

### **Description of Additional Supplementary Files**

File Name: Supplementary Data 1

Description: Gene, cell, and gRNA counts of all studies.

File Name: Supplementary Data 2

Description: Unexpected associations and potential off-target effects of NTC gRNAs in CROP-seq screen.

File Name: Supplementary Data 3

Description: Gene regulatory network inferred from CROP-seq screen.

File Name: Supplementary Data 4

Description: Top GO enrichments of inferred targets of top up-/down-regulation favored regulators in CROP-seq screen.

File Name: Supplementary Data 5

Description: Significant gene ontology enrichments of top 100 principal genes in the co-expression network of dysfunctional T cells, for different numbers of GO covariates in iterative GO pathway removal.

File Name: Supplementary Data 6

Description: Differential gene expression result in dysfunctional v.s. naive T cells.

File Name: Supplementary Data 7

Description: Node and edge properties of Fig. 7c, Fig. S13, and Fig. S14.

File Name: Supplementary Data 8

Description: Top gene ontology enrichments of the cell cycle and type I interferon response clusters in the co-expression network of dysfunctional T cells.

File Name: Supplementary Data 9

Description: Over-abundance of co-expression edges between genes in the same GO or KEGG pathways.