

Lymph node swelling combined with temporary effector T cell retention aids T cell response in a model of adaptive immunity

Supplementary File 3 : Supplementary Results A

Supplementary figures for results from baseline calibration, model validation and LN swelling simulations.

Fig A Captured phases of TC trafficking and response to AgDC stimuli. Changes in proliferation and differentiation continued after the initial stimulus was no longer present. TC recruitment and TC egress changes also accompanied the response.

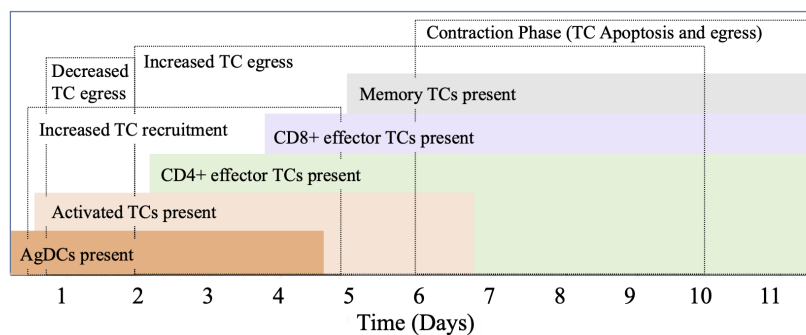


Fig B TC responses *in-silico* and *in-vivo* when proportion of cognate TCs was varied. i. The CD4⁺ magnitude of response in the dLNs of mice post-antigen injection correlated to estimated starting frequency of cognate TCs in a sample of 1×10^7 TCs [1]. ii. Results *in-silico* showed an overall increase in cognate CD4⁺ TC response with increasing F_{cog} ($n=8$). Simulations using a wider range of F_{cog} values (iii, iv) confirmed total cognate CD4⁺ TCs and CD8⁺ TCs increased linearly with F_{cog} . v. Mice were infected with VSV-M45 or VSV-ova with starting precursor CD8⁺ frequencies of 7×10^{-5} , 8×10^{-5} and 13×10^{-5} respectively. The peak number of resulting TCs as a percent of overall CD8⁺ TCs present is shown [2]. vi. Simulations using the same F_{cog} *in-silico* showed a similar increasing trend in cognate CD8⁺ TCs with similar increase rate.

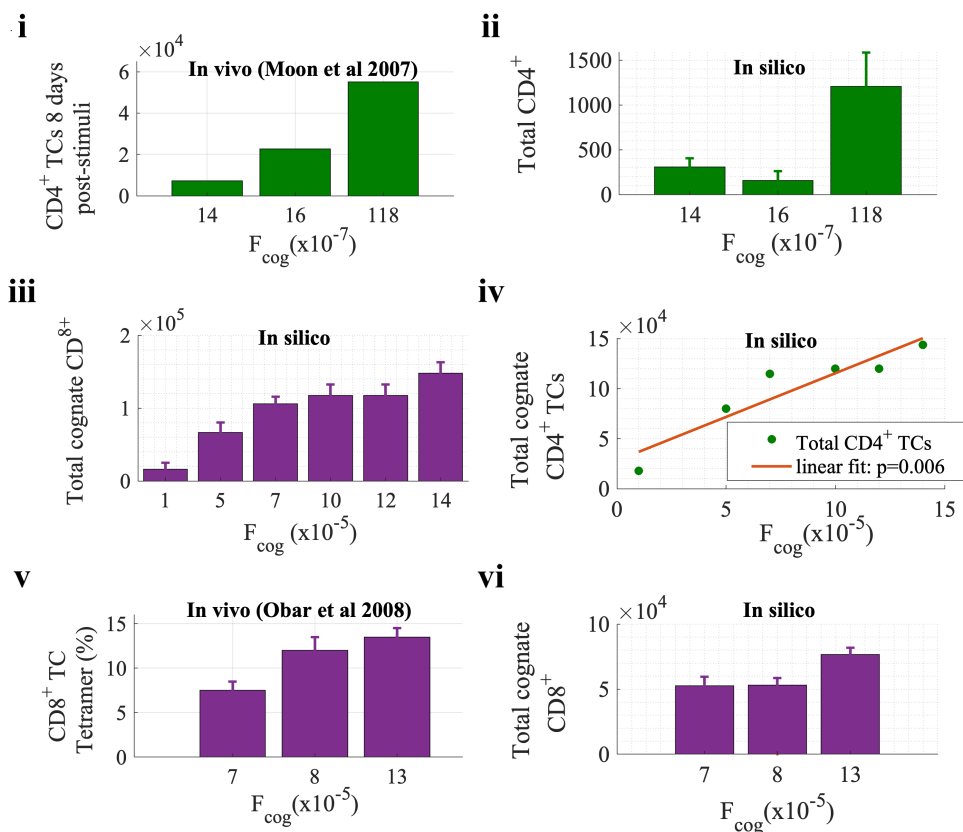


Fig C TC responses *in-silico* and *in-vivo* when a stimulus is abruptly abolished. i. The LNs of transgenic rats were injected with OT-1 CD8⁺ TCs specific for agDCs that were subsequently injected. The lifespan of the agDCs were curtailed using DT injection at 1hr and 12hrs and the change in subsequent CD8⁺ effector TC response recorded. Adapted from Prlic et al 2006 [3]. ii. The simulated disrupted input stimuli achieved by curtailing the 60hr DC influx at 12±2hr. iii-iv. The results of simulations (n=8). Mean (±SEM) CD8⁺ TCs were reduced 91% when the stimulus was curtailed at 12hrs compared to sustained entry for 60hrs. iv. individual CD8⁺ TC responses varied by a factor of 10 in an all or nothing response manner.

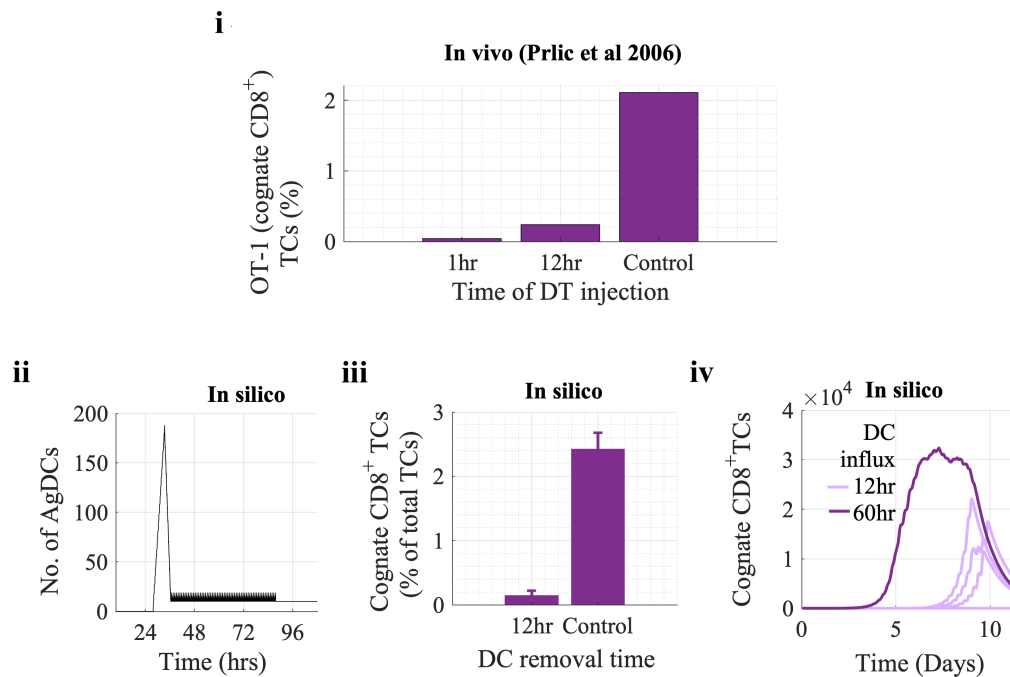


Fig D TC responses *in-silico* and *in-vivo* when the DC stimuli (no. of DCs applied as a fraction of initial TCs present, ϕ_{DC}) is varied. The estimated percentage of CD8⁺ TCs that underwent a proliferative response (i) in the LNs of chimeric mice 7 days post-injection with antigen LM-GP33 and (ii) in cell culture post-application of DCs [4]. (iii) Analysis of *in-silico* CD8⁺ TC response at low doses showed a significant response (1×10^4 total cognate CD8⁺ TCs) or no proliferative response at all (<10 cognate CD8⁺ TCs). (iv) *In-silico* simulations increasing the proportion of DCs resulted in increasing numbers of cognate CD8⁺ TCs that plateaued as the DC dose increased.

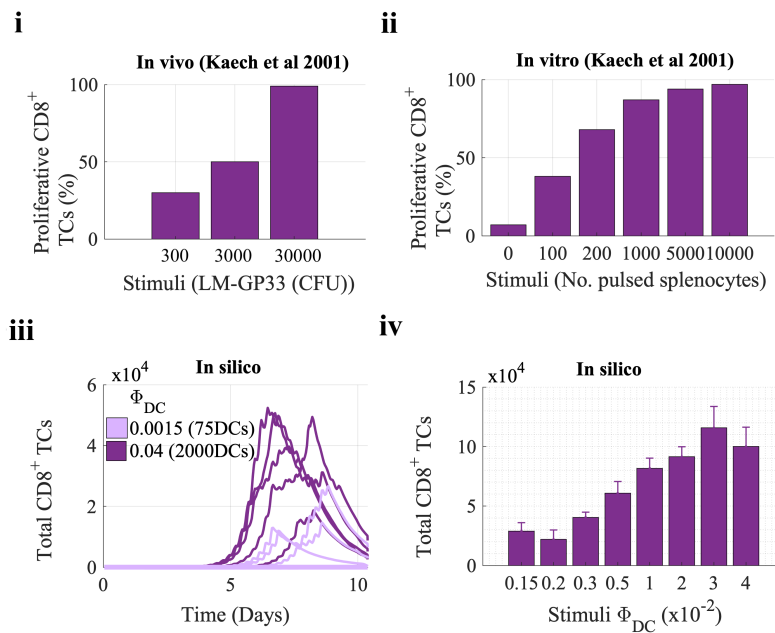
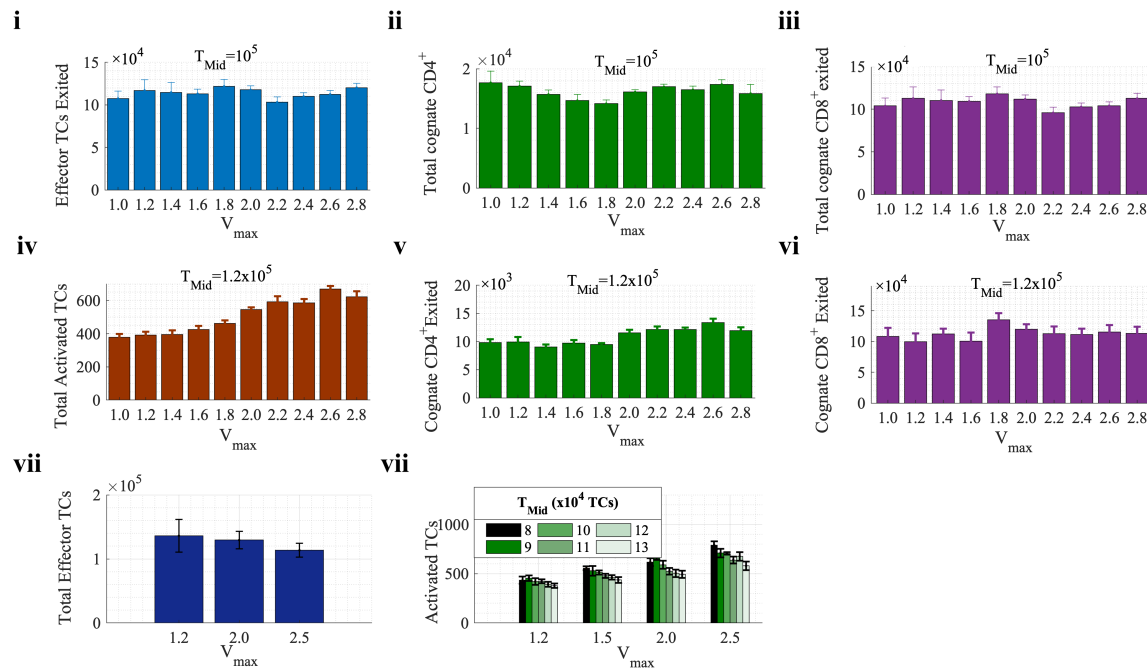


Fig E Supplementary results when varying maximal swelling (V_{max}) and TC number required to reach half V_{max} (T_{mid}). With default $T_{mid}=10^5$ TCs, no correlation was observed between V_{max} and (i) effector TCs exited, (ii) total cognate CD4⁺ TCs and (iii) total cognate CD8⁺ exited. (iv) When T_{mid} was increased to 1.2×10^5 TCs, TC activation increased with maximal swelling ($R^2=0.96$, $p=9.67 \times 10^{-6}$), (v) cognate CD4⁺ TCs exited weakly correlated with V_{max} ($R^2=0.71$, $p=0.002$) and (vi) cognate CD8⁺ TCs exited showed no significant correlation. (vii) Increasing (V_{max}) from 1.2 to 2.0 decreased effector TC number by 17% and to 2.5 by 5%. (viii) Activation of TCs increased with V_{max} but negatively correlated with T_{mid} ($R^2=0.78, 0.99, 0.84, 0.84$ for $V_{max}=1.2, 1.5, 2.0$ and 2.5 respectively, $p=1.5 \times 10^{-5}, 1.5 \times 10^{-5}, 0.01, 0.01$).



References

- [1] Moon JJ, Chu HH, Pepper M, McSorley SJ, Jameson SC, Kedl RM, et al. Naive CD4(+) T cell frequency varies for different epitopes and predicts repertoire diversity and response magnitude. *Immunity*. 2007 08;27(2):203–213.
- [2] Obar JJ, Khanna KM, Lefrançois L. Endogenous naive CD8+ T cell precursor frequency regulates primary and memory responses to infection. *Immunity*. 2008 06;28(6):859–869.
- [3] Prlic M, Hernandez-Hoyos G, Bevan MJ. Duration of the initial TCR stimulus controls the magnitude but not functionality of the CD8+ T cell response. *Journal of Experimental Medicine*. 2006;203(9):2135–2143.
- [4] Kaech SM, Ahmed R. Memory CD8+ T cell differentiation: initial antigen encounter triggers a developmental program in naïve cells. *Nature Immunology*. 2001 05;2:415–22.