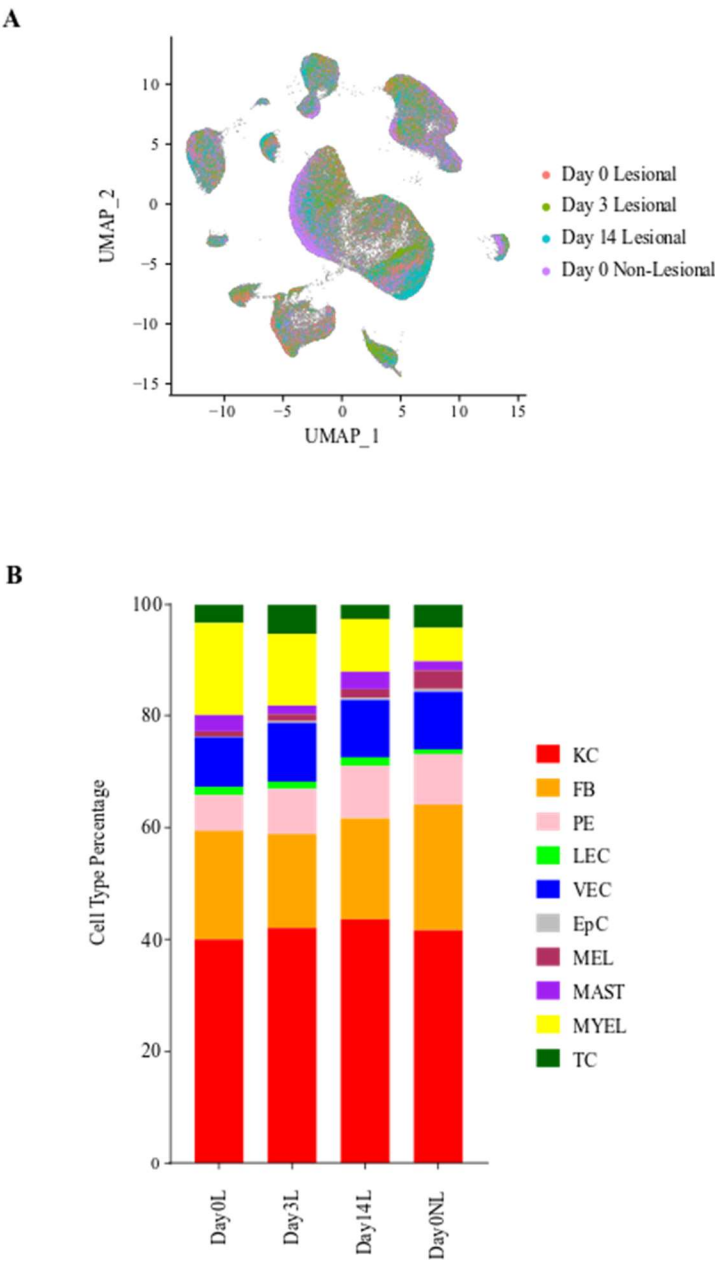


Supplementary Figures



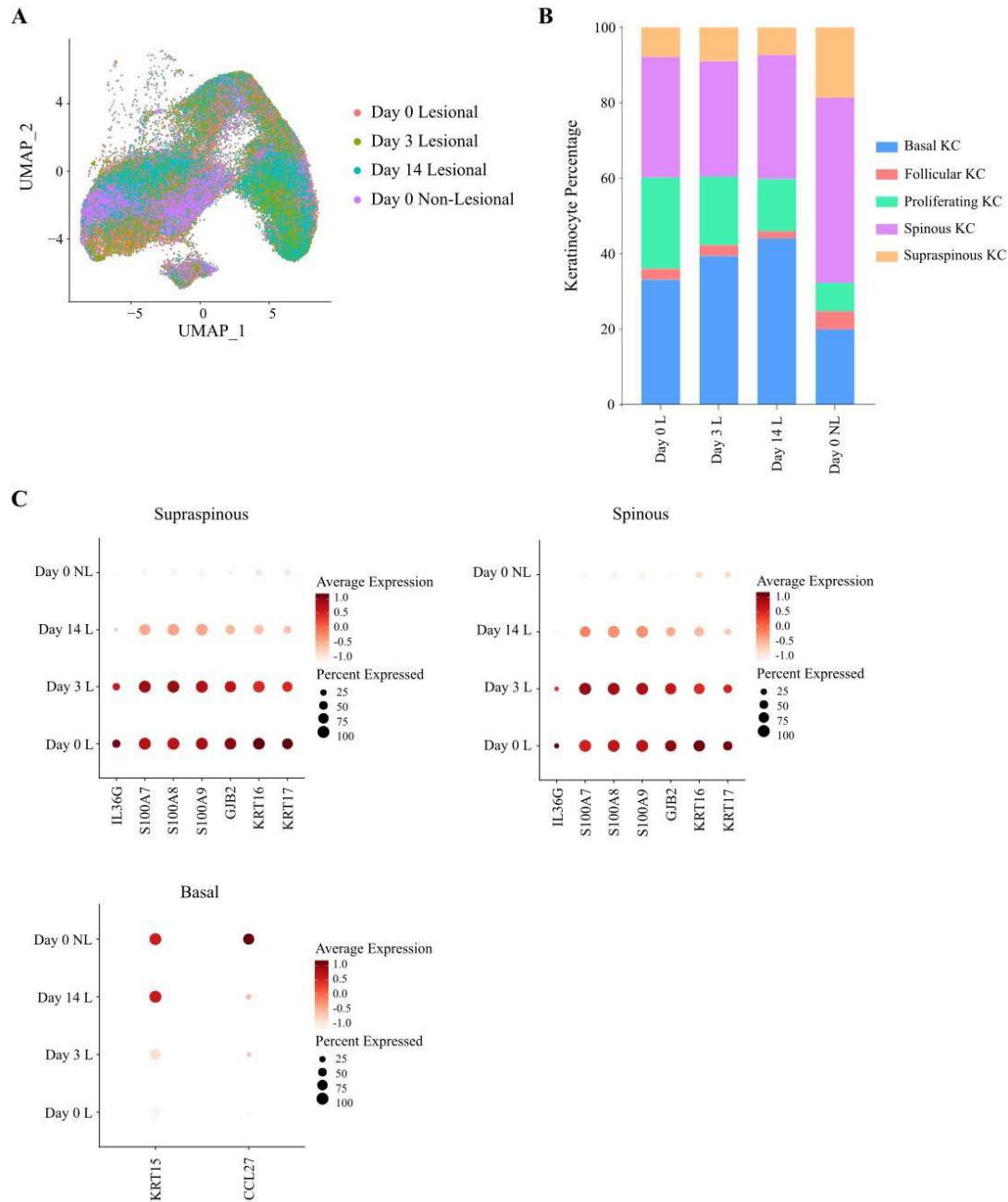
Supplementary Figure 1: Clustering and abundance of cell populations detected in treated and

untreated skin. (A) Unifold Manifold Approximation and Projection (UMAP) of 164,553 single cells

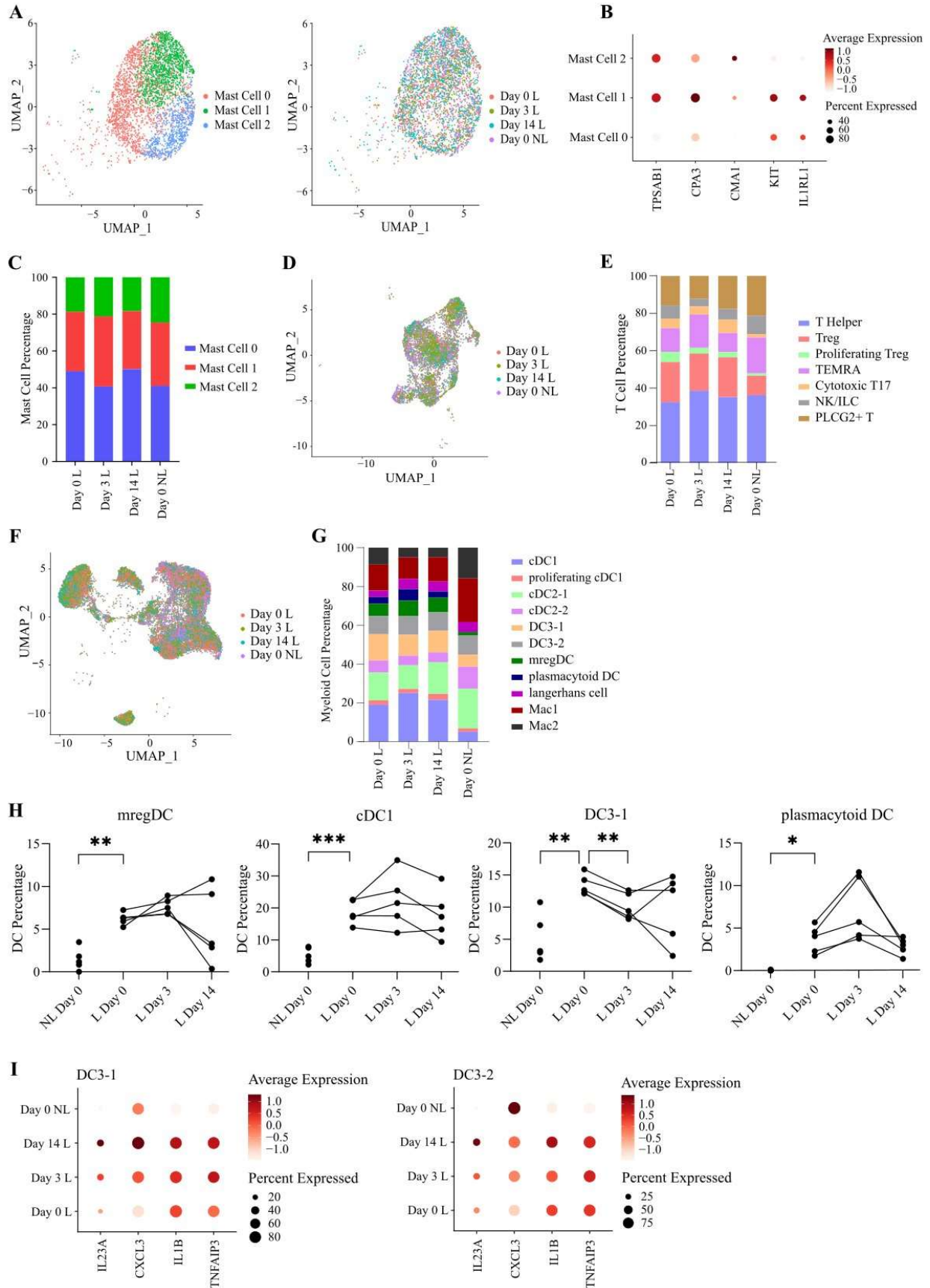
showing that cluster membership is not influenced by sample type (lesional vs non-lesional skin) or

study time point (n=5 patients). **(B)** Stacked bar chart showing the abundance of the various cell

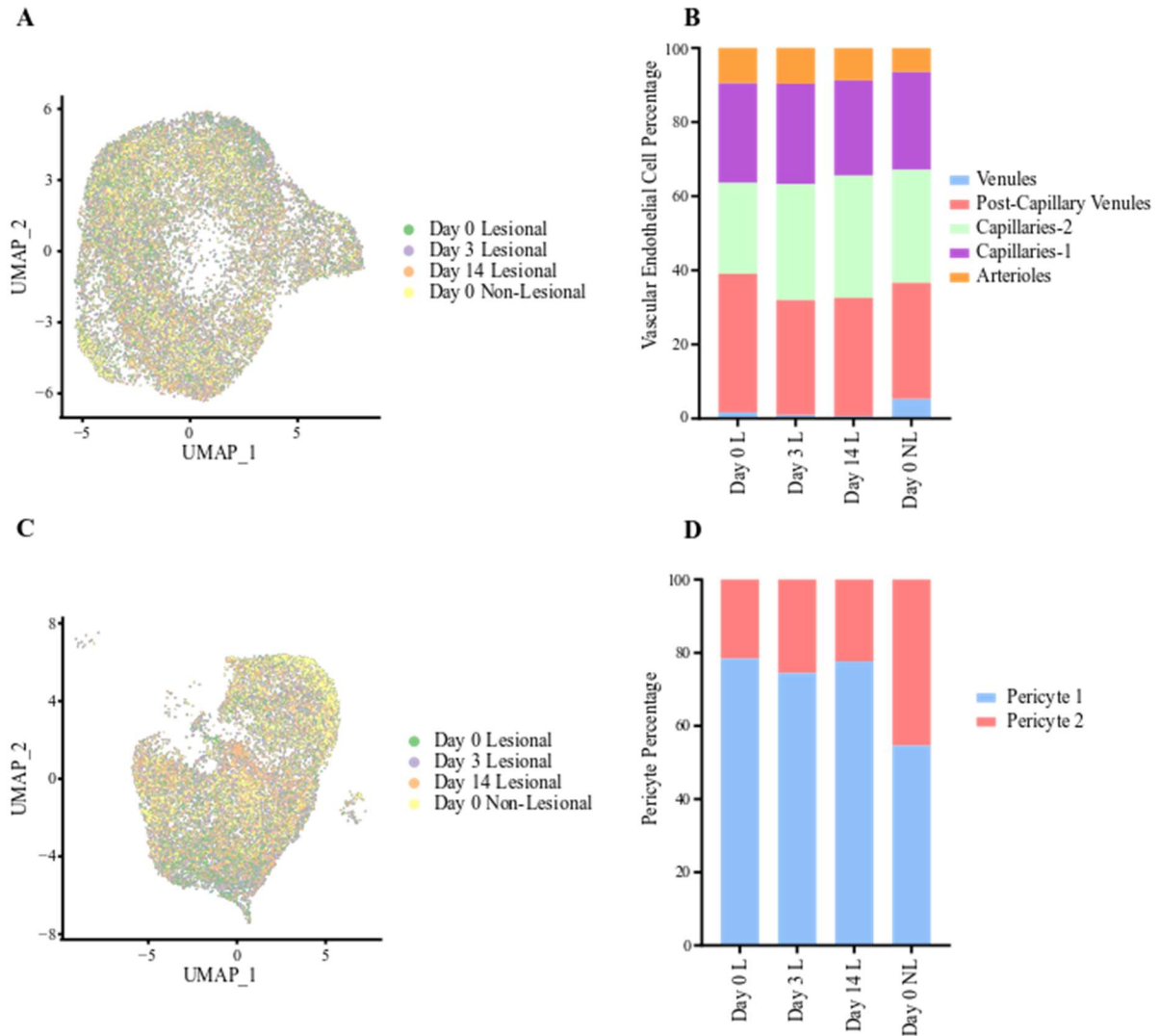
populations in the four sample groups. KC, keratinocytes; FB, fibroblasts; PE, pericytes; LEC, lymphatic endothelial cells; VEC, vascular endothelial cells; EpC, epithelial cells; MEL, melanocytes; MAST, mast cells; MYEL, myeloid cells; TC, T cells; L, lesional skin; NL, non-lesional skin.



Supplementary Figure 2: Clustering and abundance of keratinocyte populations detected in treated and untreated skin. (A) UMAP of 68,695 keratinocytes showing that cluster membership is not influenced by sample type (lesional vs non-lesional skin) or study time point (n=5 patients). **(B)** Stacked bar chart showing the abundance of the various keratinocyte populations in the four sample groups. **(C)** Dot plots showing treatment-induced gene expression changes within keratinocyte populations. KC, keratinocytes; L, lesional skin; NL, non-lesional skin.

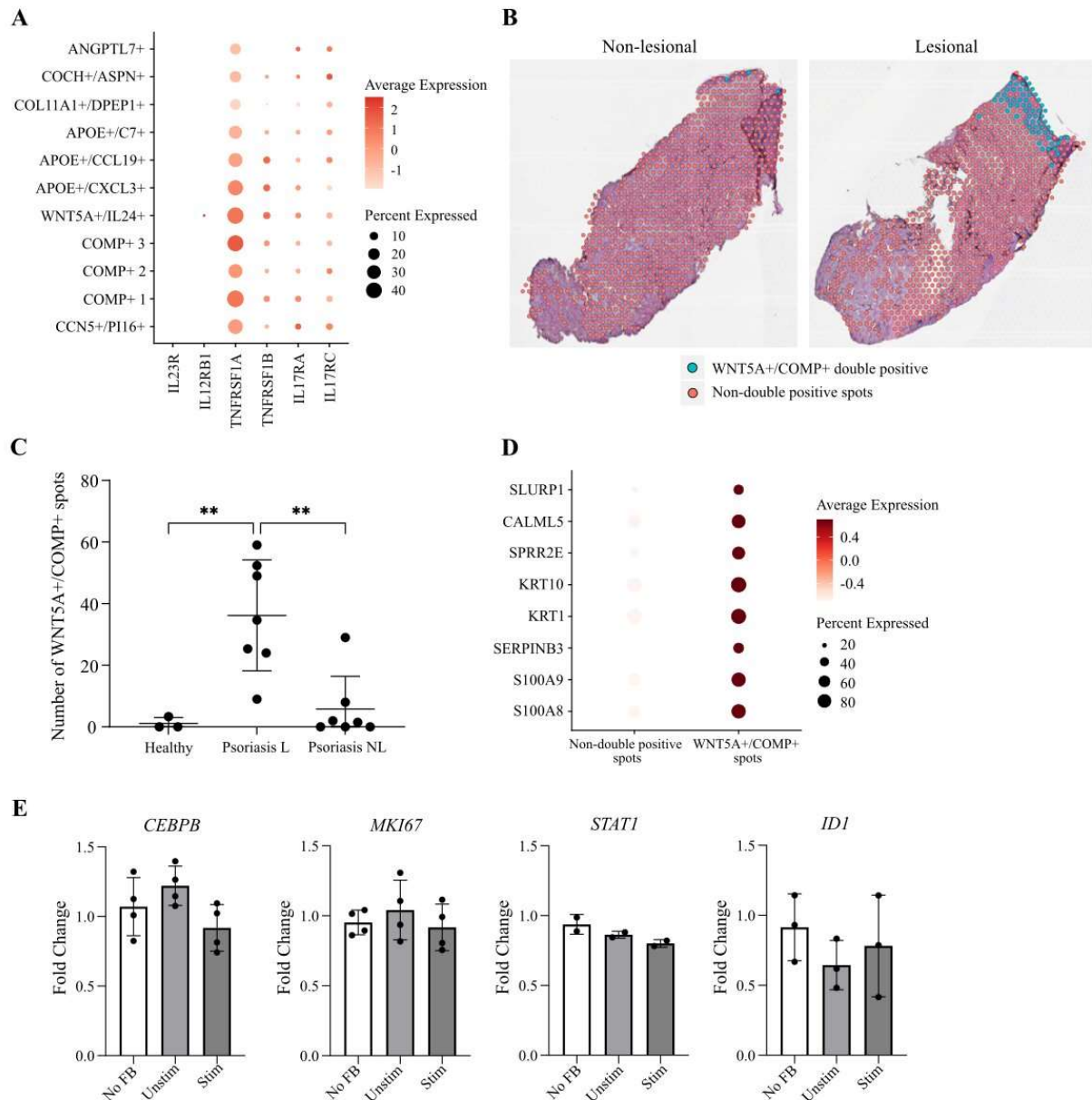


Supplementary Figure 3: Clustering and abundance of immune populations detected in treated and untreated skin. (A) UMAP of 3,755 mast cells forming three distinct sub-clusters. Cells are coloured by sub-cluster (left) or sample group (right) (n=5 patients). (B) Dot plot showing the expression of marker genes in the three sub-clusters. (C) Stacked bar chart showing the abundance of the various mast cell populations in the four sample groups. (D) UMAP of 6,263 T cells showing that cluster membership is not influenced by sample type (lesional vs non-lesional skin) or study time point. (E) Stacked bar chart showing the abundance of the various T cell populations in the four sample groups. (F) UMAP of 18,544 myeloid cells showing that cluster membership is not influenced by sample type (lesional vs non-lesional skin) or study time point. (G) Stacked bar chart showing the abundance of the various myeloid populations in the four sample groups. (H) Plot showing the abundance of myeloid populations at different time points. Every line represents a patient. * $P < 0.05$, * $P < 0.01$, * $P < 0.001$ (repeated measures ANOVA with Dunnett's post-test). (I) Dot plots showing treatment-induced gene expression changes within DC3-1 (left) and DC3-2 (right) cells. Treg, regulatory T cell; TEMRA, terminally differentiated effector memory T cell; NK, natural killer cell; ILC, innate lymphoid cell; DC, dendritic cell; Mac, macrophage; L, lesional skin; NL, non-lesional skin.



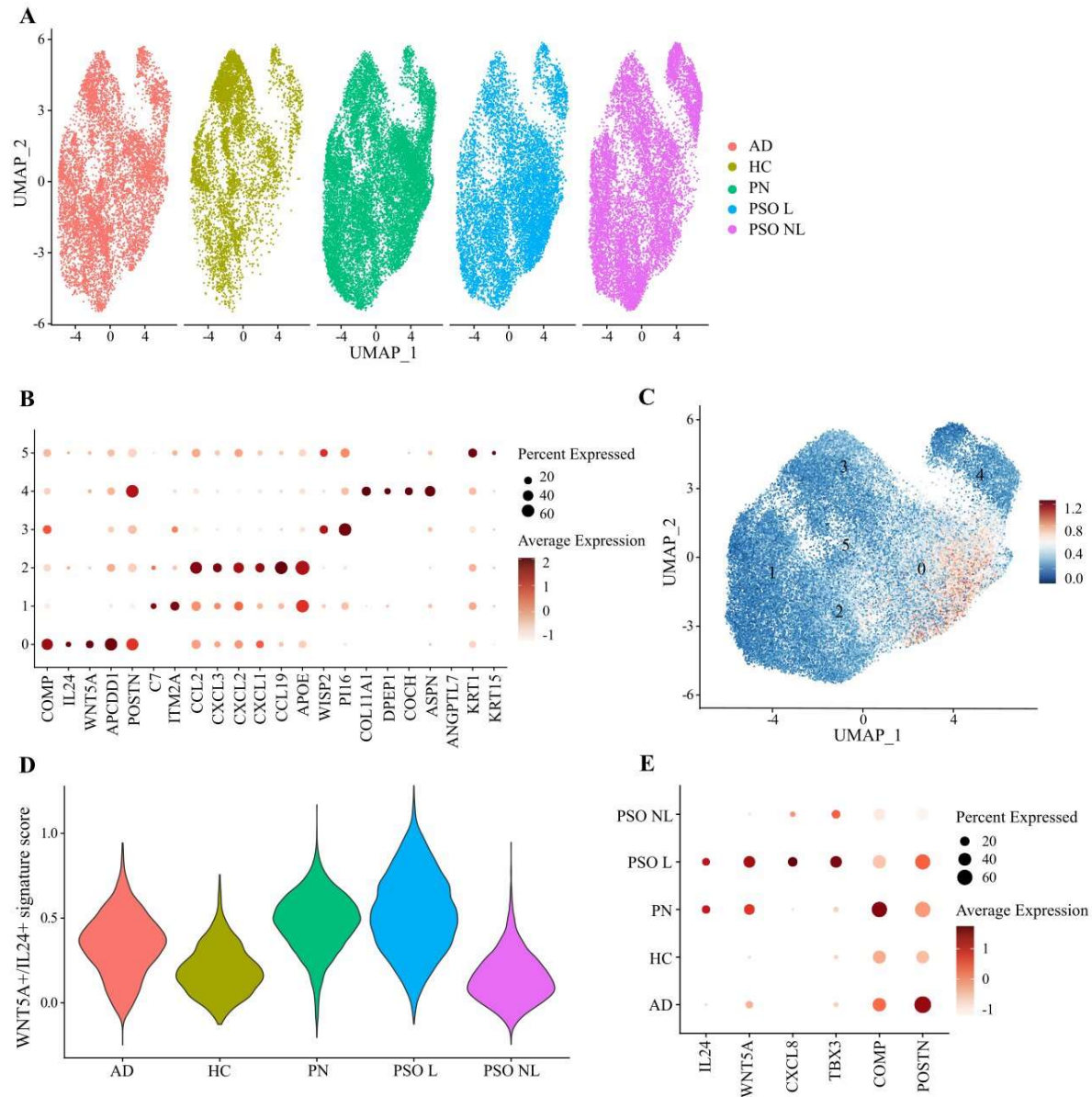
Supplementary Figure 4: Clustering and abundance of vascular endothelial cells and pericytes in treated and untreated skin. (A) UMAP of 16,420 vascular endothelial cells showing that cluster membership is not influenced by sample type (lesional vs non-lesional skin) or study time point (n=5 patients). **(B)** Stacked bar chart showing the abundance of the various vascular endothelial cell populations in the four sample groups. **(C)** UMAP of 13,507 pericytes showing that cluster membership is not influenced by sample type (lesional vs non-lesional skin) or study time point. **(D)** Stacked bar chart showing the abundance of the various pericyte populations in the four sample groups.

Supplementary Figure 5: Clustering and abundance of fibroblast populations detected in treated and untreated skin. (A) UMAP of 31,765 fibroblasts showing that cluster membership is not influenced by sample type (lesional vs non-lesional skin) or study time point (n=5 patients). (B) Stacked bar chart showing the abundance of the various fibroblast populations in the four sample groups. (C) UMAP visualization of fibroblasts from lesional skin, showing the number of DEG observed in each cluster, after 3 (left) and 14 (right) days of treatment. (D) Dot plot showing the expression of *CCL19* in fibroblasts, following treatment with risankizumab. (E) Inferred interaction between IL-24 produced by *WNT5A+/IL24+* fibroblasts and its receptor (encoded by *IL20RA* and *IL20RB*) on spinous keratinocytes. (F) NicheNet ligand activity prediction for the communication between *WNT5A+/IL24+* fibroblasts and spinous keratinocytes. Left: potential ligands expressed by *WNT5A+/IL24+* fibroblasts ranked according to their ability (Pearson correlation coefficient) to predict the gene expression changes observed between day 0 and day 14. Right: matrix showing the potential targets of the top ranked ligands and their regulatory potential in spinous keratinocytes. (G) Plot showing the abundance of COMP+ fibroblasts at different time points. Every line represents a patient. Fib, fibroblasts; L, lesional skin; NL, non-lesional skin; * $P < 0.05$ (repeated measures ANOVA with Dunnett's post-test).



Supplementary Figure 6: Spatial localization of *WNT5A*+/*IL24*+ fibroblasts and interacting partners. (A) Dot plot showing the expression of immune receptor genes in the various fibroblast populations. **(B)** Representative spatial plots from non-lesional and lesional psoriasis skin showing the localization of *WNT5A*+/*COMP*+ spots. **(C)** Number of *WNT5A*+/*COMP*+ spots across healthy (n=3), psoriasis lesional (n=7) and psoriasis non-lesional skin (n=7) conditions; ***P*<0.01 (ANOVA with Dunnett's post-test). **(D)** Dot plot showing the expression of spinous/supra-spinous keratinocyte markers in *WNT5A*+/*COMP*+ spots vs all other spots. **(E)** Real-time PCR analysis of inflammatory markers in human primary keratinocytes cultured with unconditioned medium (no FB grown), supernatants from IL-17A/TNF stimulated fibroblasts

(Stim) or control medium (supernatant from unstimulated fibroblasts, Unstim), n=4 biologically independent samples for *CEBPB* and *MKI67*, n=3 for *ID1* and n=2 for *STAT1*; (ANOVA with Dunnett's post-test); data are mean (SD). L, lesional skin; NL, non-lesional skin.



Supplementary Figure 7: Analysis of *WNT5A*+/*IL24*+ fibroblasts across inflammatory skin diseases. (A) UMAP of fibroblasts from publicly available scRNA-seq datasets of healthy (n=4), prurigo nodularis (n=7) and atopic dermatitis (n=5) skin, following integration with our day 0 psoriasis data (n=5). Cells are coloured by sample group. **(B)** Dot plot showing the expression of marker genes used for the annotation of fibroblast sub-clusters. The *WNT5A*+/*IL24*+ population corresponds to cluster 0 **(C)** UMAP of fibroblast populations confirming that the *WNT5A*+/*IL24*+ cell signature is specific to cluster 0. **(D)** Violin plot showing the *WNT5A*+/*IL24*+ signature score across sample groups. **(E)** Dot plot showing gene expression in *WNT5A*+/*IL24*+ fibroblasts across sample groups. PSO, psoriasis; L, lesional skin; NL, non-lesional skin; HC, healthy control; PN, prurigo nodularis; atopic dermatitis, AD.

Supplementary Tables

Supplementary Table 1: Patient demographics¹

	<i>Patient n.</i>	<i>Mean age (SD)</i>	<i>Sex</i>	<i>Comorbidity</i>	<i>Mean baseline PASI (SD)</i>	<i>Biologic naïve</i>
Discovery (scRNA-seq)	5	30.1 (9.6)	5M	None	23.8 (9.9)	Yes
Validation (RNA-scope)	3	41.3 (10.1)	2M 1F	None	27.7 (11.7)	Yes

¹All individuals were of European descent; M, male; F, female; PASI, psoriasis area and severity index.

Supplementary Table 2: scRNA-seq output summary statistics

<i>Sample Group</i>	<i>Mean n. of cells per sample (SD)</i>	<i>Mean n. of reads per cell (SD)</i>	<i>Mean n. of genes per cell (SD)</i>
Non-lesional skin Day 0	8970 (1325)	6967 (4427)	1900 (776)
Lesional skin Day 0	8382 (1583)	7134 (5384)	1953 (921)
Lesional skin Day 3	7906 (1522)	7138 (5552)	1886 (902)
Lesional skin Day 14	7653 (2384)	7022 (4779)	1944 (875)

Supplementary Table 3: Real-time PCR primers

<i>Target</i>	<i>Primer sequences (5' to 3')</i>
<i>CEBPB</i>	AACTCTCTGCTTCTCCCTCTG AAGCCCGTAGGAACATCTTT
<i>CXCL8</i>	GAGAAGTTTTGAAGAGGGCTGA CTTCACTGATTCTTGGATACCACA
<i>GAPDH</i> ¹	CGGAGTCAACGGATTGGTC AATGAAGGGGTCATTGATGGCA
<i>ID1</i>	CAGTTGGAGCTGAACTCGGA AACGCATGCCGCCTCG
<i>IL24</i>	TGTGGACTTTAGCCAGACCC GGTAAAACCCAGGCAAGGGA
<i>MKI67</i>	CTTTGGGTGCGACTTGACGA ACAACTCTCCACTGGGACG
<i>PKG1</i> ¹	GCGGGTCGTTATGAGAGTCG TGGGACAGCAGCCTTAATCC
<i>S100A8</i>	TTTCAGAAGACCTGGTGGGG CAGGGAGTACTTGTGGTAGACG
<i>S100A9</i>	TCCTCGGCTTTGACAGAGTG TGGTCTCTATGTTGCGTTCCA
<i>SERPINB3</i>	ACCAATGTGGTATTGCTGCCAA AACTCCTGGGTGGAAAGTCAA
<i>STAT1</i>	TCTGTGTCTGAAGTTCACCCT TCCGAGACACCTCGTCAAAC
<i>TBX3</i>	TGCACCTGGAGGCTAAAGAAC GGAAACATTGCGCTTCCCGA
<i>WNT5A</i>	AGGGCTCCTACGAGAGTGCT GACACCCCATGGCACTTG

¹Housekeeping genes