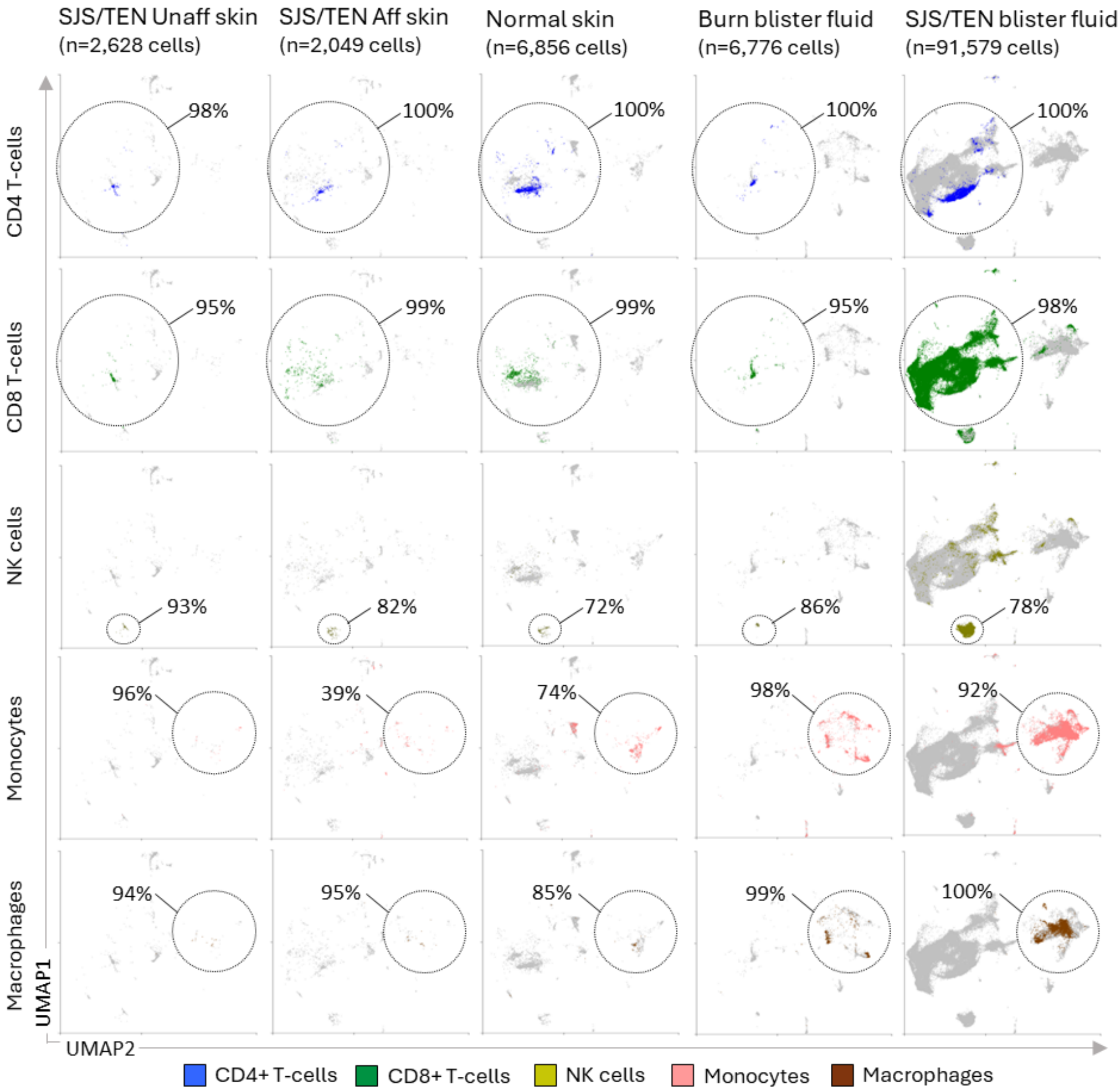
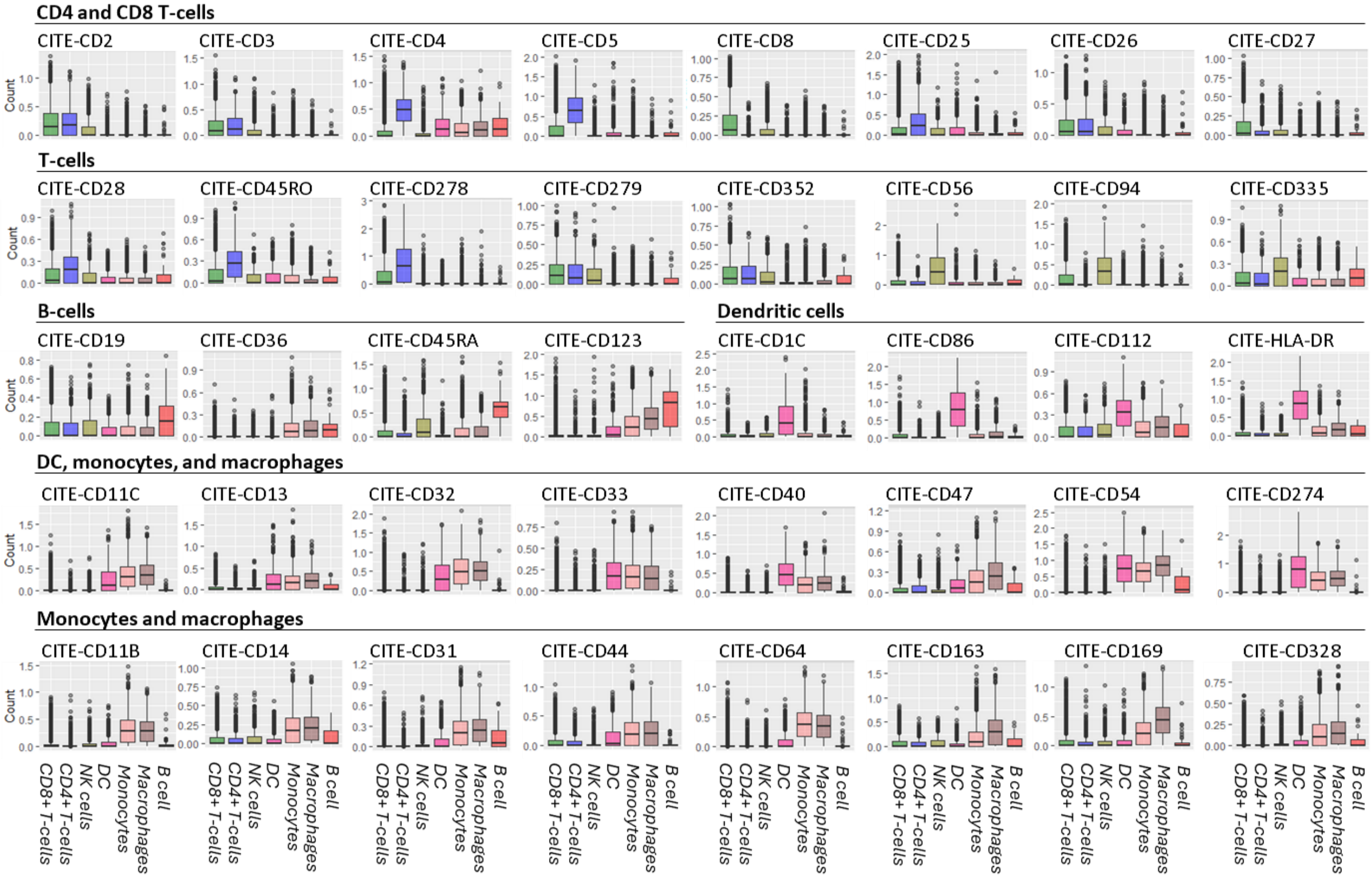
Multi-omic single-cell sequencing defines tissue-specific responses in Stevens-Johnson Syndrome and Toxic epidermal necrolysis.

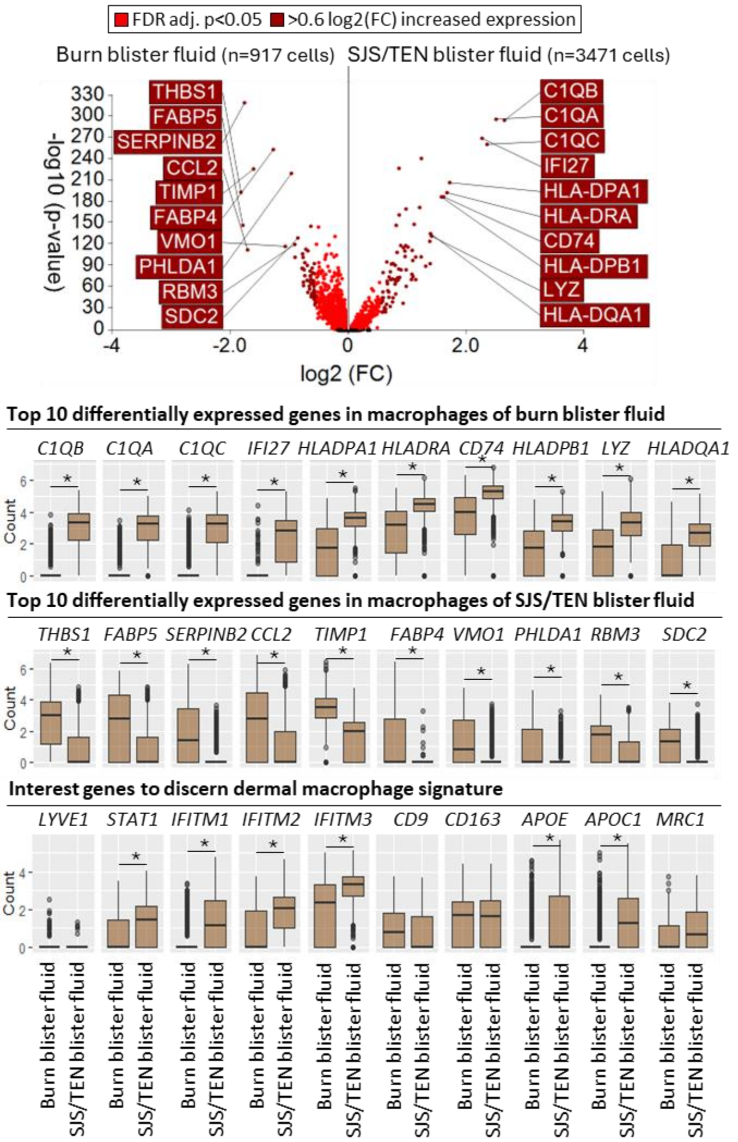
Supplementary Figures



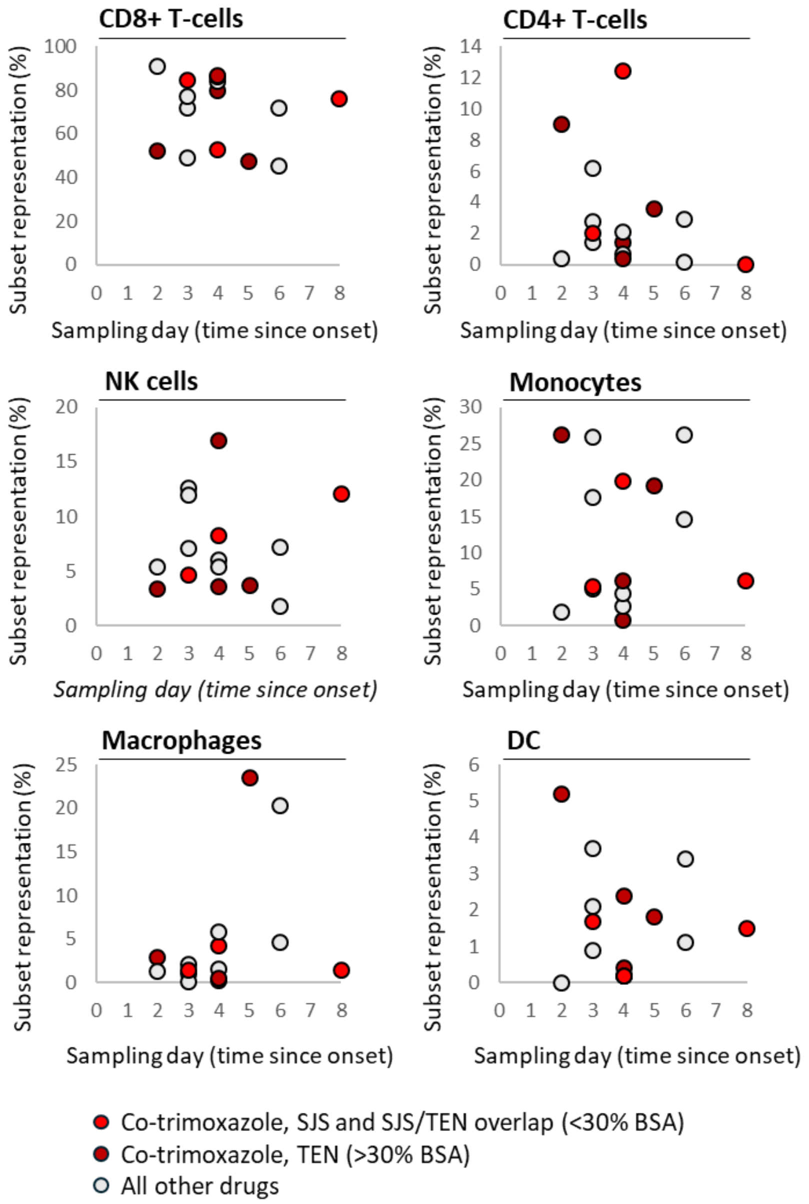
Supplementary Figure 1 | UMAP location of predominant immune subsets across sample types. Expression distribution for key cell types across SJS/TEN unaffected skin (n=1 patient, 2,628 cells), SJS/TEN affected skin (n=1 patient, 2,049 cells), normal skin from an unrelated healthy donor (n=1 donor, 6,856 cells), burn blister fluid (n=4 patients, 6,776 cells), and SJS/TEN blister fluid (n=15 patients, 91,579 cells). The majority of the UMAP locations of each subset are labeled with the percentage of each subset within that location indicated. *Unaff, unaffected; aff, affected; SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis.*



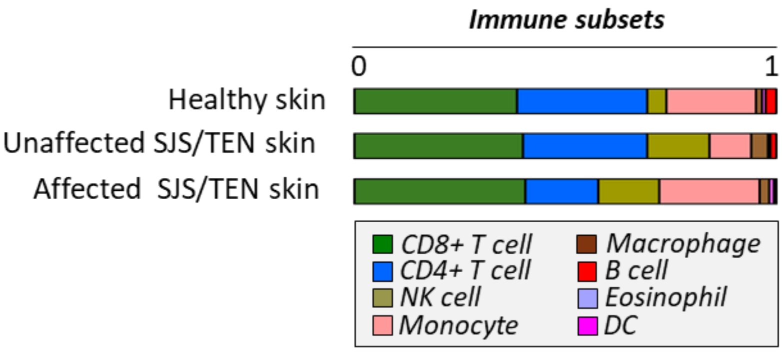
Supplementary Figure 2 | Cell surface protein expression (scCITE-seq) of key lineage and activation markers on scRNA-defined immune cell subsets. Box plots show the expression for each cell surface protein across scRNA-subsets from a representative UMAP of SJS/TEN blister fluid and 17,404 cells obtained within a single 10x run (n=4 patients, (n=11,261 CD8+ T-cells, 593 CD4+ T-cells, 727 NK cells, 536 DC, 3,177 monocytes, 1,034 macrophages, 45 B cells). Bounds of the box represent the interquartile range from the 25th to 75th percentile, the center line shows the median expression, and whiskers identify maximum and minimum values to the 10th and 90th percentile, respectively. Outliers are shown. Surface proteins are grouped into panels headed by the scRNA-defined cell type with the highest median expression for that marker. *DC, dendritic cell; NK, natural killer.*



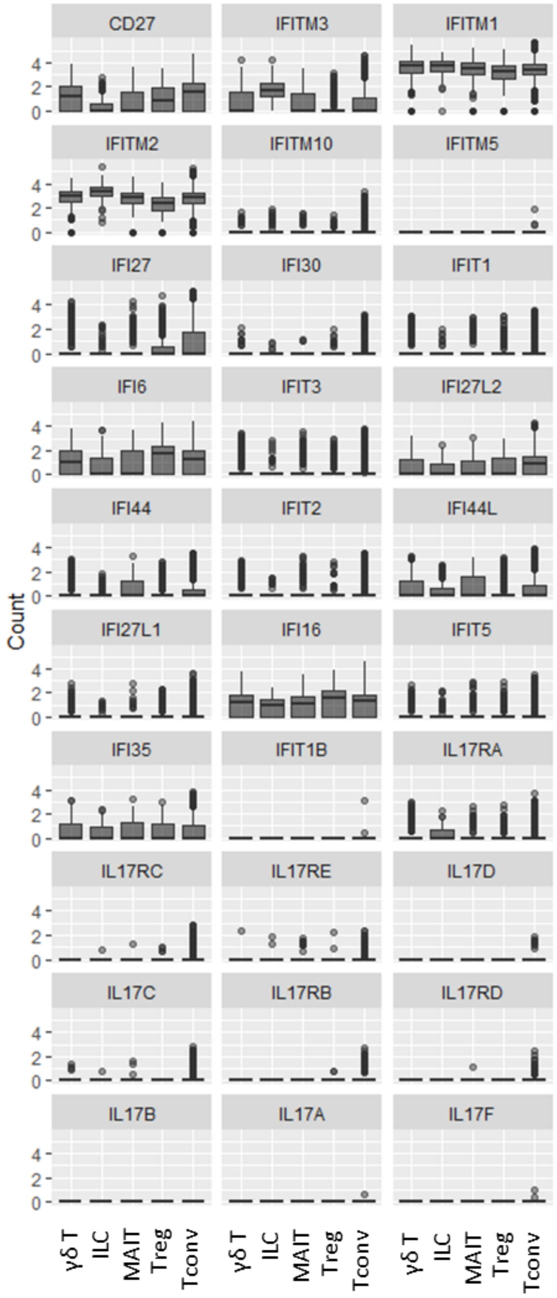
Supplementary Figure 3 | Differential signature of macrophages between burn and SJS/TEN blister fluid. (A) Differential gene expression signatures (two-tailed Wilcoxon, Hochberg adj, p<0.05) between macrophages in burn (n=4 patients, 917 cells) and SJS/TEN blister fluid (n=15 patients, 3,471 cells). Genes colored red are significantly (p<0.05) increased (light red <0.6log2FC, dark red >0.6log2FC). The top 10 genes are labeled. **(B)** Box plot expression of the top 10 significantly differentially expressed genes in burn or SJS/TEN blister fluid or interest genes that further discern the dermal macrophage signature from literature. *Indicates significant differential expression (two-tailed Wilcoxon, Hochberg adj, p<0.05 and >0.6 log2FC). For box plots, bounds of the box represent the interquartile range from the 25th to 75th percentile, the center line shows the median expression, and whiskers identify maximum and minimum values to the 10th and 90th percentile, respectively. Outliers are shown. Figure created using VGAS. Source data are provided as a Source Data file. *FDR, false discovery rate; FC, fold change; SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis.*



Supplementary Figure 4 | Relationship between drug, reaction severity, time since onset, and cell subset representation in SJS/TEN blister fluid. Scatter plots show the relationship between immune cell subset representation (CD8$^+$ T-cells, CD4$^+$ T-cells, NK cells, monocytes, macrophages, DC) and sampling day (time since onset of symptoms) for each SJS/TEN patient as outlined in Supplementary Table 1. Each dot represents an individual patient (n=15). Co-trimoxazole-induced SJS/TEN blister fluids highlighted red according to disease severity defined by the percentage BSA (light red, SJS and SJS/TEN overlap indicating BSA <30%; dark red, TEN indicating a BSA >30%). Source data are provided as a Source Data file. *BSA, Body surface area detached; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; NK, natural killer; DC, dendritic cell.*

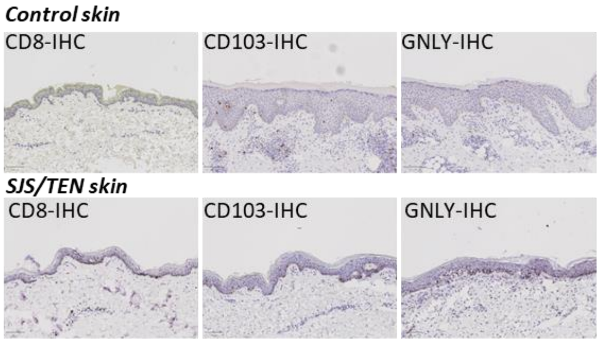


Supplementary Figure 5 | The relative proportion of immune cell subsets within immune cells of skin biopsies. The relative proportion of immune subsets in normal skin (n=1 donor, n=3,873 cells) and time-paired unaffected and affected SJS/TEN skin (n=1 patient; unaffected skin, 453 cells; affected skin, 933 cells) after removal of stromal subsets from each sample. Source data are provided as a Source Data file. *SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; NK, natural killer; DC, dendritic cell.*

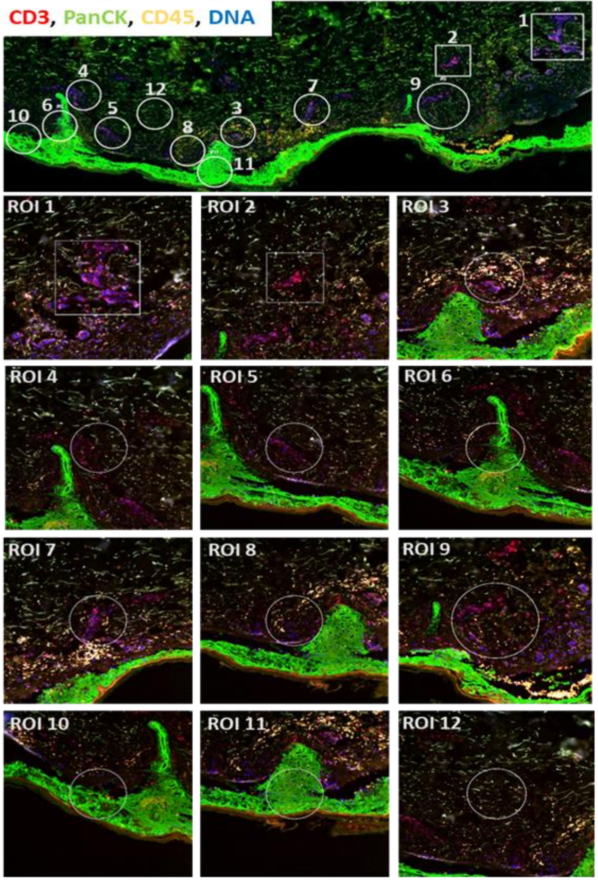


Supplementary Figure 6 | Expression of IFN and IL-17 responsive gene signatures in γδ T, ILC, MAIT, or Tconv cells in SJS/TEN blister fluid. Box plot expression of CD27 (co-stimulation) or diverse IFN- or IL-17-responding genes across $CD8^+$ T-cells in SJS/TEN blister fluid (n=15 patients) which have been re-aligned as γδ T (747 cells), ILC (159 cells), MAIT (328 cells), Treg (364 cells) or Tconv (62,169 cells) using the Azimuth PBMC reference dataset. For box plots, bounds of the box represent the interquartile range from the 25th to 75th percentile, the center line shows the median expression, and whiskers identify maximum and minimum values to the 10th and 90th percentile, respectively. Outliers are shown. Figure created using VGAS. *SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis; γδ, gamma delta; ILC, innate-like lymphoid cell; MAIT, mucosal-associated invariant T-cells; Tconv, T conventional cell.*

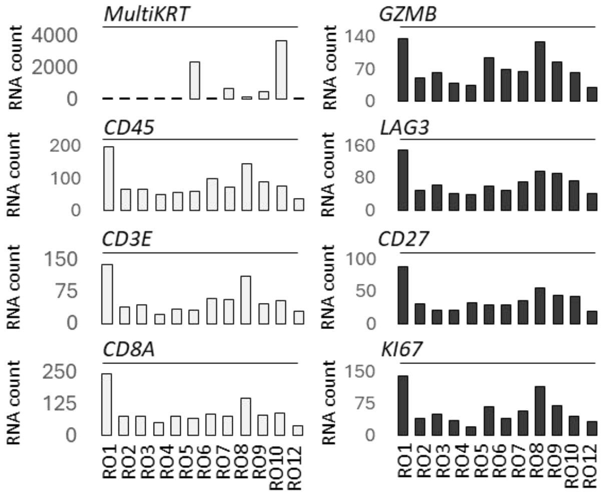
a. Immunohistochemistry on SJS/TEN affected skin



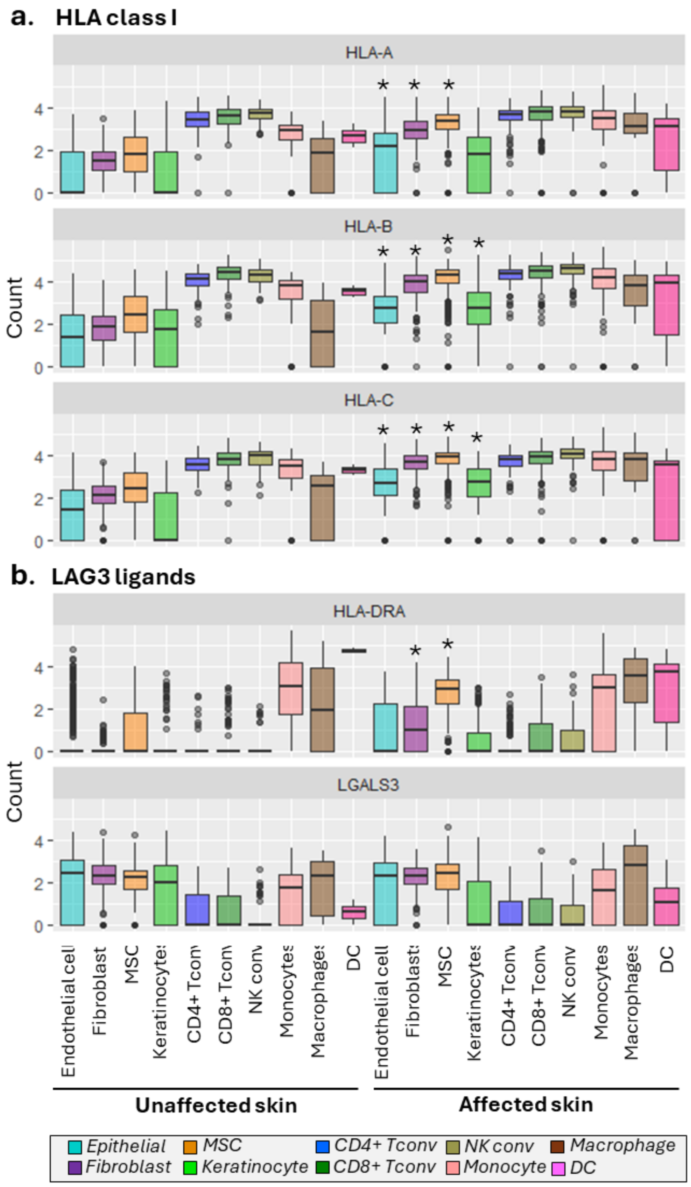
b. GeoMX spatial sequencing on SJS/TEN affected skin



c. Cell subset markers **Cytotoxic CD8 Tconv**

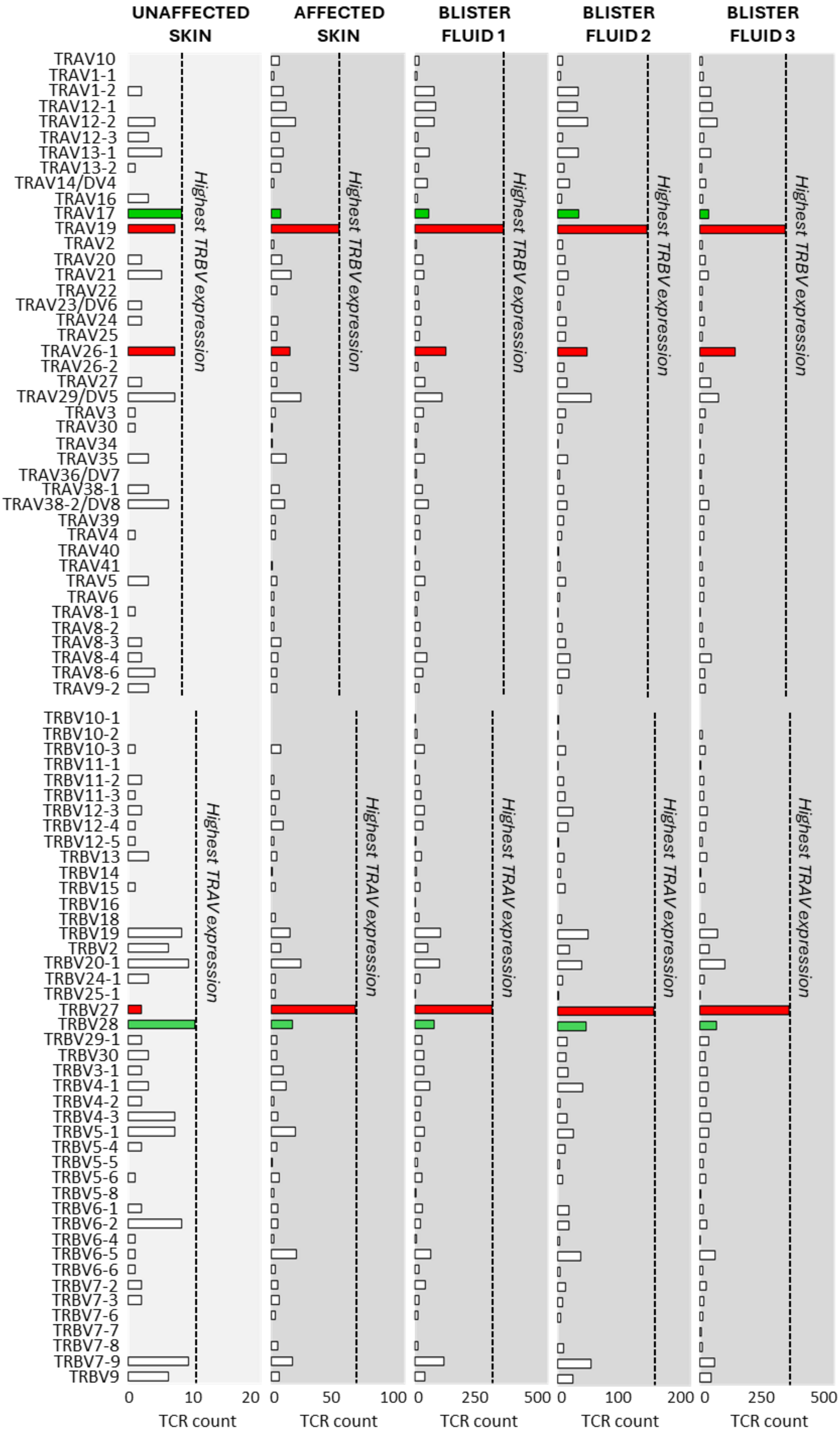


Supplementary Figure 7 | Immunohistochemistry and spatial sequencing map cytotoxic CD8$^+$ T$_{RM}$ T-cells to the dermal-epidermal junction of skin during SJS/TEN. **a** Immunohistochemistry of healthy control (n=1) and SJS/TEN affected skin (n=1) using antibodies specific for CD8, CD103, and GNLY map cytotoxic CD8$^+$ T$_{RM}$ T-cells to the dermal-epidermal boundary in SJS/TEN affected skin. **b** Nanostring GeoMX spatial sequencing on affected SJS/TEN skin biopsy (n=1) showing tissue pathology and cell subset positioning with CD3 (red), panCK (green), CD45 (yellow), and DNA (blue). Detached epidermis with formation of a subepidermal blister can be seen on the right-hand side nearest ROI 1 and ROI 9. **c** Regional expression of specific marker genes for interest cell subsets including keratinocytes (MultiKRT) and CD8$^+$ T-cells (*CD45, CD3, CD8A*) and the cytotoxic CD8$^+$ Tconv cluster including markers for cytotoxicity (*GZMB*), regulation (*LAG3*), activation (*CD27*), and proliferation (*KI67*). RNA counts were normalized using ERCC spike-in controls. Source data are provided as a Source Data file. *Tconv, T conventional cell; T$_{RM}$, tissue-resident memory; ROI, region of interest; CK, cytokeratin; ERCC, External RNA Controls Consortium.*



Supplementary Figure 8 | Differential expression of *HLA class I* and *LAG3 ligands* in cell subsets of unaffected and affected SJS/TEN patient skin. Comparative gene expression in scRNA-defined stromal and immune subsets between time-paired unaffected and affected skin from an SJS/TEN patient. **a** HLA class I (*HLA-A*, *HLA-B*, *HLA-C*). **b** LAG3 ligands (*HLA-DRA*, *LGALS3*). Cells shown for unaffected skin (epithelial cells, n=558; fibroblasts, n=594; MSC, n=673; keratinocytes, n=331; CD4+ Tconv, n=118; CD8+ Tconv, n=142; NK cells, n=67; monocytes, n=45; macrophages, n=18, DC, n=2) and affected skin (epithelial cells, n=177; fibroblasts, n=219; MSC, n=578; keratinocytes, n=108; CD4+ Tconv, n=155; CD8+ Tconv, n=356; NK cells, n=136; monocytes, n=220; macrophages, n=21, DC, n=11). Differential gene expression analyses were performed (two-tailed Wilcoxon, Hochberg adj. $p<0.05$). Asterisks (*) indicate a significant increase above 0.6log2 fold change in gene expression for that subset in affected compared to unaffected skin. Source data are provided as a Source Data file

HLA, human leukocyte antigen; MSC, mesenchymal stromal cell; NK, natural killer; DC, dendritic cell.


UNAFFECTED SKIN
AFFECTED SKIN
BLISTER FLUID 1
BLISTER FLUID 2
BLISTER FLUID 3
TRAV10
TRAV1-1
TRAV1-2
TRAV12-1
TRAV12-2
TRAV12-3
TRAV13-1
TRAV13-2
TRAV14/DV4
TRAV16
TRAV17
TRAV19
TRAV2
TRAV20
TRAV21
TRAV22
TRAV23/DV6
TRAV24
TRAV25
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TRBV7-2
TRBV7-3
TRBV7-6
TRBV7-7
TRBV7-8
TRBV7-9
TRBV9
Highest TRBV expression
Highest TRAV expression
0
10
20
0
50
100
0
250
500
0
100
200
0
250
500
TCR count
TCR count
TCR count
TCR count
TCR count

Supplementary Figure 9 | Individual TRAV and TRBV scTCR-seq counts on CD8$^+$ Tconv cells across paired samples from a single SJS/TEN patient. Individual counts for all identified TRAV and TRBV in CD8$^+$ Tconv across TCR+ cells from unaffected skin (n=79 cells), affected skin (n=235 cells), and blister fluid from three anatomical sites (blister fluid 1, n=1318 cells; blister fluid 2, n=610 cells; blister fluid 3, n=1033 cells) from a single patient with SJS/TEN. The dominant TRAV and TRBV in affected skin and blister fluid are highlighted red, and the dominant TRAV and TRBV in unaffected skin are highlighted in green. Figure created using VGAS. Source data are provided as a Source Data file. *TCR, T-cell receptor; TRAV, TCR alpha variable; TRBV, TCR beta variable; Tconv, T conventional cell.*

a. **UNAFFECTED SKIN (79 CD8+ Tconv cells with TCR expression)**

TCR	*CDR3α*	*CDR3β*	*TRAV*	*TRAJ*	*TRBV*	*TRBJ*	*Ct.*
1	CIVRVARNTGNQFYF	CASSYHTGGSGYEQYF	TRAV26-1	TRAJ49	TRBV6-2	TRBJ2-7	3
2	CATDVMNRDDKIIF	CASSLTARGSGVELFF	TRAV17	TRAJ30	TRBV13	TRBJ2-2	2
3	CAVSDRSGGGADGLTF	CASSLGLNYEQYF	TRAV8-6	TRAJ45	TRBV28	TRBJ2-7	2
4	CAASVTGNQFYF	CASSVESGGWYGYTF	TRAV29/DV5	TRAJ49	TRBV9	TRBJ1-2	2
5	CALRGWGRRALTF	CATSDDGAGTDTQYF	TRAV19	TRAJ5	TRBV24-1	TRBJ2-3	1
6	CAGAGNAGNMLTF	CASSQVRFYGYTF	TRAV27	TRAJ39	TRBV4-3	TRBJ1-2	1
7	CALTQGAQKLVF	CASSHLTGELFF	TRAV16	TRAJ54	TRBV11-2	TRBJ2-2	1
8	CAETSYGQNFVF	CASSEMSVGETQYF	TRAV5	TRAJ26	TRBV6-1	TRBJ2-5	1
9	CALRGGAAGNKLTF	CASSDNPPYTEAFF	TRAV19	TRAJ17	TRBV7-9	TRBJ1-1	1
10	CALSEVTTSGTYKYIF	CASSQDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1

AFFECTED SKIN (235 CD8+ Tconv cells with TCR expression)

TCR	*CDR3α*	*CDR3β*	*TRAV*	*TRAJ*	*TRBV*	*TRBJ*	*Ct.*
1	CALSEVTTSGTYKYIF	CASSQDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	27
2	CALSEVTTSGTYKYIF	CASSPDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	20
3	CIVRVHSGGGADGLTF	CASSPDRGGYEQYF	TRAV26-1	TRAJ45	TRBV27	TRBJ2-7	10
4	CVVNNARNNDMRF	CASSPDRGGYEQYF	TRAV12-1	TRAJ43	TRBV27	TRBJ2-7	4
5	CLNDMRF	CASSQLSGNSPLHF	TRAV25	TRAJ43	TRBV3-1	TRBJ1-6	3
6	CAGRPDSGTYKYIF	CPPSLPRDDYEQYF	TRAV35	TRAJ40	TRBV27	TRBJ2-7	3
7	CAVCQEDDYKLSF	CSARDLAVYNSPLHF	TRAV22	TRAJ20	TRBV20-1	TRBJ1-6	2
8	CAASVTGNQFYF	CASSVESGGWYGYTF	TRAV29/DV5	TRAJ49	TRBV9	TRBJ1-2	2
9	CAVSGYGGATNKLIF	CASSLGDRQSYEQYF	TRAV21	TRAJ32	TRBV7-9	TRBJ2-7	2
10	CAVSPNNNARLMF	CASSLLGVGSPLHF	TRAV21	TRAJ31	TRBV5-1	TRBJ1-6	2

BLISTER FLUID 1 (ARM, 1318 CD8+ Tconv cells with TCR expression)

TCR	*CDR3α*	*CDR3β*	*TRAV*	*TRAJ*	*TRBV*	*TRBJ*	*Ct.*
1	CALSEVTTSGTYKYIF	CASSPDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	128
2	CIVRVHSGGGADGLTF	CASSPDRGGYEQYF	TRAV26-1	TRAJ45	TRBV27	TRBJ2-7	97
3	CALSEVTTSGTYKYIF	CASSQDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	82
4	CALSEARSSASKIIF	CASSDRDRYYEQYF	TRAV19	TRAJ3	TRBV7-9	TRBJ2-7	33
5	CVVNNARNNDMRF	CASSPDRGGYEQYF	TRAV12-1	TRAJ43	TRBV27	TRBJ2-7	24
6	CALSESETSGSRLTF	CASSLWEVERAYNEQFF	TRAV19	TRAJ58	TRBV28	TRBJ2-1	18
7	CAVSLTYSGGGADGLTF	CSAKGGEQYF	TRAV8-4	TRAJ45	TRBV20-1	TRBJ2-7	17
8	CAADTGGFKTIF	CASTLSAGLNQPQHF	TRAV13-1	TRAJ9	TRBV19	TRBJ1-5	16
9	CVVNLYKLSF	CASSSQRAVDEQFF	TRAV12-1	TRAJ20	TRBV7-9	TRBJ2-1	14
10	CATGTSYGKLTF	CASSLPTLGLAGGATDNEQFF	TRAV17	TRAJ52	TRBV28	TRBJ2-1	13

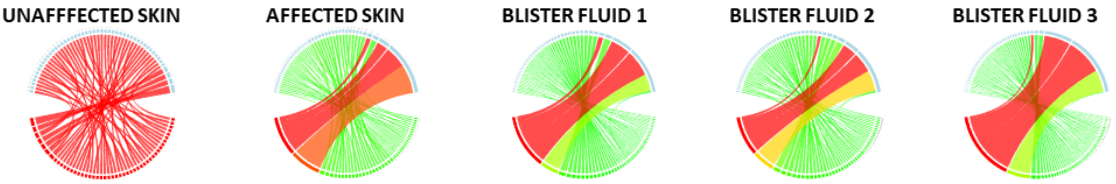
BLISTER FLUID 2 (FACE, 610 CD8+ Tconv cells with TCR expression)

TCR	*CDR3α*	*CDR3β*	*TRAV*	*TRAJ*	*TRBV*	*TRBJ*	*Ct.*
1	CALSEVTTSGTYKYIF	CASSQDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	43
2	CALSEVTTSGTYKYIF	CASSPDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	42
3	CIVRVHSGGGADGLTF	CASSPDRGGYEQYF	TRAV26-1	TRAJ45	TRBV27	TRBJ2-7	29
4	CALSEARSSASKIIF	CASSDRDRYYEQYF	TRAV19	TRAJ3	TRBV7-9	TRBJ2-7	14
5	CAMNSYSGAGSYQLTF	CASSPFYSGGDTDTQYF	TRAV14/DV4	TRAJ28	TRBV12-3	TRBJ2-3	9
6	CAADTGGFKTIF	CASTLSAGLNQPQHF	TRAV13-1	TRAJ9	TRBV19	TRBJ1-5	9
7	CATGTSYGKLTF	CASSLPTLGLAGGATDNEQFF	TRAV17	TRAJ52	TRBV28	TRBJ2-1	7
8	CAVSLTYSGGGADGLTF	CSAKGGEQYF	TRAV8-4	TRAJ45	TRBV20-1	TRBJ2-7	6
9	CALSESETSGSRLTF	CASSLWEVERAYNEQFF	TRAV19	TRAJ58	TRBV28	TRBJ2-1	6
10	CVVNLYKLSF	CASSSQRAVDEQFF	TRAV12-1	TRAJ20	TRBV7-9	TRBJ2-1	6

BLISTER FLUID 3 (FOOT, 1033 CD8+ Tconv cells with TCR expression)

TCR	*CDR3α*	*CDR3β*	*TRAV*	*TRAJ*	*TRBV*	*TRBJ*	*Ct.*
1	CALSEVTTSGTYKYIF	CASSPDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	154
2	CIVRVHSGGGADGLTF	CASSPDRGGYEQYF	TRAV26-1	TRAJ45	TRBV27	TRBJ2-7	112
3	CALSEVTTSGTYKYIF	CASSQDRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	93
4	CAVSLTYSGGGADGLTF	CSAKGGEQYF	TRAV8-4	TRAJ45	TRBV20-1	TRBJ2-7	18
5	CAVYYGNNRLAF	CASSTGGLGNQPQHF	TRAV12-2	TRAJ7	TRBV6-5	TRBJ1-5	14
6	CVVNNARNNDMRF	CASSPDRGGYEQYF	TRAV12-1	TRAJ43	TRBV27	TRBJ2-7	11
7	CATGTSYGKLTF	CASSLPTLGLAGGATDNEQFF	TRAV17	TRAJ52	TRBV28	TRBJ2-1	9
8	CAMNSYSGAGSYQLTF	CASSPFYSGGDTDTQYF	TRAV14/DV4	TRAJ28	TRBV12-3	TRBJ2-3	9
9	CAATGSGTYKYIF	CASSMQGYTMNTEAFF	TRAV29/DV5	TRAJ40	TRBV19	TRBJ1-1	8
10	CALSEARSSASKIIF	CASSDRDRYYEQYF	TRAV19	TRAJ3	TRBV7-9	TRBJ2-7	7

b.



UNAFFFECTED SKIN

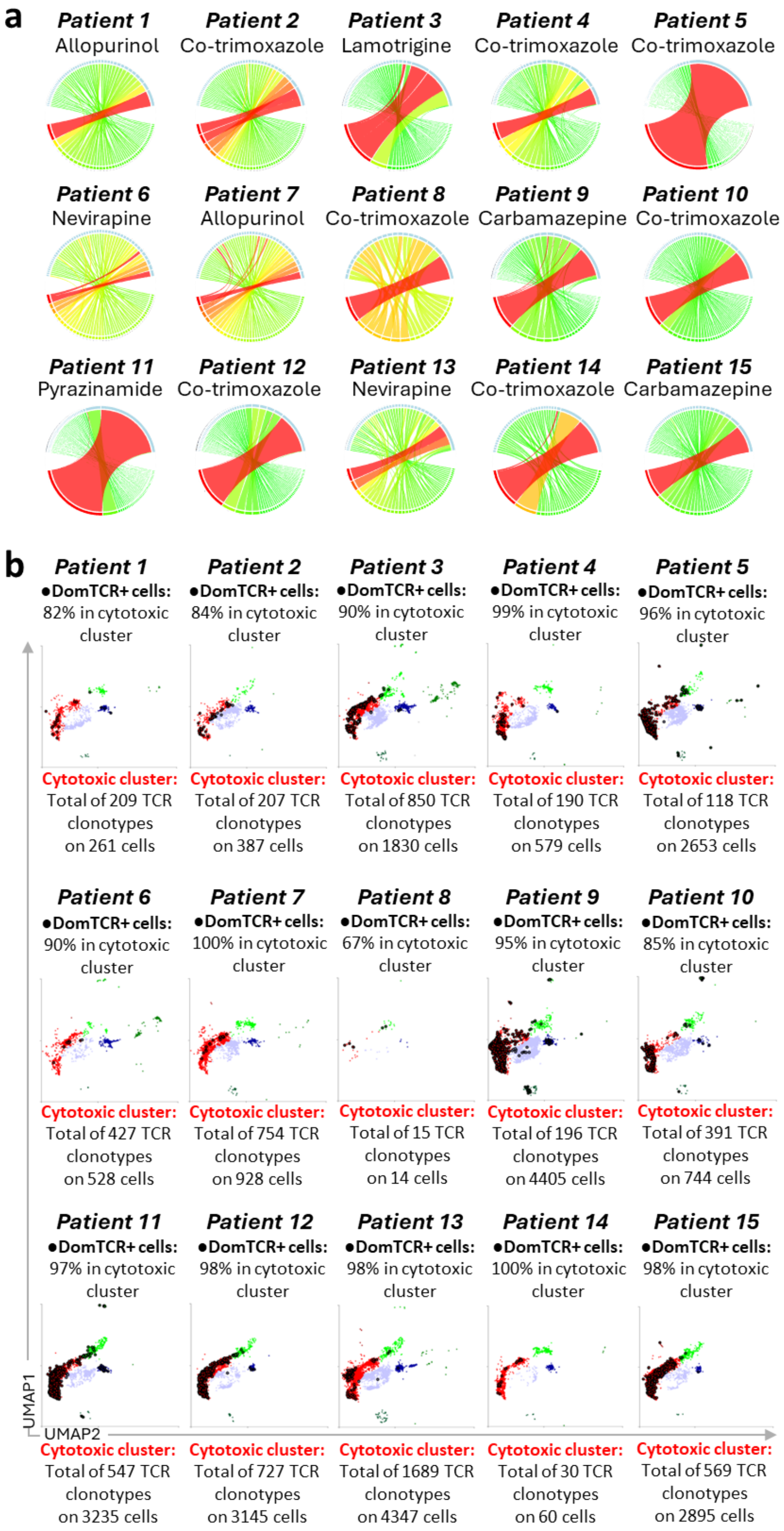
AFFECTED SKIN

BLISTER FLUID 1

BLISTER FLUID 2

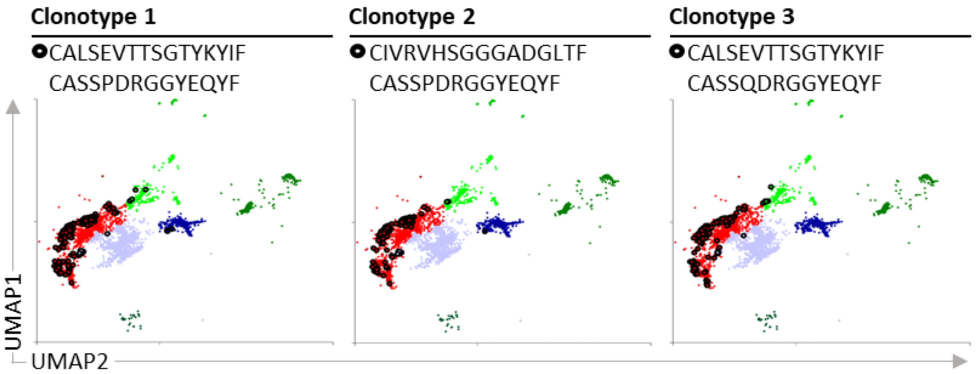
BLISTER FLUID 3

Supplementary Figure 10 | Top functional CDR3αβ clonotypes and counts in CD8$^+$ Tconv across paired samples from a single SJS/TEN patient. a Top 10 CDR3 TCRαβ clonotypes and counts in the CD8$^+$ Tconv population from unaffected skin (n=79 cells), affected skin (n=235 cells), and blister fluid from three anatomical sites (blister fluid 1, n=1318 cells; blister fluid 2, n=610 cells; blister fluid 3, n=1033 cells) from a single patient with SJS/TEN. Blue highlights indicate the same functional CDR3αβ clonotypes. **b** Circos plots show comparative clonality and CDR3α and CDR3β pairings between samples. The width of each segment is proportionate to its expression. Least to most dominant is colored green to red. Top 50 CDR3αβ clonotypes shown for each sample. Source data are provided as a Source Data file. *Tconv, T conventional cell; TCR, T-cell receptor; TRAV, TCR alpha variable; TRBV, TCR beta variable; TRAJ, TCR alpha joining; TRBJ, TCR beta joining; CDR3, complementary-determining region; Ct., count.*

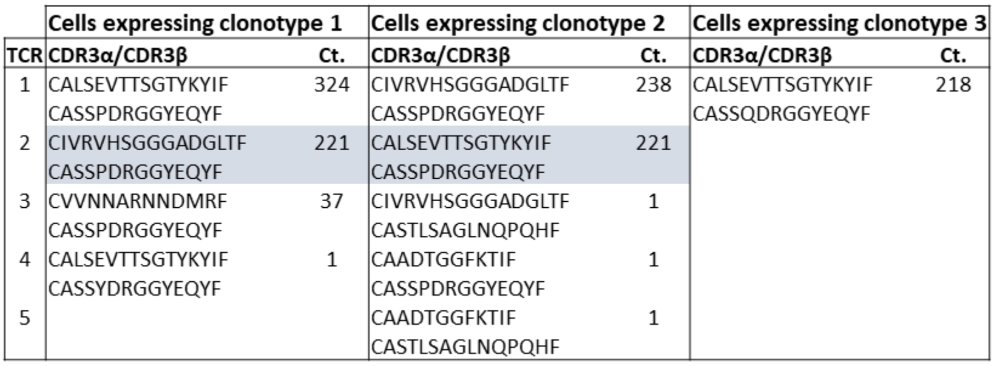

a
Patient 1
Allopurinol
Patient 2
Co-trimoxazole
Patient 3
Lamotrigine
Patient 4
Co-trimoxazole
Patient 5
Co-trimoxazole
Patient 6
Nevirapine
Patient 7
Allopurinol
Patient 8
Co-trimoxazole
Patient 9
Carbamazepine
Patient 10
Co-trimoxazole
Patient 11
Pyrazinamide
Patient 12
Co-trimoxazole
Patient 13
Nevirapine
Patient 14
Co-trimoxazole
Patient 15
Carbamazepine
b
Patient 1
●DomTCR+ cells:
82% in cytotoxic cluster
Cytotoxic cluster:
Total of 209 TCR clonotypes on 261 cells
Patient 2
●DomTCR+ cells:
84% in cytotoxic cluster
Cytotoxic cluster:
Total of 207 TCR clonotypes on 387 cells
Patient 3
●DomTCR+ cells:
90% in cytotoxic cluster
Cytotoxic cluster:
Total of 850 TCR clonotypes on 1830 cells
Patient 4
●DomTCR+ cells:
99% in cytotoxic cluster
Cytotoxic cluster:
Total of 190 TCR clonotypes on 579 cells
Patient 5
●DomTCR+ cells:
96% in cytotoxic cluster
Cytotoxic cluster:
Total of 118 TCR clonotypes on 2653 cells
Patient 6
●DomTCR+ cells:
90% in cytotoxic cluster
Cytotoxic cluster:
Total of 427 TCR clonotypes on 528 cells
Patient 7
●DomTCR+ cells:
100% in cytotoxic cluster
Cytotoxic cluster:
Total of 754 TCR clonotypes on 928 cells
Patient 8
●DomTCR+ cells:
67% in cytotoxic cluster
Cytotoxic cluster:
Total of 15 TCR clonotypes on 14 cells
Patient 9
●DomTCR+ cells:
95% in cytotoxic cluster
Cytotoxic cluster:
Total of 196 TCR clonotypes on 4405 cells
Patient 10
●DomTCR+ cells:
85% in cytotoxic cluster
Cytotoxic cluster:
Total of 391 TCR clonotypes on 744 cells
Patient 11
●DomTCR+ cells:
97% in cytotoxic cluster
Cytotoxic cluster:
Total of 547 TCR clonotypes on 3235 cells
Patient 12
●DomTCR+ cells:
98% in cytotoxic cluster
Cytotoxic cluster:
Total of 727 TCR clonotypes on 3145 cells
Patient 13
●DomTCR+ cells:
98% in cytotoxic cluster
Cytotoxic cluster:
Total of 1689 TCR clonotypes on 4347 cells
Patient 14
●DomTCR+ cells:
100% in cytotoxic cluster
Cytotoxic cluster:
Total of 30 TCR clonotypes on 60 cells
Patient 15
●DomTCR+ cells:
98% in cytotoxic cluster
Cytotoxic cluster:
Total of 569 TCR clonotypes on 2895 cells
UMAP1
UMAP2

Supplementary Figure 11 | Oligoclonal TCR CDR3αβ clonotypes were identified in the cytotoxic CD8$^+$ Tconv cluster in blister fluids from all SJS/TEN patients. a Circos plots show comparative clonality and CDR3α and CDR3β pairings of CD8+ Tconv cells in blister fluid samples from patients with SJS/TEN (n=15 patients). The width of each segment is proportionate to its expression. Least to most dominant is colored green to red. Up to the top 50 clonotypes are shown for each sample. **b** UMAPs show the expression of the dominantly-expanded TCR$^+$ cells (black circle highlight) for each patient across CD8$^+$ Tconv clusters (Patient 1, 1429 cells, 449 TCR+ cells; Patient 2, 1687 cells, 1235 TCR+ cells; Patient 3, 5470 cells, 2961 TCR+ cells; Patient 4, 2510 cells, 729 TCR+ cells; Patient 5, 5183 cells, 4327 TCR+ cells; Patient 6, 1709 cells, 701 TCR+ cells; Patient 7, 3232 cells, 1086 TCR+ cells; Patient 8, 49 cells, 26 TCR+ cells; Patient 9, 12920 cells, 9566 TCR+ cells; Patient 10, 2347 cells, 1720 TCR+ cells; Patient 11, 4866 cells, 3949 TCR+ cells; Patient 12, 4629 cells, 3719 TCR+ cells; Patient 13, 7870 cells, 6177 TCR+ cells; Patient 14, 3670 cells, 66 TCR+ cells; Patient 15, 4598 cells, 3221 TCR+ cells). The percentage of dominantly-expanded TCR$^+$ cells in the cytotoxic CD8$^+$ Tconv cluster is indicated above each UMAP. The total number of TCR clonotypes and cells in the cytotoxic CD8$^+$ Tconv cluster is indicated below each UMAP. *DomTCR, dominantly-expanded T-cell receptors; Tconv, T conventional cell; TCR, T-cell receptor; CDR, complimentary-determining region.*

a. Blister fluid: Expression of top expanded TCRs in CD8 Tconv

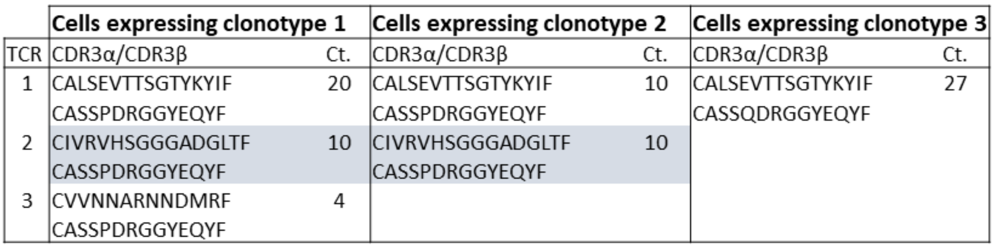


b. Blister fluid: CDR3αβ expression of CD8 Tconv cells selected by each top clonotype



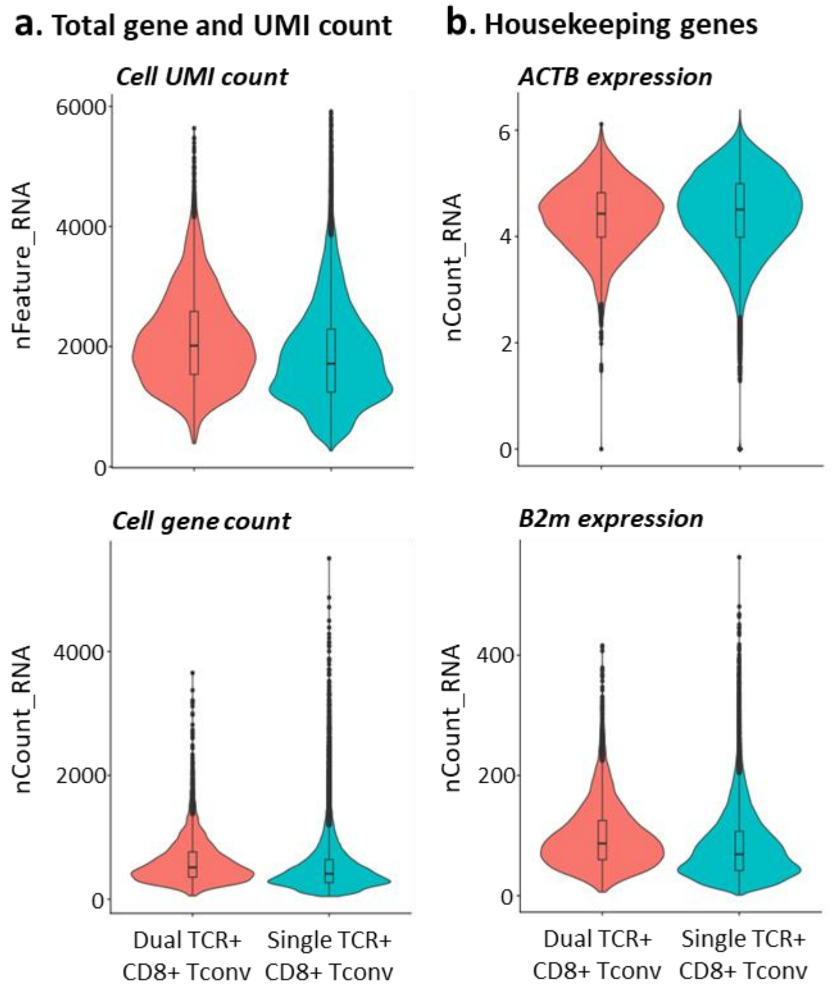
	Cells expressing clonotype 1		Cells expressing clonotype 2		Cells expressing clonotype 3	
TCR	CDR3α/CDR3β	Ct.	CDR3α/CDR3β	Ct.	CDR3α/CDR3β	Ct.
1	CALSEVTTSGTYKYIF CASSPDRGGYEQYF	324	CIVRVHSGGGADGLTF CASSPDRGGYEQYF	238	CALSEVTTSGTYKYIF CASSQDRGGYEQYF	218
2	CIVRVHSGGGADGLTF CASSPDRGGYEQYF	221	CALSEVTTSGTYKYIF CASSPDRGGYEQYF	221		
3	CVVNNARNNDMRF CASSPDRGGYEQYF	37	CIVRVHSGGGADGLTF CASTLSAGLNQPQHF	1		
4	CALSEVTTSGTYKYIF CASSYDRGGYEQYF	1	CAADTGGFKTIF CASSPDRGGYEQYF	1		
5			CAADTGGFKTIF CASTLSAGLNQPQHF	1		

c. Affected skin: CDR3αβ expression of CD8 Tconv cells selected by each top clonotype

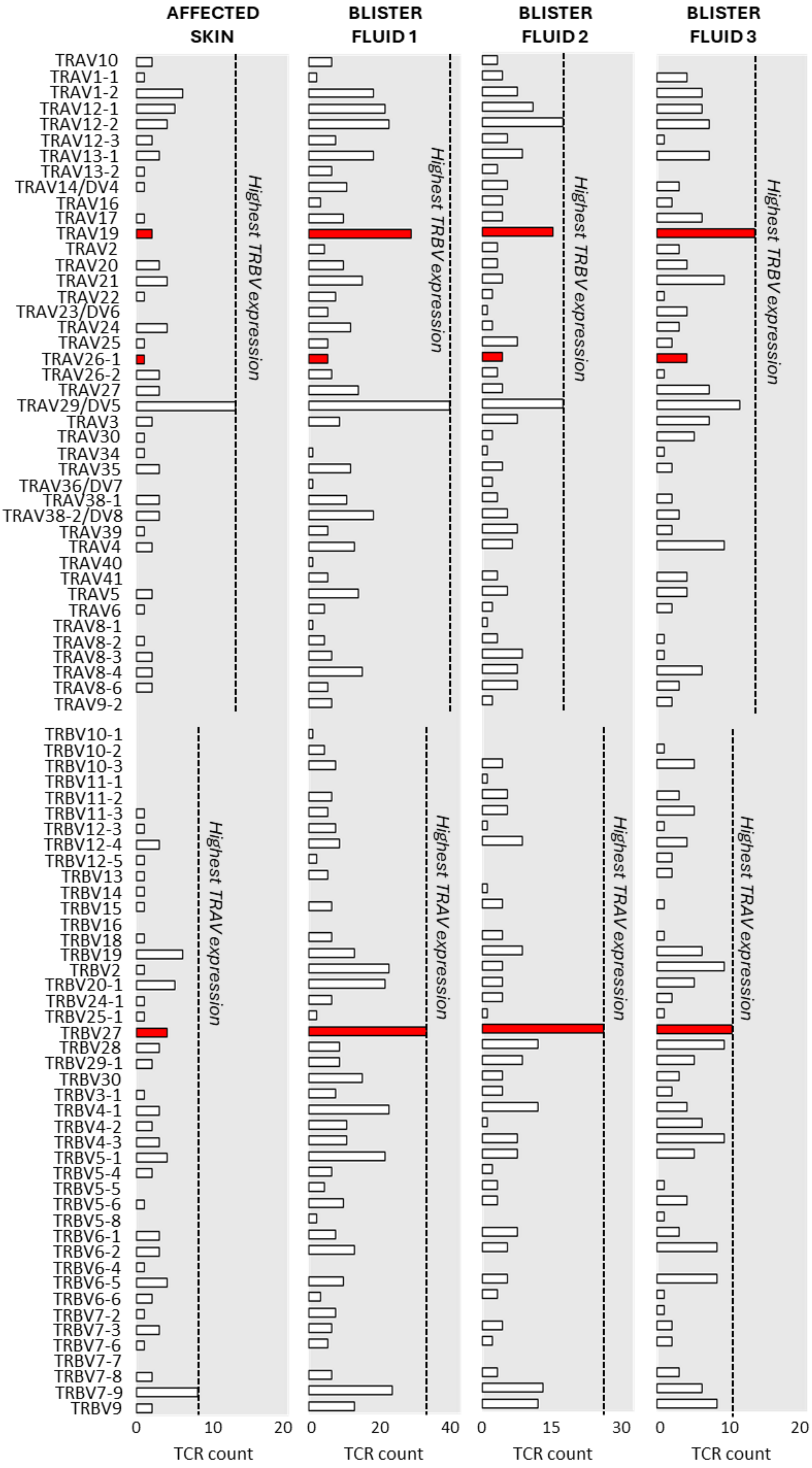


	Cells expressing clonotype 1		Cells expressing clonotype 2		Cells expressing clonotype 3	
TCR	CDR3α/CDR3β	Ct.	CDR3α/CDR3β	Ct.	CDR3α/CDR3β	Ct.
1	CALSEVTTSGTYKYIF CASSPDRGGYEQYF	20	CALSEVTTSGTYKYIF CASSPDRGGYEQYF	10	CALSEVTTSGTYKYIF CASSQDRGGYEQYF	27
2	CIVRVHSGGGADGLTF CASSPDRGGYEQYF	10	CIVRVHSGGGADGLTF CASSPDRGGYEQYF	10		
3	CVVNNARNNDMRF CASSPDRGGYEQYF	4				

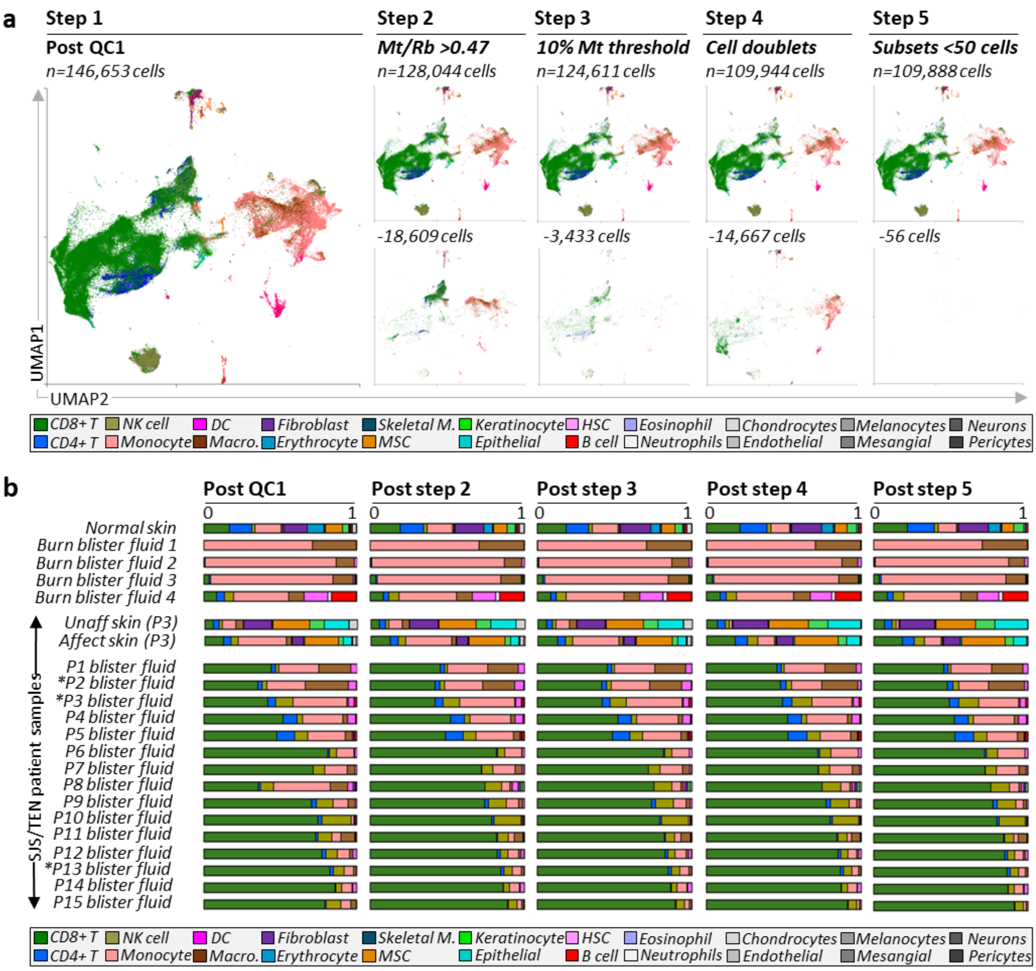
Supplementary Figure 12 | Top expanded TCRαβ clonotypes in CD8^{+} Tconv in affected skin and blister fluid have shared expression on dual TCRαβ^{+} T-cells. a Expression of each of the top 3 dominantly-expanded TCR on CD8^{+} Tconv cells in blister fluid (n=1 patient, 5470 total CD8+ Tconv, 2961 TCR+ CD8+ Tconv, 324 CD8+ Tconv express clonotype 1, 238 cells express clonotype 2, 218 cells express clonotype 3) from a patient with SJS/TEN. Cells expressing each clonotype are circled in black. **b** The TCR clonotypes and counts expressed by the same cells selected for expression of each top clonotype individually in SJS/TEN blister fluid. **c** The TCR clonotypes and counts expressed by cells selected for expression of each top clonotype individually in paired SJS/TEN affected skin (356 total CD8+ Tconv, 235 TCR+ CD8+ Tconv, 20 CD8+ Tconv express clonotype 1, 10 cells express clonotype 2, 27 cells express clonotype 3). A grey highlight indicates TCR expressed by the same cells. Source data are provided as a Source Data file. *Ct., cell count. Tconv, T conventional cell; TCR, T-cell receptor; CDR, complimentary-determining region; Ct., Count.*



Supplementary Figure 13 | Total gene and UMI count for CD8$^+$ Tconv cells in SJS/TEN blister fluid with one or two TCRαβ. a Violin plots show comparative total UMI and total gene count and **b** expression of housekeeping genes ACTB and B2m in CD8$^+$ Tconv cells of SJS/TEN blister fluid (n=15 patients) which express a single (n=44,946 cells) or dual TCRαβ (4,675 cells). The dual TCRαβ population includes cells with two CDR3α and one CDR3β, one CDR3α and two CDR3β, or two CDR3α and two CDR3β. Bounds of the box represent the interquartile range from the 25th to 75th percentile, the center line shows the median expression, and whiskers identify maximum and minimum values to the 10th and 90th percentile, respectively. Outliers are shown. *TCR, T-cell receptor; Tconv, T conventional cell; UMI, unique molecular identifier; CDR, complimentary-determining region.*


AFFECTED SKIN
BLISTER FLUID 1
BLISTER FLUID 2
BLISTER FLUID 3
TRAV10
TRAV1-1
TRAV1-2
TRAV12-1
TRAV12-2
TRAV12-3
TRAV13-1
TRAV13-2
TRAV14/DV4
TRAV16
TRAV17
TRAV19
TRAV2
TRAV20
TRAV21
TRAV22
TRAV23/DV6
TRAV24
TRAV25
TRAV26-1
TRAV26-2
TRAV27
TRAV29/DV5
TRAV3
TRAV30
TRAV34
TRAV35
TRAV36/DV7
TRAV38-1
TRAV38-2/DV8
TRAV39
TRAV4
TRAV40
TRAV41
TRAV5
TRAV6
TRAV8-1
TRAV8-2
TRAV8-3
TRAV8-4
TRAV8-6
TRAV9-2
TRBV10-1
TRBV10-2
TRBV10-3
TRBV11-1
TRBV11-2
TRBV11-3
TRBV12-3
TRBV12-4
TRBV12-5
TRBV13
TRBV14
TRBV15
TRBV16
TRBV18
TRBV19
TRBV2
TRBV20-1
TRBV24-1
TRBV25-1
TRBV27
TRBV28
TRBV29-1
TRBV30
TRBV3-1
TRBV4-1
TRBV4-2
TRBV4-3
TRBV5-1
TRBV5-4
TRBV5-5
TRBV5-6
TRBV5-8
TRBV6-1
TRBV6-2
TRBV6-4
TRBV6-5
TRBV6-6
TRBV7-2
TRBV7-3
TRBV7-6
TRBV7-7
TRBV7-8
TRBV7-9
TRBV9
Highest TRBV expression
Highest TRAV expression
0
10
20
0
20
40
0
15
30
0
10
20
TCR count
TCR count
TCR count
TCR count

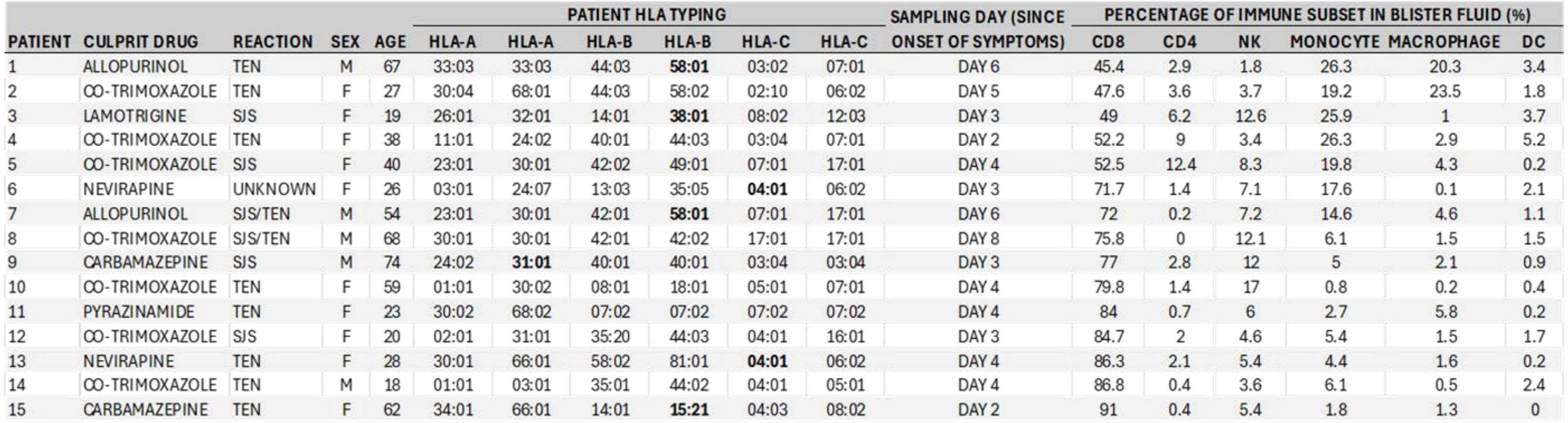
Supplementary Figure 14 | Individual TRAV and TRBV scTCR-seq counts on unexpanded cytotoxic CD8$^+$ Tconv cluster cells across samples from a single SJS/TEN patient. Individual counts for all identified TRAV and TRBV genes across unexpanded cytotoxic CD8$^+$ Tconv from paired affected skin (n=77 cells) and blister fluid (blister fluid 1, n=333 cells; blister fluid 2, n=179 cells; blister fluid 3, n=138 cells) from three anatomical sites from a single SJS/TEN patient. The dominant TRAV and TRBV of the dominantly-expanded cells in the cytotoxic CD8$^+$ Tconv cluster in affected skin and blister fluid are highlighted in red. Figure created using VGAS. Source data are provided as a Source Data file. *TCR, T-cell receptor; TRAV, TCR alpha variable; TRBV, TCR beta variable; Tconv, T conventional cell.*



Supplementary Figure 15 | Quality control analysis of the distribution and cell representation in samples pre- and post-filtering at all steps in the filtering of single-cell data. a UMAPs show the distribution of cells removed by or post QC1 (remove hashtag negative/doublets, remove cells with low UMI (<500), <100 genes, and >50% mitochondrial content), QC step 2 (remove cells with a low percentage of ribosomal genes and a high percentage of mitochondrial genes), QC step 3 (remove remaining cells with >10% mitochondrial RNA content), QC step 4 (remove RNA doublets identified by a consensus of bioinformatic algorithms), and QC step 5 (remove cell subsets with <50 cells) across normal skin (n=1 donor), burn blister fluid (n=4 patients), SJS/TEN unaffected and affected skin (n=1 patient), and SJS/TEN blister fluid (n=15 patients). The UMAP post-QC step 5 represents the final cells utilized in this study. **b** The scRNA-defined cell representation in different samples after each step in the QC analysis pipeline. The average expression is shown for patients with multiple samples from the same time point, indicated by an asterisk. Source data are provided as a Source Data file. *DC, dendritic cell; NK, natural killer; MSC, mesenchymal stromal cell; HSC, hematopoietic stem cell; QC, quality control; Mt/Rb, mitochondrial/ribosomal; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.*

Supplementary Tables

Supplementary Table 1 | Clinical data and scRNA-defined immune cell subset representation in blister fluid from patients with SJS/TEN. The culprit drug driving the reaction, sex, and age (years) of each SJS/TEN patient (n=15) is listed with the reaction phenotype as defined by literature using the percentage of the body surface area detached (SJS, <10%; SJS/TEN overlap, 10-30%; TEN >30%) if known. The HLA class I (HLA-A, B, C) expression of each patient is shown with the putative risk HLA alleles for individual drugs highlighted in black if previously reported in literature and expressed by the patient. The sampling day indicates the time since the onset of symptoms to when blister fluid was obtained. The percentage of each blister fluid formed of different scRNA-defined immune subsets is indicated, with patients ordered by the percentage of $CD8^+$ T-cells (patient 1 to patient 15, low to high). Source data are provided as a Source Data file. *SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; M, male; F, female; HLA, human leukocyte antigen; NK, natural killer; DC, dendritic cell.*

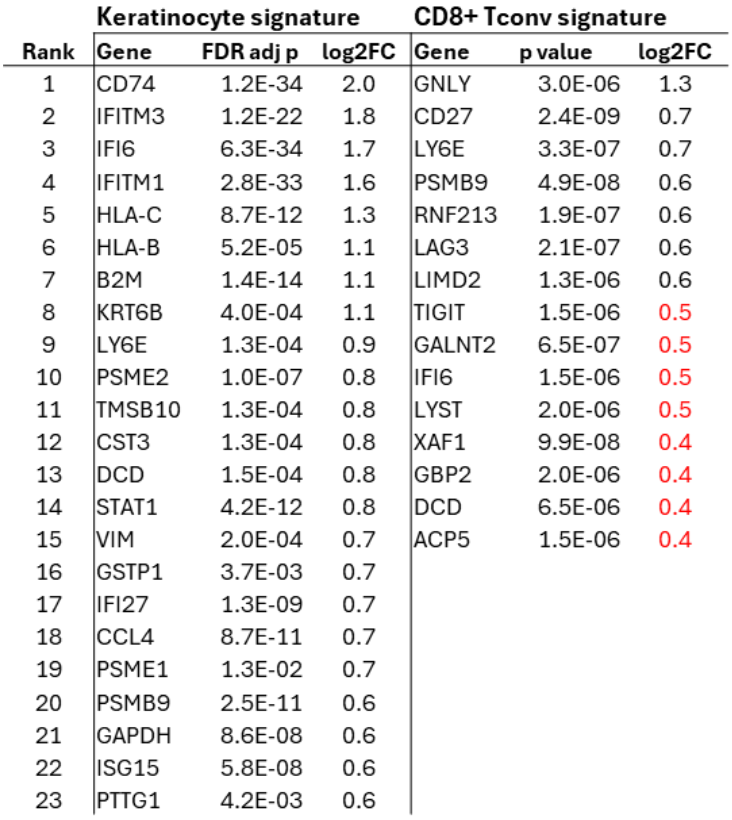


					PATIENT HLA TYPING						SAMPLING DAY (SINCE ONSET OF SYMPTOMS)	PERCENTAGE OF IMMUNE SUBSET IN BLISTER FLUID (%)					
PATIENT	CULPRIT DRUG	REACTION	SEX	AGE	HLA-A	HLA-A	HLA-B	HLA-B	HLA-C	HLA-C		CD8	CD4	NK	MONOCYTE	MACROPHAGE	DC
1	ALLOPURINOL	TEN	M	67	33:03	33:03	44:03	**58:01**	03:02	07:01	DAY 6	45.4	2.9	1.8	26.3	20.3	3.4
2	CO-TRIMOXAZOLE	TEN	F	27	30:04	68:01	44:03	58:02	02:10	06:02	DAY 5	47.6	3.6	3.7	19.2	23.5	1.8
3	LAMOTRIGINE	SJS	F	19	26:01	32:01	14:01	**38:01**	08:02	12:03	DAY 3	49	6.2	12.6	25.9	1	3.7
4	CO-TRIMOXAZOLE	TEN	F	38	11:01	24:02	40:01	44:03	03:04	07:01	DAY 2	52.2	9	3.4	26.3	2.9	5.2
5	CO-TRIMOXAZOLE	SJS	F	40	23:01	30:01	42:02	49:01	07:01	17:01	DAY 4	52.5	12.4	8.3	19.8	4.3	0.2
6	NEVIRAPINE	UNKNOWN	F	26	03:01	24:07	13:03	35:05	**04:01**	06:02	DAY 3	71.7	1.4	7.1	17.6	0.1	2.1
7	ALLOPURINOL	SJS/TEN	M	54	23:01	30:01	42:01	**58:01**	07:01	17:01	DAY 6	72	0.2	7.2	14.6	4.6	1.1
8	CO-TRIMOXAZOLE	SJS/TEN	M	68	30:01	30:01	42:01	42:02	17:01	17:01	DAY 8	75.8	0	12.1	6.1	1.5	1.5
9	CARBAMAZEPINE	SJS	M	74	24:02	**31:01**	40:01	40:01	03:04	03:04	DAY 3	77	2.8	12	5	2.1	0.9
10	CO-TRIMOXAZOLE	TEN	F	59	01:01	30:02	08:01	18:01	05:01	07:01	DAY 4	79.8	1.4	17	0.8	0.2	0.4
11	PYRAZINAMIDE	TEN	F	23	30:02	68:02	07:02	07:02	07:02	07:02	DAY 4	84	0.7	6	2.7	5.8	0.2
12	CO-TRIMOXAZOLE	SJS	F	20	02:01	31:01	35:20	44:03	04:01	16:01	DAY 3	84.7	2	4.6	5.4	1.5	1.7
13	NEVIRAPINE	TEN	F	28	30:01	66:01	58:02	81:01	**04:01**	06:02	DAY 4	86.3	2.1	5.4	4.4	1.6	0.2
14	CO-TRIMOXAZOLE	TEN	M	18	01:01	03:01	35:01	44:02	04:01	05:01	DAY 4	86.8	0.4	3.6	6.1	0.5	2.4
15	CARBAMAZEPINE	TEN	F	62	34:01	66:01	14:01	**15:21**	04:03	08:02	DAY 2	91	0.4	5.4	1.8	1.3	0

Supplementary Table 2 | Cluster marker gene signatures of Seurat-defined CD8$^+$ Tconv clusters 1-8. The top 25 genes that show significantly (two-tailed Wilcoxon rank sum test, Benjamini Hochberg adjusted $p < 0.05$) increased expression are shown in order of fold change for Seurat-defined CD8+ Tconv clusters 1-8 across cells from normal skin (n=1 donor), burn blister fluid (n=4 patients), and unaffected and affected SJS/TEN skin (n=1 patient) and SJS/TEN blister fluid (n=15 patients; total n=64,358 cells: cluster 1, n=3,295 cells; cluster 2, n=19,761 cells; cluster 3, n=36,428 cells; cluster 4, 60 cells; cluster 5, 3,395 cells; cluster 6, 280 cells; cluster 7, 743 cells; cluster 8, 381 cells). Clusters with <20 cells were removed from cluster marker analyses (n=15 cells). Red font indicates genes below significance. Genes shared or indicative of shared functional state between clusters are shaded for inactivation/quiescence (grey), IL7R (red), cytotoxicity/proliferation/activation (green), the inflammasome (yellow), and innate-like differentiation (blue). Source data are provided as a Source Data file. *Tconv, T conventional cell; FC, fold change; Adj, Hochberg adjusted p value.*

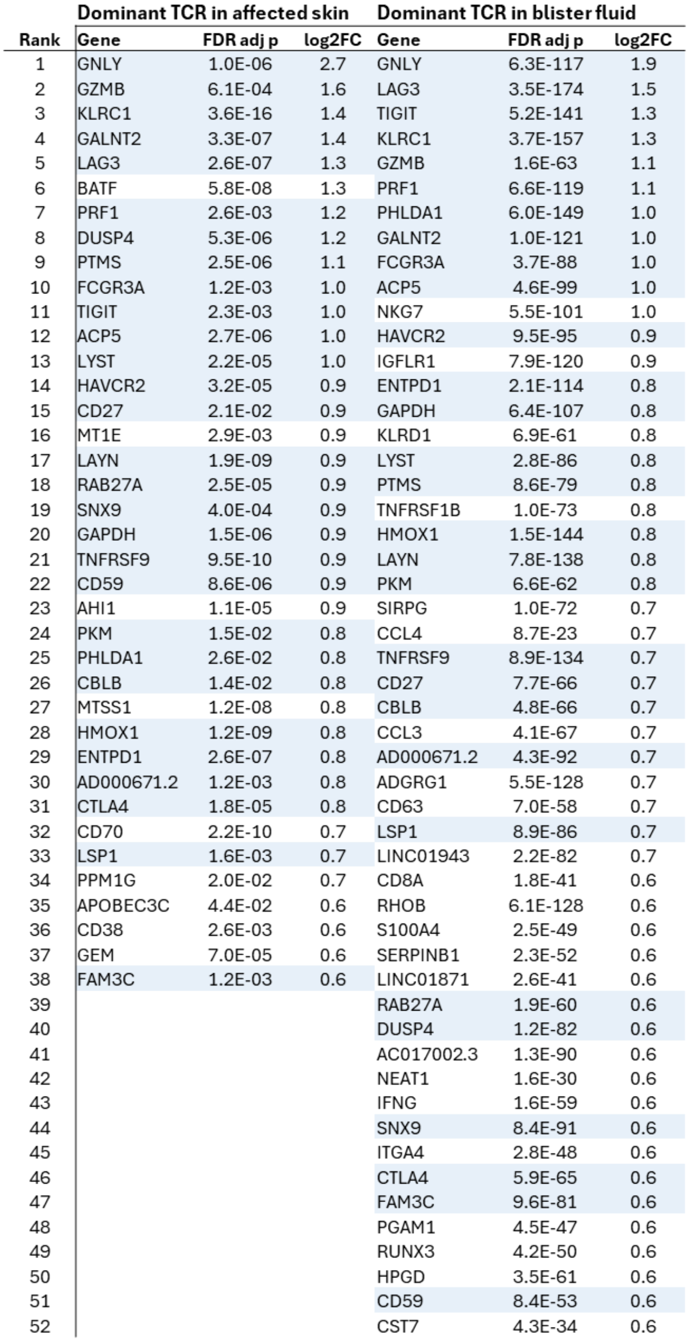
	Quiescent/inactive						Cytotoxic/proliferative			Quiescent/inactive			Inflammasome-related			Innate-like								
	CD8 Tconv cluster 1			CD8 Tconv cluster 2			CD8 Tconv cluster 3			CD8 Tconv cluster 4			CD8 Tconv cluster 5			CD8 Tconv cluster 6			CD8 Tconv cluster 7			CD8 Tconv cluster 8		
Rank	Gene	log2FC	Adj p value	Gene	log2FC	Adj p value	Gene	log2FC	Adj p value	Gene	log2FC	Adj p value	Gene	log2FC	Adj p value	Gene	log2FC	Adj p value	Gene	log2FC	Adj p value	Gene	log2FC	Adj p value
1	TYROBP	2.2	0.0E+00	IL7R	1.8	0.0E+00	GNLY	1.8	0.0E+00	AREG	2.2	2.0E-08	NEAT1	1.5	3.8E-246	CST3	2.1	5.5E-94	CST3	3.3	0.0E+00	TYROBP	2.2	0.0E+00
2	AREG	1.8	7.4E-129	CMC1	1.6	0.0E+00	GZMB	1.4	0.0E+00	IL7R	1.4	6.7E-07	MALAT1	1.4	0.0E+00	IFITM3	1.8	6.0E-46	TYROBP	3.2	0.0E+00	AREG	1.8	7.4E-129
3	FCER1G	1.8	3.1E-239	ZFP36	1.3	0.0E+00	STMN1	1.4	0.0E+00	JAML	1.3	2.5E-05	CTSD	1.1	3.6E-84	TYROBP	1.6	5.6E-55	FCER1G	3.2	0.0E+00	FCER1G	1.8	3.1E-239
4	XCL1	1.8	2.4E-299	HSPA1A	1.3	4.5E-37	KLRC1	1.3	0.0E+00	RASD1	1.2	1.0E+00	XIST	1.1	6.9E-34	FCER1G	1.6	2.0E-48	S100A8	3.0	0.0E+00	XCL1	1.8	2.4E-299
5	XCL2	1.7	2.3E-169	FOS	1.2	7.5E-274	TUBA1B	1.2	0.0E+00	BTG1	1.0	7.0E-08	RNF213	1.0	4.4E-145	HIST1H2AI	1.3	1.7E-29	IFITM3	2.8	0.0E+00	XCL2	1.7	2.3E-169
6	CMC1	1.6	1.1E-98	JUNB	1.2	0.0E+00	GALNT2	1.2	0.0E+00	RGS1	1.0	2.2E-02	SYNE2	1.0	5.4E-51	S100A8	1.2	9.2E-48	HLA-DRA	2.4	0.0E+00	CMC1	1.6	1.1E-98
7	KLRD1	1.4	1.2E-104	LTB	1.1	0.0E+00	PRF1	1.2	0.0E+00	GCHFR	1.0	1.5E-03	AKNA	0.9	3.0E-44	LYZ	1.2	9.3E-31	AIF1	2.4	0.0E+00	KLRD1	1.4	1.2E-104
8	KLRC3	1.2	9.9E-96	CXCR4	1.1	0.0E+00	KIR2DL4	1.1	0.0E+00	LGALS3	1.0	1.3E-02	IKZF3	0.9	1.4E-29	CXCL10	1.1	1.6E-85	LYZ	2.3	0.0E+00	KLRC3	1.2	9.9E-96
9	KLRB1	1.2	2.0E-162	DUSP1	1.1	0.0E+00	LGALS1	1.1	0.0E+00	FXYD7	0.9	1.1E-03	TRAC	0.9	6.6E-27	HIST1H1E	1.1	1.8E-15	C1QB	2.3	0.0E+00	KLRB1	1.2	2.0E-162
10	IFITM3	1.1	3.1E-36	DNAJB1	1.0	1.8E-222	ACP5	1.1	0.0E+00	GPR15	0.9	1.7E-04	NKTR	0.8	2.2E-07	SAT1	1.1	9.8E-14	C1QA	2.2	0.0E+00	IFITM3	1.1	3.1E-36
11	SH2D1B	1.0	0.0E+00	DUSP2	1.0	0.0E+00	LAG3	1.1	0.0E+00	AUTS2	0.9	1.0E+00	MYO1F	0.8	9.7E-21	S100A6	1.1	5.5E-40	SAT1	2.1	0.0E+00	SH2D1B	1.0	0.0E+00
12	TRDC	0.9	0.0E+00	TXNIP	0.9	0.0E+00	TYMS	1.1	0.0E+00	PLEC	0.9	1.0E+00	MYH9	0.8	3.1E-88	SERPING1	1.0	4.2E-79	FTL	2.1	0.0E+00	TRDC	0.9	0.0E+00
13	TXNIP	0.9	1.0E-30	HLA-DPB1	0.9	0.0E+00	HAVCR2	1.1	0.0E+00	ABTB1	0.9	1.0E+00	USF2	0.8	4.5E-36	TXN	1.0	3.4E-43	S100A9	2.1	0.0E+00	TXNIP	0.9	1.0E-30
14	KLRF1	0.8	0.0E+00	ZFP36L2	0.9	0.0E+00	GZMA	1.1	0.0E+00	FKBP5	0.8	1.0E+00	GRK2	0.8	1.7E-13	FTL	1.0	8.0E-24	C1QC	2.1	0.0E+00	KLRF1	0.8	0.0E+00
15	C1orf162	0.8	1.6E-113	RPL3	0.9	0.0E+00	IFI27	1.0	0.0E+00	PIK3IP1	0.8	1.0E+00	INPP5D	0.8	1.2E-14	GLUL	1.0	2.5E-24	CXCL10	2.0	0.0E+00	C1orf162	0.8	1.6E-113
16	MATK	0.7	1.6E-46	PPP1R14B	0.9	4.8E-280	CD27	1.0	0.0E+00	AC243829.4	0.8	1.0E+00	GNAS	0.8	7.5E-56	AIF1	1.0	4.3E-25	HIST1H2AI	2.0	0.0E+00	MATK	0.7	1.6E-46
17	FOS	0.7	8.1E-24	EEF1A1	0.9	0.0E+00	TUBB	1.0	0.0E+00	SLA2	0.8	3.5E-02	CNOT6L	0.8	5.4E-06	RNASE1	1.0	1.5E-31	RNASE1	1.9	0.0E+00	FOS	0.7	8.1E-24
18	DDIT4	0.7	8.1E-19	BTG1	0.9	0.0E+00	HMGN2	1.0	0.0E+00	SAMSN1	0.8	1.0E+00	MACF1	0.8	2.6E-06	HLA-DRA	1.0	1.5E-16	SERPING1	1.9	0.0E+00	DDIT4	0.7	8.1E-19
19	KIR3DL2	0.7	2.3E-62	HLA-DPA1	0.9	0.0E+00	HMGB2	0.9	0.0E+00	TCEAL4	0.8	2.3E-01	CCDC88B	0.8	2.2E-19	C1QC	1.0	1.3E-48	GLUL	1.9	0.0E+00	KIR3DL2	0.7	2.3E-62
20	BTG1	0.7	2.8E-43	JUN	0.8	0.0E+00	TIMD4	0.9	0.0E+00	GLUL	0.8	1.0E+00	MT-CO1	0.8	0.0E+00	C1QB	1.0	4.5E-37	FOS	1.9	0.0E+00	BTG1	0.7	2.8E-43
21	TMIGD2	0.7	5.2E-190	KLRB1	0.8	0.0E+00	CXCL13	0.8	5.4E-184	STOM	0.8	1.0E+00	ETS1	0.8	5.4E-55	CD14	0.9	8.5E-57	HLA-DRB1	1.9	0.0E+00	TMIGD2	0.7	5.2E-190
22	TCF7	0.7	4.6E-50	RGCC	0.8	1.2E-25	HIST1H4C	0.8	3.6E-152	RCBTB2	0.8	4.6E-04	CBLB	0.8	1.3E-43	C1QA	0.9	4.3E-38	C15orf48	1.9	0.0E+00	TCF7	0.7	4.6E-50
23	C1orf21	0.7	6.2E-54	KLRG1	0.8	0.0E+00	H2AFZ	0.8	0.0E+00	ITM2B	0.8	3.6E-06	FMNL1	0.8	3.4E-20	THBS1	0.9	3.4E-59	HIST1H1E	1.9	0.0E+00	C1orf21	0.7	6.2E-54
24	DUSP1	0.7	1.8E-28	GZMM	0.8	0.0E+00	GAPDH	0.8	0.0E+00	NT5E	0.8	9.5E-01	OGT	0.8	5.0E-05	FOS	0.9	4.6E-26	HLA-DQA1	1.8	2.0E-275	DUSP1	0.7	1.8E-28
25	IL7R	0.7	9.4E-30	TCF7	0.8	0.0E+00	UBE2C	0.8	0.0E+00	LPAR6	0.7	6.8E-01	MT-ND4	0.7	2.0E-166	LGALS1	0.9	7.0E-32	THBS1	1.8	0.0E+00	IL7R	0.7	9.4E-30

Supplementary Table 3 | Differential gene signatures of keratinocytes and CD8$^+$ Tconv in affected compared to unaffected skin. The genes in cells of affected skin compared to unaffected SJS/TEN patient skin that show significant (two-tailed Wilcoxon, Hochberg adjusted p <0.05) increased expression are shown in order of fold change. Cells from unaffected skin (keratinocytes, n=331 cells; CD8+ Tconv, n=142 cells) and affected skin (keratinocytes, n=108 cells; CD8+ Tconv, n=356 cells) are time-paired samples from n=1 patient. Red font indicates genes significantly differentially expressed but below the threshold for fold change (0.6 log2FC, 1.5 actual fold change). Source data are provided as a Source Data file. *FDR adj p, False discovery rate adjusted p-value; FC, fold change; Tconv, T conventional cell.*



	Keratinocyte signature			CD8+ Tconv signature		
Rank	**Gene**	**FDR adj p**	**log2FC**	**Gene**	**p value**	**log2FC**
1	CD74	1.2E-34	2.0	GNLY	3.0E-06	1.3
2	IFITM3	1.2E-22	1.8	CD27	2.4E-09	0.7
3	IFI6	6.3E-34	1.7	LY6E	3.3E-07	0.7
4	IFITM1	2.8E-33	1.6	PSMB9	4.9E-08	0.6
5	HLA-C	8.7E-12	1.3	RNF213	1.9E-07	0.6
6	HLA-B	5.2E-05	1.1	LAG3	2.1E-07	0.6
7	B2M	1.4E-14	1.1	LIMD2	1.3E-06	0.6
8	KRT6B	4.0E-04	1.1	TIGIT	1.5E-06	0.5
9	LY6E	1.3E-04	0.9	GALNT2	6.5E-07	0.5
10	PSME2	1.0E-07	0.8	IFI6	1.5E-06	0.5
11	TMSB10	1.3E-04	0.8	LYST	2.0E-06	0.5
12	CST3	1.3E-04	0.8	XAF1	9.9E-08	0.4
13	DCD	1.5E-04	0.8	GBP2	2.0E-06	0.4
14	STAT1	4.2E-12	0.8	DCD	6.5E-06	0.4
15	VIM	2.0E-04	0.7	ACP5	1.5E-06	0.4
16	GSTP1	3.7E-03	0.7			
17	IFI27	1.3E-09	0.7			
18	CCL4	8.7E-11	0.7			
19	PSME1	1.3E-02	0.7			
20	PSMB9	2.5E-11	0.6			
21	GAPDH	8.6E-08	0.6			
22	ISG15	5.8E-08	0.6			
23	PTTG1	4.2E-03	0.6			

Supplementary Table 4 | Differential gene signatures of CD8^{+} Tconv expressing dominantly expanded TCR compared to other TCR in affected skin or blister fluid. The genes that show significantly (two-tailed Wilcoxon, Hochberg adjusted p <0.05) increased expression above the threshold for fold-change (0.6log2FC) for dominant TCR+ CD8+ Tconv (affected skin, n=47 cells; blister fluid, n=559 cells) compared to non-dominant TCR+ CD8+ Tconv (affected skin, n=192 cells; blister fluid, n=2441 cells) are shown for single patient. Genes shared in the signature of dominantly-expanded TCR^{+} Tconv between affected skin and blister fluid highlighted blue. Source data are provided as a Source Data file. *TCR, T-cell receptor; FDR adj p, False discovery rate adjusted p-value; FC, fold change; Tconv, T conventional cell.*



	Dominant TCR in affected skin			Dominant TCR in blister fluid		
Rank	**Gene**	**FDR adj p**	**log2FC**	**Gene**	**FDR adj p**	**log2FC**
1	GNLY	1.0E-06	2.7	GNLY	6.3E-117	1.9
2	GZMB	6.1E-04	1.6	LAG3	3.5E-174	1.5
3	KLRC1	3.6E-16	1.4	TIGIT	5.2E-141	1.3
4	GALNT2	3.3E-07	1.4	KLRC1	3.7E-157	1.3
5	LAG3	2.6E-07	1.3	GZMB	1.6E-63	1.1
6	BATF	5.8E-08	1.3	PRF1	6.6E-119	1.1
7	PRF1	2.6E-03	1.2	PHLDA1	6.0E-149	1.0
8	DUSP4	5.3E-06	1.2	GALNT2	1.0E-121	1.0
9	PTMS	2.5E-06	1.1	FCGR3A	3.7E-88	1.0
10	FCGR3A	1.2E-03	1.0	ACP5	4.6E-99	1.0
11	TIGIT	2.3E-03	1.0	NKG7	5.5E-101	1.0
12	ACP5	2.7E-06	1.0	HAVCR2	9.5E-95	0.9
13	LYST	2.2E-05	1.0	IGFLR1	7.9E-120	0.9
14	HAVCR2	3.2E-05	0.9	ENTPD1	2.1E-114	0.8
15	CD27	2.1E-02	0.9	GAPDH	6.4E-107	0.8
16	MT1E	2.9E-03	0.9	KLRD1	6.9E-61	0.8
17	LAYN	1.9E-09	0.9	LYST	2.8E-86	0.8
18	RAB27A	2.5E-05	0.9	PTMS	8.6E-79	0.8
19	SNX9	4.0E-04	0.9	TNFRSF1B	1.0E-73	0.8
20	GAPDH	1.5E-06	0.9	HMOX1	1.5E-144	0.8
21	TNFRSF9	9.5E-10	0.9	LAYN	7.8E-138	0.8
22	CD59	8.6E-06	0.9	PKM	6.6E-62	0.8
23	AHI1	1.1E-05	0.9	SIRPG	1.0E-72	0.7
24	PKM	1.5E-02	0.8	CCL4	8.7E-23	0.7
25	PHLDA1	2.6E-02	0.8	TNFRSF9	8.9E-134	0.7
26	CBLB	1.4E-02	0.8	CD27	7.7E-66	0.7
27	MTSS1	1.2E-08	0.8	CBLB	4.8E-66	0.7
28	HMOX1	1.2E-09	0.8	CCL3	4.1E-67	0.7
29	ENTPD1	2.6E-07	0.8	AD000671.2	4.3E-92	0.7
30	AD000671.2	1.2E-03	0.8	ADGRG1	5.5E-128	0.7
31	CTLA4	1.8E-05	0.8	CD63	7.0E-58	0.7
32	CD70	2.2E-10	0.7	LSP1	8.9E-86	0.7
33	LSP1	1.6E-03	0.7	LINC01943	2.2E-82	0.7
34	PPM1G	2.0E-02	0.7	CD8A	1.8E-41	0.6
35	APOBEC3C	4.4E-02	0.6	RHOB	6.1E-128	0.6
36	CD38	2.6E-03	0.6	S100A4	2.5E-49	0.6
37	GEM	7.0E-05	0.6	SERPINB1	2.3E-52	0.6
38	FAM3C	1.2E-03	0.6	LINC01871	2.6E-41	0.6
39				RAB27A	1.9E-60	0.6
40				DUSP4	1.2E-82	0.6
41				AC017002.3	1.3E-90	0.6
42				NEAT1	1.6E-30	0.6
43				IFNG	1.6E-59	0.6
44				SNX9	8.4E-91	0.6
45				ITGA4	2.8E-48	0.6
46				CTLA4	5.9E-65	0.6
47				FAM3C	9.6E-81	0.6
48				PGAM1	4.5E-47	0.6
49				RUNX3	4.2E-50	0.6
50				HPGD	3.5E-61	0.6
51				CD59	8.4E-53	0.6
52				CST7	4.3E-34	0.6

Supplementary Table 5 | Unexpanded clonotypes of the cytotoxic CD8$^+$ Tconv cluster with a shared CDRβ sequence with the dominantly-expanded clonotypes. Unexpanded clonotypes from the cytotoxic CD8$^+$ Tconv cluster of blister fluids from three different anatomical sites (blister fluid 1, arm, n=333 cells; blister fluid 2, face, n=179 cells; blister fluid 3, foot, n=138 cells) from a single SJS/TEN patient are shown that have the same CDR3β CASSPDRGGYEQYF sequence as the dominantly-expanded TCR$^+$ population or a single mismatch (bold and underlined). The 'dual TCR' column indicates whether an n=1 or n=2 count clonotype is expressed on a dual TCR$^+$ cell (yes or no). TCRs expressed on the same dual TCR$^+$ cell are indicated by the same symbol (○, ●, ◊, ‡). Ct. TCR count. Source data are provided as a Source Data file.

Blister fluid 1 (ARM), 333 unexpanded cells from the cytotoxic CD8+ Tconv cluster

TCR	CDR3α	CDR3β	TRAV	TRAJ	TRBV	TRBJ	Ct.	Dual TCR+
1	CAVQAFRQTGANNLFF	CASS**H**DRGGYEQYF	TRAV20	TRAJ36	TRBV27	TRBJ2-7	1	yes ○
2	CALSEVTTSGTYKYIF	CASS**H**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1	yes ○
3	CVVATNAGGTSYGKLTF	CASSPDRGGYEQYF	TRAV10	TRAJ52	TRBV27	TRBJ2-7	1	yes
4	CALSEVTTSGTYKYIF	CASS**R**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1	no
5	CAAIDSWGKLQF	CASS**L**DRGGYEQYF	TRAV23/DV6	TRAJ24	TRBV11-2	TRBJ2-7	2	yes ‡
6	CALSEVRTSGTYKYIF	CASS**L**DRGGYEQYF	TRAV19	TRAJ40	TRBV11-2	TRBJ2-7	2	yes ‡
7	CASSMTSAGNMLTF	CASS**V**DRGGYEQYF	TRAV23/DV6	TRAJ39	TRBV27	TRBJ2-7	2	yes □
8	CALSEVTTSGTYKYIF	CASS**V**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	2	yes □

Blister fluid 2 (FACE), 179 unexpanded cells from the cytotoxic CD8+ Tconv cluster

TCR	CDR3α	CDR3β	TRAV	TRAJ	TRBV	TRBJ	Ct.	Dual TCR+
1	CALSEVTTSGTYKYIF	CASS**H**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1	yes ○
2	CAVQAFRQTGANNLFF	CASS**H**DRGGYEQYF	TRAV20	TRAJ36	TRBV27	TRBJ2-7	1	yes ○
3	CAADTGGFKTIF	CASSPDRGGYEQYF	TRAV13-1	TRAJ9	TRBV27	TRBJ2-7	1	yes ●
4	CIVRVHSGGGADGLTF	CASSPDRGGYEQYF	TRAV26-1	TRAJ45	TRBV27	TRBJ2-7	1	yes ●
5	CAVTDNYGQNFVF	CASSPDRGGYEQYF	TRAV25	TRAJ26	TRBV27	TRBJ2-7	1	yes ◊
6	CALSANSGNTPLVF	CASSPDRGGYEQYF	TRAV16	TRAJ29	TRBV27	TRBJ2-7	1	yes ◊
7	CAVQTNAGNNRKLIW	CASSPDRGGYEQYF	TRAV20	TRAJ38	TRBV27	TRBJ2-7	1	yes
8	CAVKYTGANSKLTF	CASSPDRGGYEQYF	TRAV12-2	TRAJ56	TRBV27	TRBJ2-7	1	yes
9	CAAGSSSGTYKYIF	CASSPDRGGYEQYF	TRAV13-1	TRAJ40	TRBV27	TRBJ2-7	1	yes
10	CALSEVTTSGTYKYIF	CASS**Y**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	2	no
11	CASSMTSAGNMLTF	CASS**V**DRGGYEQYF	TRAV23/DV6	TRAJ39	TRBV27	TRBJ2-7	2	yes □
12	CALSEVTTSGTYKYIF	CASS**V**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	2	yes □

Blister fluid 3 (FOOT), 138 unexpanded cells from the cytotoxic CD8+ Tconv cluster

TCR	CDR3α	CDR3β	TRAV	TRAJ	TRBV	TRBJ	Ct.	Dual TCR+
1	CALSEVTTSGTYKYIF	CASS**H**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1	yes ○
2	CAVQAFRQTGANNLFF	CASS**H**DRGGYEQYF	TRAV20	TRAJ36	TRBV27	TRBJ2-7	1	yes ○
3	CAASMTSAGNMLTF	CASS**V**DRGGYEQYF	TRAV23/DV6	TRAJ39	TRBV27	TRBJ2-7	1	yes □
4	CALSEVTTSGTYKYIF	CASS**V**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1	yes □
5	CALSEVTTSGTYKYIF	CASS**Y**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1	yes
6	CALSEVTTSGTYKYIF	CASS**F**DRGGYEQYF	TRAV19	TRAJ40	TRBV27	TRBJ2-7	1	no

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