Chromatin and transcriptional dynamics of *T-cell immunotherapy*

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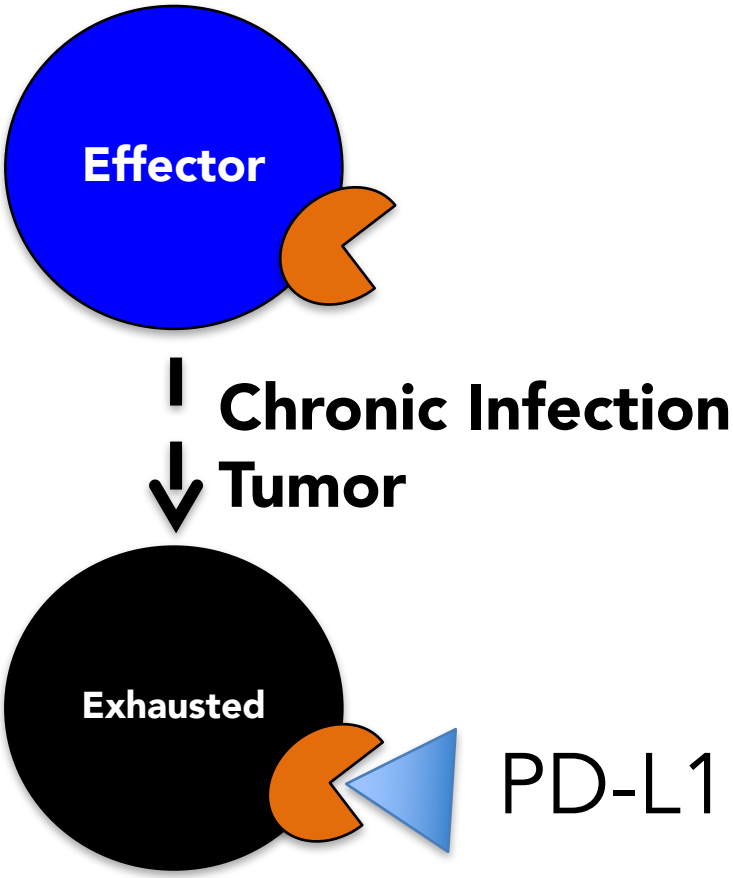
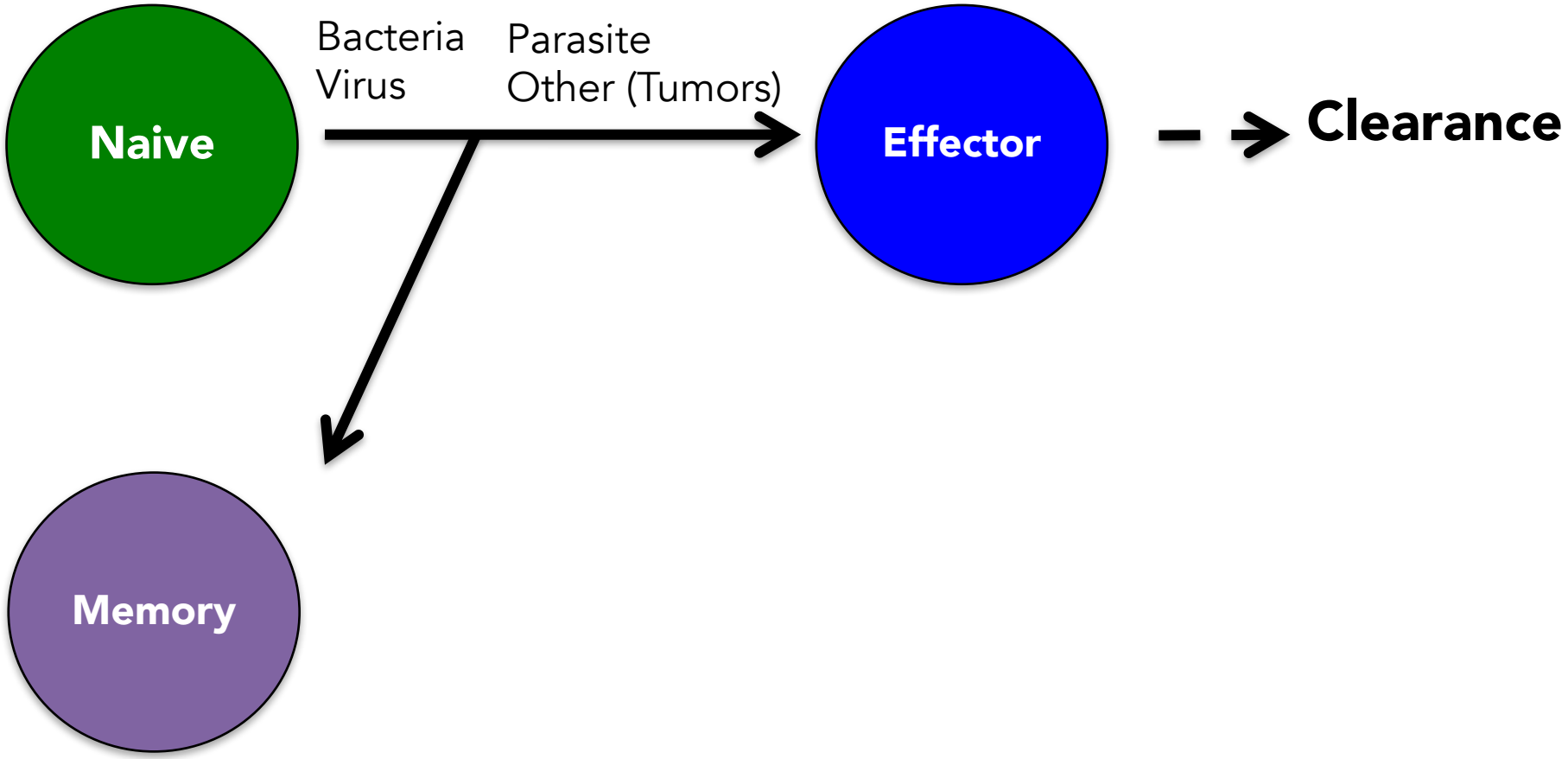
Checkpoint blockade inhibition as an anti-cancer strategy

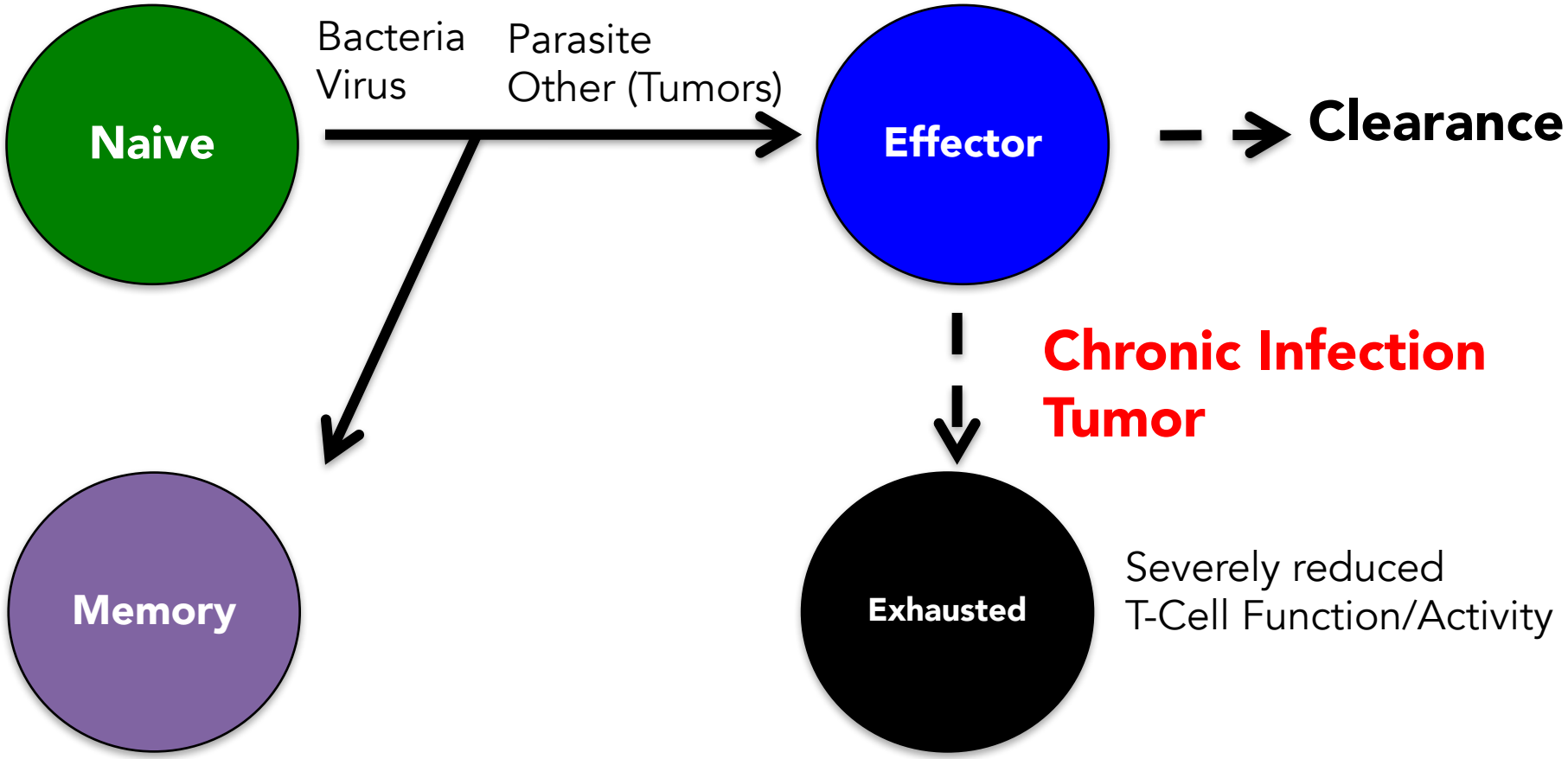


Drugs targeting PD1 and/or PD-L1 have shown efficacy in melanoma (and other cancers)

Genomics of T cell exhaustion (and reinvigoration)



Genomics of T cell exhaustion (and reinvigoration)



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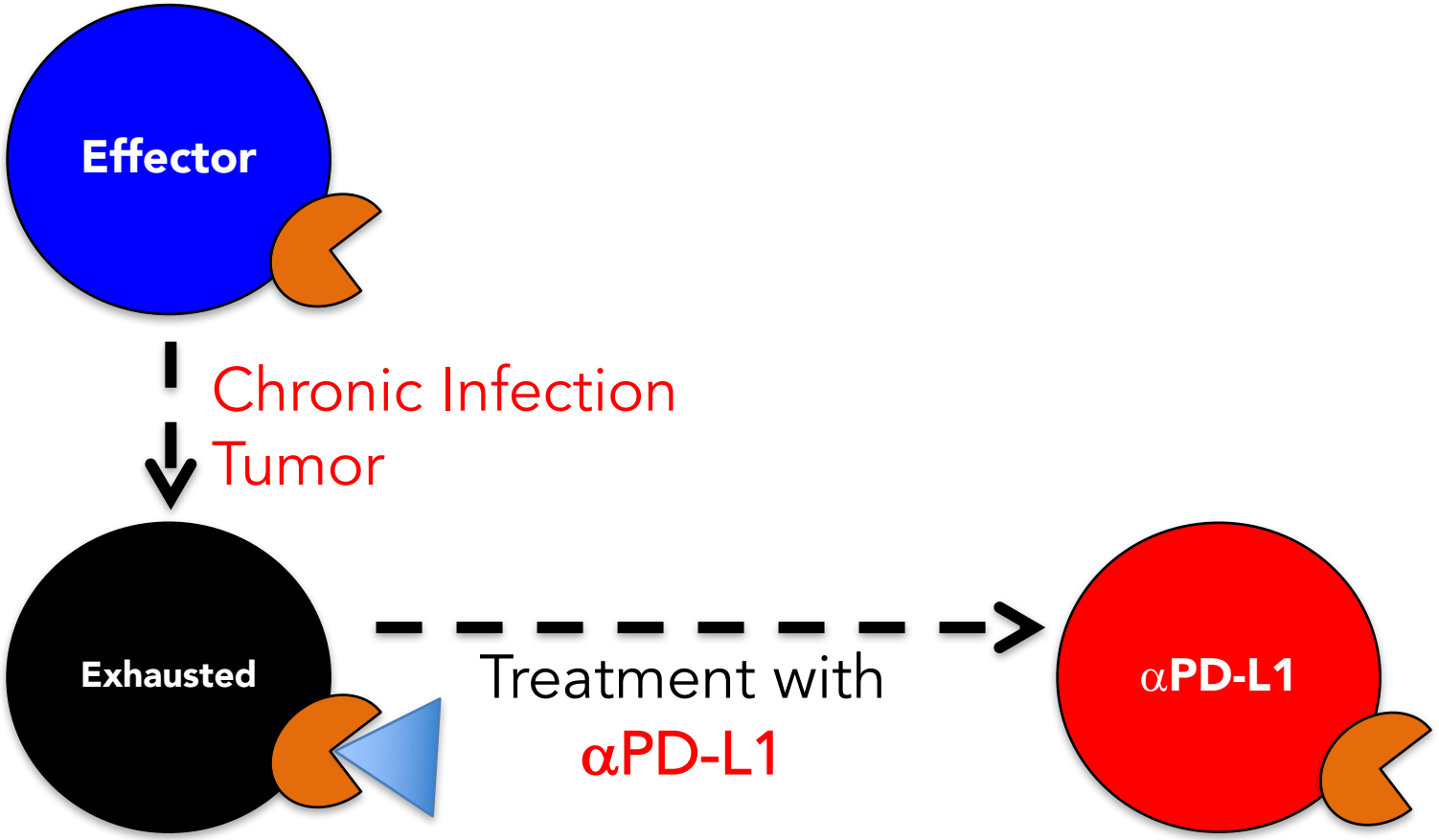
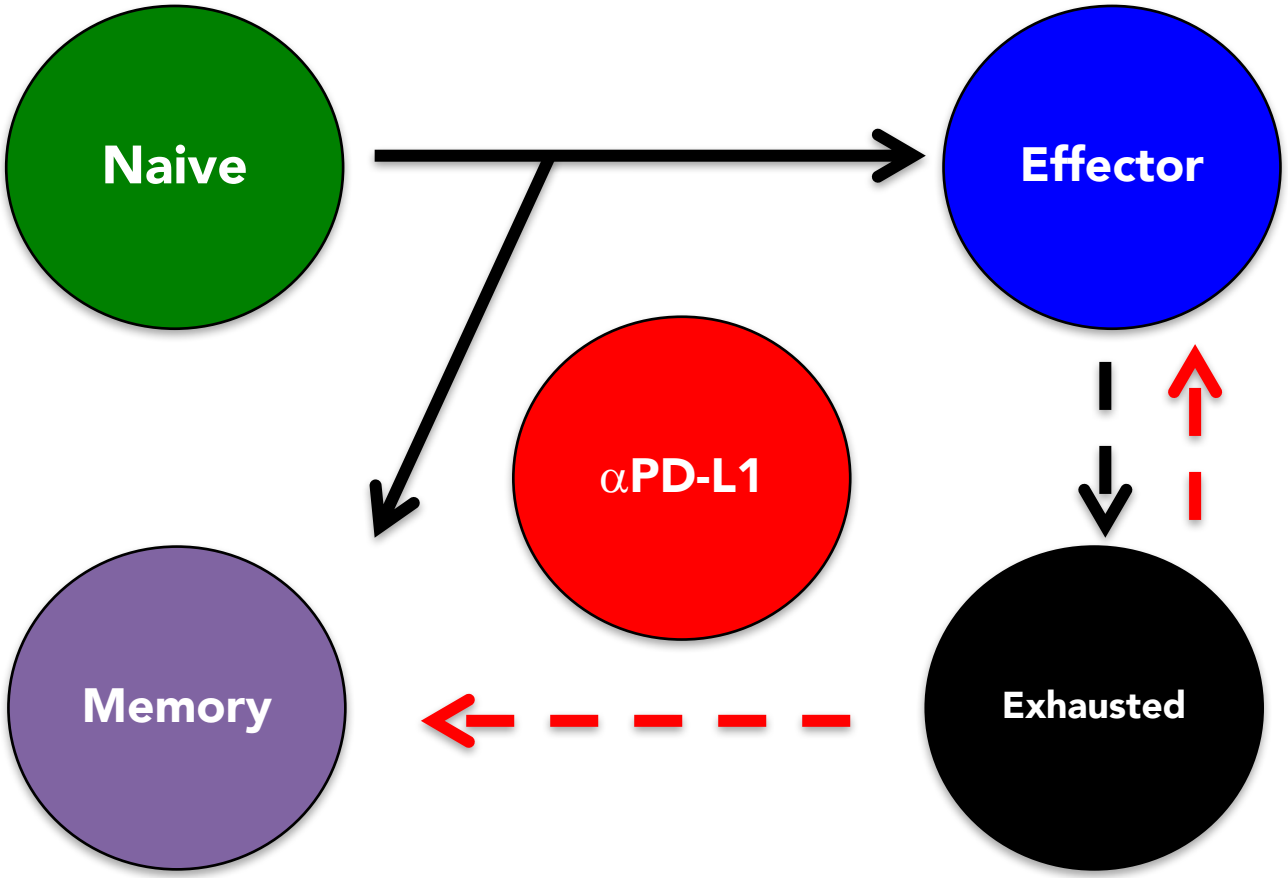
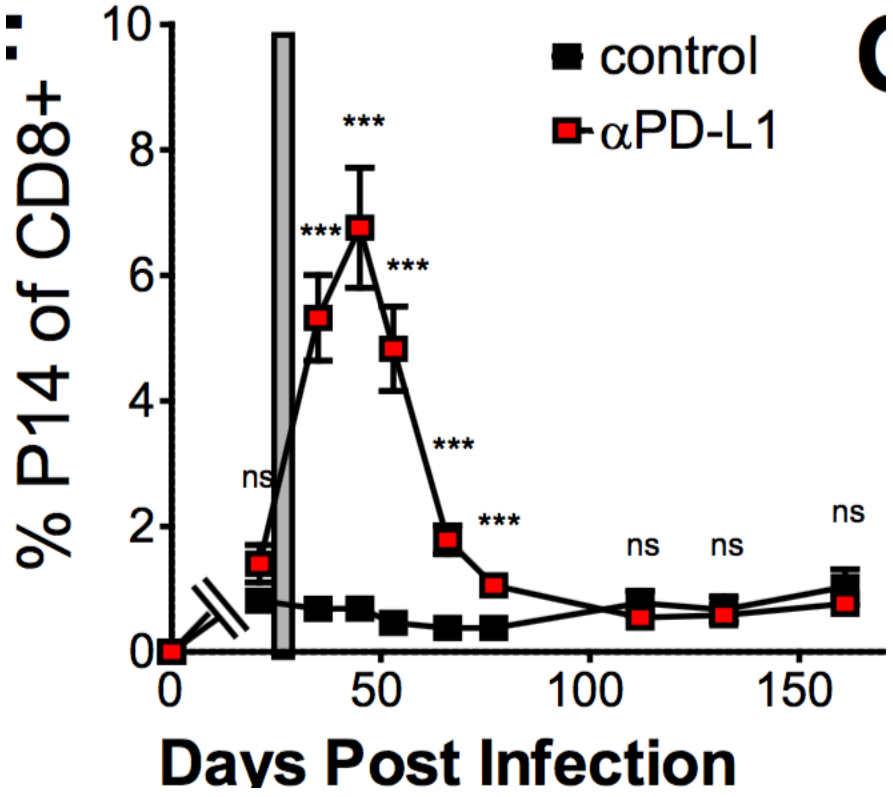


Where do exhausted and αPD-L1 cells fit?

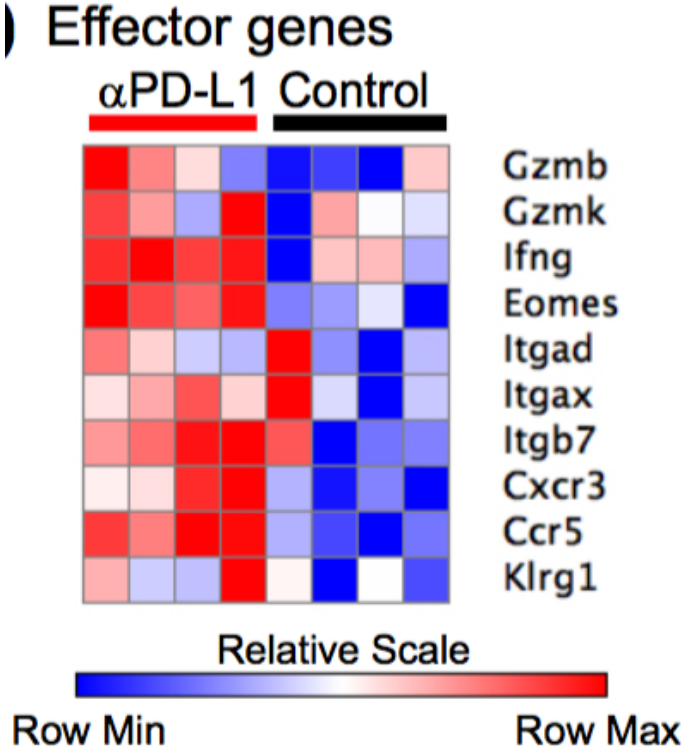


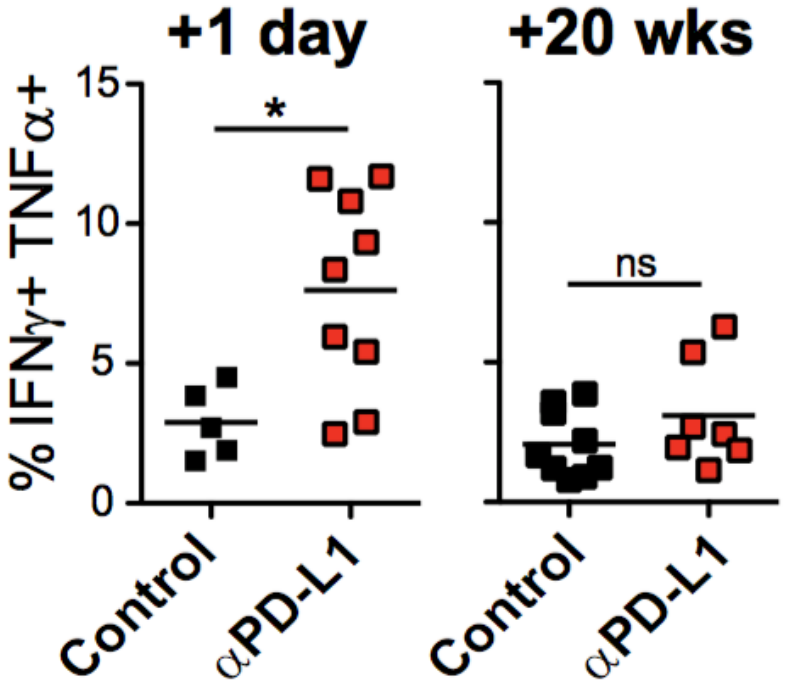
Experimental paradigm



1. Mice infected with chronic viral infection
2. T-cells allowed to exhaust
3. aPD-L1 is added for 1 day
4. Effector/cytotoxic T cell function is monitored for a really long time…

αPD-L1 treatment makes exhausted T-cells more "effector-like"





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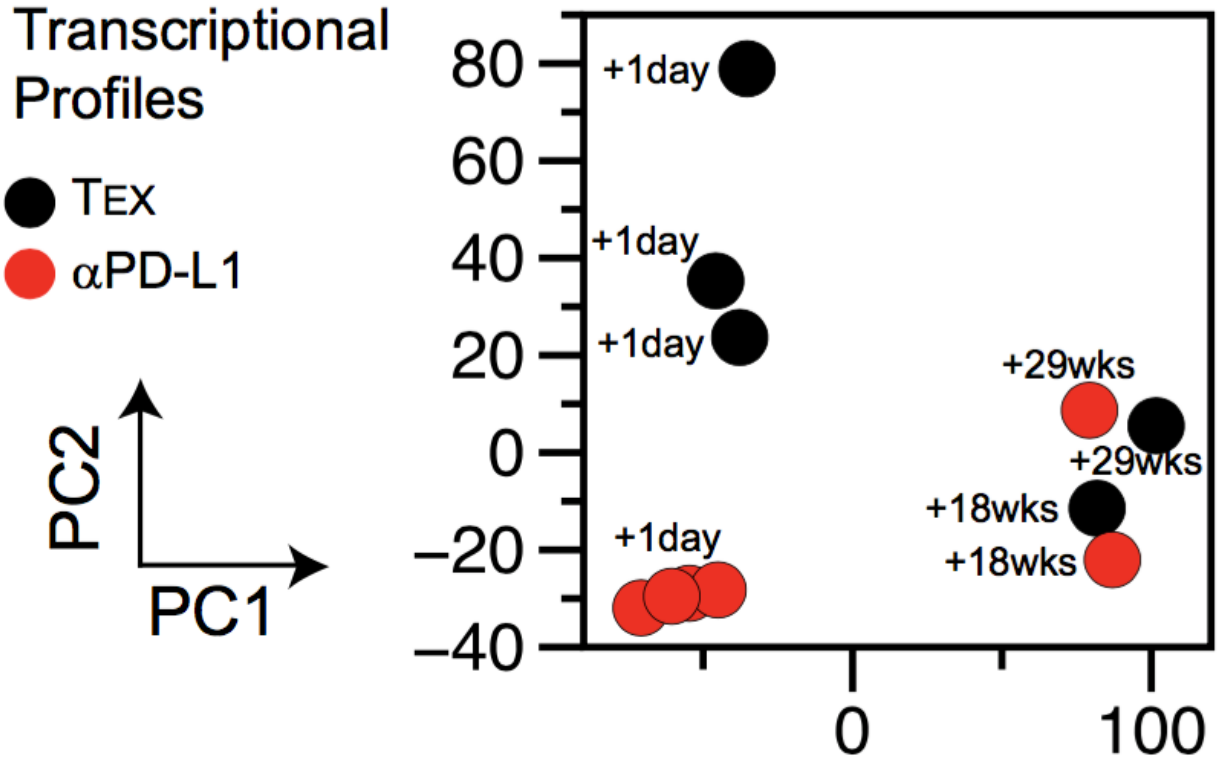
Exhausted T-cells treated with αPD-L1 rapidly remodel their transcriptome …temporarily



Each sample above was from N=3 mice yeilding 10,000 total cells/per condition

Clontech SMRTseq v4

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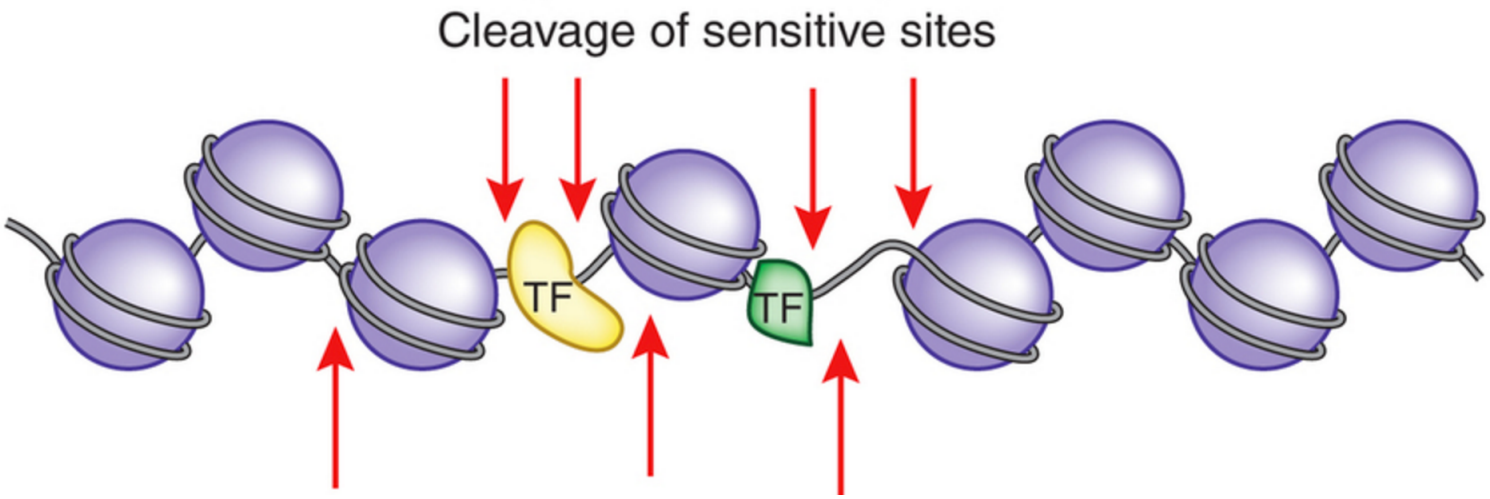
Using ATAC-seq to assess lineage specific chromatin states in T cells

Tn5 transposase on intact nuclei

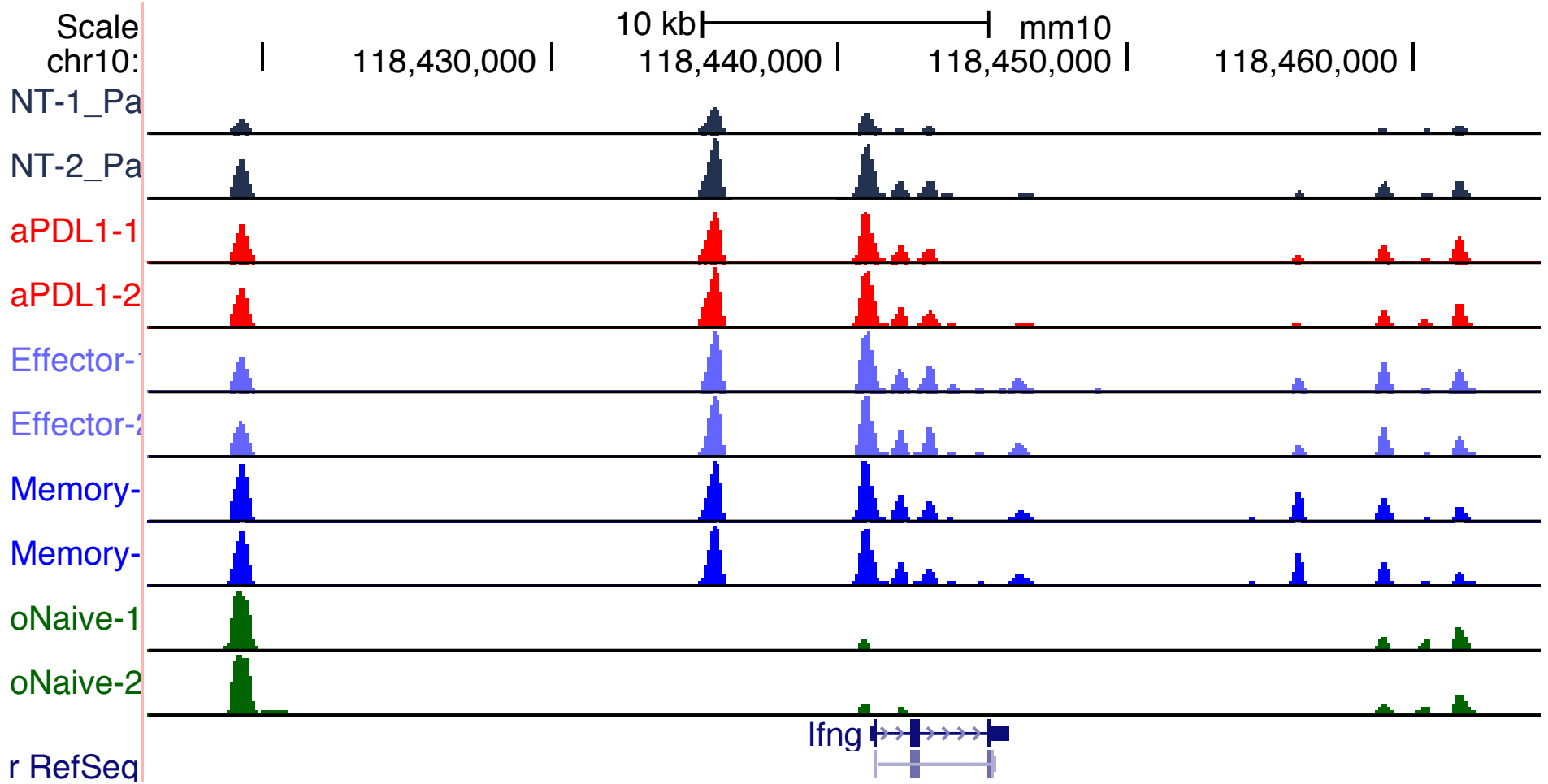
(Illumina Nextera)



Map regulatory regions and assess lineage-specific patterns

N=10 pooled mice per replicate, 2 biological replicates for 5 T-cell populations

Activated T-cell specific pattern



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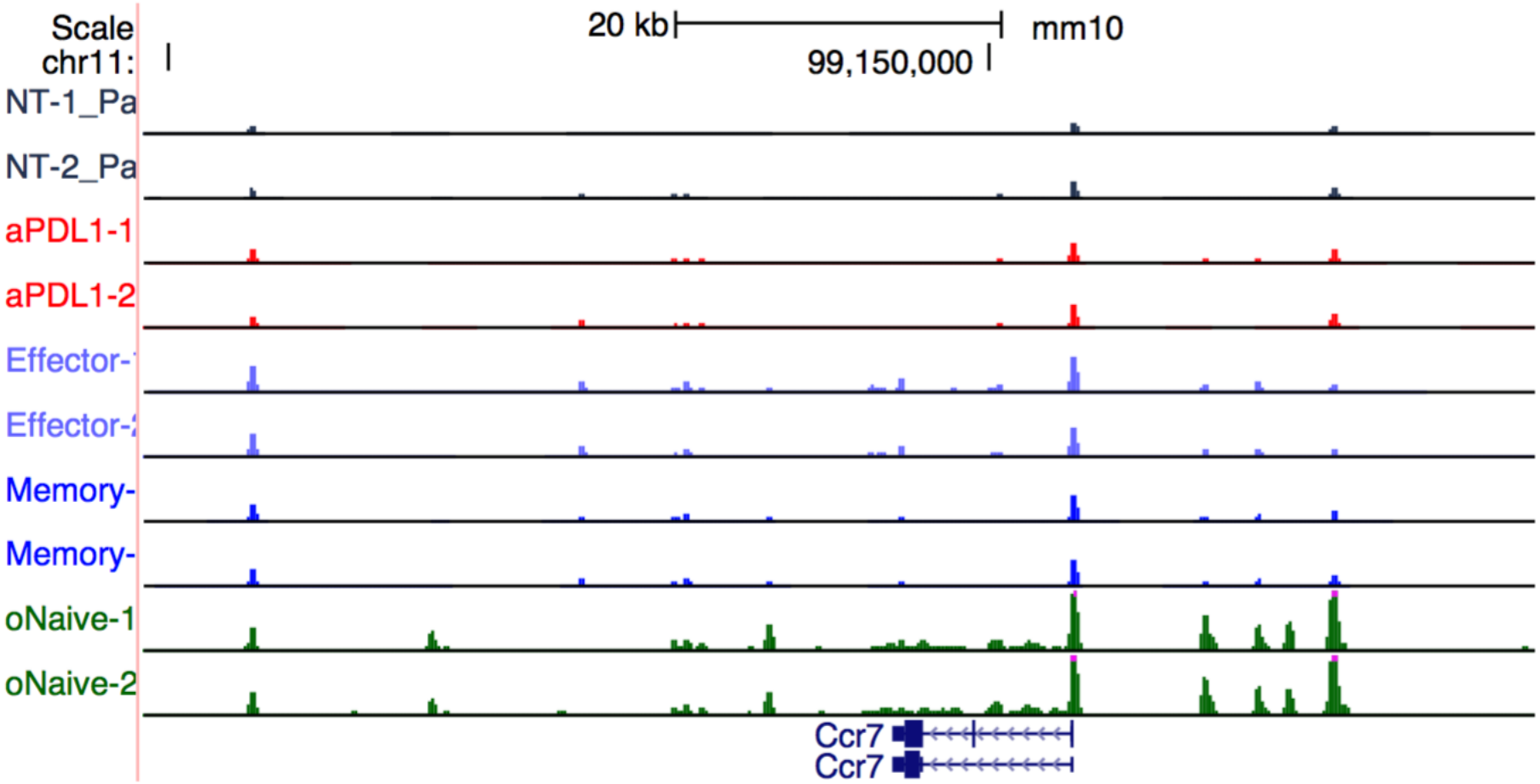
Naïve-specific patterns



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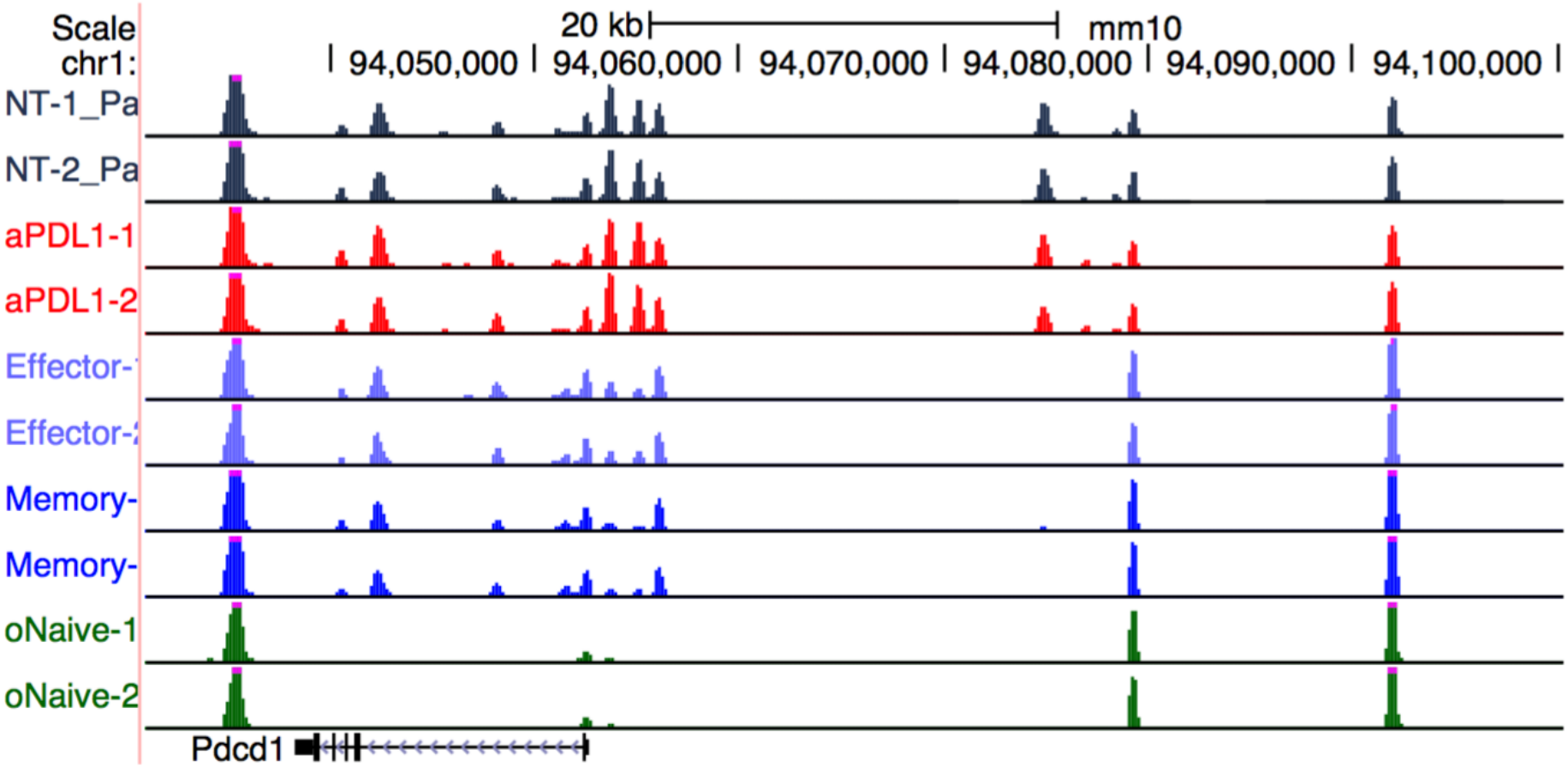
Exhausted T-cell specific pattern



This new enhancer region is critical for transcriptional upregulation of PD-1 seen in exhausted T-cells. (companion paper from Haining Lab, Dana Farber)

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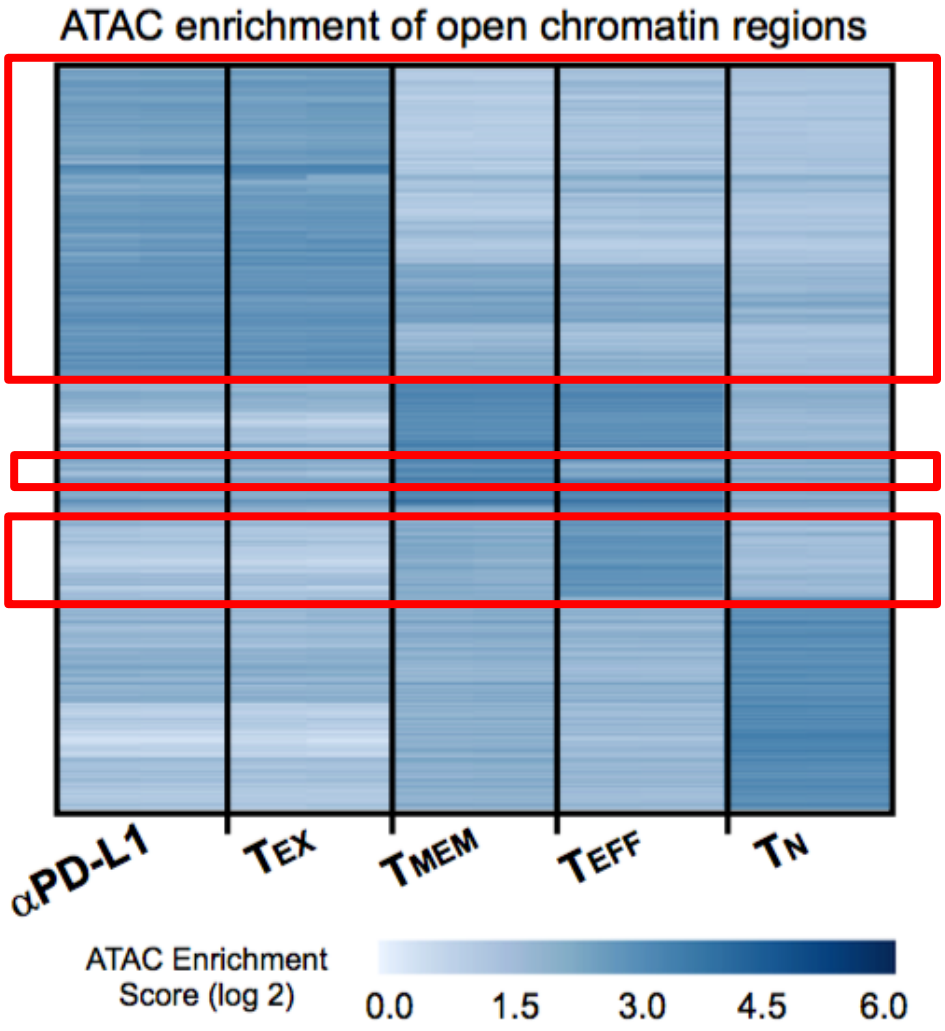
Exhausted T-cells are highly dissimilar from T_{mem}, T_{eff}, or T_{naive} cells



But similar to αPD-L1 treated cells…

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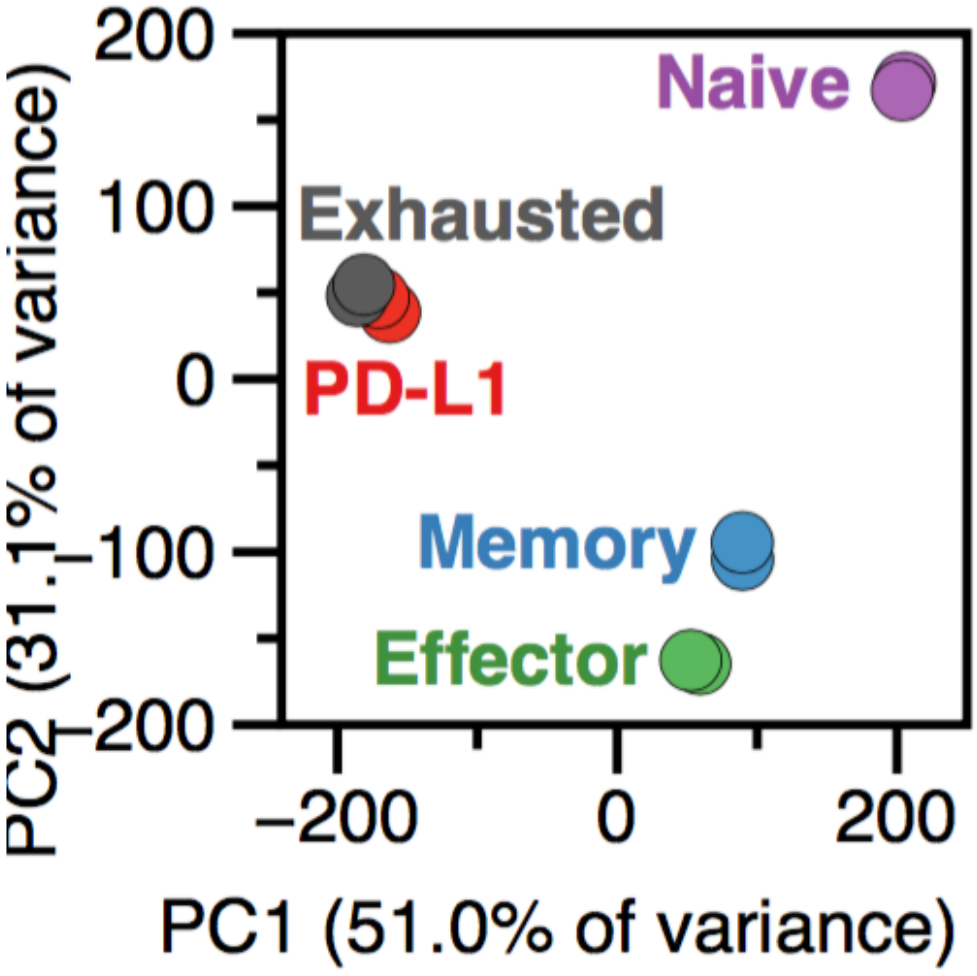
Exhausted T cells are a distinct lineage



αPDL-1 treatment does not lead to differentiation

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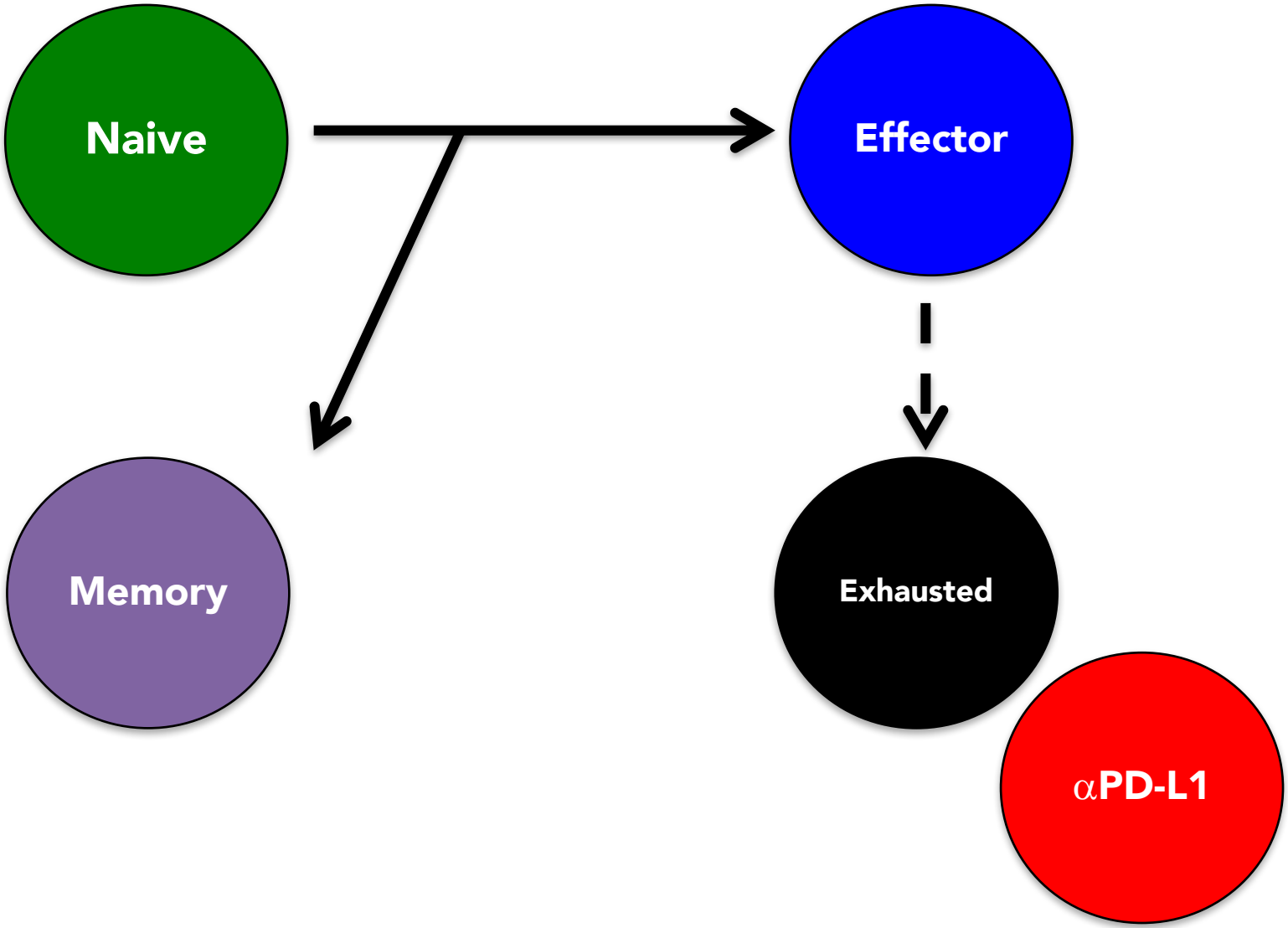
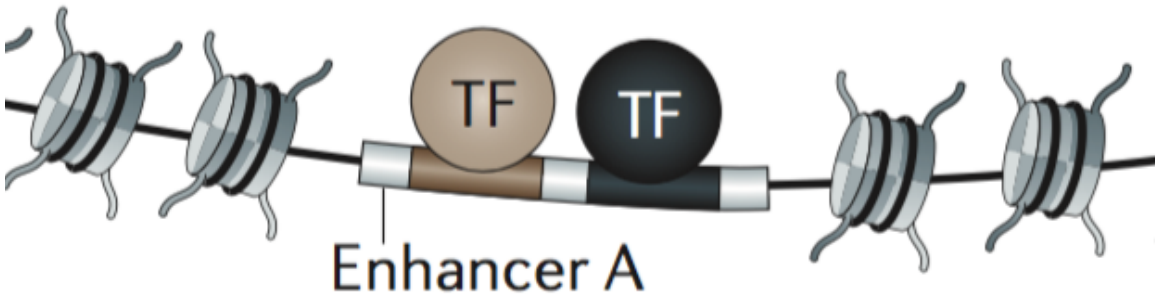
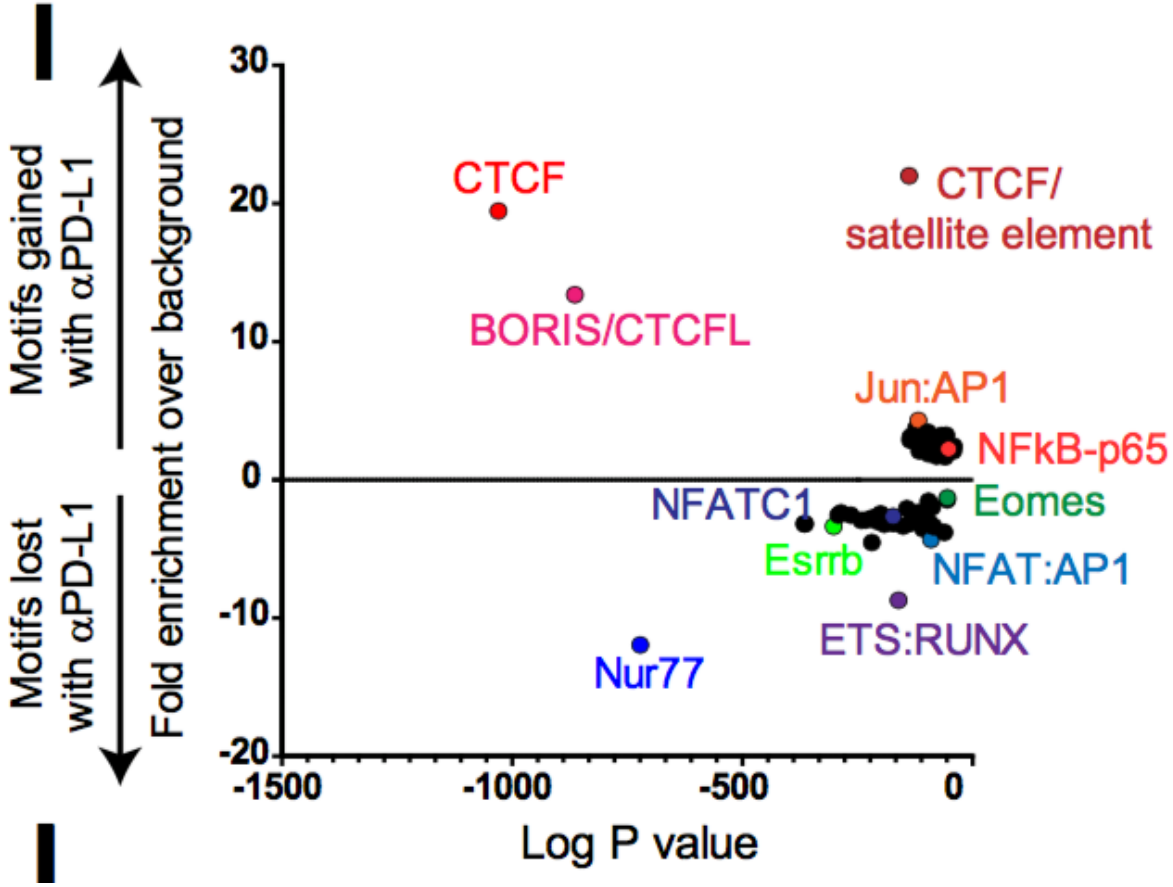
Where do exhausted and αPDL-1 cells fit?



Identifying (putative) transcription factor binding sites from ATAC-seq data



Nur77/NR4A1 motif-containing peaks are downregulated after αPDL-1 treatment



Nur77/NR4A1 is a pro-apoptotic TF in T cells

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Summary of T cell exhaustion and reinvigoration with αPD-L1

- Exhausted T cells treated with αPD-L1 rapidly (and reversibly) convert to a "more effector T cell-like transcriptome state"

- This conversion is reversible, likely due to the lack of true epigenetic or sustained signaling changes.

- αPD-L1 treated cells do not appear to undergo a lineage transition (to T_{mem} or T_{eff} or naive)

- αPD-L1 treated cells appear to downregulate Nur77, a pro-apoptotic gene, ostensibly allowing them to fight on for longer.