

Disclosure

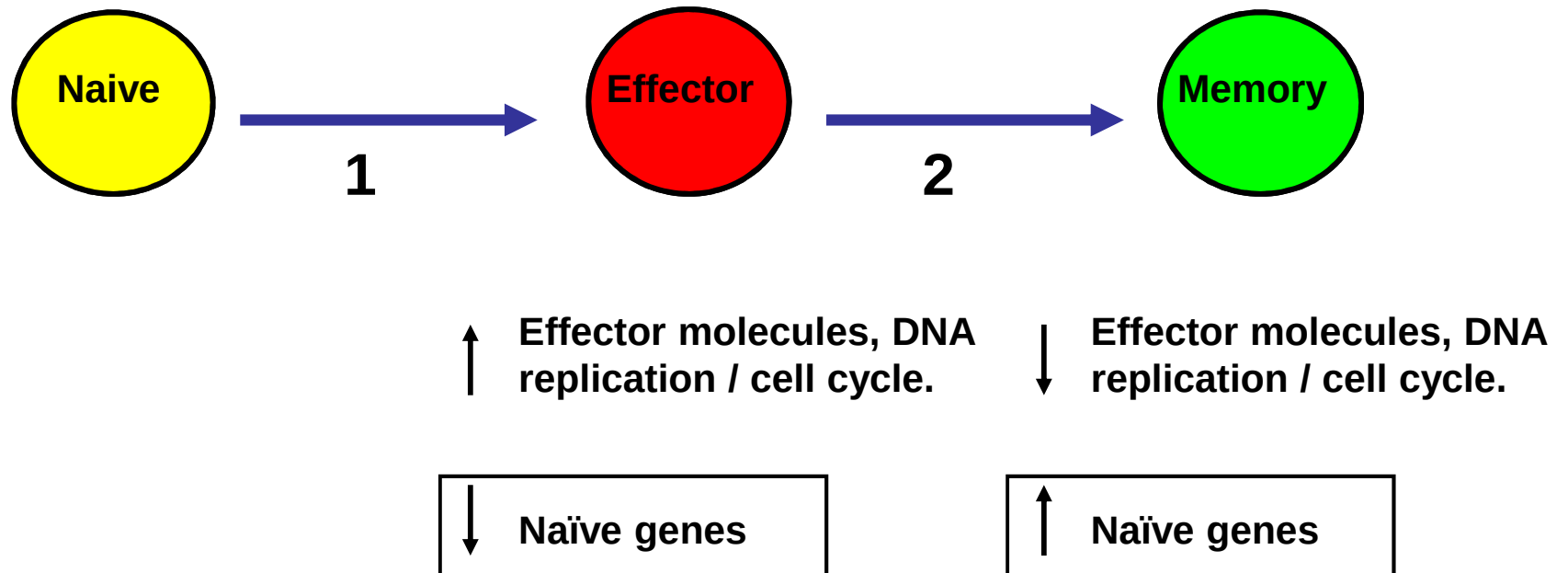
Patents on PD-1

Understanding Memory CD8 T Cell Differentiation

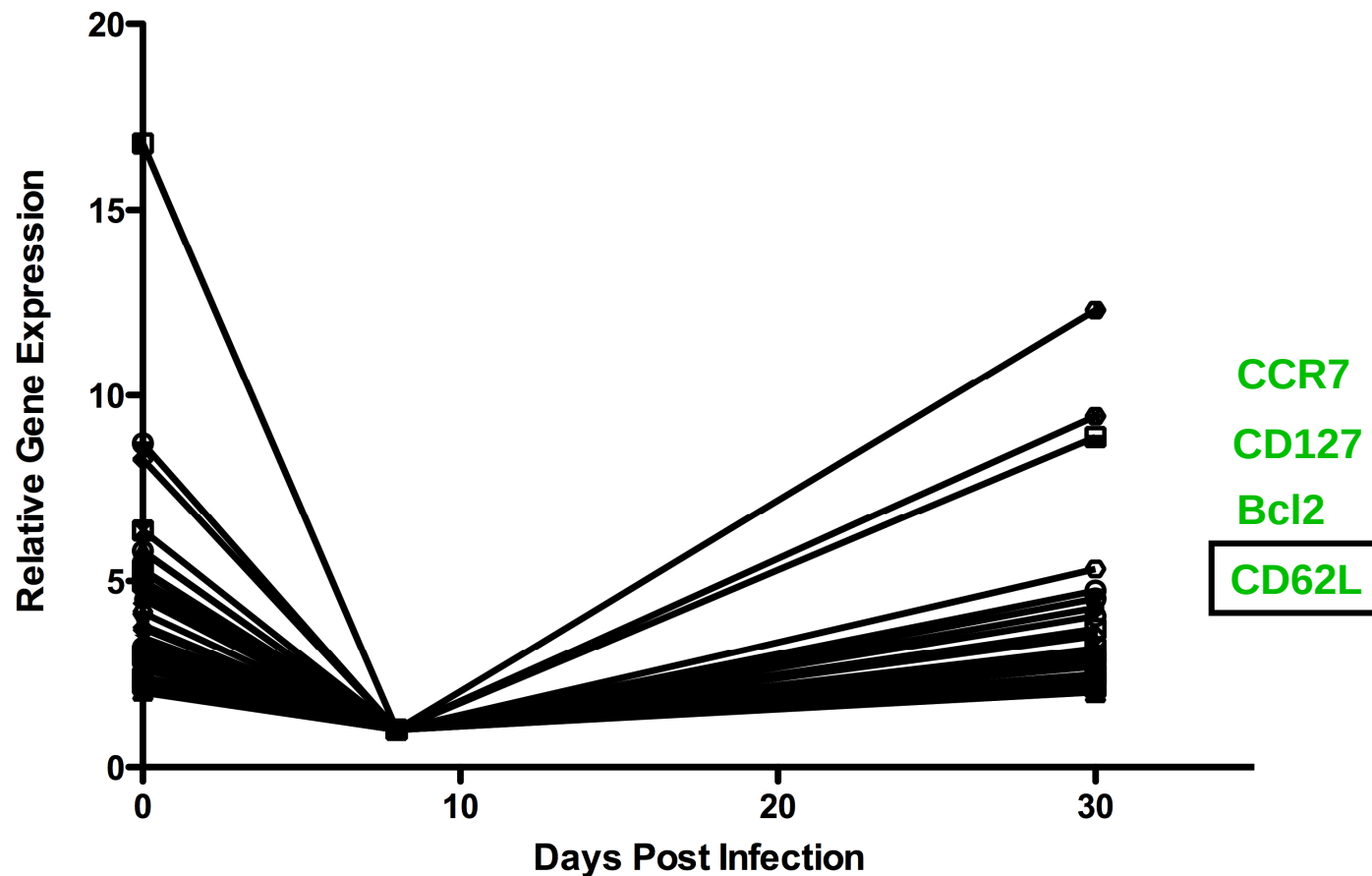
***Implications for Cancer
Immunotherapy ?***

Memory CD8 T Cell Differentiation

Two distinct stages of differentiation!



Becoming Naive Again (on-off-on)

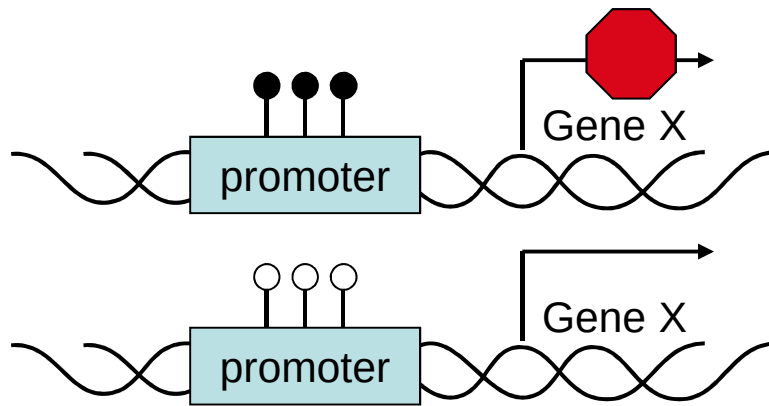


Epigenetic Regulation

Epigenetic Mark

Gene Expression

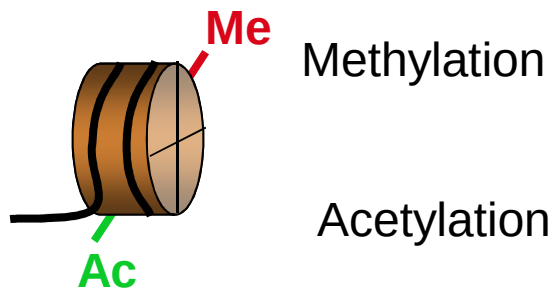
1. DNA Methylation



↓ *Transcriptional Inhibition*

↑ *Transcriptional Activation*

2. Histone Modifications

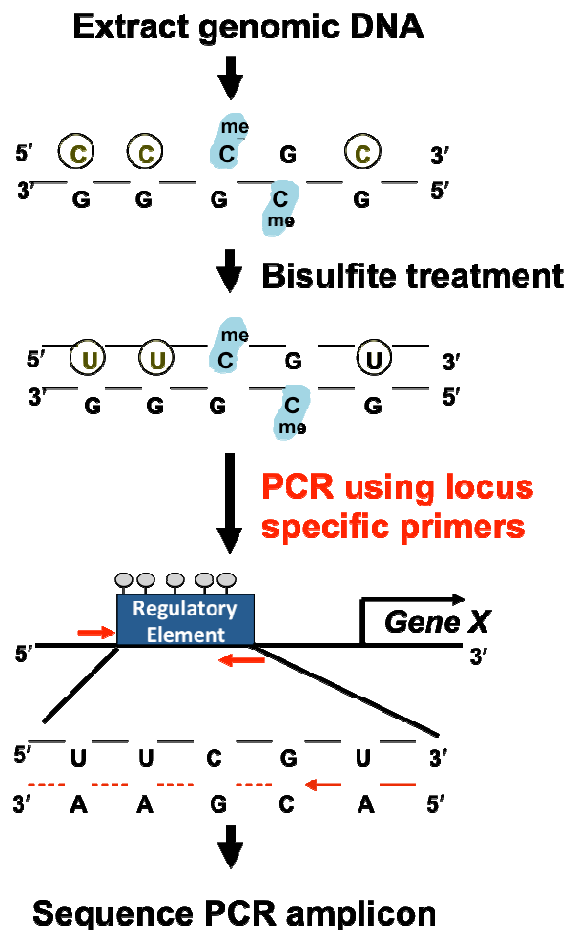


↓ *Repressive Marks*

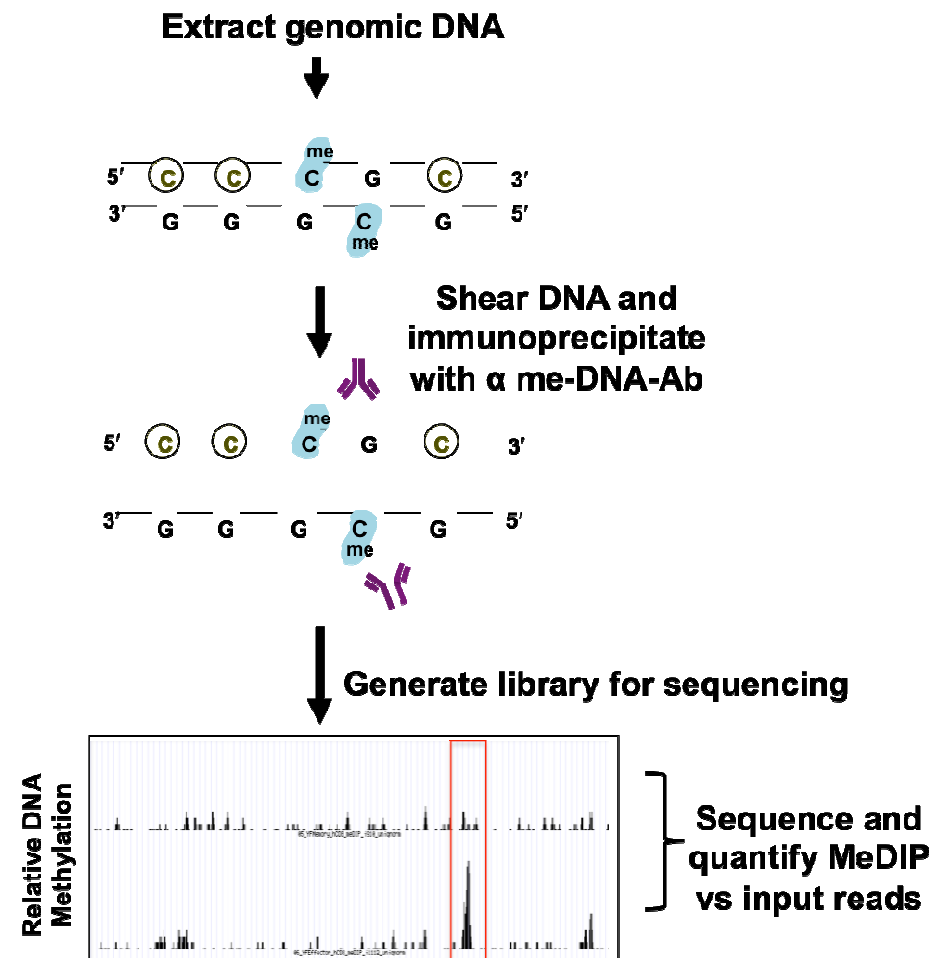
↑ *Active Marks*

DNA methylation during memory CD8 T cell differentiation

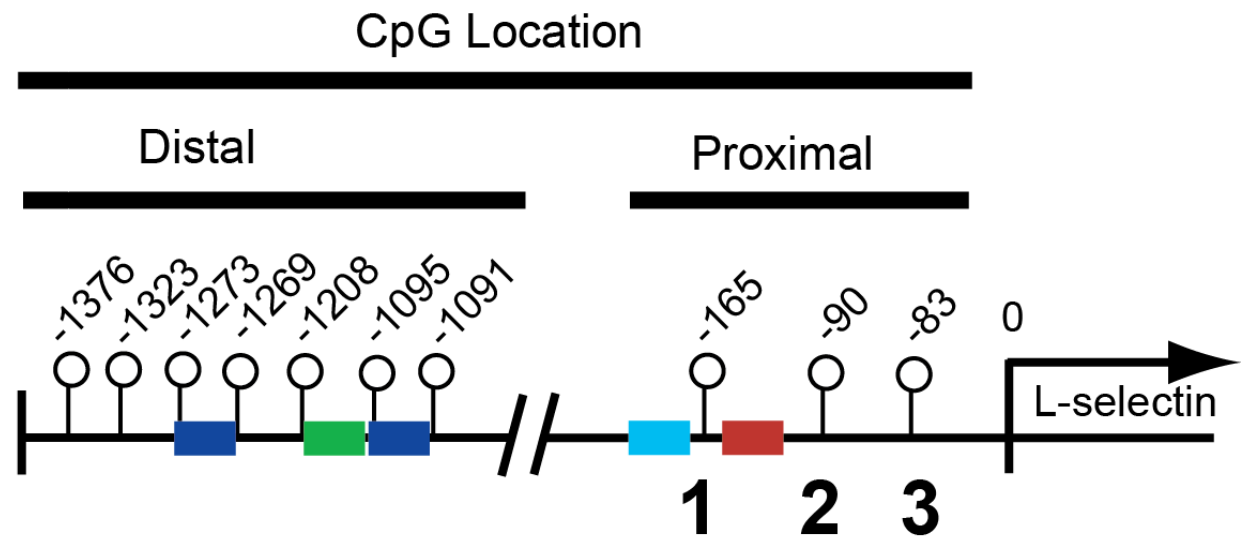
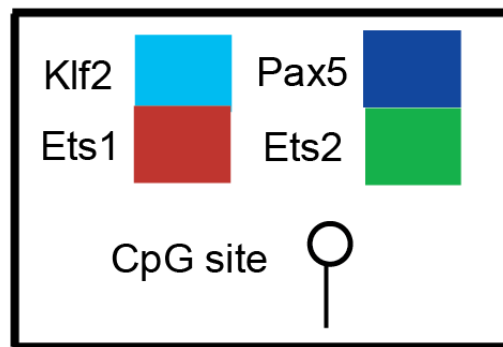
Loci Specific



Genome Wide

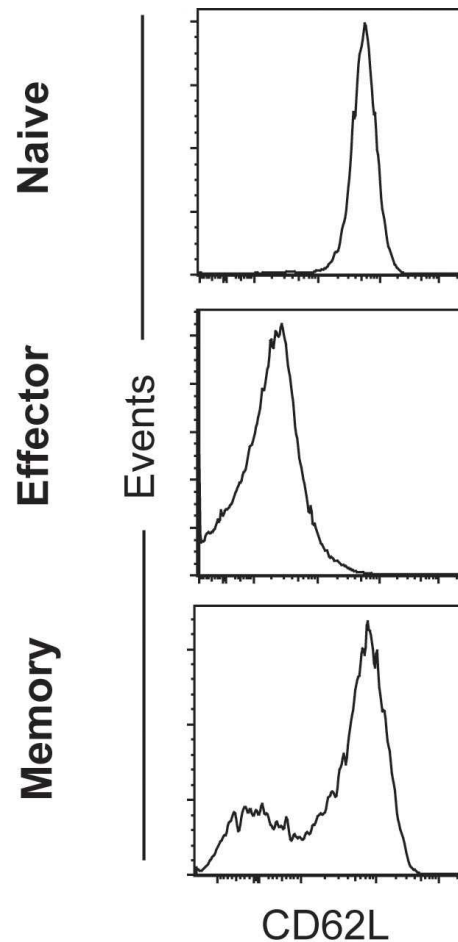


CD62L (L-selectin)

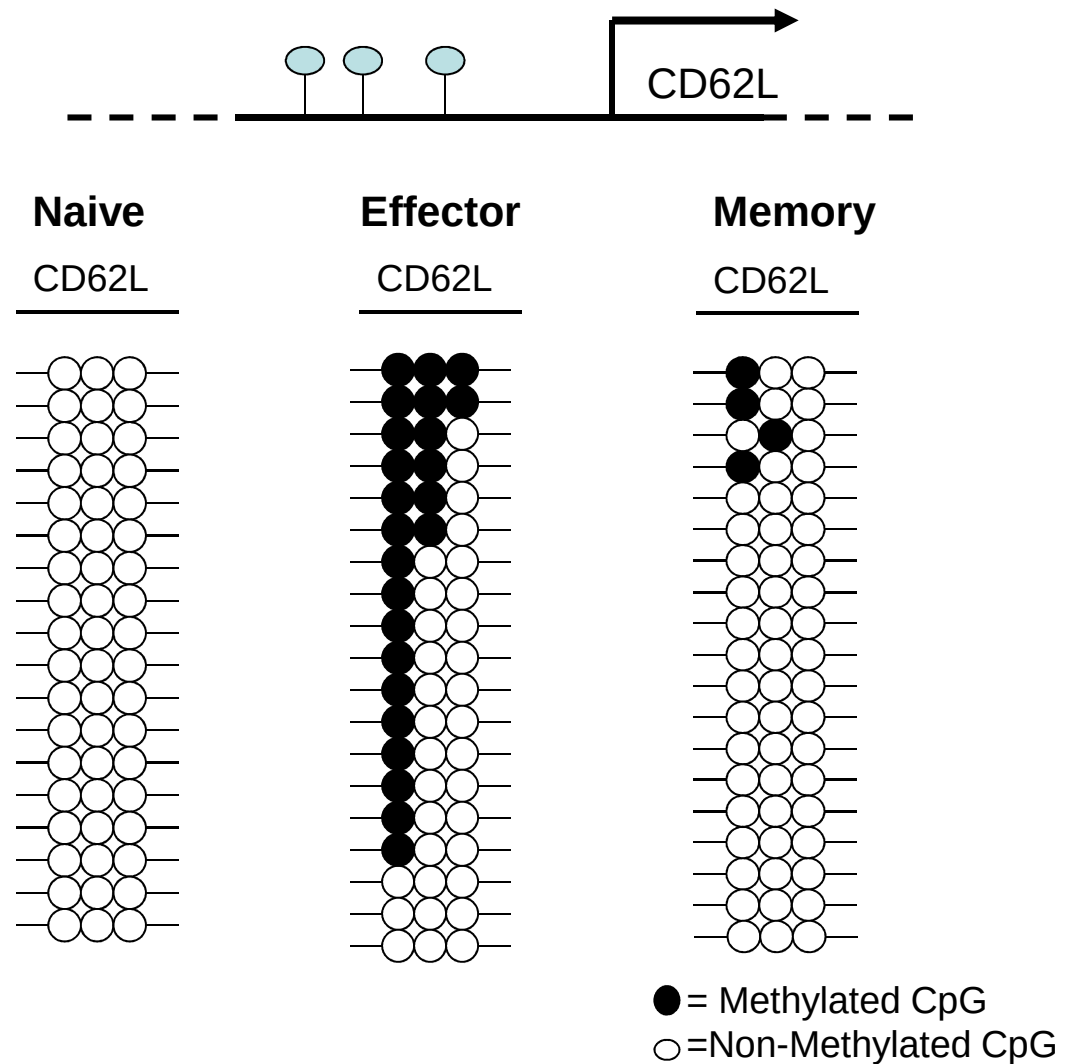


Epigenetics of Memory T Cell Differentiation

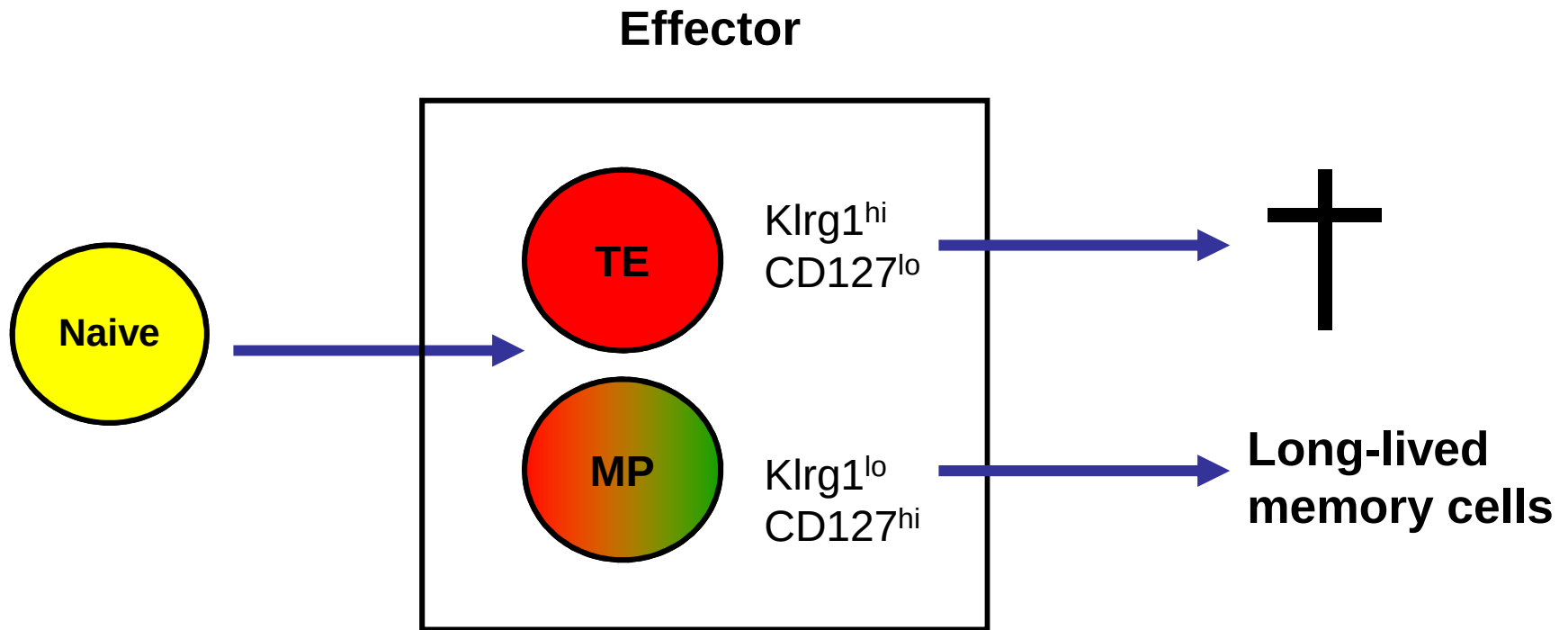
CD62L Expression



CD62L DNA Methylation

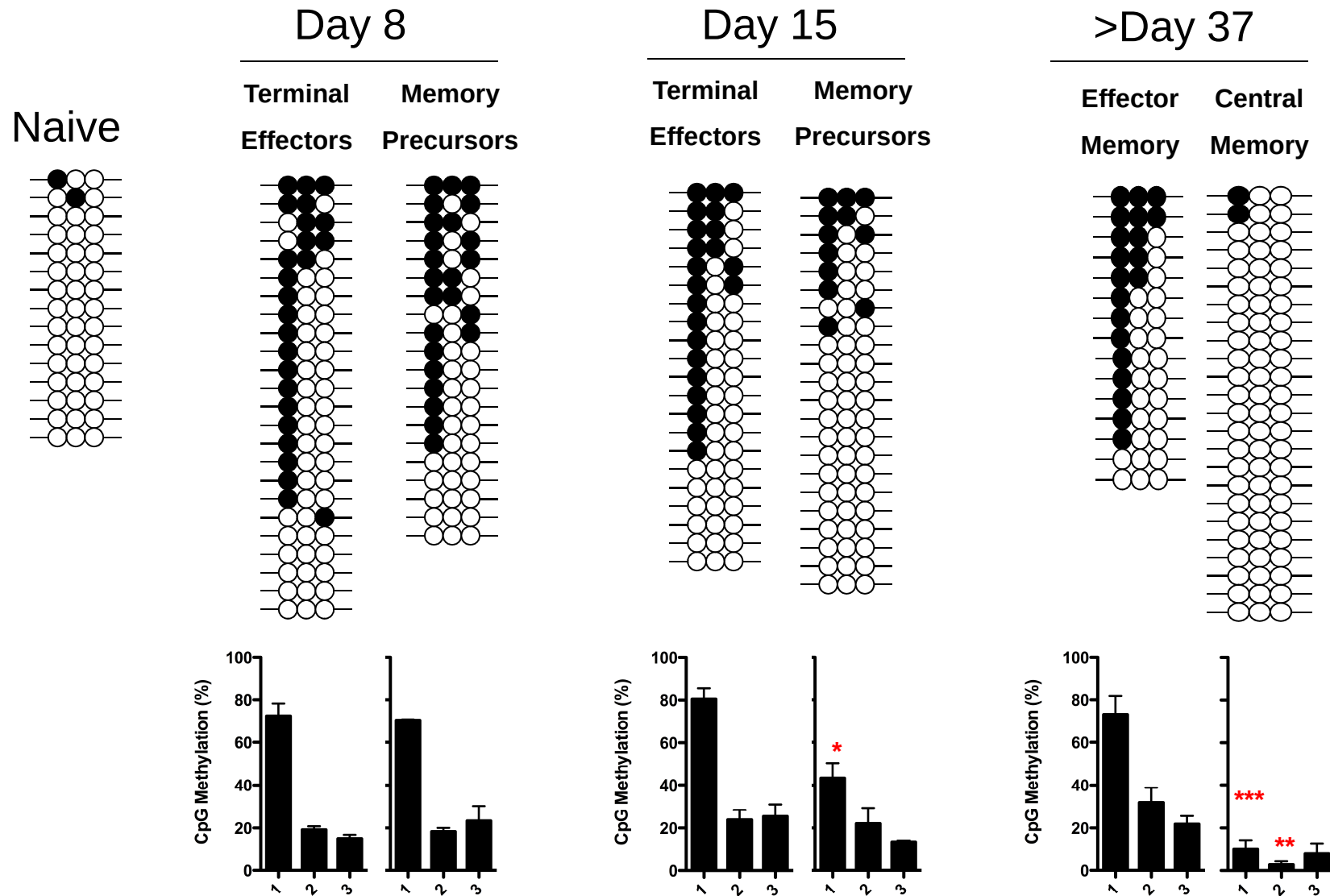


Two Effector CD8 T Cell Subsets with Distinct Memory Fates

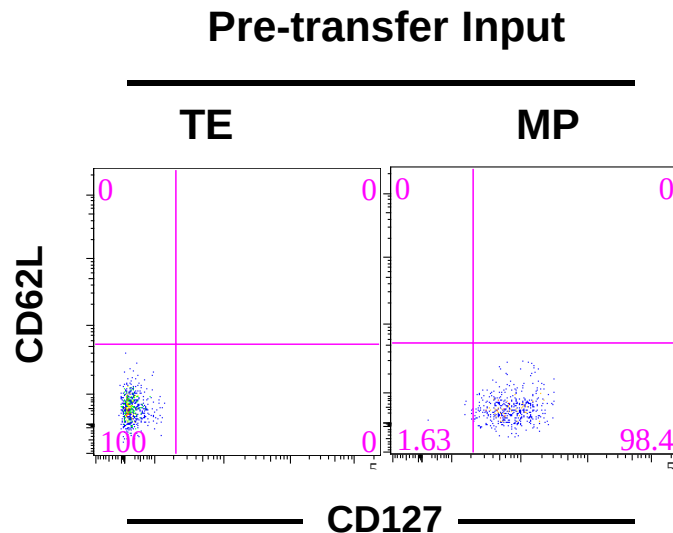
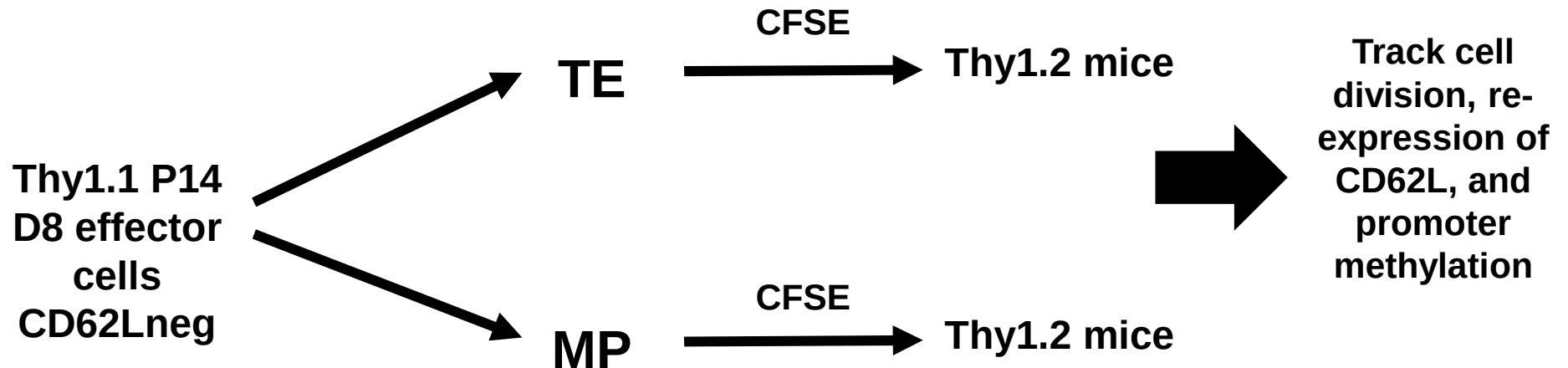


Kaech et al. *Nature Immunology* 2003
Joshi et al. *Immunity* 2007
Sarkar et al. *J. Exp. Med.* 2008

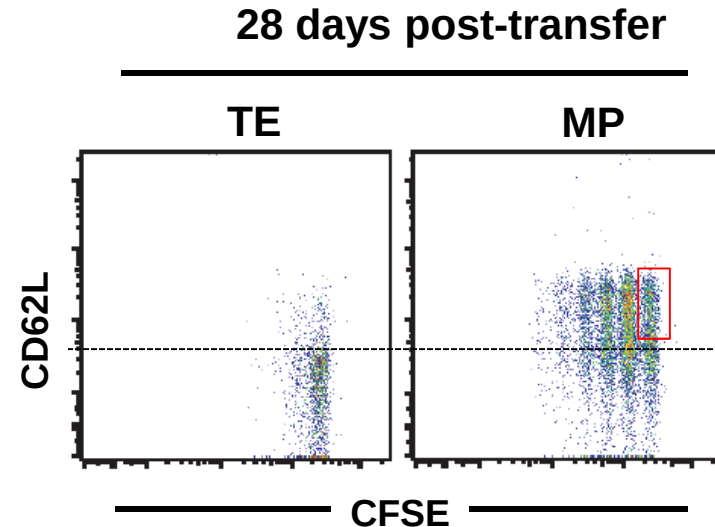
Epigenetic Evidence for E → M Differentiation



Epigenetic Evidence for E → M Differentiation

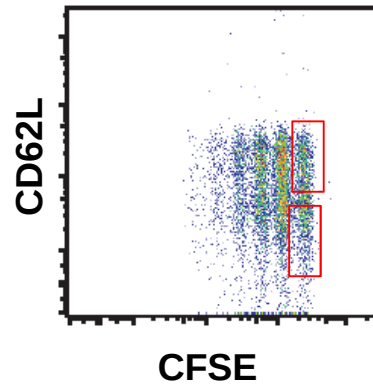


< 0.01% CD62Lhi cells < 100 cells
10⁶ cells transferred

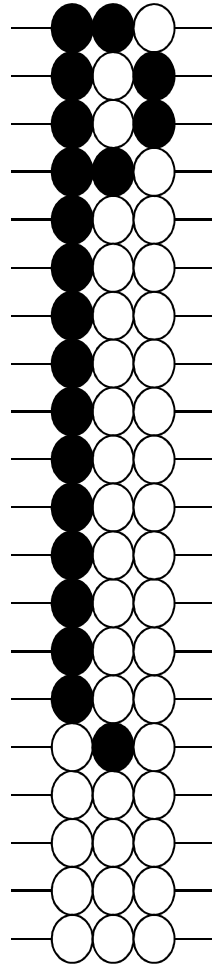


> 1000
CD62Lhi cells!

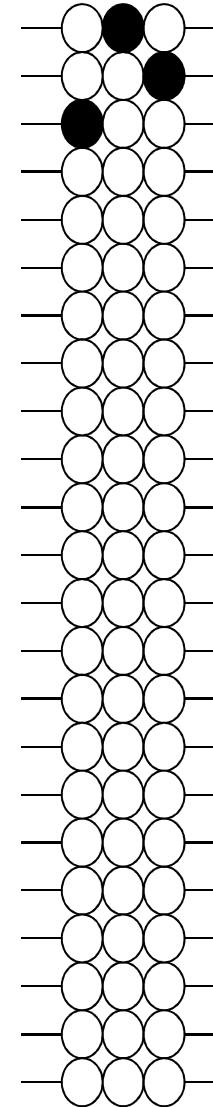
DNA methylation analysis of undivided memory cells



CD62L^{lo}



CD62L^{hi}



DNA Methyltransferases

DNMT1 - *maintenance methylation*

DNMT3a - *de novo methylation*

DNMT3b - *de novo methylation*

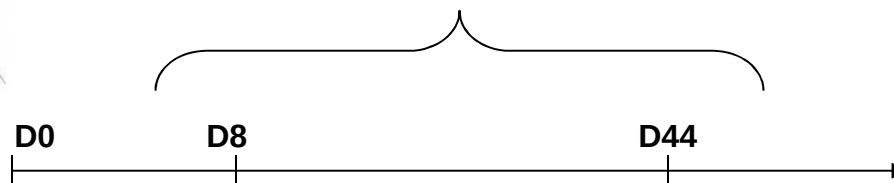
- **Effector CD8 T cells increase transcription of Dnmt3a isoforms**
- **Dnmt3a floxed mice crossed to granzyme B cre to conditionally delete Dnmt3a in activated/effector CD8 T cells**

Infect with LCMV-arm

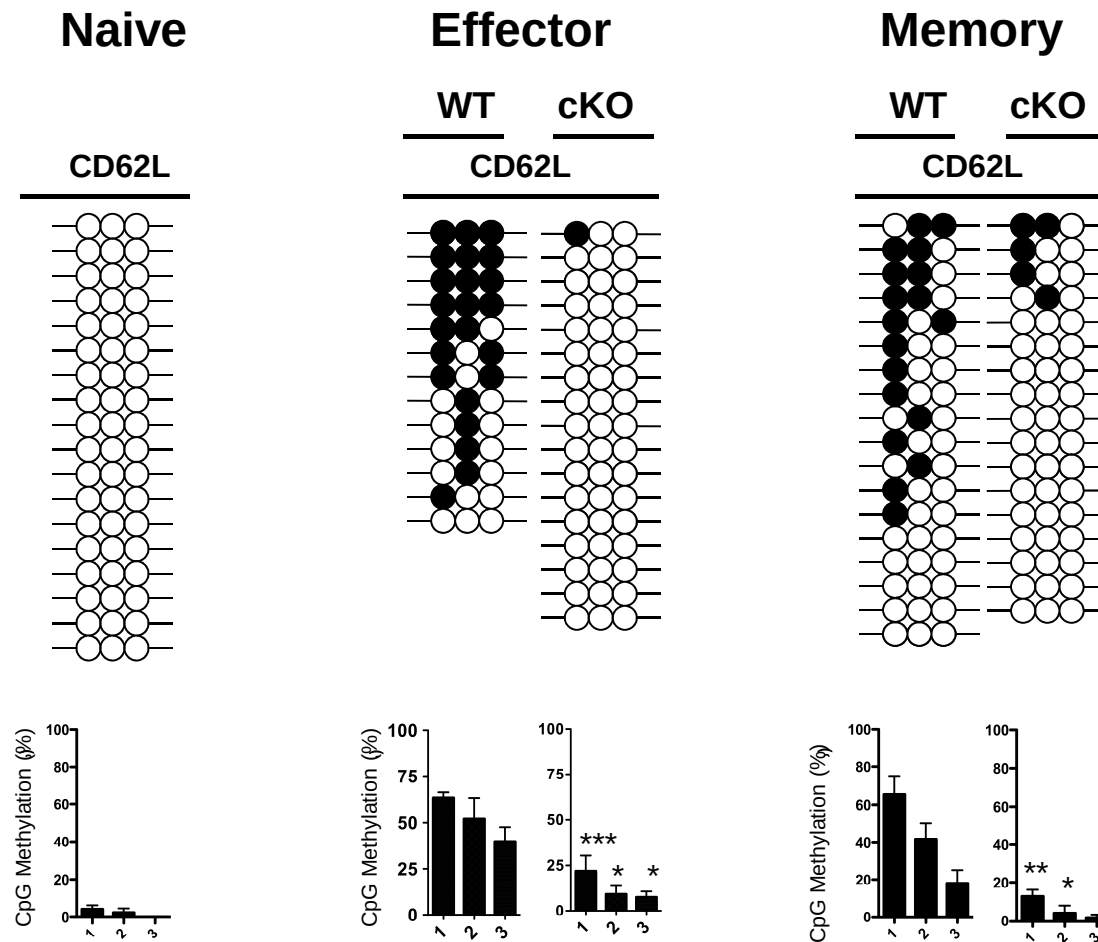


WT or cKO

Analyze phenotype and epigenetic program(s)

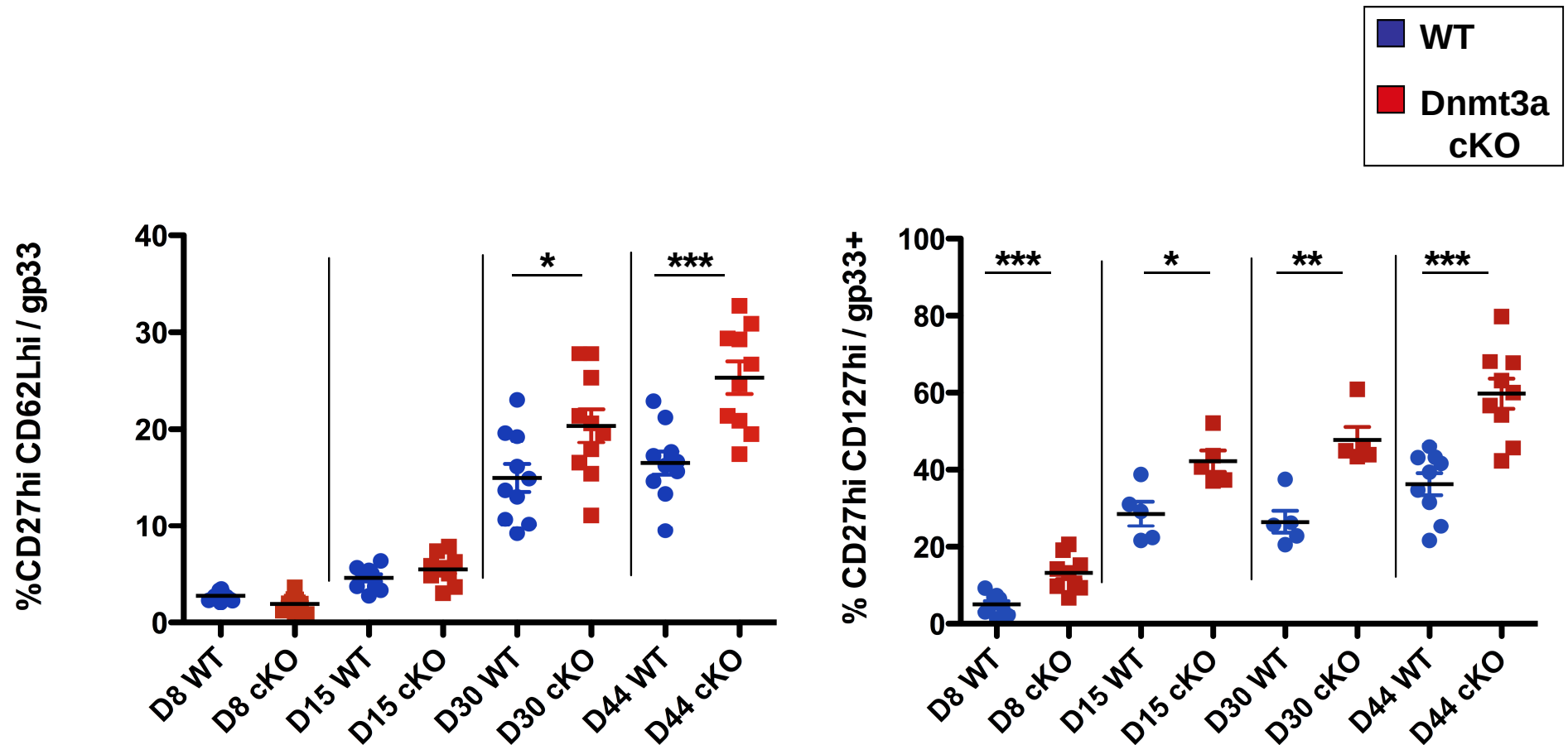


Dnmt3a Mediates *De novo* DNA Methylation of CD62L in Effector CD8 T Cells

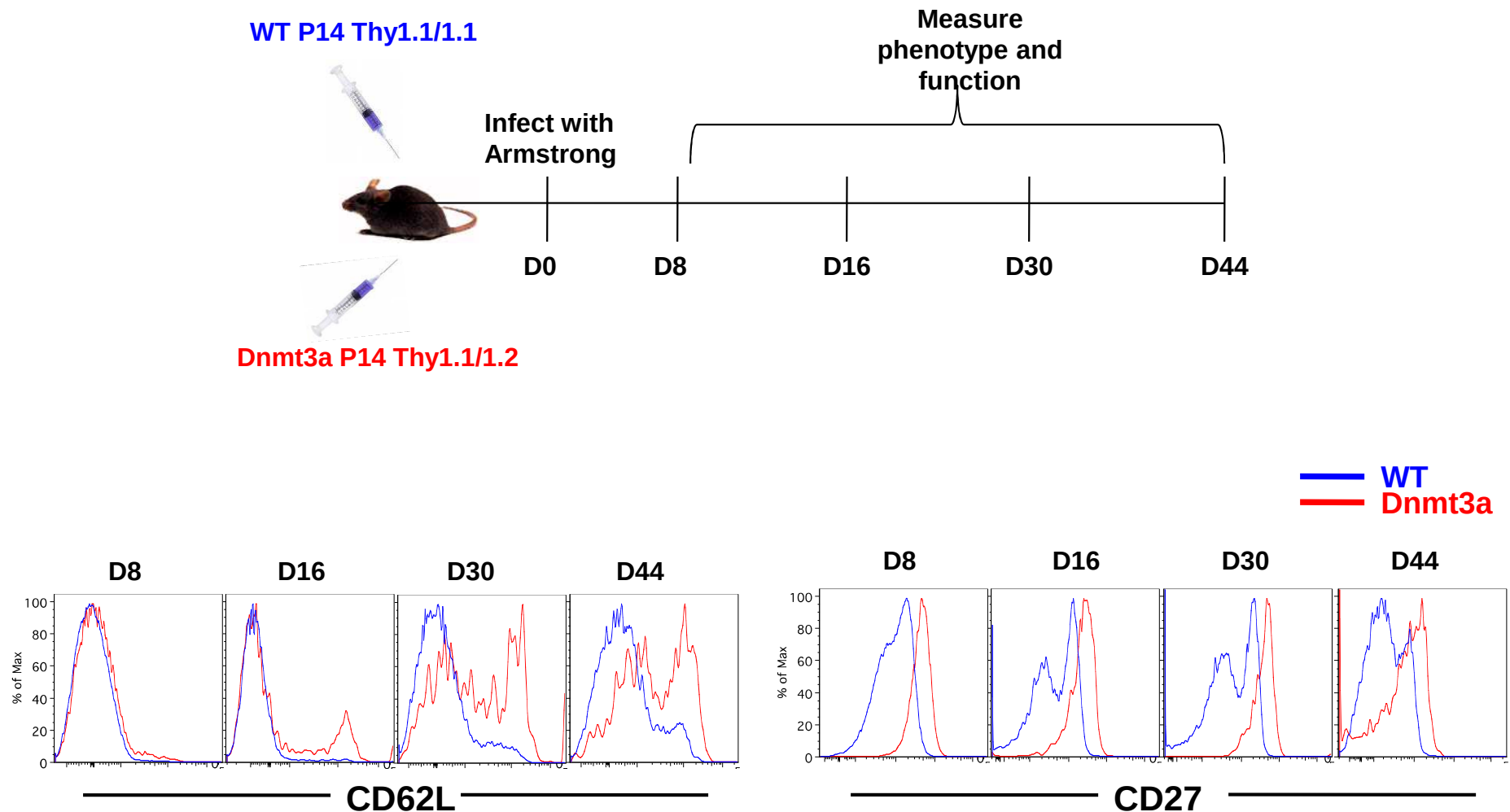


● = Methylated CpG
○ = Non-Methylated CpG

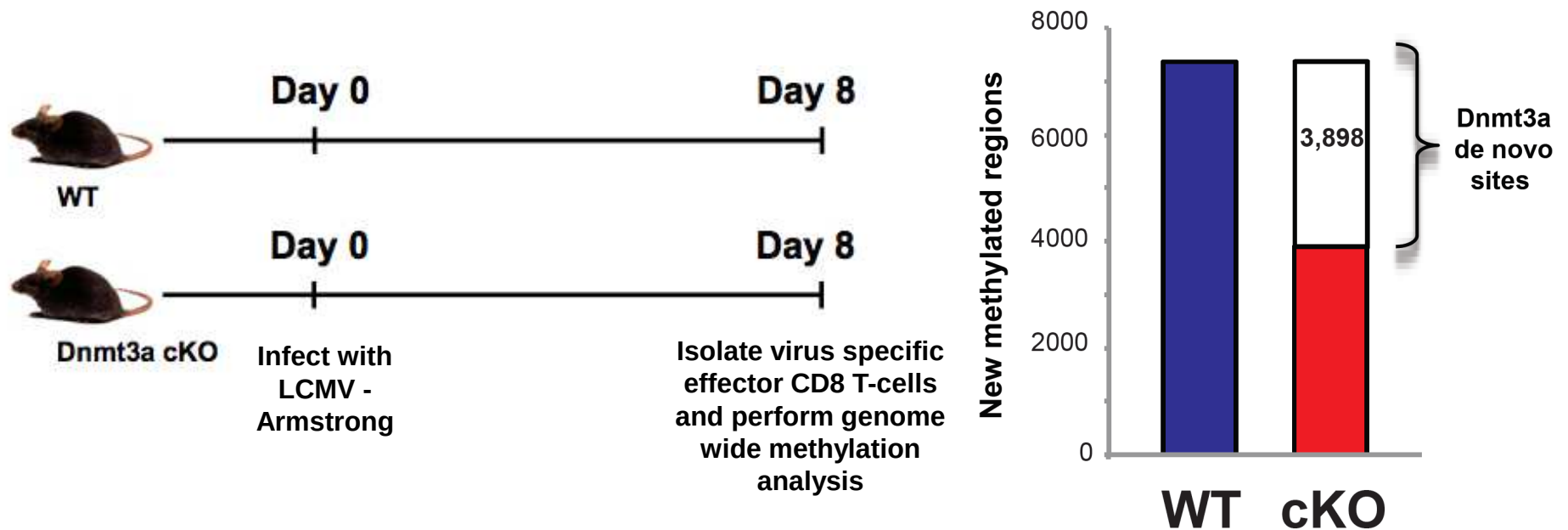
Faster Effector to Memory Differentiation in the Absence of Dnmt3a (de novo methylation)



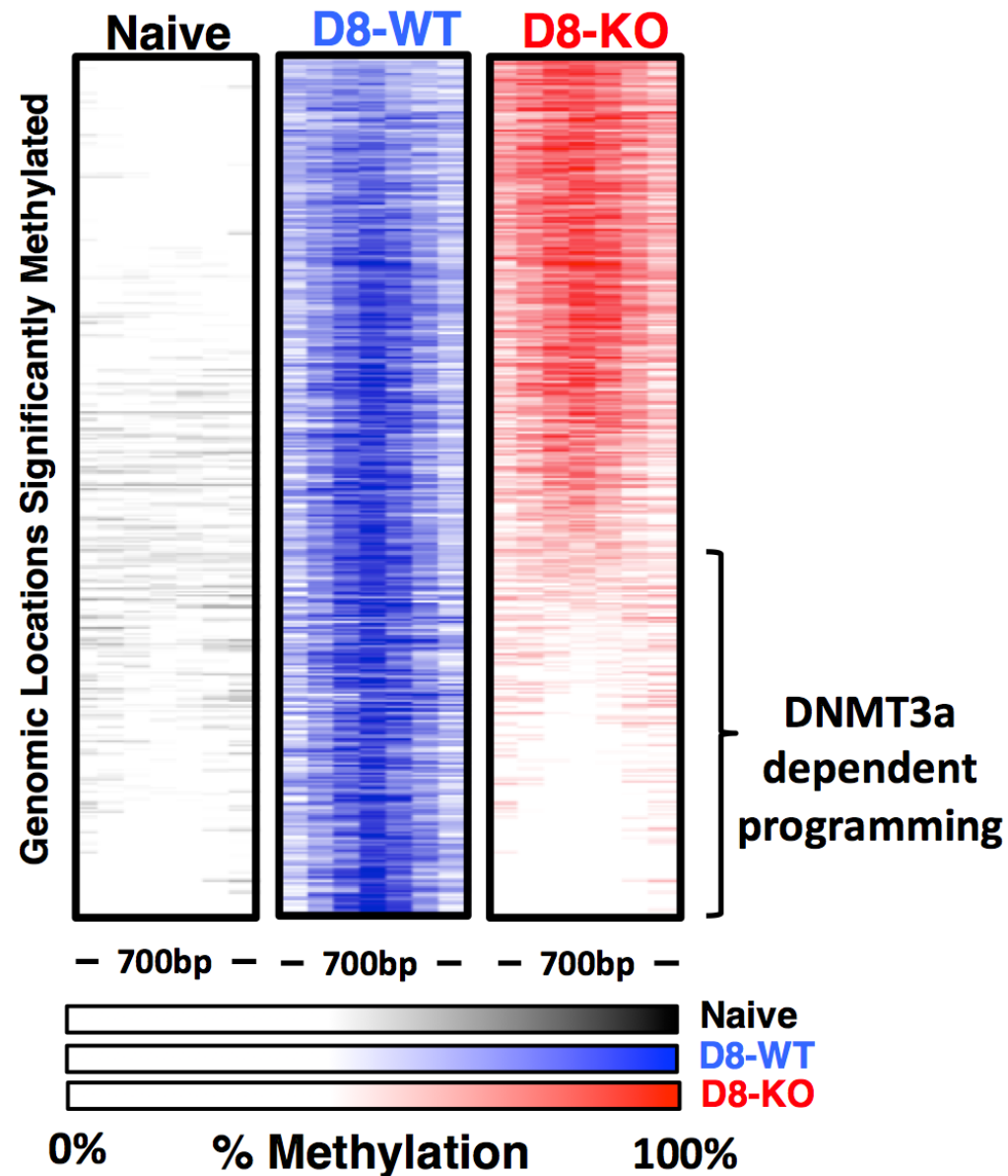
Faster Effector to Memory progression in the absence of Dnmt3a is a cell intrinsic property



Genome-wide assessment of Dnmt3a mediated de novo programming

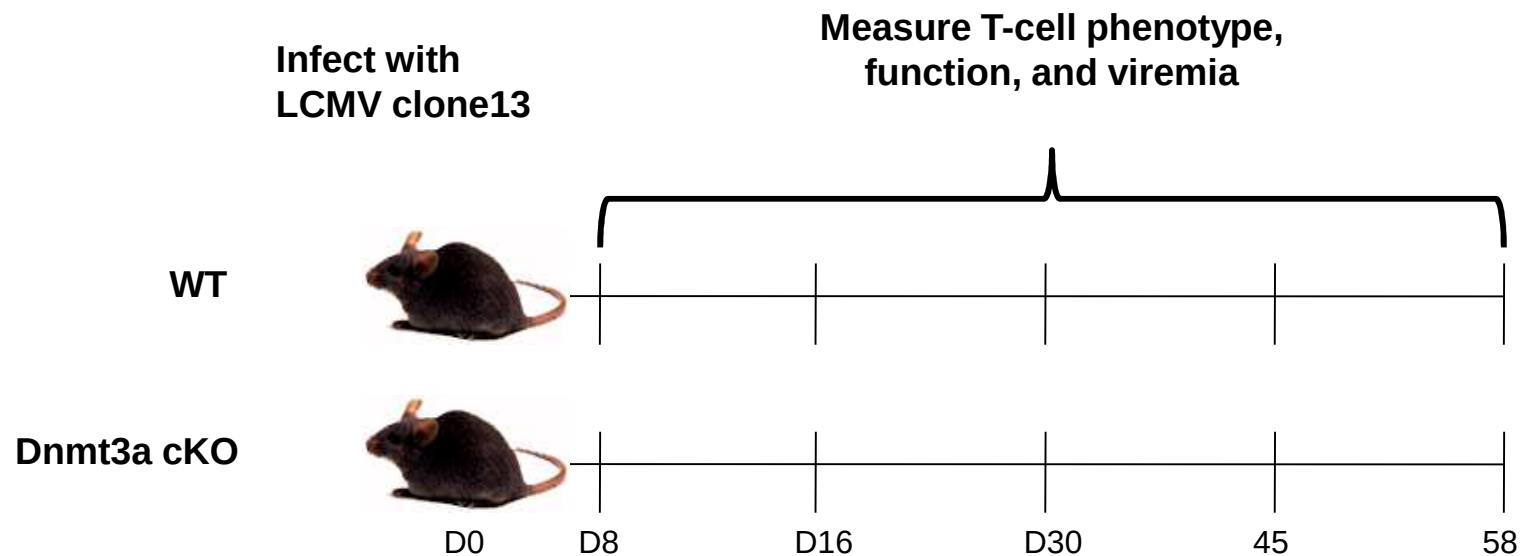


Genome-wide assessment of Dnmt3a mediated de novo programming

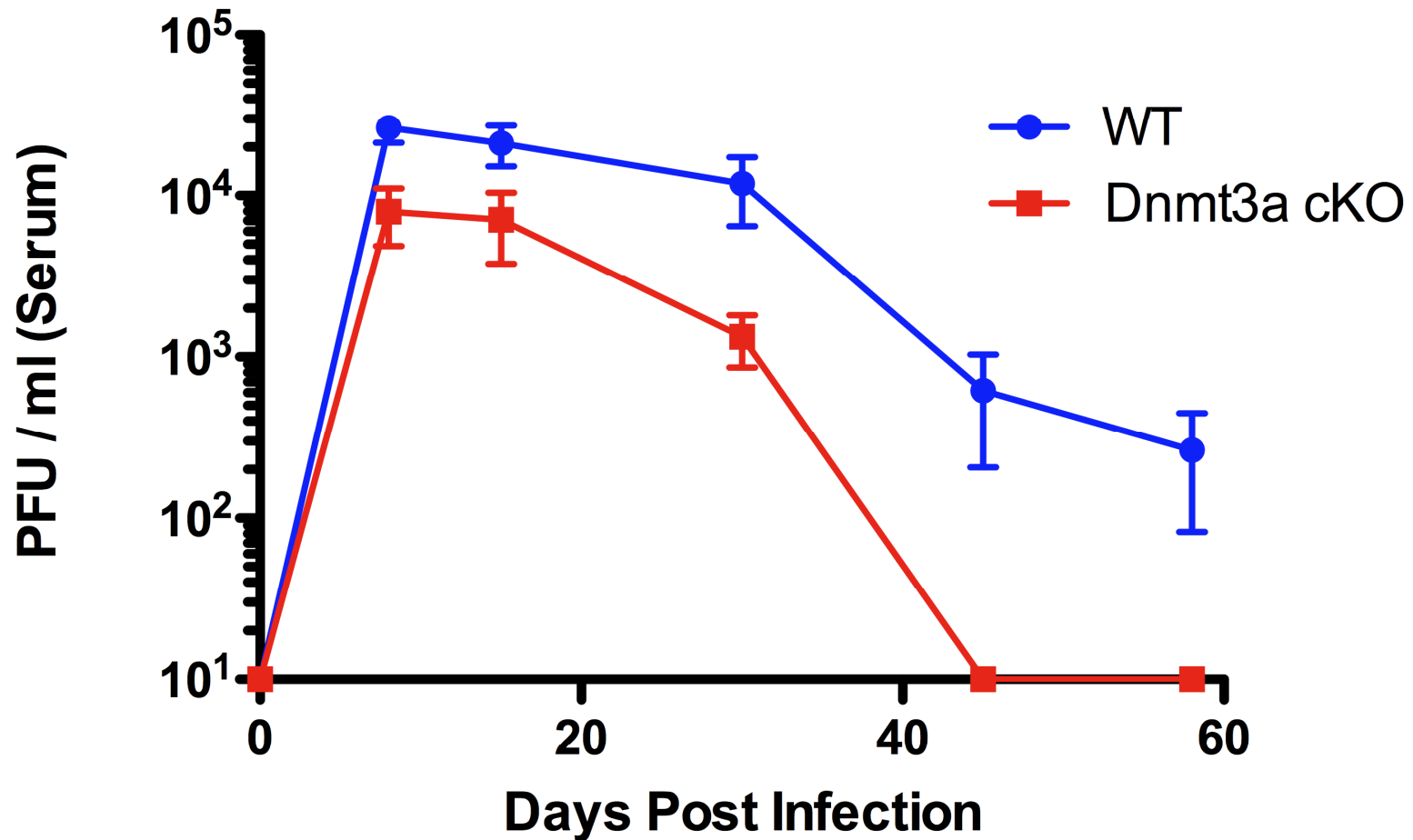


**What about chronic viral
infection ?**

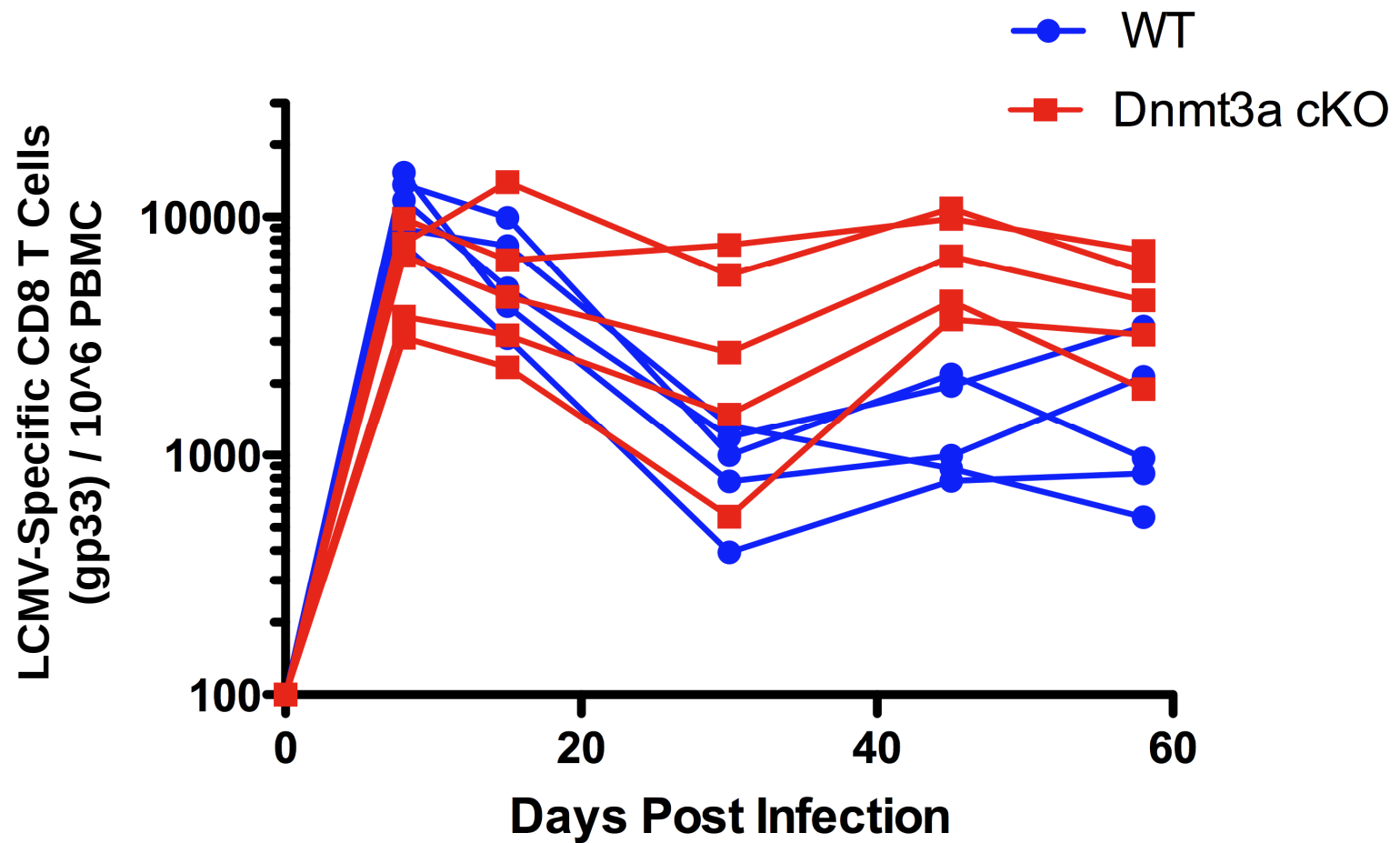
Is the exhaustion program maintained by de novo DNA methylation?



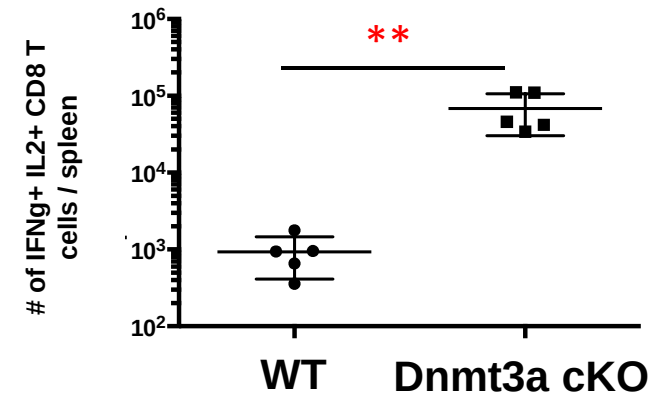
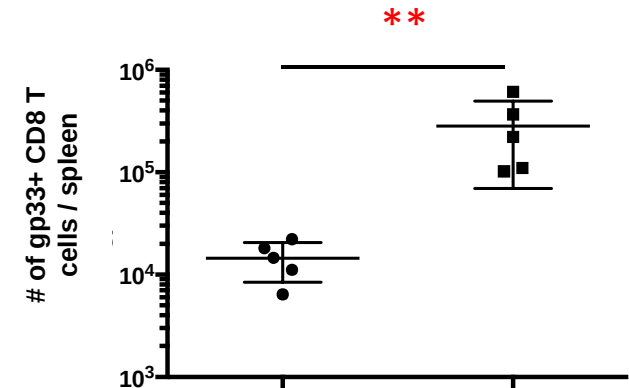
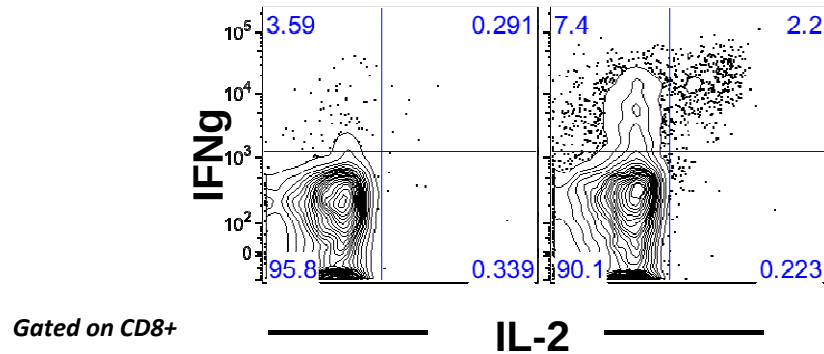
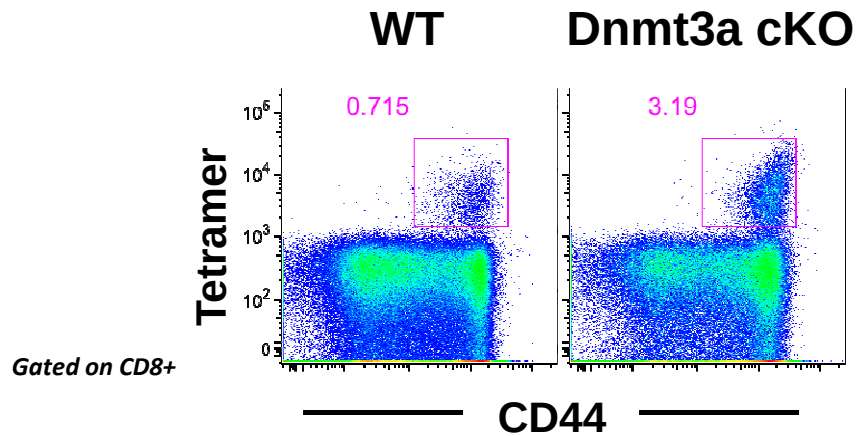
Better Viral Control in Dnmt3a cKO mice

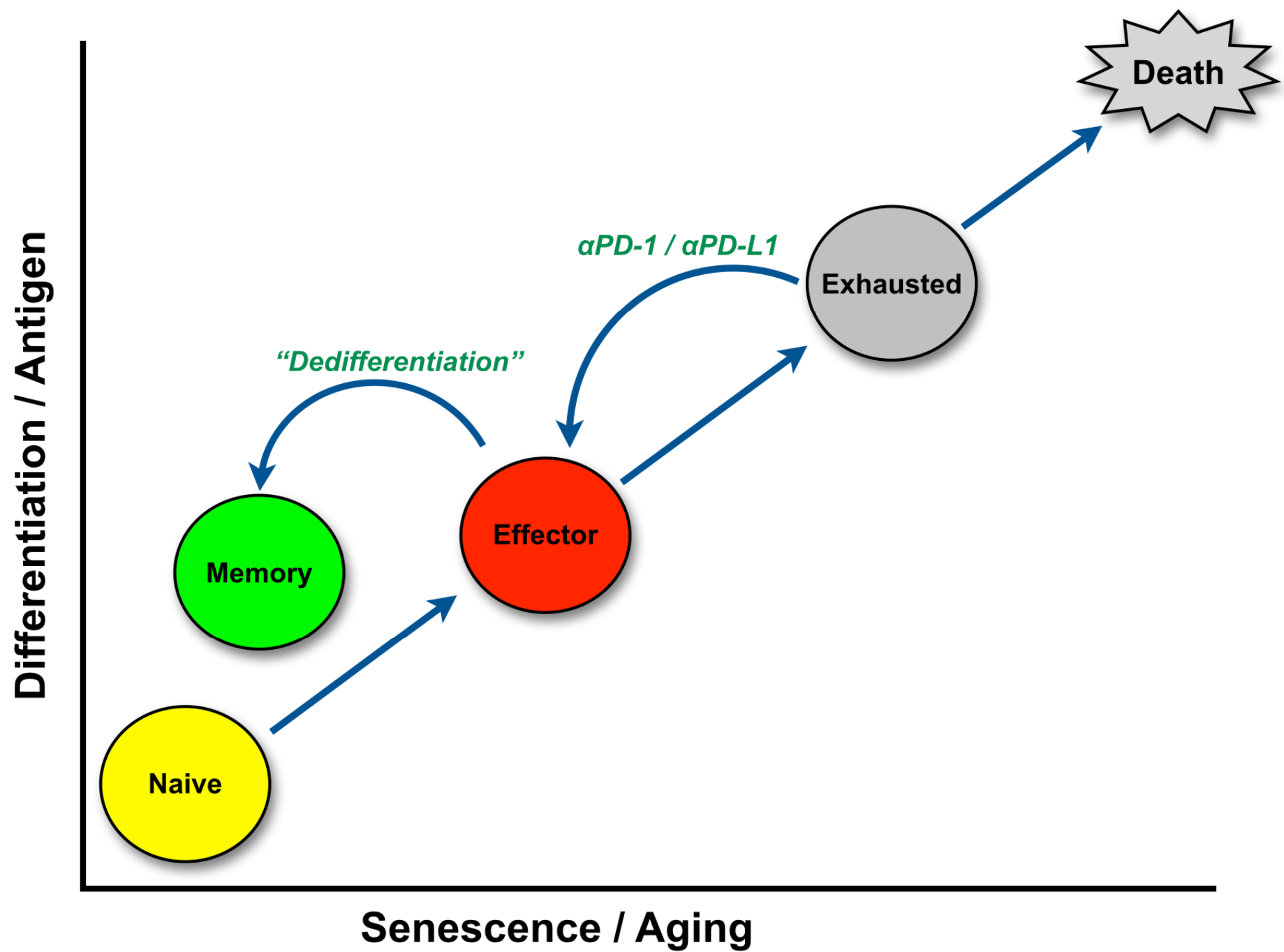


Viral Control is Coupled to Increased CD8 T Cell Responses



Increased T cell function





Acknowledgements

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