Modelling the effects of lymph node swelling on T-cell response.

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.

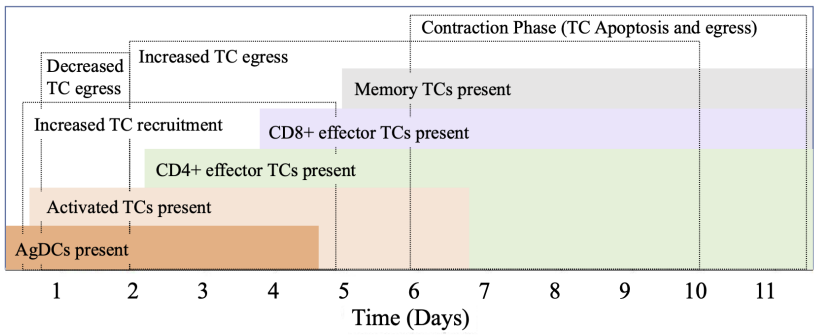


Fig B TC responses *in-silico* and *in-vivo* when proportion of cognate TCs was varied. i. The $CD4^+$ magnitude of response in the dLNs of mice post-antigen injection correlated to estimated starting frequency of cognate TCs in a sample of $1x10^7$ TCs [1]. ii. Results *in-silico* showed an overall 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 $7x10^{-5}$, $8x10^{-5}$ and $13x10^{-5}$ 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.

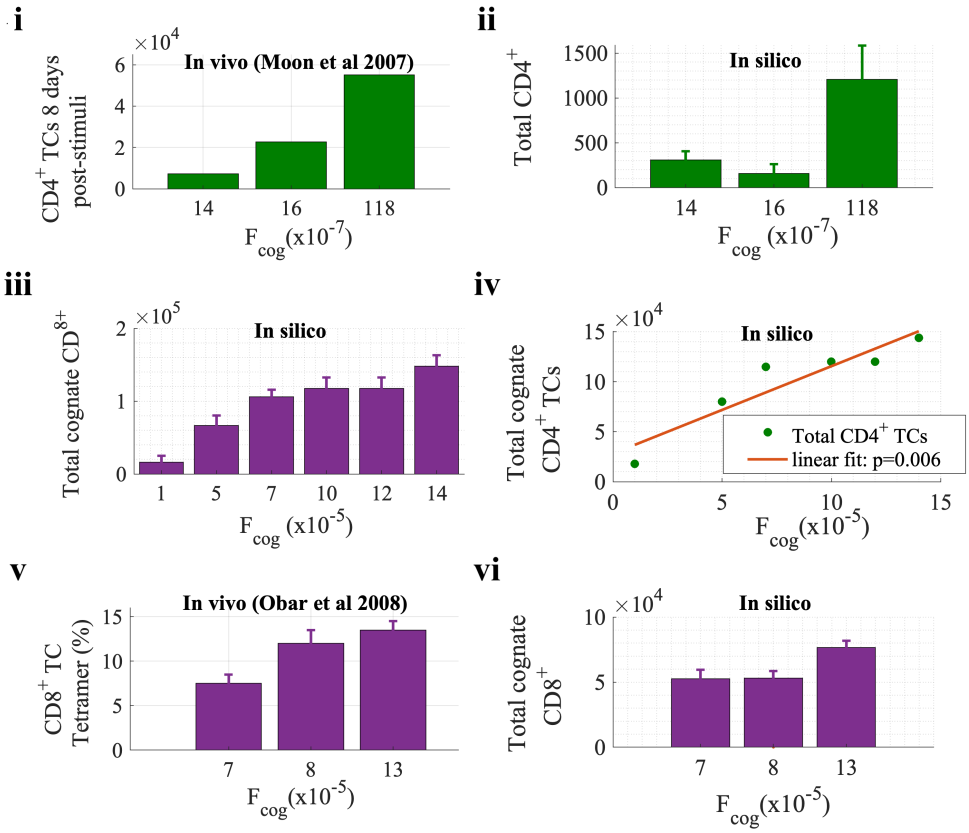


Fig C TC responses *in-silico* and *in-vivo* when a stimulus is abruptly abolished. i. The LNs of transgenic rats were injected with OT-1 $CD8^+$ TCs specific for agDCs that were subsequently injected. The lifespan of the agDCs were curtailed using DT injection at 1hr and 12hrs and the change in subsequent $CD8^+$ 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.

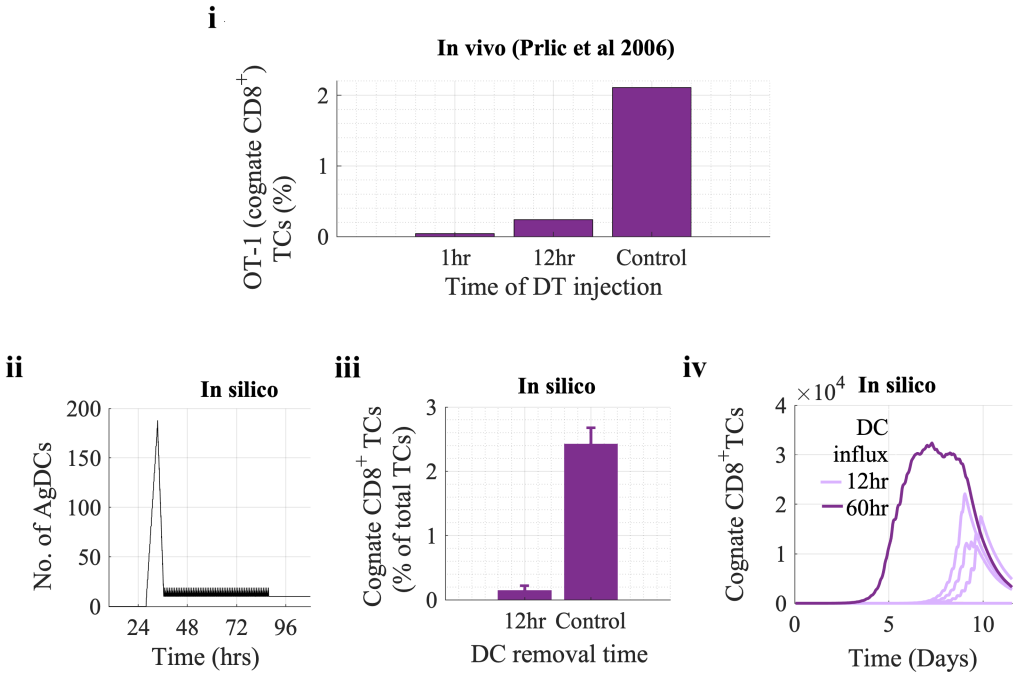


Fig D TC responses *in-silico* and *in-vivo* when the DC stimuli (no. of DCs applied as a fraction of initial TCs present, (ϕDC)) is varied. The estimated percentage of $CD8^+$ TCs that underwent a proliferative response (i) in the LNs of chimeric mice 7 days post-injection with antigen LM-GP33 and (ii) in cell culture post-application of DCs [4]. (iii) Analysis of *in-silico* $CD8^+$ TC response at low doses showed a significant response ($1x10^4$ 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.

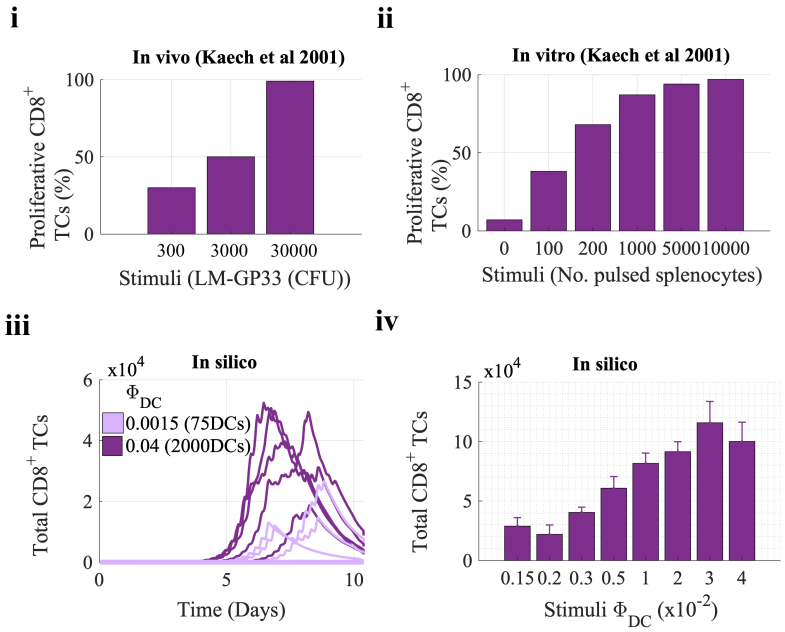
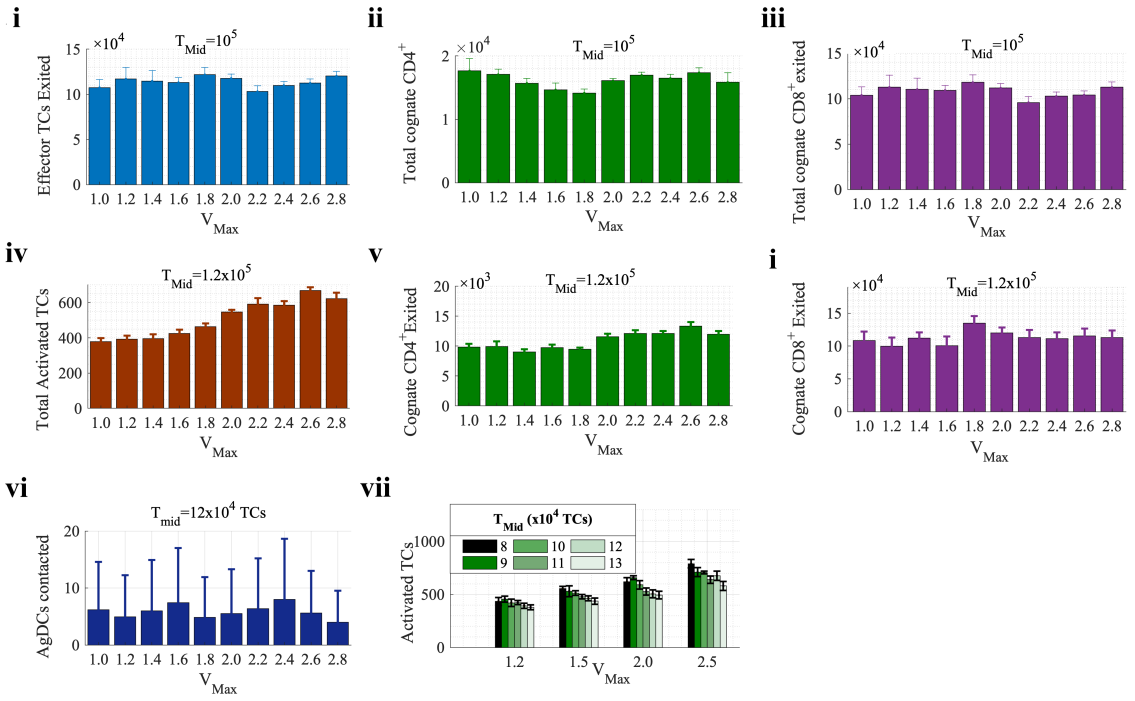


Fig E Supplementary results when varying maximal swelling (V_{max}) and TC number required to reach half V_{max} (T_{mid}). With default T_{mid}=10^5 TCs, no correlation was observed between V_{max} and (i) effector TCs exited, (ii) total cognate $CD4^+$ TCs and (iii) total cognate $CD8^+$ exited. (iv) When T_{mid} was increased to 1.2 x10^5 TCs, TC activation increased with maximal swelling (R^2=0.96, p=9.67x10^{-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) No trend was identified between number of agDCs each cognate TC has contacted and swelling at day 3. (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=1.5x10^{-5}, 1.5x10^{-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.

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