

Supplemental Methods

In vitro B cell Differentiation Assay

In brief, 10,000 CD34+ cells isolated from bone marrow aspirates of healthy donors were co-cultured in a 12-well tissue culture plate with sub-confluent human MSC in DMEM 10% FBS, 1% penicillin-streptomycin media supplemented with 20 ng/ml stem cell factor (SCF) and 10 ng/ml Flt-3. The effect of IFN- γ and TNF in isolation or in combination was evaluated by the addition of IFN- γ (5 ng/ml), TNF (5 ng/ml), and the combination of IFN- γ (5 ng/ml) and TNF (5 ng/ml) to the differentiation media. Half of the medium was replaced with fresh medium containing the cytokines every 4 days.

RNA Sequencing Analysis

The sequenced raw FastQ files were aligned with reference genome Hg38 using HISAT2 package. In total, ~12,676 protein-coding genes were considered with at least above 10 read counts in 50% of samples. Differential expression (DE) analysis between treated and non-treated groups were performed using Deseq2 package in R platform. The DE genes were identified with fold change (FC) ≥ 1.2 and false discovery rate of (FDR) < 0.05 . The Pheatmap was used to generate the heat maps for DE genes. The principal component analysis (PCA) was performed in prcomp function and the PCA plots were generated using factoextra package in R. The functional relationship between differentially expressed genes were performed by performing a gene ontology (GO) functional annotation using the clusterprofiler package in R. Over Representation Analysis (ORA) was performed to determine whether known biological functions or processes are enriched in our differentially expressed genes list. Gene Set Enrichment Analysis (GSEA) using KEGG and WikiPathways implicated by differentially expressed genes to identify the pathways that are enriched by DE genes. ClusterProfiler package in R was used for both analyses. Significant pathways were identified with a nominal p-value threshold of $P < 0.05$ and after multiple tests corrections (FDR < 0.05).

Multiplex Immunofluorescence Staining

Deparaffinization was accomplished with heat and EZ-Prep solution, followed by application of Cell Conditioning 1 (Roche). Blocking of endogenous peroxidase activity was performed with DISCOVERY Inhibitor (Roche). After primary antibody incubation, species appropriate horseradish peroxidase (HRP)-conjugated secondary antibody

(DISCOVERY OmniMap anti-rabbit HRP (Roche 760–4311) was applied followed by application of the tyramide signal amplification Opal dye. Denaturing of the primary and secondary antibodies was accomplished by heating at 93°C with Cell Conditioning 2 (Roche). Counter staining of nuclei was achieved using Spectral DAPI (Akoya). Slides were cover-slipped with VECTASHIELD Antifade mounting medium (Vector Laboratories). Stained slides were stored at 4°C. Images of stained slides were acquired with the Vectra Polaris (Akoya Biosciences) whole-slide scanner using a standardized scanning protocol. Software fluorophore signal unmixing and removal of autofluorescence followed by digital image analysis was accomplished with inForm software (Akoya Biosciences).

Cytokine Profiling

Cytokine profiling was performed using a custom multiplex panel on the Luminex platform looking at IFN- γ , IL-6, CXCL9, and CXCL13 in healthy control (n=16) and HLH (P-HLH, n=3; I-HLH, n=6; Total, n=9) patients.

Statistical Analysis

Shapiro-Wilk test was used for testing the normality of numerical variables. When comparing two groups, two-tailed Student's t-tests or Mann-Whitney test was used depending upon normality. When comparing more than two groups, one-way ANOVA with Tukey's multiple comparison tests or Kruskal-Wallis test with Dunn's multiple comparison was performed for normally distributed or non-normally distributed data, respectively. All analyses were completed at the 0.05 significance level using GraphPad Prism (v9).

Supplemental Data

Patient ID	Gender	Age at Presentation	Type of HLH	Mutation	Secondary Cause	Flow Panel A	Flow Panel B
1	Male	8 weeks old	Primary	RAB27A	-	X	
2	Male	6 months old	Primary	RAB27A	-	X	
3	Male	4 weeks old	Primary	STXBP2	-	X	X
4	Female	11 years old	Primary	PRF1	-	X	
5	Male	2 months old	Primary	UNC13D	-	X	X
6	Male	3 days old	Primary	UNC13D	-	X*	X
7	Female	7 months old	Secondary	-	Infection	X	
8	Male	8 months old	Secondary	-	Infection	X	
9	Male	11 years old	Secondary	-	Infection	X	
10	Male	15 months old	Secondary	-	Infection	X*	X*
11	Female	9 years old	Secondary	-	Infection	X	
12	Female	4 years old	Secondary	-	Infection	X	
13	Male	15 years old	Secondary	-	Infection	X	
14	Male	11 weeks old	Secondary	-	Infection	X	
15	Male	13 years old	Secondary	-	Infection	X	
16	Male	3 years old	Secondary	-	Infection	X	
17	Female	18 years old	Secondary	-	Infection	X	
18	Male	9 years old	Secondary	-	Infection	X	
19	Female	12 years old	Secondary	-	Infection	X	X*
20	Male	4 months old	Secondary	-	Infection	X	
21	Male	4 years old	Secondary	-	Infection	X	
22	Female	7 years old	Secondary	-	Infection	X	X
23	Female	1 year old	Secondary	-	Infection	X	
24	Female	2 years old	Secondary	-	Infection	X	
25	Male	2 years old	Secondary	-	Infection	X*	
26	Female	7 years old	Secondary	-	Infection	X	X
27	Male	4 years old	Secondary	-	Infection	X	
28	Male	3 years old	Secondary	-	Infection	X	
29	Male	6 years old	Secondary	-	Rheumatologic	X	
30	Male	17 years old	Secondary	-	Rheumatologic	X	
31	Female	12 years old	Secondary	-	Rheumatologic	X	
32	Male	3 years old	Secondary	-	Rheumatologic	X	
33	Male	7 years old	Secondary	-	Rheumatologic	X	
34	Female	2 years old	Secondary	-	Rheumatologic	X	
35	Female	19 years old	Secondary	-	Rheumatologic	X*	X*
36	Female	17 years old	Secondary	-	Rheumatologic	X	X
37	Female	15 years old	Secondary	-	Rheumatologic	X	
38	Male	12 years old	Secondary	-	Rheumatologic	X	
39	Female	14 years old	Secondary	-	Rheumatologic	X	
40	Female	15 years old	Secondary	-	Rheumatologic	X	
41	Female	3 years old	Secondary	-	Rheumatologic	X	X
42	Male	9 years old	Secondary	-	Rheumatologic	X*	X*

*Unable to include patient data in all analysis for Flow Panels due to missing data

Supplemental Table 1. Characteristics of patients (n=42) by HLH group and flow data analysis.

Supplemental Data

Patient ID	Gender	Age at Presentation (years)	Type of HLH	Mutation	Infection	Therapy Received	Duration of Therapy (days)
1	F	0	Primary	STXBP2	-	Dexamethasone, IVIG, Emapalumab	35
2	M	0.25	Primary	RAB27A	-	Dexamethasone, IVIG, Etoposide	15
3	F	19	Infection-Associated	-	EBV	Dexamethasone, IVIG	26
4	M	2	Primary	Unknown	-	Dexamethasone, IVIG, Etoposide, Cyclosporine, Emapalumab	47
5	M	5	Primary	IRF3	-	Cyclosporine, Solumedrol	9
6	M	14	Primary	PRF1	-	Dexamethasone, Etoposide	107

Supplemental Table 2. Characteristics of patients (n=6) with longitudinal data from peripheral blood.

Supplemental Data

Target	Clone	Fluorochrome	Catalog	Vendor
CD34	8G12	APC	340667	BD
CD38	HIT2	PerCP-Cy5.5	656050	BD
CD45	2D1	APC-H7	641408	BD
CD19	J3-119	PC7	IM3628U	BC
CD3	SK7	PE-Cy7	341101	BD
CD33	P67.6	APC	340680	BD
CD56	B159	APC	555518	BD
CD16	3G8	V450	644490	BD
CD10	HI10a	PE	555375	BD
CD20	L27	FITC	340673	BD
CD3	UCHT1	PerCP/Cy5.5	300430	BL
CD4	RPA-T4	PE-Cy7	560649	BD
CD38	HIT2	BUV496	612947	BD
CD45RA	HI100	APC	304112	BL
CCR7	G043H7	PE	353204	BL
HLA-DR	G46-6	BV711	563696	BD
CXCR5	J252D4	BV605	356930	BL
CD19	SJ25C1	BUV496	612938	BD
CD27	O323	APC-Cy7	302816	BL
IgD	IA6-2	BV421	348226	BL
Live/Dead	-	Aqua	L3224	Invitrogen
CD10	HI10a	BV421	562902	BD
CD20	2H7	FITC	555622	BD
CD19	HIB19	APC	302212	BL
CD34	561	PE	343606	BL
CD45	HI30	PerCP	304026	BL

BD = Biosciences; BC = Beckman Coulter; BL = BioLegend

Supplemental Table 3. Surface antibodies (all anti-human) used in flow cytometry.

Supplemental Data

Supplemental Table 4. RNA seq data list of upregulated differentially expressed genes.

baseMean	log2FoldChange	lfcSE	stat	pvalue	padj	gene_name	fc
3692.747872	5.514260911	0.173480136	31.78612287	1.01E-221	1.28E-217	GBP1	45.70439223
11317.80009	2.838026242	0.101118352	28.06638161	2.52E-173	1.60E-169	WARS	7.150411363
5357.01885	2.814471517	0.104667791	26.88956645	2.91E-159	1.23E-155	TAP1	7.034615238
3348.910506	3.845930622	0.173759597	22.13362998	1.50E-108	4.75E-105	GBP5	14.37939052
2884.58582	2.374785736	0.119223692	19.91874019	2.80E-88	7.09E-85	APOL6	5.186587868
445.371354	2.832983423	0.154859854	18.29385309	9.26E-75	1.96E-71	HAPLN3	7.12546133
550.5557188	2.405241839	0.134460573	17.88808256	1.46E-71	2.64E-68	LRRK2	5.297243543
2756.095839	2.66183963	0.154362551	17.24407649	1.24E-66	1.96E-63	IRF1	6.328394906
14188.80649	3.230983909	0.194365668	16.62322338	4.73E-62	6.66E-59	STAT1	9.389080703
44341.43623	1.556816694	0.094190415	16.52839821	2.29E-61	2.90E-58	HLA-B	2.942039658
980.9558149	2.531664521	0.154190564	16.41906258	1.40E-60	1.61E-57	APOL3	5.782384406
463.0639283	7.245048038	0.448460548	16.15537435	1.04E-58	1.10E-55	IFI27	151.6969258
2150.455188	2.444885325	0.152195172	16.06414505	4.55E-58	4.43E-55	PSMB9	5.444823656
1811.379561	2.980199666	0.186048187	16.01842899	9.50E-58	8.60E-55	MYOF	7.890953654
933.1988875	2.412799836	0.151768647	15.89788066	6.55E-57	5.53E-54	APOL1	5.325067585
534.7046033	2.810222234	0.185250624	15.16983949	5.60E-52	4.43E-49	ANKRD22	7.013926116
2865.794256	2.820774225	0.194791685	14.48097861	1.60E-47	1.19E-44	GBP4	7.06541462
37877.7846	1.282512905	0.089615747	14.31124487	1.86E-46	1.31E-43	HLA-A	2.432623256
1835.25003	3.678709939	0.258312303	14.24132686	5.08E-46	3.38E-43	LGALS3BP	12.80566207
157.9925909	4.641953147	0.326863704	14.20149464	8.97E-46	5.68E-43	CHAC1	24.96704452
518.91725	3.484006336	0.248696068	14.00909296	1.37E-44	8.27E-42	RARRES3	11.1889778
582.9559231	1.867924459	0.138426792	13.49395175	1.70E-41	9.77E-39	SLAMF8	3.650070827
189.1815389	3.153493997	0.237677782	13.26793766	3.55E-40	1.96E-37	TGM2	8.898079552
712.3574612	1.480026096	0.113276832	13.06556753	5.18E-39	2.73E-36	IFI35	2.789537791
2920.414051	1.890587575	0.153176378	12.34255307	5.34E-35	2.71E-32	UBE2L6	3.707862064
567.0626192	1.519342811	0.12355434	12.29696031	9.40E-35	4.58E-32	BTN3A3	2.866604379
620.796809	2.892474898	0.236676772	12.22120309	2.40E-34	1.12E-31	HBD	7.425431673
365.4390598	2.854219951	0.235595482	12.11491803	8.81E-34	3.98E-31	SDC3	7.231124175
1236.810076	1.330785196	0.110526226	12.04044727	2.18E-33	9.51E-31	JAK2	2.515395397
2308.181304	1.269057161	0.106560009	11.90931916	1.06E-32	4.47E-30	TNFAIP2	2.410040116
720.1578858	2.099009003	0.179952333	11.66425001	1.94E-31	7.93E-29	MT2A	4.284150028
2285.450547	2.589511263	0.222293197	11.6490801	2.32E-31	9.18E-29	GBP2	6.018947625
5051.899455	1.827950668	0.157460076	11.60897869	3.71E-31	1.42E-28	LAP3	3.550323947
2859.691227	1.482800558	0.129067843	11.48853595	1.51E-30	5.61E-28	TAP2	2.794907542
486.079819	2.757327882	0.248444177	11.09837999	1.28E-28	4.62E-26	GCH1	6.761427573
296.340015	2.265152459	0.206720426	10.95756478	6.11E-28	2.15E-25	ANK1	4.807052165
332.7678585	2.93337013	0.272435946	10.76719196	4.92E-27	1.64E-24	IDO1	7.638927664
2084.941549	1.122402628	0.104625626	10.72779844	7.54E-27	2.45E-24	PSTPIP2	2.177092382
5106.231461	1.719241767	0.160557772	10.70793241	9.34E-27	2.96E-24	PSME2	3.292633115
1484.831553	1.159439657	0.108616268	10.67464088	1.34E-26	4.13E-24	ITGB7	2.233706535
25411.20851	1.455956356	0.141267134	10.30640544	6.59E-25	1.99E-22	HLA-C	2.743383583
948.3970072	1.314409902	0.127861265	10.27996945	8.68E-25	2.56E-22	TNFRSF14	2.487005851
744.0692434	1.292510954	0.127506164	10.13685077	3.79E-24	1.09E-21	BTN3A1	2.449540175
110.2071156	3.08446891	0.309767848	9.957356549	2.34E-23	6.59E-21	GRIN3A	8.48237879
7448.281904	1.067204029	0.107909228	9.889831046	4.61E-23	1.27E-20	CYBB	2.095368565
4042.338916	1.21689068	0.127104363	9.573948948	1.03E-21	2.77E-19	PSMB8	2.324452073
1051.841391	2.262042868	0.238048217	9.502456691	2.05E-21	5.41E-19	SLAMF7	4.79670218
790.7440442	1.946369579	0.205943665	9.450980581	3.36E-21	8.68E-19	VAMP5	3.854034749
107.3006964	4.748765557	0.503718976	9.427410491	4.20E-21	1.06E-18	BATF2	26.88567069

2755.161001	1.593074623	0.169181404	9.416369572	4.67E-21	1.16E-18	PARP14	3.016916198
618.8611026	1.99542365	0.212484072	9.390932832	5.95E-21	1.45E-18	SES2	3.987331767
2296.932162	0.808608705	0.086894736	9.305612131	1.33E-20	3.18E-18	SQOR	1.751521509
103.3969935	3.178881322	0.344495935	9.227630867	2.77E-20	6.49E-18	CD274	9.056046225
155.9494578	3.093662339	0.338376249	9.142669875	6.09E-20	1.40E-17	FAM178B	8.536604487
6531.930355	1.540669427	0.171584599	8.979065923	2.73E-19	6.18E-17	TYMP	2.909294668
668.3356029	1.173813741	0.131340288	8.937194801	3.99E-19	8.87E-17	TAGAP	2.256072986
1437.733755	1.009055043	0.113915894	8.857895111	8.15E-19	1.78E-16	CASP1	2.012592432
1220.952336	2.800461825	0.317648752	8.816221724	1.18E-18	2.54E-16	HLA-F	6.966634255
2915.778033	1.139877521	0.129335415	8.81334414	1.21E-18	2.56E-16	PSMB10	2.203623145
237.0972027	2.385859649	0.274302703	8.697907898	3.38E-18	7.02E-16	IL12RB1	5.226552533
62041.19913	1.268568862	0.145878717	8.696051656	3.44E-18	7.02E-16	B2M	2.409224545
2088.860454	1.926062174	0.222206509	8.667892673	4.40E-18	8.85E-16	C1QC	3.8001653
5594.29707	0.990562328	0.115045038	8.610213417	7.29E-18	1.44E-15	PSME1	1.986959309
339.0379774	2.032404071	0.236472506	8.594673884	8.35E-18	1.63E-15	SPTA1	4.090859732
311.6630929	1.346892672	0.157761291	8.537535818	1.37E-17	2.63E-15	IL15RA	2.543636774
1176.970827	1.337742354	0.156988117	8.521296883	1.58E-17	2.95E-15	IFITM1	2.527554769
1600.864044	2.380127156	0.279333074	8.520749514	1.59E-17	2.95E-15	PSAT1	5.205826234
497.2110821	1.552440214	0.182355661	8.513254838	1.69E-17	3.10E-15	KCNH2	2.933128372
234.8295999	2.964435406	0.349083038	8.492063734	2.03E-17	3.67E-15	HBA1	7.805198949
206.3623691	2.386031897	0.281512806	8.475749033	2.34E-17	4.17E-15	CD209	5.227176584
114.5903813	3.174324426	0.379154494	8.372113421	5.66E-17	9.96E-15	AHSP	9.02748693
169.6939307	2.369279932	0.285243216	8.306174511	9.88E-17	1.69E-14	ADD2	5.166831845
809.8366699	1.097218724	0.133731227	8.204656044	2.31E-16	3.91E-14	PRKAR2B	2.139418504
1638.411969	1.069597403	0.130407965	8.201933077	2.37E-16	3.94E-14	CALCOCO2	2.098847583
2680.024069	0.768640801	0.093981392	8.178648785	2.87E-16	4.72E-14	ITGAL	1.703663962
1540.676146	1.077309559	0.132301872	8.142814197	3.86E-16	6.27E-14	TNFSF10	2.11009735
2021.03524	1.155343119	0.141956947	8.138686742	4.00E-16	6.41E-14	PARP9	2.227372914
1980.504069	0.911988355	0.112200492	8.128202819	4.36E-16	6.90E-14	NMI	1.881637027
88.46143294	2.602772663	0.320403961	8.123409756	4.53E-16	7.09E-14	CCND1	6.074529471
11603.39667	1.289517217	0.160373366	8.040719294	8.93E-16	1.38E-13	HLA-E	2.444462405
476.6326537	1.335670389	0.166860407	8.004717323	1.20E-15	1.83E-13	FBXO6	2.52392736
1936.895313	2.335337589	0.292745194	7.97737294	1.49E-15	2.25E-13	C1QB	5.046690415
282.3023973	3.045967865	0.383020379	7.952495572	1.83E-15	2.72E-13	CA1	8.259004321
217.9723351	2.247513056	0.282780451	7.947908175	1.90E-15	2.79E-13	NEXN	4.748635616
90.32199247	3.33901747	0.422364952	7.905526852	2.67E-15	3.88E-13	SLC6A9	10.11915887
3210.827827	1.209106312	0.153045425	7.900310054	2.78E-15	4.00E-13	BST2	2.311943774
656.3776874	1.043159352	0.132600291	7.866946184	3.63E-15	5.17E-13	IGSF6	2.060735512
129.2401977	2.329264996	0.296446162	7.857295175	3.93E-15	5.52E-13	KREMEN1	5.02549253
781.7104394	1.41846985	0.181749112	7.804548987	5.97E-15	8.31E-13	APOL2	2.673018551
1696.868633	2.19230437	0.287049521	7.637373388	2.22E-14	3.05E-12	SAMD9L	4.570349105
215.2840235	2.551125714	0.334764278	7.620662892	2.52E-14	3.44E-12	CD40	5.860914185
1234.175764	1.010969843	0.13345624	7.575290914	3.58E-14	4.79E-12	NUB1	2.015265395
2021.118279	1.19953342	0.158357573	7.574840918	3.60E-14	4.79E-12	LY6E	2.296653832
1500.141825	1.429831465	0.190772723	7.494947098	6.63E-14	8.75E-12	NLRC5	2.694152405
81.34145683	2.925000568	0.390554468	7.489353749	6.92E-14	9.04E-12	HBA2	7.594739957
4267.408012	1.279330013	0.172359142	7.422466807	1.15E-13	1.49E-11	MTHFD2	2.427262287
490.2736229	1.0987303	0.14871717	7.388052783	1.49E-13	1.91E-11	PARP12	2.141661242
125.1442199	2.834519065	0.384214517	7.377438752	1.61E-13	2.02E-11	PKLR	7.133049896
946.1609321	1.192643062	0.161843687	7.369104625	1.72E-13	2.13E-11	ALDH1A1	2.285711092
13246.3887	0.543669456	0.073785991	7.368193464	1.73E-13	2.13E-11	IFI30	1.457675365

668.1363644	1.849207663	0.252069208	7.336110891	2.20E-13	2.68E-11	ASNS	3.603022505
1114.992969	1.046628249	0.143136176	7.312115496	2.63E-13	3.17E-11	CARS	2.065696422
1341.190662	2.303248976	0.315960108	7.289682841	3.11E-13	3.71E-11	C1QA	4.935680391
116.9401053	2.330342236	0.320380637	7.273667516	3.50E-13	4.14E-11	SOCS1	5.029246393
1693.323529	1.817123375	0.249985054	7.268928069	3.62E-13	4.25E-11	SERPING1	3.523778827
640.7433359	1.714566977	0.236083329	7.26254999	3.80E-13	4.41E-11	DDX60	3.281981204
614.5755496	1.026543142	0.141383185	7.260715894	3.85E-13	4.43E-11	LILRB1	2.037137191
1454.516601	2.107063531	0.291358684	7.231854241	4.76E-13	5.44E-11	XAF1	4.308135215
134.3509586	1.707458848	0.236763394	7.211667405	5.53E-13	6.25E-11	CDH1	3.265850721
3991.581952	0.928030613	0.131215917	7.072546025	1.52E-12	1.69E-10	SLC1A5	1.902676926
1844.200824	0.688737647	0.09816868	7.015859327	2.29E-12	2.47E-10	AGPAT3	1.611872519
327.0803216	1.546650726	0.222011632	6.966530131	3.25E-12	3.49E-10	GALM	2.921381409
438.0213608	1.404075924	0.201986898	6.951321778	3.62E-12	3.82E-10	PMAIP1	2.646482152
2503.687848	0.97782932	0.141290431	6.920704467	4.49E-12	4.70E-10	SLC3A2	1.969499867
478.6437968	1.484090183	0.216285074	6.861731876	6.80E-12	7.01E-10	STX11	2.797407027
182.2631388	1.826075591	0.267089929	6.836931655	8.09E-12	8.26E-10	GIMAP5	3.545712572
525.3041342	1.050255835	0.153961046	6.821568568	9.01E-12	9.12E-10	RHOBTB3	2.070897051
411.3743198	2.194252996	0.322065256	6.813069577	9.55E-12	9.60E-10	ALDH1L2	4.576526377
725.1887929	2.159783363	0.319042492	6.76957903	1.29E-11	1.29E-09	CALHM6	4.468477509
56.64762243	2.292540298	0.338968141	6.763291356	1.35E-11	1.33E-09	KEL	4.89918
1085.826121	0.848649942	0.125844948	6.74361549	1.54E-11	1.52E-09	SCPEP1	1.800814954
1821.25472	0.855131308	0.127057473	6.730271667	1.69E-11	1.65E-09	CD38	1.808923388
1262.575508	0.637410177	0.095343847	6.685383461	2.30E-11	2.23E-09	RBCK1	1.555534268
77.37478516	2.839915122	0.425601051	6.672716417	2.51E-11	2.41E-09	ASS1	7.159779325
4369.944939	1.364470157	0.206246346	6.615730074	3.70E-11	3.52E-09	FGL2	2.57481746
366.4186507	1.77932865	0.270479557	6.578421943	4.75E-11	4.49E-09	GBP3	3.432664003
1882.351076	0.607302604	0.092664957	6.553746101	5.61E-11	5.26E-09	PAK1	1.52340824
1221.031305	0.890582459	0.136990292	6.501062577	7.98E-11	7.37E-09	MOV10	1.853924458
549.7921011	0.820606892	0.12679837	6.471746364	9.69E-11	8.89E-09	CASP7	1.766148795
3581.031215	0.834228001	0.129782936	6.427871229	1.29E-10	1.18E-08	AARS	1.782902736
2068.452773	1.015903811	0.159587774	6.365799734	1.94E-10	1.76E-08	DTX3L	2.022169333
302.9848172	1.400071313	0.219999515	6.36397454	1.97E-10	1.77E-08	KLF1	2.639146272
4241.672068	0.97413758	0.153596116	6.342201927	2.27E-10	2.02E-08	SLC7A5	1.96446652
79.8746359	2.143818271	0.339984731	6.305631043	2.87E-10	2.54E-08	SAMD4A	4.419301227
910.0596112	0.731834456	0.117775971	6.213784092	5.17E-10	4.52E-08	DNPEP	1.660749473
4473.579208	0.533033136	0.086378988	6.170865735	6.79E-10	5.89E-08	ATP6V1B2	1.446968119
716.8603745	1.967611394	0.319424674	6.159860387	7.28E-10	6.27E-08	CCL2	3.911200226
1250.259279	0.89786778	0.146020067	6.148934165	7.80E-10	6.68E-08	XRN1	1.863310082
372.9944665	1.050996513	0.171014667	6.145651309	7.96E-10	6.77E-08	TMEM268	2.07196052
325.759042	1.063836397	0.173942474	6.116024307	9.59E-10	8.10E-08	ARAP2	2.090483125
1433.255426	0.60874416	0.099567091	6.113909253	9.72E-10	8.15E-08	LRRC8D	1.524931205
987.9039917	1.643766078	0.269916774	6.089899695	1.13E-09	9.41E-08	SECTM1	3.124804817
45.30014517	2.557291791	0.422304771	6.055559788	1.40E-09	1.15E-07	TMEM56	5.886017333
315.1663809	0.947015506	0.156401335	6.055034679	1.40E-09	1.15E-07	VPS9D1	1.927880336
1449.825568	1.075848297	0.179508403	5.993303268	2.06E-09	1.68E-07	IGF2R	2.107961177
1867.186504	0.795724494	0.132802928	5.991769191	2.08E-09	1.69E-07	MVP	1.735948916
539.2356008	3.610861964	0.60744087	5.944384287	2.77E-09	2.24E-07	APOL4	12.21737098
1361.073316	1.378755144	0.235314776	5.859194936	4.65E-09	3.71E-07	PCK2	2.600438907
295.294276	1.07229264	0.183839433	5.832767332	5.45E-09	4.32E-07	SLC4A5	2.102772307
866.4133694	1.017085512	0.17617703	5.773088077	7.78E-09	6.05E-07	PARP10	2.023826355
1420.15473	0.66868646	0.116020152	5.763537183	8.24E-09	6.36E-07	LY75	1.589624992

163.1104339	1.700440398	0.295542249	5.753628816	8.73E-09	6.71E-07	RTP4	3.250001532
1067.02734	2.823571516	0.49110476	5.749428115	8.95E-09	6.83E-07	EPST11	7.079127286
7682.268249	0.736234575	0.128408897	5.733516863	9.84E-09	7.46E-07	ATF4	1.665822374
630.2726571	0.803514657	0.14047073	5.720157183	1.06E-08	7.98E-07	TIFA	1.745347924
1369.815261	0.63695634	0.111382046	5.718662572	1.07E-08	8.00E-07	LRRC8C	1.555045011
1164.518355	0.66104284	0.116446202	5.676808957	1.37E-08	1.02E-06	ANKRD44	1.581225187
129.4863649	1.911579333	0.33722924	5.668486322	1.44E-08	1.06E-06	ATF3	3.76220727
100.0897824	2.873530481	0.510858554	5.624904303	1.86E-08	1.35E-06	ADM2	7.32856372
294.1972632	1.236501202	0.219909378	5.622776131	1.88E-08	1.36E-06	ST3GAL5	2.35626402
1487.111657	0.559197734	0.10004875	5.589252607	2.28E-08	1.62E-06	EFR3A	1.473449621
139.9273025	1.357946548	0.242980973	5.588695003	2.29E-08	1.62E-06	KCNMB1	2.56320088
2509.903544	0.877761064	0.157785206	5.563012447	2.65E-08	1.87E-06	TRIM22	1.837521416
53.05345407	2.275193077	0.410433474	5.543390644	2.97E-08	2.08E-06	MT1E	4.840624138
1250.176389	0.582931392	0.106563634	5.470265713	4.49E-08	3.13E-06	RNF41	1.4978897
185.9882589	1.175220337	0.215315865	5.45812236	4.81E-08	3.33E-06	MDK	2.258273681
87.74398228	2.366037872	0.435010609	5.439034874	5.36E-08	3.67E-06	LAG3	5.15523385
33.88549763	2.694299743	0.500765483	5.380362329	7.43E-08	5.06E-06	SSPN	6.472395389
1442.254769	0.773747546	0.144361444	5.359793625	8.33E-08	5.60E-06	CIITA	1.709705152
229.4925543	2.212675769	0.412863251	5.359342985	8.35E-08	5.60E-06	C2	4.635341945
856.804219	1.211208535	0.226725857	5.342172045	9.18E-08	6.12E-06	IRF9	2.315315079
106.2791777	1.201717008	0.225184722	5.33658321	9.47E-08	6.28E-06	AIFM2	2.30013256
4315.495698	1.241905581	0.233710859	5.313854846	1.07E-07	7.08E-06	RNF213	2.365107209
814.8747725	1.124388704	0.212791178	5.284000562	1.26E-07	8.29E-06	FCGR1B	2.180091525
39.18805247	3.041076529	0.576308765	5.276818114	1.31E-07	8.58E-06	SELENBP1	8.231050277
1341.763637	0.714472122	0.135515566	5.272251318	1.35E-07	8.71E-06	CYLD	1.640882713
29.47916584	2.736626067	0.520608294	5.256593288	1.47E-07	9.44E-06	SIGLEC11	6.665097901
698.1080457	1.64402395	0.313386396	5.245996535	1.55E-07	9.89E-06	P2RX7	3.125363403
288.2585723	0.91931468	0.175525432	5.237501296	1.63E-07	1.03E-05	SLC7A7	1.8912167
251.4877849	1.022280732	0.195291361	5.234643899	1.65E-07	1.04E-05	CAMK2D	2.031127397
2656.883455	0.631287697	0.121361733	5.201703063	1.97E-07	1.24E-05	ERAP1	1.54894691
1484.394695	3.015271909	0.580578228	5.193566972	2.06E-07	1.29E-05	NCF1	8.08513526
97.67416903	1.371229347	0.264986284	5.174718195	2.28E-07	1.42E-05	C5orf56	2.586909075
236.1224053	1.244498439	0.241700088	5.148936634	2.62E-07	1.61E-05	GATA1	2.369361677
131.399158	1.759246642	0.342064651	5.143023805	2.70E-07	1.65E-05	ISG20	3.385213071
149.9020728	1.086144913	0.211832795	5.127369037	2.94E-07	1.77E-05	CXCR2	2.123059661
101.0230418	1.637654335	0.319492679	5.125796116	2.96E-07	1.77E-05	TNF	3.111595088
796.2015692	0.710924448	0.13892404	5.117360866	3.10E-07	1.84E-05	TRIM21	1.636852641
732.8056511	0.59311361	0.115912102	5.11692568	3.11E-07	1.84E-05	VRK2	1.508498864
365.1823583	0.918898636	0.179726541	5.112759803	3.17E-07	1.87E-05	APOBEC3G	1.89067139
65.98619263	1.715280392	0.337491999	5.082432757	3.73E-07	2.17E-05	CYSLTR2	3.283604552
629.2870056	1.444605917	0.284464941	5.07832675	3.81E-07	2.20E-05	ICAM1	2.721884628
2765.089898	0.645739424	0.127555771	5.06240852	4.14E-07	2.37E-05	TGFB1	1.564540954
94.20837997	1.793312726	0.354819015	5.054161841	4.32E-07	2.47E-05	SPTB	3.466098674
350.216898	0.763267462	0.151399509	5.041413059	4.62E-07	2.62E-05	KIF21B	1.697330443
129.6182449	2.771815286	0.552624463	5.015730343	5.28E-07	2.99E-05	FLT1	6.829667229
270.0395196	0.982283063	0.196406593	5.001273372	5.70E-07	3.21E-05	TUBE1	1.975589305
2429.766702	0.630205615	0.126098405	4.997728671	5.80E-07	3.25E-05	POMP	1.547785571
3053.638786	0.749169495	0.149992636	4.994708504	5.89E-07	3.29E-05	GARS	1.680824965
309.606541	1.380449415	0.276578851	4.99116042	6.00E-07	3.33E-05	GIMAP7	2.603494601
85.2595836	1.880123568	0.377109496	4.985617141	6.18E-07	3.40E-05	RHAG	3.681065876
786.0329489	0.786780655	0.158585696	4.961233432	7.00E-07	3.84E-05	JDP2	1.72522037

193.2052586	1.117346841	0.226835118	4.925810659	8.40E-07	4.55E-05	KMO	2.169476323
1507.580221	0.441097499	0.089585948	4.923735379	8.49E-07	4.58E-05	PATL1	1.357636728
334.0975521	0.989267846	0.201393907	4.912104159	9.01E-07	4.83E-05	SCIMP	1.985177277
169.3653363	1.123977849	0.228932193	4.909653976	9.12E-07	4.84E-05	IGF2BP3	2.179470761
833.4989185	0.521724674	0.106270688	4.909393975	9.14E-07	4.84E-05	RBM47	1.435670499
28.95245973	2.537414484	0.517073616	4.907259637	9.24E-07	4.87E-05	EPB42	5.805476497
455.4359314	1.483886849	0.303196519	4.894142098	9.87E-07	5.19E-05	OPTN	2.797012786
159.7246095	1.409329593	0.288074682	4.892236921	9.97E-07	5.22E-05	TCN2	2.656137059
1004.075417	3.01965911	0.620339693	4.867750919	1.13E-06	5.88E-05	KLHDC7B	8.109759384
301.3793204	0.845219155	0.174278038	4.849831711	1.24E-06	6.41E-05	FAM43A	1.796537631
2550.170655	0.765574442	0.157948469	4.846988673	1.25E-06	6.48E-05	PHGDH	1.700046776
583.0516947	0.896169296	0.184963216	4.845121722	1.27E-06	6.51E-05	SLC8A1	1.861117699
377.7043557	1.291473886	0.266795634	4.840685989	1.29E-06	6.61E-05	APOC1	2.447779979
1986.415068	0.536403146	0.111225799	4.82265041	1.42E-06	7.18E-05	LCP2	1.450352062
1636.65389	0.505043746	0.104912041	4.813973151	1.48E-06	7.47E-05	SARS	1.419166388
2114.196706	0.512123088	0.107284031	4.773525778	1.81E-06	9.06E-05	ADGRE5	1.426147389
1718.415488	0.770832795	0.161605177	4.769852104	1.84E-06	9.16E-05	PLEKHO1	1.706254434
2122.751622	2.594477308	0.543942365	4.769765098	1.84E-06	9.16E-05	HBB	6.039701749
1319.964057	0.755751266	0.158677782	4.762804586	1.91E-06	9.45E-05	GPT2	1.688510634
661.5624984	0.785553329	0.16564196	4.742477856	2.11E-06	0.000103645	GIMAP2	1.723753319
354.8747925	1.621471503	0.345430968	4.69405367	2.68E-06	0.000128504	FCGR3A	3.07688709
199.752797	1.049879793	0.225579661	4.654142091	3.25E-06	0.000152897	CAPRIN2	2.070357336
427.5807794	0.891155783	0.191491371	4.653764692	3.26E-06	0.000152897	ETV5	1.85466135
1608.827553	0.596311047	0.128203912	4.651270299	3.30E-06	0.000154187	UBA7	1.511845849
2075.786107	0.561690998	0.120907318	4.645632754	3.39E-06	0.000157876	DOCK10	1.475998237
1110.856559	0.538969458	0.11661305	4.621862302	3.80E-06	0.000175164	AIDA	1.452934291
7791.932155	0.546247323	0.118262905	4.618923591	3.86E-06	0.000177019	CTSZ	1.460282327
3681.007196	0.575698134	0.124975408	4.606491344	4.10E-06	0.000185913	TAPBP	1.490398507
4752.605702	1.044774556	0.227268902	4.597085414	4.28E-06	0.000193809	IFITM3	2.063043949
120.3670472	1.361979054	0.296921959	4.58699336	4.50E-06	0.00020269	CFH	2.570375357
104.4404173	1.335069254	0.291320465	4.582819993	4.59E-06	0.000206046	GPR84	2.52287592
351.5746547	1.01486937	0.221543303	4.580907469	4.63E-06	0.000206531	SCO2	2.020719917
1288.945939	0.538764773	0.117612397	4.580850213	4.63E-06	0.000206531	LPGAT1	1.452728168
431.5865069	0.695978347	0.152080258	4.57638852	4.73E-06	0.000210243	RHBDD1	1.619982633
4715.543716	0.575870199	0.125977489	4.5712151	4.85E-06	0.00021414	PSMA4	1.490576271
1625.446489	0.662697967	0.145028636	4.569428387	4.89E-06	0.000215083	CASP4	1.583040282
551.3427848	1.040284301	0.228041155	4.561827012	5.07E-06	0.000221482	CMPK2	2.056632898
493.7529139	0.557805479	0.122575475	4.550710328	5.35E-06	0.000232711	AP1AR	1.472028372
2519.986831	0.724014937	0.159144587	4.549416043	5.38E-06	0.000233345	CLIC4	1.651772432
2132.810947	0.511584888	0.112902813	4.531197002	5.87E-06	0.000253538	NCF2	1.42561546
980.2565966	0.611631969	0.135584294	4.511082739	6.45E-06	0.000275059	TRAFD1	1.527986682
205.6901983	0.85113442	0.189424402	4.493267028	7.01E-06	0.000298113	RILP	1.803918825
701.5437025	0.727625618	0.162173026	4.486724048	7.23E-06	0.000305363	SP110	1.655911555
413.0592358	1.334277573	0.298123437	4.475587646	7.62E-06	0.000320654	ODF3B	2.521491869
2624.483726	0.60060588	0.134230292	4.474443668	7.66E-06	0.000321308	NFE2L1	1.516353247
37.07547993	2.0643248	0.461670713	4.471422473	7.77E-06	0.000324806	ALAS2	4.182381892
1757.260135	0.415867632	0.093086436	4.467542756	7.91E-06	0.000329663	RAD23A	1.334100759
24.82989577	2.284079418	0.512704904	4.454959178	8.39E-06	0.000348457	SLC2A14	4.870532181
94.70508246	1.763573096	0.395944912	4.454087024	8.43E-06	0.000348733	XK	3.39538012
858.3878088	0.509677467	0.114535239	4.449962054	8.59E-06	0.00035434	LHFPL2	1.423731867
1612.275934	0.47687864	0.107294854	4.444562078	8.81E-06	0.000362178	SCARB2	1.391729314

198.65888	0.986244085	0.222329966	4.435947623	9.17E-06	0.00037575	EPOR	1.981020878
258.3320804	0.759388913	0.171710152	4.422504459	9.76E-06	0.000397343	MYH10	1.692773459
1085.537307	0.448542414	0.101452169	4.421220536	9.81E-06	0.000397718	CEP55	1.364660813
339.8718801	1.117841814	0.25285299	4.420915933	9.83E-06	0.000397718	FAM92A	2.170220774
1066.701102	0.564842655	0.127866004	4.417457622	9.99E-06	0.000402846	PCGF5	1.479226172
2431.304871	0.367092998	0.083308041	4.406453383	1.05E-05	0.000422509	FAM111A	1.289751387
312.9589719	0.717022608	0.162920265	4.401064585	1.08E-05	0.000431771	DNAJA4	1.643786134
2425.324313	0.87084982	0.198098027	4.396054997	1.10E-05	0.000440457	STAT2	1.828739803
563.5962489	1.188006481	0.270656004	4.389359427	1.14E-05	0.00045281	SLC7A11	2.27837699
1398.249161	0.521827614	0.119134248	4.380164598	1.19E-05	0.000470864	HAX1	1.435772942
915.3134358	0.792311138	0.181634039	4.362129157	1.29E-05	0.000509818	CCDC50	1.731846588
609.2319453	0.580708745	0.133173423	4.360545325	1.30E-05	0.000511922	DDHD1	1.495583796
224.2151485	0.888691794	0.204184884	4.352387787	1.35E-05	0.000529702	IGFBP4	1.851496464
291.1791163	0.668315577	0.153597368	4.351087419	1.35E-05	0.000531204	B3GALNT1	1.589216389
125.2584531	1.519970834	0.349386406	4.350400613	1.36E-05	0.000531225	AKR1C1	2.867852518
397.0262382	0.685069715	0.157664654	4.345106513	1.39E-05	0.000542526	USP6NL	1.607779672
3873.195513	0.387778719	0.089335871	4.340683258	1.42E-05	0.000551866	EPRS	1.308377377
66.93281073	1.307846167	0.301445135	4.338587735	1.43E-05	0.00055545	SIGLEC16	2.475716584
612.807663	1.149037422	0.26512558	4.333936473	1.46E-05	0.000565593	TRIB3	2.217658811
3903.896517	0.408509751	0.094369694	4.328823511	1.50E-05	0.000577123	DOCK8	1.327314041
1185.260188	0.42677974	0.099270995	4.299138339	1.71E-05	0.000655596	USP25	1.344229751
2465.410392	0.821801008	0.191176684	4.298646618	1.72E-05	0.000655596	FCGR1A	1.767611237
528.6342715	0.527664033	0.122823518	4.296115595	1.74E-05	0.000661131	MFSD6	1.441593122
317.8954651	1.039418723	0.243054547	4.276483354	1.90E-05	0.000720023	IL18BP	2.055399345
803.9927338	0.47726202	0.111697746	4.272799023	1.93E-05	0.000729843	APOBEC3C	1.3920992
1088.143781	0.452219258	0.10598997	4.266623143	1.98E-05	0.000748101	DECR1	1.368143216
570.9267879	0.607849491	0.142541478	4.264369214	2.00E-05	0.000753449	HTATIP2	1.523985832
41.53112148	1.512918146	0.35542188	4.256682641	2.07E-05	0.000777507	BATF3	2.853867088
888.7017809	0.423238543	0.099462819	4.255243775	2.09E-05	0.000780216	SETD7	1.34093429
950.4964936	0.453254613	0.106558222	4.253586493	2.10E-05	0.000783704	HLA-DOA	1.369125421
57.39855072	2.546925095	0.59891058	4.252596598	2.11E-05	0.000784869	HBG2	5.843874092
147.1902479	1.621597899	0.383824415	4.224843012	2.39E-05	0.000880388	CSF1	3.077156671
1848.276428	0.442296835	0.104766979	4.221719834	2.42E-05	0.000890091	CDT1	1.358765822
80.22743456	1.374541274	0.325732562	4.219846071	2.44E-05	0.000894927	TMEM150B	2.592854542
111.1214355	1.143937733	0.271166255	4.218584394	2.46E-05	0.000897355	L3MBTL4	2.209833359
544.1766481	0.756238215	0.17947989	4.213498319	2.51E-05	0.000915166	IFRD1	1.68908065
56.83406223	1.809605445	0.431042263	4.19820885	2.69E-05	0.000970823	IL15	3.505464064
1049.783097	0.995430448	0.237206467	4.196472639	2.71E-05	0.000975513	SNX10	1.993675277
260.7114415	0.890077911	0.212215493	4.194217385	2.74E-05	0.000979702	TFR2	1.853276205
1073.607869	0.591350151	0.141528298	4.178317409	2.94E-05	0.001044475	GPCPD1	1.506656097
643.9039062	1.283230379	0.307204232	4.177124678	2.95E-05	0.001044475	SIGLEC1	2.433833336
878.8230564	0.567609226	0.135937697	4.175510106	2.97E-05	0.001048981	MR1	1.482065518
578.4432303	0.775670176	0.185960515	4.171155226	3.03E-05	0.001065693	GIMAP6	1.711985136
1662.027525	0.506721333	0.121497112	4.170645071	3.04E-05	0.001065693	OGFR	1.420817575
67.06682617	1.210229278	0.290613478	4.164394874	3.12E-05	0.001092283	TUBB2A	2.313744046
418.2427624	0.663013021	0.159272735	4.162752775	3.14E-05	0.00109714	HVCN1	1.583386022
38.86082744	1.879174536	0.453708923	4.141806429	3.45E-05	0.001192477	GPT	3.678645197
288.5856189	0.705385816	0.17040787	4.13939694	3.48E-05	0.001201786	CLIC2	1.630580668
274.7492881	1.401623026	0.340607601	4.115066788	3.87E-05	0.001332227	IFIT5	2.641986375
94.97161897	1.025106001	0.249934459	4.101499266	4.10E-05	0.001401392	PBK	2.035108907
245.3353936	0.870925204	0.212559167	4.097330708	4.18E-05	0.001415414	GFI1B	1.828835361

82.41676258	1.148078258	0.280362819	4.094973294	4.22E-05	0.001422288	ABCB4	2.216184908
440.7375548	0.696182756	0.17026896	4.088723837	4.34E-05	0.001457272	ARHGEF3	1.620212177
68.68166556	1.361612316	0.335446514	4.059104089	4.93E-05	0.001637649	ARHGEF5	2.569722041
2399.098128	0.557800924	0.137458983	4.057944505	4.95E-05	0.001641491	SLC7A1	1.472023725
5838.024544	0.543077991	0.134081303	4.050363311	5.11E-05	0.00168238	PRDX1	1.457077881
24.27482376	2.397524349	0.592460675	4.046723183	5.19E-05	0.001704319	CEACAM1	5.268982356
2035.616904	0.390497036	0.09668324	4.038932022	5.37E-05	0.001757371	WDFY1	1.310844937
533.654157	0.798505172	0.197780163	4.037337019	5.41E-05	0.001764797	TRIB2	1.739298043
317.4960481	0.687534447	0.170625128	4.029502888	5.59E-05	0.001819962	FAM117B	1.610528786
168.2788651	1.038253316	0.261274437	3.973803663	7.07E-05	0.002291343	ASPHD2	2.053739667
1264.958903	0.806916645	0.203312081	3.968857343	7.22E-05	0.00232161	DAPP1	1.749468447
123.4143395	0.860248253	0.216953695	3.965123775	7.34E-05	0.002352281	SNTB2	1.815350661
867.4218287	0.3929305	0.099723151	3.940213452	8.14E-05	0.002584247	ZCCHC8	1.313057869
727.4466014	0.660445254	0.169267691	3.901779771	9.55E-05	0.002994537	LIMK1	1.580570354
229.7926802	0.633315338	0.162317322	3.901711358	9.55E-05	0.002994537	APOBEC3F	1.551125414
2250.355602	0.511127885	0.131204617	3.895654727	9.79E-05	0.003062789	EIF4EBP1	1.42516394
2832.061239	0.546026003	0.140285389	3.892251396	9.93E-05	0.003098436	CUL1	1.460058326
157.3512951	0.754656339	0.194259095	3.884792818	0.000102417	0.003179451	TTBK2	1.687229633
62.49960299	1.926512404	0.49679407	3.877889291	0.000105367	0.003263017	TNXB	3.801351422
875.3300286	1.015689579	0.262421133	3.8704565	0.000108632	0.003344344	IL1RN	2.021869074
583.9053402	0.976432327	0.252333715	3.869607074	0.000109011	0.003344344	IFIH1	1.967593681
273.548317	0.889946534	0.229988751	3.869522004	0.000109049	0.003344344	PTK2	1.853107447
4452.216178	0.421485187	0.1090094	3.866503154	0.000110407	0.003369676	SHMT2	1.339305598
3565.656737	0.458129013	0.119039181	3.848556505	0.000118816	0.003617601	LYN	1.373759076
1432.569269	1.84703589	0.481672032	3.834633874	0.000125751	0.003819588	IFI6	3.597602745
921.4568335	0.463004518	0.120985444	3.826944001	0.000129744	0.00393143	NDC80	1.37840947
142.0219931	1.526635588	0.399101329	3.825182921	0.000130675	0.003950191	CLCN4	2.881131658
114.847774	1.030710479	0.26972868	3.821286182	0.000132757	0.004003587	GDPD5	2.043030127
94.95444236	1.860074774	0.488817874	3.805251144	0.00014166	0.004241774	ADAMTS14	3.63026477
3764.806609	0.414545967	0.10918034	3.796892062	0.000146522	0.004376986	EIF2S2	1.332879138
626.4126904	0.514239287	0.136187877	3.775954943	0.000159396	0.00472812	TRAK2	1.42824085
1756.658261	0.492895363	0.130626569	3.773316302	0.000161092	0.004767265	PML	1.407266304
18.70002316	2.277223499	0.604200202	3.768988315	0.000163911	0.004839373	PLEK2	4.847441539
580.6465782	0.545632479	0.145145611	3.759207575	0.000170452	0.005020813	HEG1	1.459660121
339.4982711	1.256170722	0.336805183	3.729665645	0.000191734	0.005569961	SMPDL3A	2.388609015
82.48254187	1.033762134	0.277736282	3.722099703	0.000197573	0.005713377	GPR18	2.047356212
54.36869401	1.189429909	0.319945906	3.717596906	0.000201127	0.005802899	KLF5	2.280626048
61.02292504	1.675866568	0.451011427	3.715796243	0.000202565	0.005817881	ASB2	3.195112142
361.4321517	0.831975973	0.224081044	3.712835136	0.00020495	0.005873081	CTSO	1.78012182
757.1419035	0.556085392	0.149837771	3.711249769	0.000206238	0.005896651	TRIM56	1.470274358
31.22021432	2.036497191	0.550140878	3.701773983	0.000214097	0.006093835	NEO1	4.102482533
1025.087808	0.533608264	0.144371308	3.696082484	0.000218952	0.006218037	DESI1	1.447545066
438.4412512	0.502905255	0.136449123	3.685661309	0.00022811	0.006463614	SLC9A7	1.417064331
1162.710101	0.438811697	0.119294544	3.678388643	0.000234712	0.006635857	CCZ1B	1.355487395
226.8868091	1.043867621	0.284121211	3.67402214	0.000238762	0.006735323	ASCL2	2.061747447
670.0407978	0.642956118	0.175596415	3.661556054	0.000250688	0.007040386	FGD2	1.561525488
485.0148363	1.040661393	0.286017466	3.638454	0.00027428	0.007652039	TAPBPL	2.057170532
301.8778094	0.774638994	0.213364065	3.630597284	0.000282766	0.007871462	TNKS1BP1	1.710761914
39.23895897	1.554239251	0.428301996	3.628839614	0.000284698	0.007907863	RHEBL1	2.936788257
1456.977557	0.434337095	0.119876158	3.623215003	0.000290964	0.008031251	CMIP	1.351289785
197.4803828	1.073694614	0.296342548	3.623153748	0.000291033	0.008031251	CD276	2.10481672

241.9451309	0.745099347	0.205715554	3.621988378	0.000292347	0.008049718	PDE4B	1.676089685
266.278496	1.272836577	0.351993427	3.616080528	0.000299097	0.008199929	BCL2A1	2.416361955
387.8716227	2.283776197	0.633533662	3.604822182	0.000312367	0.008526804	GIMAP4	4.869508616
816.1559228	0.483937923	0.134330896	3.602580909	0.000315073	0.00858219	PRIM1	1.398555903
1139.034381	1.147409667	0.319227368	3.594333638	0.000325223	0.00876441	BTN3A2	2.215158096
233.8137313	0.659902056	0.183723472	3.591822251	0.000328374	0.008830536	BTN2A2	1.579975357
161.9713721	0.704523651	0.196299941	3.589016106	0.000331928	0.008907213	AKAP7	1.629606512
1758.865395	0.58601353	0.163421335	3.585905894	0.00033591	0.008975673	ITPR1	1.501093175
329.8052628	0.517868144	0.144439397	3.58536628	0.000336605	0.008975673	AMMECR1	1.431837871
608.7642137	0.553358661	0.154386656	3.584238909	0.000338063	0.008995589	CASP10	1.467498126
585.8727665	0.481888111	0.134849791	3.573517682	0.000352217	0.009352592	RARA	1.396570217
1142.362707	0.422804414	0.118370038	3.571887119	0.000354418	0.00939134	SUSD6	1.340530844
39.788183	1.327659386	0.372896605	3.560395478	0.000370297	0.009771204	RAB39A	2.509951325
473.5454838	0.500476721	0.140688329	3.557343556	0.000374624	0.009864841	ADAMDEC1	1.41468095
82.83966681	1.655903442	0.467505792	3.541995562	0.000397112	0.010392195	DUSP5	3.15120463
117.4076646	1.503915557	0.424679833	3.541292616	0.000398172	0.010398439	TMOD1	2.836114065
454.6121556	0.460409057	0.130247023	3.534891217	0.000407943	0.010631701	TPD52	1.37593189
1215.422377	0.515738853	0.146388791	3.523076106	0.000426569	0.011077131	EPG5	1.429726163
441.02109	0.544659684	0.154810161	3.518242483	0.000434415	0.011252154	PYCR1	1.458676218
1062.94409	0.583666402	0.166022995	3.515575675	0.000438802	0.011342576	ZNFX1	1.498653025
43.82371578	2.592200245	0.738221775	3.511411247	0.000445734	0.01149831	SLC4A1	6.030176563
489.0595568	1.050437801	0.300011088	3.501329924	0.000462942	0.011893768	IFI44	2.071158267
879.8297821	0.515094106	0.147184139	3.499657712	0.000465856	0.011944395	SIAH2	1.429087355
33752.65877	0.273586213	0.078298807	3.494130014	0.000475609	0.012145298	LCP1	1.208808921
1298.79759	0.474260856	0.135802741	3.492277496	0.00047892	0.012205244	LMO4	1.389206298
400.7617634	0.520505791	0.149068855	3.491713886	0.000479932	0.012206464	CYB561	1.434458063
485.6257614	0.700942723	0.201006518	3.48716415	0.000488172	0.012391146	ABI3	1.625566665
12332.07137	0.689882789	0.198243771	3.479972088	0.000501466	0.012652527	HLA-DPA1	1.613152453
535.3044439	0.617035292	0.177502205	3.476211981	0.00050855	0.012780349	DYNLT1	1.533720178
31.89996303	2.426979183	0.69830436	3.475532048	0.000509841	0.01278742	UBXN10	5.377662381
773.7952443	0.394779798	0.113674986	3.472881878	0.000514902	0.012888829	AKIRIN2	1.314742073
129.0891545	4.507965907	1.300108139	3.467377654	0.000525563	0.013108439	CXCL10	22.75270089
1118.847988	0.476483424	0.137422649	3.467284518	0.000525745	0.013108439	FANCA	1.391348112
456.6381657	0.53616661	0.154814168	3.463291629	0.00053361	0.01327839	CDC42BPA	1.45011429
768.4483051	0.369514448	0.10671301	3.462693513	0.000534797	0.013281846	RIPOR2	1.29191795
69.32967103	2.480625686	0.716681516	3.461266451	0.00053764	0.013326327	TNFAIP6	5.581394751
41.71814886	1.637861912	0.473914818	3.456025958	0.000548203	0.013561588	EPCAM	3.112042823
482.3573877	0.456247507	0.132144719	3.452635197	0.000555139	0.013685861	SFXN3	1.371968642
1074.530863	0.396377738	0.114808412	3.452514777	0.000555387	0.013685861	LIMK2	1.316199098
29.22471353	3.582002345	1.037760303	3.451666376	0.000557136	0.013702304	INHBA	11.97540336
28.40089654	1.779108754	0.515534094	3.451001155	0.000558511	0.013709501	SLC16A9	3.432140836
567.6939497	0.572148167	0.166006691	3.446536783	0.000567821	0.013911072	LRRCC1	1.486735667
72.60094997	0.987231027	0.286491818	3.445930969	0.000569096	0.013915379	SLC49A3	1.98237655
25.04052145	1.959658778	0.569958831	3.438246186	0.000585495	0.014261117	HBG1	3.889699699
61.9847641	1.291627286	0.375721023	3.437729613	0.000586613	0.014261117	FN3K	2.448040262
2803.469277	0.440046612	0.128290461	3.430080514	0.000603402	0.014557508	PSMA2	1.356648159
3165.866962	0.330511878	0.096408462	3.428245537	0.000607496	0.014628405	TARS	1.257459451
215.917756	0.687580091	0.200659963	3.426593335	0.000611204	0.014689764	TMCO4	1.61057974
1605.854142	0.344341842	0.100518142	3.425668598	0.000613288	0.01469985	SNX6	1.269571672
1020.455296	0.403248711	0.117723855	3.425378054	0.000613944	0.01469985	ELK3	1.322482573
1106.110758	0.420909642	0.123135179	3.41827286	0.000630199	0.015060566	BBX	1.338771405

1950.021059	0.301907545	0.088725966	3.402696632	0.000667243	0.015907968	GLS	1.23277332
205.6658489	0.719035256	0.211384841	3.401545973	0.000670059	0.015923005	BANK1	1.646080917
2732.595839	0.47615448	0.140007983	3.400909507	0.000671621	0.015930236	WSB1	1.391030912
48.52145298	1.165275296	0.34435984	3.383888482	0.00071467	0.01687041	GNGT2	2.242760081
420.982775	0.463037291	0.13684493	3.383664194	0.000715254	0.01687041	RIMKLB	1.378440783
2124.017867	0.382749284	0.113212839	3.380793969	0.000722767	0.017015927	PRPS2	1.303824133
2323.81962	0.333522129	0.098713884	3.378674977	0.000728361	0.01711158	CSNK1A1	1.260085938
339.5495619	0.960546779	0.284561991	3.375527337	0.000736744	0.017280733	GIMAP8	1.946047304
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555.9520698	0.466105691	0.140929077	3.30737773	0.000941738	0.021224297	RBM38	1.381375643
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333.7490317	0.829758638	0.27114532	3.060199	0.0022119	0.041018919	DDIT3	1.777387981
838.7293018	0.332419304	0.108876292	3.053183555	0.002264274	0.041867582	CBWD2	1.259123071
58.81552416	1.053124047	0.346628477	3.038192525	0.002380018	0.043879642	RYR3	2.075018281
336.1814087	1.210205628	0.399442752	3.029734852	0.002447685	0.04473648	SLFN5	2.313706118
5475.838734	0.401470362	0.132678091	3.025897928	0.00247896	0.045178615	SLC38A2	1.320853409
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2747.535358	0.353806446	0.118205003	2.99315965	0.002761053	0.049604956	BAZ2A	1.277927903
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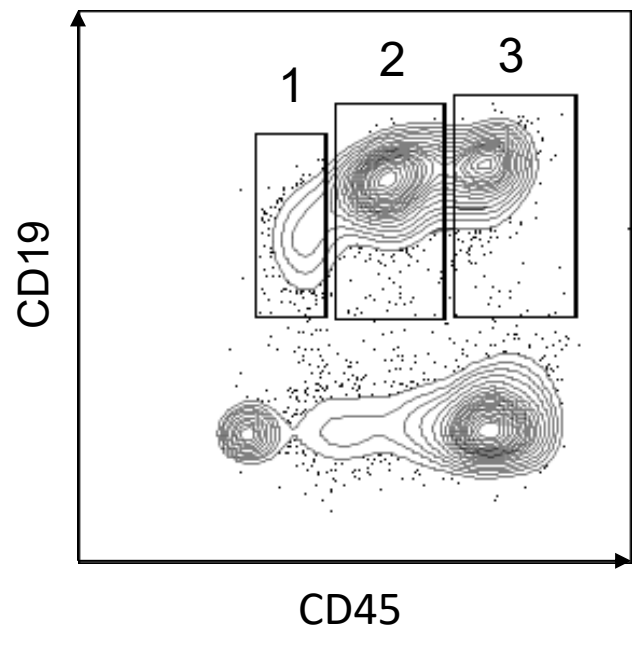
Supplemental Table 5. RNA seq data list of downregulated differentially expressed genes.

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273.381433	-1.470190869	0.209281573	-7.024941792	2.14E-12	2.34E-10	PCOLCE2	2.770585461
615.1075102	-1.717445256	0.24687316	-6.956792134	3.48E-12	3.71E-10	FCER1A	3.288535527
2940.54556	-0.749704851	0.108399089	-6.916154506	4.64E-12	4.82E-10	CD163	1.681448802
407.2367834	-1.199612144	0.183478122	-6.538175405	6.23E-11	5.80E-09	FGFR1	2.296779158
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55.3456768	-2.072403931	0.350680555	-5.909663081	3.43E-09	2.75E-07	CTTNBP2	4.205869047
1177.656483	-0.685678858	0.117587756	-5.831209652	5.50E-09	4.33E-07	ANXA3	1.608458661
862.4765766	-0.640202076	0.110570151	-5.790008175	7.04E-09	5.50E-07	CPNE2	1.558547447
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4400.263188	-0.611248335	0.112283503	-5.44379469	5.22E-08	3.59E-06	SELL	1.527580422
432.3068506	-0.861882124	0.160325558	-5.375824893	7.62E-08	5.16E-06	ENC1	1.817407735
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495.2115982	-0.913526132	0.174064406	-5.248207566	1.54E-07	9.82E-06	S100B	1.883643744
52.46906165	-3.173610265	0.614050146	-5.168324254	2.36E-07	1.46E-05	COLEC12	9.023019258
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173.2082424	-2.236331992	0.438112711	-5.104467266	3.32E-07	1.95E-05	SDC2	4.711975349
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4757.269762	-2.514223963	0.503891841	-4.989610388	6.05E-07	3.35E-05	F13A1	5.712902718
298.7974507	-1.420488394	0.286974271	-4.949880657	7.43E-07	4.05E-05	S100A12	2.676761117
4763.723046	-0.634004381	0.128351509	-4.939594275	7.83E-07	4.26E-05	ITM2C	1.551866421
1903.963323	-0.673269697	0.137083377	-4.911388319	9.04E-07	4.83E-05	PLPPR3	1.594683035
1898.264238	-0.790658588	0.163280041	-4.842346823	1.28E-06	6.58E-05	P2RY2	1.729863962
4593.243921	-0.642585374	0.132998486	-4.831523985	1.35E-06	6.89E-05	TMED9	1.561124258
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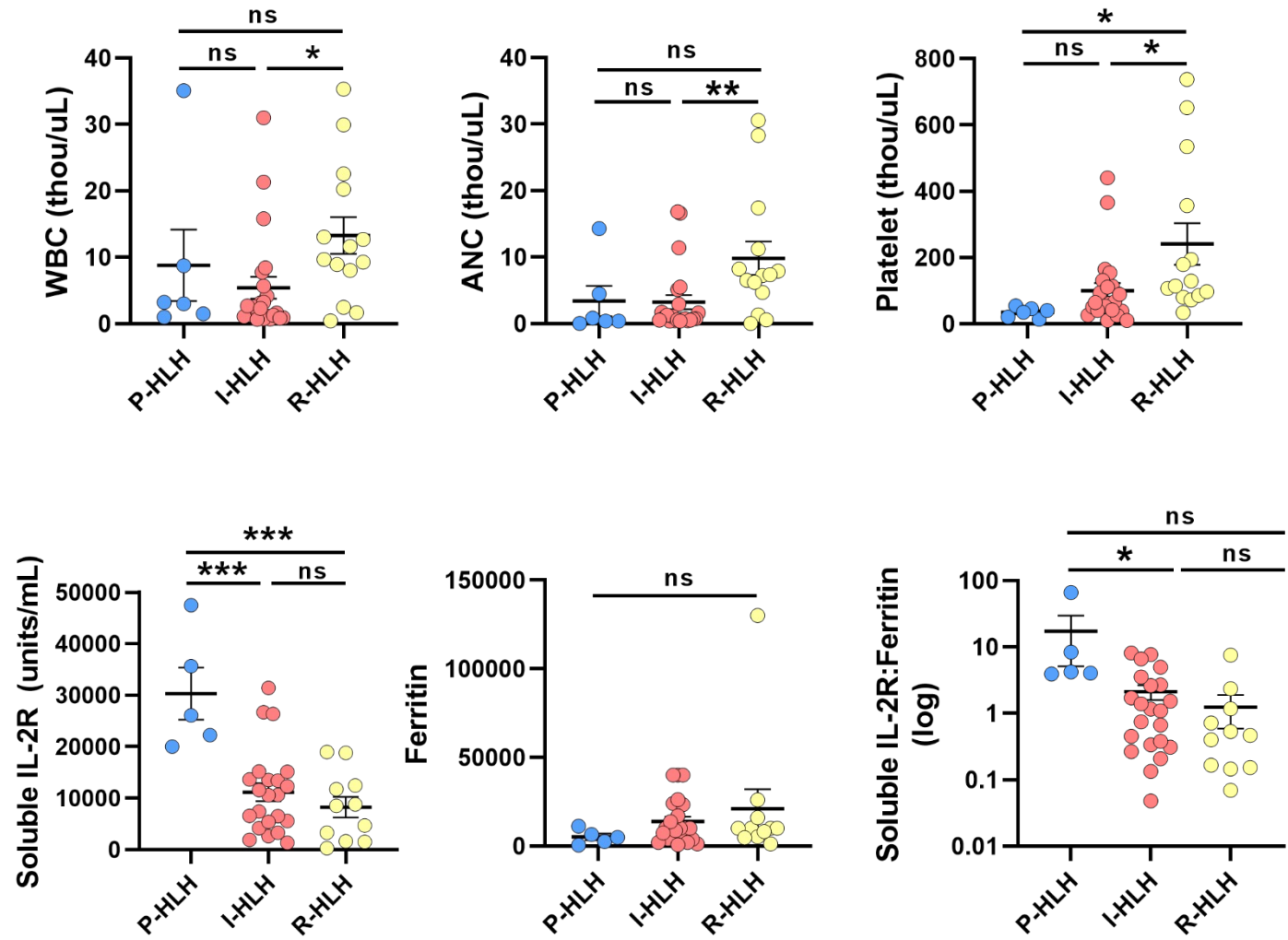
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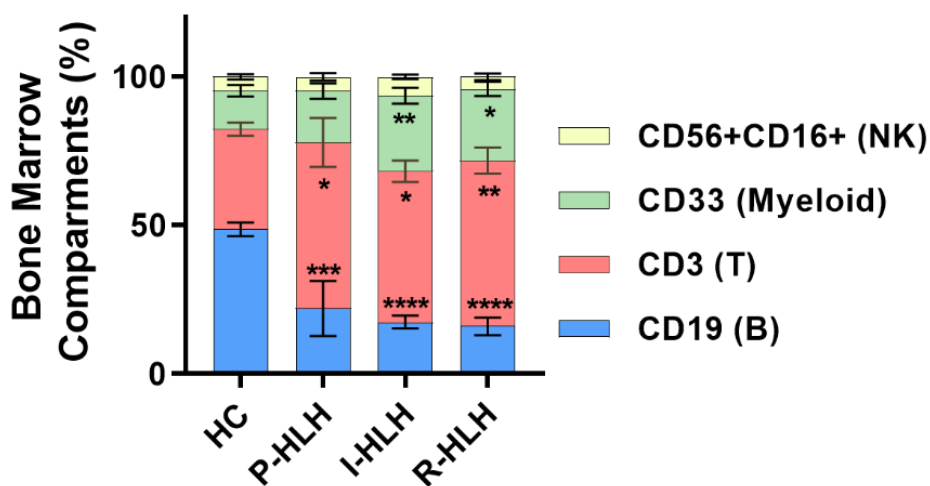
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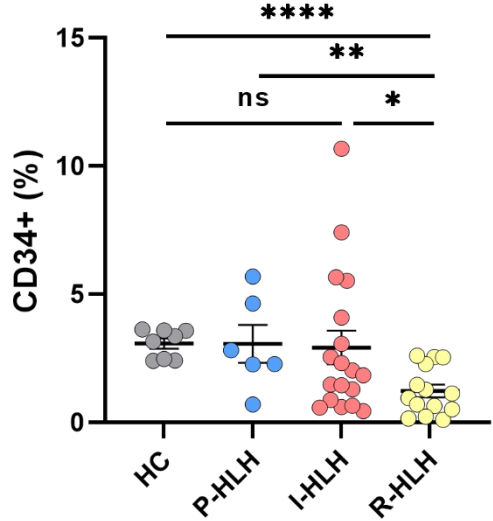
Supplemental Figure 1. Gating of hematogones in bone marrow of patient samples. Representative flow cytometry plot showing gating for Stage 1 (CD19+CD45^{dim}), Stage 2 (CD19+CD45^{intermediate}), and Stage 3 (CD19+CD45^{bright}) hematogones in a patient sample.



Supplemental Figure 2. Laboratory data obtained surrounding the time of bone marrow sampling in patient groups. For WBC, ANC, Platelet counts: P-HLH group, n= 6; I-HLH group, n=20; R-HLH group, n=14. For ferritin and soluble IL-2R: P-HLH group, n= 5; I-HLH group, n=22; R-HLH group, n=11. Kruskal-Wallis 1-way ANOVA followed by Dunn’s multiple comparison test for non-normally distributed samples and ordinary 1-way ANOVA followed by Tukey’s multiple comparison test for normally distributed samples were used for statistical comparison amongst groups. Data represent mean ± SEM; *, p < 0.05; **, p < 0.01; ***, p < 0.001; ****, p < 0.0001; ns, not significant.

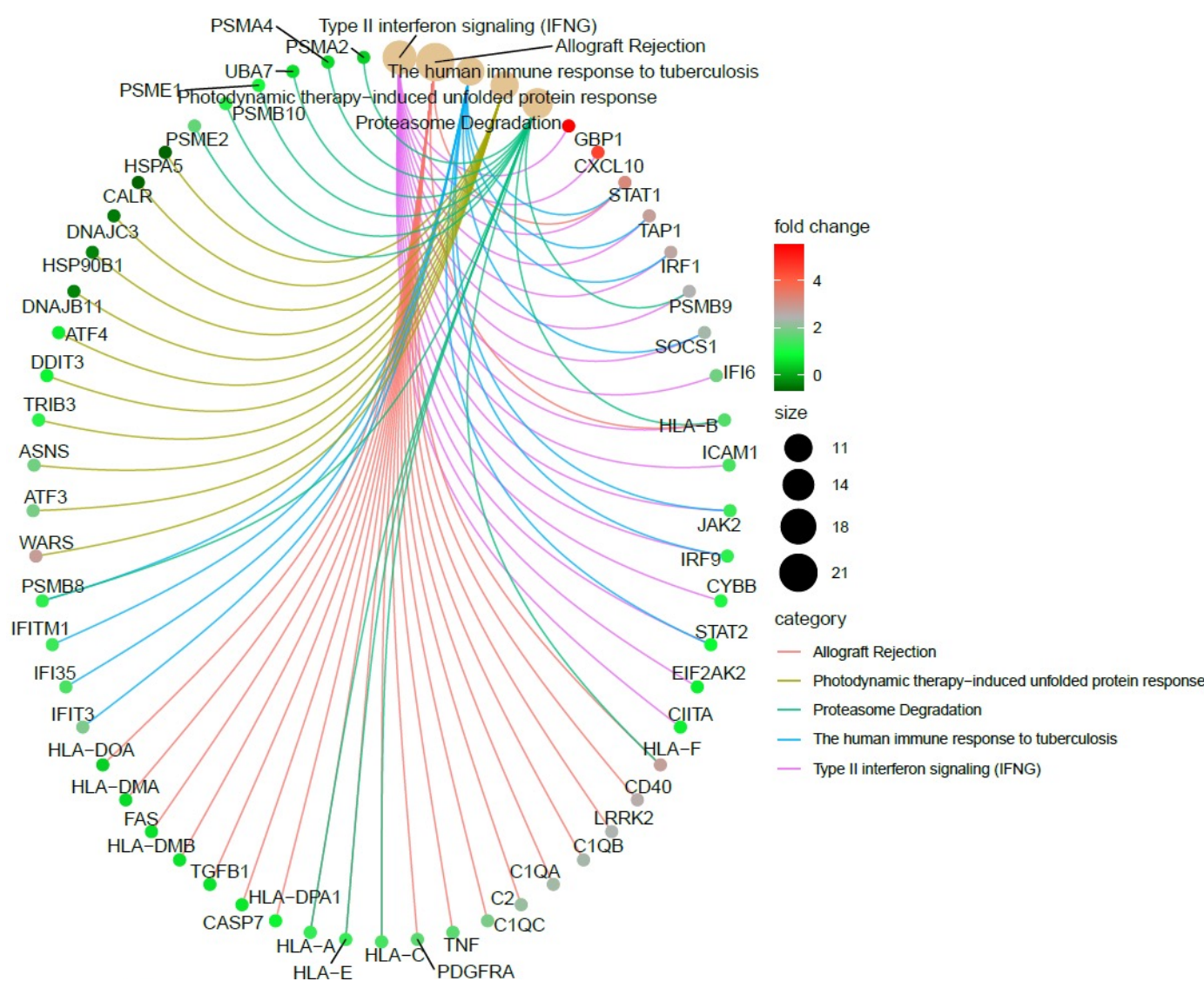


Supplemental Figure 3. Bone marrow compartment characterization. The individual percentages of CD19+ (B cell lineage), CD3+ (T cell lineage), CD33+ (myeloid lineage), and CD56+CD16+ (NK cell lineage) cells in the bone marrow compartment were normalized to the total percentages of these cells for healthy control (HC) group (n=8), P-HLH group (n=5), I-HLH group (n=19), R-HLH group (n=12). B cell compartment (HC 48.67 ± 2.38%, P-HLH 22.01 ± 9.30%, I-HLH 17.45 ± 2.21%, and R-HLH 16.03 ± 3.02%); T cell compartment (HC 33.73 ± 2.16%, P-HLH 55.92 ± 8.28%, I-HLH 50.76 ± 3.58%, and R-HLH 55.80 ± 4.40%); myeloid compartment (HC 12.89 ± 1.94%, P-HLH 17.30 ± 2.57%, I-HLH 25.48 ± 2.63%, and R-HLH 24.11 ± 2.44%); NK cell compartment (HC 4.71 ± 0.86%, P-HLH 4.76 ± 1.28%, I-HLH 6.30 ± 0.73%, and R-HLH 4.07 ± 1.08%). Kruskal-Wallis 1-way ANOVA followed by Dunn's multiple comparison test for non-normally distributed samples and ordinary 1-way ANOVA followed by Tukey's multiple comparison test for normally distributed samples were used for statistical comparison amongst groups. Data represent mean ± SEM; *, p < 0.05; **, p < 0.01; ***, p < 0.001; ****, p < 0.0001; ns, not significant.

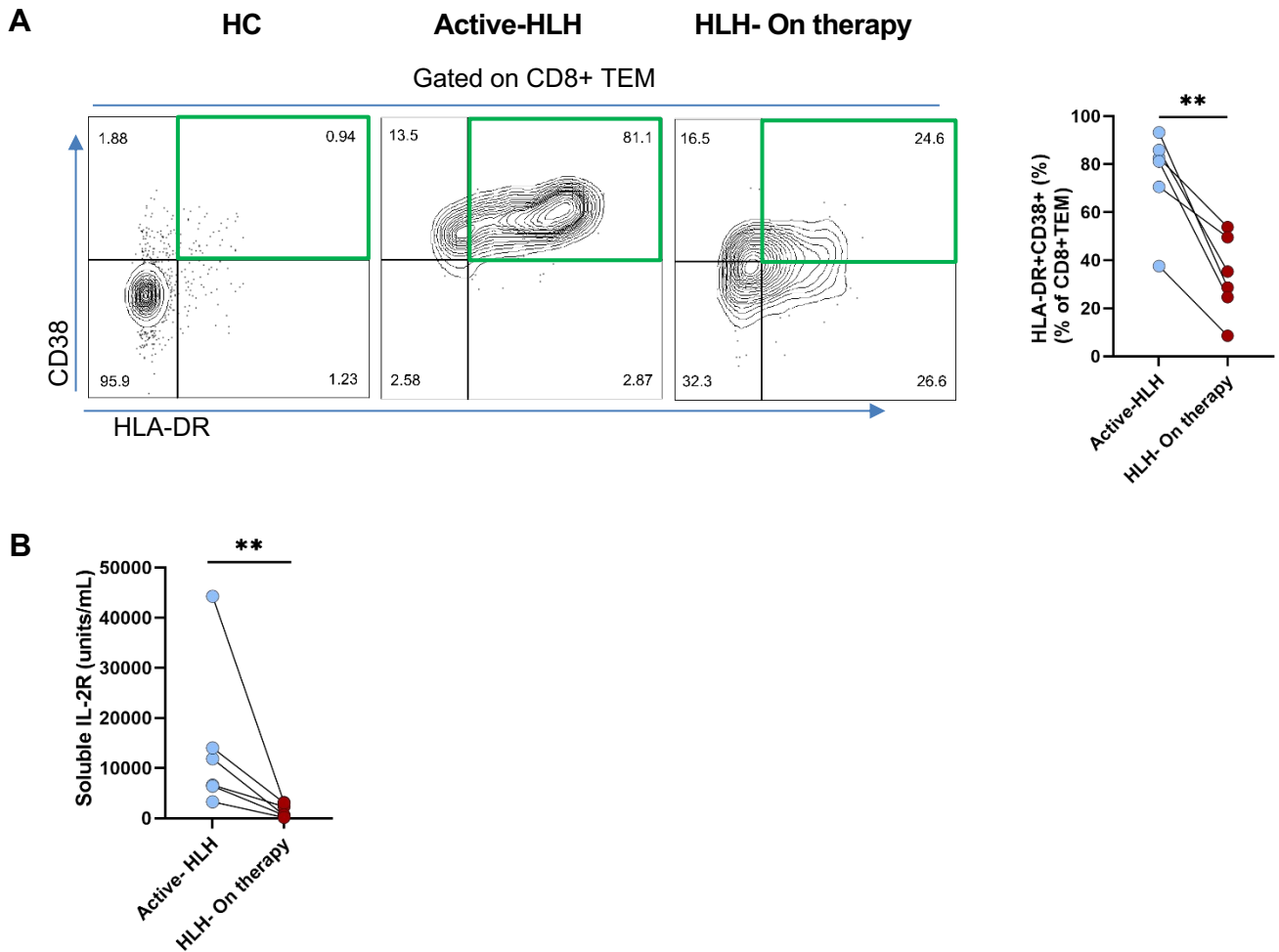


Supplemental Figure 4. CD34+ cell population in patients with HLH. Percentage of CD34+ cells identified in bone marrows of patients from each group. Healthy Control (HC) (n=8) 3.07 ± 0.20 %, P-HLH (n=6) 3.06 ± 0.74%, I-HLH (n=18) 2.91 ± 0.66%, and R-HLH (n=14) 1.22 ± 0.25%. (Kruskal-Wallis 1-way ANOVA followed by Dunn’s multiple comparison test for non-normally distributed samples and ordinary 1-way ANOVA followed by Tukey’s multiple comparison test for normally distributed samples were used for statistical comparison amongst groups. Data represent mean ± SEM; *, p < 0.05; **, p < 0.01; ***, p < 0.001; ****, p < 0.0001; ns, not significant.

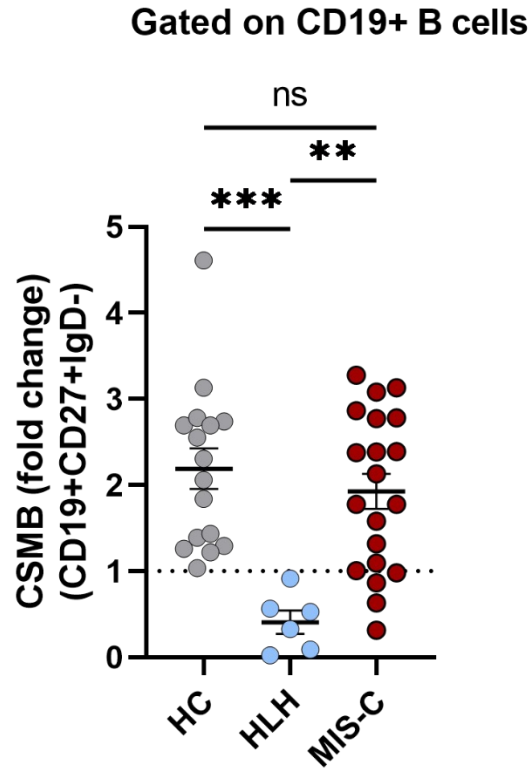
Supplemental Data



Supplemental Figure 6. The DE genes for some of the WikiPathways are expanded to show their expression in different pathways.



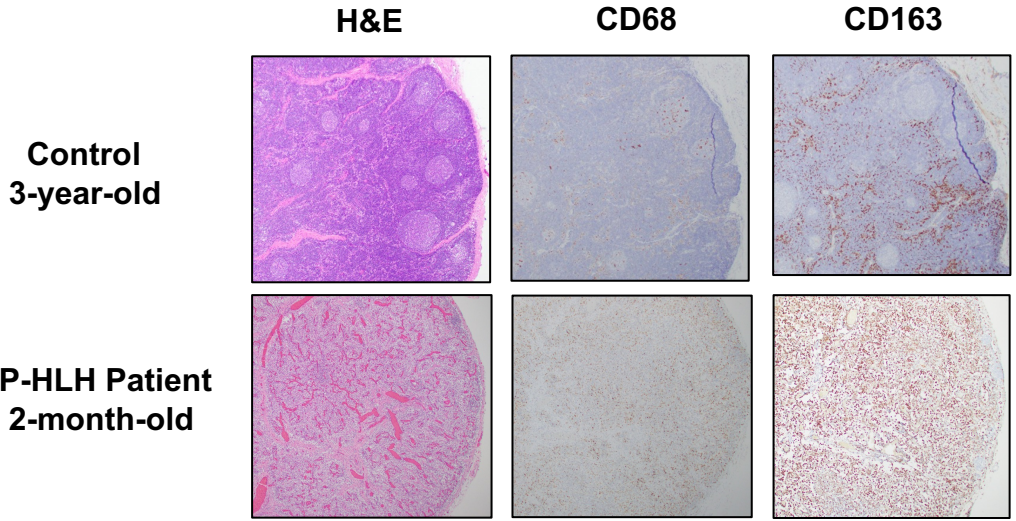
Supplemental Figure 7. T cell activation decreases during HLH therapy. (A) Flow cytometry analysis of peripheral blood mononuclear cells from healthy control (HC) and patients with active HLH and on therapy (P-HLH, n=5; I-HLH, n=1; Total, n=6). Gated on CD8+ effector memory T cells (TEM) to analyze CD38+HLA-DR+ population (green rectangle) representing T cell activation (left). (B) Quantitative soluble IL-2R values obtained at diagnosis and beginning of therapy and at a later time point towards end of therapy in same group of patients. Two-tailed Student's t-test or Mann-Whitney test was used depending on normality for statistical comparison between two groups. Data represent mean \pm SEM; *, p < 0.05; **, p < 0.01; ***, p < 0.001; ****, p < 0.0001; ns, not significant.



Supplemental Figure 8. CSMB cells are not affected in MIS-C. Age-normalized values of class switched memory B cells (CSMB, CD19+CD27+IgD-) represented as fold change were determined in the peripheral blood of healthy controls (HC) (n=16; 2.19 ± 0.24) vs. patients with HLH (P-HLH, n=5; I-HLH, n=1; Total, n=6; 0.41 ± 0.14) vs. patients with MIS-C (n=20; 1.93 ± 0.21). Kruskal-Wallis 1-way ANOVA followed by Dunn's multiple comparison test for non-normally distributed samples and ordinary 1-way ANOVA followed by Tukey's multiple comparison test for normally distributed samples were used for statistical comparison amongst groups. Data represent mean \pm SEM; *, p < 0.05; **, p < 0.01; ***, p < 0.001; ****, p < 0.0001; ns, not significant.

A

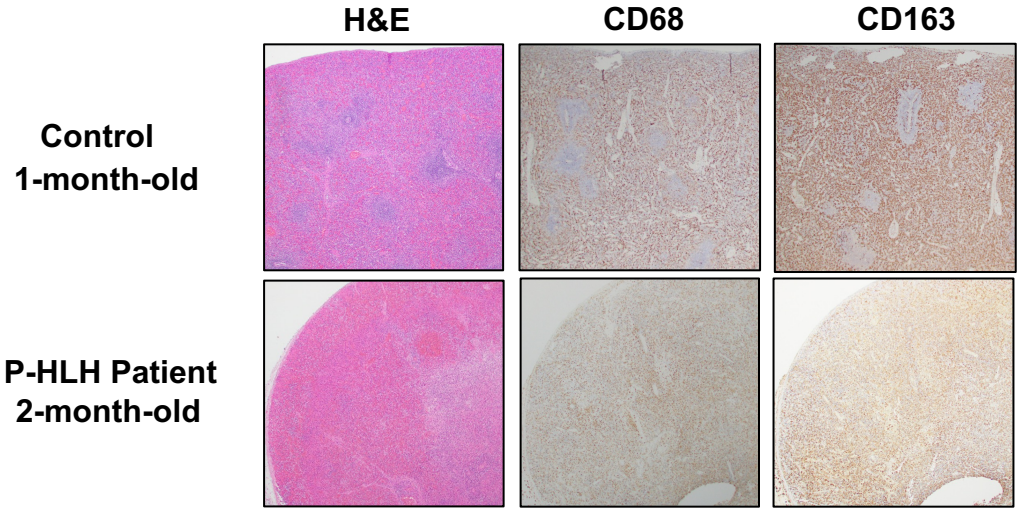
Lymph Node



400 μm

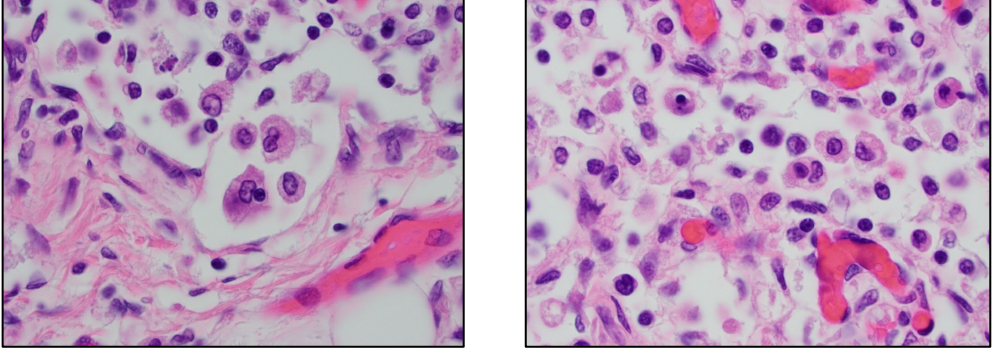
B

Spleen



400 μm

C



Supplemental Figure 9. Immunohistochemistry of lymph nodes and spleen of healthy controls and patient with P-HLH. Panel showing IHC (H&E, CD68, and CD163) images from (A) lymph node and (B) spleen of controls and a patient with active P-HLH. Scale bar represents 400 μm. (C) Hemophagocytosis (100x) shown in H&E stain of lymph node from patient with active P-HLH.