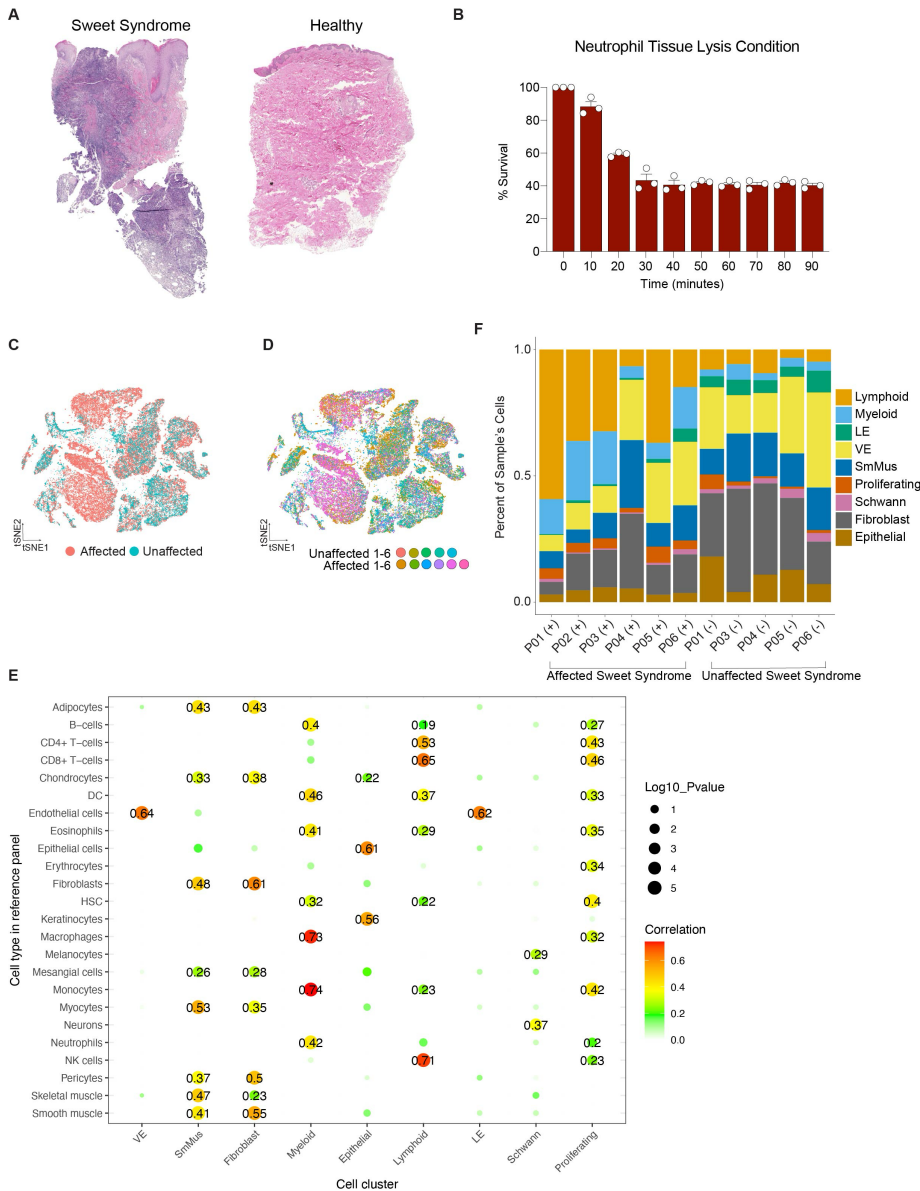
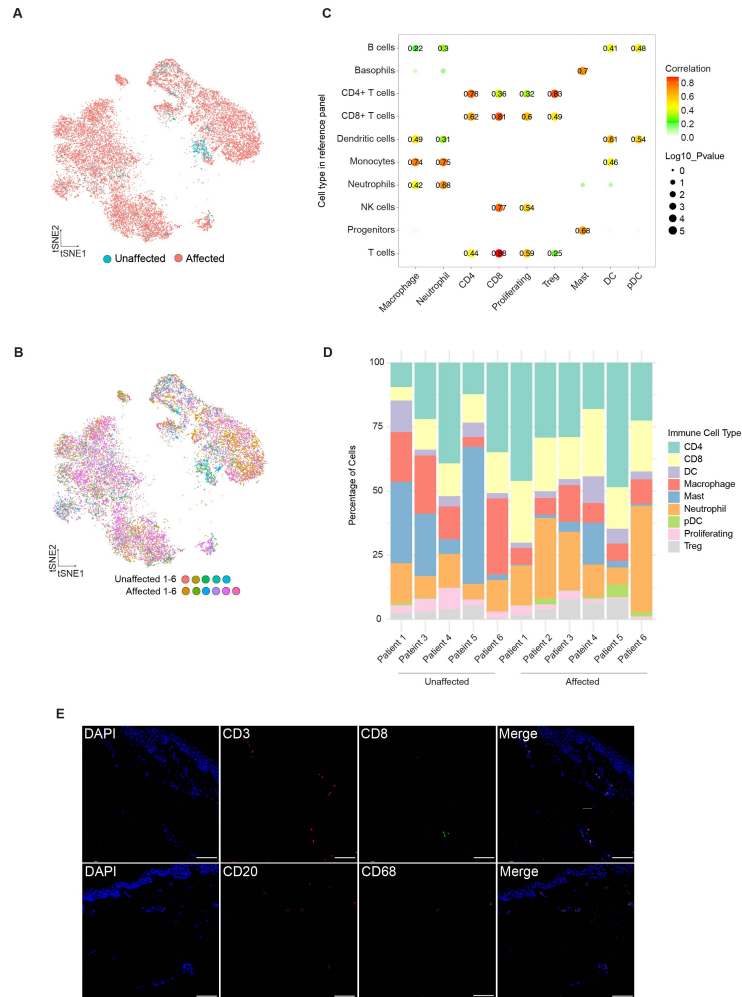


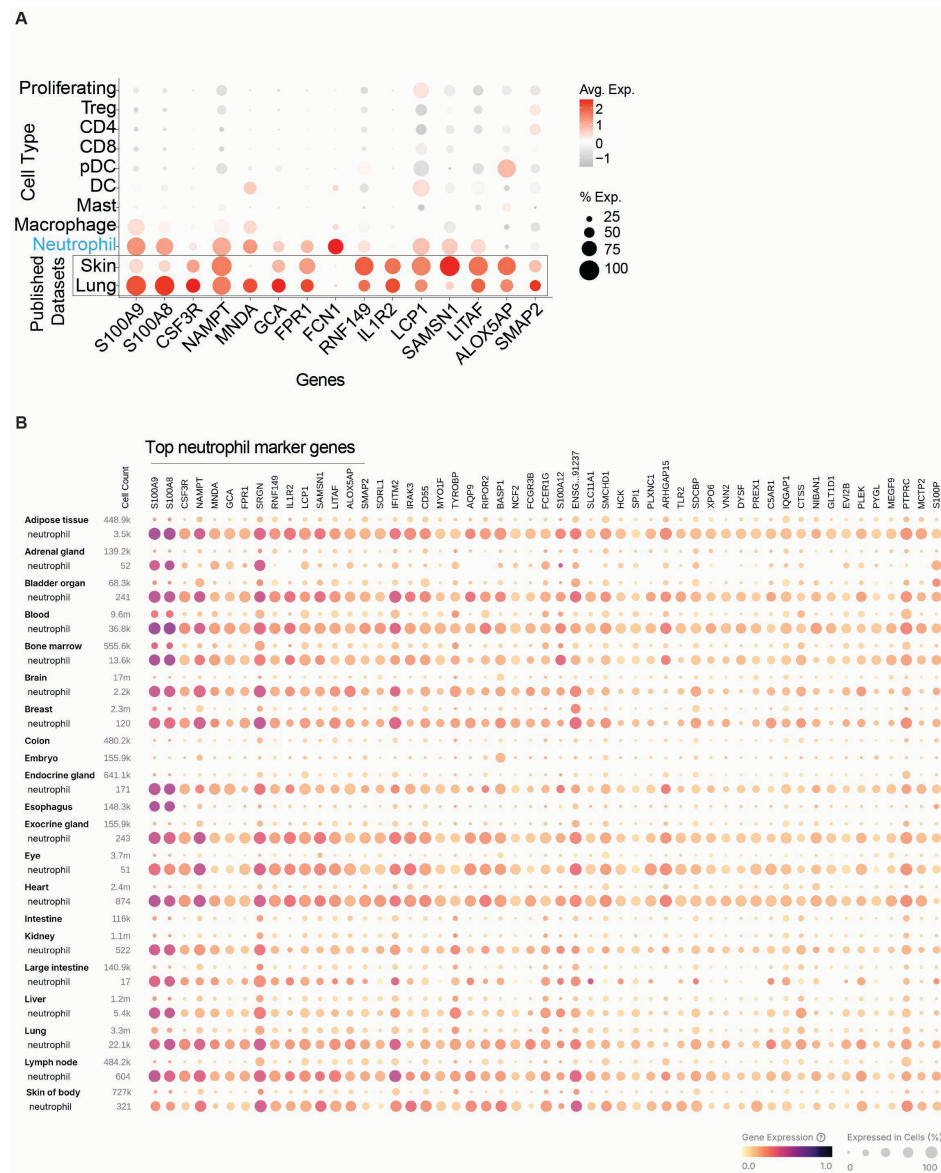


Supplemental Figure 1: Human Sweet syndrome samples. (A) H&E staining of affected and unaffected skin from Sweet syndrome patients. (B) Viability of blood neutrophils during the tissue dissociation protocol at different time points. Mean $\pm$ SEM from $n=3$ independent experiments. (C) tSNE plot demonstrating cell clusters overlap between affected and unaffected Sweet syndrome skin. (D) Cell contributions to tSNE plot from individual patient samples. (E) Cell type correlation analysis (deCS) mapping identified clusters to reference immune cell databases. Color intensity represents Pearson correlation coefficient; dot size indicates $-\log_{10}$ p-value. (F) Contributions of individual cell types in each patient sample.

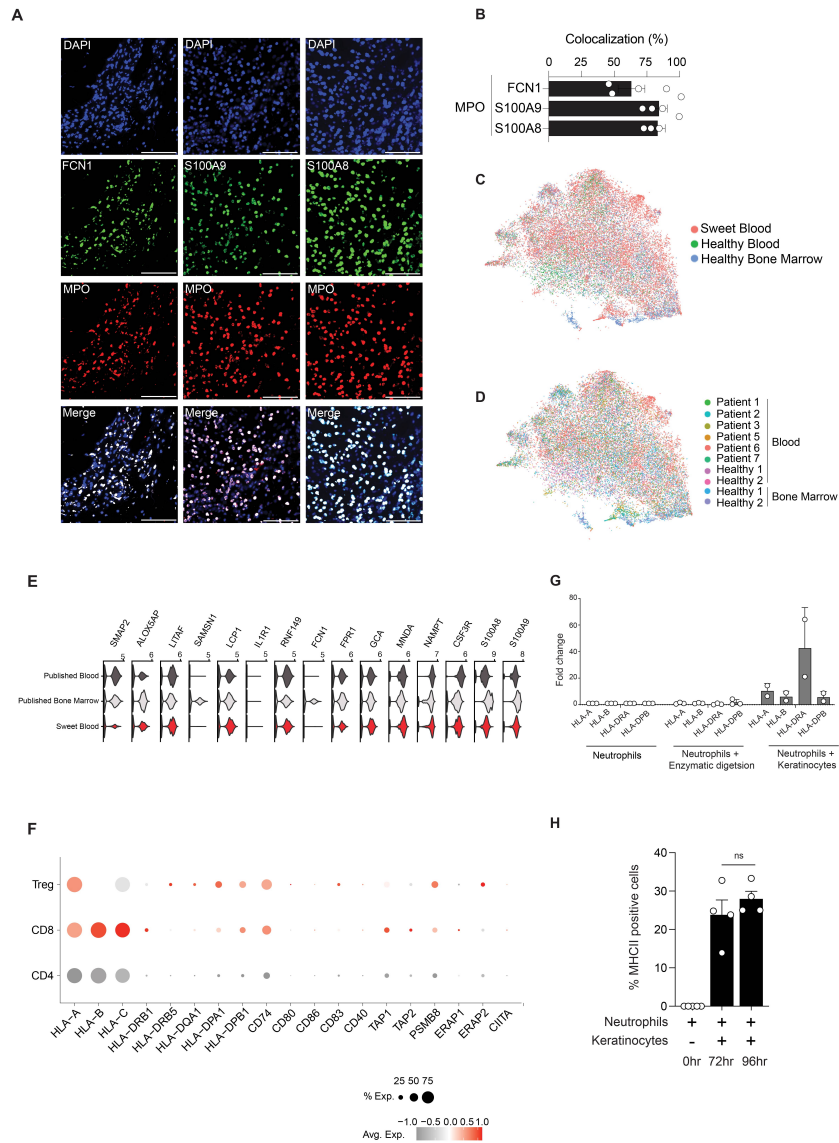


Supplemental Figure 2: Immune cell subclustering of Sweet syndrome skin

(A) tSNE plot of immune cell subcluster in unaffected and affected Sweet syndrome skin. **(B)** Contribution to tSNE plot by individual patients. **(C)** deCS correlation plot for cell type enrichment analysis of different cell clusters. Y-axis: main cell types identified from MonaccoImmune database. Color scale represents Pearson correlation coefficient, and dot sizes represent the $-\log_{10}$ transformed p value. **(D)** Contributions of individual immune cell types in each patient sample. **(E)** Representative immunofluorescence staining from 3 control human skin samples confirming populations of macrophages (CD68+), B cells (CD20+) and T cells (CD3+, CD8+) within normal human dermis. Scale bar 100μM.

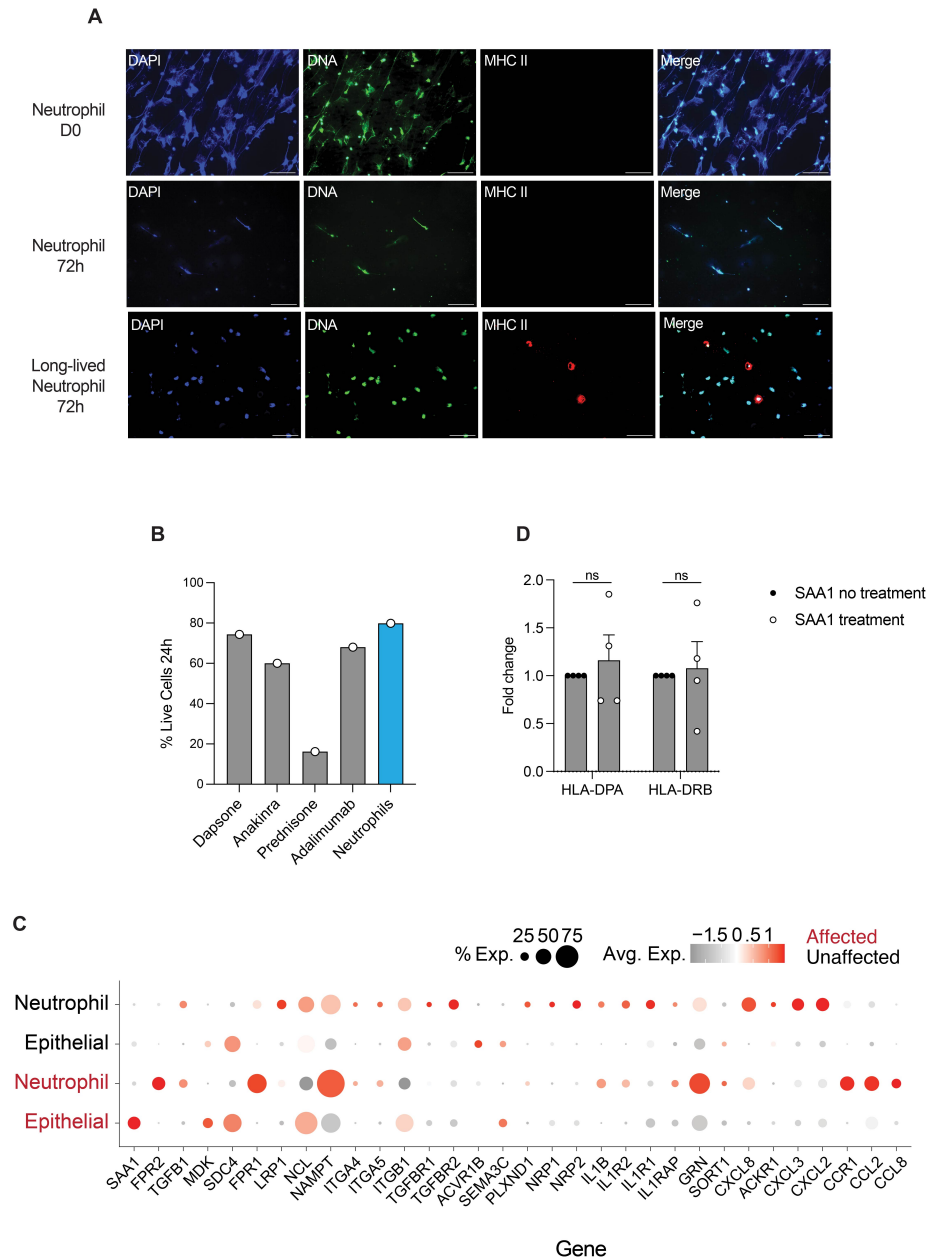


Supplemental Figure 3: Validation of neutrophil identity through marker gene expression. (A) Top 15 genes expressed in single-cell neutrophil cluster compared with other cell types and with published human neutrophil datasets. (B) Comprehensive dot plot of neutrophil marker gene expression across multiple human tissue sources from the Human Cell Atlas datasets.



Supplemental Figure 4: Characterization of Sweet syndrome neutrophils.

(A) Immunofluorescence staining of Sweet syndrome tissue demonstrating co-expression of neutrophil-specific marker genes (FCN1, S100A8, S100A9) and myeloperoxidase (MPO). (B) Quantification of Immunostaining. n=4. (C) tSNE plot neutrophil subcluster showing overlap with published purified neutrophil from blood and bone marrow. (D) Contributions by each patient sample. (E) Shared expression of most of the top 15 neutrophil-specific genes identified in our skin dataset within blood neutrophils from different sources. (F) Dot plot showing MHC genes in different T cell subsets within Sweet syndrome blood. Dot size reflects percent cells expressing the gene, and color illustrates level of gene expression. (G) qPCR analysis of MHC gene expression in healthy neutrophils following enzymatic digestion or keratinocyte co-culture (positive control). (H) Immunofluorescence quantification of MHC-II positive neutrophils after 72 or 96 hours of culture with or without keratinocytes. One-way ANOVA with individual comparisons. ns, not significant. Mean $\pm$ SEM, n=3.



Supplemental Figure 5: Long-lived neutrophils exhibit reduced spontaneous NETosis, *SAA1* and *FPR2* transcripts are induced in Sweet syndrome skin.

(A) Immunostaining depicting decreased spontaneous NETosis in long-lived neutrophils (DAPI, blue, DNA, green, MHC, red). Scale bars 100µM. (B) Effect of Sweet syndrome therapeutics on healthy neutrophil survival at 24 hours. (C) Compared to unaffected control, dot plot demonstrating induction of *SAA1* and *FPR2* transcript in affected skin keratinocytes and neutrophils, respectively. Dot size reflects percent cells expressing the gene, and color illustrates level of gene expression. (D) qPCR analysis assessing MHC class II gene expression (*HLA-DPA*, *HLA-DRB*) in neutrophils at 24 hours after treatment with and without SAA1 treatment. Two-tailed Student's T-test. ns, not significant. Mean $\pm$ SEM, n=4.