CTL immune responses to viruses

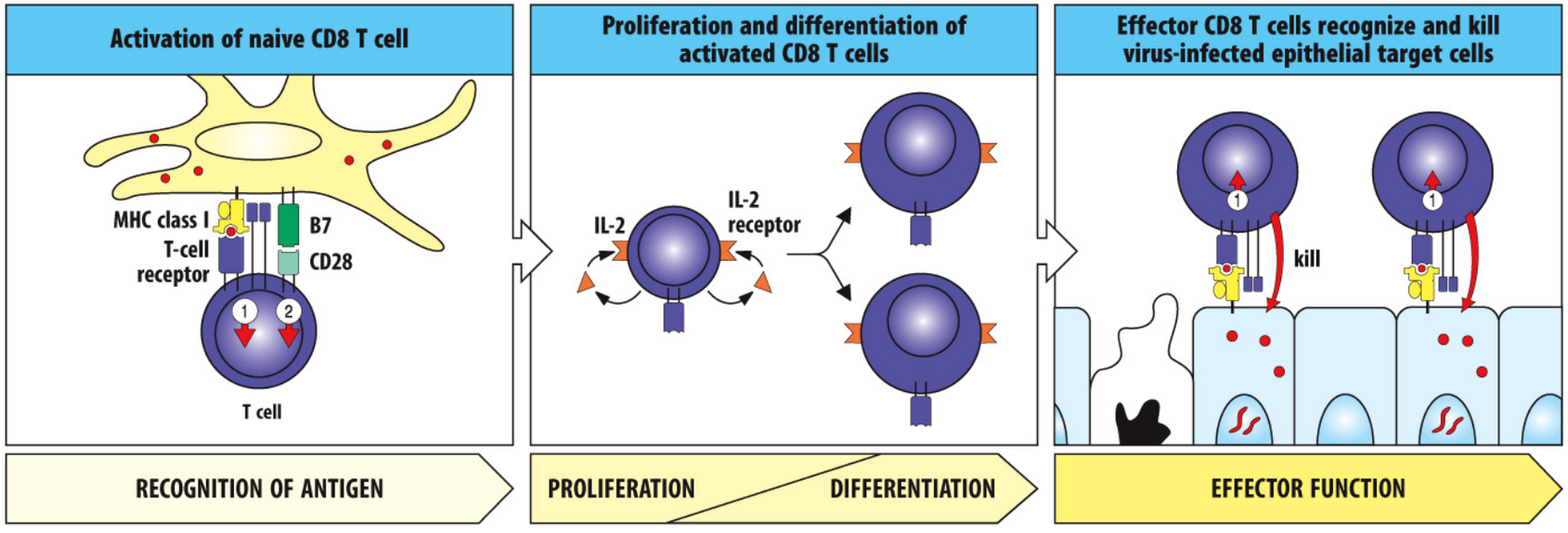


Figure 8.20 The Immune System, 4th ed. (© Garland Science 2015)

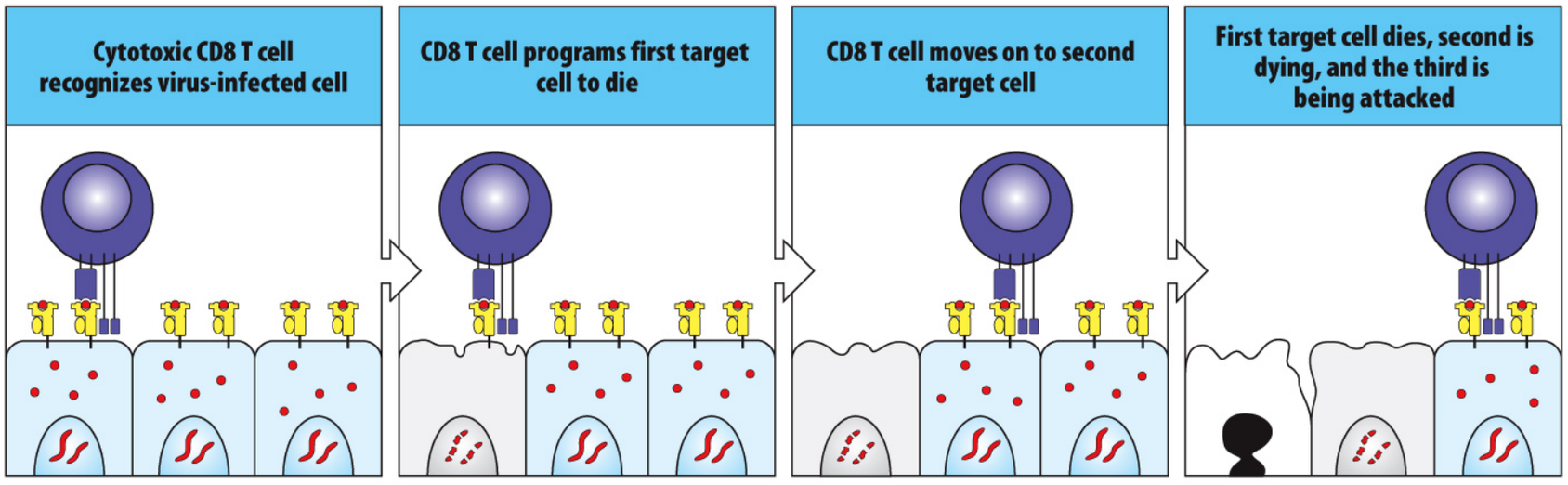
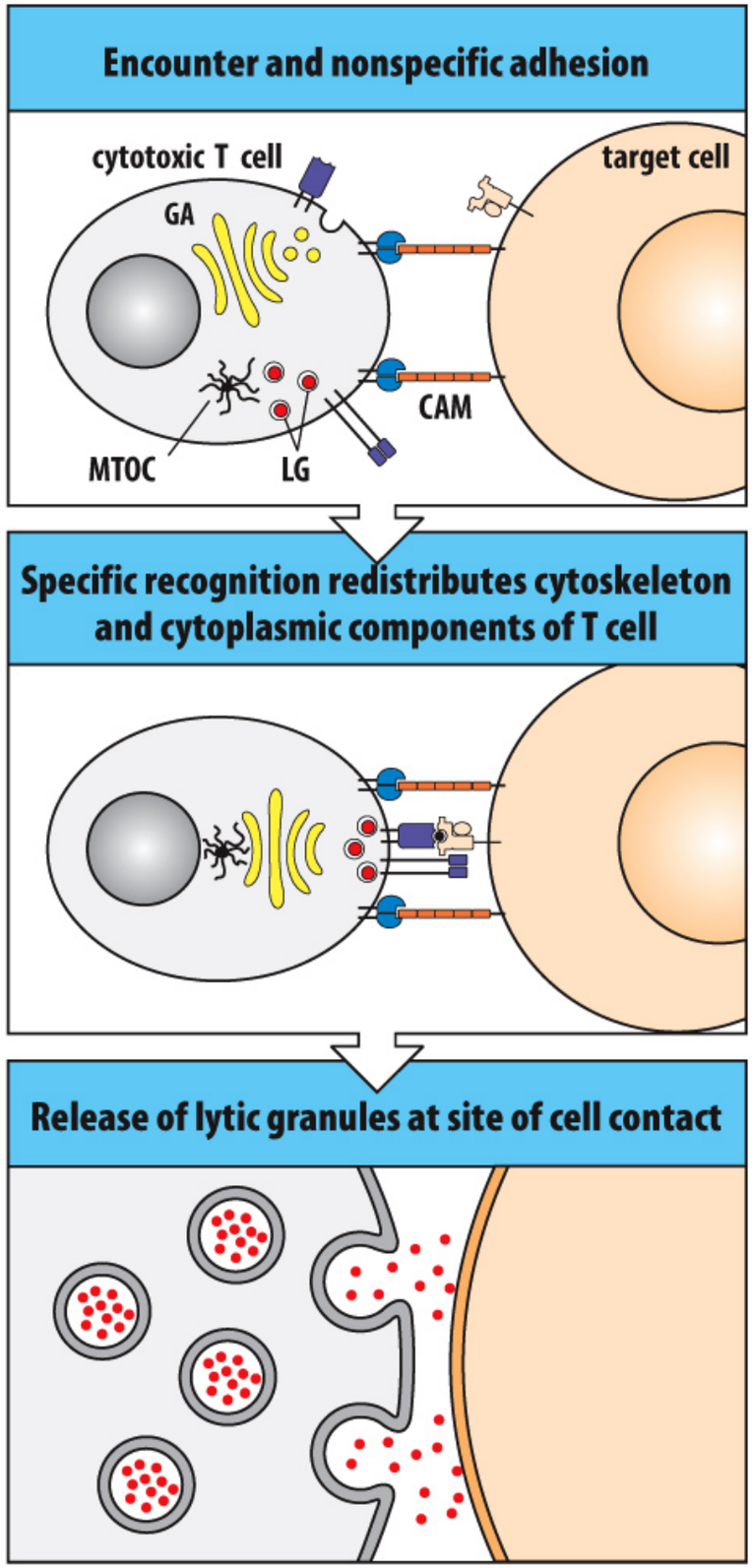
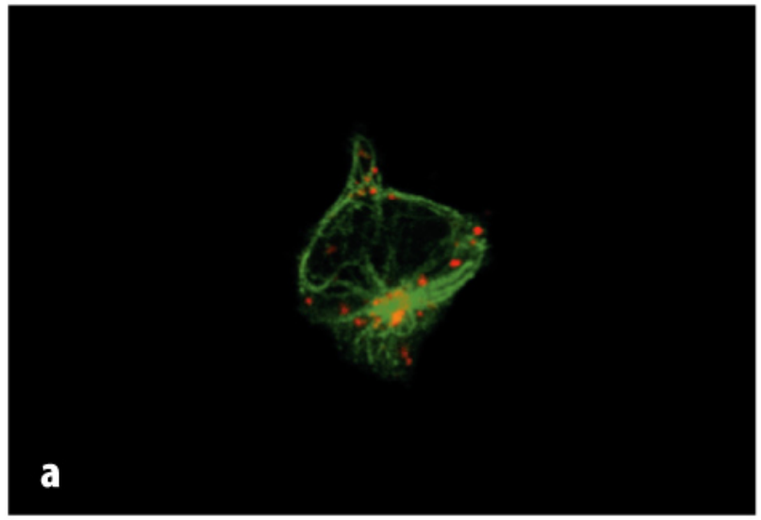
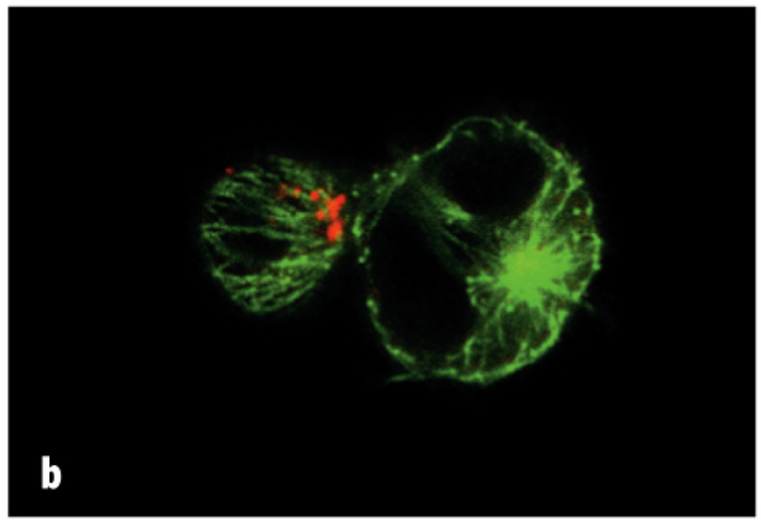


Figure 8.24 The Immune System, 4th ed. (© Garland Science 2015)

CTL Immune responses to viruses







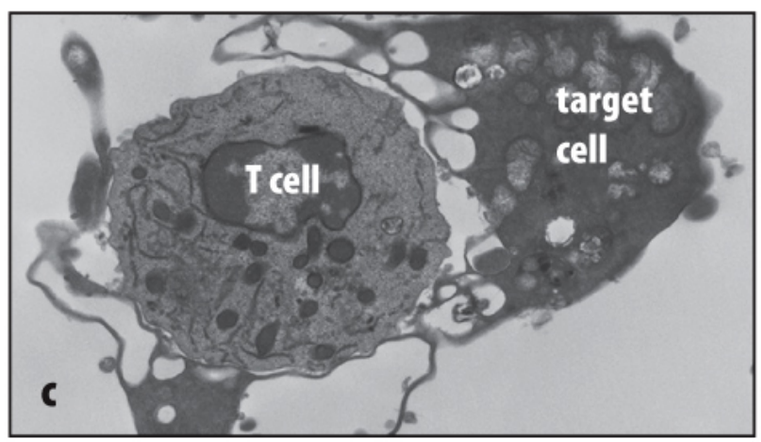
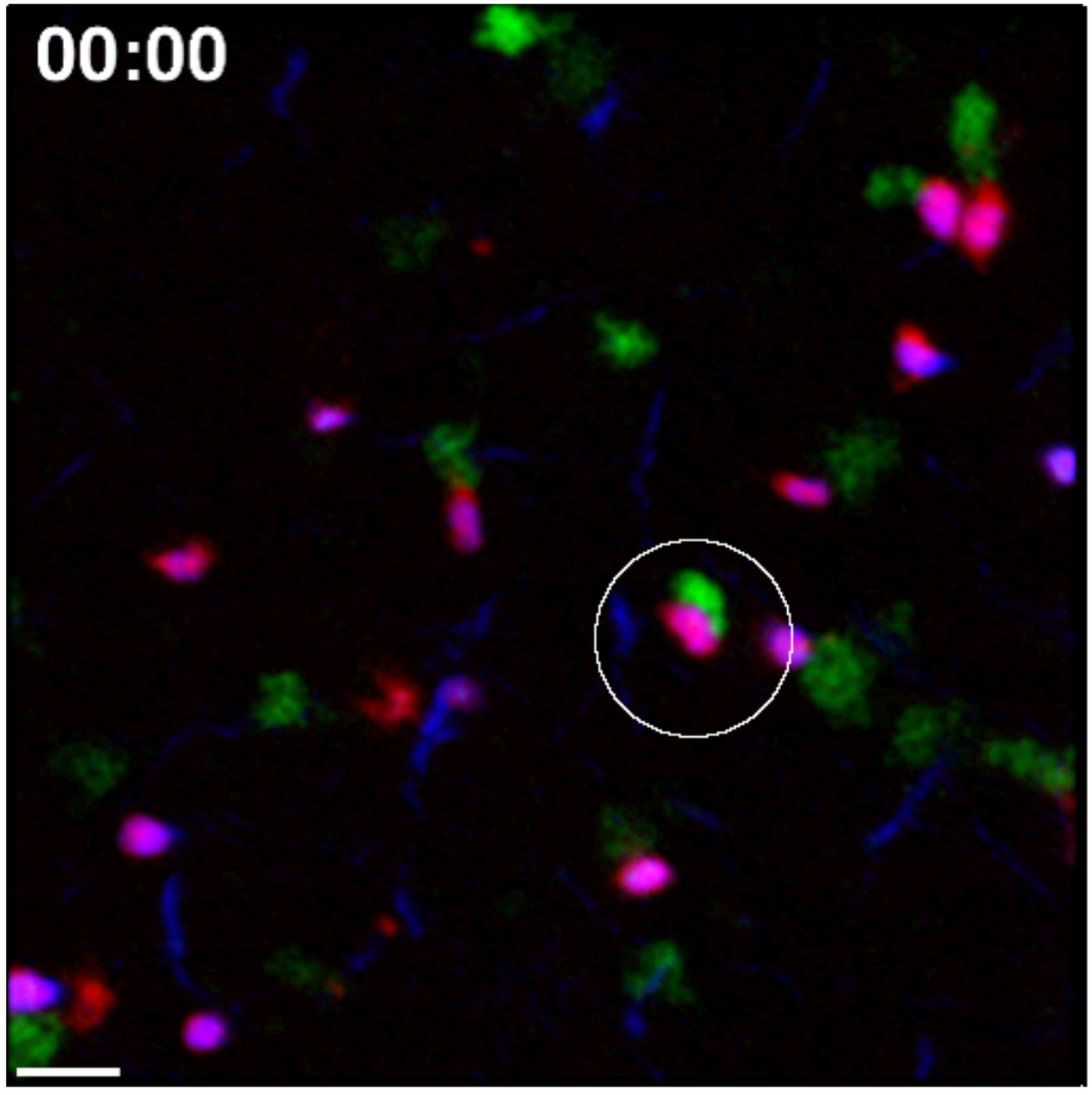


Figure 8.23 The Immune System, 4th ed. (© Garland Science 2015)

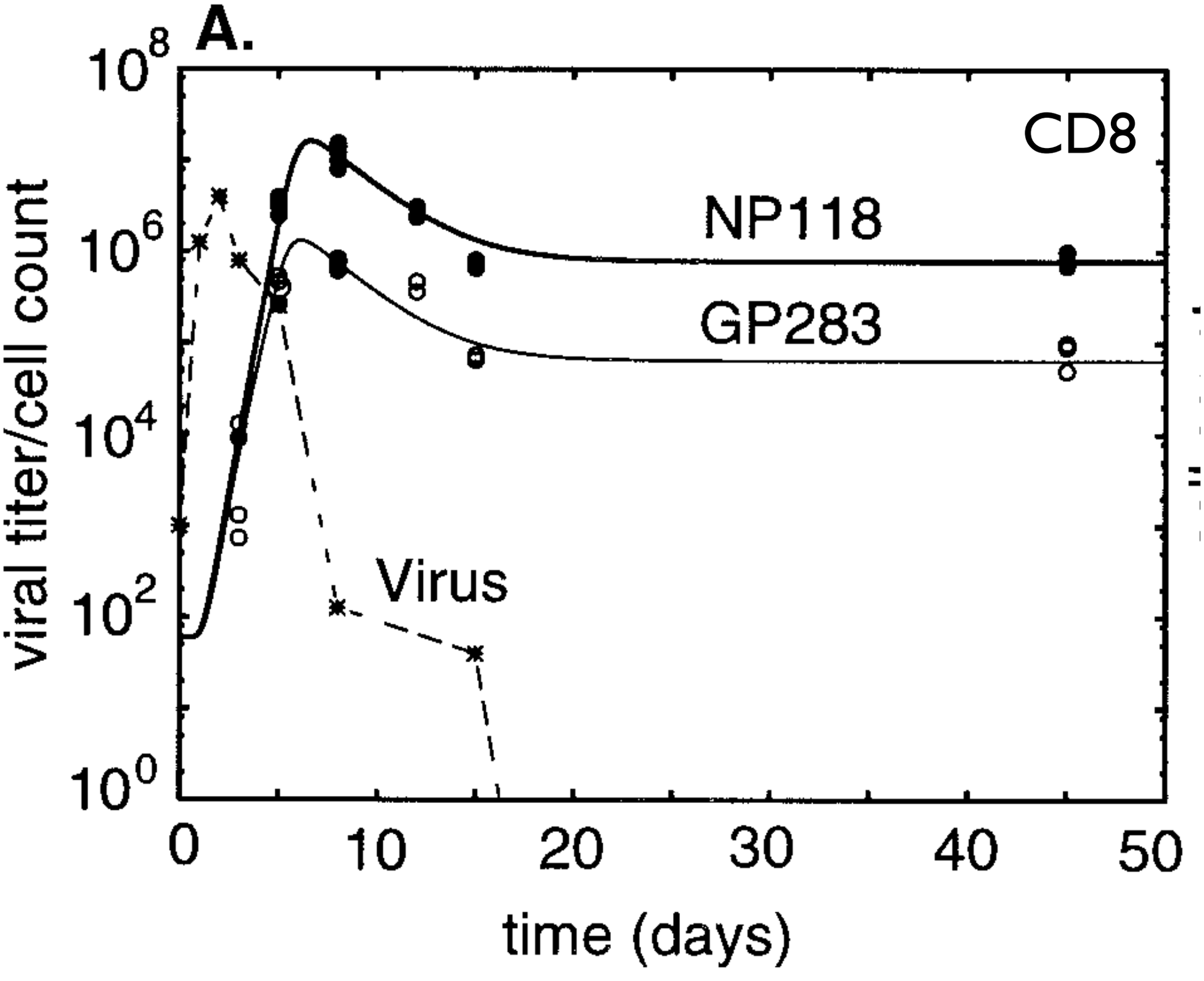
2PM movie of Ag pulsed B cells being killed by CTL



B cell (target cell): purple, CTL: green, death B cell: white

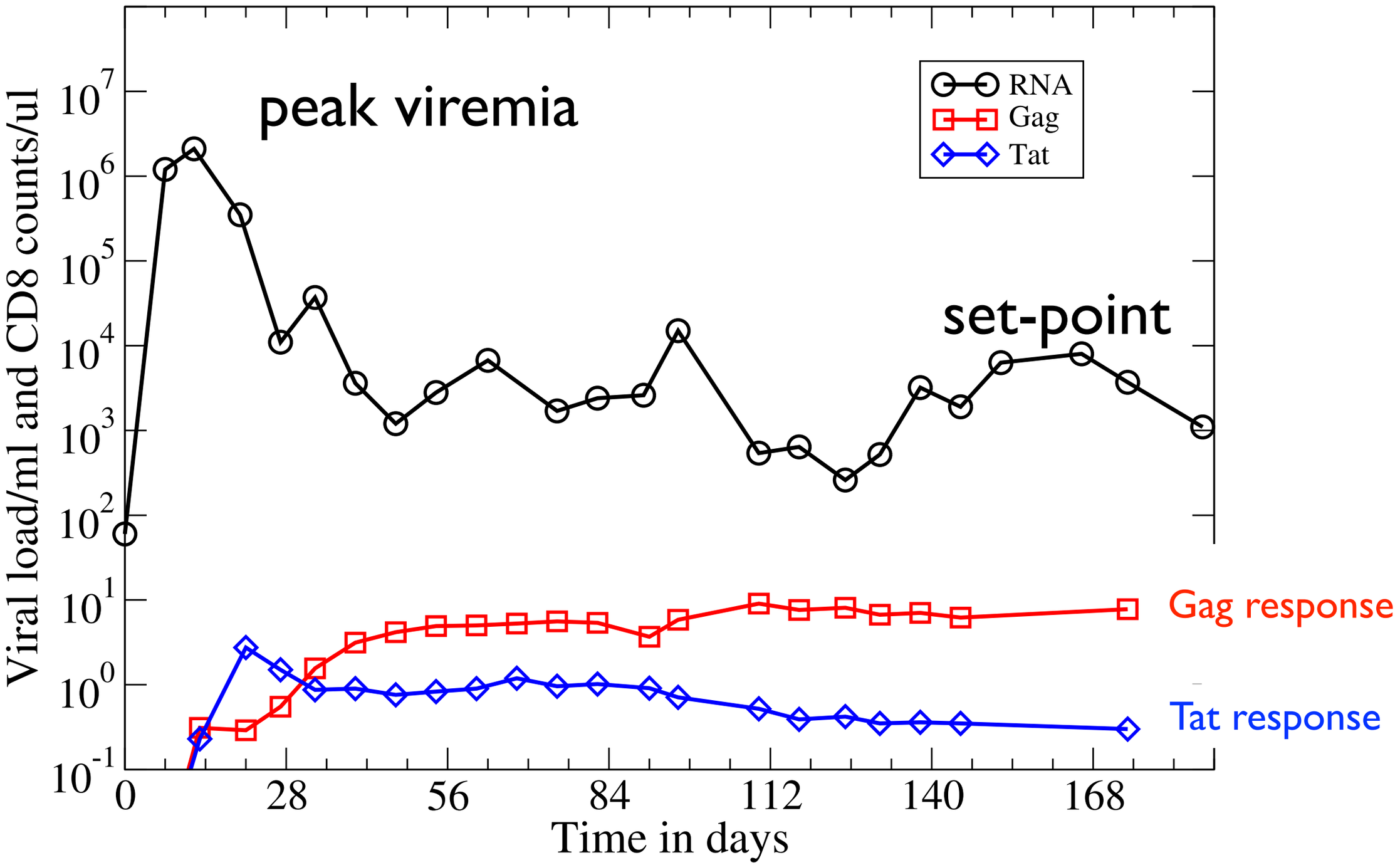
From: Mempel et al. Immunity 2006

LCMV: massive acute infection in mice



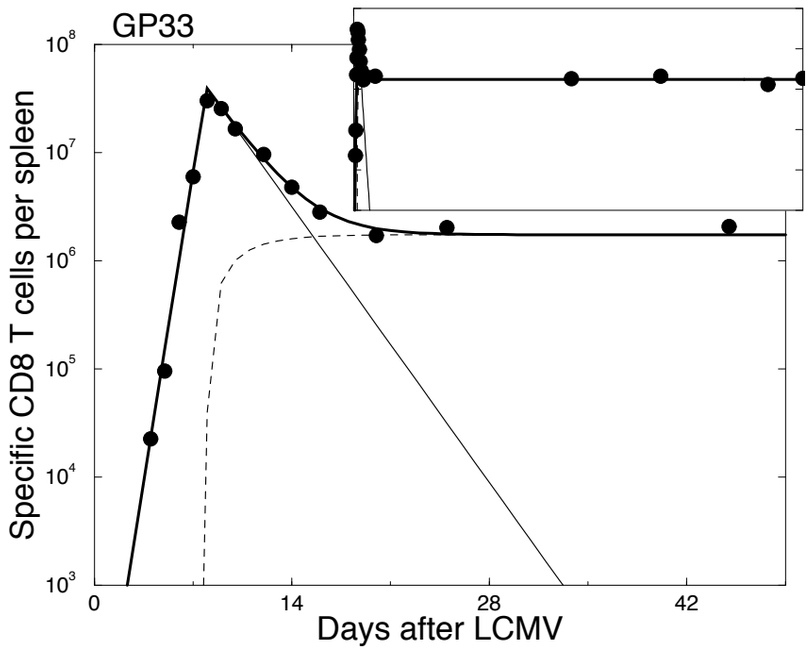
Classical model in immunology [Rafi Ahmed, Emory]

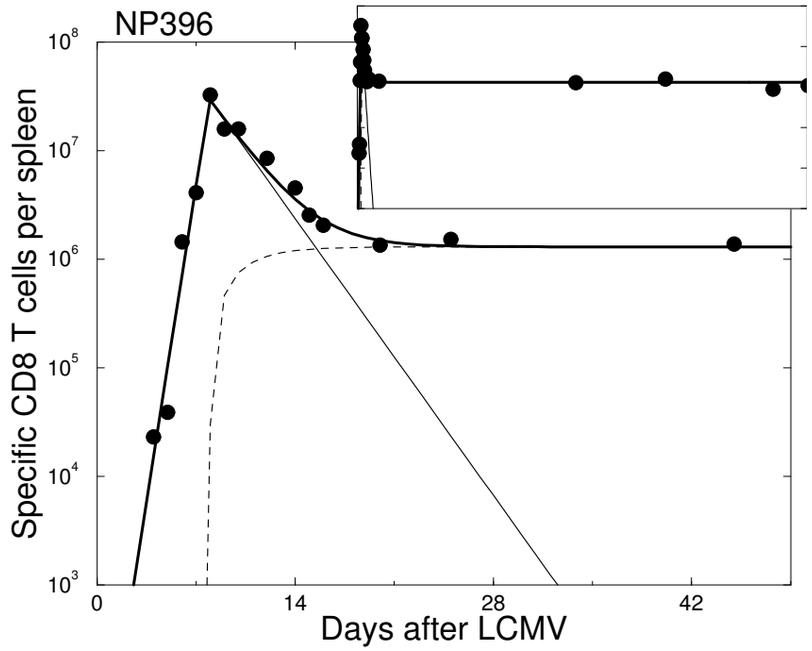
The natural history of a SIV infection becoming chronic

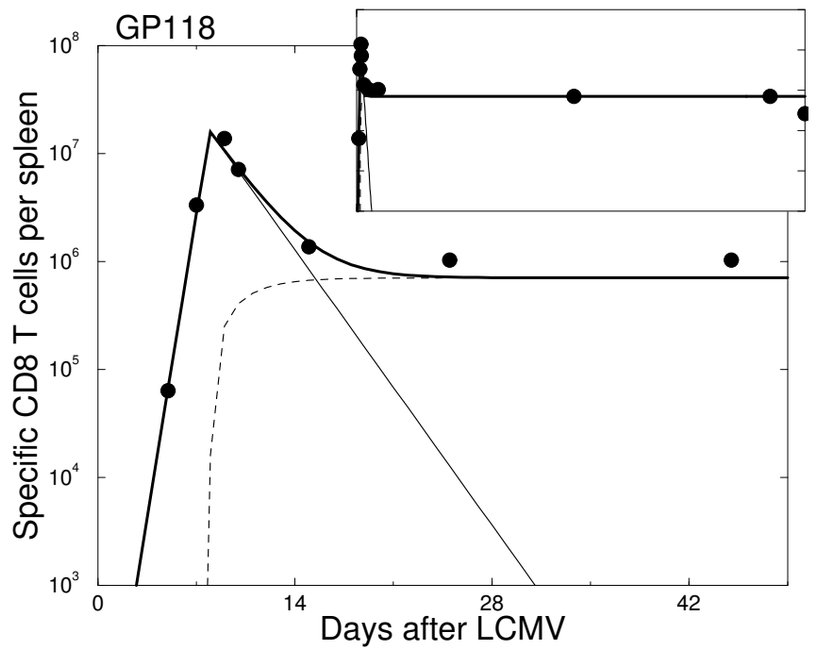


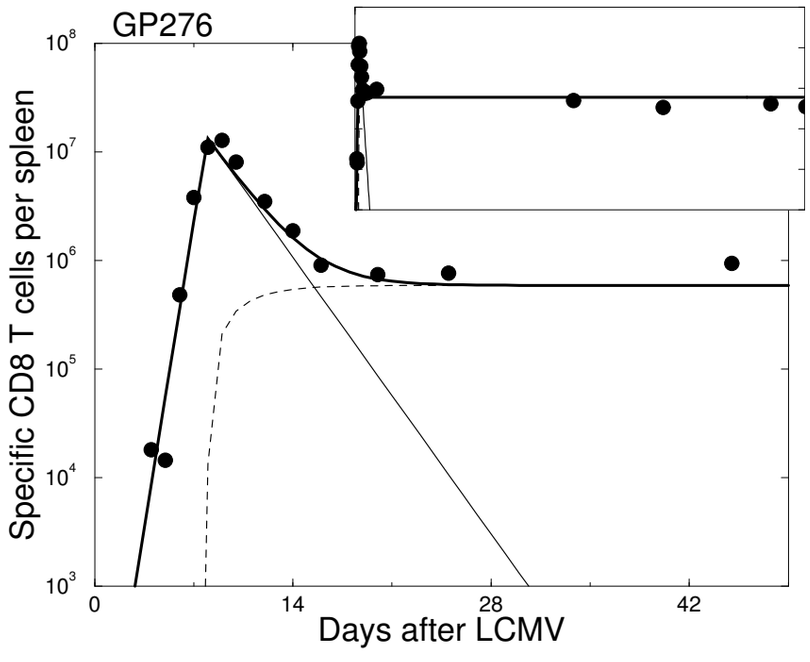
Immune response after 2 weeks, **Tat escapes**, Gag stays.
Viral contraction coincides with rise of CD8 responses and depletion of target cells (CD4 T cells)

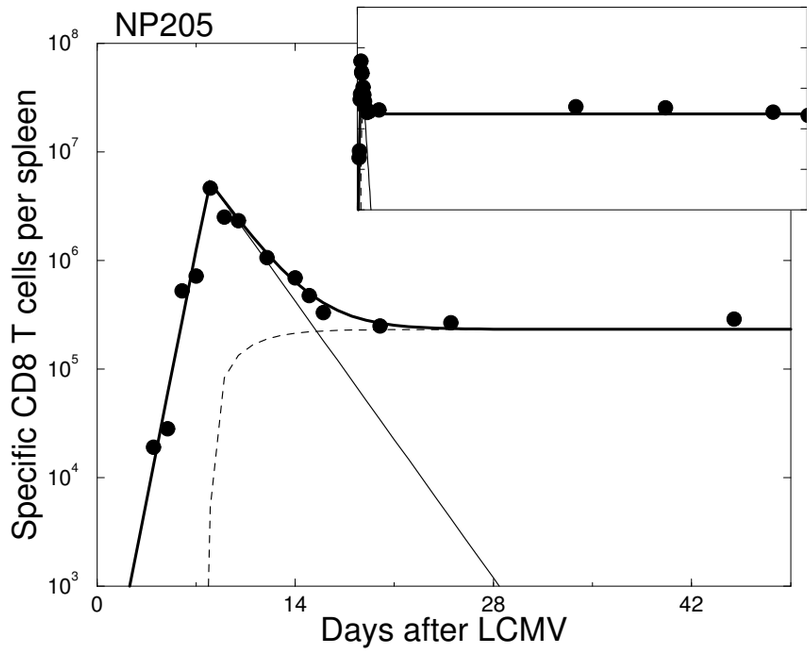
LCMV: several epitopes trigger CD8 T cells

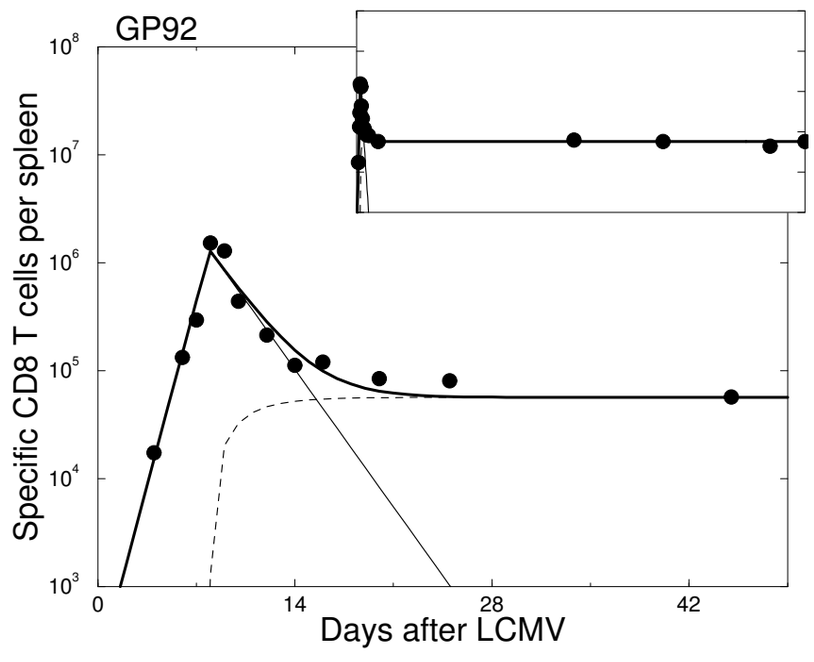








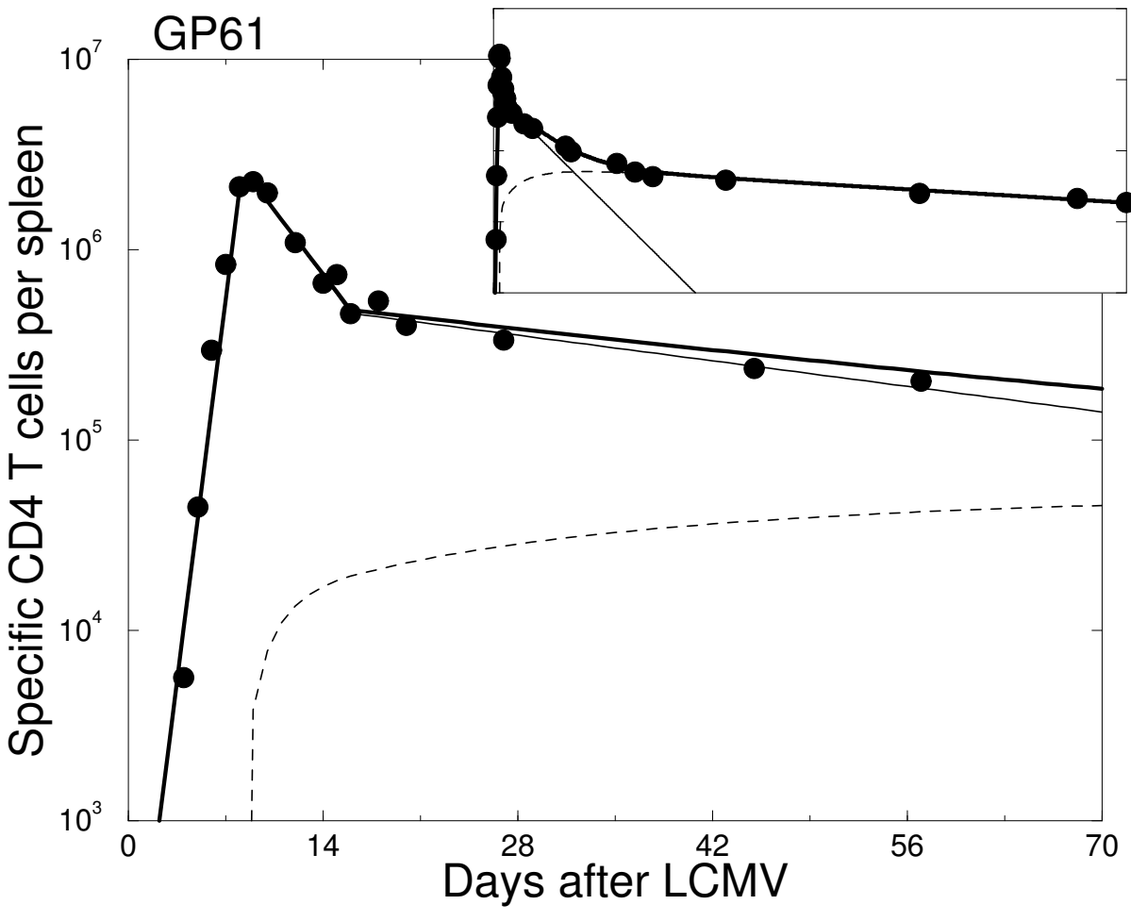




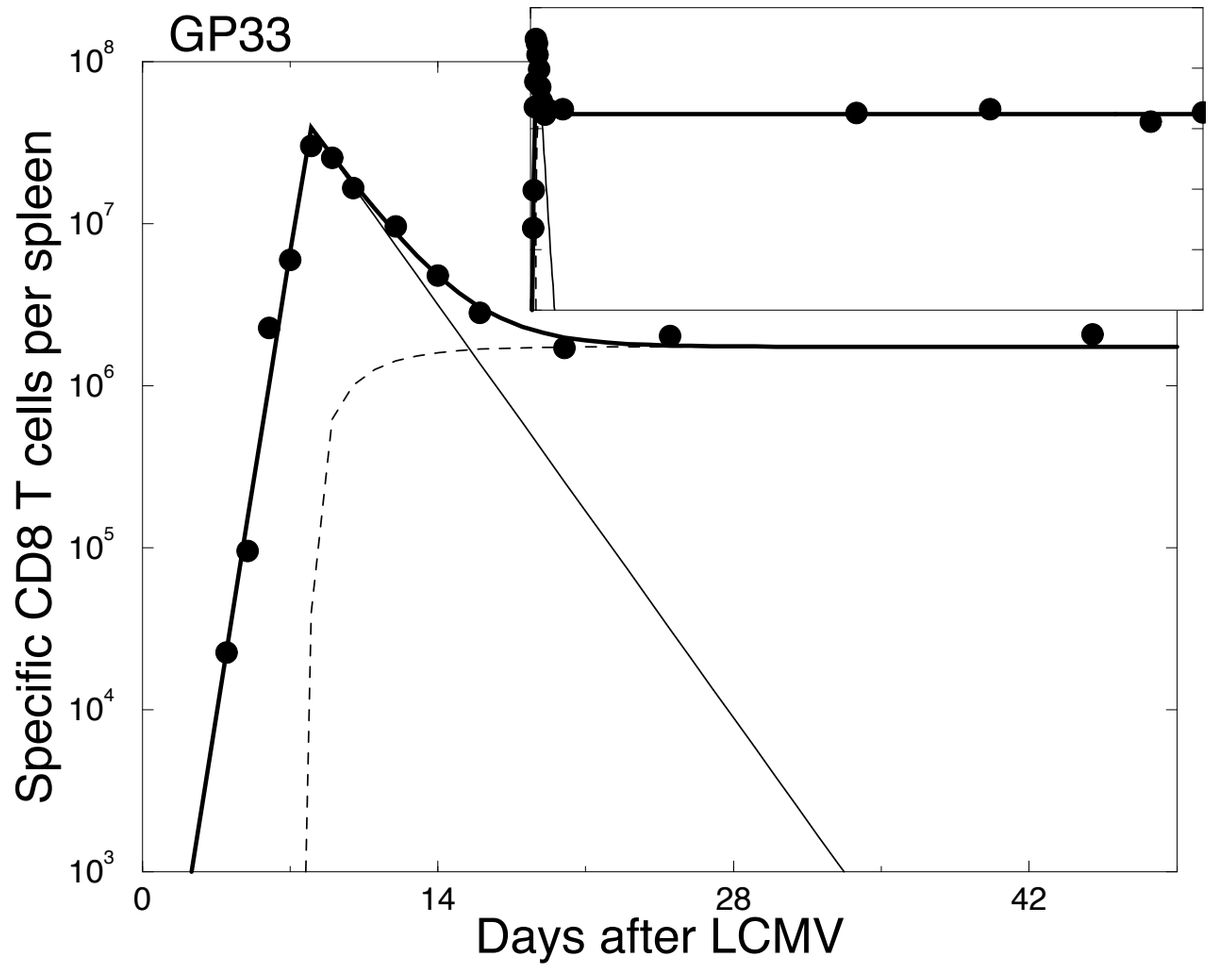
Immunodominance (within host): > 15 CD8 responses.

LCMV: programmed CD4 & CD8 responses

CD4



CD8

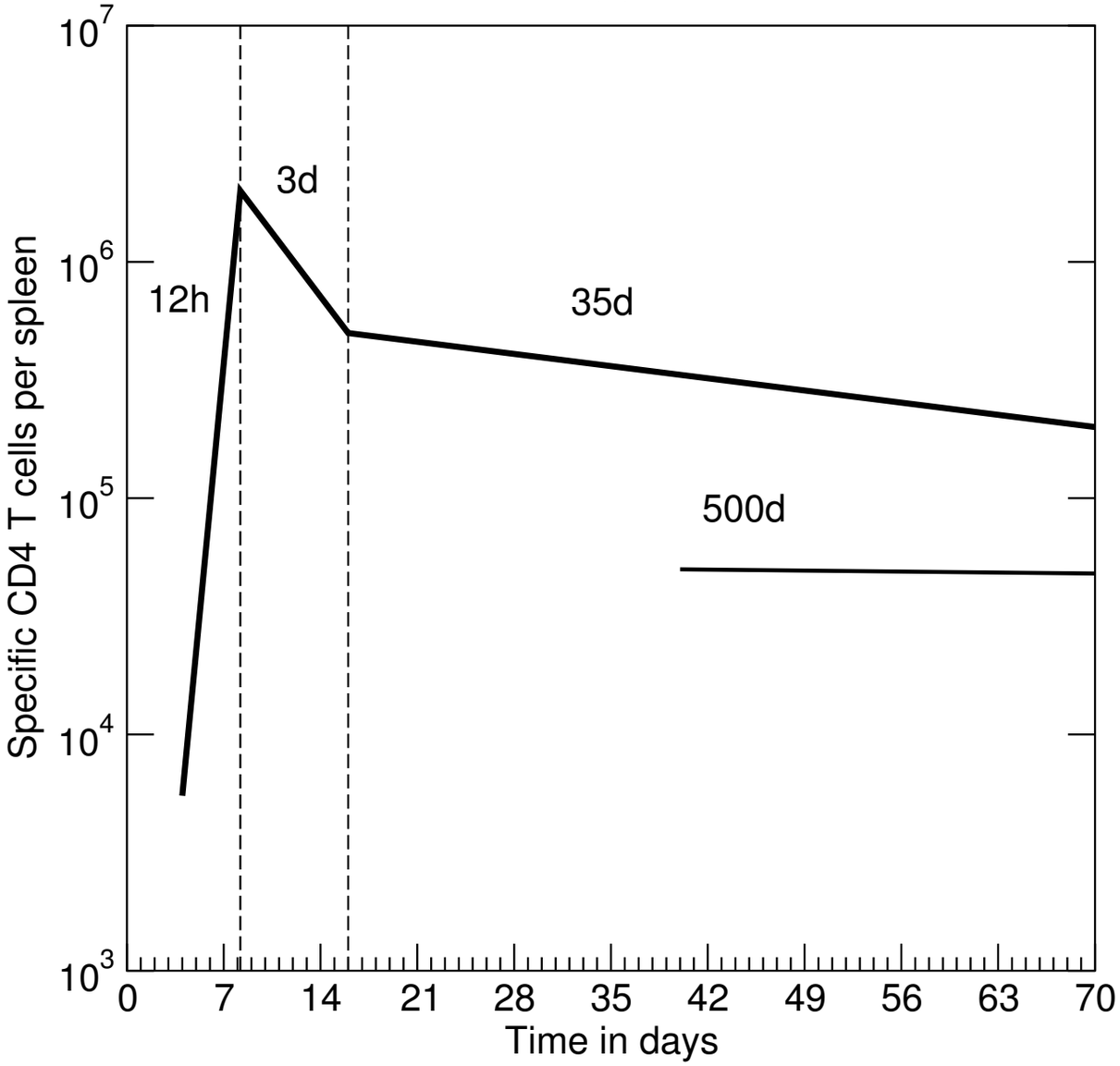


Remove Ag after one day: normal expansion

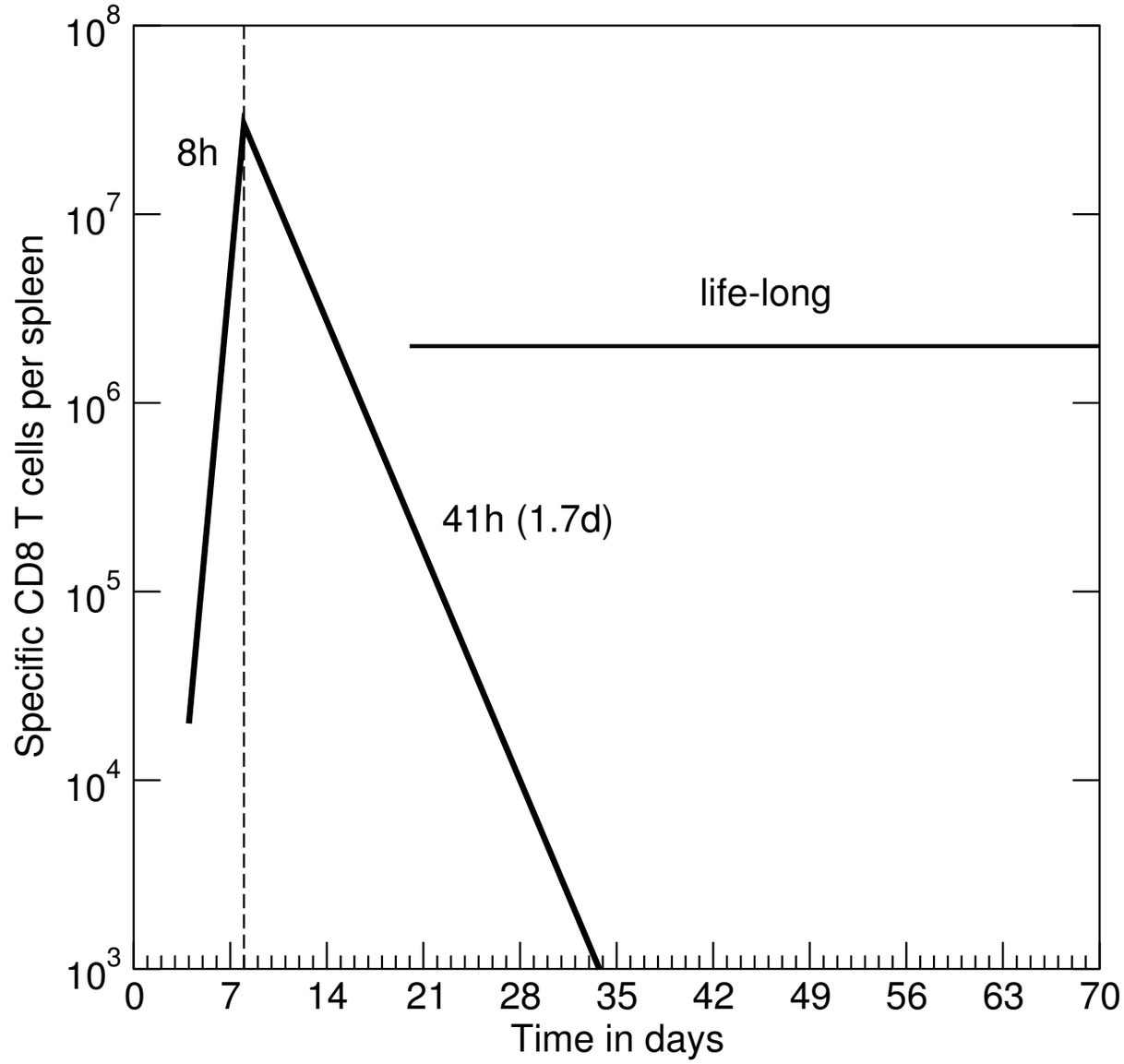
Add Ag at/after peak: normal contraction

kinetic differences between CD4 and CD8 acute responses

CD4



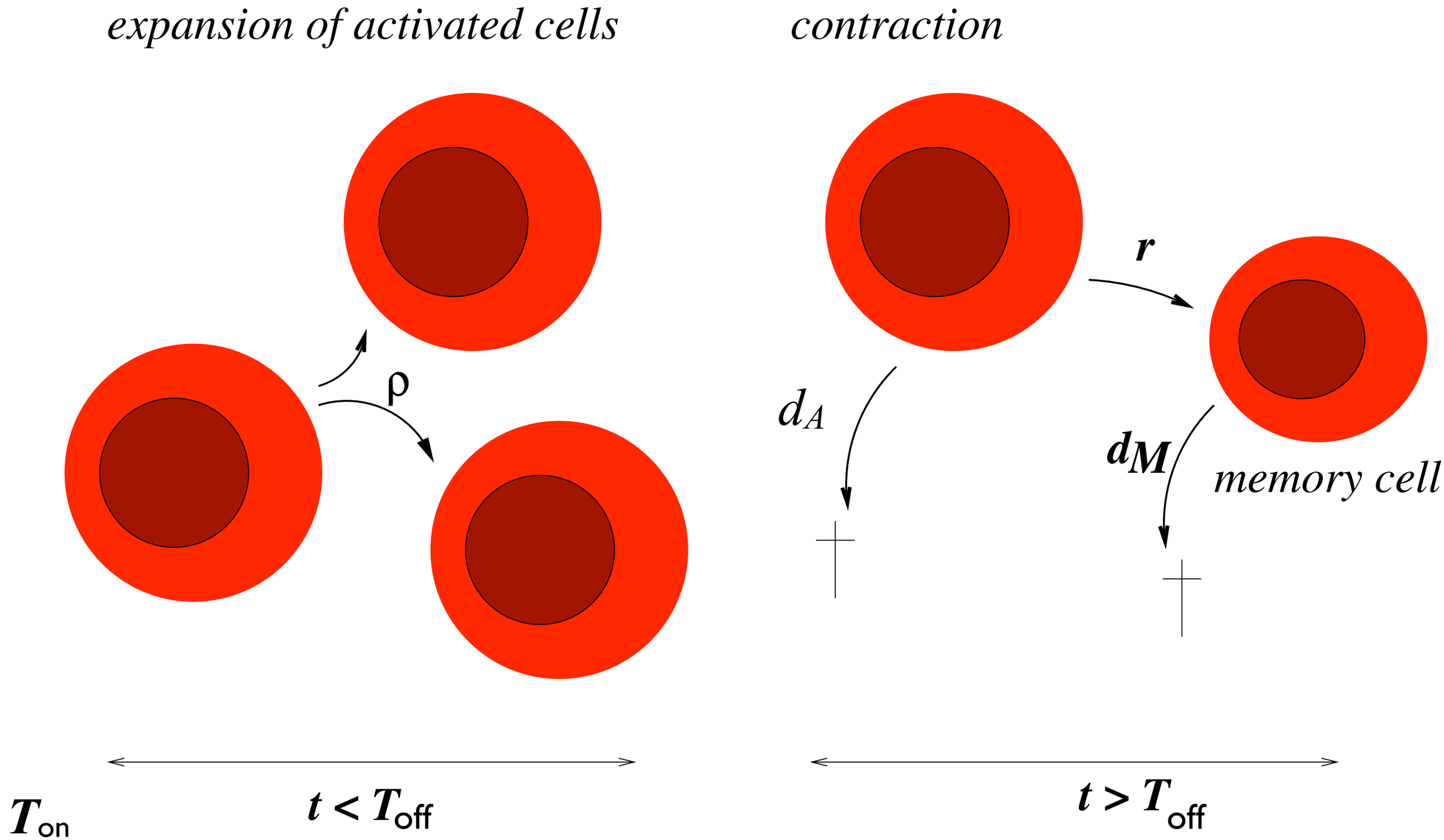
CD8



Start of contraction phase very similar

due to slower division rate less expansion for CD4s

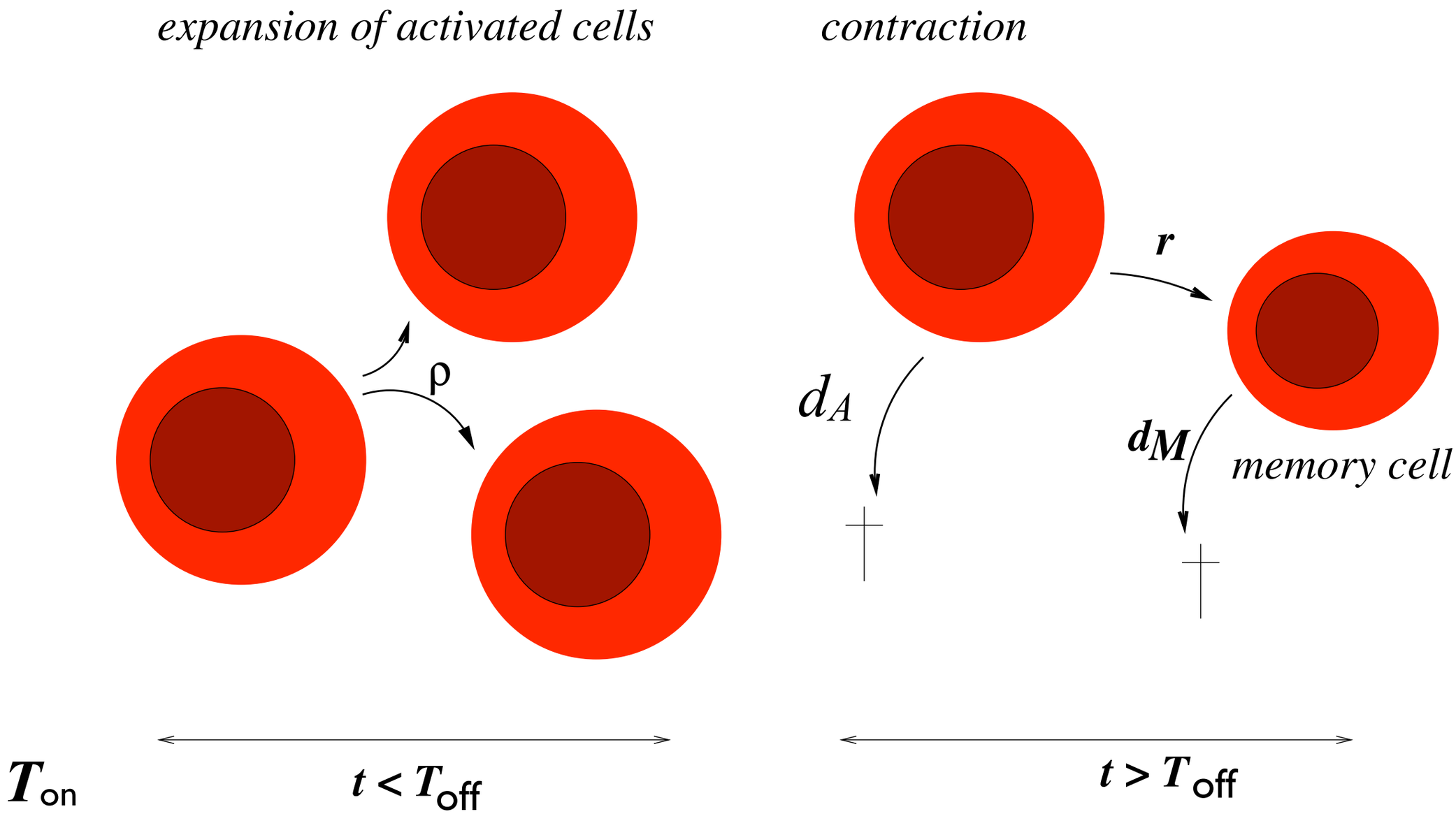
Thanks to program: simple mathematical model



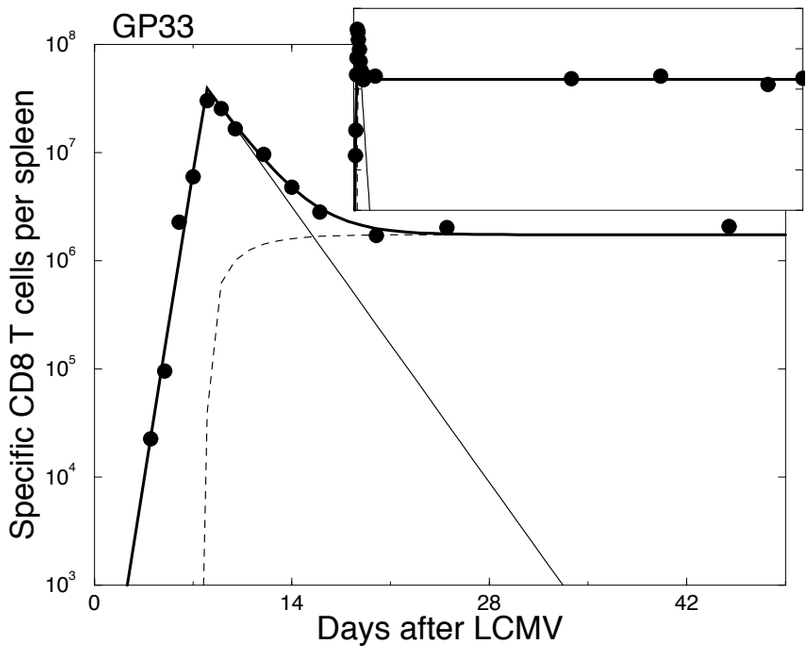
Piecewise model: different before and after peak

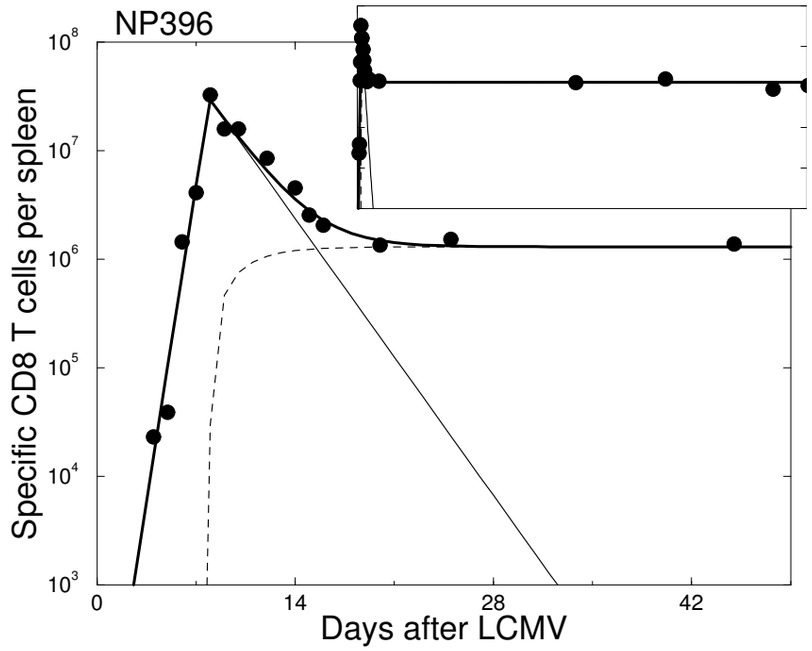
Thanks to program: simple mathematical model

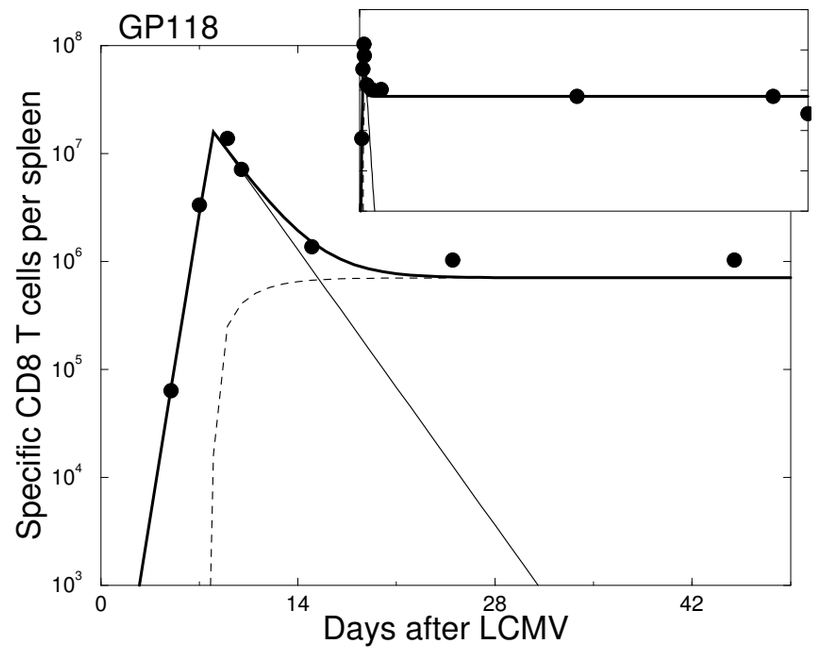
$$\begin{cases} \mathrm{d}A/\mathrm{d}t = 0 \quad \text{and} \quad \mathrm{d}M/\mathrm{d}t = 0\,, & \text{if } t \le T_{\mathrm{on}}\,, \\ \mathrm{d}A/\mathrm{d}t = pA \quad \text{and} \quad \mathrm{d}M/\mathrm{d}t = 0\,, & \text{if } T_{\mathrm{on}} < t \le T_{\mathrm{off}}\,, \\ \mathrm{d}A/\mathrm{d}t = -(d_A + r)A \quad \text{and} \quad \mathrm{d}M/\mathrm{d}t = rA - d_M M, & \text{otherwise}\,, \end{cases}$$

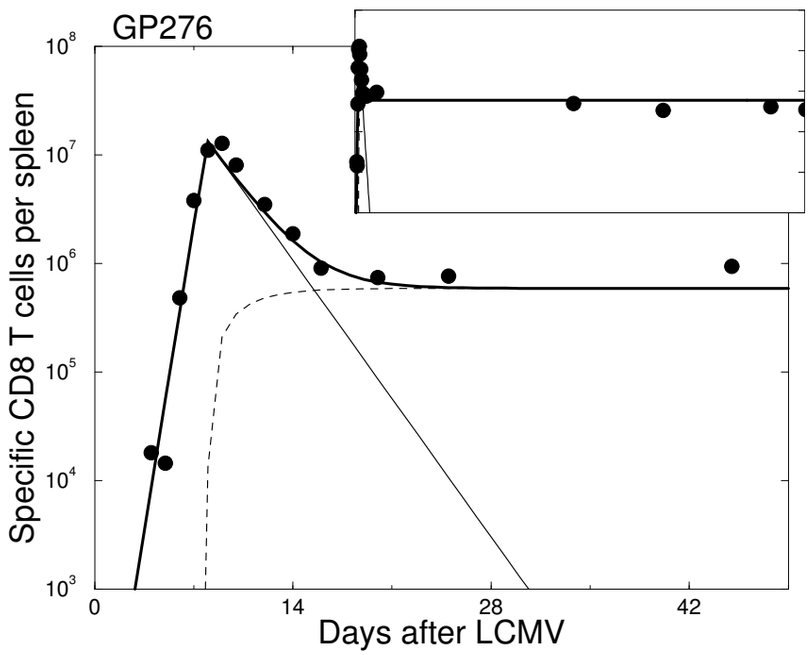


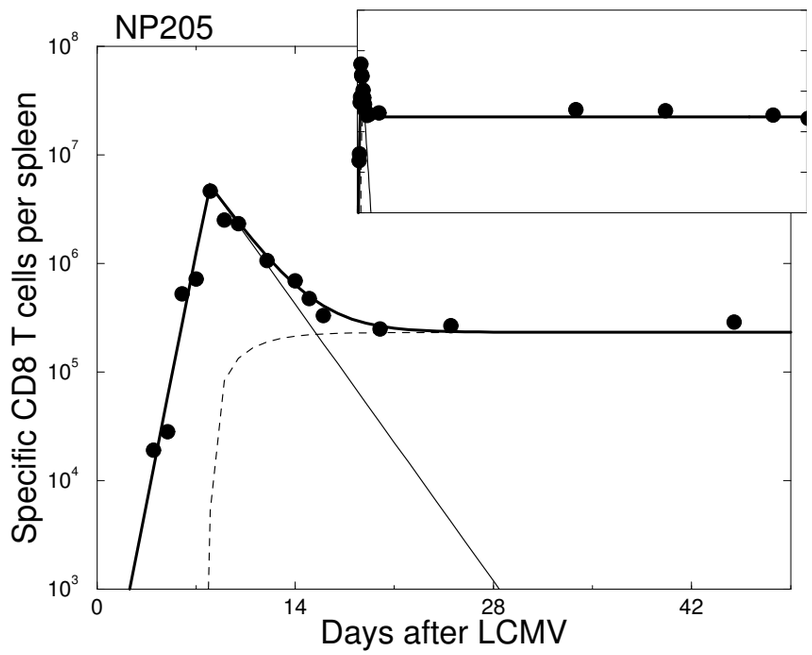
Fit model to data to see how parameters explain immunodominance (minimize SSQ)

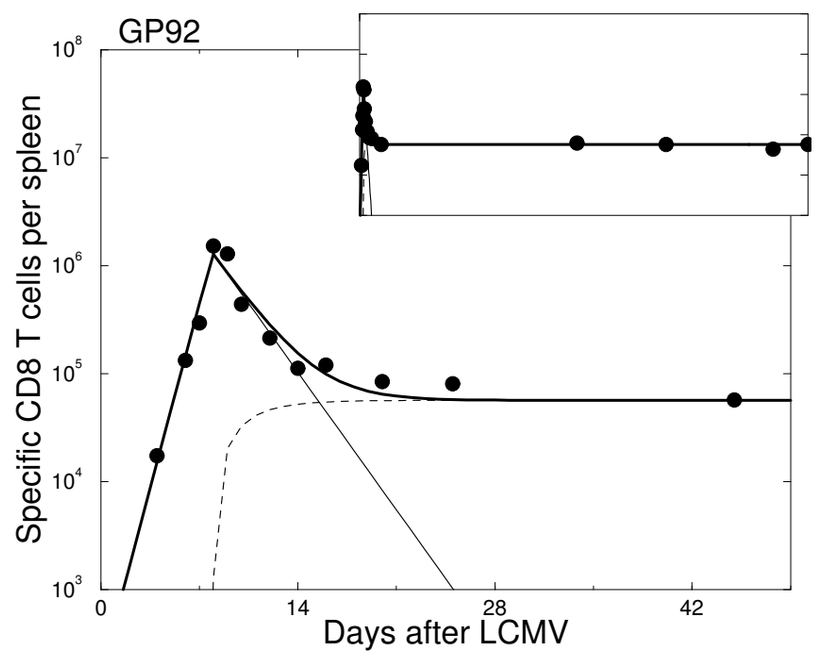










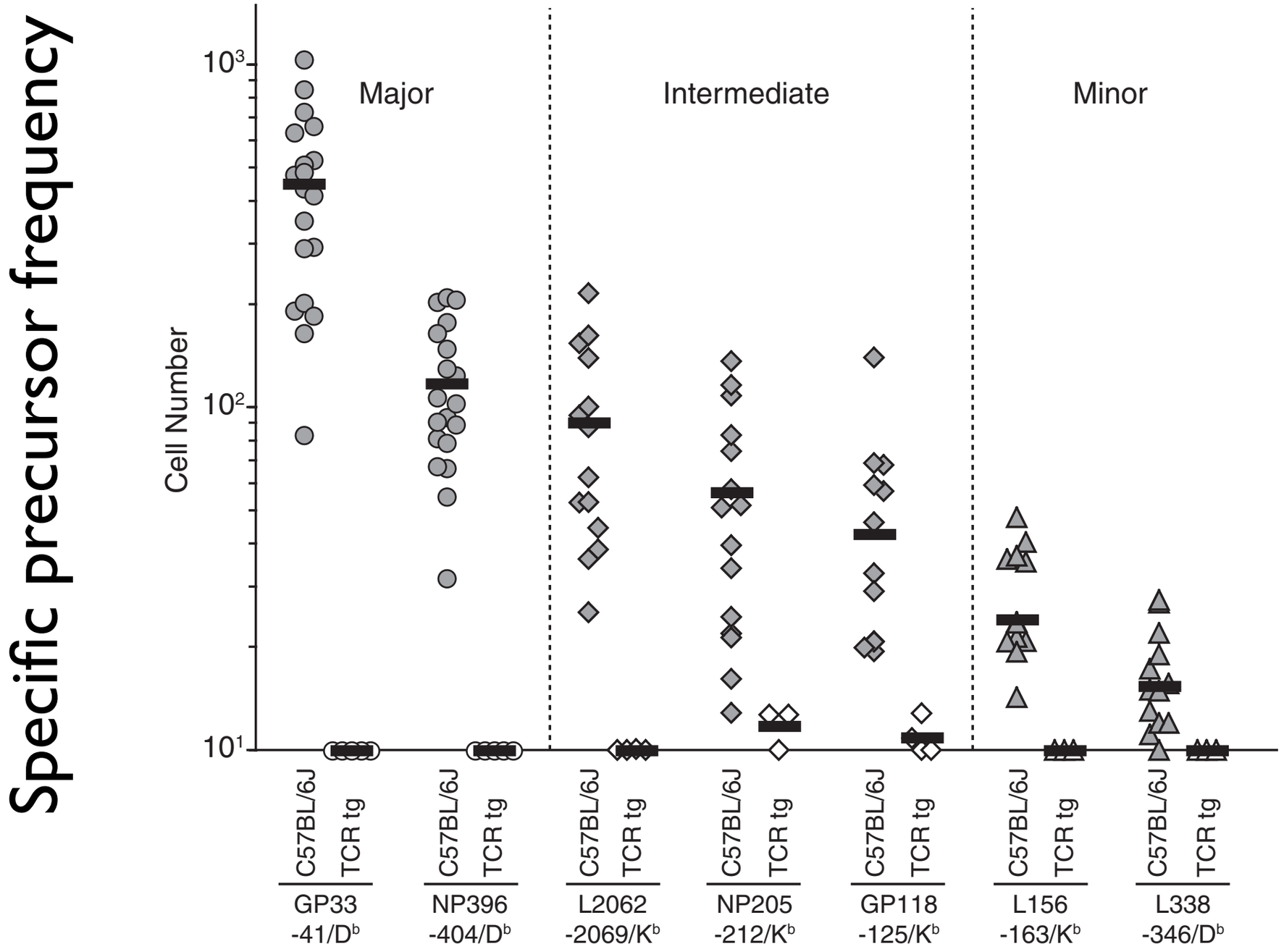


Parameter estimates

Name	Units	Value	95% C.I.
ρ_{GP33}	d^{-1}	1.89	1.73 — 2.08
ρ_{NP396}	d^{-1}	1.92	1.75 — 2.14
ρ_{GP118}	d^{-1}	1.86	1.60 — 2.21
ρ_{GP276}	d^{-1}	1.87	1.70 — 2.05
ρ_{NP205}	d^{-1}	1.52	1.37 — 1.69
ρ_{GP92}	d^{-1}	1.13	0.98 — 1.33
$A(0)_{\text{GP33}}$	cells	12.1	3.3 — 32.5
$A(0)_{\text{NP396}}$	cells	6.9	1.3 — 20.7
$A(0)_{\text{GP118}}$	cells	6.1	0.4 — 40.3
$A(0)_{\text{GP276}}$	cells	5.0	1.3 — 13.9
$A(0)_{\text{NP205}}$	cells	29.3	8.6 — 81.9
$A(0)_{\text{GP92}}$	cells	165.3	34.4 — 518.8
δ_A	d^{-1}	0.40	0.34 — 0.47
r	d^{-1}	0.018	0.015 — 0.022
T	days	7.9	7.8 — 8.1

Today you will estimates these parameters by yourself

Kotturi et al. J Immunology 2008



Goncalves et al. Molecular Immunology 2017:
GP33: 15244 and NP396: 9530 (dextramers, BM, careful expts)

Is T cell memory protective and, if so, how?

Most current vaccines provide protection via Abs (even if natural immunity is largely due to T cells).

Will we ever be able to develop vaccines triggering sufficient cellular immunity to provide protection to infection?

Malaria, AIDS, Hepatitis C

Numbers matter

Failure of vaccination to HIV/AIDS

HIV trial vaccines successfully boost $CD8^+$ T cell responses

CD8 response probably very important

(depletion expts, HLA, immune escape, reversions)

Merck trial failed and stopped (gag, pol, nef)

Acute phase of infection largely unaffected by vaccination

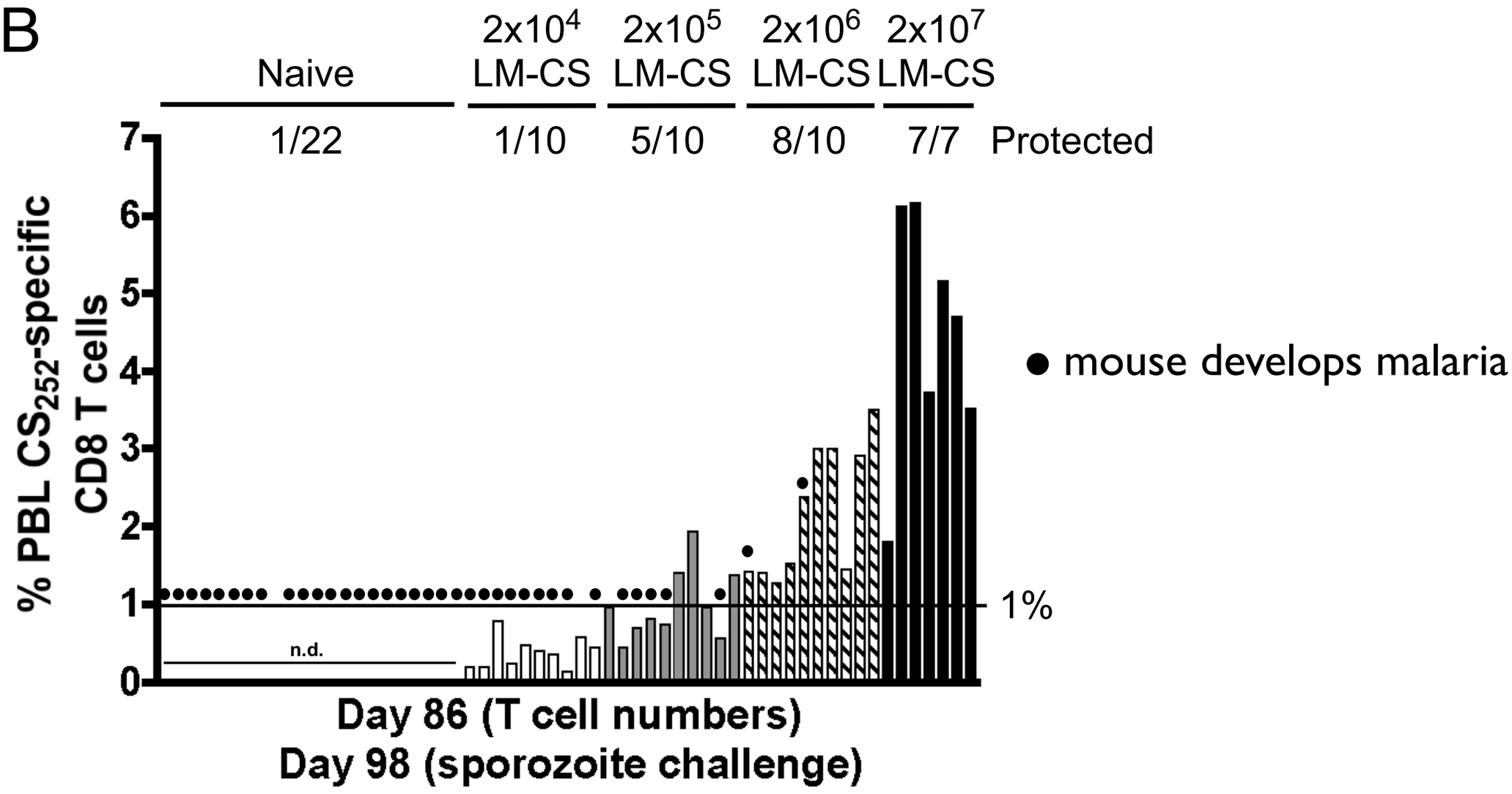
T cells do respond: failure not due to immune escape

Why are vaccines triggering cellular responses failing?

Which proteins would be protective?

Back to the drawing boards.

Long term protection by specific CTL to malaria



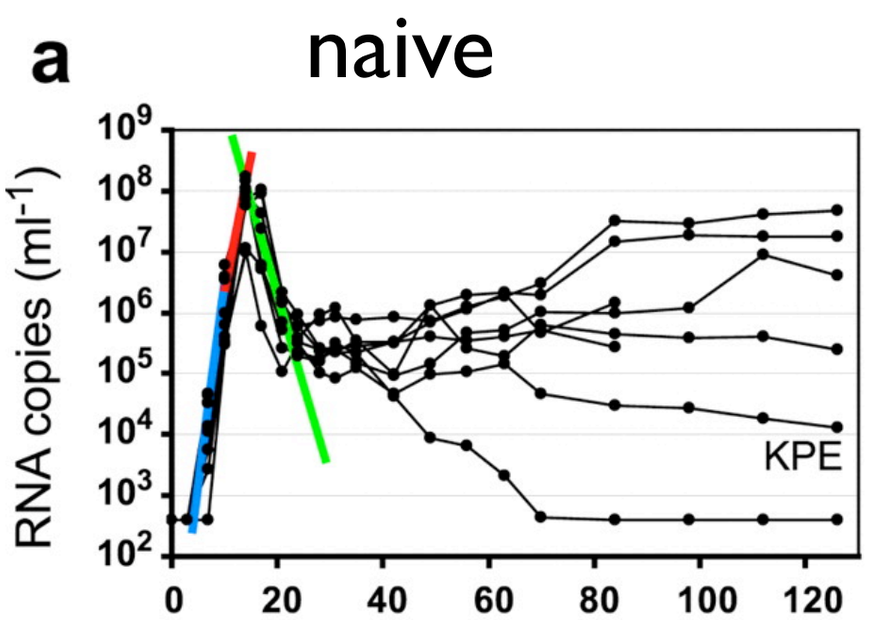
One mosquito bite: few hundred sporozoites in skin

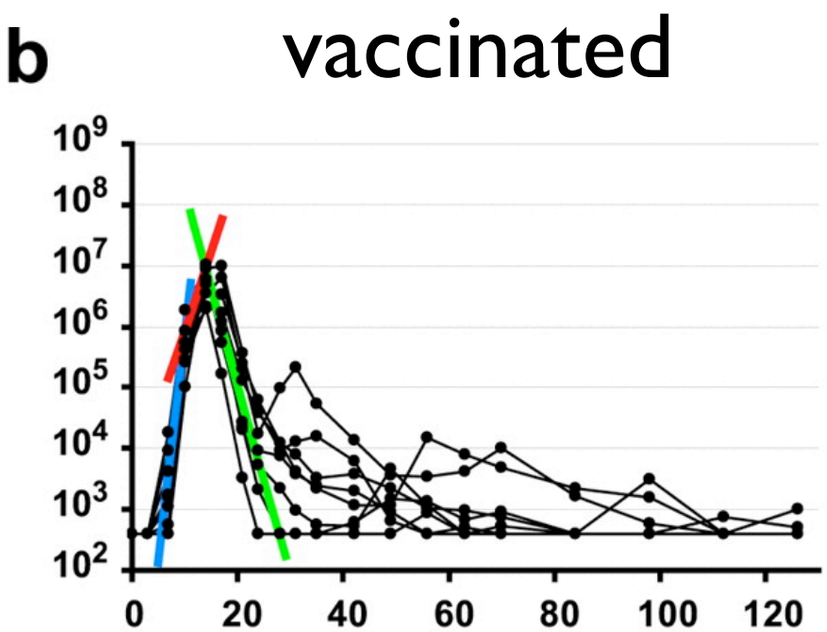
In mice only one in 10^6 (human 1:10^9) hepatocytes is infected and after two (6) days they start to produce blood stage parasites

Threshold of 1% in PBL (20% in total, 10^6 in spleen, $2x10^5$ in liver)

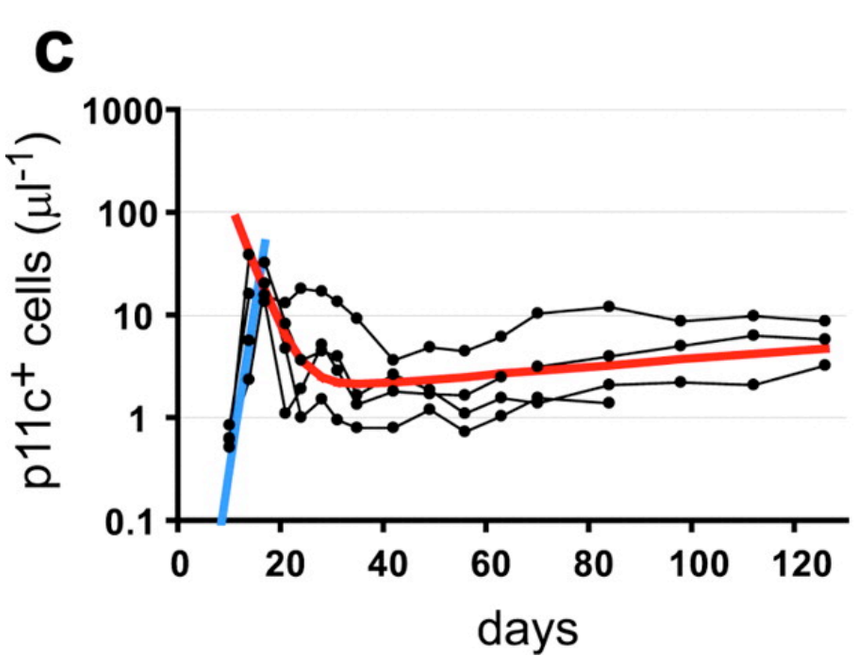
Schmidt et al PNAS 2008, PLoS Path 2010

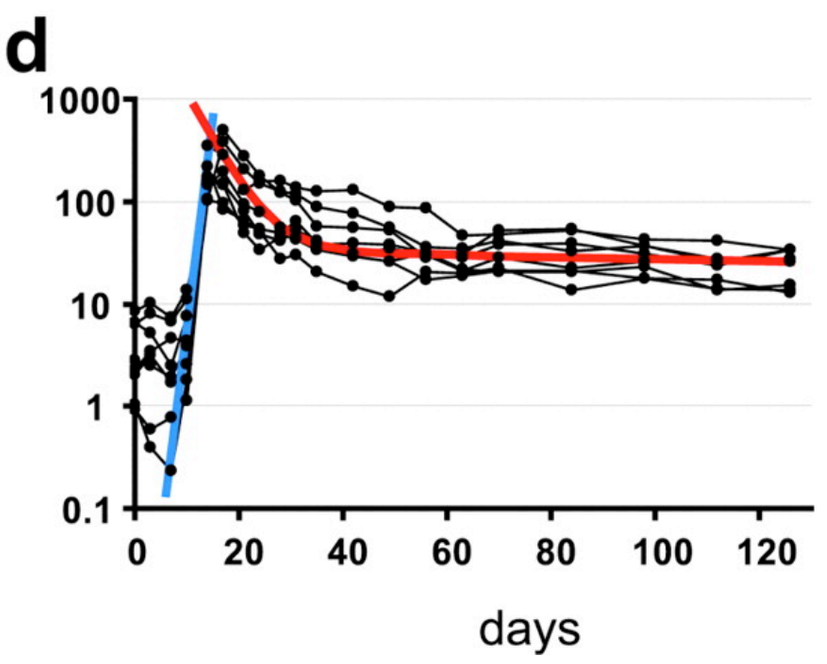
CD8 immune response to HIV/SIV





Virus rates:
replication: 1.7 d^{-1}
contraction: 0.7 d^{-1}





CD8$^+$ T cells:
expansion: 0.9 d^{-1}

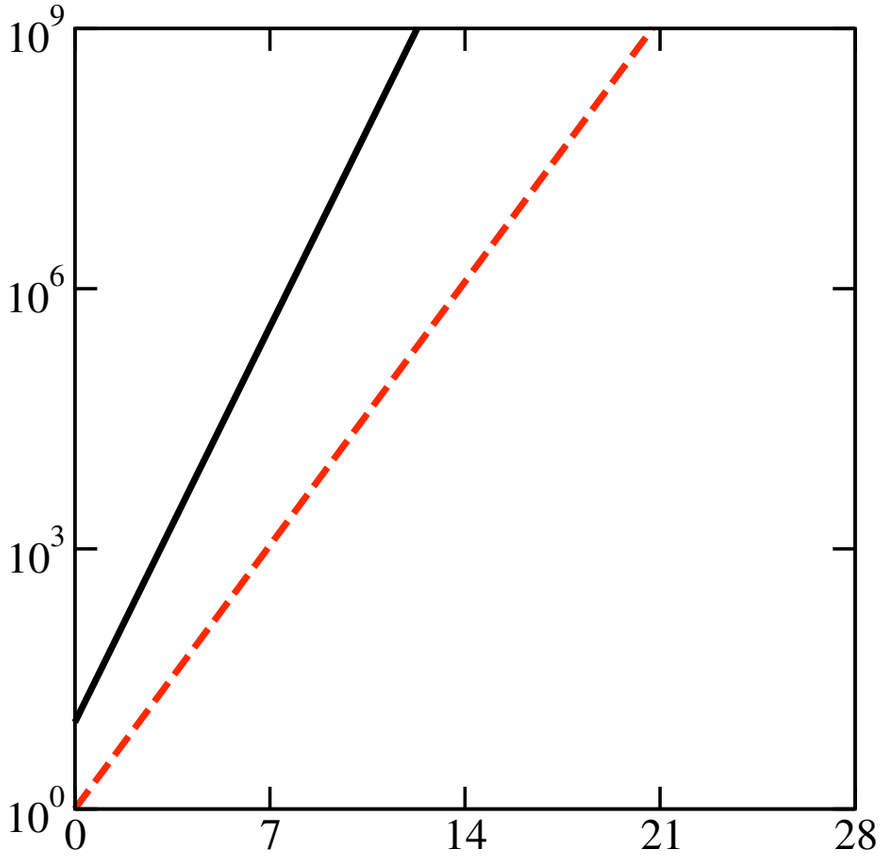
Acute SHIV-89.6P response in naive (left) or vaccinated (right) Rhesus monkeys (Data: Barouch.s00, Figure: Davenport.jv04).

A simple mathematical model

Simple model with pathogen growing faster than immune response

$$\frac{\mathrm{d}P}{\mathrm{d}t} = rP - \frac{kPE}{h+P} \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \ ,$$

where $r > \rho$, can typically not control the pathogen:



P: pathogen, **E**: response

Pilyugin.bmb00: general result for saturated responses

Mathematical explanation

At high pathogen densities the model

$$\frac{\mathrm{d}P}{\mathrm{d}t} = rP - \frac{kPE}{h+P} \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \ ,$$

approaches

$$\frac{\mathrm{d}P}{\mathrm{d}t} = rP - kE \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \ .$$

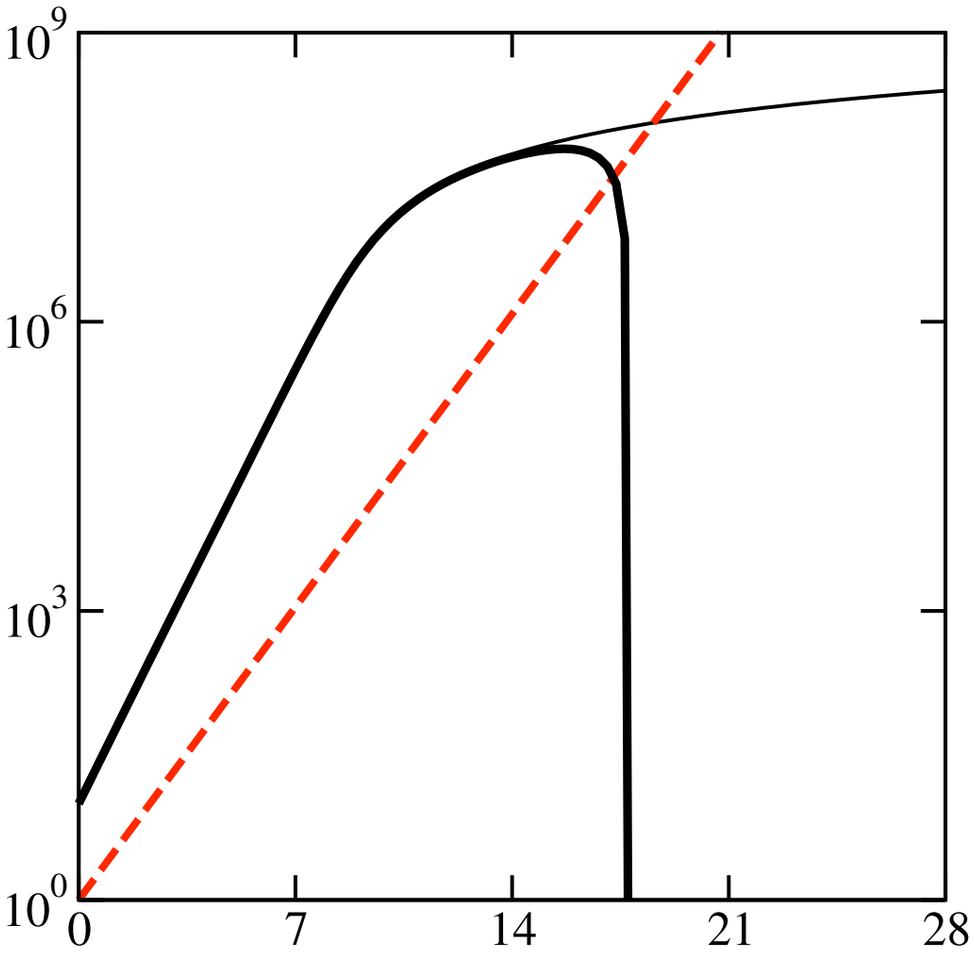
When P grows faster than E:

$$\frac{\mathrm{d}P}{\mathrm{d}t} > 0$$

See: Pilyugin.bmb00

Control only if pathogen is first limited by something else

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \frac{rP}{1+\epsilon P} - \frac{kPE}{h+P} \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \ ,$$



P: pathogen, **E**: response

P: pathogen in absence of response

SIV parameters: $r = 1.5$ d^{-1}, $\rho = 1$ d^{-1}, $k = 5$ d^{-1}.

Interpretation

CTL control only when the E:T ratio is large.

When pathogen replicates faster than CD8 T cells
this is difficult to achieve

Innate immunity or target cell limitation required to slow down pathogen

Antibodies are produced in vast amounts and can catch up

CTL can only control infections that are already controlled

(Note that this hinges upon saturation)

It's a numbers game

Individual CTL kill only a handful of target cells per day

In LCMV infected mice >10^7 CTL per spleen

HIV-infected patients can have10% specific CTL in blood,
healthy CMV+ carriers 10% cognate CD4 & CD8 T cells:
$0.1x10^{11}=10^{10}$ cognate $CD8^+$ T cells

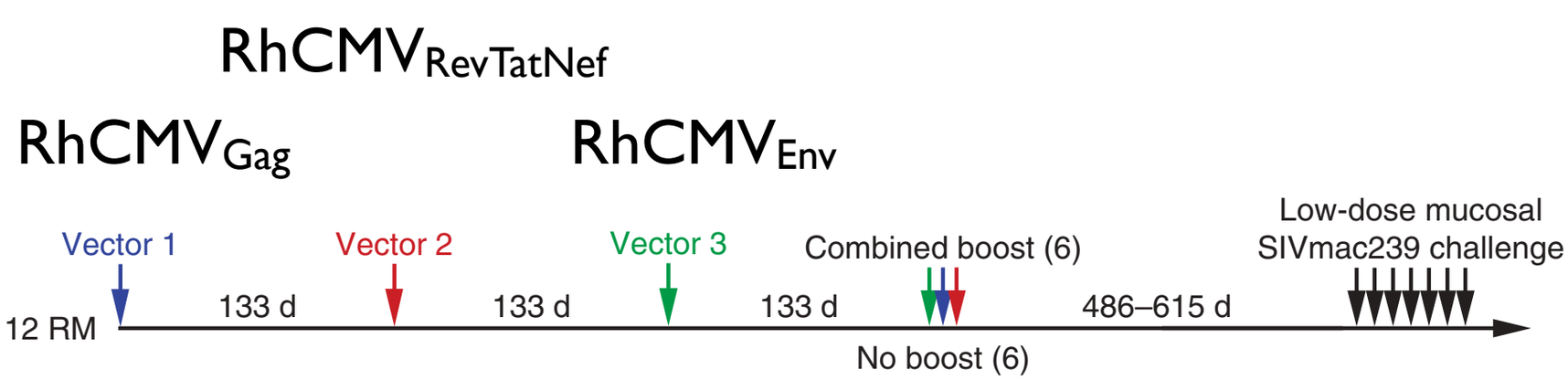
Apparently huge CTL populations required to control

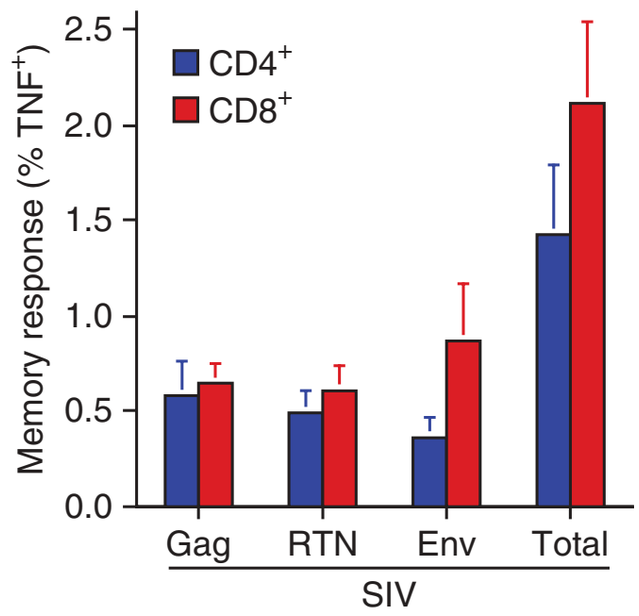
This amount of clonal expansion takes time

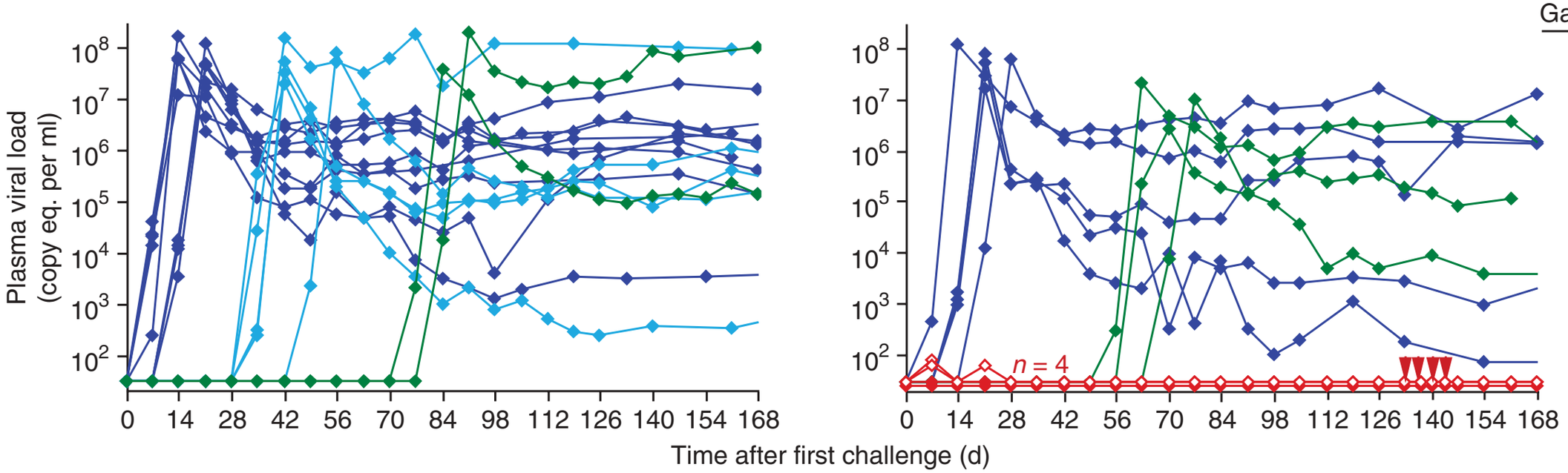
Expanding 10^3 cells into 10^{11} takes 18 days

(Every 10-fold expansion takes ln[10]=2.3 days if cells divide once d^{-1})

Persistent infection indeed works much better







SIV proteins in RhCMV causing persistent infection: 2% of the response

Challenge monkeys repeatedly with low intrarectal doses of SIVmac239

All 16 controls (left) infected, 4/12 vaccinees protected

Hansen,..., Picker, Nat Med 2009

Prime and Pull: localized T cell memory

The integration of T cell migration, differentiation and function

David Masopust and Jason M. Schenkel

Nature Reviews Immunology | AOP, published online 19 April 2013;

Sensing and alarm function of resident memory CD8+ T cells

Jason M Schenkel, Kathryn A Fraser, Vaiva Vezys & David Masopust

nature immunology 2013

A vaccine strategy that protects against genital herpes by establishing local memory T cells

Haina Shin[1] & Akiko Iwasaki[1]

15 NOVEMBER 2012 | VOL 491 | NATURE | 463

Long-lived epithelial immunity by tissue-resident memory T (T_{RM}) cells in the absence of persisting local antigen presentation

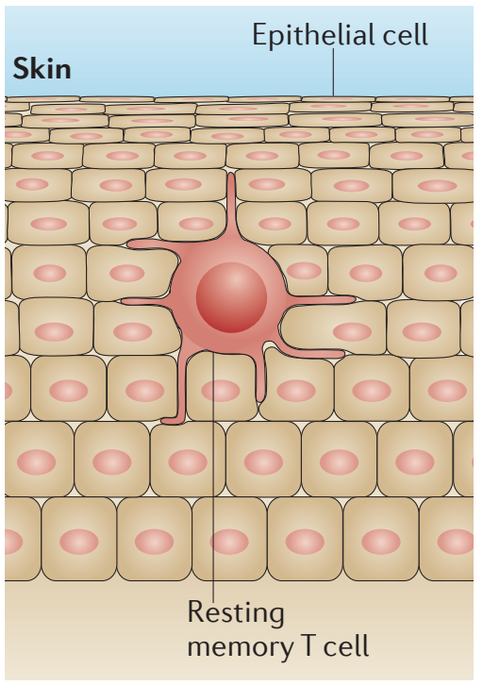
Laura K. Mackay, Angus T. Stock, Joel Z. Ma, Claerwen M. Jones, Stephen J. Kent, Scott N. Mueller, William R. Heath, Francis R. Carbone[1], and Thomas Gebhardt[1]

PNAS | **May 1, 2012** | vol. 109 | no. 18 | **7037–7042**

Tissue-resident memory CD8+ T cells continuously patrol skin epithelia to quickly recognize local antigen

Silvia Ariotti[a], Joost B. Beltman[b,1], Grzegorz Chodaczek[c,1], Mirjam E. Hoekstra[a], Anna E. van Beek[a], Raquel Gomez-Eerland[a], Laila Ritsma[d], Jacco van Rheenen[d], Athanasius F. M. Marée[e], Tomasz Zal[c], Rob J. de Boer[b], John B. A. G. Haanen[a], and Ton N. Schumacher[a,2]

PNAS 2012

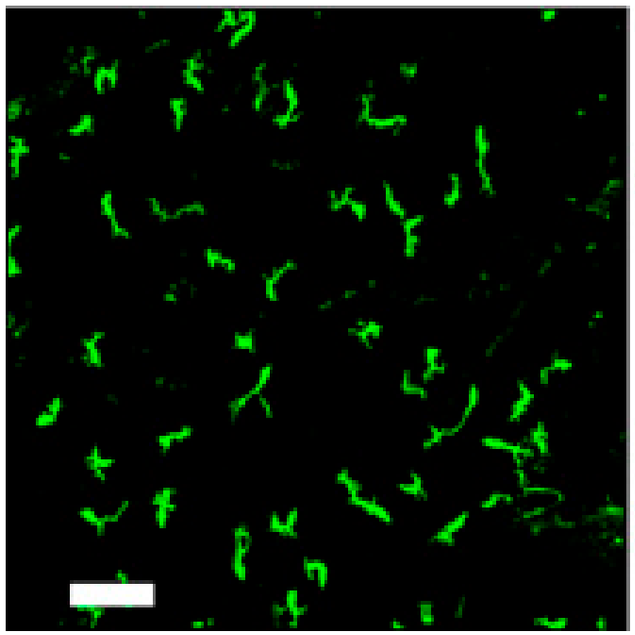


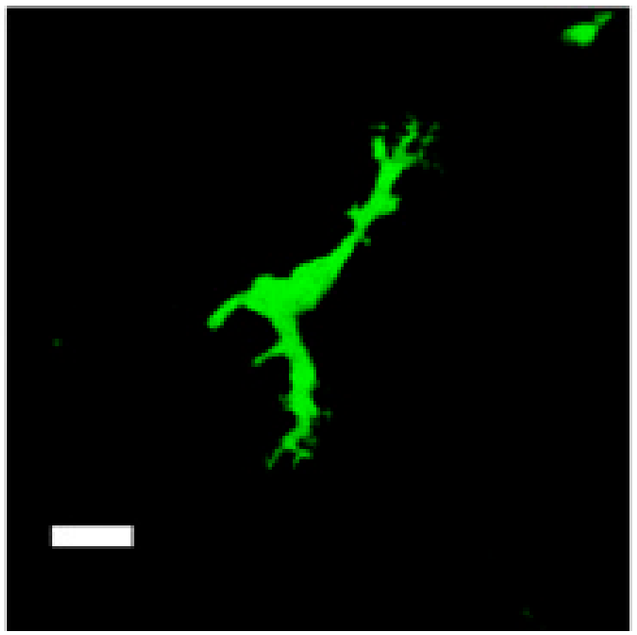
Different patterns of peripheral migration by memory CD4+ and CD8+ T cells

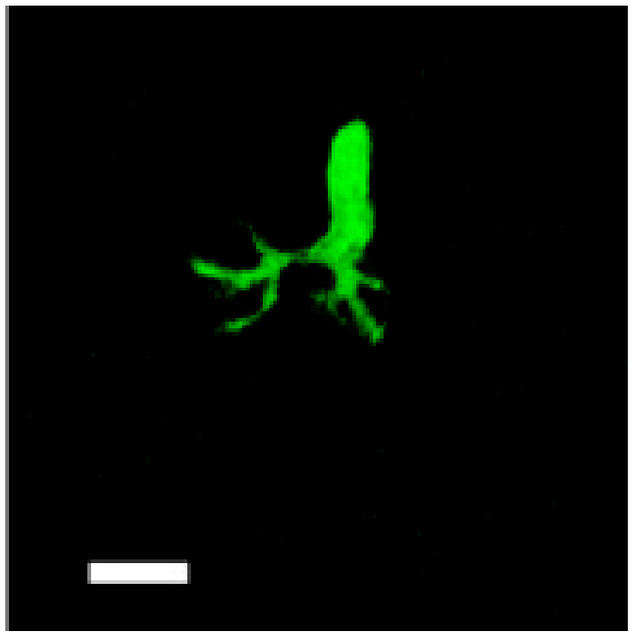
Nature 2011

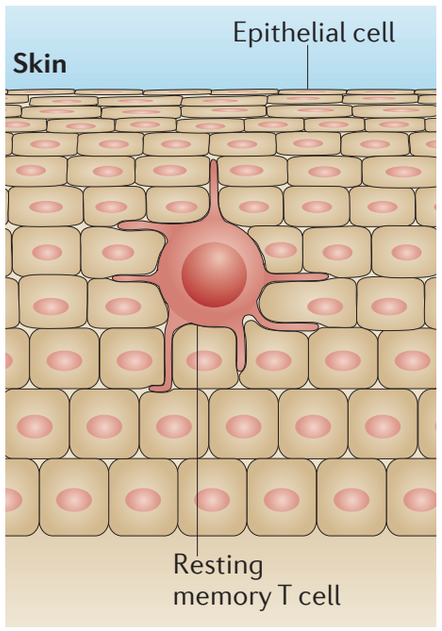
Thomas Gebhardt[1], Paul G. Whitney[1], Ali Zaid[1], Laura K. Mackay[1], Andrew G. Brooks[1], William R. Heath[1], Francis R. Carbone[1] & Scott N. Mueller[1]

Local CD8 memory T cells persist after acute infection





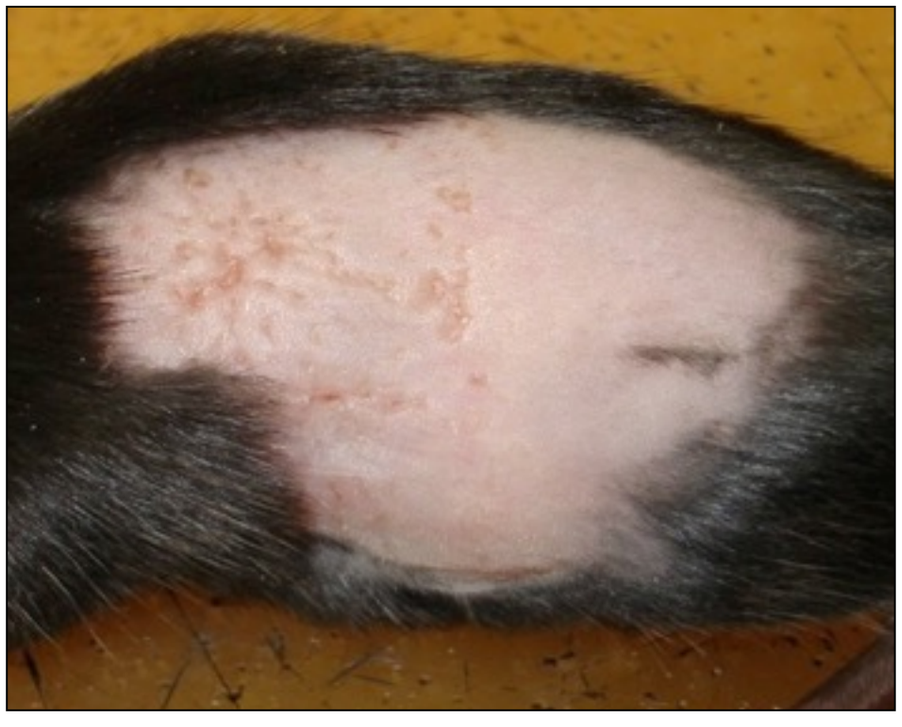




Use tattoo needle to induce very local HSV-1 infections in the epidermis layer of the skin.

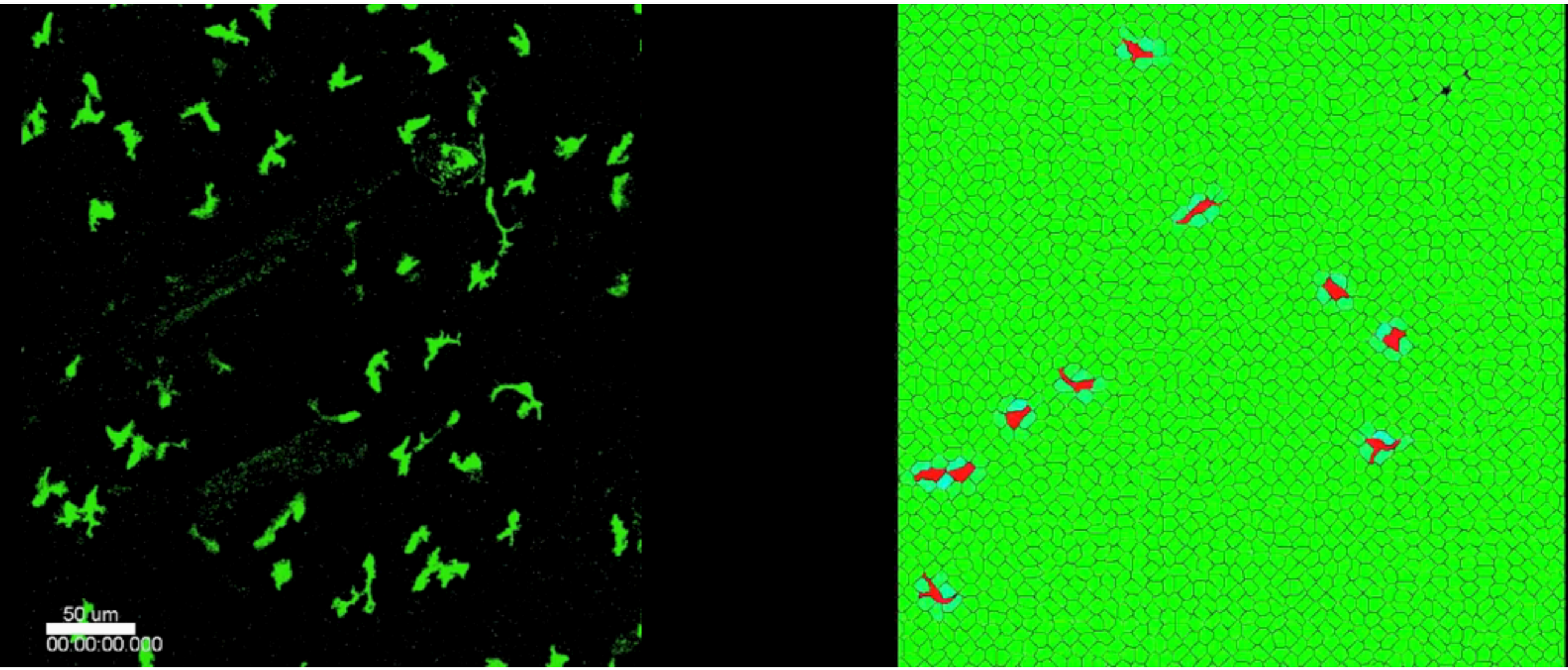
Dendritic memory $CD8^+$ T cells persist locally.

Good protection to reinfection in the same area, and no protection to reinfection on the other flank



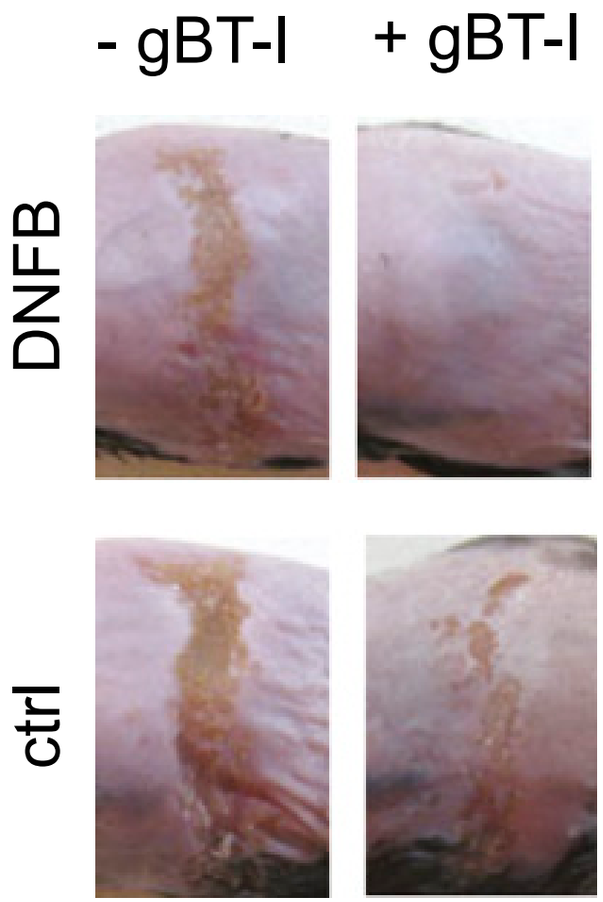
Ariotti PNAS 2012

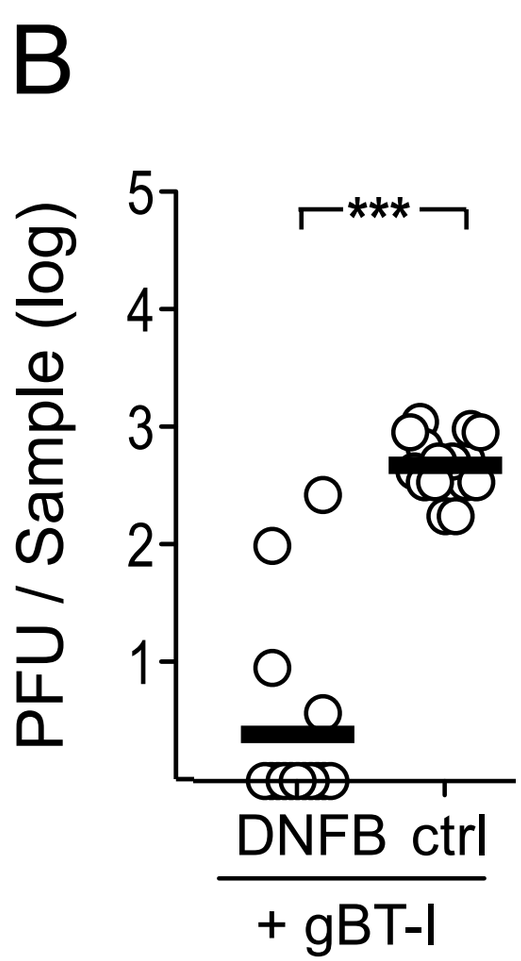
HSV specific memory T cells in skin epidermis



memory T cells squeeze themselves in between skin cells

Paint the skin of mice with 2,4-dinitrofluorobenzene (DNFB)





Mackay PNAS 2012

Transfer activated gBT-1 and paint skin with irritant.

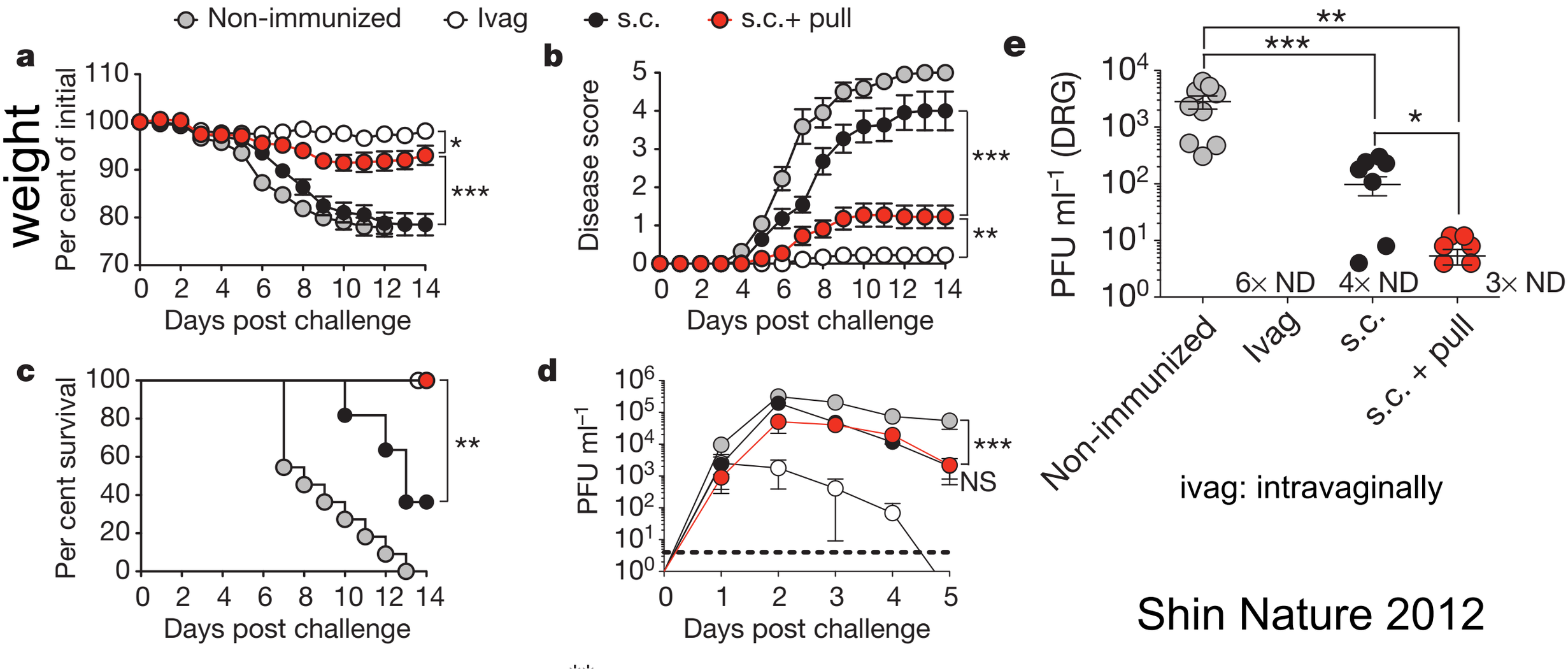
Activated $CD8^+$ T cells preferentially lodge into the inflamed skin.

Good protection to HSV infection in painted areas, but little protection to HSV infection in the other flank (ctrl)

Activated T cells home to inflamed tissues in a non-specific manner

Can we use this to improve vaccination?

Protection against lethal genital HSV infection



Shin Nature 2012

After pulling memory cells into FRT with chemokines:

good protection to lethal genital HSV

No sterilizing immunity, but protection of dorsal route ganglia (DRG)

Mackay [PNAS2012]: use **spermicide** components for pulling cognate T cells into FRT: protection from genital HSV infection.