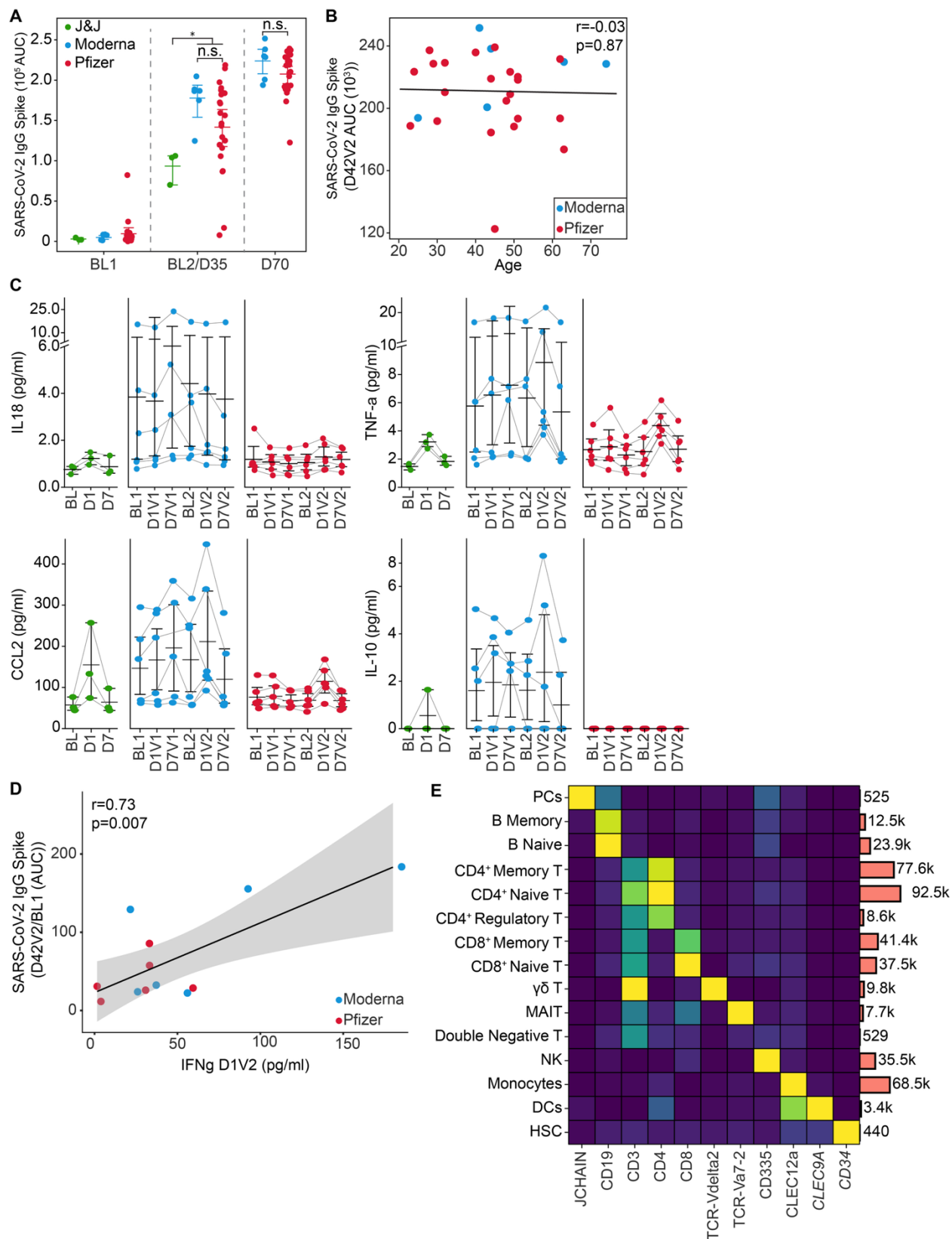
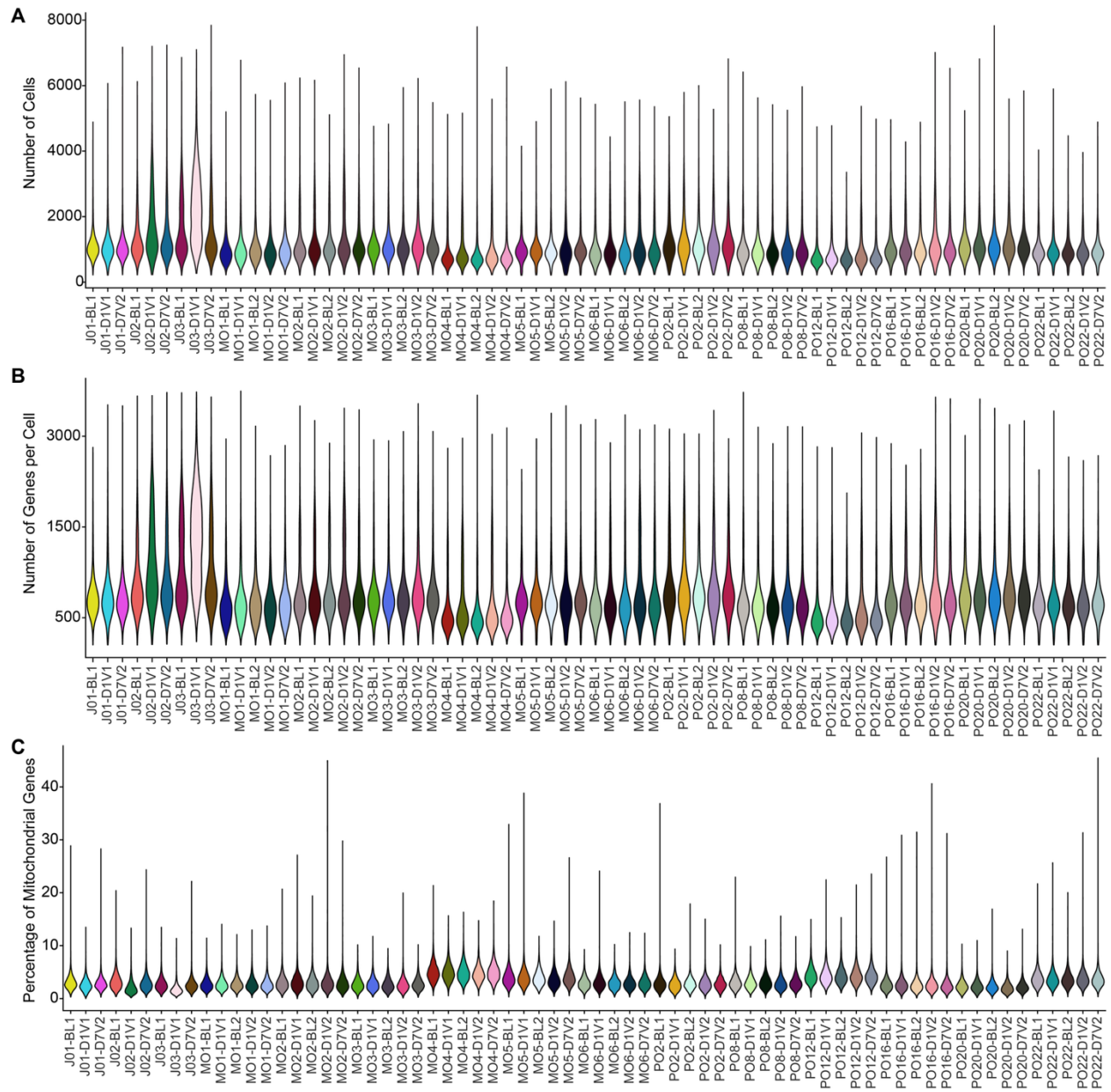




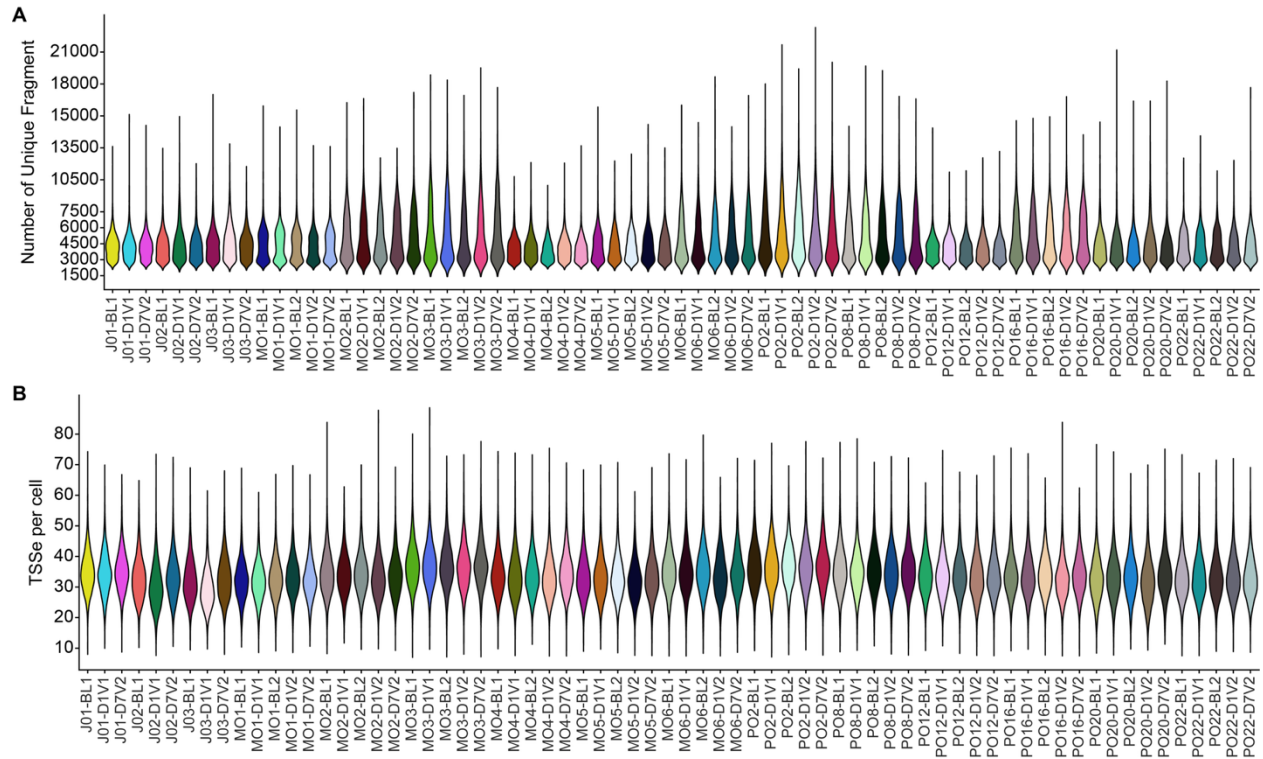
Supplementary Figure 1: Antibody titer and cytokine level after adenovirus and mRNA vaccination

(A) IgG titers against SARS-CoV-2 spike protein measured by ELISA. mRNA vaccines elicit higher antibody titer compared to J&J. (B) The correlation plot with age and antibody titer for mRNA vaccines. Pearson's correlation was used to calculate statistics. The Pearson correlation analysis examining the relationship between IFN- γ protein levels and IgG titers after booster vaccination in mRNA-vaccinated donors. (C) IL-8, TNF α , CCL2, and IL-10 cytokine levels, quantified by ELLA. (D) The Pearson correlation analysis examining the relationship between IFN- γ protein levels and IgG titers fold change (D42 vs BL1) in mRNA-vaccinated donors. (E) The heatmap shows the marker genes for single-cell annotations. (A) The statistical analysis is conducted between all mRNA vaccine recipients (Moderna and Pfizer) and adenovirus vaccine recipients. Statistical comparisons were performed using the Mann-Whitney test: n.s.: non-significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.



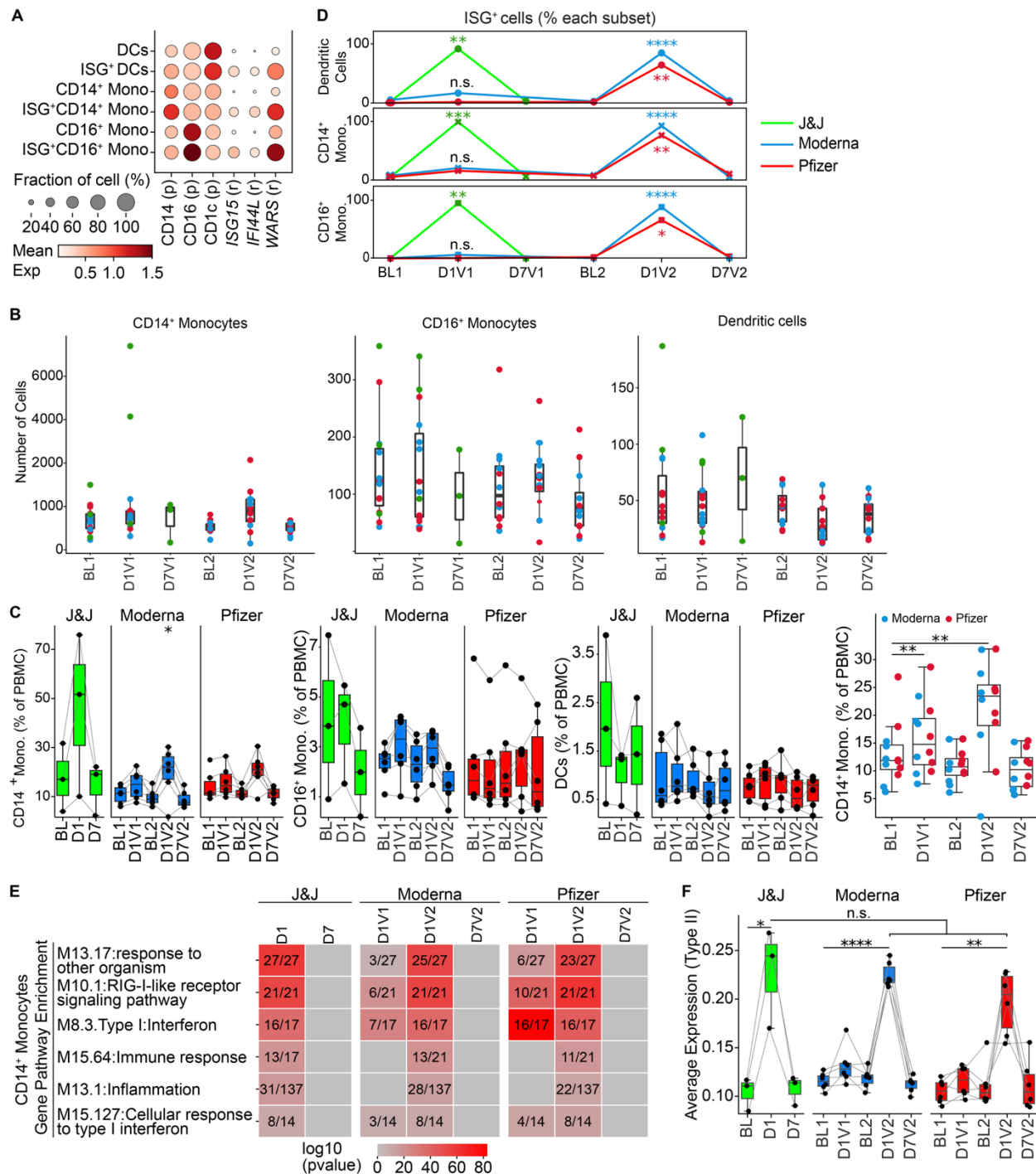
Supplementary Figure 2: The statistical and quality metrics used in RNA-seq pre-processing

(A) The number of cells per donor and time point is given as a violin plot. (B) The number of genes per cell for each donor and timepoint is given as a violin plot. (C) Mitochondrial gene percentage is given as a violin plot.



Supplementary Figure 3: The statistical and quality metrics used in ATAC-seq pre-processing, and the number of cells within the myeloid population.

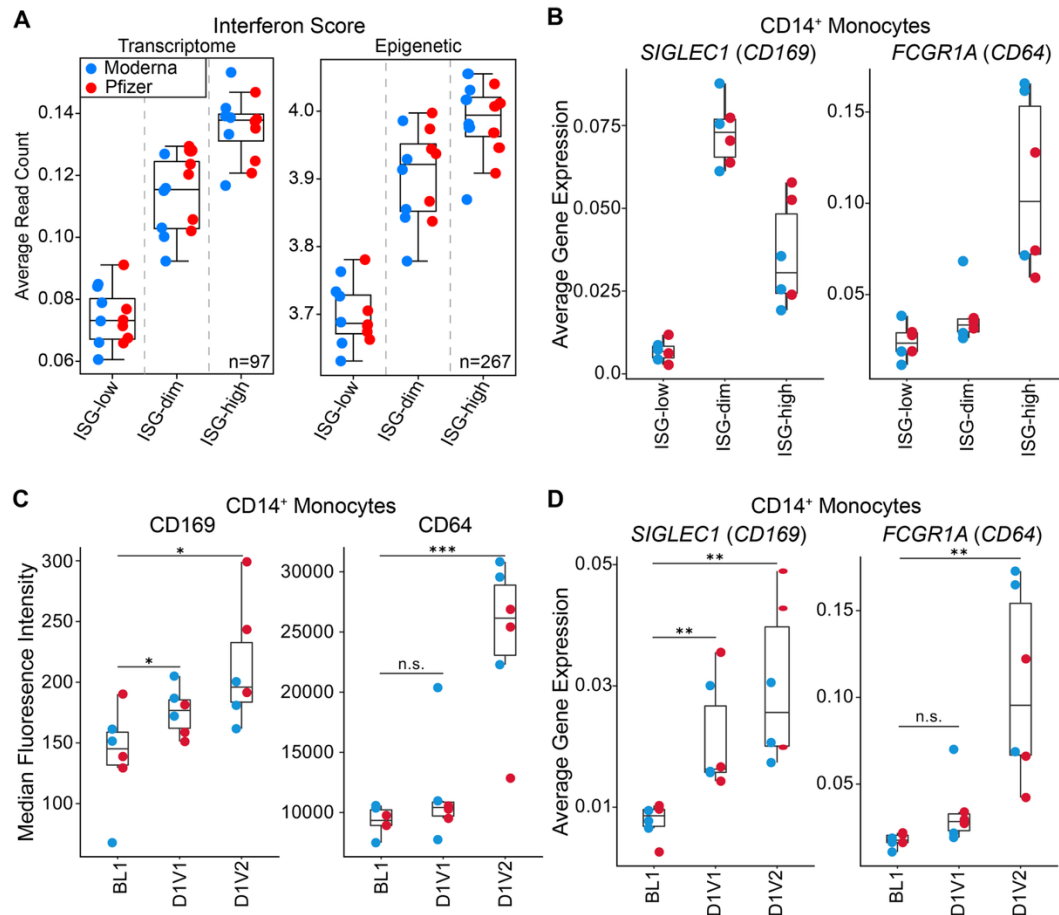
(A) The number of unique fragments per donor and time point is given as a violin plot. **(B)** The Transcription Start Site enrichment score (TSSe) for each donor and time point is given as a violin plot.



Supplementary Figure 4: Adenovirus and mRNA vaccines response in CD14⁺ monocytes.

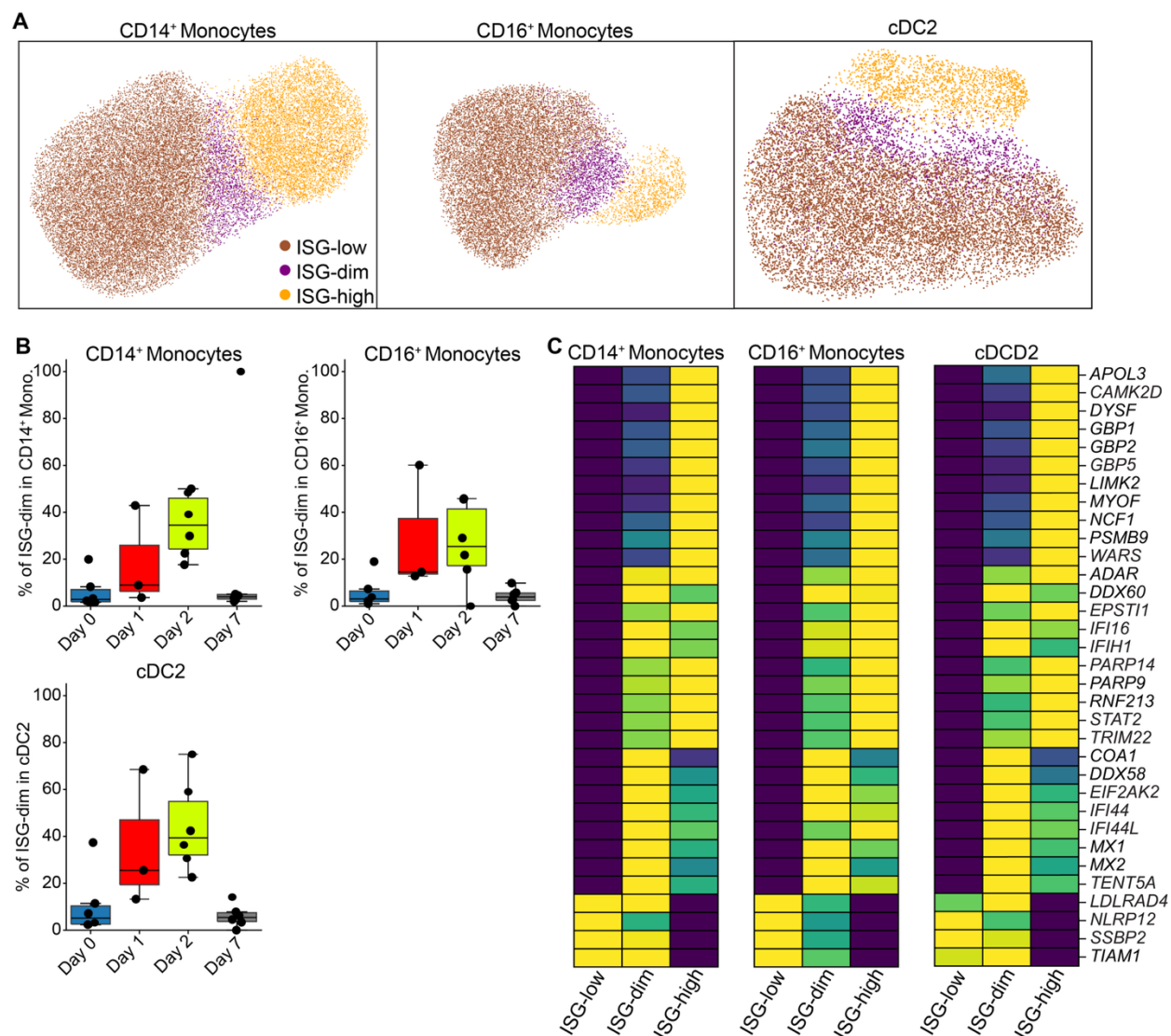
(A) The average expression of marker genes in each myeloid and ISG subsets. (B) The percentage of CD14⁺ monocytes, CD16⁺ monocytes and dendritic cells (DCs) in total PBMC (left). Significant expansion of the CD14⁺ monocytes upon mRNA vaccination (right). (C) The number of cells is given as a box plot for each time point in myeloid cells. (D) The percentage of ISG subsets within each lineage for each vaccine. (E) The heatmap shows the top 6 enriched pathways obtained by over-representation analysis using the Blood3GenModule. The number inside indicates the

number of overlaps for the respective module. **F)** Type-II interferon expression score calculated from manually curated list (n=51). **(C)** Statistical comparisons were performed using the one-sided Wilcoxon test **(D, F)** Statistical significance between timepoints was performed using a two-tailed paired t-test; statistical significance between mRNA vaccine (Pfizer and Moderna) and adenovirus was performed using a non-paired t-test: n.s. non-significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.



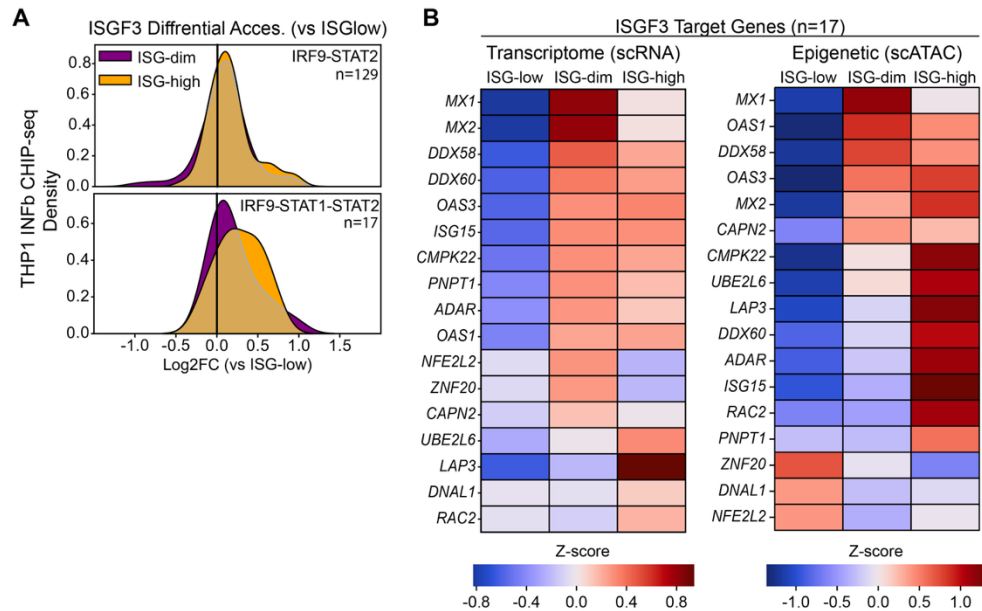
Supplementary Figure 5: The ISG transcriptome and surface protein markers to distinguish ISG-dim and ISG-high populations in CD14⁺ Monocytes.

(A) Interferon scores for cells in each ISG state. **(B)** Mean gene expression levels of *SIGLEC1* (CD169) and *FCGR1A* (CD64) across ISG states. **(C)** Fluorescence mean intensity of CD169 (ISG-dim marker) and CD64 (ISG-high marker) measured by flow cytometry in CD14⁺ monocytes from six mRNA-vaccinated donors. **(D)** Mean gene expression levels of *SIGLEC1* (CD169) and *FCGR1A* (CD64) across corresponding CD14⁺ monocytes from the same donors.



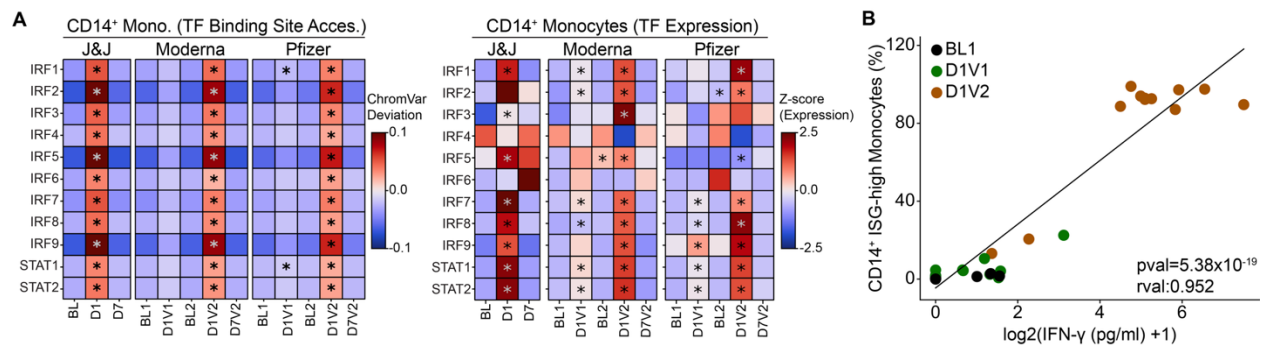
Supplementary Figure 6: Distinct ISG subset signature in publicly available data from donors vaccinated with BNT162b2.

(A) UMAP representation of ISG-low, ISG-dim, and ISG-high subsets in CD14⁺ monocytes, CD16⁺ monocytes and cDC2 cell types. **(B)** ISG-dim cell percentage within respective cell populations across different timepoints. **(C)** The heatmap displays the expression levels of marker genes for ISG states in CD14⁺ monocytes, CD16⁺ monocytes, and cDC2s.



Supplementary Figure 7: ISGF3 Transcription factor epigenetic dynamic changes

A) Kernel density estimation plots show the distribution of accessibility of transcription factor binding sites in ISG-dim and ISG-high compared to the ISG-low subset. IRF9-STAT2 and IRF9-STAT1-STAT2 (ISGF3) peaks were identified by intersecting each TF motif of overlapping peaks of CHIP-seq data. **B)** The heatmap shows the expression and accessibility of the genomic region targeted by the ISGF3 complex in three ISG states.



Supplementary Figure 8: IFNG cytokine levels correlates with ISG-high CD14⁺ Monocyte

(A) Longitudinal binding site activity of the IRFs and STATs calculated by ChromVAR (left); corresponding gene expression levels (right) of same TFs (right). **(B)** Pearson correlation between ISG-high state percentage in CD14⁺ monocytes and IFN- γ cytokine levels per sample. **(A)** Statistical significance between timepoints were performed using one-tailed paired t-test, $*P < 0.05$.