

Supplementary Materials

Aberrant STAT signaling and T cell dysregulation define a targetable pediatric sepsis endotype

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SUPPLEMENTAL CLINICAL METHODS

Study Setting and Eligibility: Patients were enrolled in the Pediatric Intensive Care Unit (75 beds) and Cardiac Intensive Care Unit (38 beds) at Children's Hospital of Philadelphia. Both units are combined medical and surgical ICUs.

Inclusion Criteria: Patients >40 weeks post-conceptual age and <18 years old were eligible if they exhibited new dysfunction of ≥ 2 organ systems defined by modified Proulx criteria (Table S11) within the preceding three calendar days. MODS defined by Proulx criteria is strongly associated with both short- and long-term PICU outcomes (1).

Exclusion Criteria: Patients were excluded if they had limitations of care orders (DNR/DNI) at the time of eligibility, clinical suspicion for brain death, or prior enrollment in the study.

Clinical Definitions

- **MODS Onset:** Defined as the calendar day a patient first met criteria for concurrent dysfunction of ≥ 2 organ systems.
- **Sepsis Classification:** Sepsis was identified as the MODS inciting diagnosis based on clinical suspicion for infection by the primary treating team combined with positive microbiologic or virologic testing. Patients with "culture-negative sepsis" were classified as sepsis if they developed organ dysfunction in the setting of clinical suspicion for infection and received sepsis-directed therapies (antibiotics/antivirals), in concordance with international pediatric sepsis guidelines (2, 3).
- **Immunocompromised Status:** Defined as a diagnosis of active malignancy, prior hematopoietic cell transplant, or primary immune deficiency syndrome.
- **Outcome Measures:** Daily organ dysfunction was scored using the PELOD-2 score from MODS onset through day +28. The primary outcome was the cumulative PELOD-2 score. This metric incorporates both the severity and duration of organ failure and is associated with meaningful differences in long-term mortality (4) and health-related quality of life (5) in pediatric patients with sepsis.

SUPPLEMENTAL LABORATORY METHODS

Biospecimen Processing: Blood samples were obtained in sodium heparin tubes and processed on-site within one hour of acquisition. Platelet-poor heparin plasma was separated by centrifugation, snap-frozen on dry ice, and stored at -80°C. Peripheral Blood Mononuclear Cells were isolated by density gradient centrifugation using SepMate tubes (STEMCELL Technologies, Vancouver, Canada). Whole blood was mixed 1:1 with PBS, layered onto Lymphoprep gradient. SepMate tubes were centrifuged, and the buffy coat suspension was collected and washed. Red blood cells were lysed using ACK lysis buffer. Cells were resuspended in complete RPMI (RPMI 1640 supplemented with 10% FBS, 1% L-Glutamine, 1% Pen-Strep) for counting, then resuspended in 500µl of freezing media (90% FBS, 10% DMSO) and frozen in Mr. Frosty containers at -80°C before transfer to liquid nitrogen.

Spectral Flow Cytometry: Full staining protocols for each panel are provided below. Details of the flow cytometry antibodies and buffers required for these protocols are available in **Table S2** (immune phenotyping panel) and **Table S10** (phosphoflow cytometry panel). All samples were acquired on a Cytex Aurora spectral flow cytometer at Children's Hospital of Philadelphia.

Fluorescence-Activated Cell Sorting: For scRNA-seq, cryopreserved PBMCs were thawed and stained with Live/Dead Blue (Thermo Fisher, Catalog #L34961) and anti-CD45 (BD Biosciences, Clone HI30, Catalog #751472). Using a Cytex Aurora CS cell sorter, live singlet CD45⁺ cells were sorted into 1.5mL Eppendorf tubes containing 500µl of PBS + 20% FBS to ensure high viability. Sorted cells were washed twice with PBS + 10% FBS to remove sheath fluid EDTA prior to 10X library preparation.

Single-Cell Library Preparation: Single-cell gene expression and TCR libraries were prepared using the Chromium Next GEM Single Cell 5' Reagent Kits v2 and Single Cell Human TCR Amplification Kit per manufacturer instructions. Libraries were sequenced on an Illumina NovaSeq 6000 S2 flow cell. Demultiplexing and alignment to the GRCh38 reference genome were carried out using the Cell Ranger v8.0 pipeline (10X Genomics), generating both transcriptomic and V(D)J clonotype data for downstream analysis.

PROTOCOL FOR THAWING AND STAINING HUMAN PBMCs FOR IMMUNE PROFILING ANALYSIS

PBMC Thawing Protocol

1. Prepare 15mL conical tubes with 10mL cRPMI (warmed 37°C water bath).
2. Obtain cryovials from liquid nitrogen (LN). Keep on dry ice until immediately before thaw.
3. Swirl 2 vials in 37°C water bath for ~30 seconds. Partially thawed pellet should remain.
4. Add 1mL warm cRPMI to cryovial and mix. Transfer all contents into 15mL tube.
5. Wash cryovial with 2mL warm cRPMI and transfer contents to 15mL tube.
6. Spin @ 800xg for 4 mins at room temperature (RT).
7. Decant supernatant into waste and tap vial ridge to remove excess media.
8. Resuspend cells in 1mL warm cRPMI.
9. Count cells: 10µL Trypan blue + 10µL Cell suspension.
10. Spin @ 800xg for 4 mins at RT.
11. Decant supernatant into waste and tap vial ridge to remove excess media.
12. Resuspend cells in warm cRPMI at a concentration of 5×10^6 cells/mL.
13. Plate 200µL/well, or 1×10^6 cells/well, in a 96-well round bottom plate.

PBMC Staining Protocol

1. Spin at 800xg for 4 mins, RT. Flick plate to discard supernatant.
2. Wash cells with 150µL of PBS.
3. Spin at 800xg for 4 mins, RT. Flick plate to discard supernatant.
4. Resuspend cells in 50µL **LD/Fc stain mixture**.
5. Incubate at 4°C for 15 minutes.
6. Wash cells with 150µL of PBS.
7. Spin at 800xg for 4 mins, RT. Flick plate to discard supernatant.
8. Resuspend cells in 50µL **SS antibody mixture** in FACS Buffer + Brilliant Stain Buffer.
9. Incubate at 4°C for 30 minutes in the dark.
10. Wash with 150µL FACS buffer.
11. Spin @ 800xg for 4 mins, RT. Flick plate to discard supernatant.
12. Resuspend cells in 50µL of **Fix/Perm reagent**.
13. Incubate at RT for 20 minutes in the dark.
14. Wash with 150µL Perm buffer.
15. Spin @ 800xg for 4 mins, RT. Flick plate to discard supernatant.
16. Resuspend cells in 50µL **ICS antibody mixture** in Perm Buffer + Brilliant Stain Buffer.
17. Incubate at 4°C for 60 minutes in the dark.
18. Wash with 150µL of Perm Buffer.
19. Spin @ 800xg for 4 mins, RT. Flick plate to discard supernatant.
20. Resuspend pellets in 100µL **1.6% PFA fixative** and transfer to bullet tubes.
21. Cells can be held at 4°C overnight prior to acquisition.

PROTOCOL FOR THAWING AND STAINING HUMAN PBMCs FOR AURORA CS SORTING

PBMC Thawing Protocol

1. Prepare 15mL conical tubes with 10mL cRPMI (warmed 37°C water bath).
2. Obtain PBMC cryovials from LN and keep on dry ice until immediately before thaw.
3. Swirl 2 vials in 37°C water bath for ~30 seconds. Partially thawed pellet should remain.
4. Add 1mL warm cRPMI to cryovial and mix. Transfer all contents into 15mL tube.
5. Wash cryovial with 2mL warm cRPMI and transfer contents to 15mL tube.
6. Spin @ 800xg for 4 mins at RT.
7. Decant supernatant into waste and tap vial ridge to remove excess media.
8. Resuspend cells in 1mL warm cRPMI.
9. Count cells with 10µL trypan blue + 10µL cell suspension.
10. Lift 1×10^6 live cells into a new labeled tube for staining.

PBMC Staining Protocol

1. Spin at 800xg for 4 mins, RT. Decant/tap to remove excess media.
2. Wash cells with 1mL of FACS buffer.
3. Spin at 800xg for 4 mins, RT. Decant/tap to remove excess media.
4. Resuspend cells in 100µL **Stain Mixture**.
5. Incubate at RT for 30 minutes in the dark.
6. Wash cells with 1mL of FACS buffer.
7. Spin at 800xg for 4 mins, RT. Decant/tap to remove excess media.
8. Resuspend cells in 500µL FACS Buffer and pass through blue cell strainer into FACS tube.
9. Cover and keep on wet ice. Cells are ready for sorting.

Prepare Sort Tubes and Resuspension Media

1. Prepare three 1.5ml eppendorf tubes with 500µL of PBS + 20% FBS for each sample.
2. Prepare 10% FBS Resuspension Media.

Cell Washing and Resuspension

1. After sorting, spin down cells in microcentrifuge 800xg for 5 mins, 4 degrees.
2. Aspirate supernatant and wash with 500µL PBS + 10% FBS.
3. Spin down cells in microcentrifuge 800xg for 5 mins, 4 degrees.
4. Aspirate supernatant and wash with 500µL PBS + 10% FBS.
5. Spin down cells in microcentrifuge 800xg for 5 mins, 4 degrees.
6. Goal concentration is 1200 cells per microliter. Calculate resuspension volume.
7. Aspirate supernatant and resuspend in PBS + 10% FBS.
8. Cover and keep on wet ice. Cells are ready for 10x processing.

PROTOCOL FOR THAWING AND STAINING HUMAN PBMCs FOR PHOSPHOFLOW CYTOMETRY

PBMC Stimulation Protocol

1. Prepare a 2µg/mL solution of anti-CD3 in sterile PBS.
 - InVivoMAb Anti-Human CD3, BioXCell, UCHT1 (Leu-4) (T3), BE0231
2. Add 200µL of diluted anti-CD3 solution to stimulation wells of a flat bottom 96 well plate.
3. Add 200µL of PBS to unstimulated wells in the same flat bottom 96 well plate.
4. Cover the plate with a plate sealer and store at 4°C overnight.

PBMC Thawing Protocol

5. Prepare 15mL conical tubes with 10mL cRPMI (warmed 37°C water bath).
6. Obtain PBMC cryovials from LN and keep on dry ice until immediately before thaw.
7. Swirl 2 vials in 37°C water bath for ~30 seconds. Partially thawed pellet should remain.
8. Add 1mL warm cRPMI to cryovial and mix. Transfer all contents into 15mL tube.
9. Wash cryovial with 2mL warm cRPMI and transfer contents to 15mL tube.
10. Spin @ 800xg for 4 mins at RT.
11. Decant supernatant into waste and tap vial ridge to remove excess media.
12. Resuspend cells in 1mL warm cRPMI.
13. Count cells with 10µL trypan blue + 10µL cell suspension.
14. Spin @ 800xg for 4 mins at RT.
15. Decant supernatant into waste and tap vial ridge to remove excess media.
16. Resuspend cells in warm cRPMI at a concentration of 2.5×10^6 cells/mL.

PBMC Stimulation Protocol Continued

17. Remove anti-CD3 flat bottom plate from 4°C and carefully aspirate coating solution and PBS from wells.
18. Plate 100µL/well, or 2.5×10^5 cells/well, in the 96-well flat bottom plate coated with anti-human CD3 antibody and PBS.
19. Prepare a 2µg/mL of an anti-human CD28 in AIM-V media. *Add cytokine if desired here.*
 - BD FastImmune Anti-Human CD28/CD49d, BD, L293/L25, 347690
20. Add 100µL of stimulation media to each stimulated well.
21. Add 100µL of AIM-V media to each unstimulated well.
22. Incubate at 37°C, 5% CO₂ for 24 hours.

PBMC Staining Protocol

23. Spin at 800xg for 4 mins, RT. Flick plate to discard supernatant.
24. Resuspend cells in 50µL of **pFlow surface stain mixture** and incubate at RT for 30 minutes.
25. Wash cells with 150µL of FACS Buffer.
26. Spin at 800xg for 4 minutes at RT. Flick plate to discard supernatant.
27. Resuspend cells in 100µL of **1.6% PFA** and incubate at RT for 15 minutes.
28. Spin at 800xg for 4 minutes at RT. Flick plate to discard supernatant.
29. Add 150µL/well of **cold MeOH**.
30. Wrap plate in foil and incubate at -20°C overnight.
31. Spin at 800xg for 5 minutes at RT. Flick plate to discard supernatant.
32. Wash cells with 200µL of Perm Buffer.

33. Spin at 800xg for 4 minutes at RT. Flick plate to discard supernatant.
34. Wash cells with 200 μ L of Perm Buffer.
35. Spin at 800xg for 4 minutes at RT. Flick plate to discard supernatant.
36. Resuspend cells in 50 μ L of **pFlow ICS stain mixture** and incubate at RT for 60 minutes.
37. Wash cells with 150 μ L of Perm Buffer.
38. Spin at 800xg for 4 minutes at RT. Flick plate to discard supernatant.
39. Resuspend cells in 125 μ L of **1.6% PFA**.
40. Cover and keep on wet ice. Cells are ready for acquisition.

SUPPLEMENTAL COMPUTATIONAL METHODS

Statistical Framework: Categorical variables were analyzed by χ^2 test. Comparisons of continuous variables between two groups were performed using the Wilcoxon rank-sum test with Benjamini-Hochberg adjustment to control the false discovery rate. Comparisons of continuous variables across three or more groups were performed using the Kruskal-Wallis test. Pairwise comparisons were subsequently performed using Dunn's post-hoc test with Benjamini-Hochberg adjustment to control the false discovery rate.

Identification of subgroups: We constructed linear mixed effects models for each protein to determine the association between normalized protein expression and cumulative PELOD-2 score, with age and sex modeled as fixed effects and day from MODS onset modeled as a random effect. Proteins which were significantly associated with cumulative PELOD-2 score after Benjamini-Hochberg correction (FDR $p < 0.05$) were retained for further analysis. This supervised feature selection strategy was explicitly selected to discover endotypes relevant to clinical outcomes. We used consensus clustering to define subgroups and identified optimal k via the Monte Carlo reference-based consensus clustering algorithm (6) which uses the proportion of ambiguous clustering (PAC) score to test the hypothesis that $k=n$ clusters is more informative than $k=1$. Optimal number of clusters in the MODS data ($k=3$) was confirmed by Monte Carlo bootstrapping, elbow method, and gap statistic. To ensure that this approach did not yield circular artifacts, the biological validity of the resulting clusters was confirmed using orthogonal data modalities (e.g., spectral flow cytometry, scRNA-seq) not included in the clustering model. The clinical and proteomic datasets contained no missing data elements, thus imputation was not necessary for our analyses.

Sensitivity analysis of patient clustering algorithms: To verify that the identified patient subgroups were robust to the choice of clustering algorithm, we performed a sensitivity analysis using spectral clustering, a graph-theoretic approach that partitions data based on topological connectivity. We constructed a k -nearest neighbor graph ($k=19$) using the severity-associated protein feature set and partitioned the resulting Laplacian matrix into three clusters. Concordance between the primary Consensus Clustering and Spectral Clustering was quantified using the Adjusted Rand Index (ARI) and overall percent agreement. We observed a high degree of concordance between methods (ARI: 0.73; Concordance: 91%), confirming that the subgroups reflect stable intrinsic structures within the proteomic data rather than artifacts of a specific algorithm. Concordance was visualized by projecting cluster assignments onto the first two principal components of the proteomic dataset, as shown in **Figure S2**.

Competing risk survival analysis: We fit a proportional subdistribution hazards regression model to assess the effect of covariates on the subdistribution of death and survival to PICU discharge in a competing risk setting and then estimated the cumulative incidence function from this model for each subgroup and outcome using the Fine and Gray model (7). We then tested the hypothesis that the subdistribution hazard differed between Group C and Group A/B for both death and survival to PICU discharge.

Model reduction via ordinal elastic net: We defined a parsimonious protein signature to classify subgroups by training an ordinal elastic net model (8) for feature selection using the

severity-associated proteins previously identified through linear mixed effects modeling. This approach fit a semi-parallel elementwise link multinomial-ordinal regression model with elastic net penalty which defines coefficients for each protein:subgroup and then shrinks the model to a single coefficient for each protein via elastic net penalty to minimize Gini index. We assessed the performance of the parsimonious elastic net protein set to discriminate the three subgroups using PCA, linear mixed effects post-estimation, and polytomous discrimination index (9).

Analysis of spectral flow cytometry data: *Data preprocessing:* Raw .fcs files were compensated on-instrument (Cytek Aurora) using single-stain controls. Post-acquisition, data were arcsinh transformed (10) and quality controlled using flowAI (11) to automatically remove acquisition anomalies related to flow rate, signal instability, and dynamic range. *Metaclustering:* We performed FlowSOM metaclustering (12) to identify 14 immune cell populations by surface and intracellular marker expression. PBMCs were first clustered into k=60 FlowSOM metaclusters and then combined in a stepwise fashion to generate the 14 canonical populations identified in the figure and used for downstream analysis. Metacluster similarity was determined by surface and intracellular marker expression and tSNE-CUDA (13) proximity and then confirmed with manual gating. Proliferation and activation markers were analyzed using bivariate plots. *Phosphoflow analysis:* Phosphoflow cytometry data were analyzed using FlowJo v10.9 (BD Biosciences). T cells were identified via manual gating as Live singlet CD3⁺CD19⁻CD56⁻ events. Major lineage subsets (CD4⁺ and CD8⁺) were subsequently identified. Within each lineage, non-naïve T cells (Tnn) were defined by excluding the naïve population (CD45RA⁺CD27⁺) to include central memory, effector memory, and TEMRA subsets.

Pathway enrichment analysis: We first performed pathway enrichment analysis by subgroup by analyzing estimated protein expression in Group C patients (adjusted for age, sex, and PELOD-2 score) with Ingenuity Pathway Analysis (Qiagen) (14). We then analyzed pathway expression in the protein dataset in bulk by GSEA (15) and at the individual patient level using GSVA (16), with a focus on enrichment of five canonical proinflammatory pathways using Human Molecular Signatures Database (MSigDB) Hallmark gene sets (17):

- “TNF Signaling via NFκB” (HALLMARK_TNFA_SIGNALING_VIA_NFKB),
- “IL-6/JAK/STAT3 Signaling” (HALLMARK_IL6_JAK_STAT3_SIGNALING),
- “IL-2/JAK/STAT5 Signaling” (HALLMARK_IL2_STAT5_SIGNALING),
- “IFN-γ Response” (HALLMARK_INTERFERON_GAMMA_RESPONSE),
- “PI3K/AKT/mTOR Signaling” (HALLMARK_PI3K_AKT_MTOR_SIGNALING).

We also applied GSVA to single cell transcriptomics data in a similar approach using UCell (18) and extended our analysis to include relevant immunometabolic pathways using MSigDB KEGG and Hallmark gene sets:

- “KEGG Glycolysis” (KEGG_GLYCOLYSIS_GLUONEOGENESIS)
- “KEGG Oxidative Phosphorylation” (KEGG_OXIDATIVE_PHOSPHORYLATION)
- “KEGG mTOR” (KEGG_MTOR_SIGNALING_PATHWAY)
- “Glycolysis” (HALLMARK_GLYCOLYSIS),
- “Oxidative Phosphorylation” (HALLMARK_OXIDATIVE_PHOSPHORYLATION).

A list of the gene sets used in GSEA and GSVA analysis in this manuscript are included in **Table S14**. Throughout the manuscript, we refer to Hallmark pathways as “modules” as opposed to

“gene sets” because the analytic approach is applied to both proteomics data (via GSVA) and transcriptomics data (via UCell).

Single cell transcriptomics analytic pipeline: Transcriptomic data were analyzed using the Seurat 5.0 preprocessing and integration pipeline (19). After review of standard quality control metrics, cells with less than 200 genes, greater than 3 median absolute deviations above the median, and >10% mitochondrial RNA content were removed from downstream analysis. After normalization and scaling using the scTransform function in Seurat, we performed anchor-based RPCA integration across samples and conditions using the top 3000 genes as anchors. Following linear dimension reduction using PCA, the data was clustered using the Louvain algorithm and projected into 2D coordinates using the RunUMAP function in Seurat. The cell identities were then inferred using the scType package (20) followed by curated manual annotation using canonical marker genes to define 14 immune cell populations by transcriptional profile. Results of each quality control and integration step are shown in **Figure S5**. Pseudobulk analysis was performed by condition, sample, and cell type using Seurat’s AggregateExpression function. Differential expression analysis was performed using the FindMarkers function in Seurat. Cell-cell communication analysis was performed using CellChat (21). To assess associations between effector cell pathways and T cell immunometabolic states, we employed generalized linear mixed-effects models, treating module enrichment scores as fixed effects and patient identity as a random effect.

T cell receptor sequencing analytic pipeline: T-cell receptor (TCR) sequencing data were analyzed using the scRepertoire package (22). VDJ output from the Cell Ranger pipeline (10x Genomics) were integrated with single-cell RNA sequencing gene expression data using the combineExpression() function. Clonotypes were defined based on CDR3 amino acid sequences and visualized using clonotype homeostasis and proportional abundance plots. Diversity was quantified using Shannon diversity (23). To further characterize TCR sequence features, clonotype-level annotation was performed using the TCR Repertoire Explorer (TRex) package (24).

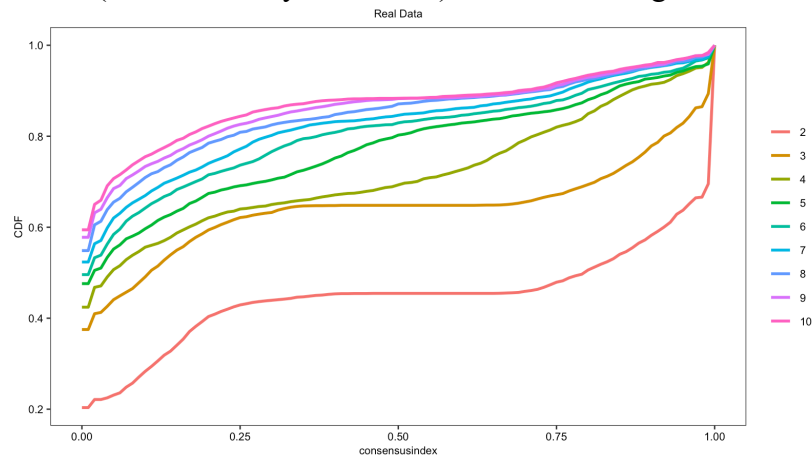
Immune Dictionary cytokine signature analysis: To assess cytokine-specific transcriptional responses in our scRNA-seq dataset, we applied the Immune Dictionary framework, which maps cytokine signaling to downstream gene expression profiles in specific immune cell types. Single-cell transcriptomic data were scored using curated cytokine-response gene signatures derived from the published experimental datasets (25). A list of the gene sets used in this analysis are included in **Table S15**. Module enrichment scores were computed using UCell for each cytokine response transcriptional signature, enabling cell-specific quantification of cytokine signaling activity.

Sensitivity analysis of corticosteroid effect: To assess the potential confounding effect of corticosteroid treatment on transcriptional signatures, we performed a sensitivity analysis comparing lineage-specific IL-6/JAK/STAT3 module enrichment scores between Group C patients who received corticosteroids (n=4) and those who did not (n=5). We calculated Cliff’s Delta (δ), a non-parametric effect size measure quantifying the difference between two distributions, to estimate the magnitude of separation between treated and untreated groups. Effect magnitudes were interpreted using standard thresholds (26): negligible ($|\delta| < 0.15$), small

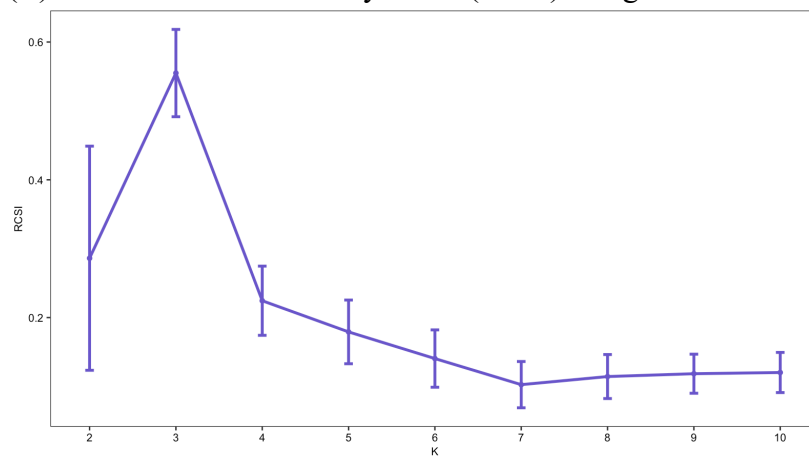
($0.15 \leq |\delta| < 0.33$), medium ($0.33 \leq |\delta| < 0.47$), and large ($|\delta| \geq 0.47$). A positive δ indicates higher scores in the "No Steroids" group (consistent with steroid-mediated suppression), while a negative δ indicates higher scores in the "Yes Steroids" group (consistent with a lack of response to corticosteroids).

Figure S1. Supporting evidence for $k=3$ clusters in Figure 2A.

(A) This cumulative distribution function (CDF) plot demonstrates increased cluster stability up to $k=3$ (as indicated by flatter line), with decreasing cluster stability with finer clustering.



(B) Relative Cluster Stability Index (RCSI) is highest at $k=3$.



(C) M3C calculates empirical p -values from reference distributions to test the null hypothesis that $k=1$. In our analysis, at $k=3$ the null hypothesis is rejected ($p=0.038$).

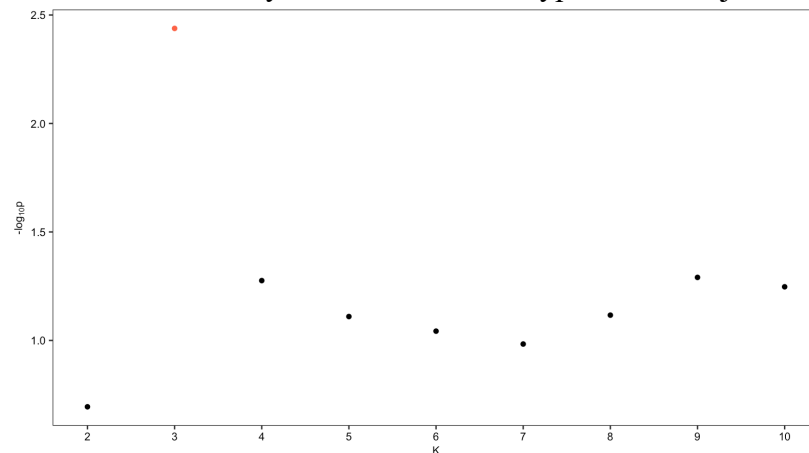
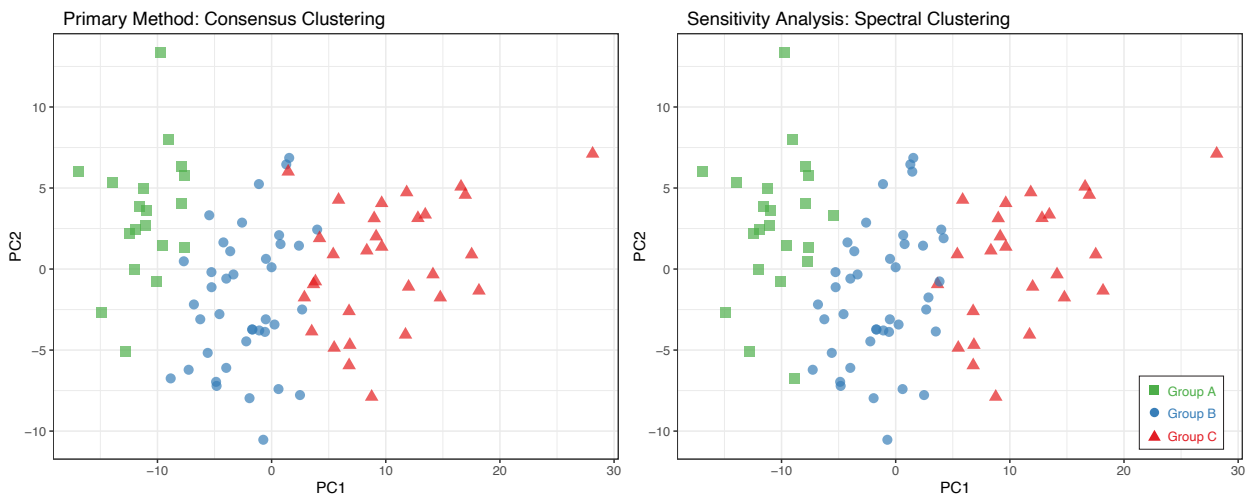


Figure S2. Sensitivity analysis of patient clustering algorithms.

(A) To verify that the identified patient subgroups were robust to the choice of clustering algorithm, we performed a sensitivity analysis using Spectral Clustering. On PCA, we see a high degree of concordance between consensus clustering and spectral clustering, suggesting that these groups reflect stable intrinsic structures within the proteomic data rather than artifacts of a specific algorithm.



(B) We quantified concordance between our primary analysis (consensus clustering) and sensitivity analysis (spectral clustering) using the Adjusted Rand Index (ARI) and overall percent agreement. The confusion matrix below shows the high degree of concordance between methods (ARI: 0.73, concordance: 90.9%).

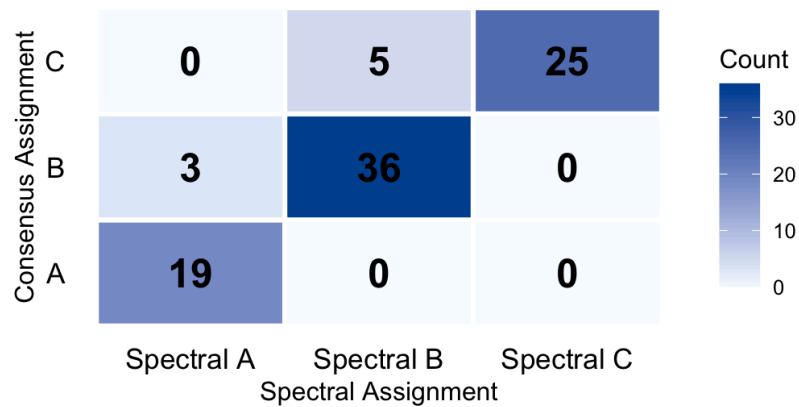
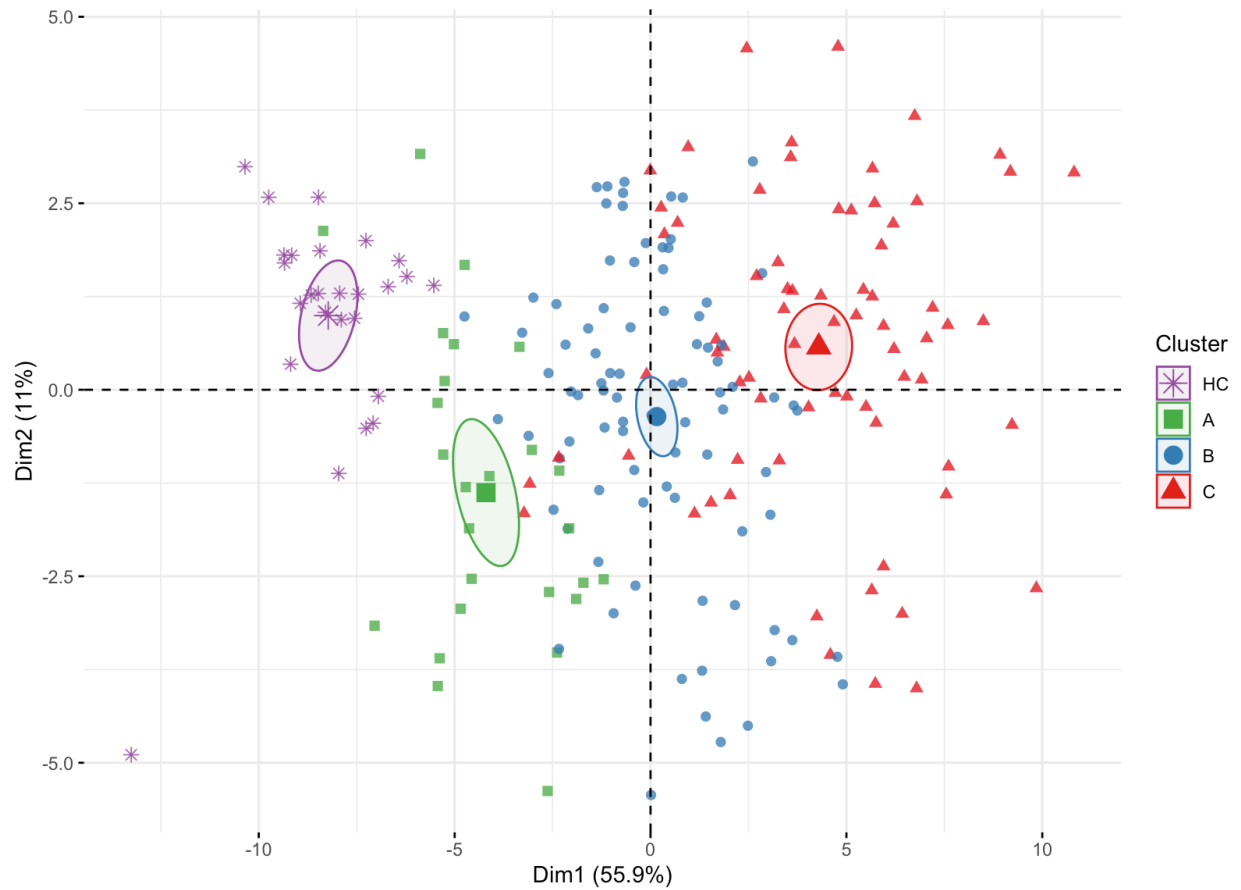


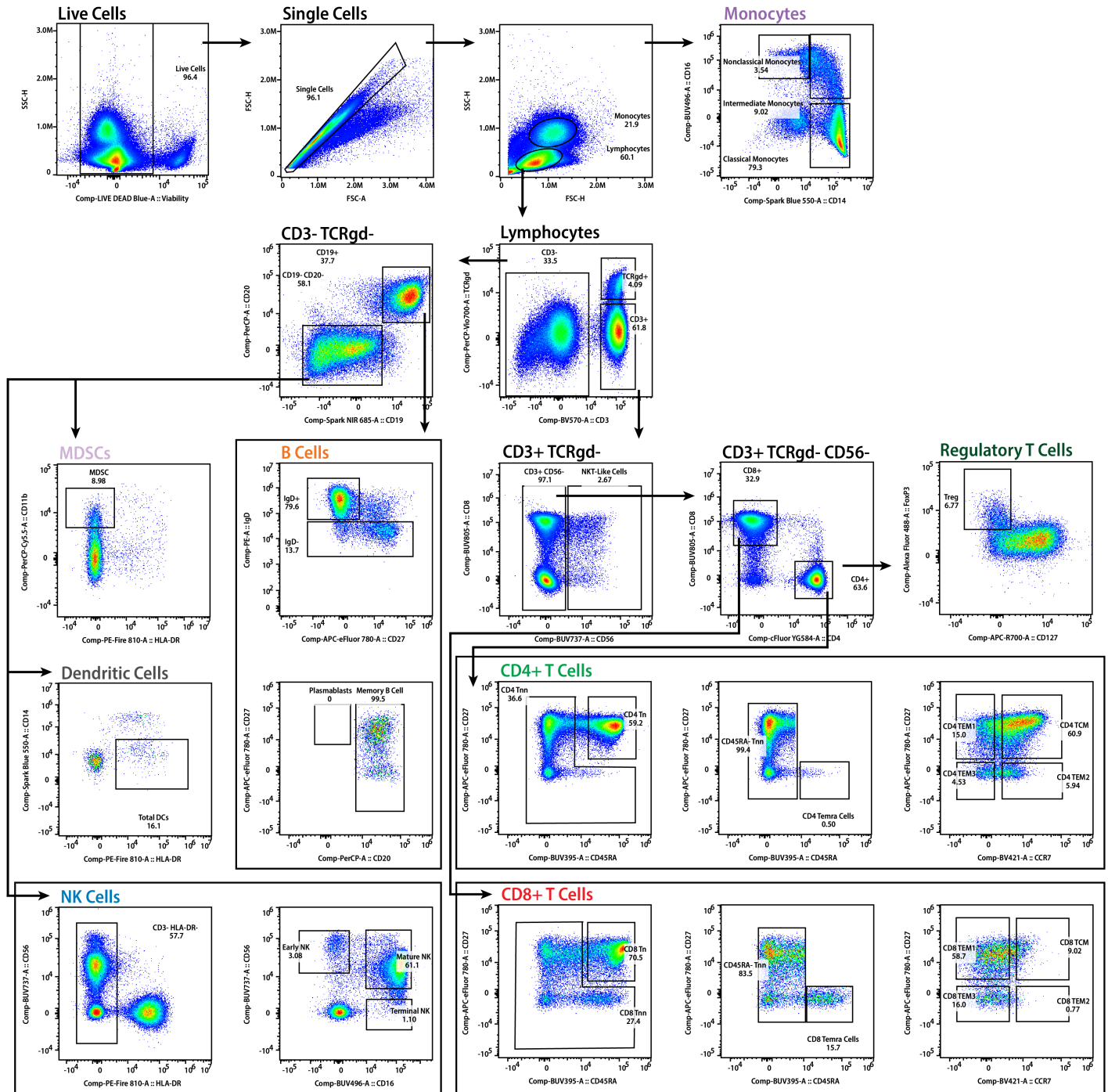
Figure S3. PCA resolving three subgroups based on expression of 24 elastic net derived severity-associated proteins.



PCA dimensionality reduction demonstrates effective resolution of three MODS subgroups based on expression of 24 elastic net derived severity-associated proteins, with the majority of variance within the dataset defined by Dimension 1 as expected.

Figure S4. Representative gating strategy and phenotype plots for spectral flow immune phenotyping panel.

(A) Canonical gating strategy



(B) Representative spectral flow cytometry immune phenotyping plots, demonstrating concordance between manually gated subsets and tSNE projection.

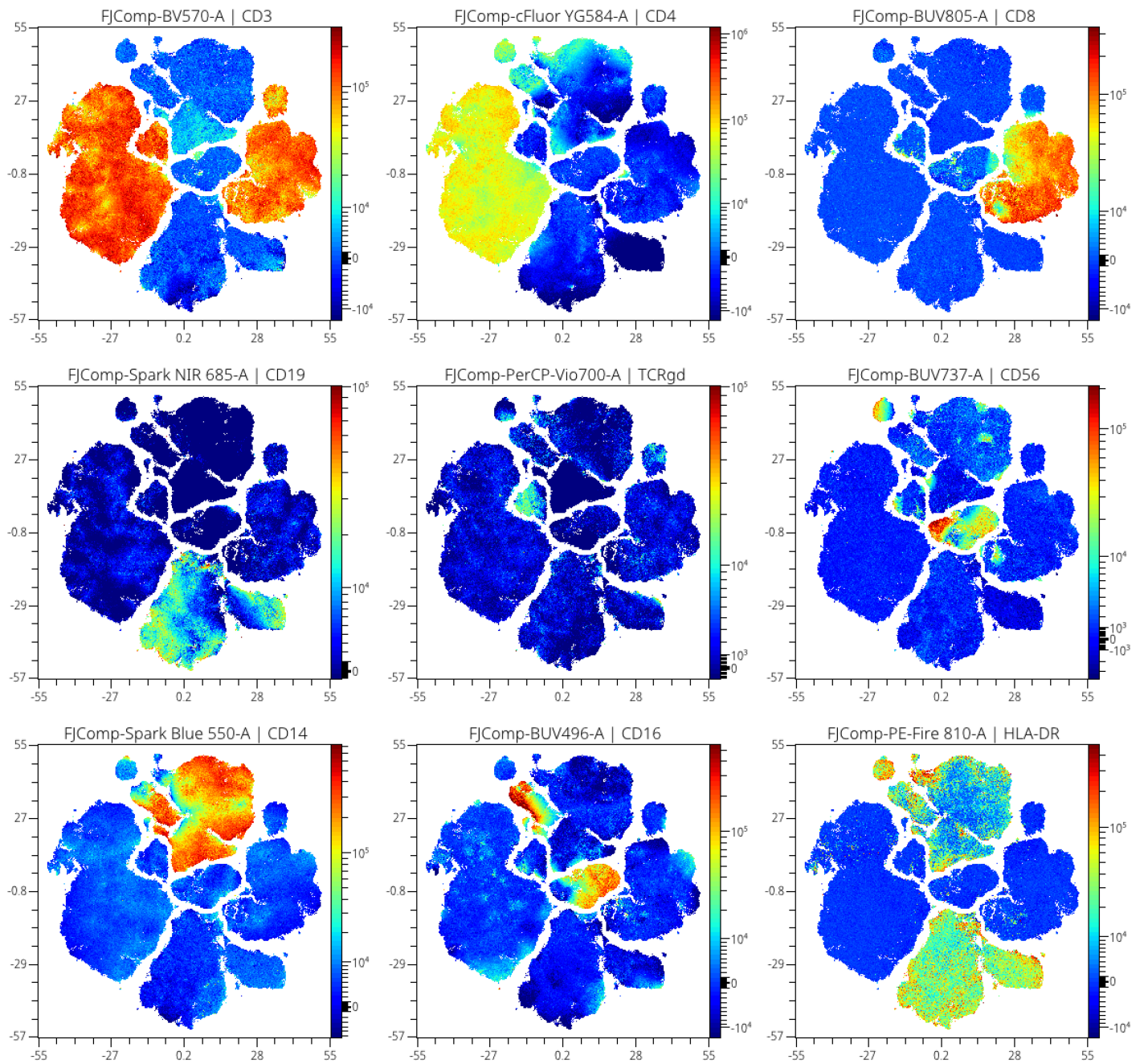
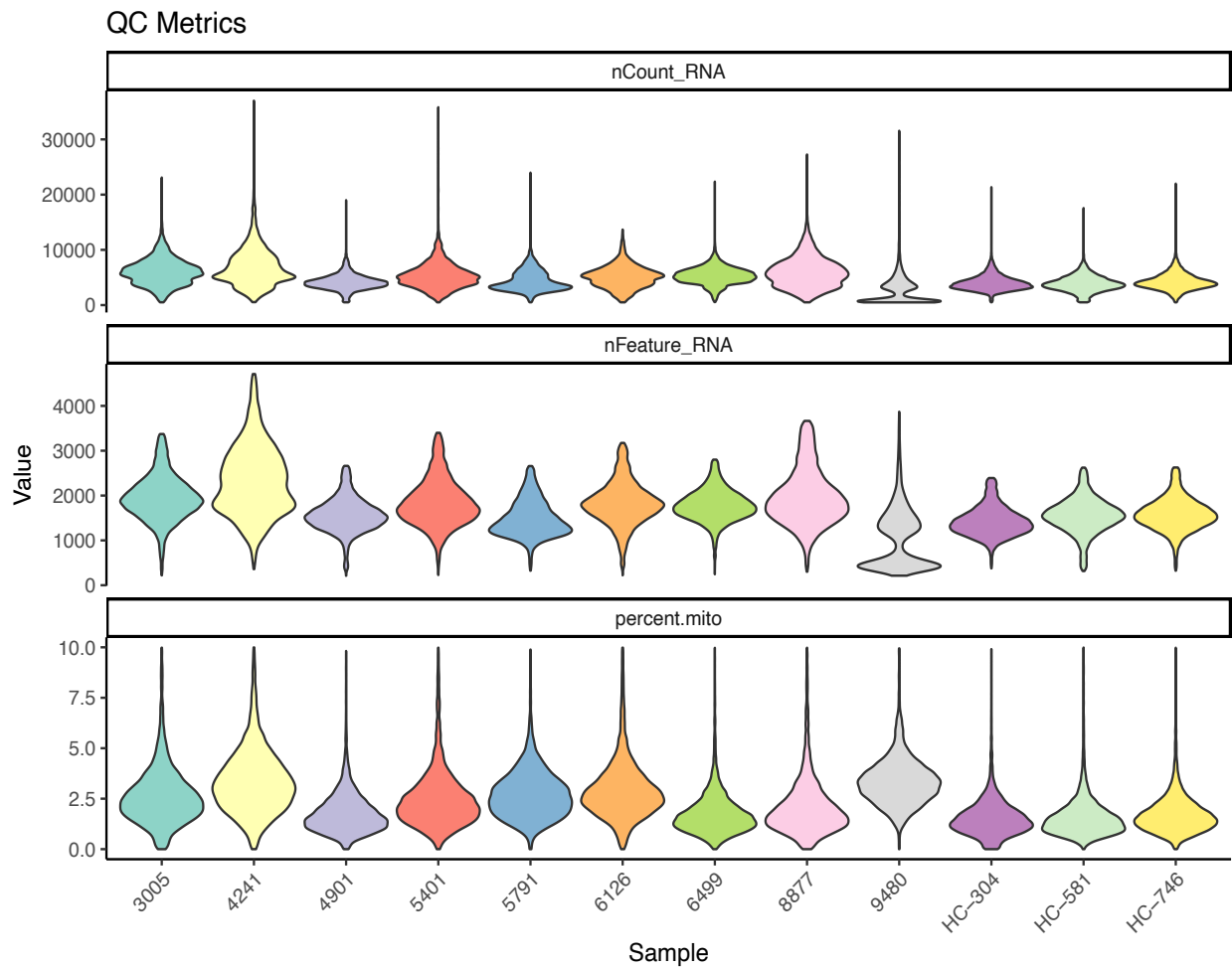


Figure S5. Results from single cell transcriptomics quality control and integration steps.

(A) Quality Control

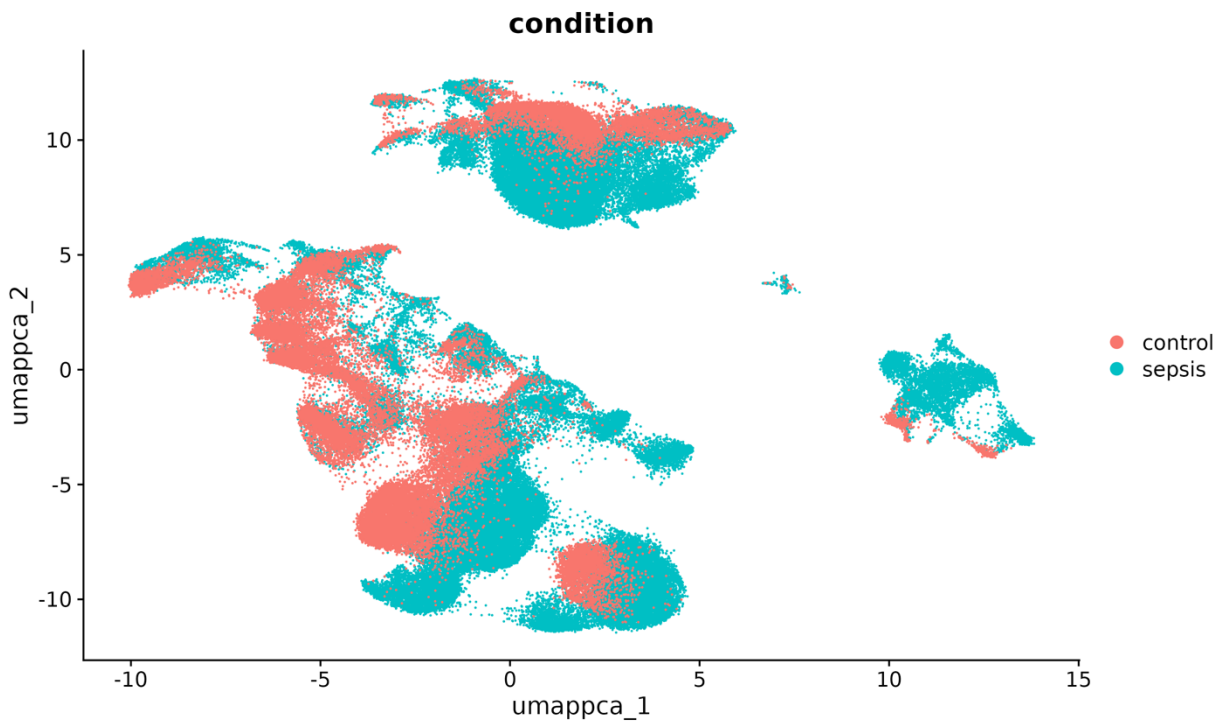
After review of standard quality control metrics, cells with less than 200 genes, greater than 3 median absolute deviation above the median, and >10% mitochondrial RNA content were removed from downstream analysis.

After applying these quality control steps, sample quality was consistent across groups.

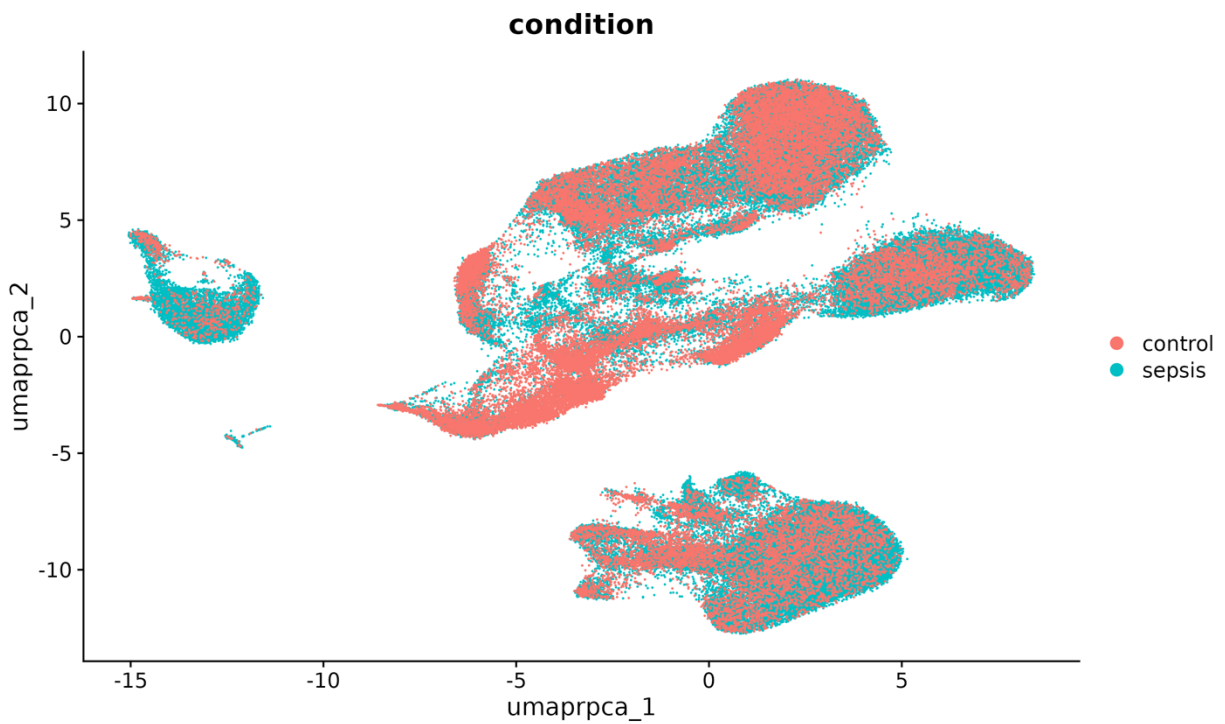


(B) RPCA Integration

Unintegrated data demonstrates differences between Group C Patients and HC Participants.



Integration with RPCA resolves discrepancies between Group C Patients and HC Participants.



After integration, each RPCA cluster contains cells from MODS patients and HC participants.

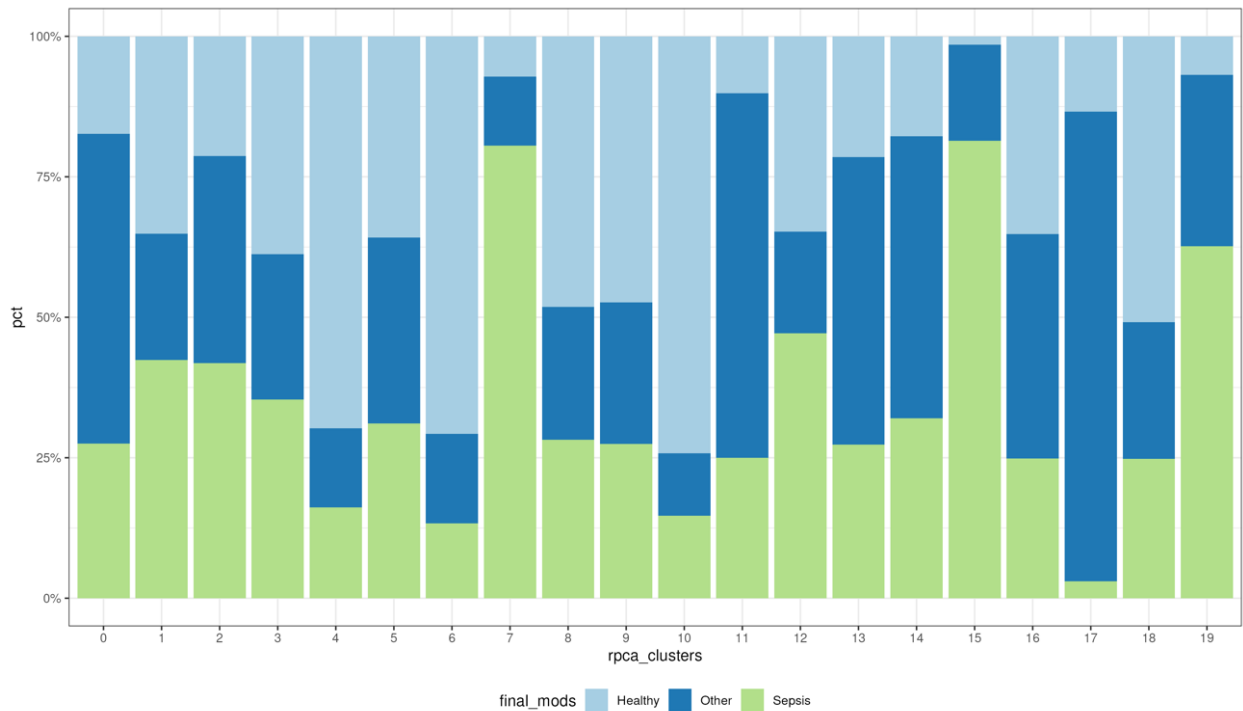


Table S1. 1472 proteins measured in proteomics panel used in MODS and HC cohorts.

Due to its size, Table S1 is available in the supplemental spreadsheet.

Table S2. Antibodies used in 35-marker spectral flow immune phenotyping panel.

MARKER	FLUOROPHORE	VENDOR	CLONE	CATALOG NO.
CD45RA	BUV395	BD Biosciences	H100	740298
Live/Dead	LD Blue	Thermo Fisher	N/A	L34961
CD16	BUV496	BD Biosciences	3G8	612944
CD26	BUV563	BD Biosciences	L272	749181
CD39	BUV661	BD Biosciences	TU66	749967
CD56	BUV737	BD Biosciences	NCAM16.2	612767
CD8	BUV805	BD Biosciences	SK1	612889
CCR7	BV421	BioLegend	G043H7	353208
CD123	Super Bright 436	Thermo Fisher	6H6	62-1239-42
CD161	eFluor 450	Thermo Fisher	HP-3G10	48-1619-41
ICOS	BV480	BD Biosciences	DX29	746248
Ki67	BV510	BD Biosciences	B56	563462
CD3	BV570	BioLegend	UCHT1	300436
CCR4	BV605	BioLegend	L291H4	359418
CD95	BV650	BioLegend	DX2	305642
CCR6	BV711	BioLegend	G034E3	353436
CXCR5	BV750	BD Biosciences	RF8B2	747111
PD-1	BV785	BioLegend	EH12.2H7	329930
Foxp3	Alexa Fluor 488	BioLegend	259D	320212
CD14	Spark Blue 550	BioLegend	63D3	367148
CD20	PerCP	BioLegend	2H7	302324
CD11b	PerCP-Cy5.5	BioLegend	ICRF44	301328
TCR $\gamma\delta$	PerCP-eFluor 710	Thermo Fisher	B1.1	46-9959-42
IgD	PE	BioLegend	IA6-2	348204
CD4	eFluor YG584	CYTEK	SK3	R7-20041-100T
Tbet	PE-Cy5	Thermo Fisher	4B10	15-5825-80
CD25	PE-Alexa Fluor 700	Thermo Fisher	CD25-3G10	MHCD2524
CXCR3	PE-Cy7	BioLegend	G025H7	353720
HLA-DR	PE-Fire 810	BioLegend	L243	307683
CRTH2	APC	BioLegend	BM16	350110
CD11c	Alexa Fluor 647	BioLegend	3.9	301620
CD19	Spark NIR 685	BioLegend	HIB19	302270
CD127	APC-R700	BD Biosciences	HIL-7R-M21	565185
CD27	APC-eFluor780	Thermo Fisher	O323	47-0279-42
CD38	APC/Fire 810	BioLegend	HIT2	303550

Table S3. PCA loadings in Figure 1D, using the full proteomics dataset.

DIMENSION 1 (TOP 25 PROTEINS)	
PROTEIN NAME	CONTRIBUTION
POLR2F	0.92969158
MAD1L1	0.91356503
TXLNA	0.89474736
ELOA	0.86811405
DPY30	0.86400025
EGLN1	0.85809847
ZBTB17	0.85543741
APBB1IP	0.85335406
PXN	0.85301337
GPKOW	0.85281899
DFFA	0.85090827
OGFR	0.84328415
HDGF	0.841057
PLAUR	0.84001585
NUDC	0.83925242
INPP1	0.83863173
GFER	0.83484888
CKAP4	0.8330877
RAD23B	0.82862877
SRP14	0.82675401
NMNAT1	0.82477831
NBN	0.82470521
EZR	0.82439488
DCTPP1	0.82416125
HEXIM1	0.82383476

DIMENSION 2 (TOP 25 PROTEINS)	
PROTEIN NAME	CONTRIBUTION
ARHGEF12	0.92927293
DBNL	0.91717031
CASP3	0.91624786
PPP1R12A	0.90434238
SRC	0.90335717
CRKL	0.90060822
NT5C3A	0.89589151
PLXNA4	0.89309739
MAP2K6	0.88974514
CA13	0.88624933
TBC1D23	0.88578306
CLIP2	0.88413467
TJAP1	0.88285037
SKAP2	0.87773049
AXIN1	0.87715071
PDLIM7	0.87685547
MANF	0.87614294
CIAPIN1	0.87457034
MYO9B	0.87420508
SNAP29	0.87219403
MAP3K5	0.87165308
DNAJA2	0.86881494
CORO1A	0.86234331
CRACR2A	0.86216539
SNAP23	0.85969907

Table S4. Severity-associated proteins identified through linear mixed-effects model after adjustment for age, sex, and day from MODS onset.

Due to its size, Table S4 is available in the supplemental spreadsheet.

Table S5. Etiology of MODS and computed subgroup for each MODS patient.

HASHED PATIENT ID	MODS ETIOLOGY	DETAILED ETIOLOGY	SUBGROUP
1018	Cardiopulmonary Bypass	Cardiopulmonary Bypass	B
1168	Sepsis	Culture Negative Sepsis	B
1234	Sepsis	Culture Negative Sepsis	C
1344	Cardiopulmonary Bypass	Cardiopulmonary Bypass	B
1426	Sepsis	Culture Negative Sepsis	B
1501	Non-infected	Exacerbation of Chronic Disease	B
1521	Sepsis	Bacterial Sepsis	B
1523	Non-infected	Cardiac Arrest	B
1568	Non-infected	No Cause Identified	B
1620	Non-infected	No Cause Identified	B
1670	Sepsis	Culture Negative Sepsis	B
1677	Non-infected	Exacerbation of Chronic Disease	C
1845	Sepsis	Viral Sepsis	A
1947	Non-infected	No Cause Identified	B
1973	Non-infected	Cardiac Arrest	A
2040	Non-infected	Postoperative Status	C
2056	Cardiopulmonary Bypass	Cardiopulmonary Bypass	B
2166	Non-infected	No Cause Identified	A
2243	Cardiopulmonary Bypass	Cardiopulmonary Bypass	B
2274	Non-infected	No Cause Identified	C
2309	Cardiopulmonary Bypass	Cardiopulmonary Bypass	B
2314	Non-infected	No Cause Identified	C
2393	Sepsis	Culture Negative Sepsis	B
2439	Cardiopulmonary Bypass	Cardiopulmonary Bypass	B
2726	Non-infected	No Cause Identified	C
2997	Non-infected	No Cause Identified	A
3005	Sepsis	Bacterial Sepsis	C
3134	Sepsis	Bacterial Sepsis	C
3227	Sepsis	Viral Sepsis	C
3365	Sepsis	Culture Negative Sepsis	C
3502	Cardiopulmonary Bypass	Cardiopulmonary Bypass	B
3596	Non-infected	No Cause Identified	B
3638	Sepsis	Bacterial Sepsis	B
3645	Non-infected	No Cause Identified	B
3783	Non-infected	No Cause Identified	C
3986	Sepsis	Culture Negative Sepsis	B
4130	Sepsis	Viral Sepsis	B
4241	Sepsis	Culture Negative Sepsis	C
4464	Non-infected	No Cause Identified	B
4638	Non-infected	No Cause Identified	B
4798	Sepsis	Viral Sepsis	B
4807	Sepsis	Culture Negative Sepsis	B
4868	Sepsis	Viral Sepsis	B
4901	Sepsis	Culture Negative Sepsis	C
5017	Non-infected	No Cause Identified	A
5368	Sepsis	Culture Negative Sepsis	A
5401	Non-infected	No Cause Identified	C
5522	Sepsis	Culture Negative Sepsis	B
5565	Sepsis	Bacterial Sepsis	B
5700	Sepsis	Viral Sepsis	B
5734	Sepsis	Viral Sepsis	A
5791	Non-infected	No Cause Identified	C
5842	Sepsis	Culture Negative Sepsis	A
5859	Cardiopulmonary Bypass	Cardiopulmonary Bypass	C
5909	Non-infected	Asphyxial Injury	C
5931	Sepsis	Viral Sepsis	C
6126	Sepsis	Bacterial Sepsis	C
6134	Non-infected	Neurologic Disease	A
6468	Sepsis	Culture Negative Sepsis	C
6499	Sepsis	Bacterial Sepsis	C
6564	Non-infected	Oncologic Disease	A

HASHED PATIENT ID	MODS ETIOLOGY	DETAILED ETIOLOGY	SUBGROUP
6606	Sepsis	Viral Sepsis	B
6698	Non-infected	Toxic Exposure	B
7184	Non-infected	Neurologic Disease	A
7331	Sepsis	Culture Negative Sepsis	C
7343	Non-infected	Cardiac Arrest	C
7411	Non-infected	Toxic Exposure	C
7433	Non-infected	Heart Failure	B
7632	Non-infected	Exacerbation of Chronic Disease	B
7639	Non-infected	Cardiac Arrest	B
7791	Trauma	Traumatic Injury	A
7810	Non-infected	Exacerbation of Chronic Disease	A
7919	Non-infected	Cardiac Arrest	A
7977	Trauma	Traumatic Injury	A
8047	Non-infected	Cardiac Arrest	B
8823	Non-infected	Cardiac Arrest	C
8825	Sepsis	Bacterial Sepsis	B
8877	Non-infected	Pulmonary Embolus	C
8893	Trauma	Traumatic Injury	A
9129	Trauma	Traumatic Injury	A
9222	Non-infected	Neurologic Disease	A
9328	Non-infected	Postoperative Status	B
9345	Non-infected	Neurologic Disease	A
9480	Sepsis	Culture Negative Sepsis	C
9484	Non-infected	Oncologic Disease	B
9630	Sepsis	Culture Negative Sepsis	C
9712	Sepsis	Viral Sepsis	C
9948	Non-infected	No Cause Identified	C

Table S6. Immunocompromised diagnoses by subgroup.

HASHED PATIENT ID	IMMUNOCOMPROMISED DIAGNOSIS	COMPUTED SUBGROUP	SURVIVAL TO PICU DISCHARGE
5368	Cancer, solid tumor	A	Yes
6564	Cancer, leukemia	A	Yes
1521	Very early onset inflammatory bowel disease	B	Yes
3596	Hematopoietic cell transplant	B	Yes
5522	Cancer, solid tumor	B	No
5565	Cancer, solid tumor	B	Yes
7433	Cancer, solid tumor	B	No
9484	Cancer, leukemia	B	Yes
3227	Hematopoietic cell transplant	C	Yes
6499	Common variable immunodeficiency	C	No
9630	Cancer, solid tumor	C	Yes

Table S7. 368 proteins measured in proteomics panel used in IEI cohort.

Due to its size, Table S7 is available in the supplemental spreadsheet.

Table S8. Leading edge analysis of protein expression in Group C patients compared to HC participants.

HALLMARK PATHWAY	FDR ADJUSTED P-VALUE	LEADING EDGE ENRICHMENT
HALLMARK_IL6_JAK_STAT3_SIGNALING	0.004779285	IL6, CCL7, PLA2G2A, REG1A, JUN, HMOX1, IL4R, TNFRSF12A, TNFRSF1A, TNFRSF1B, CXCL10, CXCL9, IL2RA, IL15RA, IL18R1, LTBR, CSF1, CD38, CXCL11, ACVRL1, IL1B, CD14, TNF, CXCL13, IL12RB1, TGFB1, CSF2RA, FAS, IFNGR1
HALLMARK_XENOBIOTIC_METABOLISM	0.005617107	PTS, FABP1, IGFBP1, FBP1, REG1A, HMOX1, TNFRSF1A, NINJ1, AHCY, CES1, ARG1, DDC, IGFBP4, EPHA2, GSTA3, DCXR
HALLMARK_INFLAMMATORY_RESPONSE	0.008012074	IL6, CCL7, CXCL8, CSF3, CCL20, LIF, TIMP1, IL10, BST2, IL4R, OSM, TNFRSF1B, CXCL10, NAMPT, CXCL9, CCL2, IL15, PLAUR, CLEC5A, LDLR, IL15RA, PVR, IL18R1, ADM, LAMP3, CSF1, MSR1, LYN, CXCL11, IL1B, CX3CL1, SLAMF1, CD14
HALLMARK_INTERFERON_ALPHA_RESPONSE	0.016318021	BST2, IL4R, GBP2, CXCL10, IL15, CASP1, LAMP3, CSF1, CD74, OGFR, PSME2, LAP3, CXCL11
HALLMARK_TNFA_SIGNALING_VIA_NFKB	0.030735353	IL6, AREG, CCL20, LIF, SERPINB8, JUN, CXCL10, NAMPT, FOSB, NINJ1, CCL2, PLAUR, CEBPB, LDLR, IL15RA, TNC, SOD2, CSF1, CCN1, B4GALT1, PTX3, CXCL11, KYNU, IL1B, CCL4, TNF, NFKBIE, VEGFA, TANK, F3, IL18, ICAM1
HALLMARK_INTERFERON_GAMMA_RESPONSE	0.031250000	IL6, CCL7, BST2, IL4R, CXCL10, NAMPT, CXCL9, CCL2, IL15, CASP1, IL15RA, CD274, SOD2, IL18BP, CD38, CD74, OGFR, PSME2, VAMP5, LAP3, CXCL11
HALLMARK_OXIDATIVE_PHOSPHORYLATION	0.035126235	NDUFS6, GRPEL1, ACAA1, POLR2F, BAX, COX5B
HALLMARK_UNFOLDED_PROTEIN_RESPONSE	0.035144814	IGFBP1, ZBTB17, EIF4EBP1, CCL2, CEBPB, NPM1, FUS, PREB, BAG3, VEGFA
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	0.038038038	IL6, AREG, CXCL8, SDC1, PRSS2, TIMP1, JUN, FSTL3, TNFRSF12A, TFPI2, SFRP1, TNFRSF11B, THBS2, MMP3, IL15, ACTA2, TGM2, PLAUR, COL4A1, TNC, BGN, PVR, CAPG, IGFBP4, VCAN, IGFBP2
HALLMARK_ESTROGEN_RESPONSE_LATE	0.044102564	AREG, KRT19, AGR2, TFPI2, SORD, FKBP4, MDK, TFF1, IGFBP4, CA12, DCXR, SLC16A1, TFF3, BLVRB, MAPT, FABP5, FKBP5

Table S9. Sensitivity analysis of corticosteroid effects on IL-6/JAK/STAT3 signaling by cell type.

CELL SUBSET	MEDIAN MODULE ENRICHMENT SCORE		CLIFF'S DELTA (δ)	EFFECT MAGNITUDE
	NO STEROIDS (N=5)	YES STEROIDS (N=4)		
Naive CD8 ⁺ T cells	-0.00326	0.005823	-0.11232	negligible
CD8 ⁺ CM cells	-0.00572	0.008703	-0.23267	small
CD8 ⁺ EM cells	0.020369	0.027366	-0.09088	negligible
CD8 ⁺ EMRA cells	0.009158	0.003892	0.06261	negligible
Naive CD4 ⁺ T cells	0.018118	0.028621	-0.10488	negligible
Effector CD4 ⁺ T cells	0.03926	0.044894	-0.05697	negligible
TCR $\gamma\delta$ ⁺ T cells	0.040752	0.035835	0.056015	negligible
NK-T cells	0.006283	0.022906	-0.17376	small
NK cells	0.019151	0.028349	-0.10808	negligible
Naive B cells	0.021713	0.00994	0.13029	negligible
Immature B cells	0.046097	0.041441	0.05601	negligible
Memory B cells	0.020756	-0.00845	0.293559	small
Plasma cells	0.022026	0.01702	0.04128	negligible
Classical Monocytes	0.122681	0.038143	0.423969	medium
Non-classical Monocytes	0.091807	0.077438	0.096315	negligible

Cliff's Delta (δ) is a non-parametric effect size measure quantifying the difference between two distributions. We interpreted effect magnitudes using standard thresholds (26): negligible ($|\delta| < 0.15$), small ($0.15 \leq |\delta| < 0.33$), medium ($0.33 \leq |\delta| < 0.47$), and large ($|\delta| \geq 0.47$). A positive δ indicates higher scores in the "No Steroids" group (consistent with steroid-mediated suppression), while a negative δ indicates higher scores in the "Yes Steroids" group (consistent with a lack of response to corticosteroids).

Table S10. Antibodies used in 13-marker T cell phosphoflow cytometry panel.

MARKER	FLUOROPHORE	VENDOR	CLONE	CATALOG NO.
CD4	BUV395	BD	RPA-T4	564724
Live/Dead Aqua	V500	Thermo Scientific	N/A	L34966
CD14	V500	BD	M5E2	561391
CD16	V500	BD	3G8	561394
CD19	V500	BD	HIB19	561121
CD8a	BV605	BioLegend	RPA-T8	301040
CD45RA	BV650	BD	HI100	563963
CD27	BV785	BioLegend	O323	302832
pSTAT1	AF488	BD	4A	612596
pSTAT3	PE	BD	4/P STAT3	612569
pSTAT5	PE-Cy7	BD	47	560117
Total STAT3	APC	BD	M59-50	560392
CD3	APC-R700	BD	UCHT1	565119

Table S11. Modified Proulx criteria used for screening and enrollment in the MODS cohort.

ORGAN SYSTEM	CLINICAL AND LABORATORY CRITERIA FOR ORGAN DYSFUNCTION ¹
Respiratory Dysfunction	i) Respiratory rate > 90 breaths per min (age < 1yr) or > 70 breaths per min (age ≥ 1yr) OR ii) PaO₂ < 40 mmHg (5.3kPa) in absence of cyanotic congenital heart disease OR iii) PaCO₂ ≥ 65 mmHg (8.7kPa) OR iv) PaO₂/FiO₂ < 200 in absence of cyanotic congenital heart disease (where P/F ratio is based on simultaneous measurements) OR v) Mechanical ventilation (1) Must be for > 24hrs post-operative if intubated just for surgery/procedure (2) Includes new HFNC ≥ 6L/min, non-invasive ventilation (e.g. CPAP, BiPAP), and VV ECMO (3) Includes patients with tracheostomy who do NOT require mechanical ventilation at baseline (4) For subjects with non-invasive ventilation at baseline, intubation would qualify as Respiratory Dysfunction
Cardiovascular Dysfunction	i) Systolic blood pressure < 40 mmHg (age < 1yr) or < 50 mmHg (age ≥ 1yr) OR ii) Heart rate < 50 or > 220 (age < 1yr), < 40 or > 200 (age ≥ 1yr) OR iii) Cardiac arrest OR iv) pH < 7.2 with normal PaCO₂ OR v) Continuous vasoactive drug infusion for hemodynamic support (excluding dopamine infusion ≤ 5ug/kg/min) OR vi) VA ECMO OR vii) Ventricular assist device
Hematologic Dysfunction	i) Hemoglobin < 5g/dL (50g/L) OR ii) White blood cell count < 3,000/mm³ (3x10⁹/L) OR iii) Platelet count < 20,000/mm³ (20x10⁹) OR iv) PT > 20 seconds OR aPTT > 60 seconds (in absence of anticoagulation therapy)
Gastrointestinal Dysfunction	i) Gastrointestinal bleeding AND one of the following believed to be the result of gastroduodenal bleeding: (1) Drop in hemoglobin ≥ 2g/dL (20g/L) over 24 hours OR (2) Blood transfusion OR (3) Hypotension with blood pressure < 5th percentile of age OR (4) Gastric or duodenal surgery
Renal Dysfunction	i) Serum BUN ≥ 100mg/dL (36 mmol/L) OR ii) Serum creatinine ≥ 2 mg/dL (177 umol/L) without pre-existing renal disease OR iii) Dialysis and/or hemofiltration
Neurological Dysfunction	i) Fixed, dilated pupils OR ii) Glasgow coma score (GCS) < 5 in the absence of neuromuscular blocking drugs
Hepatic Dysfunction	i) Total bilirubin > 3mg/dL (60 umol/L)

- ¹ MODS criteria derived from Proulx *et al*, (27).

Table S12. Age range and sex for each healthy control participant.

HASHED PARTICIPANT ID	AGE RANGE (YEARS)	SEX
HC-105	6-10	M
HC-175	11-15	M
HC-182	0-5	F
HC-304	6-10	M
HC-335	11-15	M
HC-411	11-15	M
HC-417	16-20	M
HC-439	11-15	M
HC-500	6-10	M
HC-534	11-15	F
HC-549	0-5	F
HC-581	11-15	F
HC-598	11-15	F
HC-665	16-20	M
HC-679	6-10	F
HC-698	6-10	F
HC-730	6-10	M
HC-746	6-10	F
HC-778	6-10	M
HC-782	0-5	F
HC-841	0-5	F
HC-919	16-20	M
HC-937	0-5	M
HC-963	11-15	F
HC-979	6-10	M

Median age of HC cohort: 10 years.

Table S13. Final set of 1448 proteins which met quality control thresholds in all three experiments and were included in downstream analyses.

Due to its size, Table S13 is available in the supplemental spreadsheet.

Table S14. Gene sets used in GSEA and GSVA analysis.

GENE SET	GENE SYMBOLS
HALLMARK_ TNFA_ SIGNALING_ VIA_NFKB	ABCA1, ACKR3, AREG, ATF3, ATP2B1, B4GALT1, B4GALT5, BCL2A1, BCL3, BCL6, BHLHE40, BIRC2, BIRC3, BMP2, BTG1, BTG2, BTG3, CCL2, CCL20, CCL4, CCL5, CCN1, CCND1, CCNL1, CCRL2, CD44, CD69, CD80, CD83, CDKN1A, CEBPB, CEBPD, CFLAR, CLCF1, CSF1, CSF2, CXCL1, CXCL10, CXCL11, CXCL2, CXCL3, CXCL6, DENND5A, DNAJB4, DRAM1, DUSP1, DUSP2, DUSP4, DUSP5, EDN1, EFNA1, EGR1, EGR2, EGR3, EHD1, EIF1, ETS2, F2RL1, F3, FJX1, FOS, FOSB, FOSL1, FOSL2, FUT4, G0S2, GADD45A, GADD45B, GCH1, GEM, GFPT2, GPR183, HBEGF, HES1, ICAM1, ICOSLG, ID2, IER2, IER3, IER5, IFIH1, IFIT2, IFNGR2, IL12B, IL15RA, IL18, IL1A, IL1B, IL23A, IL6, IL6ST, IL7R, INHBA, IRF1, IRS2, JAG1, JUN, JUNB, KDM6B, KLF10, KLF2, KLF4, KLF6, KLF9, KYNU, LAMB3, LDLR, LIF, LITAF, MAFF, MAP2K3, MAP3K8, MARCKS, MCL1, MSC, MXD1, MYC, NAMPT, NFAT5, NFE2L2, NFIL3, NFKB1, NFKB2, NFKBIA, NFKBIE, NINJ1, NR4A1, NR4A2, NR4A3, OLR1, PANX1, PDE4B, PDLIM5, PER1, PFKFB3, PHLDA1, PHLDA2, PLAU, PLAUR, PLEK, PLK2, PLPP3, PMEPA1, PNRC1, PPP1R15A, PTGER4, PTGS2, PTPRE, PTX3, RCAN1, REL, RELA, RELB, RHOB, RIGI, RIPK2, RNF19B, SAT1, SDC4, SERPINB2, SERPINB8, SERPINE1, SGK1, SIK1, SLC16A6, SLC2A3, SLC2A6, SMAD3, SNN, SOCS3, SOD2, SPHK1, SPSB1, SQSTM1, STAT5A, TANK, TAP1, TGIF1, TIPARP, TLR2, TNC, TNF, TNFAIP2, TNFAIP3, TNFAIP6, TNFAIP8, TNFRSF9, TNFSF9, TNIP1, TNIP2, TRAF1, TRIB1, TRIP10, TSC22D1, TUBB2A, VEGFA, YRDC, ZBTB10, ZC3H12A, ZFP36
HALLMARK_ IL6_ JAK_STAT3_ SIGNALING	A2M, ACVR1B, ACVRL1, BAK1, CBL, CCL7, CCR1, CD14, CD36, CD38, CD44, CD9, CNTFR, CRLF2, CSF1, CSF2, CSF2RA, CSF2RB, CSF3R, CXCL1, CXCL10, CXCL11, CXCL13, CXCL3, CXCL9, DNNT, EBI3, FAS, GRB2, HAX1, HMOX1, IFNAR1, IFNGR1, IFNGR2, IL10RB, IL12RB1, IL13RA1, IL15RA, IL17RA, IL17RB, IL18R1, IL1B, IL1R1, IL1R2, IL2RA, IL2RG, IL3RA, IL4R, IL6, IL6ST, IL7, IL9R, INHBE, IRF1, IRF9, ITGA4, ITGB3, JUN, LEPR, LTB, LTBR, MAP3K8, MYD88, OSMR, PDGFC, PF4, PIK3R5, PIM1, PLA2G2A, PTPN1, PTPN11, PTPN2, REG1A, SOCS1, SOCS3, STAM2, STAT1, STAT2, STAT3, TGFB1, TLR2, TNF, TNFRSF12A, TNFRSF1A, TNFRSF1B, TNFRSF21, TYK2
HALLMARK_ IL2_STAT5_ SIGNALING	ABCB1, ADAM19, AGER, AHCY, AHNAK, AHR, ALCAM, AMACR, ANXA4, APLP1, ARL4A, BATF, BATF3, BCL2, BCL2L1, BHLHE40, BMP2, BMPR2, CA2, CAPG, CAPN3, CASP3, CCND2, CCND3, CCNE1, CCR4, CD44, CD48, CD79B, CD81, CD83, CD86, CDC42SE2, CDC6, CDCP1, CDKN1C, CISH, CKAP4, COCH, COL6A1, CSF1, CSF2, CST7, CTLA4, CTSZ, CXCL10, CYFIP1, DCPS, DENND5A, DHRS3, DRC1, ECM1, EEF1AKMT1, EMP1, ENO3, ENPP1, EOMES, ETFBKMT, ETV4, F2RL2, FAH, FGL2, FLT3LG, FURIN, GABARAPL1, GADD45B, GALM, GATA1, GBP4, GLIPR2, GPR65, GPR83, GPX4, GSTO1, GUCY1B1, HIPK2, HK2, HOPX, HUWE1, HYCC2, ICOS, IFITM3, IFNGR1, IGF1R, IGF2R, IKZF2, IKZF4, IL10, IL10RA, IL13, IL18R1, IL1R2, IL1RL1, IL2RA, IL2RB, IL3RA, IL4R, IRF4, IRF6, IRF8, ITGA6, ITGAE, ITGAV, ITIH5, KLF6, LCLAT1, LIF, LRIG1, LRRC8C, LTB, MAFF, MAP3K8, MAP6, MAPKAPK2, MUC1, MXD1, MYC, MYO1C, MYO1E, NCOA3, NCS1, NDRG1, NFIL3, NFKBIZ, NOP2, NRPI, NT5E, ODC1, P2RX4, P4HA1, PDCD2L, PENK, PHLDA1, PHTF2, PIM1, PLAGL1, PLEC, PLIN2, PLPP1, PLSCR1, PNP, POU2F1, PRAF2, PRKCH, PRNP, PTCH1, PTGER2, PTH1R, PTRH2, PUS1, RABGAP1L, RGS16, RHOB, RHOH, RNH1, RORA, RRAGD, S100A1, SCN9A, SELL, SELP, SERPINB6, SERPINC1, SH3BGR2, SHE, SLC1A5, SLC29A2, SLC2A3, SLC39A8, SMPDL3A, SNX14, SNX9, SOCS1, SOCS2, SPP1, SPRED2, SPRY4, ST3GAL4, SWAP70, SYNGR2, SYT11, TGM2, TIAM1, TLR7, TNFRSF18, TNFRSF1B, TNFRSF21, TNFRSF4, TNFRSF8, TNFRSF9, TNFSF10, TNFSF11, TRAF1, TTC39B, TWSG1, UCK2, UMPS, WLS, XBP1
HALLMARK_ INTERFERON_ GAMMA_ RESPONSE	ADAR, APOL6, ARID5B, ARL4A, AUTS2, B2M, BANK1, BATF2, BPGM, BST2, BTG1, C1R, C1S, CASP1, CASP3, CASP4, CASP7, CASP8, CCL2, CCL5, CCL7, CD274, CD38, CD40, CD69, CD74, CD86, CDKN1A, CFB, CFH, CIITA, CMKLR1, CMPK2, CMTR1, CSF2RB, CXCL10, CXCL11, CXCL9, DDX60, DHX58, EIF2AK2, EIF4E3, EPSTI1, FAS, FCGR1A, FGL2, FPR1, GBP4, GBP6, GCH1, GPR18, GZMA, HELZ2, HERC6, HIF1A, HLA-A, HLA-B, HLA-DMA, HLA-DQA1, HLA-DRB1, HLA-G, ICAM1, IDO1, IFI27, IFI30, IFI35, IFI44, IFI44L, IFIH1, IFIT1, IFIT2, IFIT3, IFITM2, IFITM3, IFNAR2, IL10RA, IL15, IL15RA, IL18BP, IL2RB, IL4R, IL6, IL7, IRF1, IRF2, IRF4, IRF5, IRF7, IRF8, IRF9, ISG15, ISG20, ISOC1, ITGB7, JAK2, KLRK1, LAP3, LATS2, LCP2, LGALS3BP, LY6E, LY8MD2, MARCHF1, METTL7B, MT2A, MTHFD2, MVP, MX1, MX2, MYD88, NAMPT, NCOA3, NFKB1, NFKBIA, NLRC5, NMI, NOD1, NUP93, OAS2, OAS3, OASL, OGFR, P2RY14, PARP12, PARP14, PDE4B, PELI1, PFKP, PIM1, PLA2G4A, PLSCR1, PML, PNP, PNPT1, PSMA2, PSMA3, PSMB10, PSMB2, PSMB8, PSMB9, PSME1, PSME2, PTGS2, PTPN1, PTPN2, PTPN6, RAPGEF6, RBCK1, RIGI, RIPK1, RIPK2, RNF213, RNF31, RSAD2, RTP4, SAMD9L, SAMHD1, SECTM1, SELP, SERPING1, SLAMF7, SLC25A28, SOCS1, SOCS3, SOD2, SP110, SPPL2A, SRI, SSPN, ST3GAL5, ST8SIA4, STAT1, STAT2, STAT3, STAT4, TAP1, TAPBP, TDRD7, TNFAIP2, TNFAIP3, TNFAIP6, TNFSF10, TOR1B, TRAFD1, TRIM14, TRIM25, TRIM26, TXNIP, UBE2L6, UPP1, USP18, VAMP5, VAMP8, VCAM1, WARS1, XAF1, XCL1, ZBP1, ZNFX1
HALLMARK_ PI3K_AKT_ MTOR_ SIGNALING	ACACA, ACTR2, ACTR3, ADCY2, AKT1, AKT1S1, AP2M1, ARF1, ARHGDI, ARPC3, ATF1, CAB39, CAB39L, CALR, CAMK4, CDK1, CDK2, CDK4, CDKN1A, CDKN1B, CFL1, CLTC, CSNK2B, CXCR4, DAPP1, DDIT3, DUSP3, E2F1, ECSIT, EGFR, EIF4E, FASLG, FGF17, FGF22, FGF6, GNA14, GNGT1, GRB2, GRK2, GSK3B, HRAS, HSP90B1, IL2RG, IL4, IRAK4, ITPR2, LCK, MAP2K3, MAP2K6, MAP3K7, MAPK1, MAPK10, MAPK8, MAPK9, MAPKAP1, MKNK1, MKNK2, MYD88, NCK1, NFKBIB, NGF, NOD1, PAK4, PDK1, PFN1, PIK3R3, PIKFYVE, PIN1, PITX2, PLA2G12A, PLCB1, PLCG1, PPP1CA, PPP2R1B, PRKAA2, PRKAG1, PRKAR2A, PRKCB, PTEN, PTPN11, RAC1, RAF1, RALB, RIPK1, RIT1, RPS6KA1, RPS6KA3, RPTOR, SFN, SLA, SLC2A1,

GENE SET	GENE SYMBOLS
	SMAD2, SQSTM1, STAT2, TBK1, THEM4, TIAM1, TNFRSF1A, TRAF2, TRIB3, TSC2, UBE2D3, UBE2N, VAV3, YWHAB
HALLMARK_ OXIDATIVE_ PHOSPHOR_ YLATION	ABCB7, ACAA1, ACAA2, ACADM, ACADSB, ACADVL, ACAT1, ACO2, AFG3L2, AIFM1, ALAS1, ALDH6A1, ATP1B1, ATP5F1A, ATP5F1B, ATP5F1C, ATP5F1D, ATP5F1E, ATP5MC1, ATP5MC2, ATP5MC3, ATP5ME, ATP5MF, ATP5MG, ATP5PB, ATP5PD, ATP5PF, ATP5PO, ATP6AP1, ATP6V0B, ATP6V0C, ATP6V0E1, ATP6V1C1, ATP6V1D, ATP6V1E1, ATP6V1F, ATP6V1G1, ATP6V1H, BAX, BCKDHA, BDH2, CASP7, COX10, COX11, COX15, COX17, COX4I1, COX5A, COX5B, COX6A1, COX6B1, COX6C, COX7A2, COX7A2L, COX7B, COX7C, COX8A, CPT1A, CS, CYB5A, CYB5R3, CYC1, CYCS, DECR1, DLAT, DLD, DLST, ECH1, ECHS1, EC11, ETFA, ETFB, ETFDH, FDX1, FH, FXN, GLUD1, GOT2, GPI, GPX4, GRPEL1, HADHA, HADHB, HCCS, HSD17B10, HSPA9, HTRA2, IDH1, IDH2, IDH3A, IDH3B, IDH3G, IMMT, ISCA1, ISCU, LDHA, LDHB, LRPPRC, MAOB, MDH1, MDH2, MFN2, MGST3, MPC1, MRPL11, MRPL15, MRPL34, MRPL35, MRPS11, MRPS12, MRPS15, MRPS22, MRPS30, MTRF1, MTRR, MTX2, NDUFA1, NDUFA2, NDUFA3, NDUFA4, NDUFA5, NDUFA6, NDUFA7, NDUFA8, NDUFA9, NDUFAB1, NDUFB1, NDUFB2, NDUFB3, NDUFB4, NDUFB5, NDUFB6, NDUFB7, NDUFB8, NDUFC1, NDUFC2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NNT, NQO2, OAT, OGDH, OPA1, OXA1L, PDHA1, PDHB, PDHX, PDK4, PDP1, PHB2, PHYH, PMPCA, POLR2F, POR, PRDX3, RETSAT, RHOT1, RHOT2, SDHA, SDHB, SDHC, SDHD, SLC25A11, SLC25A12, SLC25A20, SLC25A3, SLC25A4, SLC25A5, SLC25A6, SUCLA2, SUCLG1, SUPV3L1, SURF1, TCIRG1, TIMM10, TIMM13, TIMM17A, TIMM50, TIMM8B, TIMM9, TOMM22, TOMM70, UQCRI0, UQCRI1, UQCRB, UQCRC1, UQCRC2, UQCRFS1, UQCRH, UQCRCQ, VDAC1, VDAC2, VDAC3
HALLMARK_ GLYCOLYSIS	ABCB6, ADORA2B, AGL, AGRN, AK3, AK4, AKR1A1, ALDH7A1, ALDH9A1, ALDOA, ALDOB, ALG1, ANG, ANGPTL4, ANKZF1, ARPP19, ARTN, AURKA, B3GALT6, B3GAT1, B3GAT3, B3GNT3, B4GALT1, B4GALT2, B4GALT4, B4GALT7, BIK, BPNT1, CACNA1H, CAPN5, CASP6, CD44, CDK1, CENPA, CHPF, CHPF2, CHST1, CHST12, CHST2, CHST4, CHST6, CITED2, CLDN3, CLDN9, CLN6, COG2, COL5A1, COPB2, CTH, CXCR4, CYB5A, DCN, DDIT4, DEPDC1, DLD, DPYSL4, DSC2, ECD, EFNA3, EGFR, EGLN3, ELF3, ENO1, ENO2, ERO1A, EXT1, EXT2, FAM162A, FBP2, FKBP4, FUT8, G6PD, GAL3ST1, GALE, GALK1, GALK2, GAPDHS, GCLC, GFPT1, GFUS, GLCE, GLRX, GMPPA, GMPPB, GNE, GNPD1, GOT1, GOT2, GPC1, GPC3, GPC4, GPR87, GUSB, GYS1, GYS2, HAX1, HDLBP, HK2, HMMR, HOMER1, HS2ST1, HS6ST2, HSPA5, IDH1, IDUA, IER3, IGFBP3, IL13RA1, IRS2, ISG20, KDELR3, KIF20A, KIF2A, LCT, LDHA, LDHC, LHPP, LHX9, MDH1, MDH2, ME1, ME2, MED24, MERTK, MET, MIF, MIOX, MPI, MXI1, NANP, NASP, NDST3, NDUFV3, NOL3, NSDHL, NT5E, P4HA1, P4HA2, PAM, PAXIP1, PC, PDK3, PFKFB1, PFKP, PGAM1, PGAM2, PGK1, PGLS, PGM2, PHKA2, PKM, PKP2, PLOD1, PLOD2, PMM2, POLR3K, PPFIA4, PPIA, PPP2CB, PRPS1, PSMC4, PYGB, PYGL, QSOX1, RARS1, RBCK1, RPE, RRAGD, SAP30, SDC1, SDC2, SDC3, SDHC, SLC16A3, SLC25A10, SLC25A13, SLC35A3, SLC37A4, SOD1, SOX9, SPAG4, SRD5A3, STC1, STC2, STMN1, TALDO1, TFF3, TGFA, TGFBI, TKT1L, TPBG, TPI1, TPST1, TXN, UGP2, VCAN, VEGFA, VLDLR, XYLT2, ZNF292
KEGG_ GLYCOLYSIS_ GLUCONEO_ GENESIS	ACSS1, ACSS2, ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7, AKR1A1, ALDH1A3, ALDH1B1, ALDH2, ALDH3A1, ALDH3A2, ALDH3B1, ALDH3B2, ALDH7A1, ALDH9A1, ALDOA, ALDOB, ALDOC, BPGM, DLAT, DLD, ENO1, ENO2, ENO3, FBP1, FBP2, G6PC1, G6PC2, GALM, GAPDH, GCK, GPI, HK1, HK2, HK3, LDHA, LDHAL6A, LDHAL6B, LDHB, LDHC, PCK1, PCK2, PDHA1, PDHA2, PDHB, PFKL, PFKM, PFKP, PGAM1, PGAM2, PGAM4, PGK1, PGK2, PGM1, PGM2, PKLR, PKM, TPI1
KEGG_ OXIDATIVE_ PHOSPHOR_ YLATION	ATP12A, ATP4A, ATP4B, ATP5F1A, ATP5F1B, ATP5F1C, ATP5F1D, ATP5F1E, ATP5MC1, ATP5MC1P5, ATP5MC2, ATP5MC3, ATP5ME, ATP5MF, ATP5MG, ATP5PB, ATP5PD, ATP5PF, ATP5PO, ATP6AP1, ATP6V0A1, ATP6V0A2, ATP6V0A4, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V0D2, ATP6V0E1, ATP6V0E2, ATP6V1A, ATP6V1B1, ATP6V1B2, ATP6V1C1, ATP6V1C2, ATP6V1D, ATP6V1E1, ATP6V1E2, ATP6V1F, ATP6V1G1, ATP6V1G2, ATP6V1G3, ATP6V1H, COX10, COX11, COX15, COX17, COX4I1, COX4I2, COX5A, COX5B, COX6A1, COX6A2, COX6B1, COX6B2, COX6C, COX6CP3, COX7A1, COX7A2, COX7A2L, COX7B, COX7B2, COX7C, COX8A, COX8C, CYC1, LHPP, MT-ATP6, MT-ATP8, MT-CO1, MT-CO2, MT-CO3, MT-CYB, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, NDUFA1, NDUFA10, NDUFA11, NDUFA2, NDUFA3, NDUFA4, NDUFA4L2, NDUFA5, NDUFA6, NDUFA7, NDUFA8, NDUFA9, NDUFAB1, NDUFB1, NDUFB10, NDUFB2, NDUFB3, NDUFB4, NDUFB5, NDUFB6, NDUFB7, NDUFB8, NDUFB9, NDUFC1, NDUFC2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NDUFV3, PPA1, PPA2, SDHA, SDHB, SDHC, SDHD, TCIRG1, UQCRI0, UQCRI0P1, UQCRI1, UQCRB, UQCRC1, UQCRC2, UQCRFS1, UQCRH, UQCRLH, UQCRCQ
KEGG_ MTOR_ SIGNALING_ PATHWAY	AKT1, AKT2, AKT3, BRAF, CAB39, CAB39L, DDIT4, EIF4B, EIF4E, EIF4E1B, EIF4E2, EIF4EBP1, HIF1A, IGF1, INS, MAPK1, MAPK3, MLST8, MTOR, PDPK1, PGF, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIK3R3, PIK3R5, PRKAA1, PRKAA2, RHEB, RICTOR, RPS6, RPS6KA1, RPS6KA2, RPS6KA3, RPS6KA6, RPS6KB1, RPS6KB2, RPTOR, STK11, STRADA, TSC1, TSC2, ULK1, ULK2, ULK3, VEGFA, VEGFB, VEGFC, VEGFD
SUBSPACE_ LYMPHOID_ PROTECTIVE	ARL14EP, BPGM, BTN3A2, BUB3, CAMK4, CASP8, CCNB1IP1, CD247, CD3E, CD3G, DBT, DDX6, DYRK2, JAK1, KLRB1, MAP4K1, NCR3, PIK3R1, PLCG1, PPP2R5C, SEMA4F, SIRT1, SMAD4, SMYD2, TP53BP1, TRIB2, ZAP70, ZCCHC4, ZNF831

Table S15. Gene sets used in Immune Dictionary cytokine signature analysis.

GENE SET	GENE SYMBOLS
IMMUNE_Dictionary_CD8_IL1B	SOCS3, BCL3, GADD45G, IGFBP4, GZMB, CRIP1, SOCS1, ARID5B, EMP3, SERPINB1, STAT3, SSH2, IFNGR1, GZMA, SBNO2, RGS10, ARID5A, FRMD4B, CYSLTR2, FAM241A, VARS, RGCC, NDRG3, HSD11B1, MXD1, DAPL1, CABLES1, ELOVL6, CARs, PLAC8, SKAP2, GBP2, C15orf48, FAM46A, ZBP1, AARS, MTHFD2, GPR171, CDKN2D, GPR18, NEB, RASGRP2, PIM1, FAM78A, FLOT1, THEMIS, ETV6, FAM102A, PPA1, PRELID2, ADGRE5, SMPDL3A, NSG2, ZNF281, BATF, BIN1, PPM1H, PJA1, ARL5C, ID3, CLIC4, RAMP1, CEBPB, KLHL6, TDRP, NARS, CD226, STAP1, SEMA4D, CRLF2, MAP3K8, SERPINB9, CCR9, MAPKAPK2, PPP1R16B, ICAM1, TREML2, CHST11, TSPAN32, RASGRP1, RRAS2, FKBP5, SLC41A1, CD96, SETBP1, USP6NL, GNGT2, RPAIN, S100A9, TRIB3, ITGAE, S100A8, LAMP2, YARS, IARS, LPP, RNF19A, MFSD6, DTX3L, C5orf30, SLC30A4, KIF1B, SEMA7A, ATP2B4, JAK3, SLC7A1, ACTN2, LARS, RCN3, RAB37, AHR, IDH2, SLC7A5, CLTB, MYD88, BCL2L11, PIM2, SPEF2, ABI3, SLC1A4, KIF23, CREM, TIMP2, ZFP1, LILRB4, SHMT2, GGT1, AKT2, SLPI, IRF8, ABCA2, CD55, CNDP2, TTC39B, RAB27A, TEX2, PDCD1, CKS2, MAP3K5, XPOT, GBP5, CPNE3, TRNP1, TESC, CXXC5, EPOP, MLXIP, EMC9, ANKRD28, RAPGEF3, RRP1B, GPR68, BTBD11, KCNA2, RRAGD, ALDH18A1, GPR146, PLEKHO1, HSPBAP1, LYPD6B, PLSCR1, MEX3A, CCR5, EIF4EBP1, GPRIN3, ACSS2, HSPA1A, HEXB, SLC15A2, TNIP2, AUTS2, BIRC3, MUC1, GADD45B, KCTD12, DBP, ABCB1, ODC1, GALNT10, ZC3H12D, MYO1F, TRPS1, RNF157, CEP164, KSR1, NTRK3, FGFR1, PSAT1, IL12RB2, CSRP1, SERPINI1, CCL17, FAM184A, IER3, FAS, EPHB2, AGFG2, SNX10, DGAT1, DLG3, JCHAIN, MUS81, BAHD1, RUNX2, IFITM10, ART4, FCGRT, SMPD5, HIST1H1D, METRNL, FRY, SLC15A1, CIART
IMMUNE_Dictionary_CD8_IL33	CD79A, HSPA1A, BCL3, DHX58, FCMR, MS4A1, EBF1, SERPINB1
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GENE SET	GENE SYMBOLS
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GENE SET	GENE SYMBOLS
	SPOUT1, SLC1A4, TRMT11, SLC16A2, UCK2, KLF6, RASGRP2, AHNAK, PUSL1, HIST1H4A, BTG2, RCN1, XPOT, GEMIN6, PROS1, XAF1, ZFP36L2, TECPR1, ACP5, TNP2, PCSK4, TMEM97, CAD, POLR3H, NME2, SMYD5, NFIL3, DYRK4, WARS, IPO4, YBX3, FAM46A, HLABMB, BIN1, F2R, TFDPI, ARHGAP26, DGKA, SLC7A5, PDXK, ISG20, SPECC1, PITRM1, TRAT1, YPEL3, TMTC4, PLXNA1, POLR1B, GEMIN5, THOP1, ETFBKMT, JUN, CDH1, CD7, CLUH, S100A11, TSC22D3, SCRN2, PECR, SLC25A33, AR, FOS, HGH1, MCRIP2, NEK1, TSPAN4, ABHD14A, CHAC1, SYCE2, OSBPL6, ANGPTL4, GADD45G, HSPA1A, IPCEF1, IL18R1, NEURL3, AQP9, ASNS, P2RX7, WEE1, KPNA2, TOP1MT, CIART, ARMC6, HK2, EFNA5, MTRR, FANCE, TADA2A, PDE7A, C7orf50, FRMD4B, SPN, TXNRD3, ARL5C, VCPKMT, ADGRE5, WDR59, C16orf74, PIK3IP1, SH2D1A, SLAMF6, GRAMD1A, BAG2, ARHGEF18, BSN, DDC, TRAF1, FRMD6, MXD4, MALT1, TP53INP1, SMPDL3A, KIF21B, SH3BP2, TMEM71, MADD, SLC12A7, CHEK1, LIPT2, TIMM23, ZNF566, RRAGD, FIGNL1, STIM1, NUTF2, CD55, RSAD1, TDRP, FOXO1, CDH13, MTFP1, AARSD1, THRB, SESN2, DUSP1, CXCR4, SLC6A9, POU2F2, SUV39H2, PYCR1, ESYT2, NETO2, S100A1, SELENOP, ZBTB20, GPT2, RGS2, SLC25A15, MYO19, PLEC, U2AF1L4, TLCD1, TUBA1A, CCL5, ACS2, IKZF2, MYO1F, ST3GAL1, UBE2L6, DTX1, NEB, C19orf57, LRRC32, RNF144A, GATA1, CDKN2D, ALPL, BCL9L, JUNB, LRP8, SGK1, SNRNP35, MMACHC, GGT1, TPST1, FRMD8, MAP2, RAPGEF4, DCLRE1A, PGLYRP1, TGIF2, DOCK11, PRODH, ANXA2, RETREG1, GOLM1, JAKMIP1, DAP, F2RL2, DDIT4, ACY1, IGKC, SGIP1, RACGAP1, DNAJB1, ATP1B1, CD9, FAM69B, FRY, USP2, ZNF428, TRMT5, TECPR2, COL15A1, UPRT, HEXB, EHD3, RABGAP1L, OAS1, PRF1, ENG
IMMUNE_ DICTIONARY_ CD8_IL6	IFIT3, ISG20, RSAD2, IFIT3, WDR90, PRIM1, MX1
IMMUNE_ DICTIONARY_ CD8_IL7	BCL2, EIF5A, REXO2, PPA1, PHGDH, RAN, BST2, PPP1R14B, ENO1, NME1, CDK6, SOCS1, NCL, SRM, ISG15, PAZG4, SHMT2, RANBP1, LTA, MTHFD2, EIF2S2, HSPD1, NOP56, C1QBP, CCT3, IL7R, JAML, GNL3, IFI35, NARS, TUBB4B, NOP58, MRTO4, SNRPD1, TUBA4A, CYCS, RTP4, EBNA1BP2, DKC1, TCF7, TIMM8A, METTL1, CARS, PIM1, DDX39A, CHCHD1, IGFBP4, BYSL, EIF2S1, KLRD1, PSAT1, RNF213, RRP9, SLC7A5, PLAC8, CISH, MYC, TIMM10, MARS, APEX1, GAR1, NOLC1, FKBP4, STIP1, SLC29A1, RGS10, IFRD2, MYBBP1A, HSPA9, SLC7A1, PHB, IARS, LAP3, PRPF31, RRP15, AIMP2, UCHL3, RRP1B, EPRS, ISG20, AARS, SMC4, NOC2L, ZBP1, EIF4EBP1, NSUN2, GALK1, RUVBL1, EEF1E1, RRS1, ATAD3A, DCTPP1, GARS, CORO2A, CNDP2, CDCA7, PPA1, TIMM9, CCDC86, NDUFAF4, XAF1, GADD45G, IRF7, UNG, ST6GALNAC4, GZMB, NOP16, NIFK, ZNF593, GCSH, WDR12, MAP3K8, BTG2, ODC1, LGALS3BP, MRPS18B, AGPAT3, ATP8A2, UTP18, CD3EAP, HERPUD1, YARS, TSC22D3, YPEL3, FTSJ3, OSM, GRWD1, NOP2, RPF2, SSSCA1, EIF1AX, IFIT1B, IPO5, NAF1, UCK2, ALDH18A1, MOV10, RMI2, PUSL1, LTV1, CLIC4, SOCS3, SIGMAR1, LARS, PNO1, TIMM50, SHMT1, TP11, SLC19A1, RUVBL2, PUS7, RCL1, IFIT3, FLT3LG, IPO4, MTHFD1, COMTD1, TARS, AEN, UMPS, SMYD5, TMEM238, CD7, CTPS1, FASN, AATF, SETBP1, SCO2, ZNHIT6, DAPL1, NEFH, ARL5C, XPOT, PIK3IP1, USP18, PPAT, CHCHD4, POLR3D, TMEM158, NOC4L, ACTN1, YDJC, PRMT7, TMA16, TRMT61A, HSPA1A, FAPB5, SMYD2, PIM2, CLUH, DCTD, TFAP4, TMEM97, MXD4, CD28, WARS, NEURL3, DDIT3, CXCR4, PRELID2, TRIB3, POLD2, RFLNB, TNF, FBXO17, ZDHHC8, MCM2, RRP12, PLA2G12A, USP50, ADAM19, IL2RA, CA12, HIRIP3, CIART, BCL3, ACOT7, WDR36, NOL10, SPATA5, RCC1, POLR1B, SLC30A4, TDRP, JUN, ARMC6, PIM3, CCR9, EPOP, DAP, DYRK4, PISD, C15orf48, TEX2, SLC1A4, MCM5, POLR3H, DHX58, HK2, TSPAN4, AMPD2, SOCS2, TMEM71, NSUN5, ZMYND19, FEN1, EEF1AKMT4, TP53INP1, FOS, IKZF4, SLC12A7, MRM3, GPR174, IFIT3, WEE1, THOP1, SCML4, IKBKE, CASTOR1, LIF, USP31, OAS2, SENP3, FAM46C, OAS1, SYNE1, PCSK4, CD55, ITGAE, ACS2, TXNRD3, PCMTD2, LDLR, ASNS, LIPT2, SYCE2, CD79A, IFT80, LYPD6B, POP1, C7orf50, TADA2A, GOLM1, GSDME, PHF11, ACTN2, LMNB2, AMZ1, ZER1, GPT2, SLC25A15, RGS2, MTFP1, RAPGEF4, SNTB2, CHAC1, TTC28, SUV39H2, ST3GAL1, DZIP1, OASL, HERC3, RHOB, CHEK1, FBXL20, MYO1F, DTL, FIGNL1, CARD6, HBEGF, SLC26A11, TRIM5, SLC25A40, EMC9, RSAD2, CEP164, SGSH, MFSD2A, SQLE, HLA-DOA, NETO2, HSF4, TLE1, RCN3, CDC14B, SNX8, ABCA1, PCK2, CALCRL, SESN2, SLC28A2, PYCR1, TLR7, UBE3D, UBE2L6, EPHX1, PER2, TOB1, TFDPI, HID1, TLCD1, HSD17B11, BTBD11, RRAGD, MYO19, THRA, MYB, KCNA2, PHLDA3, NUTF2, ART4
IMMUNE_ DICTIONARY_ CD8_IL12	STAT1, SOCS1, IRF1, GBP6, GBP7, GBP2, PPA1, GADD45G, ZBP1, RTP4, PIM2, IRF8, ST6GALNAC4, IRGM, GBP4, SOCS3, BCL3, AHR, GZMB, CD274, GBP5, GBP6, PRNP, IFNG, FURIN, POP1, IL2RA, HSPA1A, C3orf33, SETBP1, PDP1, CXCR4, TNKS1BP1, PTGER3, FOS, HDAC6
IMMUNE_ DICTIONARY_ CD8_IL27	ZBP1, GBP2, PLAC8, IRF7, ISG15, IFIT3, XAF1, TSC22D3, FOS, BCL3, IL12RB1, GBP4, OAS1, CYSLTR2, IFIT3, GZMA, GADD45G, GBP6, IL18BP, GZMB, ITGAX, OAS2, RGS2
IMMUNE_ DICTIONARY_ CD8_OSM	LARS2, IGFBP4, DTX1, SOCS3, TRNP1, BCL3, NEB, NME2, HSPA1A, ISG20, FOS, RSAD2, IFIT1B, SKAP2, USP18, JUN, KLF6, IFIT3, IFIT3, GADD45G, SLFN5, DHX58, CHST11, CMPK2, SERPINB1, RHOB, SPATS2, PPP1R15A, PRELID2, PHF11, IGSF23, DYNLT1, DUSP1
IMMUNE_ DICTIONARY_ CD8_IL10	BCL3, CEBPD

GENE SET	GENE SYMBOLS
IMMUNE_ DICTIONARY_ CD8_IL22	FOS, HBB
IMMUNE_ DICTIONARY_ CD8_IFNB	ISG15, IFIT3, IFIT1B, ISG20, SLFN5, ZBP1, USP18, PHF11, RNF213, IRF7, BST2, RTP4, IFI16, RSAD2, XAF1, HERC6, GBP7, PPA1, IFI35, PARP14, GBP2, OAS3, DAXX, SAMHD1, JAML, EIF2AK2, IFI16, IFI16, DDX60, IFIT3, MX1, PLAC8, IFI16, TOR3A, TRAFD1, IFI16, PSMB10, OASL, DHX58, IFIT2, IFITM3, CMPK2, PSMB8, IFIH1, LY6E, HLA-E, STAT1, PARP9, GBP6, LGALS3BP, CCND2, SLFN13, GBP6, PHF11, TAPBP, IFIT1, SMCHD1, CXCL10, PML, SOCS1, DDX58, SAMD9L, PHF11, PSME1, OAS2, EPST11, CD86, CLIC4, IFI16, HELZ2, NMI, C19orf12, GADD45G, PSME2, OAS1, SELENOW, GZMA, CHMP4B, ATP8A2, TSPO, DTX3L, SP110, PARP12, THY1, STAT2, IFI16, NCOA7, CTSS, CASP8, PSMB9, ZUFSP, CRIP1, SLCO3A1, NAMPT, ASB13, GBP6, LGALS9, GBP5, UBA7, NAA20, USP25, GBP6, UBE2L6, CCRL2, HSPA5, EMP3, TREML2, TAP1, MOV10, TMBIM6, KLF2, TRIM25, S100A10, SDC3, ASCC3, IFI44, ZNFX1, ETNK1, CALHM6, KLRD1, PARP10, PARP11, MITD1, VARS, TOR1AIP1, TRIM5, CD274, CNP, TCF7, TLR7, GIMAP1-GIMAP5, MAX, RNF114, TBRG1, DDX24, DBNL, IRGM, ADAR, CYCS, EOMES, PLA2G16, ST6GALNAC4, MS4A6A, TMEM184B, GBP4, B4GALT5, TOR1AIP2, HSH2D, PCGF5, NLRC5, S1PR1, PHGDH, RASGRP2, PHIP, ZFP36L2, AIDA, TCOF1, HLA-A, ZCCHC2, ZNF365, CTSD, PHF11, TRIM6-TRIM34, SPI40, PHC2, OGFR1, DESI2, TDRD7, KEAP1, TNFSF10, RBL1, ARF4, TRIM21, IL18BP, GZMB, ITPR1, OGFR, GPR18, FAM111A, YPEL3, TAPBP, LUZP1, TECPR1, TRIM56, TNP2, ACP5, PGD, IGFBP4, ADGRE5, MTHFD2, IFNGR1, IL12RB1, ETV6, LIPG, ACTN1, DUSP28, SLC25A22, CYSLTR2, PIM1, MORC3, AHNAK, SETDB2, FNBP4, RFC3, ATP10A, KIF21B, IRF9, PSME2, ARL5C, NEURL3, UBALD2, GBP6, FLNA, PNPT1, TMEM140, MVB12A, PLSCR3, CARS, RFLNB, ZYX, MXD4, RMI2, BCL3, HDAC7, MYD88, TTC39B, CD5, SLFN12L, SOCS3, PAPD7, MLKL, PDLIM2, CD7, TMEM192, GNG2, SLAMF7, C9orf3, AP1S3, STIM1, JAKMIP1, POU2F2, RBM43, MAP2K1, TLR3, SEPT9, FOS, IRF8, LGALS8, GMPBP, C6orf106, SNX2, C19orf66, TMEM106A, RABEPK, N4BP1, HK1, CISH, GCH1, MPEPA1, GRINA, SLFN13, RAMP1, GM2A, SLC7A1, GOLM1, SHMT2, CD200R1L, CXCR4, AARS, SLC7A5, ISOC1, CEBPB, XDH, HVCN1, ANKFY1, LAMP2, LASP1, IFITM10, EVI2A, MAFK, IARS, VPS54, ZMIZ1, DDIT3, P2RY14, BBC3, MYO1G, CXCR3, ATM, PPP1R15A, PGLYRP1, MAP7, TRIM14, NLRC3, PLCXD2, SGK1, IFI16, RETREG1, EHD4, CITED4, YARS, SIT1, APOBEC1, SSBP3, SORL1, SEMA7A, ANXA5, CPNE3, LIF, MAP3K8, TBXA2R, RCN3, PPM1K, PHLPP1, PEAK1, OSM, UBALD1, COX18, SNTB2, SH3BP2, ACTN2, WARS, PRKCE, STOML1, ARHGAP26, CCNYL1, STK26, OR2V1, VWA5A, ABCA2, CITED2, INSL6, CD72, SGSH, CD55, CCDC107, RACGAP1, UBASH3B, MYO1F, SLC17A9, RGS2, FURIN, SYNE1, TRIM5, CEP164, DHRS7, NBEAL2, CXXC5, HADH, IL10RA, TTC28, CDC42EP3, TPCN1, G0S2, SERPINI1, CARD19, GRN, ELK3, RHOB, SKI, N4BP2, TRIB2, SLC12A6, ILDR1, IZUMO4, BTBD11, MTM1, PLEKHG2, PPCDC, PINK1, SLC26A11, GPSM2, MIER3, GPRIN3, CENPA, MAST3, ITGA6, SYTL2, PIGA, CMTR1, ACSS2, TNS1, RASA4, SFXN3, ITGAE, NMRAL1, DUSP1, CD44, ZFC3H1, ANXA2, GALNT10, MAN2A2, CSTA, CGAS, PRELID2, TMIE, PGM2L1, FCGRT, SESN1, MAPK3, GNG12, SH3GLB2, MILR1, MYB, LITAF, LPIN1, ADAMTS6, CD9, TOB1, PCMTD2, CDC14B, FBXL20, AAED1, CDC25B, ZER1, NUDT14, PKD1, TUBA8, MTURN, CASP4, MAPRE2, CEP97, QRF, FRY, HID1, PEA15, RNF157, IFNG, RANBP10, LMO2, CXorf21, RNF130, HS3ST3B1, SMAD3, IL15RA, ZFH2, AGRN, PLEKHA5, ITM2A, GOLIM4, SAMD1, ARHGAP5, PAQR7, TAGAP, SLC25A40, ARMC3, NRM, RTN4RL1, SKAP2, MCEE, CTDSP2, LATS2, DTWD1, RASSF3, IL3RA, ETHE1, TRIB3, ABTB1, PLIN3, ARRB1, HDAC5, LAG3, GSN, STK39, TESK1, PACS2, P2RX4, METTL27, MOSPD3, MXRA8, SLC2A3, IZUMO1R, SPECC1, DHRS1, SLC43A2, VIPR1, SLC28A2, CHKA, FAM168A, TMEM141, IFNGR2, TRAT1, FRAT2, CHIC1, NR4A2, LRRC75B, TNFAIP8L1, KCNJ8, PXYP1, STRADA, SPICE1, ARHGAP18, HIST4H4, MAP3K3, HIST1H1D, HAUS4, SFMBT2, ALS2, WBP1, FAP, SHISA2, GAS7, CALCRL, ELOVL7, AGFG2, COL23A1, NIPAL3, ACCS, MNS1, CHAC1, UNC5CL, DDC, CASTOR1, SOX4
IMMUNE_ DICTIONARY_ CD8_IFNG	GBP2, GBP6, STAT1, GBP7, ZBP1, IRF1, SAMHD1, RTP4, ISG15, SOCS1, GBP6, BST2, CD274, IFIT3, GBP6, IRGM, TAPBP, GBP6, RNF213, PARP14, GBP5, IRF7, PARP9, DTX3L, PPA1, IL18BP, PLA2G16, XAF1, GBP4, IRF8, ISG20, IFIT1B, GBP6, NAMPT, OAS3, WARS, USP18, IFIT3, INSL6, TRAFD1, ST6GALNAC4, PARP10, IFI44, STAT2, IFIH1, OAS1, FOS, UBE2L6, PLSCR3, BCL3, NME2, CXCL10, CMPK2, MTUS2
IMMUNE_ DICTIONARY_ CD8_TNFA	IGFBP4, BCL3, CRIP1, NFKBIA, VARS, KLF2, RELB, PPA1, NFKB2, DDIT4, ZBP1, SOCS3, MAPKAPK2, GBP2, GADD45G, CARS, SDHAF1, JUN, ISG15, BIRC3, FKBP5, KLF6, TRNP1, BTG2, GZMB, BATF, AARS, SHMT2, XAF1, HSPA1A, ODC1, FOS, MTHFD2, NFKBIE, IARS, BBC3, MARS, ARID5B, CLIC4, ETV6, SKAP2, ST6GALNAC4, ICAM1, TNFRSF9, YARS, ISG20, ADGRE5, GBP5, FAM46A, MXD4, NEB, INSL6, PRELID2, PLSCR3, C15orf48, PLCG2, CYSLTR2, TRIB3, KSR1, EIF4EBP1, PPP1R15A, SLC7A5, GZMA, RHOB, SERPINB1, RGS2, CD55, CHST11, SLC1A4, SPATS2, SHMT1, CABLES1, MID1IP1, EPOP, ACTN2, SLC28A2, S100A6, CDC25B, CD83, CCL5, IFITM10, EMC9, C3orf33, IL12RB1, FOSB, TOB1, PDCD1LG2, NR4A2, VIPR1, OAS2, MYO10, CIART, ASNS, IL18BP, NOX1, EPHX1, ABCB6, SYT6
IMMUNE_ DICTIONARY_ CD8_TL1A	NFKBIA, RELB, NFKB2, ICAM1, CD82, BCL3, IKBKE, CD83, NFKBIE, BIRC3, TNFRSF9, TNFRSF25, UTF1, MGLL, FOS, LAD1, HSPA1A, GADD45G, ULBP1, PDCD1LG2, LIPT1, EFCAB2, DENND5A, SORCS2, DUSP1, ADAMTSL2, ZBTB46, CMTR2

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