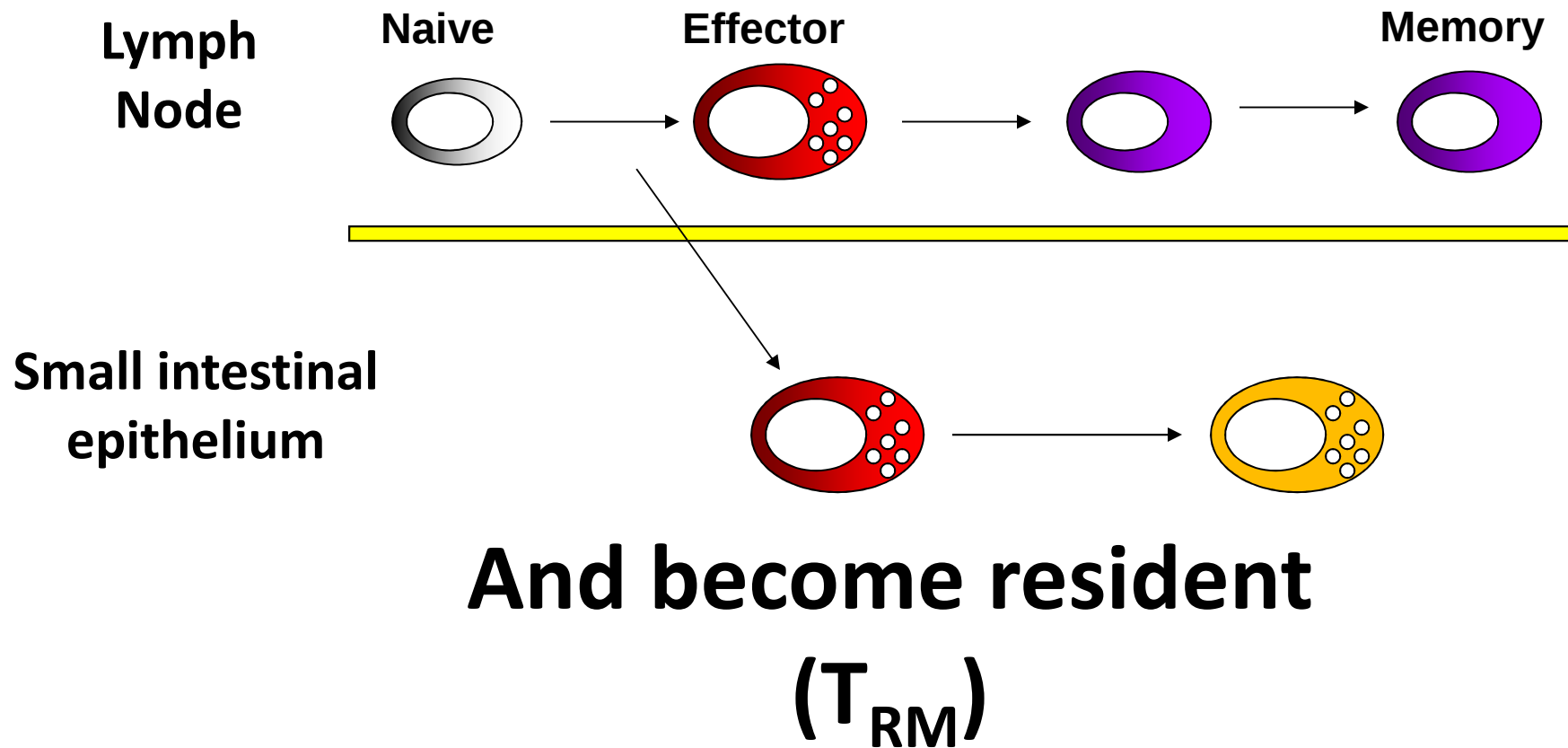


Harvest tissues.
Where did they go?

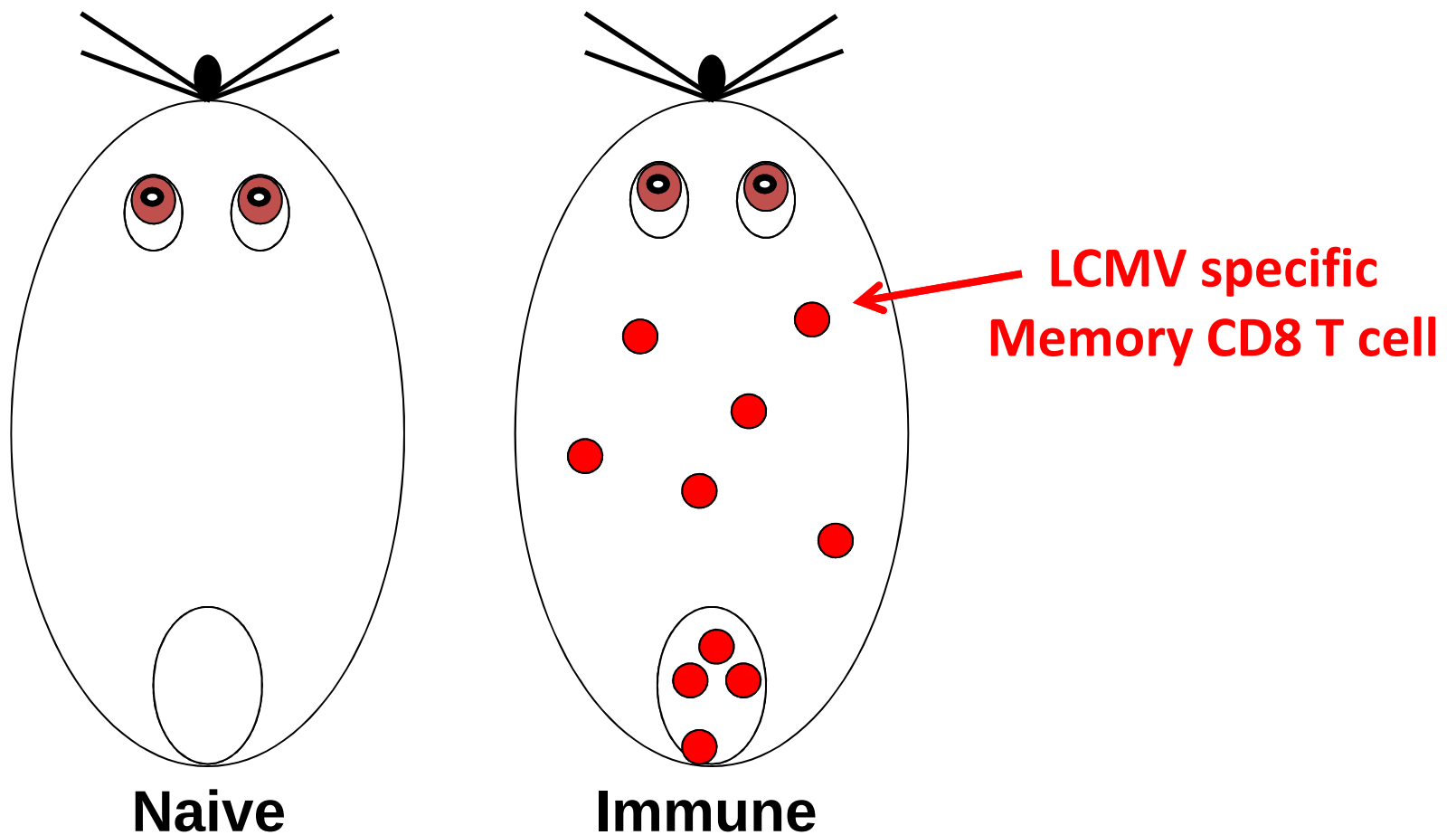


Masopust, et al.,
J Exp Med 2010

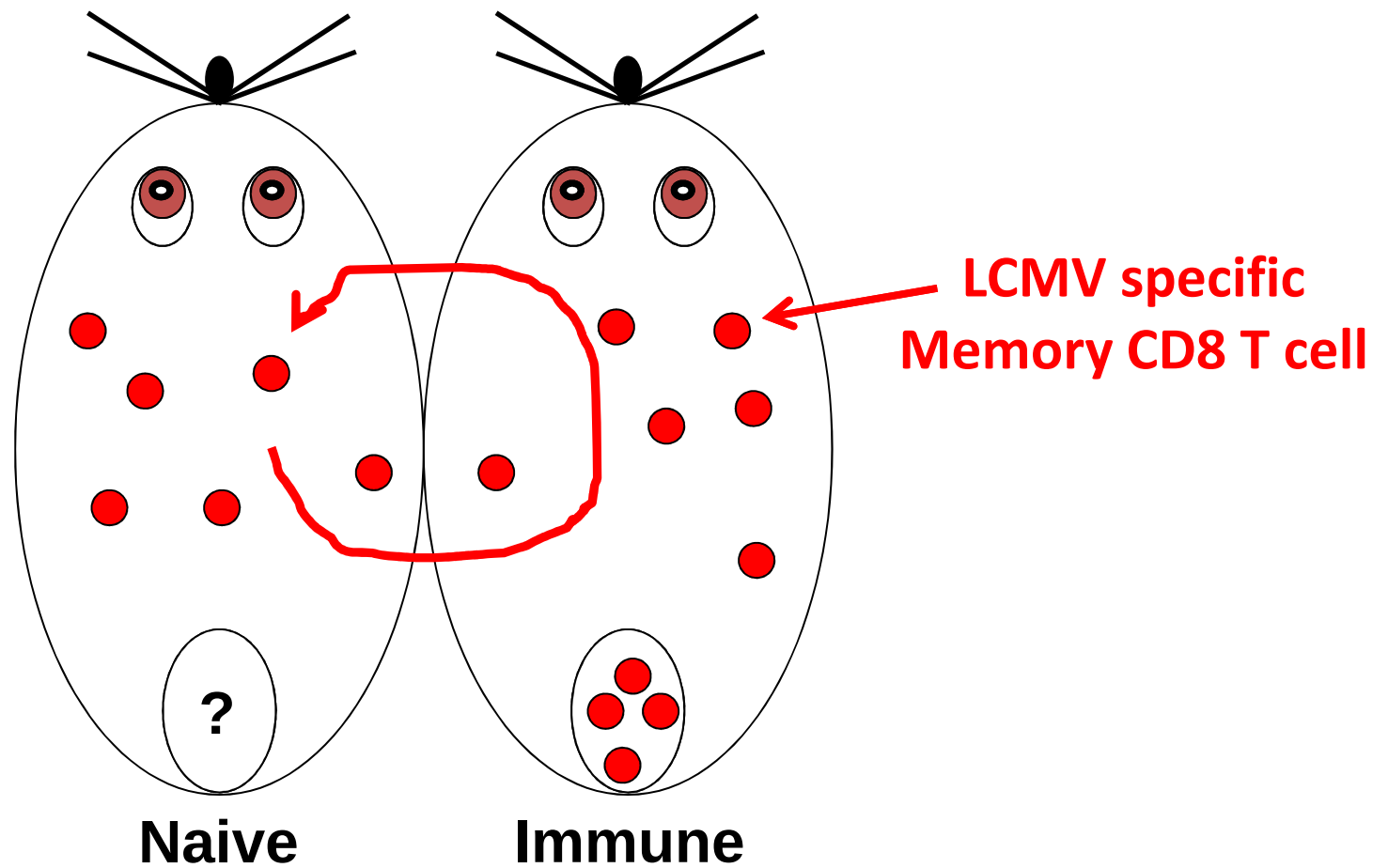
CD8 T cells migrate to the gut shortly following activation



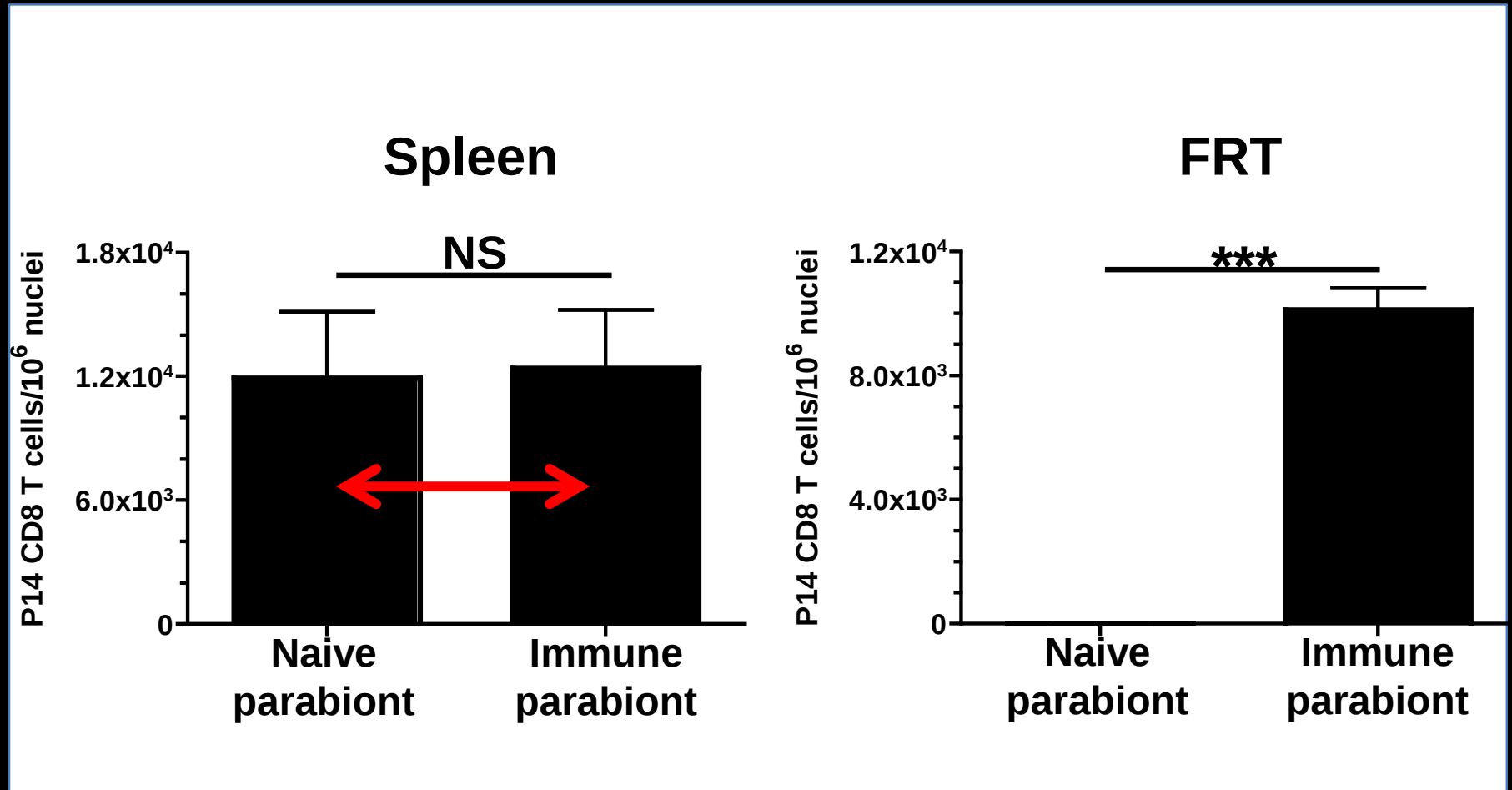
Defining memory CD8 T cell recirculation in tissue



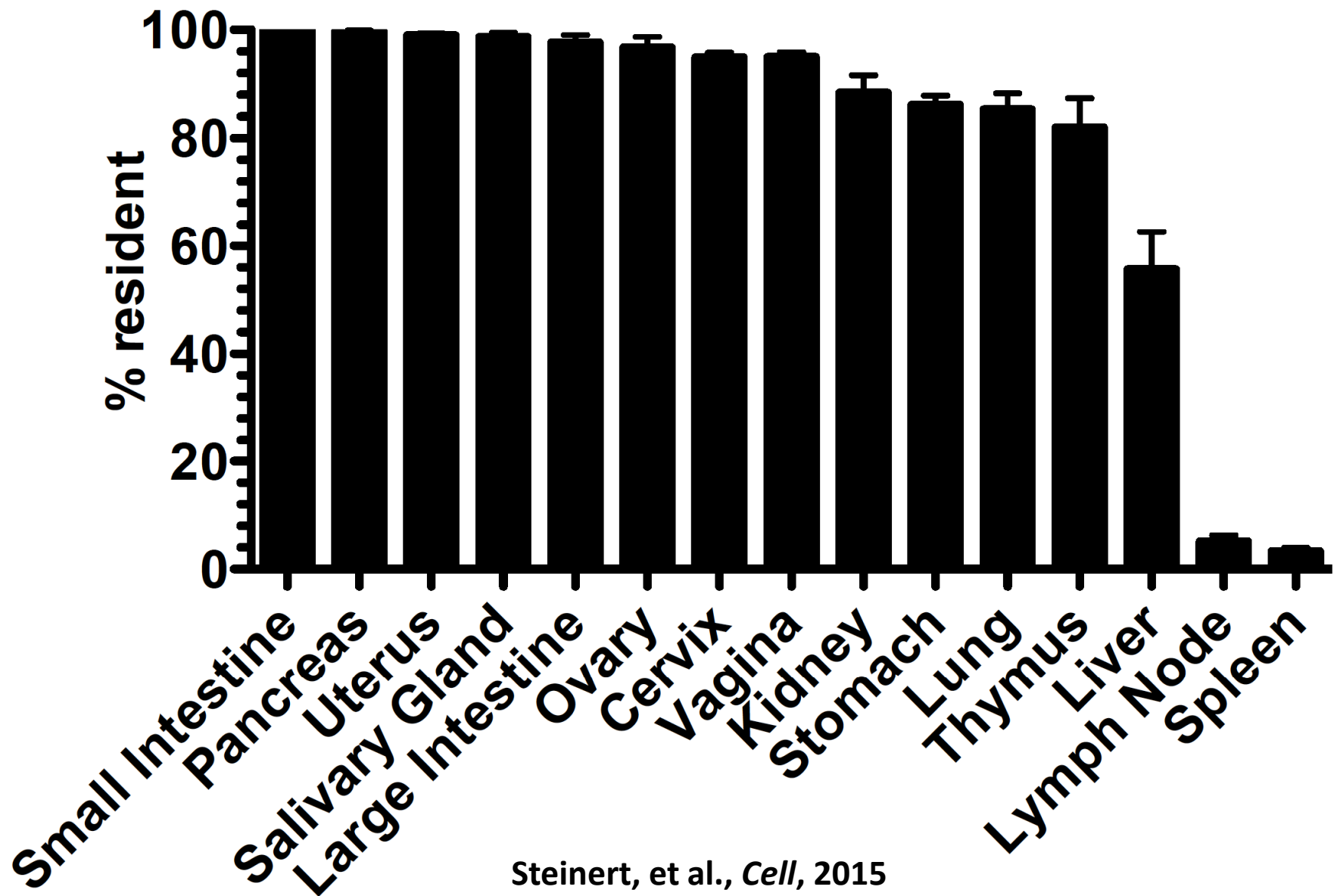
Parabiosis



Memory CD8 T cells in the FRT are resident



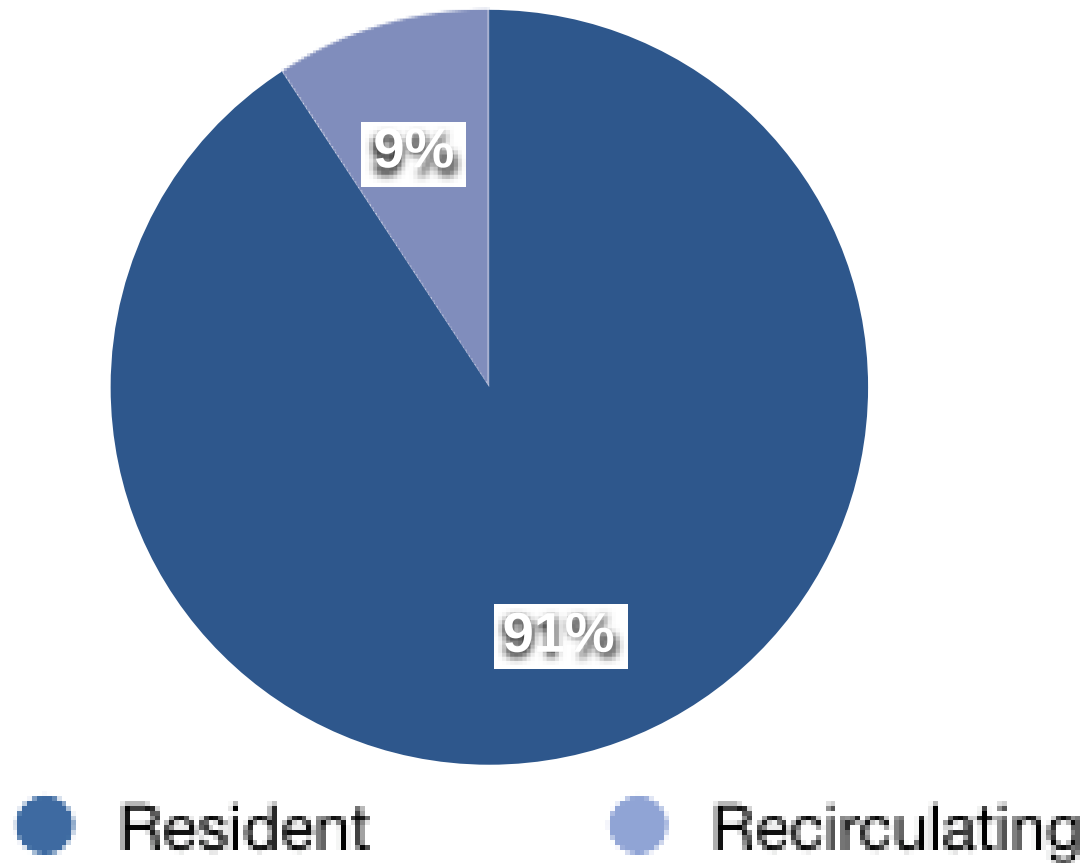
T_{RM} dominate nonlymphoid tissues



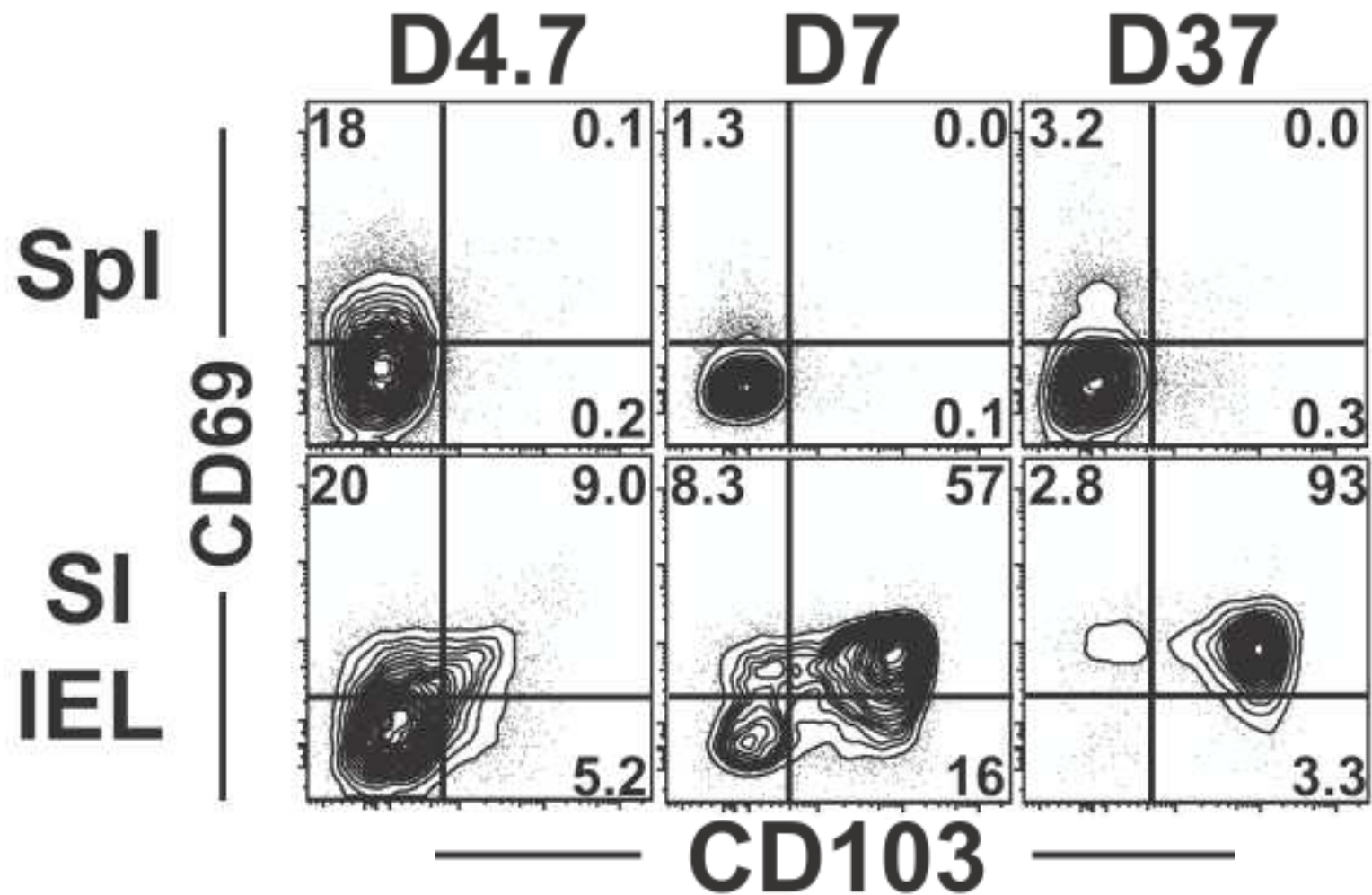
Steinert, et al., *Cell*, 2015

T_{RM} outnumber recirculating memory CD8 T cells in non-lymphoid tissues

LCMV-specific memory CD8 T cells, ~150 days after infection



IELs acquire unique signatures in situ (gated on memory P14 CD8 T cells)



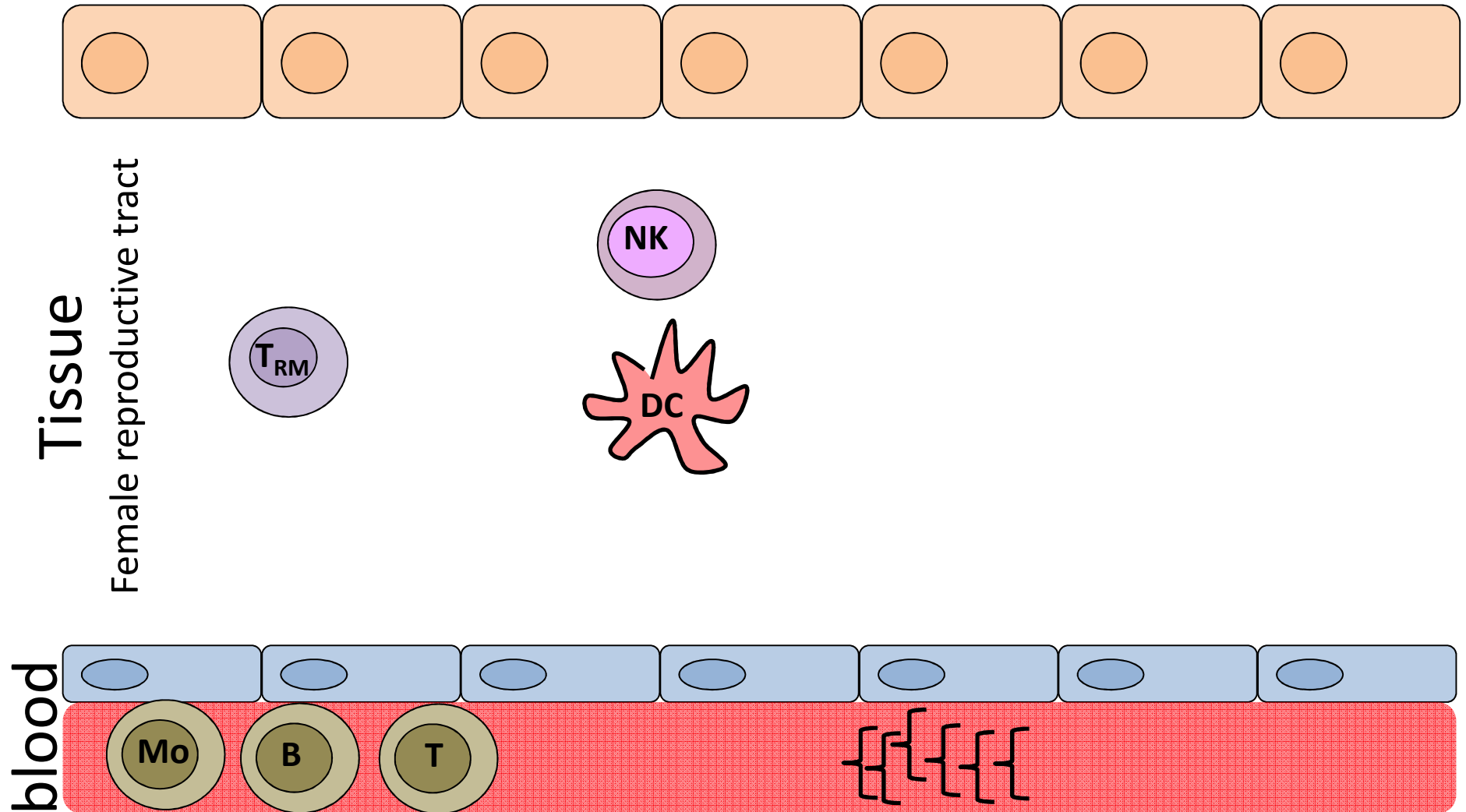
Evidence for T_{RM} within tumors

TILs bear phenotypic markers of tissue resident memory T cells

Correlate with favorable prognosis

- Djenidi F, et al., J Immunol, 2015
- Wang B, et al., J Urol, 2015
- Webb JR, et al., Clin Cancer Res, 2014

Immunize mouse to establish T_{RM} (with LCMV, natural mouse viral pathogen)

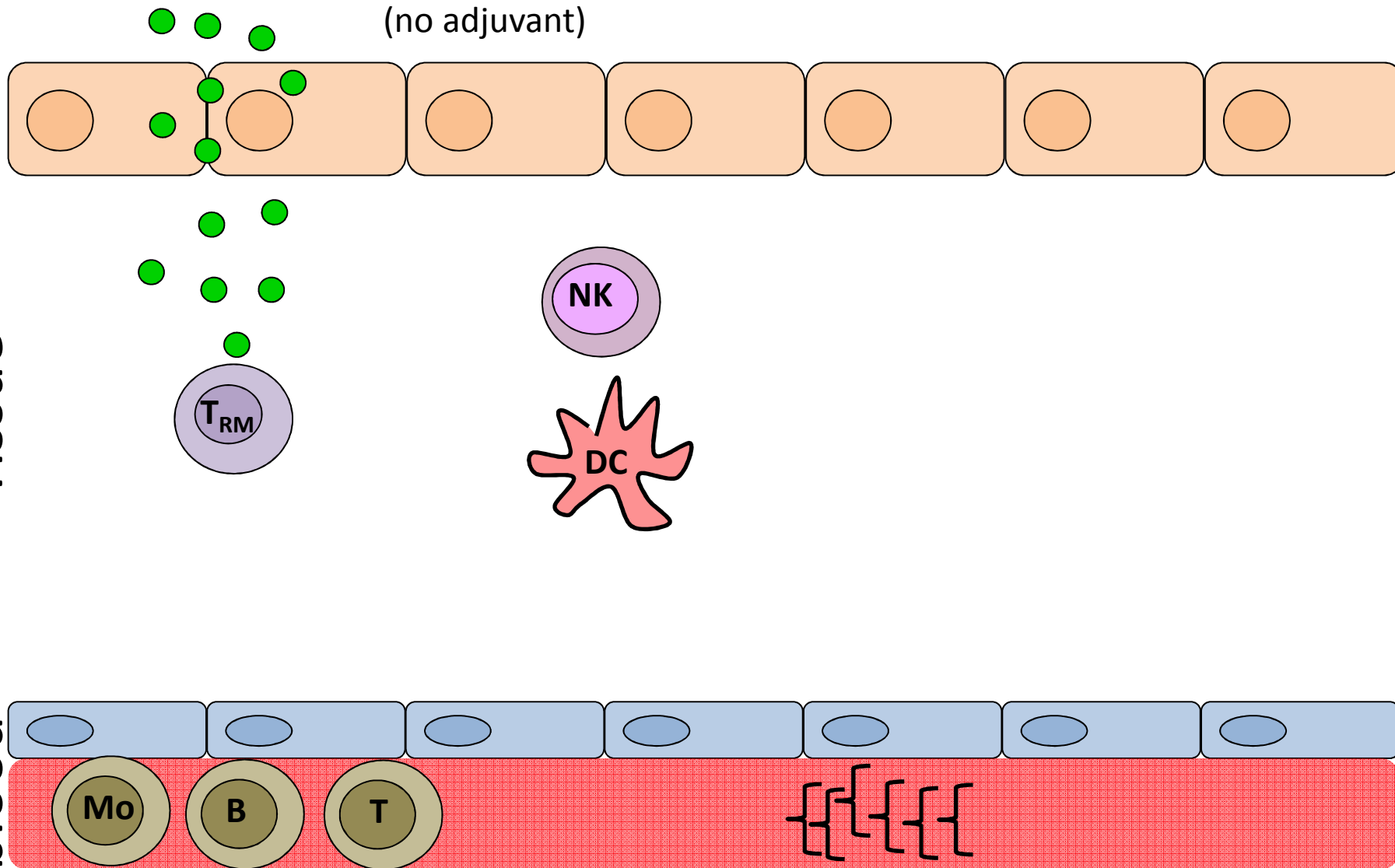


Add LCMV 8-mer peptides
to trigger T_{RM}
re-activation

(no adjuvant)

Tissue

blood

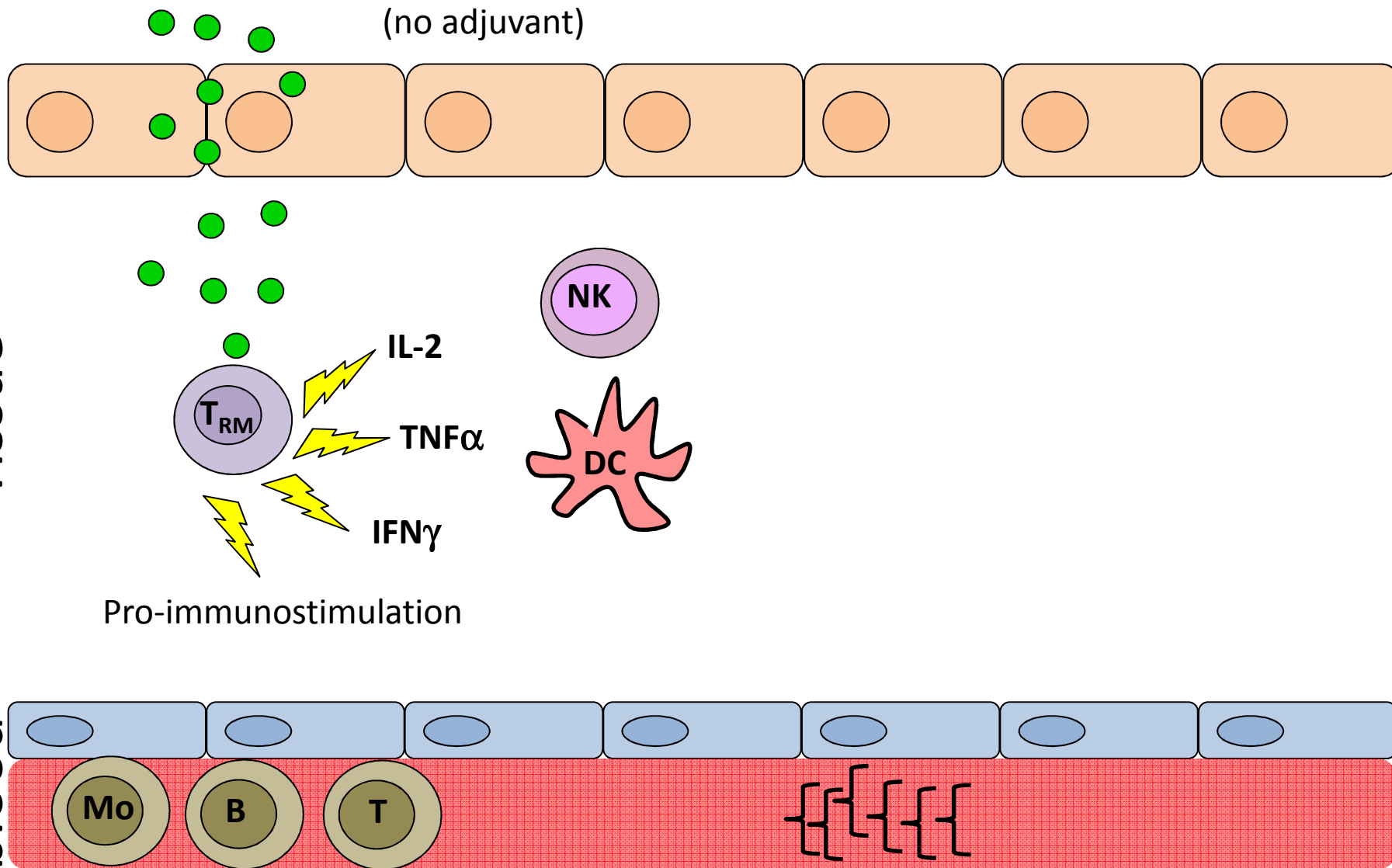


Add peptides
that trigger T_{RM}
activation

(no adjuvant)

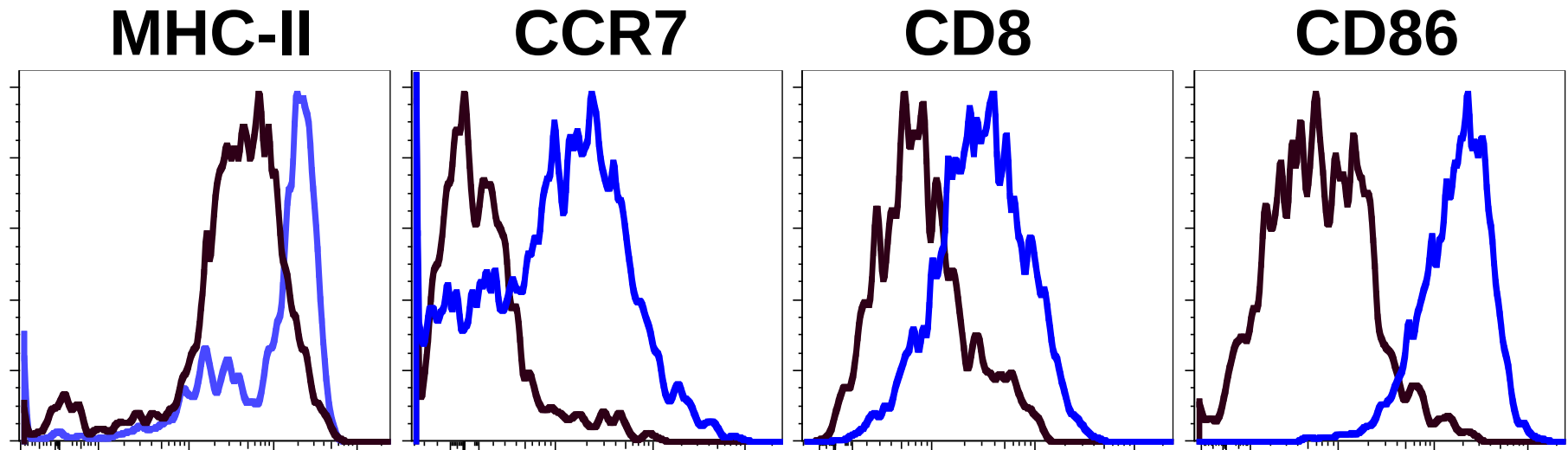
Tissue

blood



Local DC activation after local T_{RM} reactivation

12h after Ag exposure

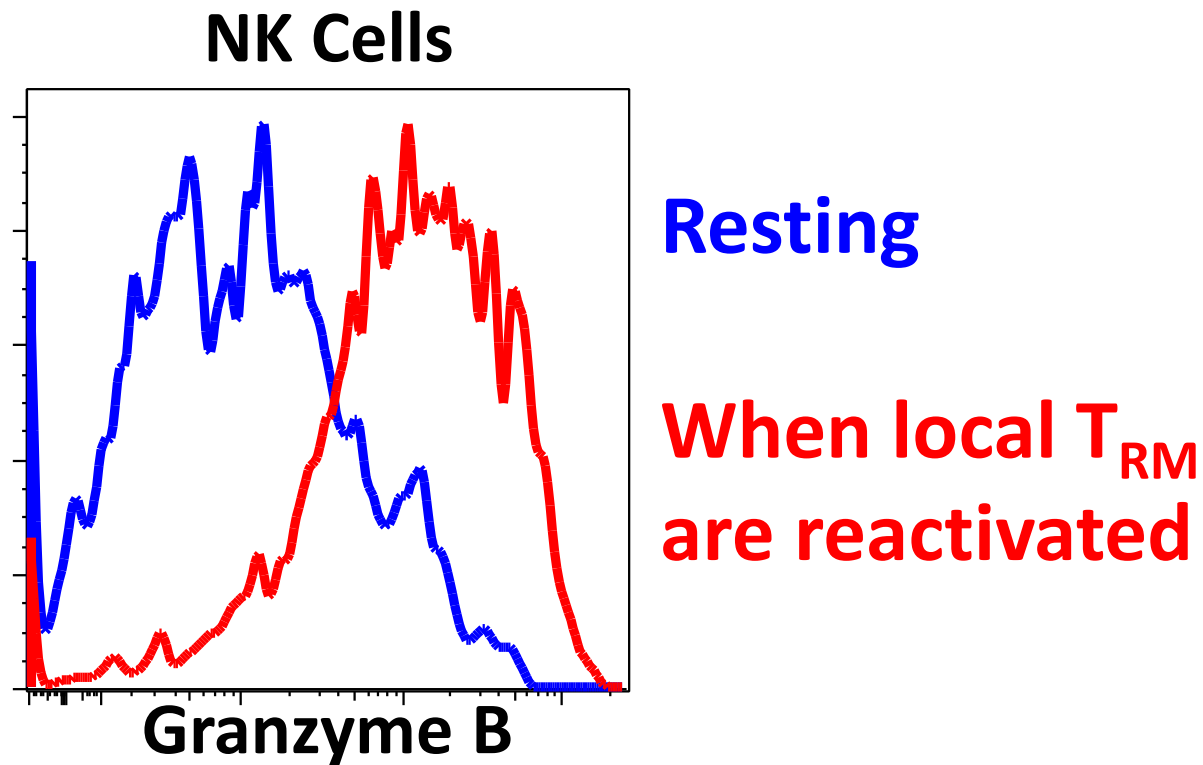


Memory

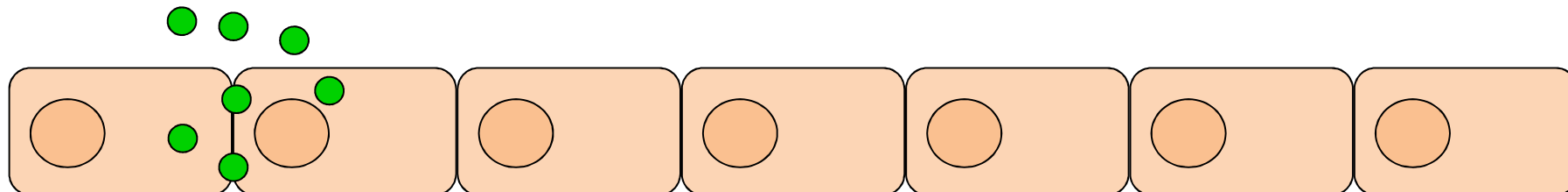
Memory + peptide

Schenkel, et al., *Science*, 2014

NK cells upregulate granzyme B after local memory CD8 T cell Ag-recognition

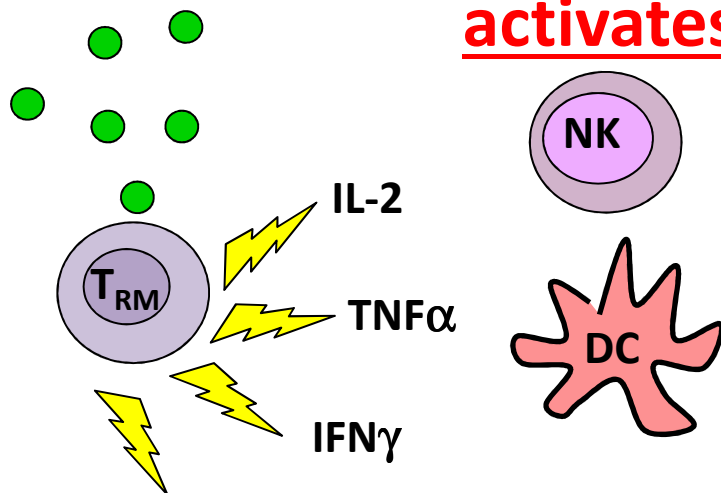


Add peptides
that trigger T_{RM}
activation



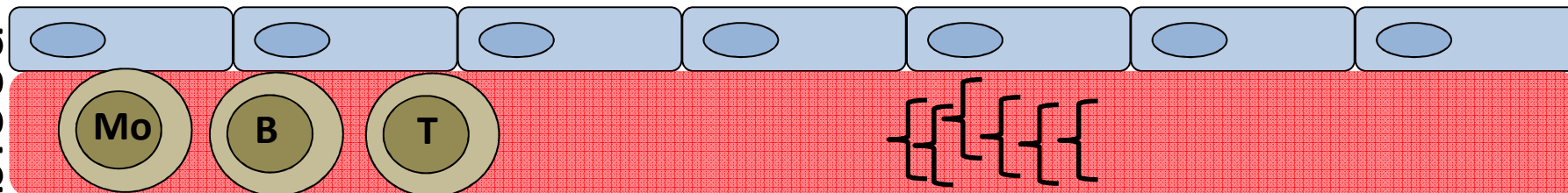
activates

Tissue



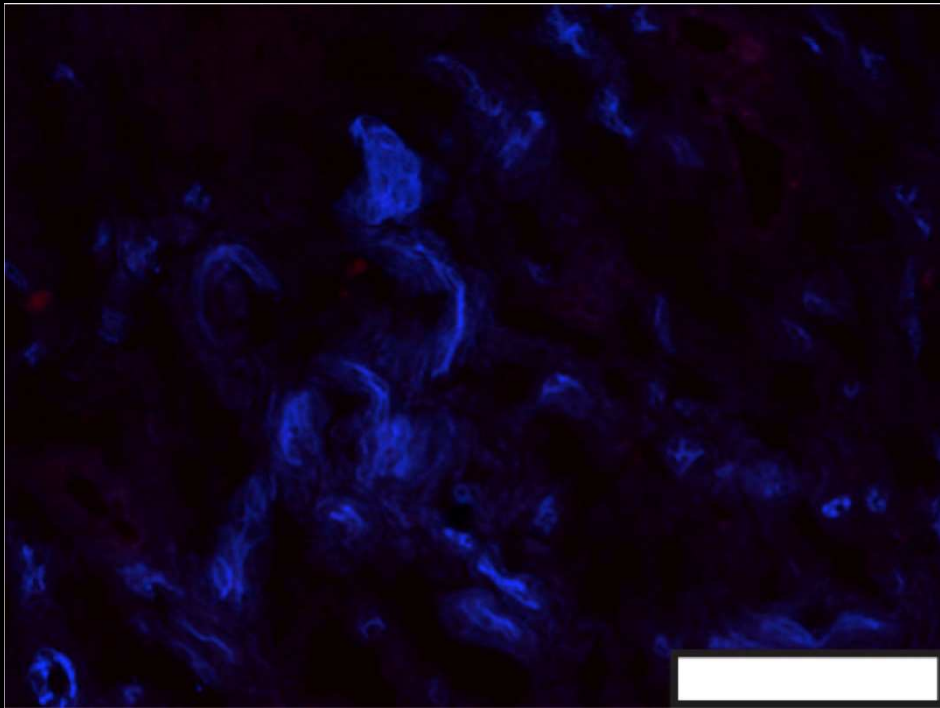
Pro-immunostimulation

blood

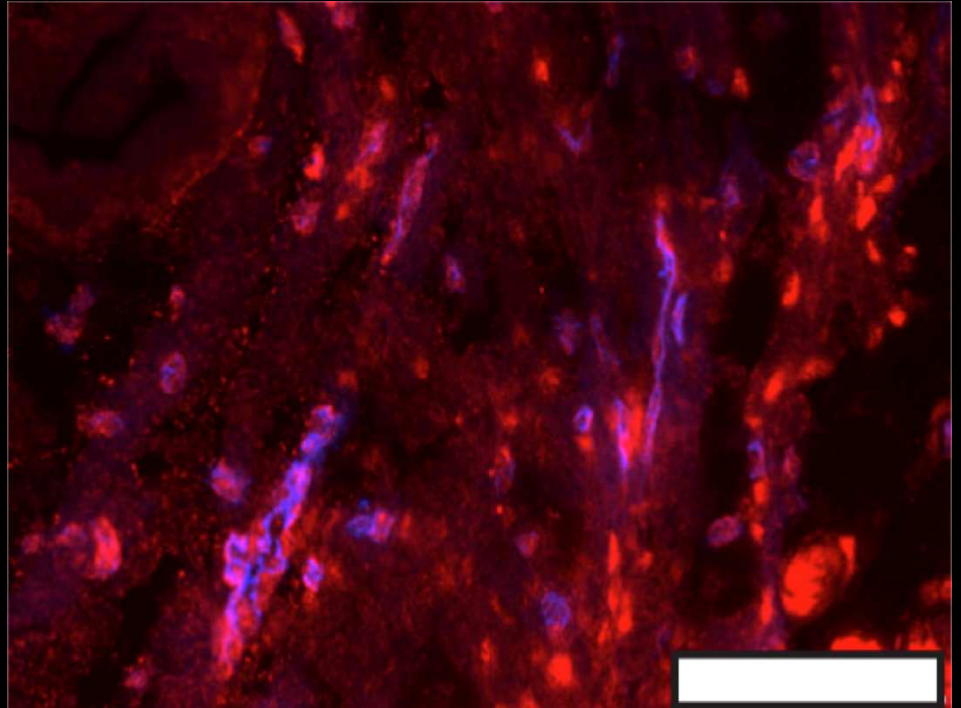


Peptide reactivation of T_{RM} induces chemokine expression (12h)

No peptide



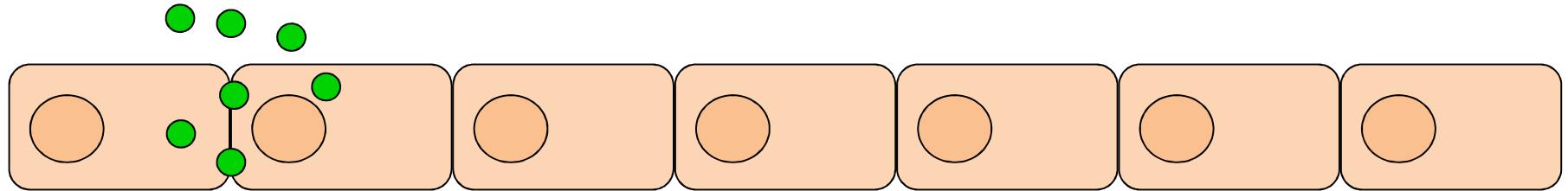
After peptide



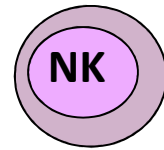
CD31 CXCL9

Schenkel, et al. *Nature Immunology*, 2013

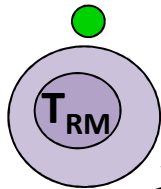
Add peptides
that trigger T_{RM}
activation



activates



Tissue



IL-2

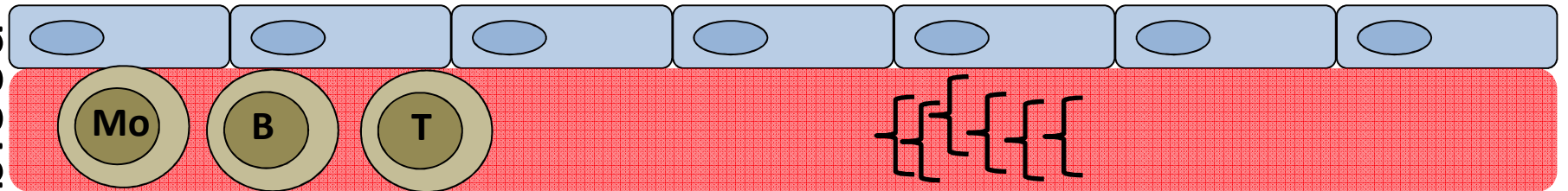
TNF α

IFN γ

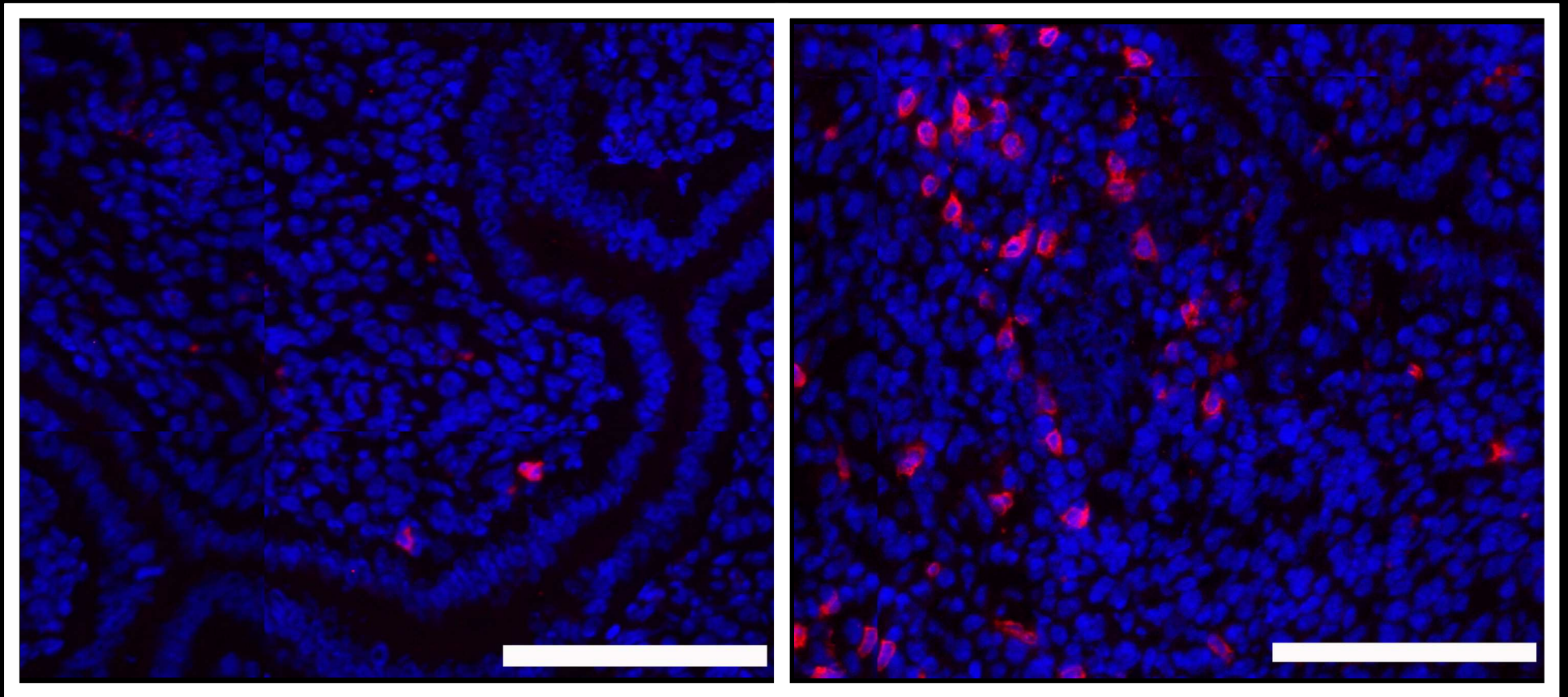
Pro-immunostimulation

VCAM-1
chemokines

blood



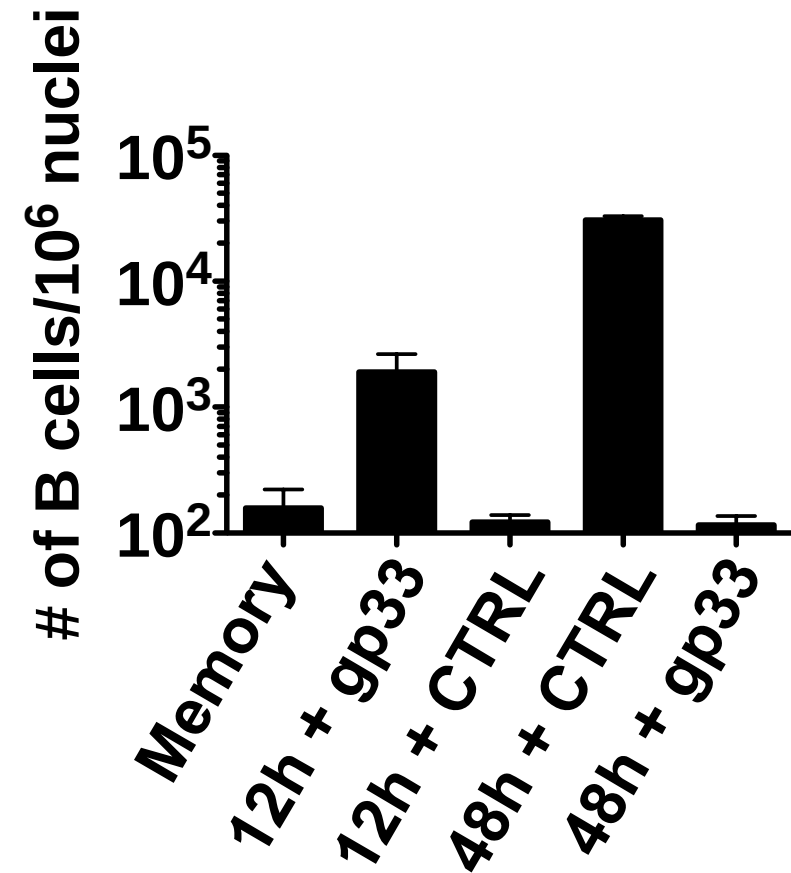
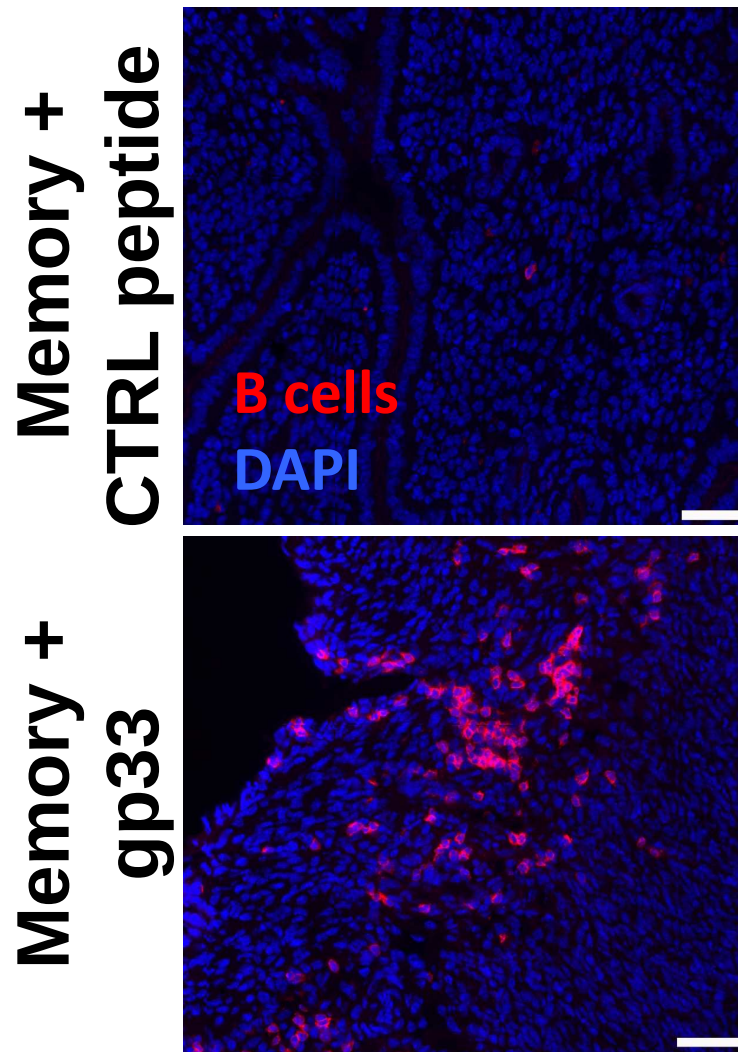
CD8 T cells are recruited



DAPI OT-I

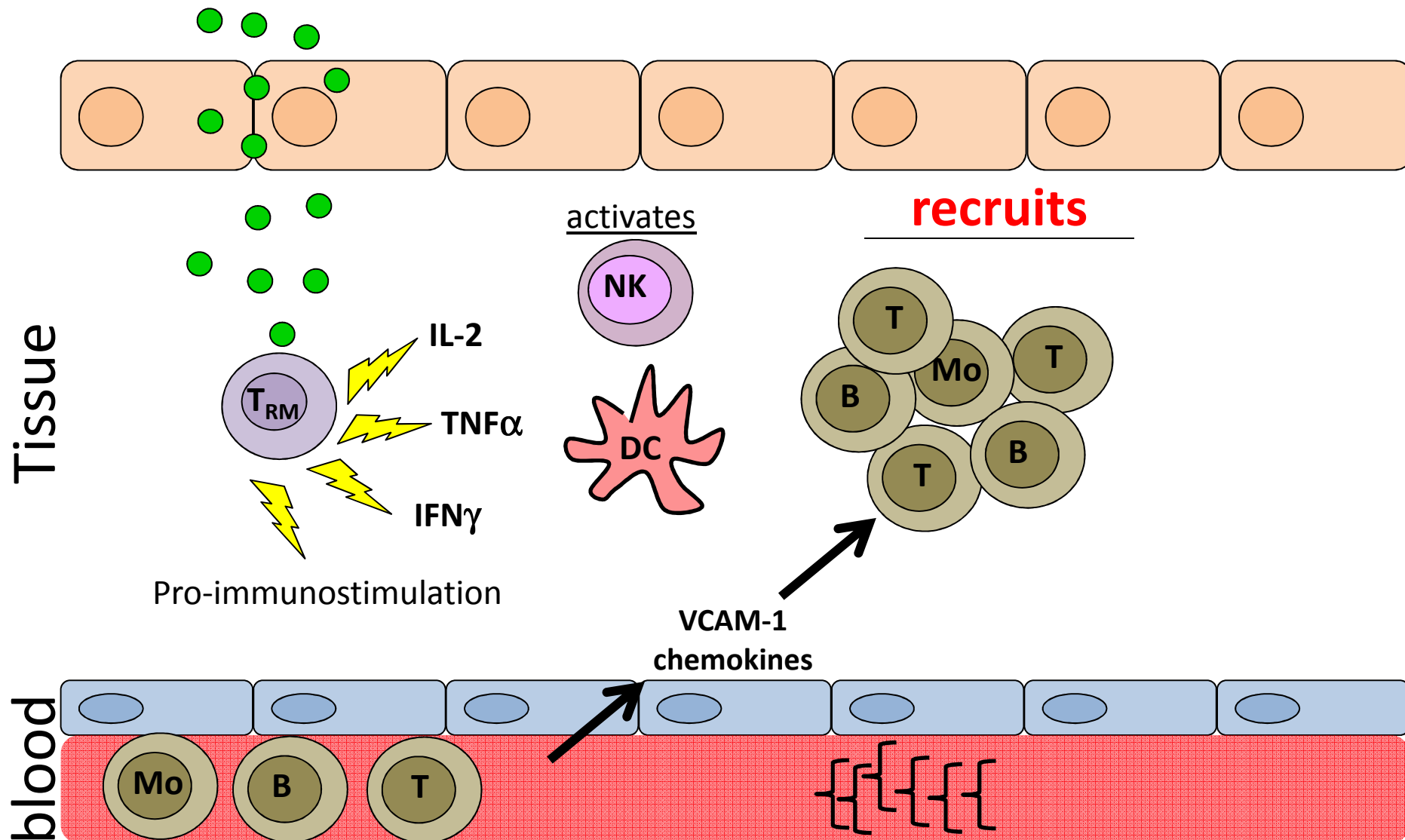
After peptide reactivation of T_{RM}

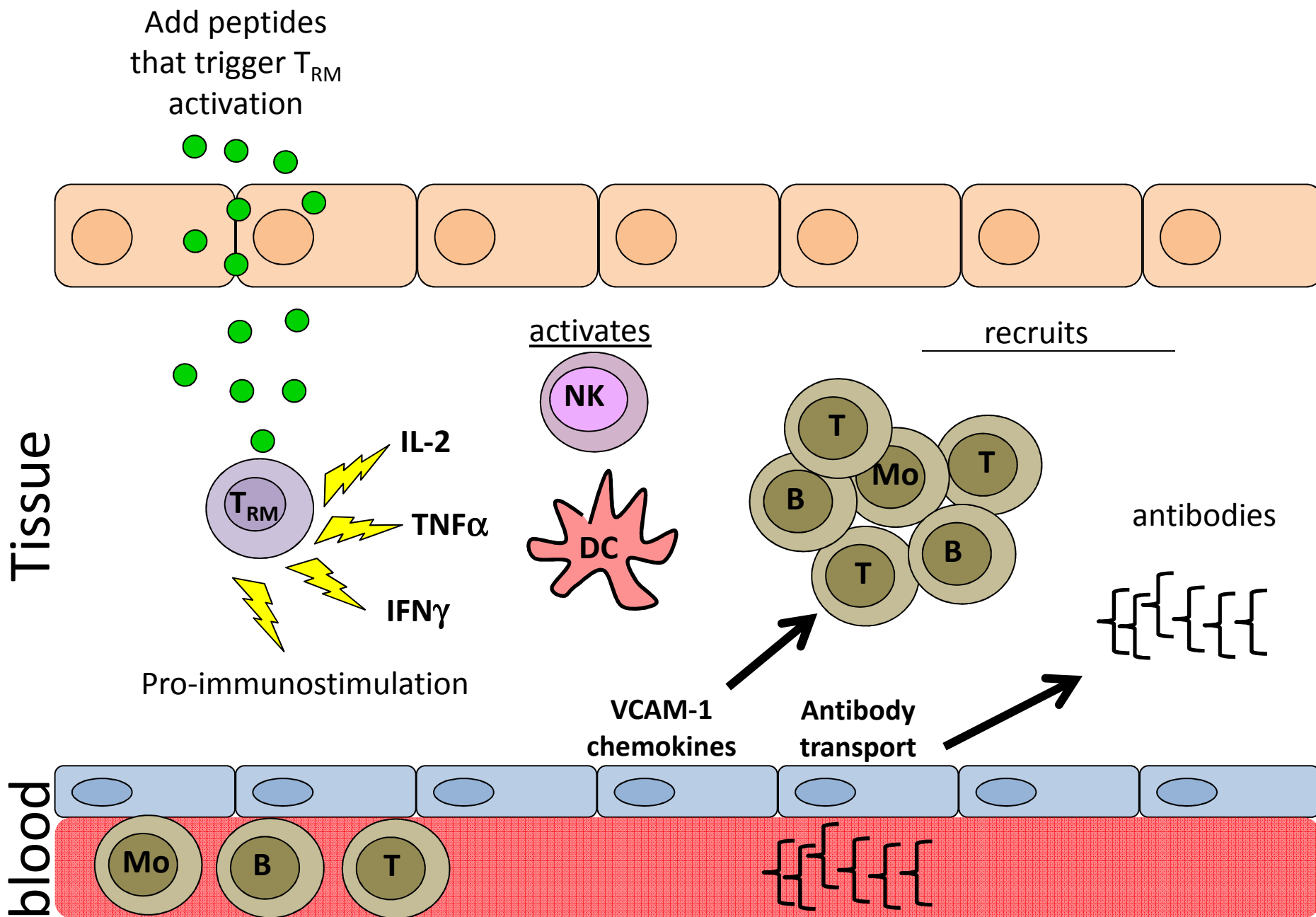
B cells are recruited after T_{RM} re-activation



Dependent on P14-derived IFN γ

Add peptides
that trigger T_{RM}
activation

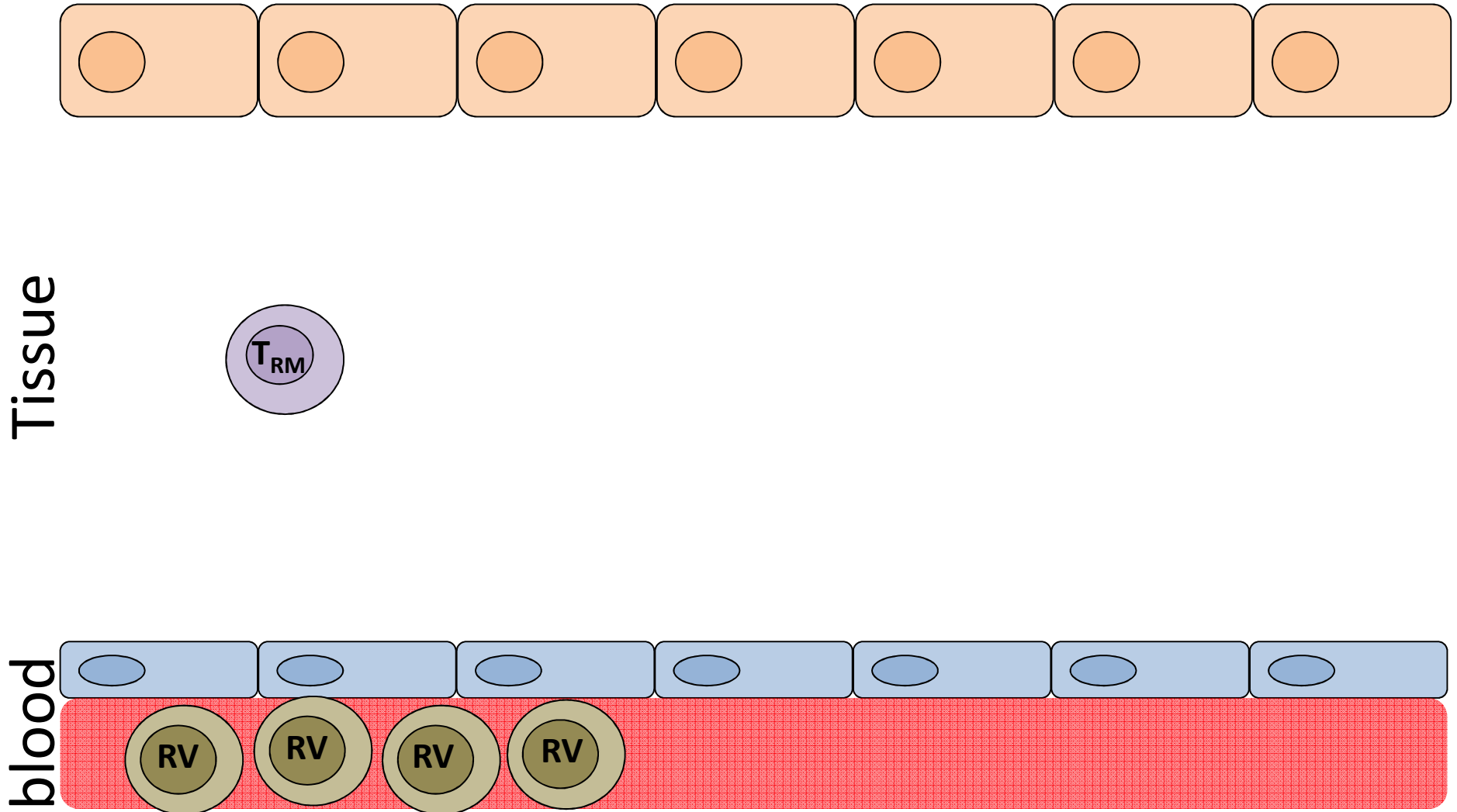




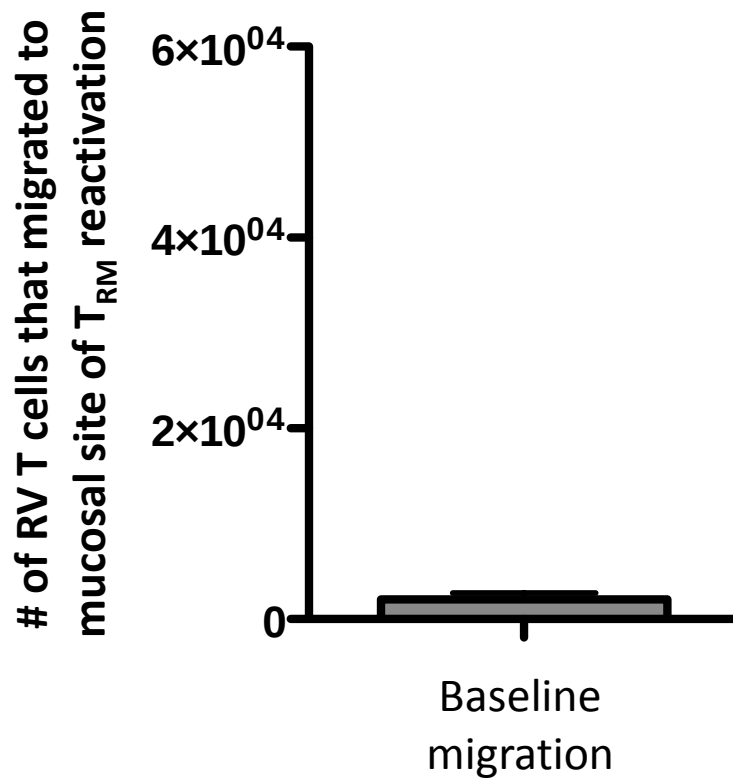
**Memory CD8 T cells are
sensitive Ag-detectors**

And sound the alarm

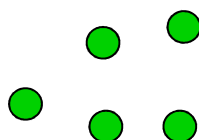
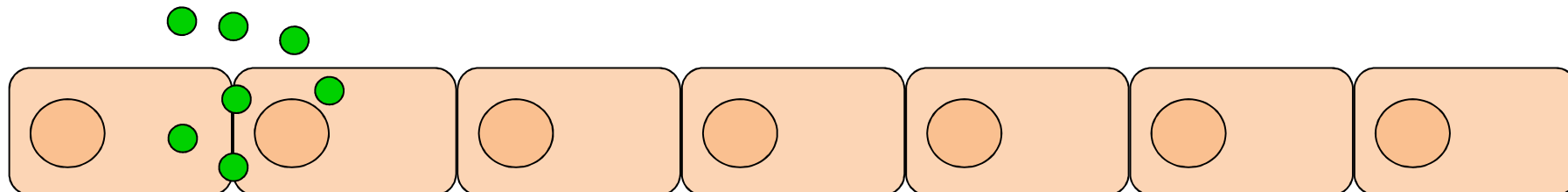
**We transferred RV transduced T cells i.v.
(T cells cultured with α CD3/ α CD28/IL-2)**



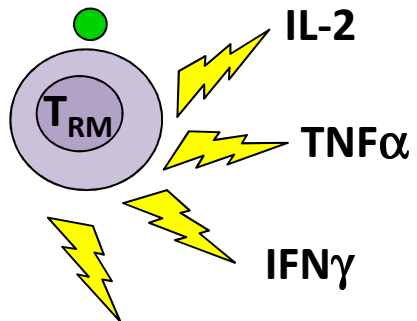
Cultured T cells migrate poorly to female reproductive tract



Add peptides
that trigger T_{RM}
activation

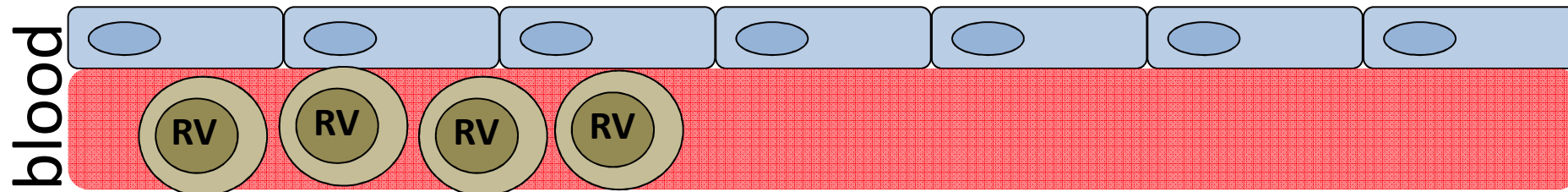


Tissue



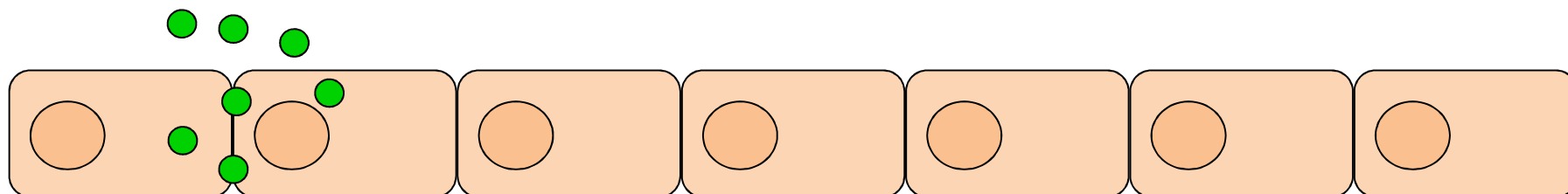
Pro-immunostimulation

VCAM-1
chemokines



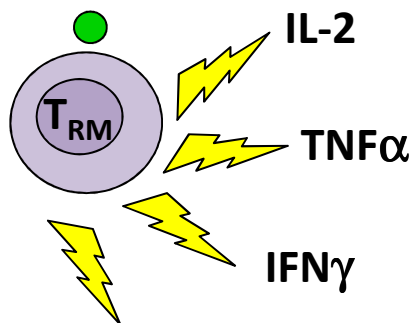
blood

Add peptides
that trigger T_{RM}
activation

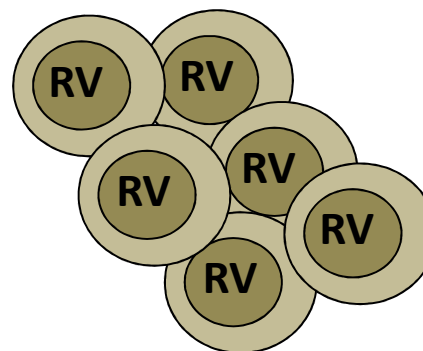


Could T_{RM} be exploited to recruit RV T cells?

Tissue

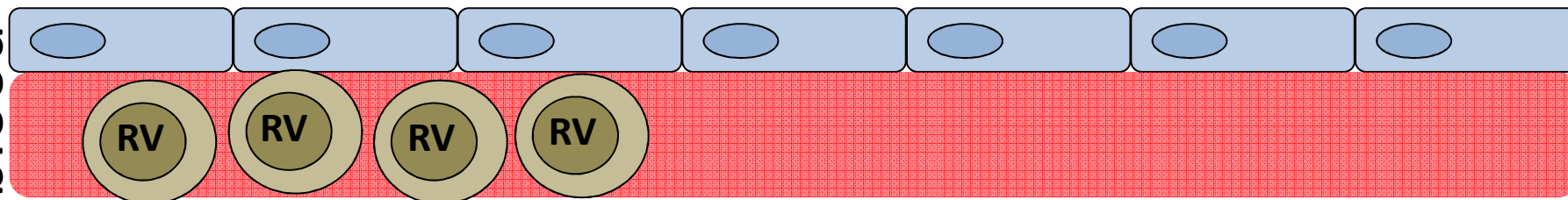


Pro-immunostimulation

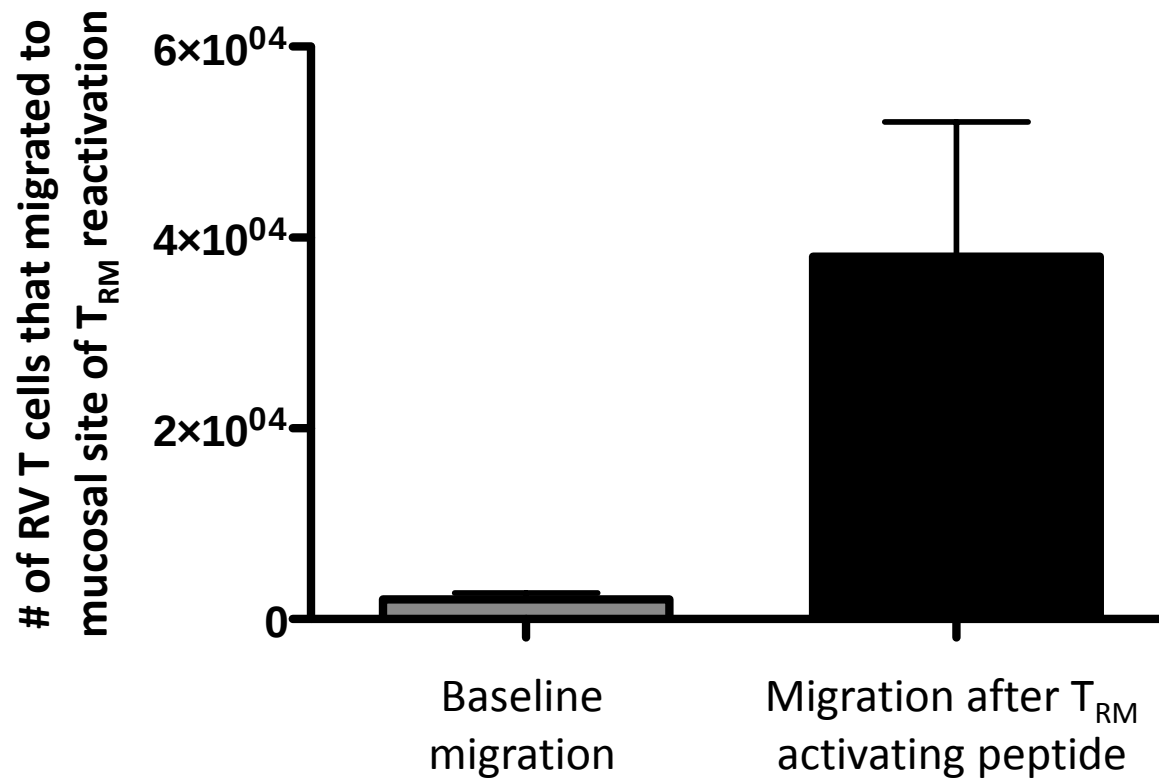


VCAM-1
chemokines

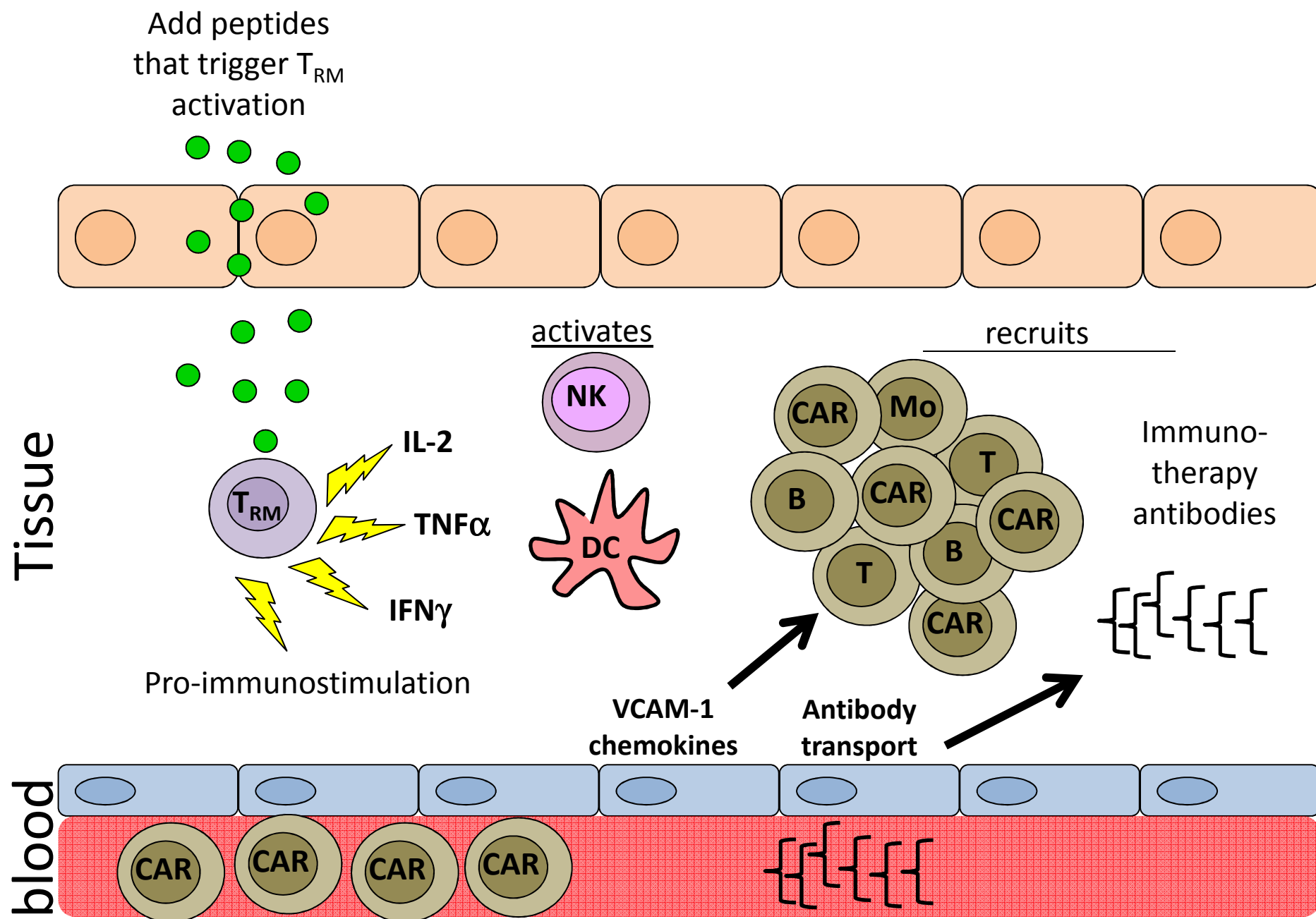
blood



T_{RM} reactivation recruits RV transduced, cultured T cells



unpublished



Take home messages:

Migration to tissues depends on T cell differentiation state

Many tissues are relatively closed to resting CD8 T cell migration

T_{RM} = unique lineage, parked within tissues

T_{RM} reactivation promotes

- Immunostimulatory environment**
- Leukocyte recruitment**

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Rafi Ahmed



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of Allergy and
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