

Supplemental Material

Supplemental Table 1. Fold changes and adjusted p-values for dtDHR vs healthy skin by bulk transcriptional profiling.

	SJS/TEN		DRESS		MDE	
Genes	Log ₂ FC	P _{adj}	Log ₂ FC	P _{adj}	Log ₂ FC	P _{adj}
<i>ABCF1</i>	0.37	0.00044	0.18	0.23884	0.34	0.02497
<i>AHR</i>	-0.67	4.35E-09	-0.86	2.36E-09	-0.69	7.52E-06
<i>ALAS1</i>	0.71	0.00532	0.32	0.37049	0.22	0.59649
<i>ARG1</i>	0.07	0.91347	-0.43	0.56904	-0.23	0.81697
<i>B2M</i>	1.39	2.35E-11	0.78	0.00576	0.96	0.00092
<i>CASP1</i>	1.33	1.27E-07	0.38	0.31163	0.44	0.25391
<i>CASP10</i>	1.15	2.02E-08	0.47	0.12147	0.51	0.09958
<i>CASP2</i>	-0.21	0.11885	0.08	0.6409	-0.16	0.40135
<i>CASP3</i>	0.37	0.01393	0.24	0.24864	0.01	0.9674
<i>CASP8</i>	0.31	0.17328	0.56	0.05058	0.11	0.7812
<i>CCL11</i>	-0.7	0.23626	-0.7	0.34956	-0.26	0.80918
<i>CCL13</i>	1.15	0.00187	2.64	3.26E-09	2.19	5.07E-06
<i>CCL16</i>	-0.46	0.39357	-0.64	0.35612	-1.01	0.15695
<i>CCL18</i>	1.17	0.05954	3.55	1.40E-06	3.26	3.05E-05
<i>CCL2</i>	2.23	6.67E-06	0.78	0.29443	0.97	0.18967
<i>CCL20</i>	1.06	0.04466	-0.41	0.53001	-0.38	0.61761
<i>CCL22</i>	0.07	0.85219	0.93	0.07381	0.29	0.65991
<i>CCL23</i>	0.63	0.15642	1.62	0.0017	0.8	0.18774
<i>CCL24</i>	-1.15	0.02584	0.19	0.74875	-1.28	0.06318
<i>CCL26</i>	-0.69	0.19748	1.46	0.02095	0.82	0.24308
<i>CCL27</i>	-1.28	0.01275	-0.03	0.97711	0.59	0.39491
<i>CCL5</i>	2.56	4.97E-10	3.29	1.51E-10	2.08	0.00019
<i>CCL7</i>	2.67	9.57E-06	-0.29	0.64728	-0.54	0.47286
<i>CCL8</i>	3.82	6.74E-13	0.81	0.32491	0.81	0.36449
<i>CCR1</i>	1.87	4.12E-08	1.06	0.02487	0.85	0.10218
<i>CCR10</i>	-0.52	0.31476	-0.7	0.29366	-0.95	0.15695
<i>CCR2</i>	1.47	2.84E-05	1.34	0.0035	0.59	0.28214
<i>CCR4</i>	-0.52	0.1842	0.05	0.91423	-0.78	0.13454
<i>CCR5</i>	2.31	2.60E-09	2.51	2.13E-07	1.71	0.00146
<i>CCR6</i>	-0.59	0.16193	-0.94	0.07618	-0.91	0.10215
<i>CCR7</i>	1.05	0.0042	1.05	0.02727	0.32	0.61356
<i>CD14</i>	1.94	6.27E-10	1.34	0.00134	1.08	0.01968
<i>CD1A</i>	-2.04	2.02E-09	-1.08	0.02198	-0.92	0.0746
<i>CD1D</i>	-0.14	0.76198	-0.47	0.42263	-0.53	0.39491
<i>CD209</i>	1.64	2.06E-06	2.37	4.06E-08	1.89	3.81E-05

<i>CD244</i>	-0.26	0.64182	-0.42	0.56074	-0.77	0.29908
<i>CD27</i>	0.64	0.13446	1.05	0.0483	0.32	0.6481
<i>CD274</i>	2.86	9.98E-09	1.24	0.08623	1.07	0.16226
<i>CD276</i>	0.45	0.04954	0.27	0.39301	0.22	0.53892
<i>CD28</i>	0.2	0.58633	0.76	0.08704	-0.12	0.83123
<i>CD3D</i>	0.72	0.05186	1.4	0.00169	0.37	0.51987
<i>CD3E</i>	1.04	0.0016	1.86	2.86E-06	0.92	0.05338
<i>CD4</i>	0.82	0.00109	0.98	0.00225	0.64	0.0793
<i>CD40</i>	1.62	3.58E-07	1.04	0.01832	0.91	0.05483
<i>CD40LG</i>	-0.87	0.01895	-0.04	0.95796	-0.41	0.46475
<i>CD44</i>	0.14	0.4412	0.41	0.08623	0.5	0.03977
<i>CD45R0</i>	1.76	1.27E-08	1.35	0.00107	1.05	0.02113
<i>CD45RA</i>	1.28	0.00082	0.89	0.09254	0.44	0.47286
<i>CD69</i>	-0.35	0.41903	-0.45	0.42263	-1.18	0.03049
<i>CD7</i>	2.24	4.06E-09	2.31	1.32E-06	1.16	0.04251
<i>CD80</i>	0.97	0.04263	0.6	0.34573	0.24	0.7812
<i>CD86</i>	1.24	0.00038	0.33	0.52397	0.09	0.90695
<i>CD8A</i>	1.5	0.00053	2.17	3.94E-05	0.86	0.18774
<i>CD8B</i>	0.04	0.91989	0.57	0.31665	-0.42	0.49368
<i>CSF1</i>	0.65	0.0094	0.05	0.90964	0.02	0.9674
<i>CSF1R</i>	0.84	0.00738	0.68	0.11767	0.3	0.55045
<i>CSF2</i>	-0.51	0.32133	-0.42	0.52874	-0.51	0.48421
<i>CTLA4_all</i>	0.91	0.01926	0.81	0.12147	-0.15	0.79948
<i>CTLA4-TM</i>	1.93	9.30E-09	1.93	4.54E-06	0.86	0.09907
<i>CX3CL1</i>	1.12	0.0061	-0.14	0.80613	0.1	0.90259
<i>CX3CR1</i>	0.03	0.93785	-0.04	0.95796	-0.15	0.81697
<i>CXCL1</i>	2.24	1.47E-06	1.92	0.00156	1.69	0.0107
<i>CXCL10</i>	6.08	4.57E-25	3.74	3.09E-07	4.4	2.83E-09
<i>CXCL11</i>	4.87	1.18E-16	2.36	0.00224	2.79	0.00037
<i>CXCL2</i>	0.54	0.23289	-0.1	0.88672	-0.7	0.23087
<i>CXCL9</i>	5.16	1.62E-26	4.42	9.29E-13	4.14	4.13E-11
<i>CXCR3</i>	0.48	0.31476	0.98	0.09254	0.03	0.98174
<i>CXCR4</i>	-0.37	0.3531	-0.05	0.95796	-1.14	0.0233
<i>EEF1G</i>	-1.06	4.16E-10	-0.77	0.00068	-0.63	0.01067
<i>FADD</i>	0.19	0.41993	0.24	0.43138	0.04	0.92515
<i>FAS</i>	-0.24	0.21427	-0.39	0.12707	-0.35	0.18774
<i>FASLG</i>	0.83	0.07712	0.92	0.12739	0.14	0.88671
<i>FOXP3</i>	-0.68	0.1764	-0.93	0.14349	-0.96	0.15695
<i>G6PD</i>	0.34	0.13446	0.03	0.95546	0.3	0.35699
<i>GAPDH</i>	0.34	0.0065	0.65	2.32E-05	0.32	0.07553
<i>GATA3</i>	-2.07	7.18E-13	-1.19	0.0019	-0.55	0.217
<i>GNLY</i>	2.1	4.99E-06	2.44	1.81E-05	0.7	0.3657
<i>GUSB</i>	-0.24	0.14718	-0.25	0.25504	-0.41	0.06318
<i>GZMA</i>	2.53	2.02E-08	3.4	1.41E-09	1.9	0.00271

<i>GZMB</i>	3.52	2.93E-13	3.14	1.66E-07	2.06	0.00231
<i>GZMK</i>	0.67	0.13446	1.87	0.00028	0.34	0.65258
<i>HLA-DRA</i>	1.31	4.99E-06	1.11	0.00361	0.93	0.02706
<i>HLA-DRB1</i>	1.52	0.00773	0.89	0.25504	0.72	0.39491
<i>HLA-DRB3</i>	1.87	4.90E-14	1.75	3.17E-08	1.55	5.07E-06
<i>HLA-E</i>	1.08	3.77E-08	0.69	0.00999	0.63	0.03049
<i>HOBIT</i>	0.78	0.17116	1.28	0.06735	0.22	0.84621
<i>HPRT1</i>	0.07	0.6427	0.06	0.7705	-0.07	0.77838
<i>ICAM1</i>	1.78	7.47E-07	0.96	0.06098	0.7	0.2045
<i>ICAM3</i>	0.58	0.01584	0.83	0.00636	0.04	0.93891
<i>ICOS</i>	0.33	0.49333	0.44	0.46214	-0.4	0.53892
<i>ICOSLG</i>	-0.2	0.47955	-0.47	0.21011	-0.34	0.39491
<i>IDO1</i>	4.9	5.34E-16	1.77	0.03974	2.43	0.00318
<i>IFNA2</i>	-0.57	0.37334	-1.18	0.13209	-1.17	0.15695
<i>IFNG</i>	0.85	0.13461	-0.02	0.97016	-0.64	0.37218
<i>IFNGR1</i>	-0.07	0.62885	-0.08	0.65189	-0.08	0.73077
<i>IL10</i>	2.18	1.16E-13	2.2	1.86E-09	1.62	3.81E-05
<i>IL10RA</i>	1.4	6.25E-08	1.15	0.00085	0.63	0.10892
<i>IL12A</i>	0.59	0.03904	0.09	0.85687	-0.08	
<i>IL12B</i>	-0.2	0.71122	-0.48	0.50051	-0.87	0.217
<i>IL12RB1</i>	1	0.01823	0.91	0.10681	0.22	0.7812
<i>IL13</i>	-0.24	0.62591	-0.13	0.87424	-0.25	0.75271
<i>IL13RA1</i>	0.19	0.24394	0.29	0.17223	0.1	0.69168
<i>IL15</i>	0.61	0.05186	0.09	0.85687	0.02	0.9674
<i>IL16</i>	-0.39	0.14336	-0.17	0.63734	-0.84	0.01355
<i>IL17B</i>	-0.39	0.41579	-0.8	0.19572	-1.04	
<i>IL17F</i>	-0.74	0.23219	-1.16	0.13209	-1.09	0.18256
<i>IL18</i>	-0.42	0.19224	-1.02	0.00951	-0.6	0.17757
<i>IL18R1</i>	0.19	0.44589	0.49	0.12147	-0.44	0.18774
<i>IL18RAP</i>	0.61	0.14718	0.48	0.37407	-0.08	0.90332
<i>IL1A</i>	0.67	0.17018	-0.44	0.46214	-0.64	0.31628
<i>IL1B</i>	2.1	0.29502	-0.38	0.53866	-0.57	0.39491
<i>IL1R1</i>	0.31	0.08775	0.07	0.82098	0.12	0.69168
<i>IL1R2</i>	1.47	0.00041	1.21	0.02727	0.16	0.87036
<i>IL1RAP</i>	-0.15	0.46243	-0.4	0.12739	-0.25	0.37768
<i>IL1RN</i>	2.06	7.03E-10	0.45	0.37049	0.25	0.69168
<i>IL2</i>	-0.7	0.22115	-0.94	0.19572	-1.21	0.10218
<i>IL20</i>	-0.34	0.54514	-0.52	0.45454	-0.46	0.57255
<i>IL21</i>	-0.25	0.6427	-0.27	0.74073	-0.67	0.37768
<i>IL21R</i>	0.58	0.17825	0.56	0.31364	-0.1	0.87316
<i>IL22</i>	-0.06	0.90813	-0.81	0.24908	-0.71	0.35632
<i>IL22RA2</i>	0.08	0.79164	0.11	0.83983	0.29	
<i>IL23A</i>	0.15	0.76362	-0.38	0.53001	-0.72	0.24546
<i>IL23R</i>	-0.55	0.3531	-0.88	0.238	-1.08	0.15695

<i>IL27</i>	-0.05	0.92253	-0.84	0.24908	-1.22	0.0963
<i>IL2RA</i>	0.68	0.07539	0.74	0.13656	0.09	0.90623
<i>IL2RB</i>	1.22	0.00078	1.62	0.00036	0.59	0.28747
<i>IL2RG</i>	1.38	3.62E-06	1.73	3.30E-06	0.86	0.05451
<i>IL32</i>	1.77	2.33E-08	2.03	3.84E-07	1.28	0.00446
<i>IL4</i>	0.1	0.84699	-0.46	0.46214	-0.6	0.3657
<i>IL4R</i>	1.52	6.74E-13	1.44	8.99E-08	1.17	3.81E-05
<i>IL5</i>	-0.53	0.39621	-0.76	0.34349	-1.01	0.20744
<i>IL6</i>	0.19	0.78598	-1.37	0.07174	-1.39	0.0793
<i>IL6R</i>	0.68	0.00201	0.33	0.2887	-0.07	0.86651
<i>IL6ST</i>	-0.08	0.61889	-0.42	0.02095	-0.42	0.03043
<i>IL7</i>	-0.26	0.53046	-0.66	0.19634	-0.56	0.30684
<i>IL7R</i>	0.37	0.2676	0.8	0.0565	-0.21	0.67804
<i>IL8</i>	2.78	5.02E-06	1.2	0.16186	0.5	0.69168
<i>IL9</i>	-0.56	0.29405	-0.32	0.6409	-0.25	0.7812
<i>ITGAE</i>	0.44	0.38169	-0.14	0.85687	-0.85	
<i>ITGAL</i>	2.11	1.26E-10	2.26	4.06E-08	1.51	0.00092
<i>ITGAM</i>	1.5	3.64E-12	1.26	4.90E-06	0.9	0.00318
<i>ITGAX</i>	1.84	3.05E-10	1.26	0.00116	1.05	0.01352
<i>ITGB2</i>	2.14	1.24E-18	2.17	3.02E-12	1.45	1.23E-05
<i>JAK1</i>	-0.04	0.7744	-0.03	0.88917	-0.15	0.51031
<i>JAK2</i>	1.07	0.00024	0.29	0.49169	0.48	0.27762
<i>JAK3</i>	1.93	1.04E-12	2.39	3.02E-12	1.51	3.81E-05
<i>KIR_Activating_Subgroup_1</i>	-0.35	0.6059	-1.11	0.17451	-1.17	0.16967
<i>KIR_Activating_Subgroup_2</i>	-0.74	0.25829	-1.1	0.19057	-1.57	0.05483
<i>KIR_Inhibiting_Subgroup_1</i>	-0.33	0.62591	-1.01	0.24908	-1.24	0.15695
<i>KIR_Inhibiting_Subgroup_2</i>	2.14	3.77E-08	0.87	0.12739	0.96	
<i>KLRAP1</i>	-0.32	0.07035	-0.45	0.04813	0.03	0.92515
<i>KLRB1</i>	-0.53	0.18372	-0.58	0.26219	-0.33	0.5942
<i>KLRC1</i>	0.79	0.11076	0.11	0.89295	-0.23	0.75271
<i>KLRC4</i>	-0.17	0.73979	-0.56	0.4018	-0.64	0.3657
<i>KLRD1</i>	1.45	1.18E-05	1.95	1.84E-06	0.79	
<i>KLRF1</i>	-0.34	0.47955	-0.79	0.19572	-0.97	0.12301
<i>KLRF2</i>	-0.44	0.46641	-0.7	0.35854	-1.05	0.17757
<i>KLRG1</i>	-0.77	0.03965	-0.79	0.11613	-0.8	0.12599
<i>KLRG2</i>	-0.44	0.3706	-0.62	0.3232	-0.84	0.18967
<i>LAMP1</i>	-0.24	0.07539	-0.52	0.00134	-0.13	0.51031
<i>MICA</i>	0.25	0.23219	0.01	0.97672	-0.17	0.59649
<i>MICB</i>	0.61	0.05186	0.21	0.63734	0.02	0.9674
<i>NLRP3</i>	0.15	0.62591	-0.23	0.55677	-0.31	0.47813
<i>NOS2</i>	-0.31	0.6059	-0.95	0.20324	-1.45	0.05017
<i>OAZ1</i>	0.48	0.00059	0.22	0.27318	0.25	0.217
<i>PDCD1</i>	-0.02	0.96186	-0.43	0.5434	-0.89	0.20471
<i>PDCD1LG2</i>	1.62	3.58E-07	1	0.02198	0.87	0.06593

<i>PDCD2</i>	0.52	0.01577	0.38	0.19572	0.33	0.28838
<i>PECAMI</i>	-0.11	0.6427	-0.32	0.31665	-0.55	0.08864
<i>POLR1B</i>	0.1	0.62591	-0.19	0.49301	0.07	0.84621
<i>POLR2A</i>	-0.1	0.37428	-0.12	0.42113	0.01	0.93891
<i>PRF1</i>	2.33	2.60E-09	2.34	1.84E-06	1.17	0.04878
<i>SIPR1</i>	-0.14	0.60804	-0.35	0.3232	-0.64	0.07553
<i>sCTLA4</i>	-0.11	0.54454	0.01	0.95796	-0.13	
<i>SELE</i>	0.98	0.05024	-0.31	0.61062	0.05	0.9674
<i>SELL</i>	1.89	4.87E-06	1.66	0.0019	0.71	0.27762
<i>SELPLG</i>	0.29	0.47955	0.29	0.58015	-0.26	0.67804
<i>STAT1</i>	3.1	2.59E-30	2.3	4.28E-11	2.24	3.10E-10
<i>STAT2</i>	2.03	2.59E-16	1.19	0.00028	1.34	5.67E-05
<i>STAT3</i>	0.81	2.40E-07	0.58	0.00636	0.7	0.00141
<i>STAT4</i>	0.66	0.02693	0.67	0.09254	-0.02	0.94982
<i>STAT5A</i>	0.68	0.00038	0.57	0.02841	0.5	0.07567
<i>STAT5B</i>	-0.24	0.05736	-0.23	0.17451	-0.35	0.04156
<i>STAT6</i>	0.47	2.46E-06	0.32	0.02198	0.32	0.03043
<i>TBP</i>	-0.5	0.00251	-0.55	0.01158	-0.55	0.01686
<i>TBX21</i>	0.46	0.35639	0.46	0.45454	-0.17	0.81697
<i>TGFB1</i>	1.19	6.86E-13	1.03	1.09E-06	0.65	0.00662
<i>TGFBR1</i>	0.46	0.00389	0.22	0.32491	0.03	0.92732
<i>TGFBR2</i>	0.47	0.03978	-0.02	0.95796	-0.07	0.86651
<i>TNF</i>	1.15	0.00172	0.39	0.45454	0.27	0.67689
<i>TNFRSF1B</i>	1.81	6.65E-19	1.44	3.17E-08	0.92	0.00142
<i>TNFRSF4</i>	-0.5	0.369	-1.05	0.12739	-1.16	0.10218
<i>TNFRSF9</i>	0.59	0.18988	0.1	0.88672	-0.12	0.86651
<i>TNFSF10</i>	1.8	4.35E-09	0.96	0.02459	1	0.02706
<i>TNFSF11</i>	-1.17	0.01344	-0.69	0.29512	-0.67	
<i>TNFSF4</i>	-0.4	0.37535	-0.84	0.13523	-0.91	0.12599
<i>TUBB</i>	0.21	0.18372	0.29	0.16043	0.27	0.21303
<i>TYROBP</i>	2.51	4.46E-23	2.03	5.71E-10	1.55	8.77E-06
<i>VCAMI</i>	0.82	0.01321	0.75	0.09268	0.71	0.13247

Significance = $P_{\text{adj}} < 0.05$ and $|\text{Log}_2\text{FC}| \geq 1$

Supplemental Table 2. Fold changes and adjusted p-values for SJS/TEN vs MDE and SJS/TEN vs

DRESS by bulk transcriptional profiling; showing genes with $P_{adj} < 0.1$ and $|\text{Log}_2\text{FC}| \geq 1$.

	SJS/TEN vs. MDE	
Genes	Log₂FC	P_{adj}
<i>CCL8</i>	3.01	8.45E-05
<i>CCL7</i>	3.20	8.45E-05
<i>IL1RN</i>	1.81	1.21E-04
<i>GATA3</i>	-1.52	2.09E-04
<i>CCL27</i>	-1.88	0.016
<i>IDO1</i>	2.48	0.018
<i>IL8</i>	2.28	0.018
<i>CCL18</i>	-2.08	0.031
<i>CD274</i>	1.79	0.031
<i>CD86</i>	1.16	0.038
<i>IL1R2</i>	1.31	0.046
<i>CXCL11</i>	2.09	0.046
<i>CD1A</i>	-1.12	0.046
<i>CTLA4-TM (membrane-bound form)</i>	1.08	0.047
<i>CCL26</i>	-1.51	0.047
<i>PRF1</i>	1.16	0.052
<i>CTLA4_all (common probe)</i>	1.06	0.052
<i>IFNG</i>	1.49	0.052
<i>IL1A</i>	1.31	0.052
<i>CCL13</i>	-1.04	0.052
<i>CCR1</i>	1.03	0.052
<i>CCL20</i>	1.44	0.052
<i>ITGAE</i>	1.29	0.052
<i>ICAM1</i>	1.08	0.052
<i>GZMB</i>	1.46	0.052
<i>KIR_Inhibiting_Subgroup_2</i>	1.18	0.052
<i>GNLY</i>	1.40	0.052
<i>CXCL2</i>	1.24	0.052
<i>IL6</i>	1.58	0.054
<i>SELL</i>	1.18	0.056
<i>CD7</i>	1.08	0.061
<i>CX3CL1</i>	1.01	0.086
<i>IL1B</i>	2.67	0.096
<i>CCL2</i>	1.26	0.096

	SJS/TEN vs. DRESS	
Genes	Log₂FC	P_{adj}
<i>CCL8</i>	3.01	8.52E-05
<i>CCL7</i>	2.96	3.58E-04
<i>IDO1</i>	3.14	3.58E-04
<i>IL1RN</i>	1.61	8.77E-04
<i>CCL26</i>	-2.15	0.001
<i>CCL13</i>	-1.49	0.004
<i>CCL18</i>	-2.37	0.006
<i>CXCL11</i>	2.52	0.006
<i>CXCL10</i>	2.34	0.020
<i>CX3CL1</i>	1.26	0.044
<i>CD274</i>	1.62	0.050
<i>GZMK</i>	-1.20	0.061
<i>CCL20</i>	1.47	0.061
<i>CCL2</i>	1.45	0.078
<i>SELE</i>	1.29	0.079
<i>IL6</i>	1.56	0.079

There were no differentially expressed genes between DRESS and MDE with $P_{adj} < 0.1$ and $|\text{Log}_2\text{FC}| \geq 1$.

Supplemental Table 3. Prospective study patient demographic and clinical data

dtDHR (severity of rash if MDE)	Age/ Sex	Race/ Ethnicity ^a	HLA-A & HLA-B	Suspected culprit drug(s)	Infection testing/results	Histopathologic description	Immunosuppressive treatment prior to study sampling ^b
SJS/TEN 1	45M	Black or African- American/ Non- hispanic	HLA-A: 03:01 32:01 HLA-B: 44:02 44:03	Bupropion	Mycoplasma negative	Lymphocyte- mediated interface dermatitis	No
SJS/TEN 2	47M	NA ^c	HLA-A: 02:01 02:05 HLA-B: 44:02 49:01	Sulfamethoxazole /trimethoprim	None	Full-thickness epidermal necrosis and mild superficial perivascular lymphocytic infiltrate	Systemic steroids
SJS/TEN 3	37F	White/ Non- hispanic	HLA-A: 03:01 32:01 HLA-B: 44:02 51:05	Ceftaroline, Gentamycin	Mycoplasma negative HSV negative HBV negative HIV negative	Lymphocyte- mediated interface dermatitis	No
MDE 1 (mild)	50M	White/ Non- hispanic	HLA-A: 03:01 68:01 HLA-B: 44:02 44:03	Oxacillin	HAV negative HBV negative HCV negative HIV negative	Focal interface dermatitis with marked dermal edema and scattered interstitial lymphocytes, neutrophils and eosinophils	Topical steroid
MDE 2 (severe)	56M	White/ Non- hispanic	HLA-A: 02:01 33:03 HLA-B: 44:02 50:01	Allopurinol	Mycoplasma negative CMV negative EBV negative	Spongiotic dermatitis with pityriasiform scale, superficial perivascular lymphocytic infiltrate, and eosinophils	Systemic steroids
MDE 3 (mild)	75F	White/ Non- hispanic	HLA-A: 02:01 29:01/ 29:02 HLA-B: 44:01 44:02	Ceftazidime	None	Spongiotic dermatitis with hyperkeratosis and acanthosis, with perivascular and interstitial lymphohistiocytic infiltrate	Topical steroid

^aRace/Ethnicity as patient-reported in the medical record

^bImmunosuppressive treatment (one or more doses) administered for dtDHR prior to study sample collection

^cNot available

Supplemental Table 4. Marker list used to define T cell clusters in scRNAseq + CITEseq + TCRseq.

Cluster number	Cluster name	Markers
1	CD8 ⁺ Naïve	CD45RA ⁺ CD45RO ⁻ IL7Rα ^{high} <i>SIPRI</i> ⁺ <i>KLF2</i> ⁺ <i>CCR7</i> ⁺
2	CD8 ⁺ TCM	CD45RA ⁻ CD45RO ⁺ IL7Rα ^{high} <i>SIPRI</i> ⁺ <i>KLF2</i> ⁺ CD62L ^{high}
3	CD8 ⁺ TMM (migratory memory) (<i>I</i>)	CD45RA ⁻ IL7Rα ^{high} <i>SIPRI</i> ^{low} <i>KLF2</i> ⁺ CD62L ^{low} <i>CCR7</i> ⁺
4	CD8 ⁺ CD103 ⁻ TRM (non-functional)	CD45RA ⁻ CD45RO ⁺ IL7Rα ^{high} <i>SIPRI</i> ⁻ <i>KLF2</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ CD103 ⁻ CD69 ⁺ <i>CX3CRI</i> ⁻ Not cytotoxic*
5	CD8 ⁺ CD103 ⁻ TEMRA	CD45RA ⁺ IL7Rα ^{low} CD62L ^{low} <i>CCR7</i> ⁻ CD103 ⁻ CD69 ⁻ <i>CX3CRI</i> ⁺
6	CD8 ⁺ CD103 ⁺ TEMRA	CD45RA ⁺ IL7Rα ^{low} CD62L ^{low} <i>CCR7</i> ⁻ CD103 ⁺ CD69 ⁻ <i>CX3CRI</i> ⁺
7	CD8 ⁺ T effectors	CD45RO ⁻ IL7Rα ^{low} <i>SIPRI</i> ⁻ <i>KLF2</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ <i>CX3CRI</i> ⁺
8	CD8 ⁺ TEM	CD45RA ⁻ CD45RO ⁺ IL7Rα ^{low} <i>SIPRI</i> ⁻ <i>KLF2</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ CD69 ⁻ <i>CX3CRI</i> ⁺
9	CD8 ⁺ CD103 ⁺ TRM	CD45RA ⁻ IL7Rα ^{low} <i>SIPRI</i> ⁻ <i>KLF2</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ CD103 ⁺ CD69 ⁺ <i>CX3CRI</i> ⁻ Cytotoxic*
10	CD8 ⁺ CD103 ⁻ TRM	CD45RA ⁻ IL7Rα ^{low} <i>SIPRI</i> ⁻ <i>KLF2</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ CD103 ⁻ CD69 ⁺ <i>CX3CRI</i> ⁻ Cytotoxic*
11	CD8 ⁺ CD56 ⁺ T cells	CD45RA ⁺ CD45RO ⁻ IL7Rα ^{low} CD62L ^{low} <i>CCR7</i> ⁻ CD56 ⁺
12	γδ T cells	CD4 ⁻ CD8 ⁻ <i>TRDV2</i> ⁺
13	CD4 ⁺ Naïve	CD45RA ⁺ CD45RO ⁻ IL7Rα ^{med} <i>SIPRI</i> ⁺ <i>KLF2</i> ⁺ CD62L ^{high} <i>CCR7</i> ^{high}
14	CD4 ⁺ CD45RA ⁺ CD62L ^{low}	CD45RA ⁺ CD45RO ⁻ IL7Rα ^{med} <i>SIPRI</i> ⁺ <i>KLF2</i> ⁺ CD62L ^{low} <i>CCR7</i> ⁺
15	CD4 ⁺ CD45RA ⁻ CD62L ^{low}	CD45RA ⁻ CD45RO ⁻ IL7Rα ^{med} <i>SIPRI</i> ⁺ <i>KLF2</i> ⁺ CD62L ^{low} <i>CCR7</i> ^{low}
16	CD4 ⁺ TCM	CD45RA ⁻ CD45RO ⁺ IL7Rα ^{high} <i>SIPRI</i> ⁺ <i>KLF2</i> ⁺ CD62L ^{med}
17	CD4 ⁺ CD103 ⁻ TRM	CD45RA ⁻ CD45RO ⁺ IL7Rα ^{high} <i>SIPRI</i> ⁻ <i>KLF2</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ CD103 ⁻ CD69 ⁺
18	CD4 ⁺ CD103 ⁺ TRM	CD45RA ⁻ CD45RO ⁺ IL7Rα ^{high} <i>SIPRI</i> ⁻ <i>KLF2</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ CD103 ⁺ CD69 ⁺
19	CD4 ⁺ T effectors	IL7Rα ^{low} <i>SIPRI</i> ⁻ CD62L ^{low} <i>CCR7</i> ⁻ <i>CX3CRI</i> ⁺
20	CD4 ⁺ Treg 1	CD69 ⁺ FAS ⁺ <i>FOXP3</i> ⁺
21	CD4 ⁺ Treg 2	FAS ⁺ <i>FOXP3</i> ⁺ <i>CTLA4</i> ⁺ <i>IL2RA</i> ⁺
22	Proliferating	<i>TUBA1B</i> ⁺ <i>STMN1</i> ⁺

Gene name is italicized if RNA was used; protein name is not italicized if protein was used.

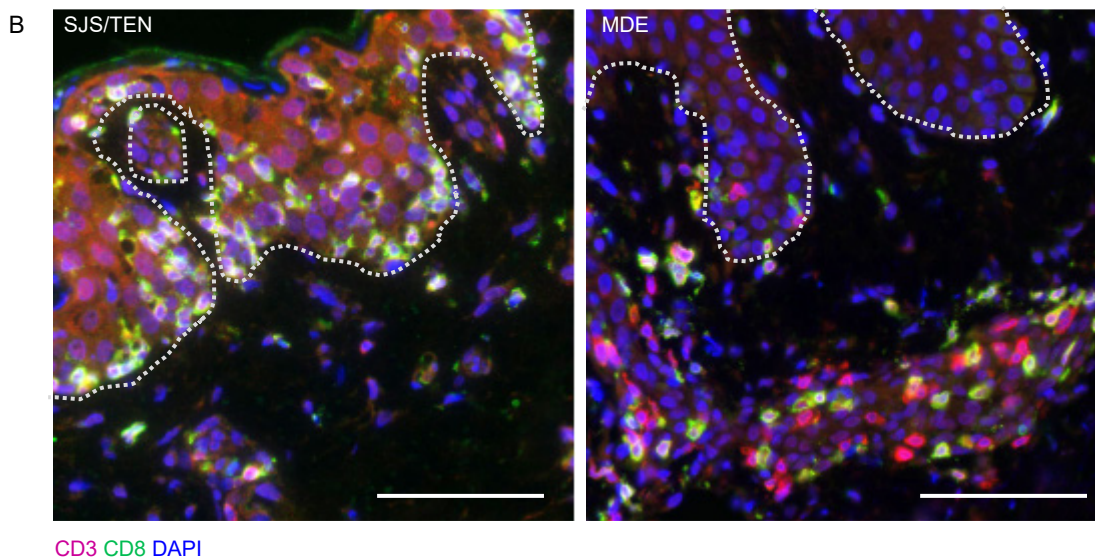
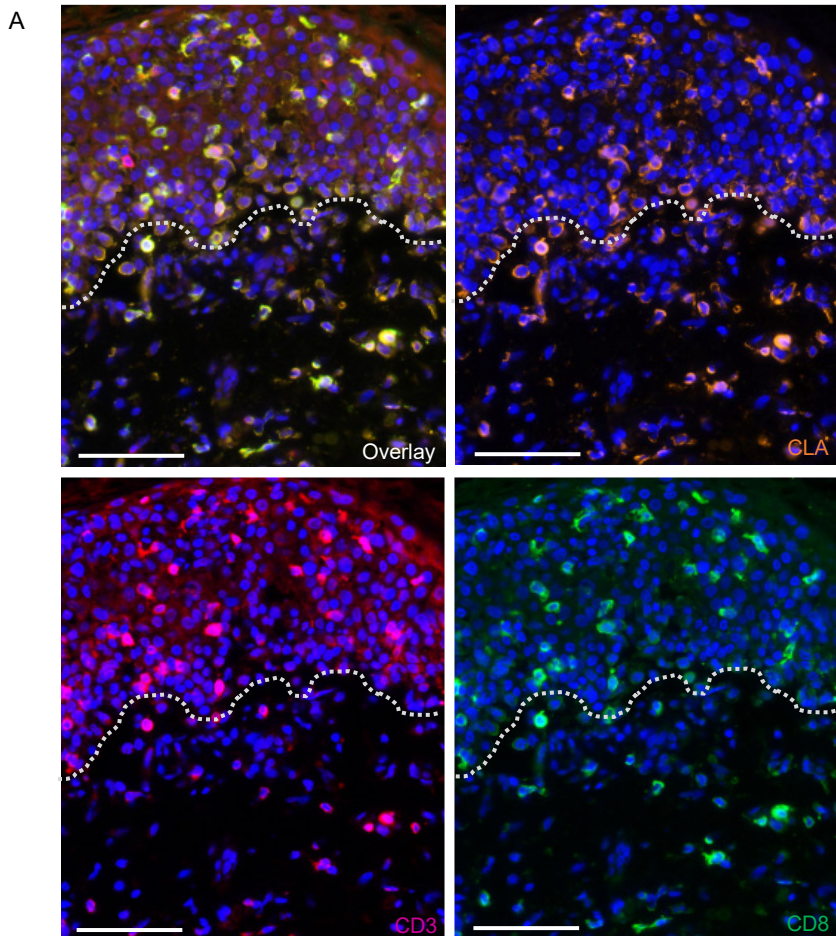
*Cytotoxic defined as expressing a combination of *GNLY*⁺ *GZMA*⁺ *GZMB*⁺ *PRFI*⁺ and/or *NKG7*⁺ based on the heatmap.

Supplemental Table 5. Clinical and histopathologic characteristics of lymphopenic AML patients with MDE.

Age/ Sex	Chemotherapy	No. days after chemotherapy that skin was biopsied	Day of Biopsy		Histopathologic description
			WBC (K/ μ l)	Absolute lymphocyte count (K/ μ l) ^b	
48M	Amonafide + Daunorubicin	20	0.12	0.166	Mild superficial and deep perivascular predominantly lymphoid infiltrate with scattered eosinophils
67M	Cytarabine + Daunorubicin + Bortezomib	16	0.19	0.109	Superficial and mid-perivascular predominantly lymphoid infiltrate
54F	Cytarabine	14	0.10	0.10	Spongiosis with superficial perivascular chronic inflammation ^a with dermal hemorrhage
44M	Mitoxantrone + Etoposide + Cytarabine	6	0.2	0.12	Lymphocyte-mediated interface dermatitis
56F	Mitoxantrone + Etoposide	32	0.11	0.103	Mixed lymphocyte-mediated interface and spongiotic dermatitis
64F	Mitoxantrone + Etoposide + Cytarabine	42	0.33	0.05	Focal vacuolar interface changes with perivascular chronic inflammation ^a with eosinophils
62M	Cytarabine + Daunorubicin	8	0.52	0.468	Spongiotic and interface dermatitis with perivascular lymphocytic infiltrate
65F	Cytarabine + Daunorubicin	23	0.97	0.165	Spongiosis with lymphocytic exocytosis, focal minimal interface change, superficial perivascular chronic inflammation
45M	Etoposide + Cytarabine + Daunorubicin	6	0.42	0.244	Perivascular chronic inflammation ^a with eosinophils
59M	Cytarabine + Idarubicin	17	0.57	0.542	Superficial dermal edema with perivascular chronic inflammation ^a
70M	Amonafide + Cytarabine	38	0.45	0.432	Superficial mid-dermal infiltrate with lymphoid and plasma cells
57M	Daunorubicin + Cytarabine	10	0.13	0.095	Subacute spongiotic dermatitis

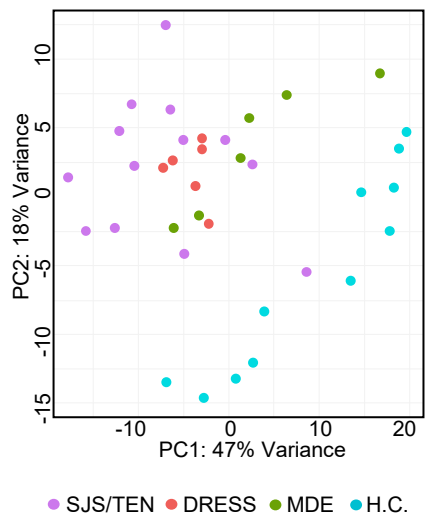
^a "Chronic inflammation" on pathology refers to either lymphocytic or lymphohistocytic infiltrate

^b Absolute lymphocyte count is reported from the day of biopsy, or day after biopsy if differential was not obtained on the day of biopsy.

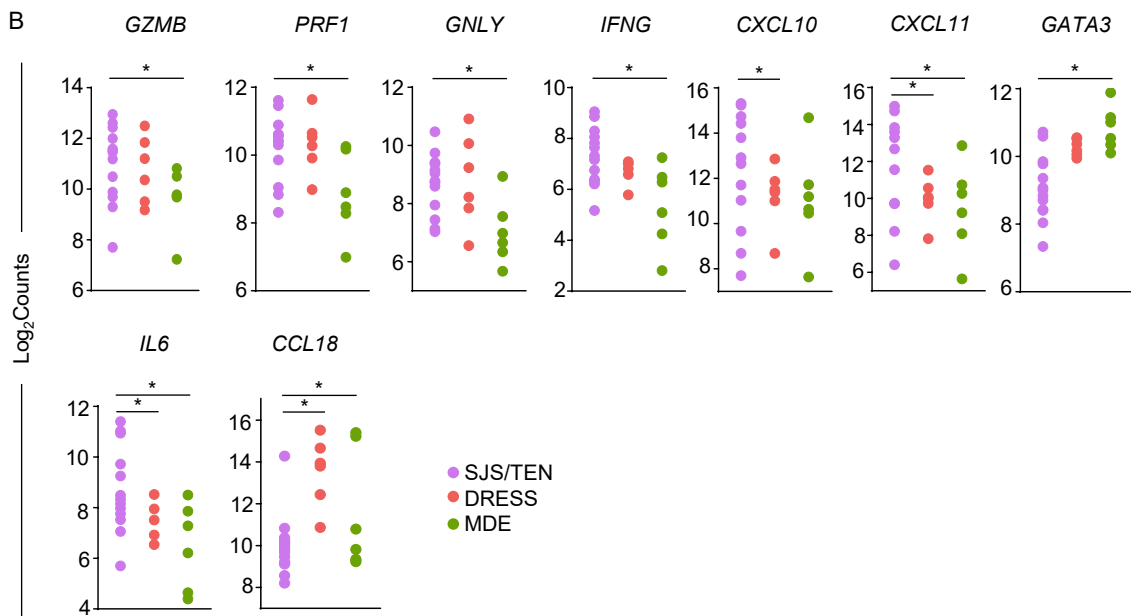


Supplemental Figure 1. Visualization of T cell infiltrate in dtDHR skin samples. (A) Representative immunofluorescence images of CD3 (magenta), CD8 (green) and CLA (orange) with overlay, of an early (non-blistered) SJS/TEN sample showing a predominantly epidermal CD8⁺ skin homing (CLA⁺) T cell infiltrate. (B) Representative immunofluorescence overlay images of CD3 (magenta) and CD8 (green) staining showing a CD8⁺ T cell infiltrate predominantly in the epidermis in SJS/TEN compared to a mixed CD8⁺ and CD8⁻ T cell infiltrate predominantly around vessels and in the papillary dermis in MDE. (A,B) Gray dotted line depicts dermoepidermal junction. White lines = 100 μ m.

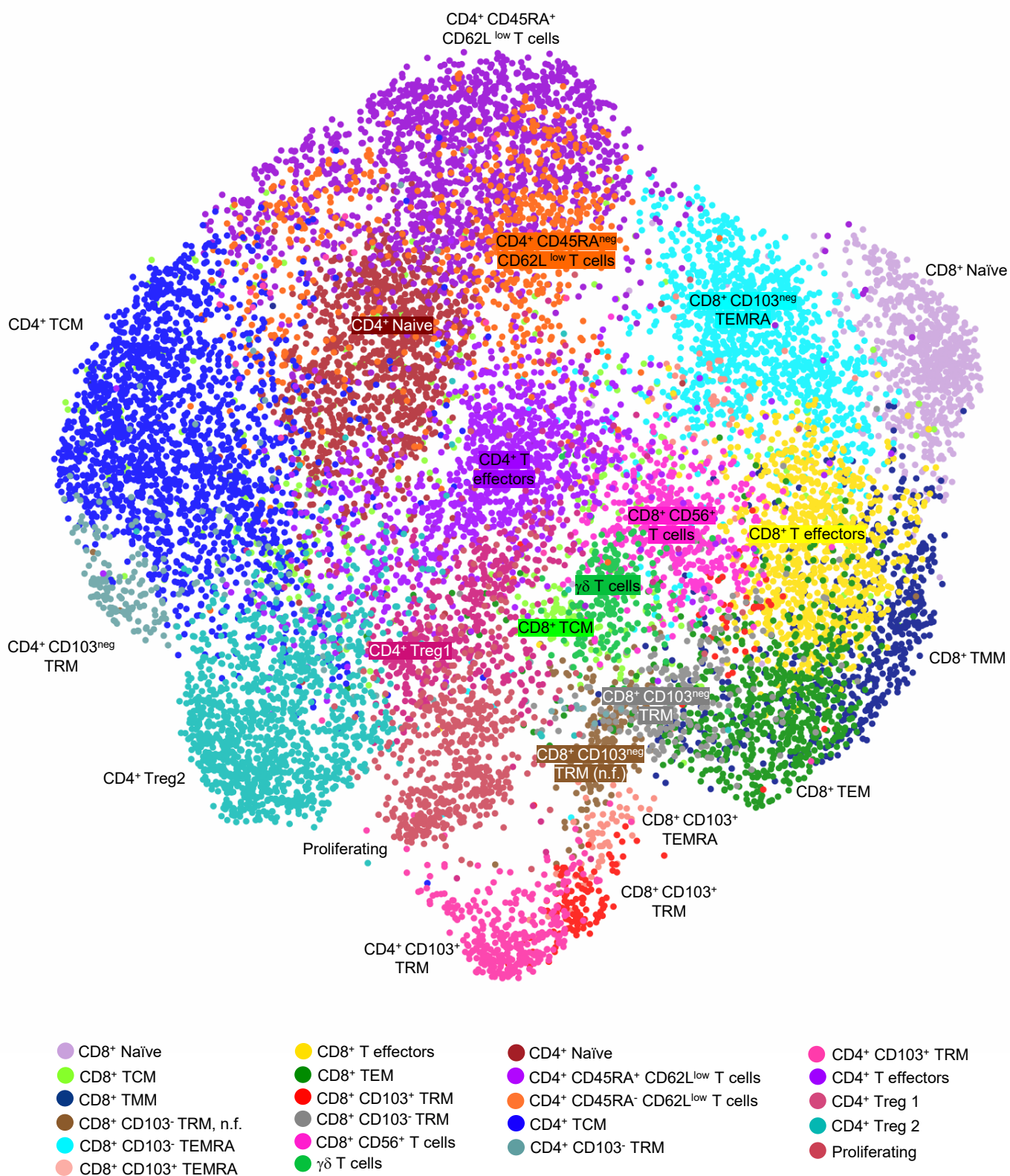
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B

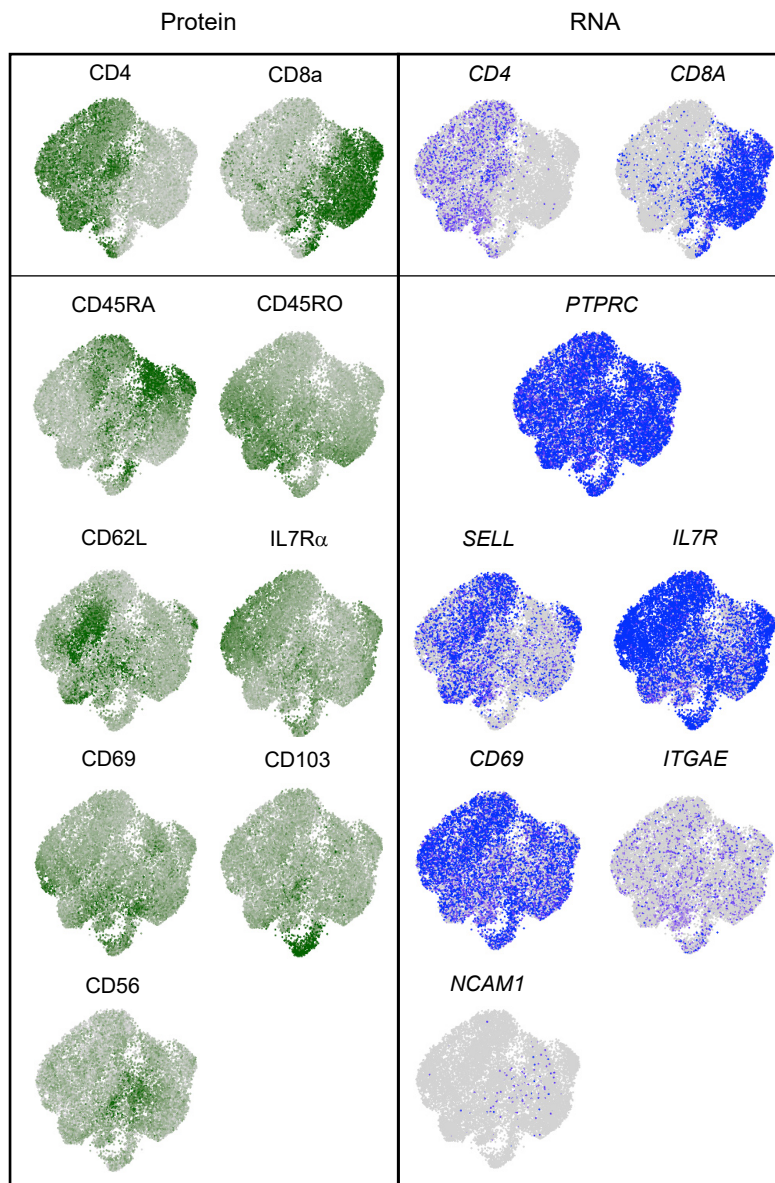


Supplemental Figure 2. Bulk transcriptional profiling with differential gene expression analysis between dtDHR. (A) PCA plot from bulk transcriptional profiling of SJS/TEN (N=13), DRESS (N=6), MDE (N=6) and healthy control (H.C.) (N=11). **(B)** Log2counts of genes relevant for T cell functionality and/or Treg recruitment and development in SJS/TEN compared to DRESS and MDE. *Significance defined as $|\text{Log}_2\text{FC}| \geq 1$ and $P_{\text{adj}} < 0.1$, DESeq2, Wald test



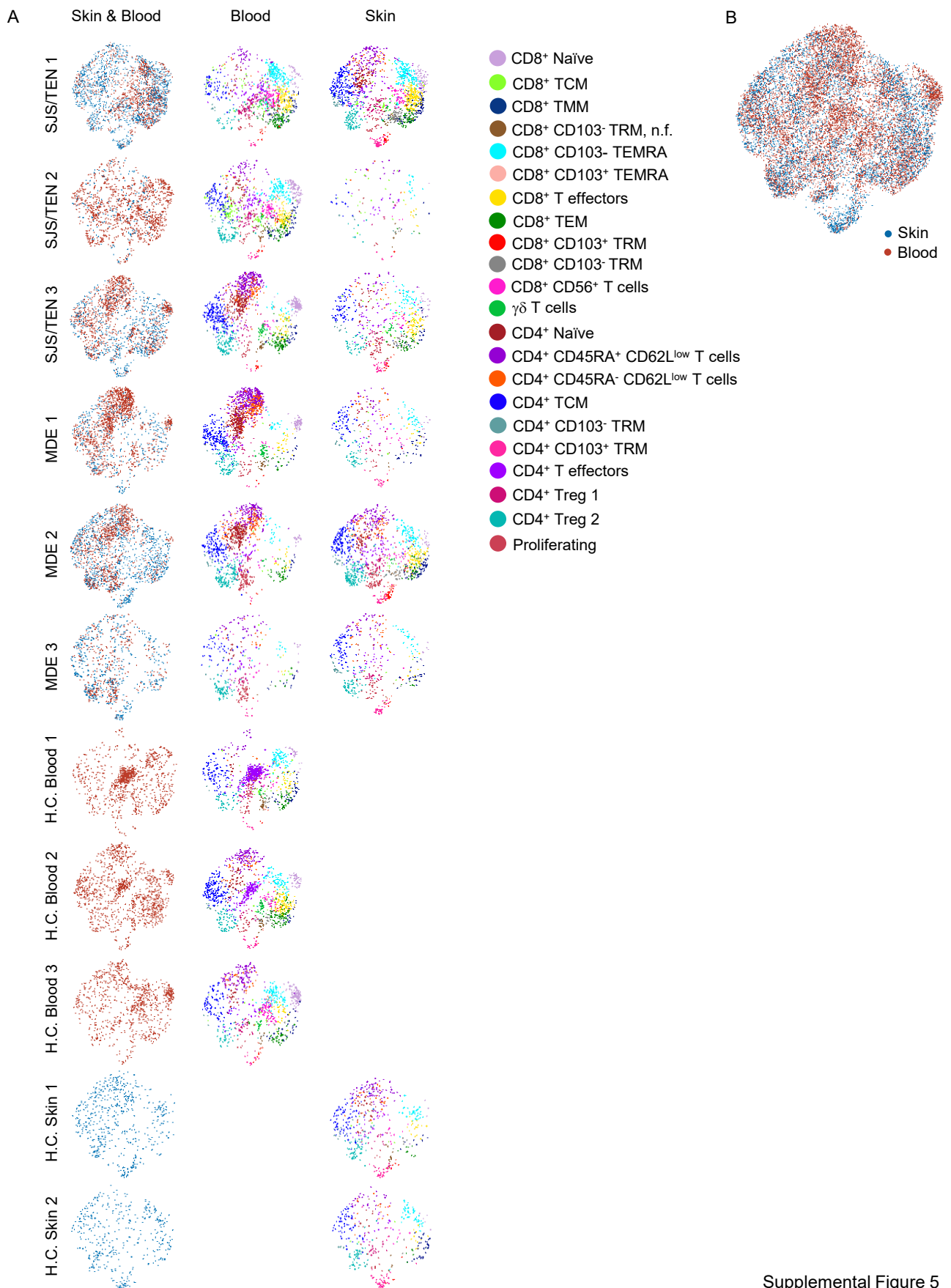
Supplemental Figure 3

Supplemental Figure 3. T cell clusters identified by scRNAseq + CITEseq of prospectively collected skin and blood samples from dtDHR and healthy control patients. UMAP showing 22 identified T cell clusters from integrating scRNAseq + CITEseq across 3 SJS/TEN, 3 MDE, 3 healthy control skin and 3 healthy control blood samples. 1 healthy control skin sample was excluded due to low number of cells. Healthy control blood and skin were not paired.



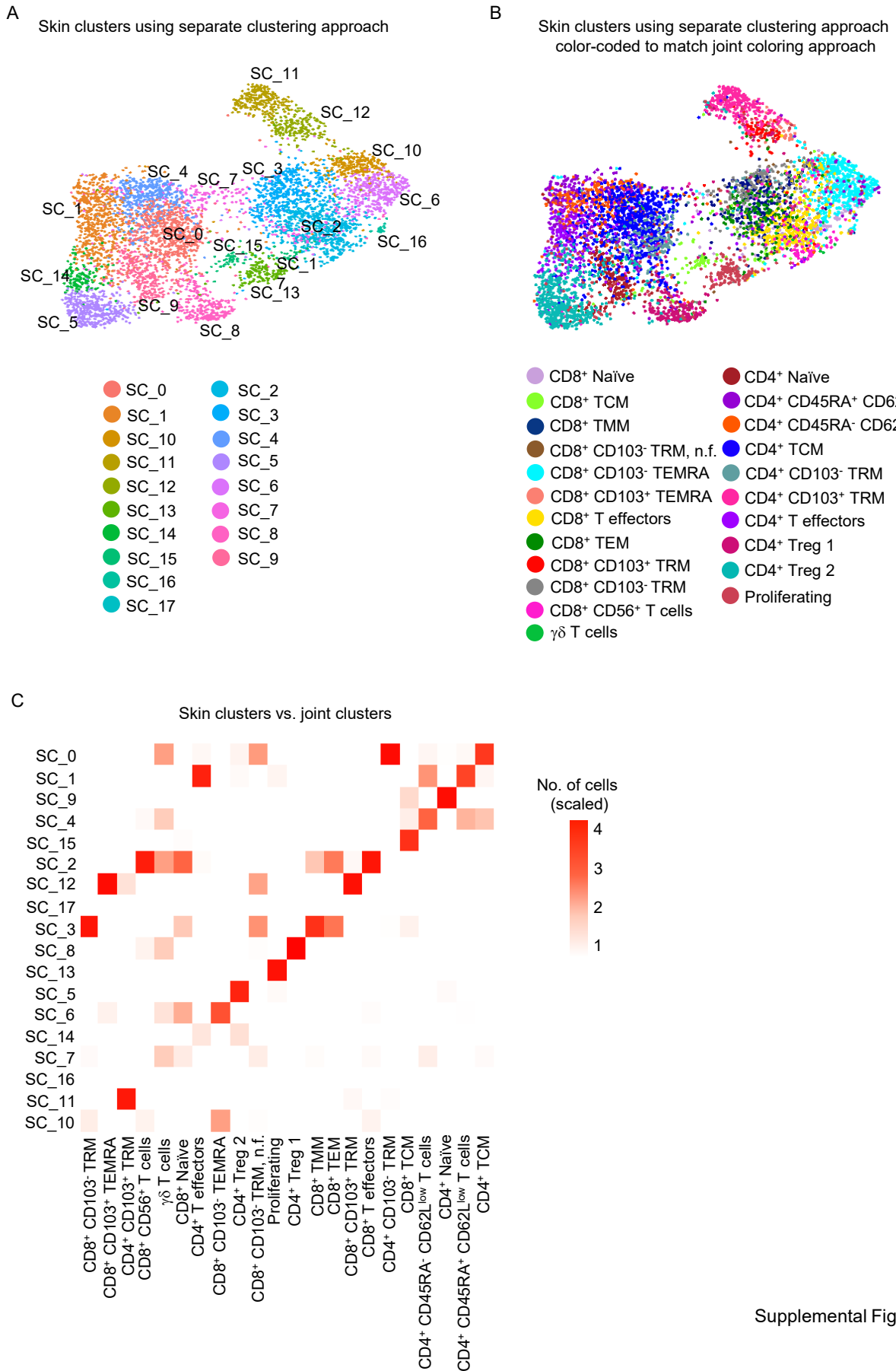
Supplemental Figure 4. Comparison of key T cell phenotypic markers between CITEseq and scRNAseq.

UMAPs of each key T cell phenotypic marker with improved resolution using protein (green) compared to RNA (blue). Distribution was largely comparable for CD4 and CD8 between the two modalities, though protein allowed for superior resolution so was used in defining each cluster. CITEseq allowed for discrimination between the isoforms of CD45RA and CD45RO that was not possible with scRNAseq alone. Cells positive for CD62L, IL7R α , CD69, CD103 and CD56 were more clearly identifiable using CITEseq compared to scRNAseq alone.



Supplemental Figure 5

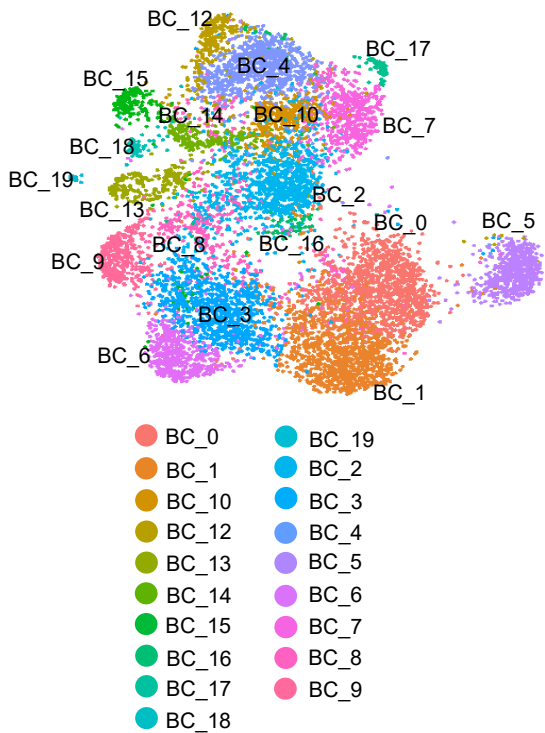
Supplemental Figure 5. Distribution of cells in skin and blood of each patient using the joint (skin + blood) clustering analysis. (A) UMAPs showing combined skin (blue) and blood (red) per patient and healthy controls (H.C.) with comparative UMAPs showing skin and blood separately by cluster per patient. **(B)** UMAP showing all T cells from all samples by skin (blue) and blood (red).



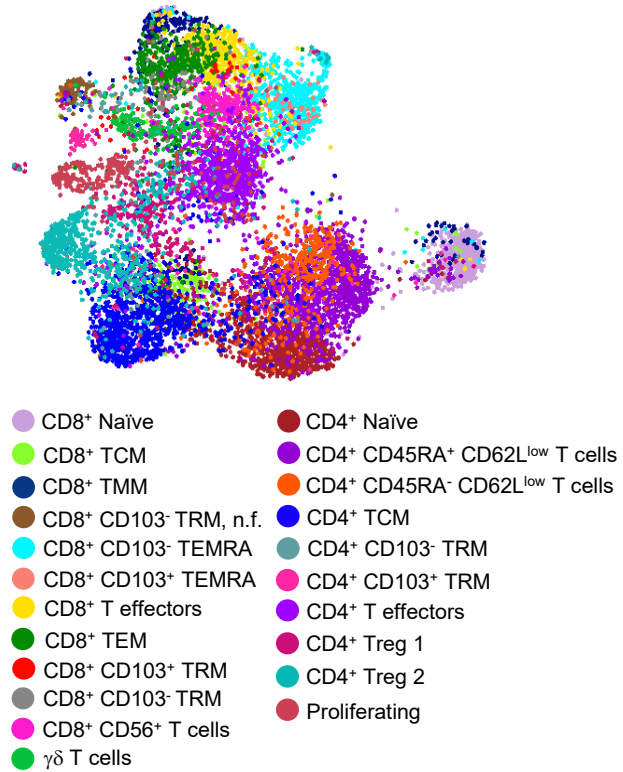
Supplemental Figure 6

Supplemental Figure 6. Skin-specific analysis mirrors joint clustering results. **(A)** UMAP showing skin-specific clustering (18 clusters) when skin is analyzed separately. **(B)** UMAP showing skin analyzed separately but now each cell is labelled using the annotations from the joint (skin + blood) clustering approach. **(C)** Heatmaps comparing clusters between joint (skin + blood) clustering approach and skin-specific clustering approach. Heatmaps show the number of cells that fall into each skin-specific cluster versus each joint cluster. The near diagonalization of both heatmaps indicates a considerable match between the joint clustering approach and tissue-specific clustering approach.

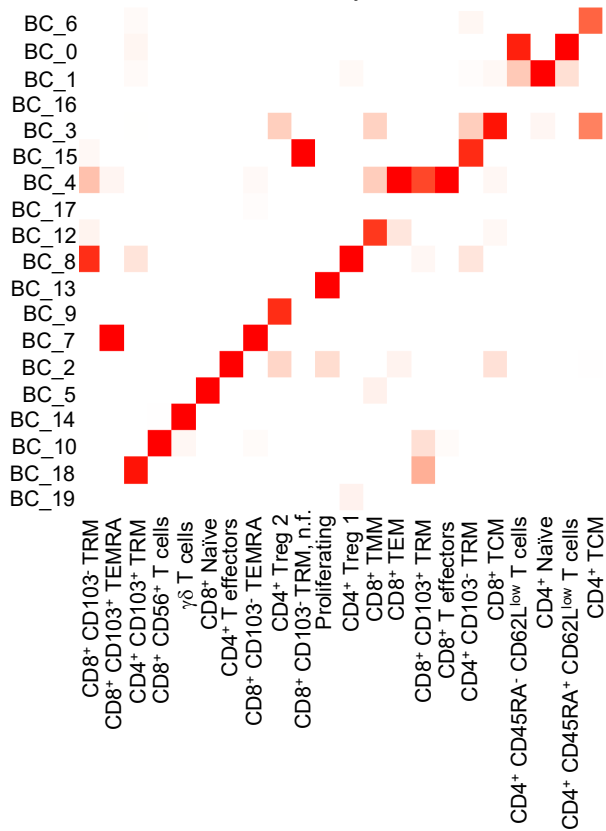
A Blood clusters using separate clustering approach



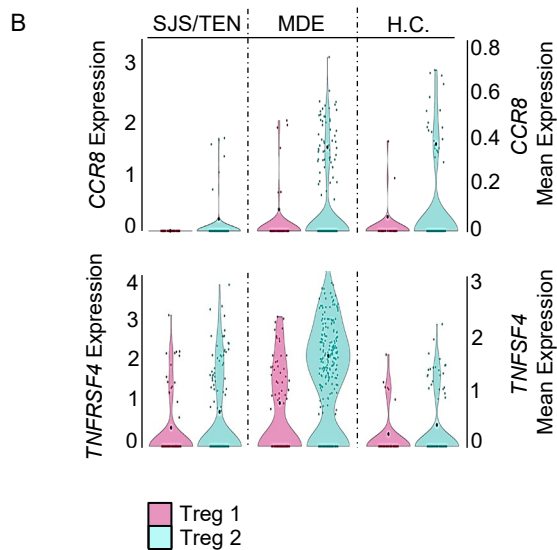
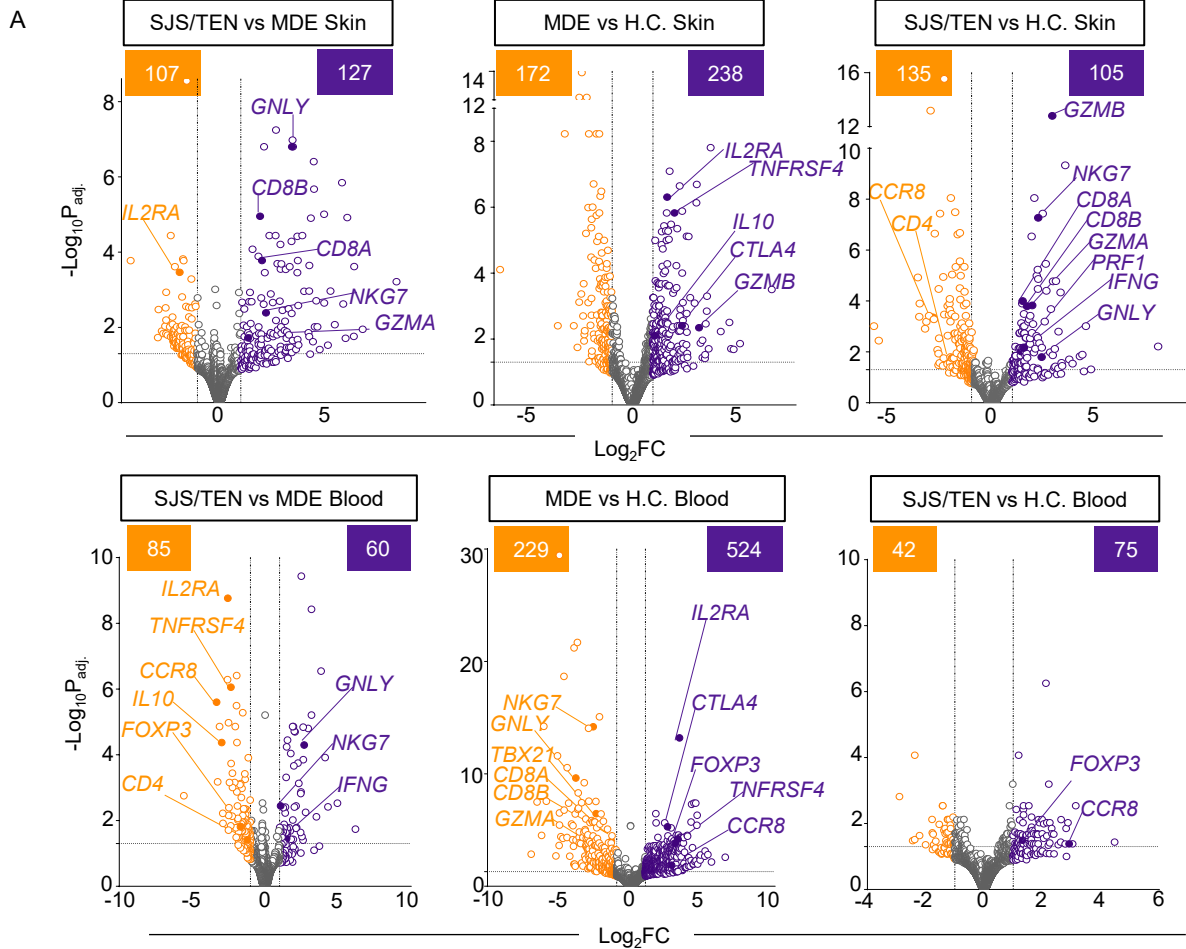
B Blood clusters using separate clustering approach color-coded to match joint coloring approach



C Blood clusters vs. joint clusters

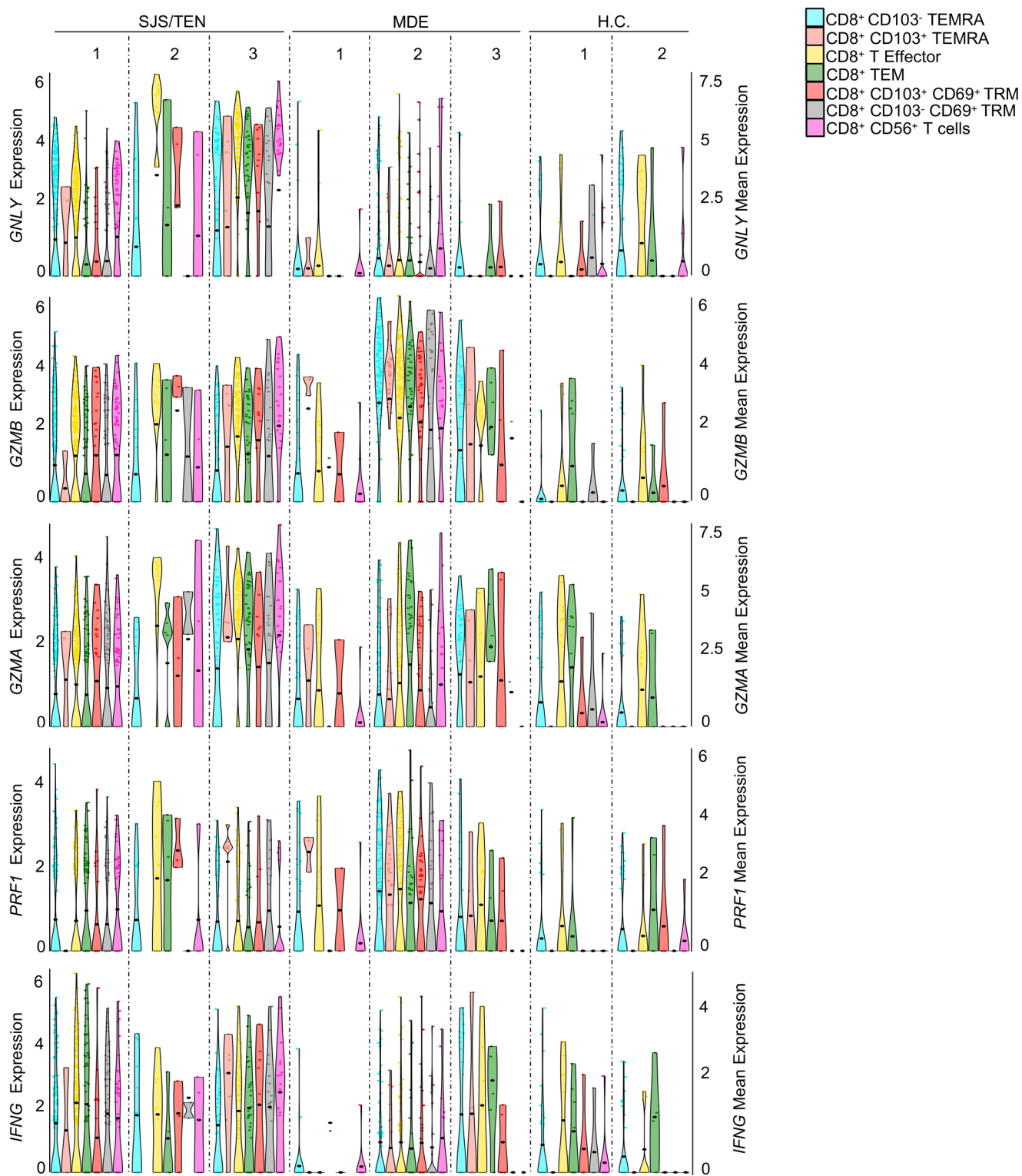


Supplemental Figure 7. Blood-specific analysis mirrors joint clustering results. **(A)** UMAP showing blood-specific clustering (19 clusters) when blood is analyzed separately. **(B)** UMAP showing blood analyzed separately but now each cell is labelled using the annotations from the joint (skin + blood) clustering approach. **(C)** Heatmaps comparing clusters between joint (skin + blood) clustering approach and blood-specific clustering approach. Heatmaps show the number of cells that fall into each blood-specific cluster versus each joint cluster. The near diagonalization of both heatmaps indicates a considerable match between the joint clustering approach and tissue-specific clustering approach.



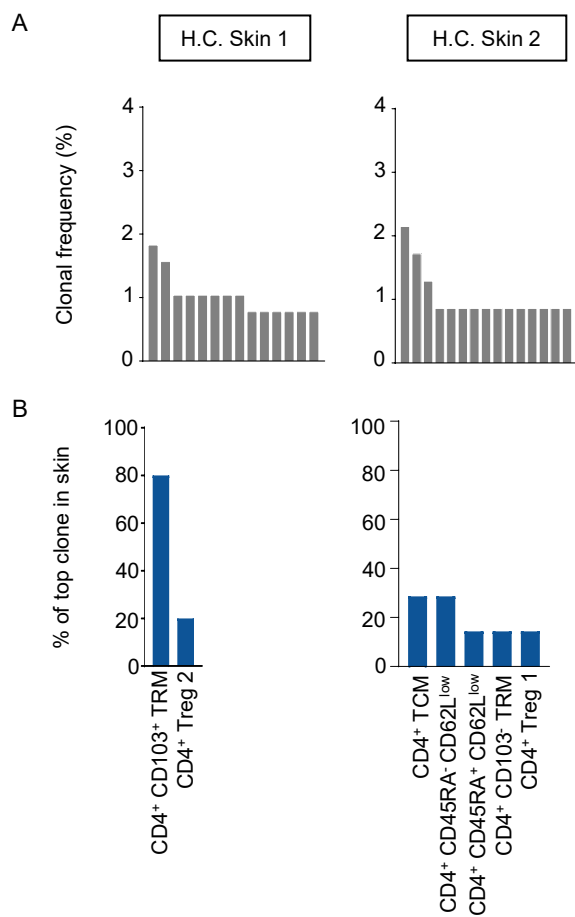
Supplemental Figure 8. MDE displays a pro-Treg profile compared to SJS/TEN and healthy controls. (A)

Volcano plots highlighting selected significantly differentially expressed genes between pooled SJS/TEN, MDE and healthy control (H.C.) skin and blood by pseudo-bulk analysis. Significance defined as $\text{Log}_2\text{FC} \geq \pm 1$ and $P_{\text{adj}} < 0.05$, DESeq2, Wald test. **(B)** Violin plots showing expression (left y-axis) of *CCR8* and *TNFRSF4* in Treg clusters in SJS/TEN, MDE and H.C. skin. Violin plots show gene expression (left y-axis) and mean expression (right y-axis and visualized by black dot).



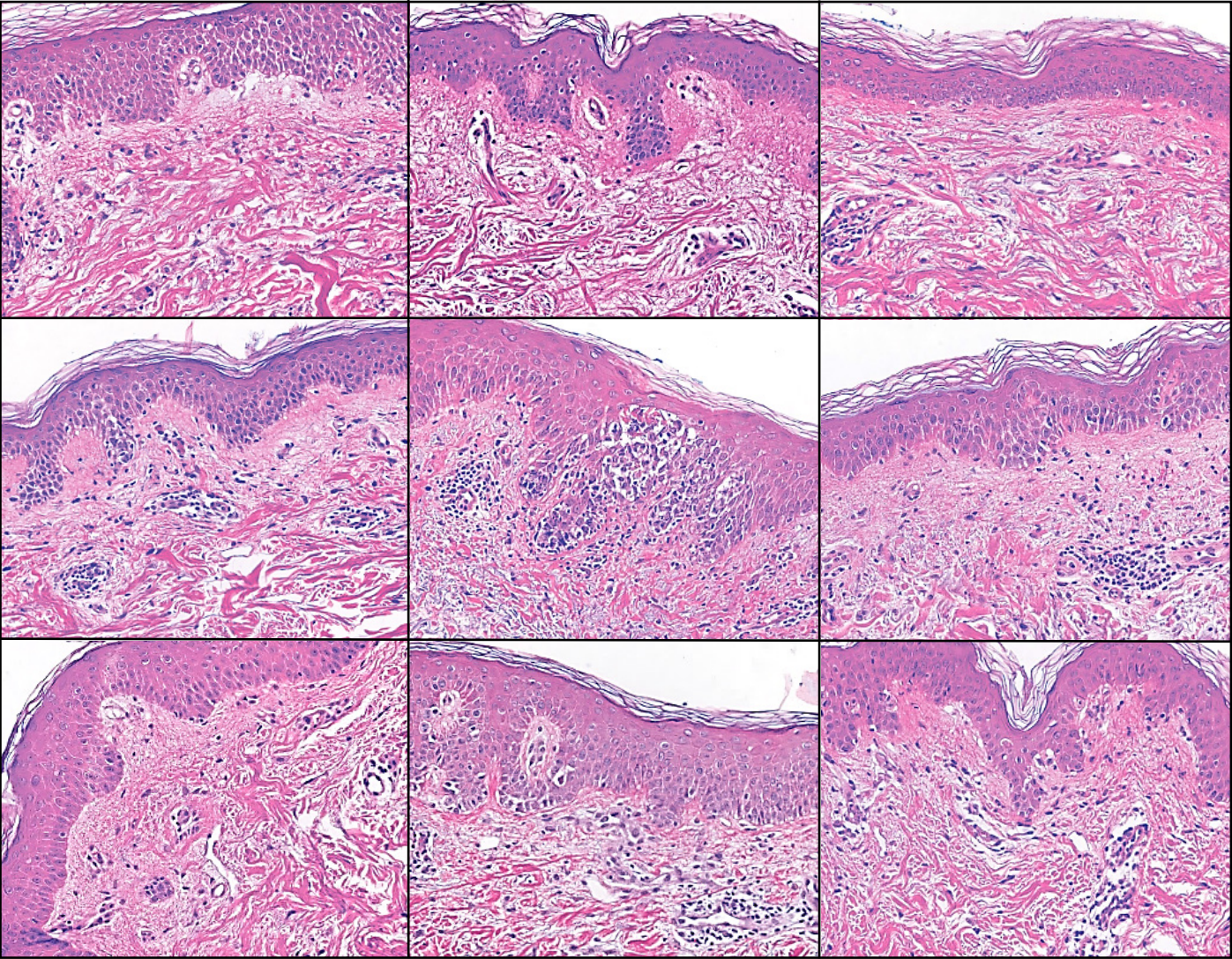
Supplemental Figure 9

Supplemental Figure 9. Expression of cytotoxic markers in skin at a single cell level per cytotoxic CD8⁺ T cell cluster for each patient. Violin plots showing expression (left y-axis) of *GNLY*, *GZMB*, *GZMA*, *PRFI*, and *IFNG* in skin of each cytotoxic CD8⁺ T cell cluster of each patient. Mean expression (right y-axis) is visualized with black dots.

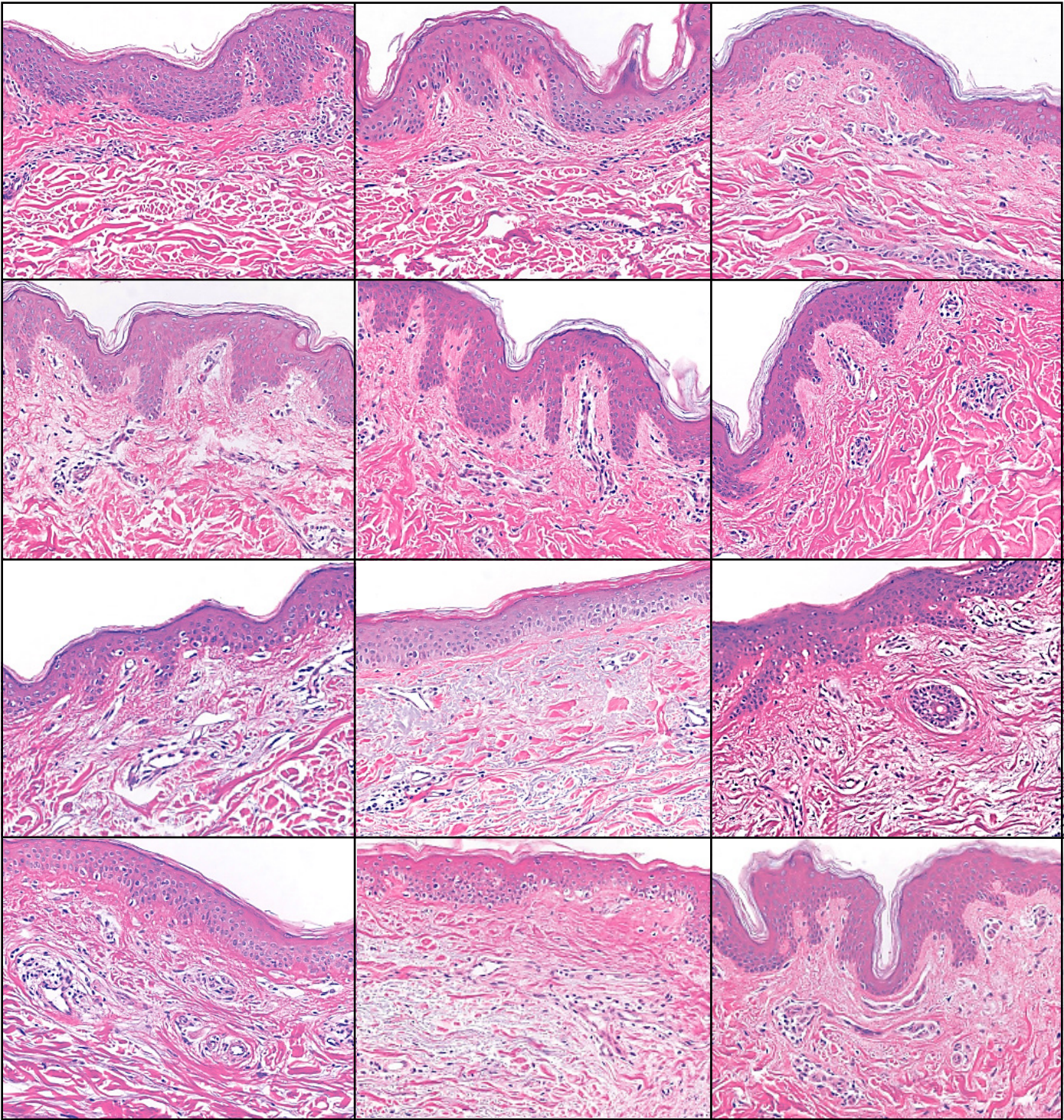


Supplemental Figure 10. TCRseq analysis of healthy control skin. (A) Clonal frequency (percentage) of the top 15 clones in skin of each healthy control. **(B)** Bar graph showing percent distribution across T cell phenotypic clusters of the top clone in skin.

Lymphopenic MDE

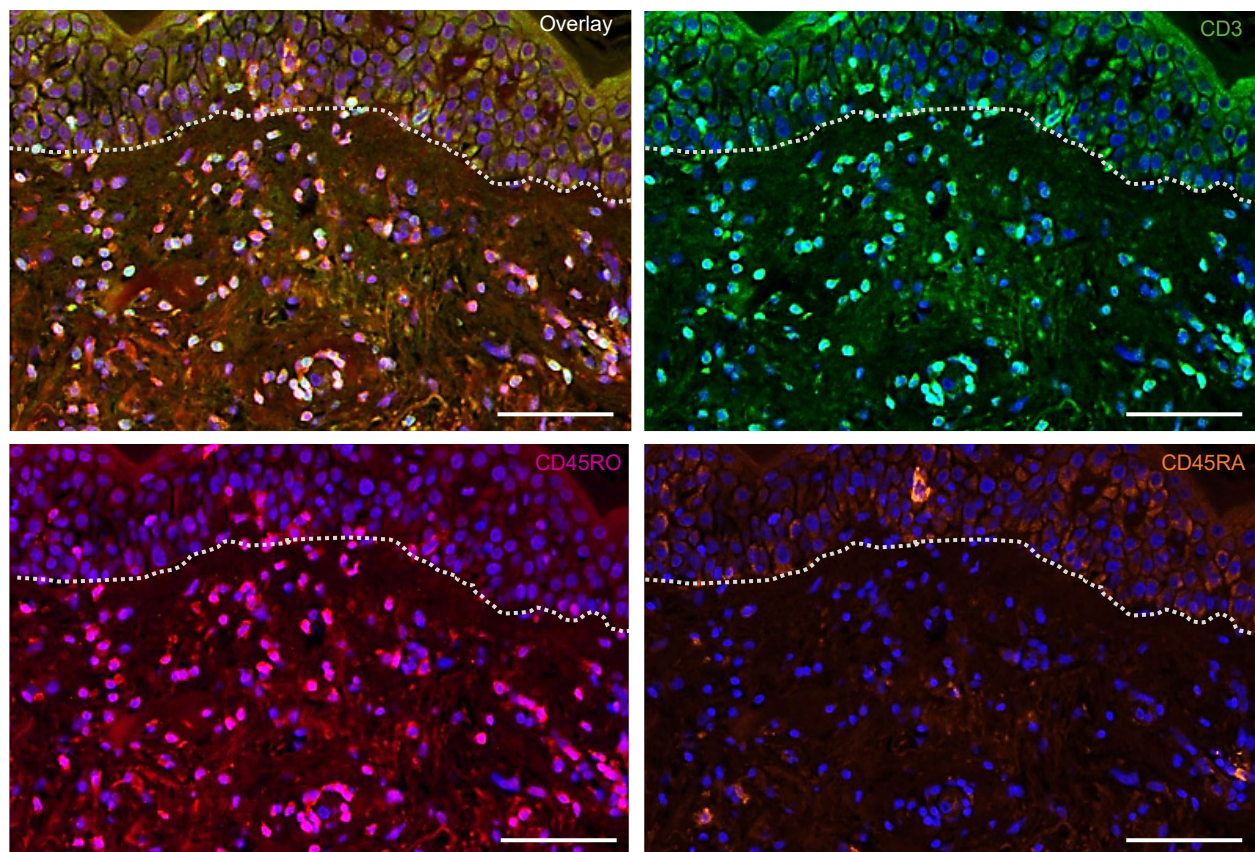


Healthy

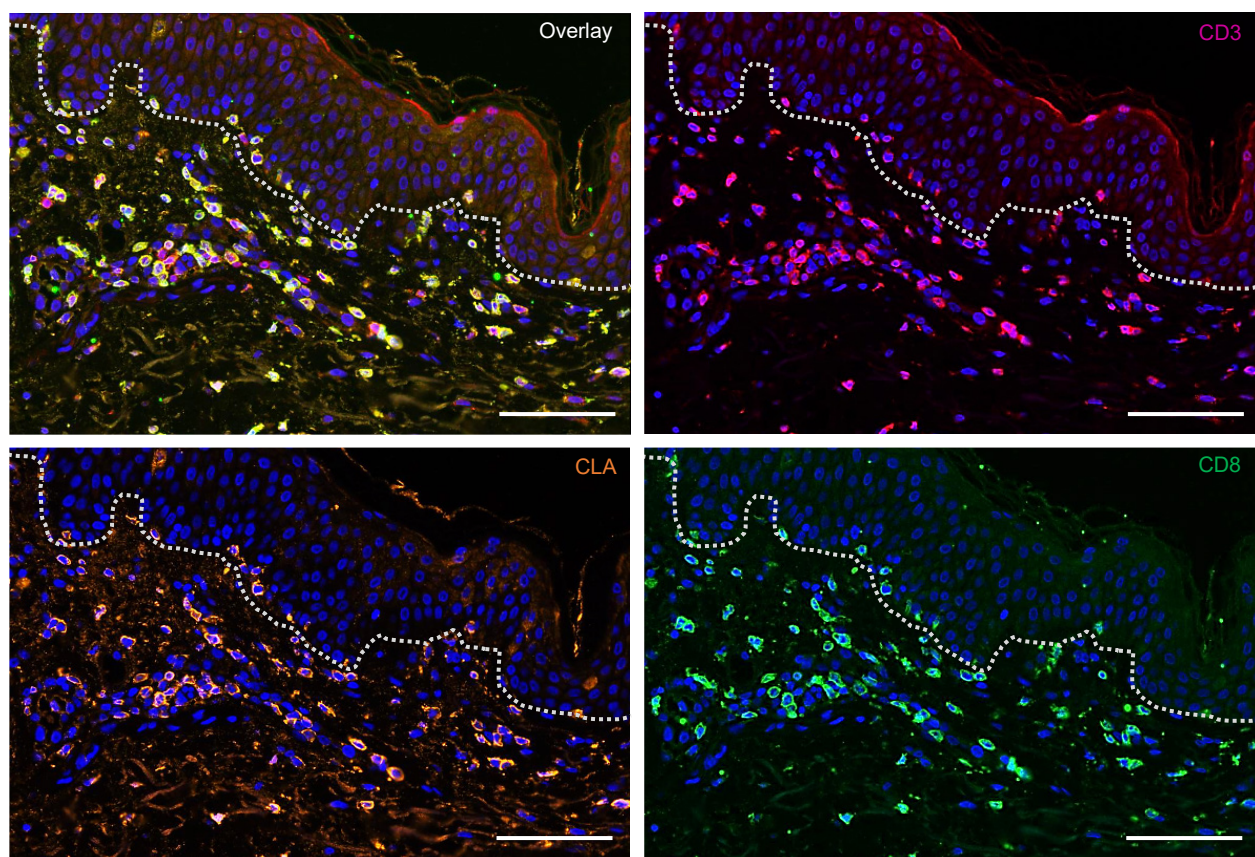


Supplemental Figure 11. Representative skin histology from lymphopenic MDE patients and healthy controls. Representative images of hematoxylin and eosin stained skin samples from lymphopenic MDE patients (N=9) and healthy controls (N=12) are shown. Black bar = 100 μ m. Disclosure: Top left image of lymphopenic MDE and row 2 middle image of healthy were shown in Figure 5B.

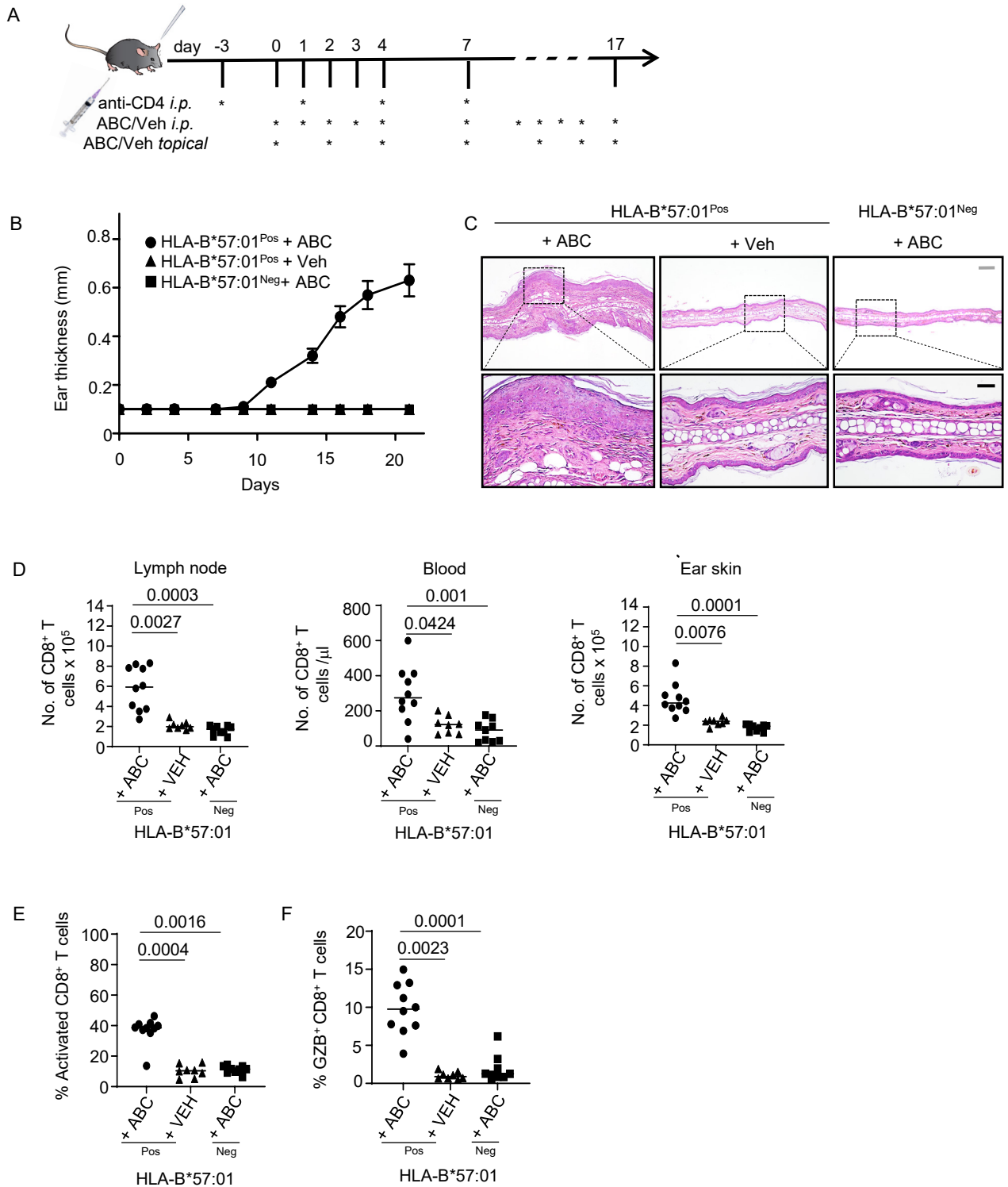
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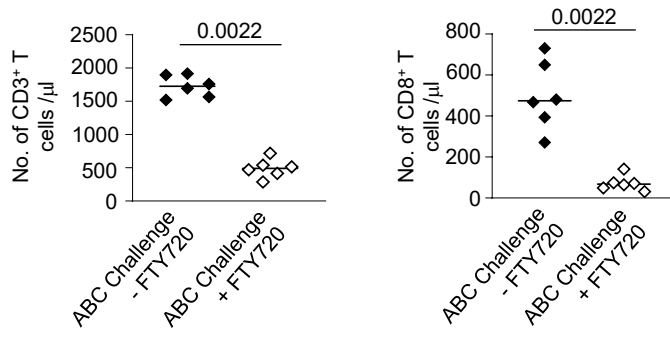
Supplemental Figure 12. Characterization of T cell infiltrate in skin of lymphopenic MDE patients by immunofluorescence staining. (A) Representative images showing overlay, CD3 (green), CD45RO (magenta), CD45RA (orange) and DAPI nuclear stain (blue) in a lymphopenic MDE patient. **(B)** Representative images showing overlay, CD3 (magenta), CLA (orange), CD8 (green) and DAPI nuclear stain (blue) in a lymphopenic MDE patient. N=5 lymphopenic and healthy patients each stained. Gray dotted line depicts dermoepidermal junction. White lines = 100 μ m.



Supplemental Figure 13. Abacavir induces CD8⁺ T cell mediated dermatitis in HLA-B*57:01^{pos} mice.

(A) Schematic of the primary exposure mouse model. HLA-B*57:01^{pos} and HLA-B*57:01^{neg} mice were depleted of CD4⁺ T cells and then treated topically to ear skin and systemically by i.p. injection with abacavir (ABC) or vehicle control (Veh) for 17 days. Mice developed ear dermatitis as determined by **(B)** ear thickness (mean with SEM) and **(C)** histology (gray bar = 200 μ m, black bar = 50 μ m). **(D)** Total number of CD8⁺ T cells in cervical lymph nodes, blood, and ear skin by flow cytometry. **(E)** Percent activated (defined as CD44^{high}CD62L^{low}CD69⁺) CD8⁺ T cells in ear skin by flow cytometry. **(F)** Percent granzyme B (GZB) producing CD8⁺ T cells in ear skin by flow cytometry. **(D-F)** Gated on CD3⁺CD8⁺ T cells. Lines show median. Significance defined as $P < 0.05$, Kruskal-Wallis test followed by Dunn's multiple comparisons test comparing HLA-B*57:01^{pos} mice receiving ABC to each control. **(A-F)** Pooled results from two independent experiments shown.

Blood



Supplemental Figure 14. FTY720 depletes circulating T cells in mice.

Total number of CD3⁺ T cells per μ l and CD8⁺ T cells per μ l in blood post-challenge on day 107, with and without systemic treatment with FTY720 (assessed by flow cytometry). Lines show median. Significant, $P < 0.05$, two-tailed Mann-Whitney test. Pooled results from two independent experiments shown.

Supplemental Figure 15. Schematic of scRNAseq + CITEseq analysis workflow. Data were demultiplexed using hashtag oligo (HTO) counts then both protein (ADT/CITE-seq) and RNA counts were quality filtered. Protein and RNA data were integrated then underwent dimensionality reduction. Individual and multimodal UMAPs were generated using Weighted Nearest Neighbor (WNN) method and compared to ensure proper integration, then clustering was performed on integrated data. From there, differential abundance analysis and pseudobulk differential expression analysis were performed, then cluster specific visualization and differential gene expression analysis was performed. In parallel, VDJ (TCRseq) analysis was performed in concert with clustering and gene expression analysis.

References

- 1 Watanabe, R. *et al.* Human skin is protected by four functionally and phenotypically discrete populations of resident and recirculating memory T cells. *Sci Transl Med* **7**, 279ra239, doi:10.1126/scitranslmed.3010302 (2015).