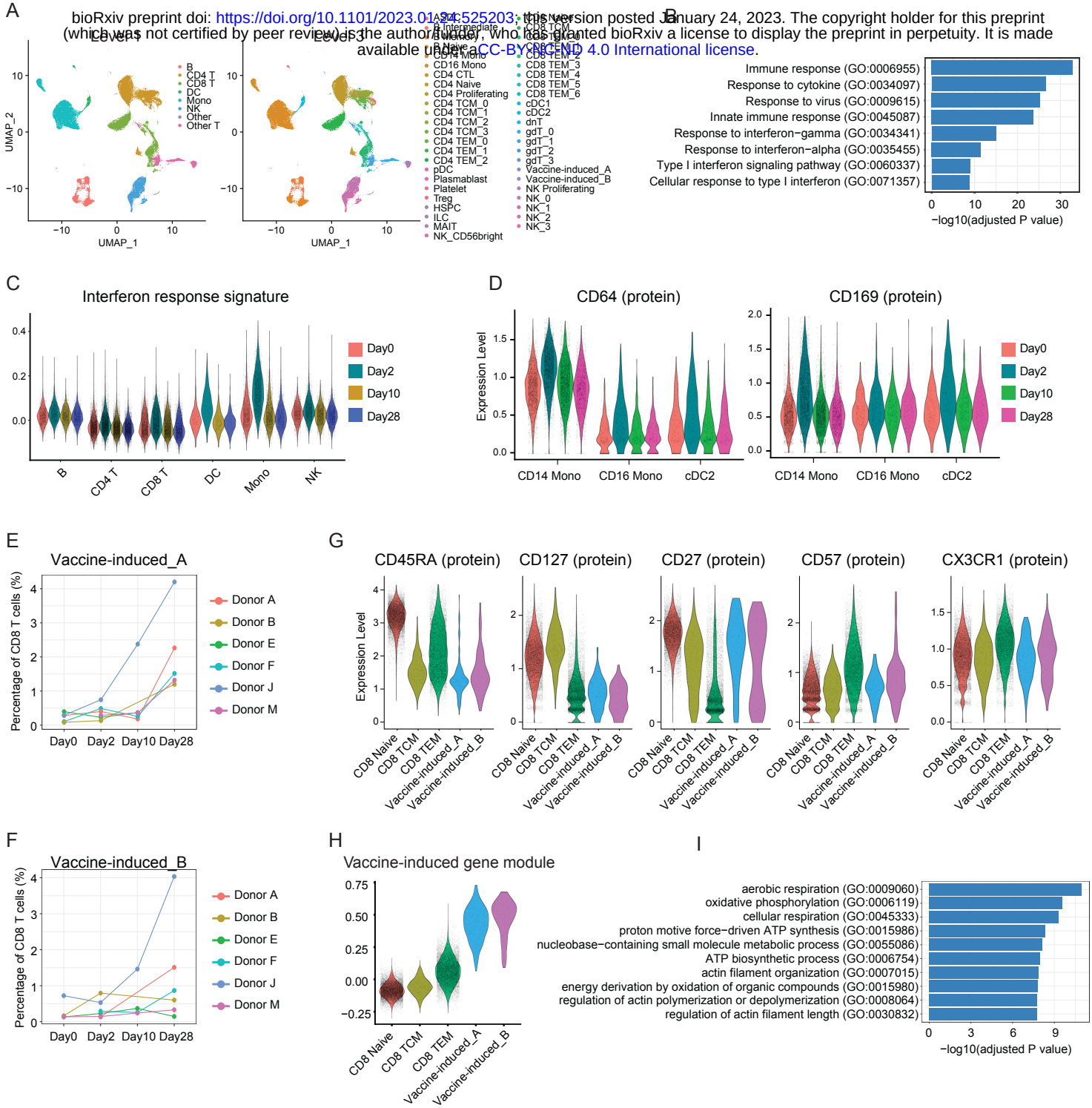
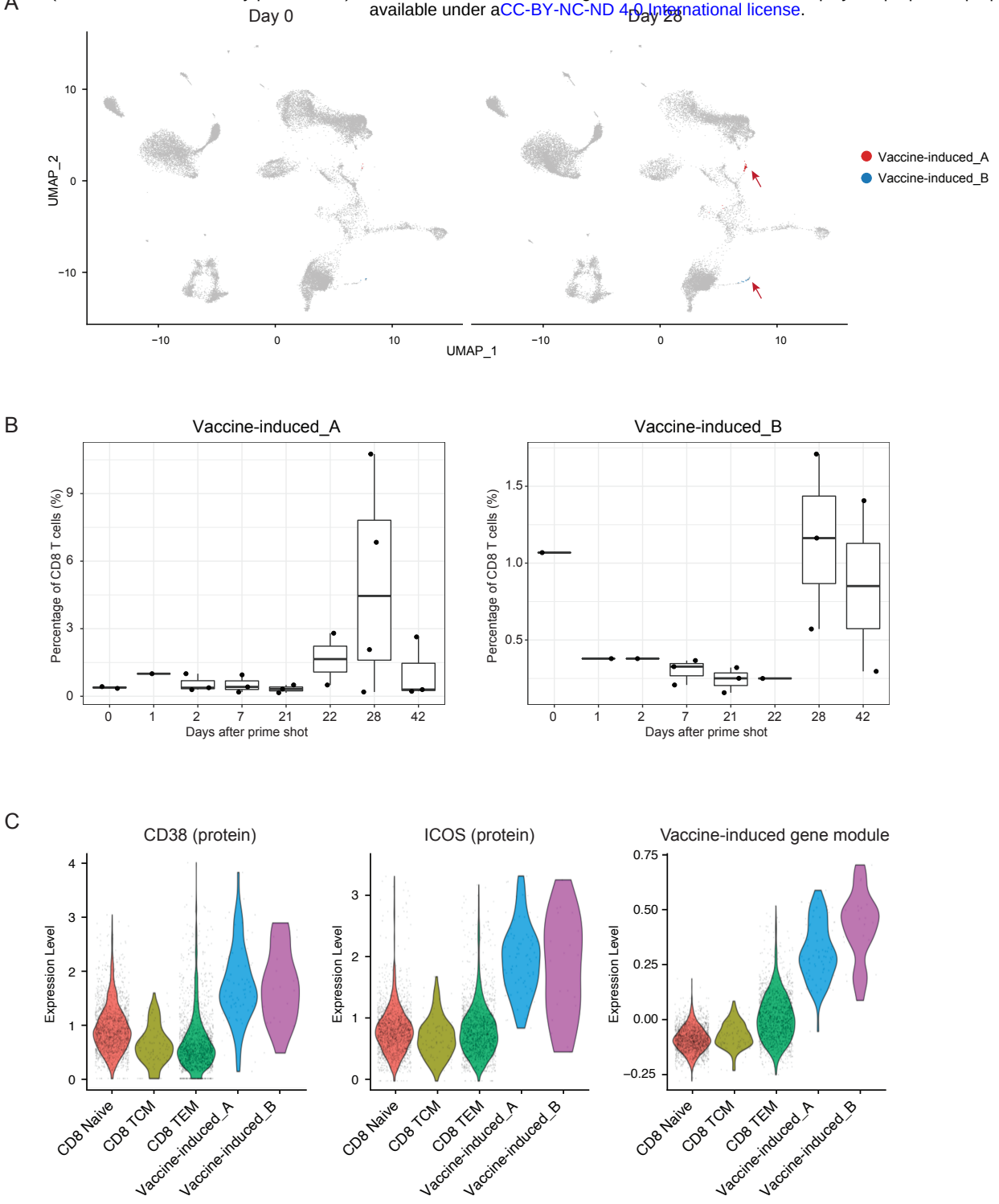
Supplementary Figure 1



Supplementary Figure 1

(A) UMAP visualizations of 113,897 single cells profiled with CITE-seq and clustered on the weighted combination of both RNA and protein modalities. Cells are colored with either level 1 or level 3 annotations. **(B)** Enriched GO terms for activated (Day 2 vs Day 0) genes in CD14+ Monocytes. **(C)** Violin plots of interferon response signatures in selected cell types across four timepoints. **(D)** Violin plots of protein upregulation of CD64 and CD169 in single cells in selected cell types, across four timepoints. **(E-F)** Percentage of CD8+ T cells in vaccine-induced groups for each donor across four timepoints. **(G)** Violin plots showing the protein expression of CD45RA, CD127, CD27, CD57 and CXC3R1 in selected cell types. **(H)** Violin plots comparing upregulated gene module scores in vaccine-induced group A and B cells, as well as selected other subsets. **(I)** Enriched GO terms for the 197 signature vaccine-induced gene set.

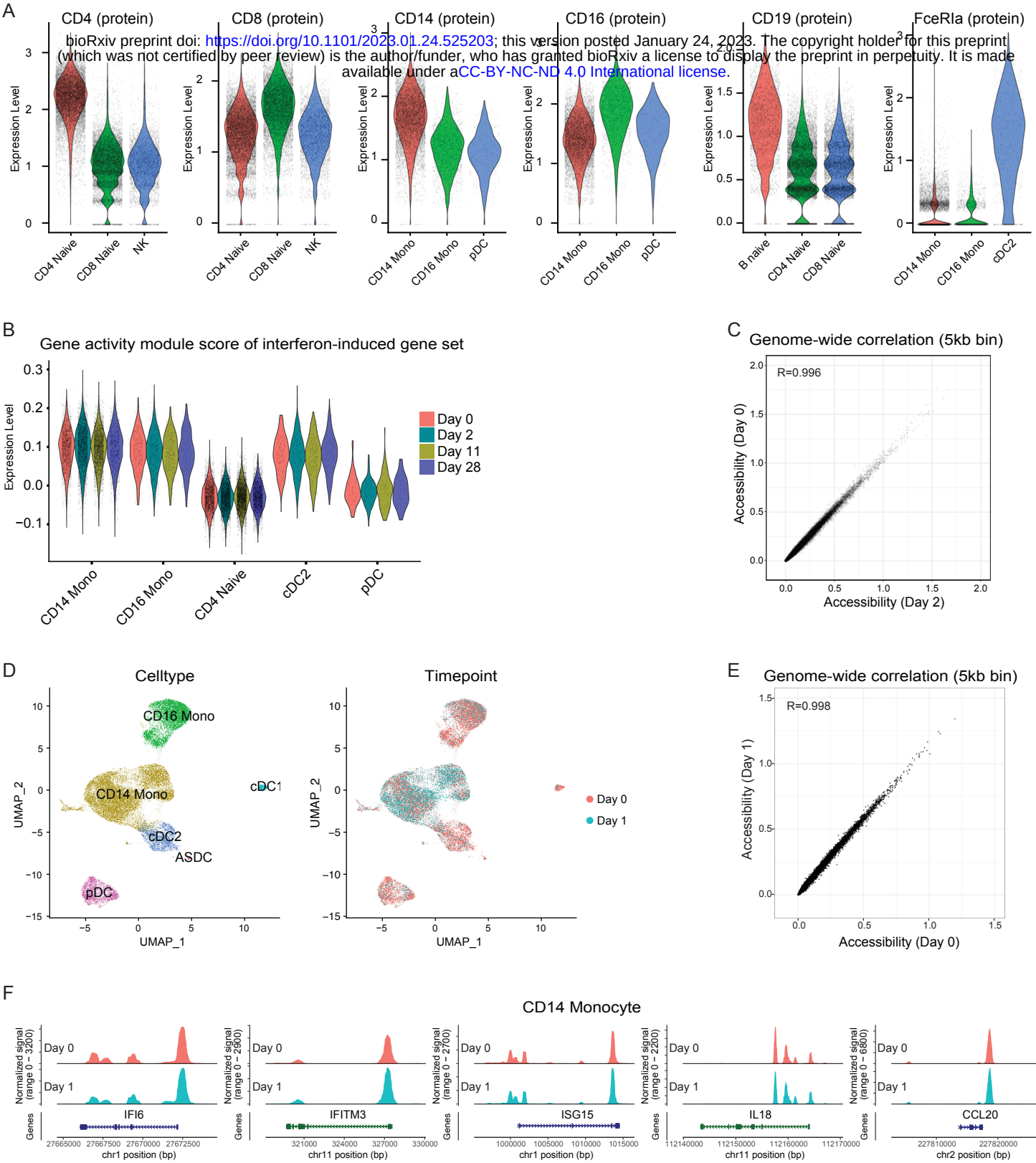
Supplementary Figure 2



Supplementary Figure 2

(A) UMAP visualization of CITE-seq data derived from human PBMC from Arunachalam et al. on Day0 and Day28, after reference mapping to the CITE-seq data in Figure 1B. Cells matching gene signature for vaccine-induced group A and B cells are highlighted in red and blue. **(B)** Boxplots showing the percentage of CD8+ T cells that fall in vaccine-induced group A (left) or group B cells (right) for each donor across eight timepoints. Each dot represents one donor. **(C)** Violin plots showing protein expression of CD38 and ICOS, along with a gene module score for vaccine-induced cells in selected CD8+ T cell subsets.

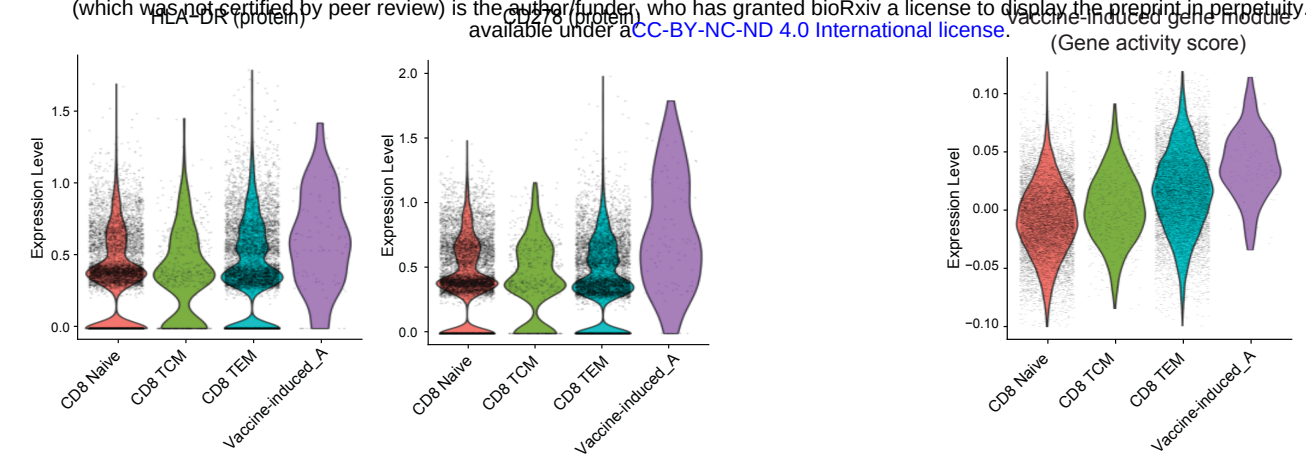
Supplementary Figure 3



Supplementary Figure 3

(A) Violin plots showing the expression of canonical surface proteins in the ASAP-seq dataset. Cells are grouped by bridge integration-derived labels. Proteins visualized include markers of CD4 and CD8 T cells, CD14 and CD16 monocytes, B cells and cDC2 cells. **(B)** Violin plots showing the gene 'activity scores', which are derived from scATAC-seq data, of the interferon-induced gene set shown in Figure 1C. **(C)** Scatter plot showing the correlation between pseudobulk chromatin accessibility of CD14 monocytes from Day 0 and Day 2 samples. Each point corresponds to a 5KB genomic bin. **(D)** UMAP visualization of the scATAC-seq profiles of myeloid cells from a trivalent inactivated seasonal influenza vaccine (TIV) study. Cells are colored by annotations (Left) or timepoints (right). **(E)** Scatter plot showing the correlation comparing pseudobulk chromatin accessibility of CD14 monocytes in the TIV dataset between Day 0 and Day 1. Each point corresponds to a 5KB genomic bin. **(F)** Visualization of open chromatin accessibility at representative loci on Day 0 and Day 1 in CD14 monocytes from the TIV study. Despite extensive transcriptional activation at these genes on Day 1, chromatin accessibility patterns do not change.

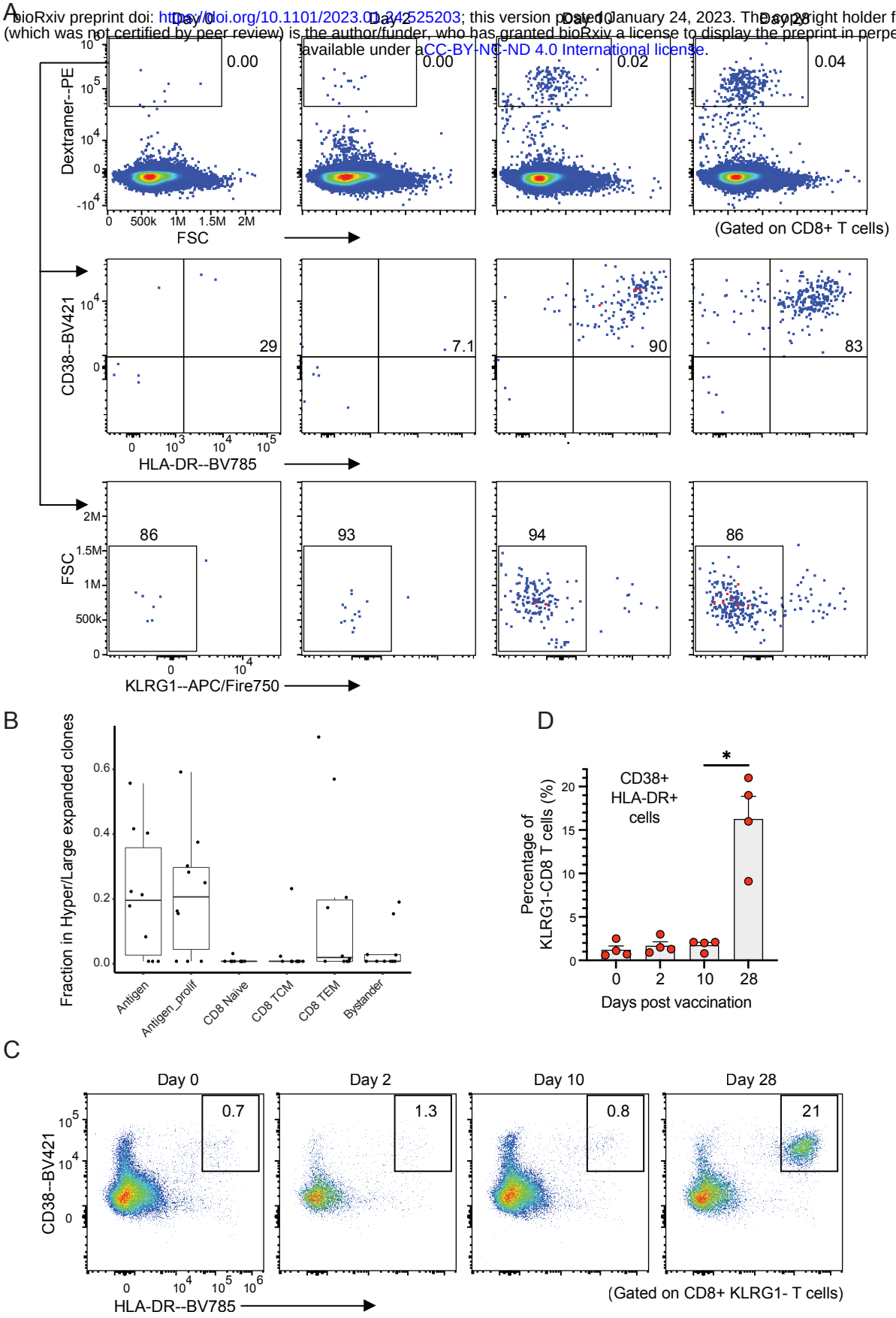
Supplementary Figure 4



Supplementary Figure 4

(A) Violin plots showing the protein upregulation of HLA-DR and CD278 (ICOS) in the vaccine-induced group A cells identified in the ASAP-seq dataset. Cells are grouped by their bridge integration-derived labels. **(B)** Violin plots showing the module score of the 197 signature vaccine-induced gene set in the ASAP-seq dataset. The module score is calculated based on gene activity scores, which are derived from scATAC-seq data.

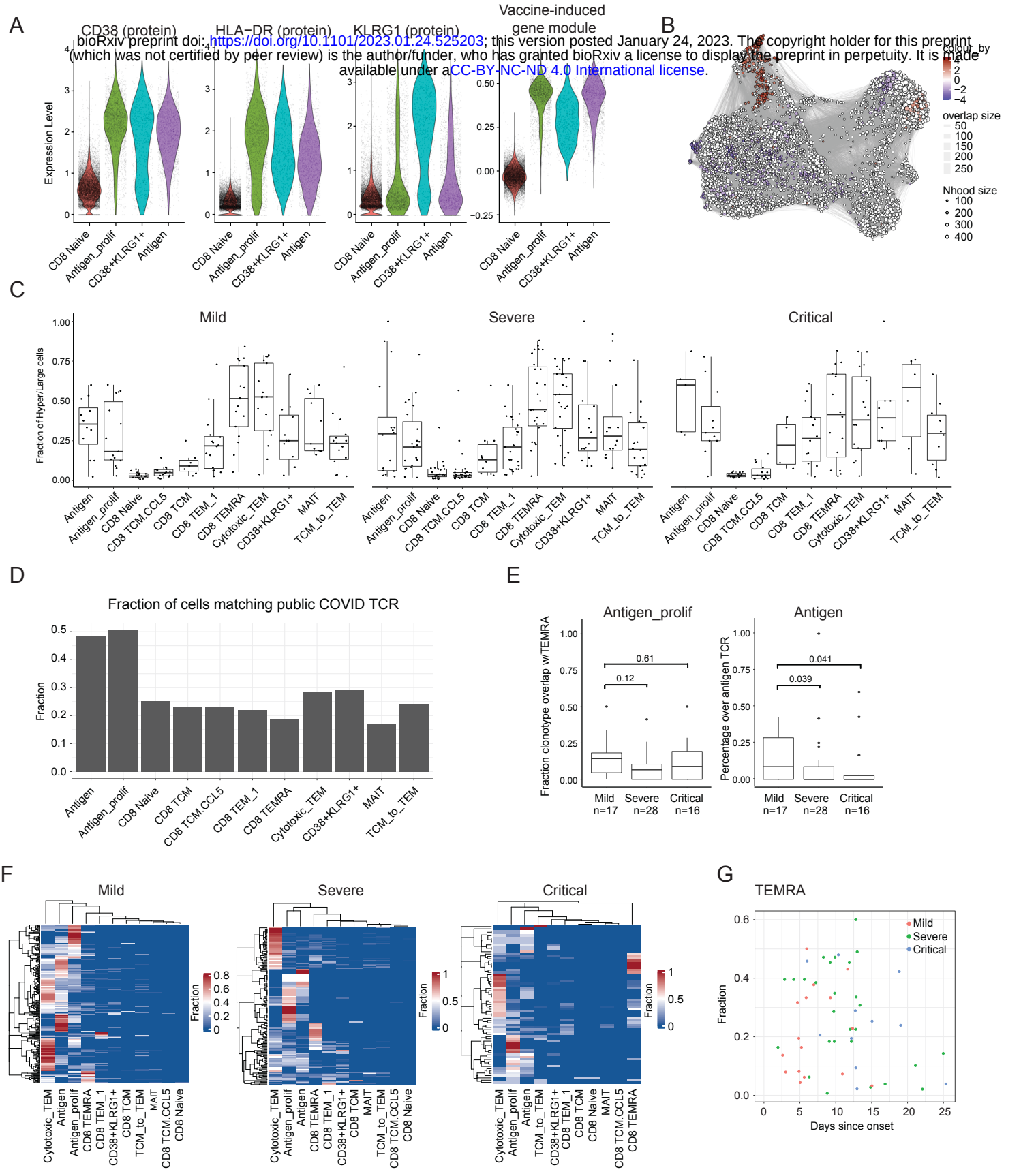
Supplementary Figure 5



Supplementary Figure 5

(A) Flow cytometry data generated during validation of individual dextramer reagents, with the progressive emergence of cells in the Dex+ gate across time points for a single donor. CD8+ cells were used as input. Middle and bottom row show CD38, HLA-DR, and KLRG1 abundance from the parent gate of Dex+CD8+ cells. **(B)** Boxplots indicate the fraction of cells harboring a hyper- or large-expanded TCR clone in each cluster. Each dot represents one biological sample. **(C)** Exemplary flow cytometry plots indicating the percentage of cells in CD38+HLA-DR+ gate of a single donor, from a parent gate of CD8+ KLRG1- cells. **(D)** Boxplot shows the percentage of CD38+HLA-DR+ cells in each donor, as a fraction of the CD8+KLRG1- gate exemplified in (C). Data represents n=4 donors with variable HLA haplotypes. p-value (p=0.0286) was calculated using a Mann-Whitney test.

Supplementary Figure 6



Supplementary Figure 6

(A) Violin plots showing the protein expression of CD38 and HLA-DR, along with the signature gene module score for the vaccine-induced cells, in the COMBAT dataset. **(B)** Milo analysis of differential abundance changes between healthy and SARS-CoV-2 infected CD8+ T cells groups from the COMBAT dataset. UMAP visualization of the Milo differential abundance testing results. Each node represents a neighborhood. The size of nodes is proportional to the number of cells in the neighborhood. Neighborhoods are colored by their log fold changes for SARS-CoV-2 infected versus healthy groups. Only neighborhoods showing significant enrichment (SpatialFDR < 0.1 and logFC > 2) are colored. **(C)** Boxplots showing the fraction of cells harboring a hyper or large expanded TCR clone within each cluster. Each dot represents one biological sample. **(D)** Barplot showing the fraction of cells within each cluster harboring TCR matching SARS-CoV-2 antigens in public databases. **(E)** Fraction of TCR clonotypes identified in either antigen cells (right) or antigen_prolif cells (left), that are also identified in TEMRA cells. Boxplots show variation across diseased donors. **(F)** Heatmaps show the distribution of cells harboring expanded antigen-specific TCR sequences among all cell states. Each row corresponds to one expanded clone, clones that are shared between molecular states will exhibit a positive fraction in multiple columns. **(G)** Scatter plot showing the lack of a potentially confounding correlation between the fraction of CD8 T cells in the TEMRA state, and the sample collection time since onset. Each dot represents one donor and is colored by disease state.