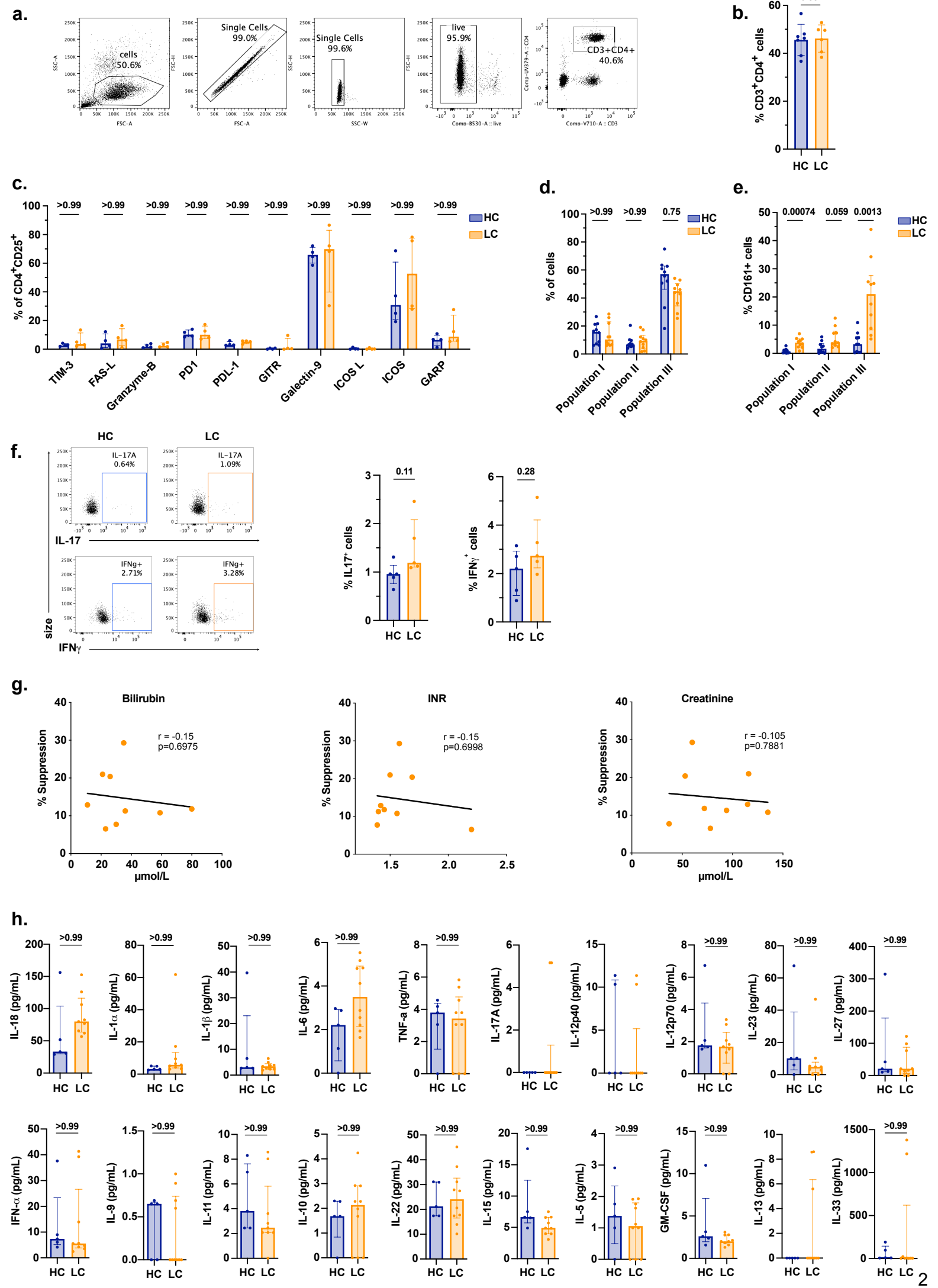


Supplementary Material

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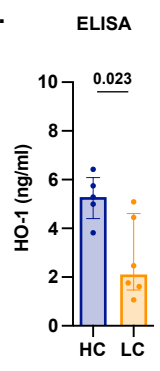
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Supplementary Figure 1.

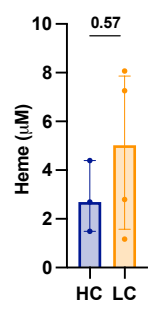


Supplementary Figure 2.

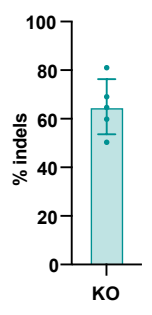
a.



b.



Supplementary Figure 3.



Supplementary Table 1.

Top 15 differentially expressed genes ($p < 0.01$) between Tregs of liver cirrhotic patients (LC) and healthy controls (HC).

	Gene	Ensembl ID	log2r	p-value	q-value
1	<i>EBF4</i>	ENSG00000088881	-1.321376	0.000001	0.005725
2	<i>GPR15</i>	ENSG00000154165	2.100661	0.000001	0.005725
3	<i>HLA-H</i>	ENSG00000206341	2.095677	0.000003	0.022216
4	<i>LRRC37A3</i>	ENSG00000176809	1.429746	0.000005	0.023532
5	<i>SV2A</i>	ENSG00000159164	0.681124	0.000008	0.033876
6	<i>SPARC</i>	ENSG00000113140	-2.09316	0.000015	0.047453
7	<i>ARMC10</i>	ENSG00000170632	-0.87305	0.000017	0.047453
8	<i>CCND3</i>	ENSG00000112576	-0.680468	0.000019	0.047889
9	<i>PIK3C2B</i>	ENSG00000133056	0.840302	0.000026	0.057316
10	<i>MLLT3</i>	ENSG00000171843	-0.881823	0.000037	0.074275
11	<i>BMF</i>	ENSG00000104081	1.214842	0.000119	0.210555
12	<i>CHCHD3</i>	ENSG00000106554	-0.510803	0.000126	0.210555
13	<i>NRGN</i>	ENSG00000154146	-1.810251	0.000146	0.215613
14	<i>MCUB</i>	ENSG00000005059	-0.581298	0.000151	0.215613
15	<i>EDAR</i>	ENSG00000135960	-1.344782	0.000163	0.216792

Supplementary Table 2.

Top 15 downregulated canonical pathways (C2) in LC patients.

	ID	setSize	enrichmentScore	NES	pvalue	p.adjust	rank
1	KEGG_RIBOSOME	81	-0.581	-2.584	0.00004	0.0084	6231
2	REACTOME_EUKARYOTIC_TRANSLATION_ELONGATION	87	-0.571	-2.575	0.00004	0.0084	6231
3	REACTOME_EUKARYOTIC_TRANSLATION_INITIATION	111	-0.471	-2.215	0.00004	0.0084	5086
4	KEGG_PENTOSE_PHOSPHATE_PATHWAY	19	-0.654	-2.076	0.00036	0.0311	1851
5	REACTOME_ACTIVATION_OF_THE_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND_EIFS_AND_SUBSEQUENT_BINDING_TO_43S	55	-0.495	-2.043	0.00010	0.0124	5078
6	REACTOME_RESPONSE_OF_EIF2AK4_GCN2_TO_AMINO_ACID_DEFICIENCY	94	-0.446	-2.038	0.00004	0.0084	5086
7	REACTOME_SELENOAMINO_ACID_METABOLISM	109	-0.433	-2.028	0.00004	0.0084	5086
8	KEGG_PEROXISOME	70	-0.441	-1.908	0.00017	0.0187	4483
9	REACTOME_MISMATCH_REPAIR	15	-0.638	-1.898	0.00318	0.0997	2272
10	REACTOME_PURINE_CATABOLISM	17	-0.614	-1.892	0.00310	0.0997	1738
11	REACTOME_RESPONSE_TO_ELEVATED_PLATELET_CYTOSOLIC_CA2	107	-0.398	-1.860	0.00004	0.0084	1561
12	HALLMARK_FATTY_ACID_METABOLISM	134	-0.383	-1.855	0.00004	0.0084	2795
13	REACTOME_MITOCHONDRIAL_FATTY_ACID_BETA_OXIDATION	32	-0.506	-1.841	0.00170	0.0730	2539
14	REACTOME_METABOLISM_OF_NUCLEOTIDES	92	-0.396	-1.803	0.00030	0.0270	3165
15	REACTOME_NONSENSE_MEDIATED_DECAY_NMD	107	-0.364	-1.699	0.00043	0.0327	5086

Top 15 upregulated canonical pathways (C2) in LC patients.

	ID	setSize	enrichmentScore	NES	pvalue	p.adjust	rank
1	HALLMARK_INTERFERON_ALPHA_RESPONSE	96	0.605	2.462	0.00001	0.0084	4558
2	HALLMARK_INTERFERON_GAMMA_RESPONSE	193	0.508	2.272	0.00001	0.0084	2436
3	REACTOME_RIP_MEDIATED_NFKB_ACTIVATION_VIA_ZBP1	16	0.790	2.190	0.00003	0.0084	2018
4	REACTOME_ZBP1_DAI_MEDIATED_INDUCION_OF_TYPE_I_IFNS	20	0.706	2.077	0.00005	0.0086	2018
5	REACTOME_RORA_ACTIVATES_GENE_EXPRESSION	17	0.679	1.914	0.00064	0.0422	4065
6	REACTOME_INTERFERON_ALPHA_BETA_SIGNALING	56	0.512	1.896	0.00006	0.0098	4546
7	REACTOME_TRANSPORT_OF_MATURE_TRANSCRIPT_TO_CYTOPLASM	79	0.474	1.869	0.00007	0.0102	4525
8	REACTOME_EXPORT_OF_VIRAL_RIBONUCLEOPROTEINS_FROM_NUCLEUS	33	0.559	1.856	0.00095	0.0535	4327
9	PID_CD40_PATHWAY	28	0.572	1.827	0.00147	0.0701	3475
10	REACTOME_DDX58_IFIH1_MEDIATED_INDUCION_OF_INTERFERON_ALPHA_BETA	60	0.481	1.803	0.00042	0.0327	3551
11	REACTOME_NS1_MEDIATED_EFFECTS_ON_HOST_PATHWAYS	40	0.516	1.785	0.00174	0.0734	4327
12	REACTOME_INTERFERON_SIGNALING	178	0.402	1.780	0.00006	0.0099	4546
13	REACTOME_METABOLISM_OF_FAT_SOLUBLE_VITAMINS	35	0.529	1.779	0.00209	0.0795	1751
14	REACTOME_SUMOYLATION_OF_UBIQUITINYLATION_PROTEINS	39	0.516	1.776	0.00201	0.0795	5421
15	REACTOME_REGULATION_OF_GLUKOKINASE_BY_GLUKOKINASE_REGULATORY_PROTEIN	31	0.542	1.773	0.00247	0.0884	4327

Top 15 downregulated ontology gene sets (C5) in LC patients.

ID		setSize	enrichmentScore	NES	pvalue	p.adjust	rank
1	GOBP_GLUCCOSE_6_PHOSPHATE_METABOLIC_PROCESS	22	-0.662	-2.186	0.000	0.0245	3079
2	GOBP_RESPONSE_TO_OXYGEN_RADICAL	23	-0.639	-2.139	0.000	0.0245	1183
3	GOBP_CYTOPLASMIC_TRANSLATION	136	-0.439	-2.130	0.000	0.0234	5086
4	GOCC_INTRACILIARY_TRANSPORT_PARTICLE_B	18	-0.666	-2.086	0.000	0.0648	4341
5	GOCC_CYTOSOLIC_RIBOSOME	93	-0.456	-2.077	0.000	0.0234	5086
6	GOCC_T_CELL_RECEPTOR_COMPLEX	94	-0.449	-2.047	0.000	0.0234	4450
7	GOBP_PLATELET_AGGREGATION	61	-0.472	-1.983	0.000	0.0245	2724
8	GOCC_PLATELET_ALPHA_GRANULE_LUMEN	50	-0.491	-1.980	0.000	0.0379	1314
9	GOBP_CELLULAR_AMINO_ACID_CATABOLIC_PROCESS	94	-0.432	-1.971	0.000	0.0234	2871
10	GOBP_PLATELET_ACTIVATION	110	-0.415	-1.948	0.000	0.0234	2724
11	GOCC_CYTOSOLIC_SMALL_RIBOSOMAL_SUBUNIT	40	-0.506	-1.941	0.001	0.0835	5085
12	GOCC_PLATELET_ALPHA_GRANULE	70	-0.446	-1.927	0.000	0.0245	1314
13	GOBP_ALPHA_AMINO_ACID_CATABOLIC_PROCESS	78	-0.426	-1.880	0.000	0.0355	2871
14	GOCC_MICROBODY_LUMEN	45	-0.476	-1.876	0.001	0.0835	4408
15	GOBP_HEMOSTASIS	193	-0.353	-1.799	0.000	0.0239	2724

Top 15 upregulated ontology gene sets (C5) in LC patients.

ID		setSize	enrichmentScore	NES	pvalue	p.adjust	rank
1	GOMF_HELICASE_ACTIVITY	149	0.463	2.006	0.000	0.0234	3554
2	GOBP_REGULATION_OF_VIRAL_GENOME_REPLICATION	81	0.499	1.975	0.000	0.0234	2353
3	GOBP_NEGATIVE_REGULATION_OF_VIRAL_GENOME_REPLICATION	53	0.535	1.959	0.000	0.0245	2353
4	GOBP_REGULATION_OF_RIG_I_SIGNALING_PATHWAY	19	0.664	1.928	0.001	0.0835	2291
5	GOMF_DNA_HELICASE_ACTIVITY	69	0.500	1.922	0.000	0.0234	2278
6	GOMF_ATP_DEPENDENT_ACTIVITY_ACTING_ON_RNA	75	0.490	1.910	0.000	0.0234	3554
7	GOBP_DEFENSE_RESPONSE_TO_SYMBIONT	246	0.405	1.858	0.000	0.0234	2602
8	GOCC_NUCLEAR_PORE	85	0.453	1.804	0.000	0.0427	4390
9	GOBP_DNA_GEOMETRIC_CHANGE	90	0.439	1.764	0.000	0.0598	2278
10	GOBP_RESPONSE_TO_VIRUS	330	0.366	1.725	0.000	0.0234	2606
11	GOBP_NUCLEAR_EXPORT	146	0.394	1.703	0.000	0.0450	3510
12	GOBP_HISTONE_METHYLATION	144	0.391	1.686	0.000	0.0652	3981
13	GOBP_MRNA_TRANSPORT	115	0.402	1.677	0.001	0.0985	4648
14	GOBP_PROTEIN_LOCALIZATION_TO_NUCLEUS	278	0.343	1.595	0.000	0.0257	6184
15	GOMF_HISTONE_BINDING	209	0.352	1.587	0.000	0.0756	3489

Supplementary Table 3. Per-figure summary of applied statistical tests.

Figure		Mean (normal distribution) / Median (non-normal distribution)	SD (normal distribution) / IQR (non-normal distribution)	Data transformation (nominal or log10 transformed)	Statistical test applied	p-value	adjusted p-value	n-numbers HC	LC
Figure 1									
1a	% Tregs FACS			N/A	N/A	N/A		N/A	N/A
1b	% Tregs	Mean: HC 6.63%; LC 4.97%	SD: HC 1.18; LC 1.97	nominal	Unpaired t-test	0.0137		13	15
1c	% Annexin	Median: HC 0.39%; LC 8.53%	iQR: HC 2.94; LC 8.92	log10 transformed	unpaired t-test	0.0106		8	7
1d	Phenotype			log10 transformed	multiple unpaired t-tests and Bonferroni adjustment				
	FoxP3	Median: HC 92%; LC 88.2%	IQR: HC 3.65; LC 12.5			0.34	>0.99	17	15
	CD161	Median: HC 4.81; LC 14.8%	IQR: HC 3.44; LC 11.3			0.000006	0.00006	10	10
	CD62L CD27	Median: HC 79.75%; LC 71.45%	IQR: HC 11.13; LC 18.48			0.0056	0.056	10	10
	CD62L	Median: HC 89.65%; LC 86.9%	IQR: HC 5.65; LC 8.58			0.122	>0.99	10	10
	CD27	Median: HC 85.55%; LC 75.8%	IQR: HC 17.63; LC 14.9			0.053	0.53	10	10
	CXCR3	Median: HC 82.85%; LC 82.5%	IQR: HC 5.3; LC 17			0.55	>0.999	10	10
	CD39	Median: HC 42.6%; LC 27%	IQR: HC 40.8; LC 47.1			0.062	0.62	17	19
	CTLA-4	Median: HC 21.6%; LC 10.7%	IQR: HC 10.43; LC 7.85			0.00097	0.0097	14	11
	Helios	Median: HC 64.3%; LC 46.3%	IQR: HC 23.2; LC 17.8			0.00022	0.0022	17	19
	HLA-DR	Median: HC 36.2%; LC 29.2%	IQR: HC 35; LC 29.35			0.39	>0.99	10	10
1e	IL17+ cells after cytokine mixes	Median: Mix 1. HC 1.55%; LC 5.39% Median: Mix 2. HC 0.99%, LC 3.78%	IQR: Mix 1. HC 1.72; LC 5.36 IQR: Mix 2. HC 2.53, LC 2.97	log10 transformed	Two-way repeated measures ANOVA with Bonferroni's multiple comparison test interaction p-value ANOVA (patient group HC/LC vs. Mixes)	0.71	0.0055 0.0015	10	10
	IFNg+ cells after cytokine mixes	Median: Mix 1. HC 3.7%; LC 6.015% Median: Mix 2. HC 4.78%, LC 4.64%	IQR: Mix 1. HC 1.97; LC 4.79 IQR: Mix 2. HC 3.72, LC 4.42	log10 transformed	Two-way repeated measures ANOVA with Bonferroni's multiple comparison test interaction p-value ANOVA (patient group HC/LC vs. Mixes)	0.083	0.044 >0.99	10	10
1f	Suppression			nominal	Two-way repeated measures ANOVA with Bonferroni's multiple comparison test interaction p-value ANOVA (patient group HC/LC vs. Treg:Teff ratio)	<0.0001	<0.0001 <0.0001 0.0003	20	20
	1:1	Mean: HC 20.17%; LC 71.29%	SD: HC 14.32; LC 10.54		1:1				
	1:5	Mean: HC 13.51; LC 40.59%	SD: HC 17.46; LC 15.45		1:5				
	1:10	Mean: HC 10.33%; LC 31.05%	SD: HC 14.24; LC 15.96		1:10				
1g	Suppression ACR vs. NASH			log10 transformed	Two-way repeated measures ANOVA with Bonferroni's multiple comparison test interaction p-value ANOVA (disease aetiology vs. Treg:Teff ratio)	0.7476	0.3397 >0.99 >0.99	5	5
	1:1	Mean: HC 27.68%; LC 14.75% Median: HC 30.44% ; LC 11.89%	SD: HCC 12.72; LC 5.73; IQR: HC 27.44; LC 10.66		1:1				
	1:5	Mean: HC 4.07%; LC 6.31% Median: HC 4.33%; LC 4.37%	SD: HC 3.29; LC 5.62; IQR: HC 7.32; LC 9.41		1:5				
	1:10	Mean: HC 1.07%; LC 1.82% Median: HC 0%; LC 2.68%	SD: HC 1.36; LC 3.04; IQR: HC 2.68; LC 4.56		1:10				
1h	Correlation MELD vs. Supp				Simple linear regression Pearson correlation coefficient r=-0.821				20
1i	TSDR			N/A	N/A	N/A			
	CpG 44	Mean: Teff 94.98%; HC 32.4%; LC 30.85%	SD: Teff 2.051; HC 21.49; LC 37.9						
	CpG 43	Mean: Teff 93%; HC 32.23%; LC 29.55%	SD: Teff 1.46; HC 20.9; LC 34.74						
	CpG 42	Mean: Teff 93.64%; HC 38.11%; LC 31.82%	SD: Teff 0.83; HC 25.57; LC 37.46						
	CpG 41	Mean: Teff 95.58%; HC 40.24%; LC 32.17%	SD: Teff 0.55; HC 26.77; LC 38.32						

	CpG 40 CpG 39 CpG 38 CpG 37 CpG 36 CpG 35 CpG 34	Mean: Teff 96.5%; HC 41%; LC 32.15% Mean: Teff 97.02%; HC 40.43%; LC 33.22% Mean: Teff 96.3%; HC 40.47%; LC 32.32% Mean: Teff 97.1%; HC 39.96%; LC 33.17% Mean: Teff 95.58%; HC 38.96%; LC 30.88% Mean: Teff 96.38%; HC 41.64%; LC 33.48% Mean: Teff 96.44%; HC 35.4%; LC 29.35%	SD: Teff 0.62; HC 25.79, LC 38.56 SD: Teff 0.95; HC 25.38; LC 38.97 SD: Teff 0.19; HC 26.44; LC 38.22 SD: Teff 0.75; HC 24.92; LC 38.54 SD: Teff 1.71; HC 25.27; LC 37.59 SD: Teff 0.28; HC 26.63; LC 39.15 SD: Teff 1.16; HC 24.04; LC 36.50					
Figure 2								
2a	MFI ROS	Median: HC 552.3; LC 1363	IQR: HC 369.9; LC 5781	log10 transformed	unpaired t-test with Welch's correction	0.009		8 7
2b	MFI Lipid Peroxidation	Median: HC 398.8; LC 790	IQR: HC 324.4; LC 6244	log10 transformed	unpaired t-test with Welch's correction	0.0134		8 7
2c	MFI Free Thiols	Median: HC 2034; LC 910	IQR: HC 2641.5; LC 839	log10 transformed	unpaired t-test	0.1484		8 7
2d	Colocalisation Nox2 subunits	Median: HC 0; LC 0.640	IQR: HC 0.1045; LC 0.7910	nominal	Mann-Whitney test	0.0492		5 7
2e	MFI MitoSox	Median: HC 29.35; LC 52.55	IQR: HC 13.92; LC 25.6	log10 transformed	unpaired t-test	<0.0001		12 16
2f	Seahorse							9 6
2g	Basal OCR	Median: HC 95.56; LC 44.34	IQR: HC 116.53; LC 39.85	log10 transformed	unpaired t-test	0.0281		9 6
	Max. OCR	Median: HC 329.1; LC 144.3	IQR: HC 467.7; LC 172.12	log10 transformed	unpaired t-test	0.0576		9 6
	ATP Production	Median: HC 75.39; LC 21.77	IQR: HC 115.04; LC 10.98	log10 transformed	unpaired t-test	0.0008		9 6
	Basal ECAR	Median: HC 68.71; LC 91.24	IQR: HC 33.91; LC 50.43	log10 transformed	unpaired t-test	0.1225		9 6
	Max. ECAR	Median: HC 17.99; LC 5.11	IQR: HC 27.42; LC 4.34	log10 transformed	unpaired t-test	0.025		9 6
	OCR/ECAR	Median: HC 1.93; LC 0.6108	IQR: HC 1.54; LC 0.2	log10 transformed	unpaired t-test	0.0018		9 6
2h	EM Mitochondria			log10 transformed	linear mixed effect model	0.026		3 3
2i / 2j / 2k	RNA Seq			N/A	N/A			
Figure 3								
3a	Nrf2WB	Mean: HC 0.58; LC 0.54	SD: HC 0.101; LC 0.14	nominal	unpaired t-test	0.5938		6 5
3b	Nrf2 nuclear translocation	-PGJ2 Mean: HC 0.5; LC 0.76 +PGJ2 Mean: HC 0.91; LC 0.73	SD: HC 0.13; LC 0.14 SD: HC 0.29; LC 0.10	nominal	Two-way repeated measures ANOVA with Bonferroni's multiple comparison test interaction p-value ANOVA (patient group HC/LC vs. PGJ2) -/+ PGJ2: HC -/+ PGJ2: LC HC vs LC (-PGJ2)	0.0027 0.0009 >0.99 0.083		5 5
3c	HO-1 WB	Median: HC 0.11; LC 0.0043	IQR: HC 0.16; LC 0.015	log10 transformed	unpaired t-test	0.0198		6 5
3d	Bach1 WB	Median: HC 0.66; LC 0.52	IQR: HC 0.78; LC 0.51	log10 transformed	unpaired t-test	0.714		7 5
3e	Nrf2 targets			log10 transformed	multiple unpaired t-tests with Bonferroni adjustment			15 12
	NQO1	Median: HC 1.57; LC 1.05	IQR: HC 0.33; LC 0.7			0.000393	0.001179	
	GCLM	Median: HC 1.37; LC 0.40	IQR: HC 1.41; LC 0.76			0.000949	0.002848	
3f	SOD1	Median: HC 0.75; LC 0.82	IQR: HC 0.29; LC 0.42			0.332385	0.997155	
3g	RNA Seq			N/A	N/A			
	Nrf2KO MFI FoxP3	Mean: HC 4520; LC 2955	SD: HC 297.8; LC 176.8	nominal	multiple unpaired t-tests with Bonferroni adjustment	0.0014	0.0042	3 3
	Nrf2KO MFI CD39	Mean: HC 1247; LC 908.3	SD: HC 128.5; LC 27.02	nominal	multiple unpaired t-tests with Bonferroni adjustment	0.0111	0.0333	3 3
3h	Nrf2KO MFI CTLA4	Mean: HC 972; LC 794.3	SD: HC 55.57; LC 45.94	nominal	multiple unpaired t-tests with Bonferroni adjustment	0.013	0.039	3 3
3i	Nrf2KO Annexin	Mean: HC 10.20%; LC 14.65%	SD: HC 1.73; LC 0.69	nominal	unpaired t-test	0.0007		5 5
	Nrf2KO Suppression	1:1 'Mean: HC 45.14%; LC 18.57% 1:2 'Mean: HC 25.57%; LC 14.86%	SD: HC 4.22; LC 4.28 SD: HC 3.69; LC 3.58	nominal	Two-way repeated measures ANOVA with Bonferroni's multiple comparison interaction p-value ANOVA (Treg Teff ratio vs. patient group HC/LC)	<0.0001 <0.0001 <0.0001		7 7
3j	CRISPR KO efficiency	Median: WT 22.05%, NC 15.6%, KO 76.1%	IQR: WT 15.2, NC 29.2, KO 21.35	log10 transformed	ordinary one-way ANOVA with Bonferroni's multiple comparison test WT vs. NC WT vs. KO NC vs. KO		>0.99 0.0001 <0.0001	WT 10, NC 11, KO 12
3k	CRISPR suppression	1:1 Mean: WT 96.42%, NC 96.57%, KO 96.76 %	SD: WT 4.52, NC 4.35, KO 3.04	nominal	Linear mixed effect model with Bonferroni's multiple comparison test interaction p-value ANOVA (genotype vs. Treg Teff ratio)	0.7543		WT 4, NC 3, KO 4

		1:5 'Mean: WT 90.52%, NC 90.92%, KO 92.15% 1:10 'Mean: WT 79.54%, NC 78.74%, KO 86.34% 1:20 Mean: WT 45.7%, NC 57.79%, KO 57.05%	SD: WT 7.85, NC 7.34, KO 5.71 SD: WT 10.06, NC 11.27, KO 5.12 SD: WT 0.74, NC 24.06, KO 23.81		1:1 - WT vs. NC 1:1 - WT vs. KO 1:1 - NC vs. KO 1:5 - WT vs. NC 1:5 - WT vs. KO 1:5 - NC vs. KO 1:10 - WT vs. NC 1:10 - WT vs. KO 1:10 - NC vs. KO 1:20 - WT vs. NC 1:20 - WT vs. KO 1:20 - NC vs. KO	>0.99 >0.99 >0.99 >0.99 >0.99 >0.99 >0.99 0.8643 >0.99 >0.99 >0.99 >0.99		
3i	CRISPR viability	0uM: 'Mean: WT 58.57%, NC 55.17%, KO 53.7% 40uM: 'Mean: WT 56.07%, NC 54.07%, KO 38.17% 70uM: 'Mean: WT 52.17%, NC 50.5%, KO 32.27%	SD: WT 3.33, NC 1.76, KO 5.72 SD: WT 1.35, NC 3.3, KO 9.53 SD: WT 1.91, NC 1.7, KO 8.95	nominal	Two-way repeated measures ANOVA with Bonferroni's multiple comparison interaction p-value ANOVA (genotype vs. concentration) 0uM - WT vs. NC 0uM - WT vs. KO 0uM - NC vs. KO 40uM - WT vs. NC 40uM - WT vs. KO 40uM - NC vs. KO 70uM - WT vs. NC 70uM - WT vs. KO 70uM - NC vs. KO	0.054 >0.99 0.7819 >0.99 >0.99 0.0014 0.004 >0.99 0.0005 0.0012	WT 3, NC 3, KO 3	
Figure 4								
4a	Serum: MFI FoxP3	Median: HC 836; LC 773	IQR: HC 882.5; LC 870	log10 transformed	unpaired t-test	0.8959		5 5
4b	Serum: AnnexinV	Median: HC 5.41%; LC 14.2%	IQR: HC 4.14; LC 6.83	log10 transformed	unpaired t-test	0.0151		7 7
4c	Serum: IL-17+ / IFNg	IL-17: Median: HC 0.51; LC 0.9 IFNg: Median: HC 2.0; LC 2.61	IQR: HC 0.23; LC 0.465 IQR: HC 1.1; LC 0.665	log10 transformed	multiple unpaired t-tests with Bonferroni adjustment IL-17 IFNg	0.0123 0.1845	0.0246 0.369	5 5
4d	Serum: % Suppression	1:1 Mean: HC 37.57%; LC 16.75% 1:5 Mean: HC 26.47%; LC 12.45% 1:10 Mean: HC 21.11%; LC 10.71%	SD: HC 8.44; LC 4.74 SD: HC 8.43; LC 5.26 SD: HC 9.27; LC 5.44	nominal	Two-way repeated measures ANOVA with Bonferroni multiple comparison test interaction p-value ANOVA (Treg Teff ratio vs. patient group HC/LC serum) 1:1 1:5 1:10	<0.0001 <0.0001 0.0027 0.0374		9 9
4e	Serum: Seahorse Basal OCR Max OCR ATP Production Basal ECAR Max ECAR OCR/ECAR	Median: HC 60.90; LC 81.53 Median: HC 141; LC 162 Median: HC 58.91; LC 74.01 Median: HC 14.18; LC 22.25 Median: HC 15.21; LC 19.14 Median: HC 6.45; LC 5.71	IQR: HC 12.67; LC 37.1 IQR: HC 96.8; LC 102.1 IQR: HC 19.28; LC 19.69 IQR: HC 2.67; LC 9.19 IQR: HC 4.07; LC 7.36 IQR: HC 1.581; LC 1.057	log10 transformed log10 transformed log10 transformed log10 transformed log10 transformed log10 transformed	unpaired t-test unpaired t-test unpaired t-test unpaired t-test unpaired t-test unpaired t-test	0.0627 0.6277 0.0752 0.0131 0.016 0.3956		5 6
Supp. Fig. 1								
S1a	Gating			N/A	N/A			
S1b	%CD3CD4	Mean: HC 45.60%; LC 46.13%	SD: HC 6.49; LC 5.69	nominal	unpaired t-test	0.88		7 6
S1c	Extended phenotype TIM-3 FAS-L Granzyme B PD1 PDL-1 GITR Galectin-9	Median: HC 2.79%; LC 4.12% Median: HC 4.34%; LC 7.12% Median: HC 2.14%; LC 2.5% Median: HC 10.5%; LC 10.43% Median: HC 3.1%; LC 5.49% Median: HC 0.395%; LC 0.54% Median: HC 66.15%; LC 70.15%	IQR: HC 1.72; LC 8.89 IQR: HC 9.52; LC 11.84 IQR: HC 2.56; LC 2.66 IQR: HC 4.78; LC 8.76 IQR: HC 2.48; LC 1.87 IQR: HC 0.785; LC 7.35 IQR: HC 10.9; LC 43.12	log10 transformed	multiple unpaired t-tests with Bonferroni adjustment	0.294 0.553 0.512 0.991 0.177 0.318 0.719	>0.99 >0.99 >0.99 >0.99 >0.99 >0.99 >0.99	4 4

	ICOS L ICOS GARP	Median: HC 0.17%; LC 0.082% Median: HC 31.15%; LC 52.95% Median: HC 6.735%; LC 9.12%	IQR: HC 1.03; LC 0.84 IQR: HC 40.08; LC 49.1 IQR: HC 7.16; LC 18.20			0.380 >0.99 0.411 >0.99 0.277 >0.99		
S1d	Miyara population	Population I: Median: HC 15.8%; LC 10.39% Population II: Median: HC 6.87%; LC 9.43% Population III: Median: HC 57.15%; LC 44.9%	IQR: HC 14.25; LC 16.43 IQR: HC 4.19; LC 9.39 IQR: HC 16.6; LC 15.9	log10 transformed	multiple unpaired t-test with Bonferroni adjustment Population I Population II Population III	0.63 >0.99 0.958 >0.99 0.251 0.754	10	10
S1e	CD161 within Miyara populations	Population I: Median: HC 0.62%; LC 3.78% Population II: Median: HC 1.61%; LC 3.94% Population III: Median: HC 3.22%; LC 21%	IQR: HC 1.051; LC 2.88 IQR: HC 3.16; LC 5.11 IQR: HC 5.55; LC 19.32	log10 transformed	multiple unpaired t-test with Bonferroni adjustment Population I Population II Population III	0.000245 0.000736 0.01998 0.0599 0.000425 0.00127	10	10
S1f	Baseline cytokine expression	IL-17: Median: HC 0.96 ; LC 1.19 IFNg: Median: HC 2.2 ; LC 2.73	IQR: HC 0.37 ; LC 0.975 IQR: HC 1.84 ; LC 1.98	log10 transformed	multiple unpaired t-test with Bonferroni adjustment IL-17+ IFNg+	0.0548 0.1096 0.1402 0.2804	5	5
S1g	Correlation MELD components vs. Supp			nominal	Simple linear regression: Bilirubin Simple linear regression: INR Simple linear regression: Creatinine	pearson coefficient r=0.1513 pearson coefficient r=0.1501 pearson coefficient r=0.105		9 9 9
S1h	Cytokines in Serum							
	IL-18	Median: HC 33.27; LC 79.95	IQR: HC 74.1; LC 52.51	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.053 >0.99	5	9
	IL-1 alpha	Median: HC 3.15; LC 5.770	IQR: HC 2.115; LC 9.54	log10 transformed	unpaired t-test with Welch's correction with Bonferroni adjustment for multiple comparison	0.0546 >0.99	5	9
	IL-1 beta	Median: HC 3.00; LC 3.43	IQR: HC 20.85; LC 2.13	log10 transformed	unpaired t-test with Welch's correction with Bonferroni adjustment for multiple comparison	0.3533 >0.99	5	9
	IL-6	Median: HC 2.21; LC 3.50	IQR: HC 2.36; LC 2.775	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.1407 >0.99	5	10
	TNF-alpha	Median: HC 3.79; LC 3.425	IQR: HC 2.845; LC 4.773	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.6919 >0.99	5	10
	IL-17A			N/A	N/A		5	10
	IL12p40			N/A	N/A		5	9
	IL12p70	Median: HC 1.76; LC 1.69	IQR: HC 2.795; LC 1.91	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.6507 >0.99	5	9
	IL-23	Median: HC 10.06; LC 4.77	IQR: HC 35.93; LC 6.42	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.2451 >0.99	5	9
	IL-27	Median: HC 20.96; LC 20.96	IQR: HC 166.94; LC 81.285	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.8651 >0.99	5	9
	IFN-alpha	Median: HC 7.34; LC 5.55	IQR: HC 18.195; LC 22.72	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.803 >0.99	5	9
	IL-9	Median: HC 0.65; LC 0	IQR: HC 0.67; LC 0.74	log10 transformed	unpaired t-test with Welch's correction with Bonferroni adjustment for multiple comparison	0.2613 >0.99	5	10
	IL-11	Median: HC 3.81; LC 2.47	IQR: HC 5.18; LC 3.74	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.5041 >0.99	5	9
	IL-10	Median: HC 1.68; LC 2.13	IQR: HC 1.45; LC 2.913	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.1794 >0.99	5	10
	IL-22	Median: HC 21.18; LC 24.05	IQR: HC 13.64; LC 16.11	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.9808 >0.99	5	10
	IL-15	Median: HC 6.65; LC 4.89	IQR: HC 6.82; LC 2.64	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.0591 >0.99	5	9
	IL-5	Median: HC 1.38; LC 1.060	IQR: HC 1.835; LC 1.798	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.5608 >0.99	5	10
	GM-CSF	Median: HC 2.600; LC 1.990	IQR: HC 5.1; LC 1.06	log10 transformed	unpaired t-test with Welch's correction with Bonferroni adjustment for multiple comparison	0.2738 >0.99	5	9
	IL-13			N/A	N/A		5	10
	IL-33	Median: HC 8.870; LC 4.610	IQR: HC 137.3; LC 617.415	log10 transformed	unpaired t-test with Bonferroni adjustment for multiple comparison	0.7944 >0.99	5	9
Supp. Fig.2								
S2a	HO-1 ELISA	Median: HC 5.29; LC 2.11	IQR: HC 1.68; LC 3.136	log10 transformed	unpaired t-test with Welch's correction	0.0232	5	6
S2b	Heme	Median: HC 2.69; LC 5.025	IQR: HC 2.906; LC 6.286	log10 transformed	unpaired t-test	0.5737	3	4
Supp. Fig.3	Indels HO-1 KO cells			N/A	N/A			

Supplementary Table 4. Summary of fluorochrome-conjugated antibodies.

Target	Antibody clone	Fluorochrome	Company	Cat. Nr.	RRID tag
<u>Human:</u>					
CD3	OKT3	BV711	Biologend	317328	AB_2562907
CD4	SK3	PercP	Biologend	344624	AB_2563326
CD4	SK3	BUV395	BD Biosciences	563550	AB_2738273
CD4	RPA-T4	BV605	Biologend	300556	AB_2564391
CD8	HIT8a	Pacific Blue	Biologend	300928	AB_10612929
CD25	2A3	APC	BD Biosciences	340907	AB_2819021
CD25	CD25-4E3	PE	Thermo Fisher - eBioscience	12-0257-42	AB_2043825
CD25	M-A251	PE	BD Biosciences	555432	AB_395826
CD45RA	JS-83	FITC	Thermo Fisher - eBioscience	11-9979-42	AB_11151708
FOXP3	PCH101	FITC	Thermo Fisher - eBioscience	11-4776-42	AB_1724125
FOXP3	PCH101	PE	Thermo Fisher - eBioscience	12-4776-42	AB_1518782
FOXP3	236A/E7	PECF594	BD Biosciences	563955	AB_2738507
CD127	eBioRDR5	eFluor450	Thermo Fisher - eBioscience	48-1278-42	AB_1963566
CD127	A019D5	PECy7	Biologend	351320	AB_10897098
CD127	A019D5	BV510	Biologend	351332	AB_2562304
CCR6	R6H1	PECy7	Thermo Fisher - eBioscience	25-1969-42	AB_1257138
CD161	HP-3G10	eFluor450	Thermo Fisher - eBioscience	48-1619-42	AB_10854273
CD27	O323	eFluor450	Thermo Fisher - eBioscience	48-0279-42	AB_10852844
CD62L	DREG-56	PECy7	Biologend	304822	AB_830801
HLA-DR	LN3	PECy7	Thermo Fisher - eBioscience	25-9956-42	AB_1582284
CD39	eBioA1	PECy7	Thermo Fisher - eBioscience	25-0399-42	AB_1582280
CD39	A1	APC/Cy7	Biologend	328226	AB_2571981
ICOS-L	MIH12	PE	Thermo Fisher - eBioscience	12-5889-42	AB_10853668
CTLA-4	14D3	PE	Thermo Fisher - eBioscience	12-1529-42	AB_10805626
CTLA-4	BN13	BV605	Biologend	369610	AB_2632779
Granzyme-B	GB11	PE	Thermo Fisher - eBioscience	GRB04	AB_1500188
PD-1	eBioJ105	PE	Thermo Fisher - eBioscience	12-2799-42	AB_11042478
CD274 (PDL-1)	MIH-1	PECy7	Thermo Fisher - eBioscience	25-5983-42	AB_1907368
GITR	eBioAITR	PE	Thermo Fisher - eBioscience	12-5875-42	AB_2572634
GARP	G14D9	eFluor660	Thermo Fisher - eBioscience	50-9882-42	AB_2574406
Helios	22F6	PE	Biologend	137216	AB_10660749
Helios	22F6	PE/Cy7	Biologend	137236	AB_2565990
CXCR3	G025H7	Pacific Blue	Biologend	353724	AB_2561442
CD178 (FAS-L)	NOK-1	PE	Biologend	306407	AB_2100664
TIM-3	F38-2E2	PE	Biologend	345006	AB_2116576
HO-1	23	AF647	BD Biosciences	566391	AB_2739722
IL-17A	BL168	BV605	Biologend	512326	AB_2563887
IFNg	4S.B3	PE/Cy7	Biologend	502528	AB_2123323
<u>Murine:</u>					
CD3	145-2C11	APC	Thermo Fisher - eBioscience	17-0031-82	AB_469315
CD4	GK1.5	FITC	Thermo Fisher - eBioscience	11-0041-82	AB_464892
CD8	53-6.7,	eFluor450	Thermo Fisher - eBioscience	48-0081-82	AB_1272198
CD25	PC61.5,	eFluor780	Thermo Fisher - eBioscience	47-0251-82	AB_1272179
FoxP3	FJK-16s,	PE	Thermo Fisher - eBioscience	12-5773-82	AB_465936
CTLA-4	UC10-4B9	PECy7	Thermo Fisher - eBioscience	25-1522-82	AB_2688105
CD39	24DMS1	PercP-eFluor710	Thermo Fisher - eBioscience	46-0391-82	AB_10717953