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Received: December 23, 2025.

Accepted: July 13, 2026.

Citation: Angelica Johansson, Daniel Nilsson, Filippa Wikström, Lina M. Olsson, Ida Hammer, Anna Janska, Anna Sandström Gerdtsen, Anna Porwit, Peter Hollander, Mats Jerkeman and Sara Ek. Integrated spatially guided transcriptomics and multiplex imaging identify a high-risk CD163⁺/CD11c⁻ subgroup in diffuse large B-cell lymphoma.

Haematologica. 2026 July 23. doi: 10.3324/haematol.2025.300429 [Epub ahead of print]

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Integrated spatially guided transcriptomics and multiplex imaging identify a high-risk CD163+/CD11c- subgroup in diffuse large B-cell lymphoma

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Short title: Multi-Modal Investigation of High-Risk CD163+/CD11c- DLBCL

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Funding Information

We gratefully acknowledge the support from Mrs. Berta Kamprad's Cancer Foundation to the L2CancerBridge program at CREATE Health Cancer Center, FBKS-2021-6-(320)/Berta

Kamprad foundation, 21 1561 and 24 3636, Pj/Swedish Cancer Society, the Crafoord Foundation, and the Cancera Foundation. The study was supported by the grant No. MCL 7005-24 from LLS (now Blood Cancer United). All financial support was granted to S.E.

Acknowledgement

The authors acknowledge that the study was performed by the SpatialOmics@LU facility and with preparative assistance and dual IHC staining by Lena Tran at the HistoCore at Lund University. Sequencing was performed at Clinical Translational Genomics, Lund University. The authors would like to acknowledge the expertise and support with NGS services provided by Clinical Genomics Stockholm facility at the Science for Life Laboratory (jointly hosted by

Department of Microbiology, Tumor and Cell biology at Karolinska Institutet and Department of Gene Technology at School of Engineering Sciences in Chemistry, Biotechnology and Health at KTH Royal Institute of Technology) and the Genomic Medicine Center Karolinska at the Karolinska University Hospital. The authors thank all patients who have made the study possible, and all technical staff involved in collecting and assembling the Biobank of Lymphomas in Southern Sweden tissue cohort and for providing the associated clinical information.

Data availability

The data generated in this study are available upon reasonable request from the corresponding author.

Code availability

The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author.

Conflict of Interests

Mats Jerkeman has received research support from AbbVie, AstraZeneca, BMS, Roche, and honoraria from AbbVie, AstraZeneca, BeOne, BMS, Galapagos, Genmab, Kite/Gilead, Lilly, and Roche. All other authors declare no potential conflicts of interest.

Author contributions

A. Johansson: Data curation, formal analysis, investigation, visualization, writing and revision of the manuscript. D. Nilsson: Formal analysis, investigation, methodology, visualization, writing and revision of the manuscript. F. Wikström: Formal analysis, investigation. L. M. Olsson: Formal analysis, investigation, methodology. I. Hammer: Formal analysis, investigation. A. Janska: Formal analysis, investigation. A. S. Gerdtsen: Supervision, writing, review & editing. A. Porwit: Supervision, review & editing. P. Hollander: Supervision, resources, review & editing. M. Jerkeman: Funding acquisition, project administration, resources, supervision, review & editing. S. Ek: Conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, supervision, writing and revision of the manuscript.

Abstract

Emerging data identify infiltrating immune cells in diffuse large B-cell lymphoma (DLBCL) as prognostic biomarkers with tentative implications for therapeutic stratification. To elucidate the tumor immune microenvironment (TIME) and molecular features governing outcome, we integrated data from multiplex immunofluorescence imaging of CD163⁺ and CD11c⁺ cells with spatially guided transcriptional profiling of infiltrating CD3⁺ and CD163⁺ immune cells alongside CD20⁺ malignant cells across a cohort of 561 DLBCL cases. For quantification of cell densities, a multi-step workflow was used, incorporating machine-learning classifiers to improve accuracy, and the underlying biology was explored through cancer and immune-focused gene expression analysis. We identified a subgroup of patients with a CD163^{low}/CD11c^{high} TIME and favorable prognosis. By contrast, a CD163^{high}/CD11c^{low} TIME exhibited poor outcome independent of established clinicopathological risk factors. To verify the clinical utility, we showed that these subgroups can be identified with a routine pathology dual IHC staining. The high-risk CD163/CD11c subgroup had abundant expression of M2-like markers (*MRC1*, *SIGLEC1*, *MARCO*) and showed evidence of T-cell exhaustion, with higher levels of *LAG3*. Of tentative translational value, the low-risk TIME expressed the checkpoint inhibitor *CTLA4*. Multivariate modelling identified a high-risk gene signature with prognostic value in independent public datasets of CHOP and R-CHOP-treated DLBCL, underscoring the robust and broad prognostic impact of CD163⁺ and CD11c⁺ cells across clinical studies.

The combined analysis of CD163 and CD11c have the potential for implementation in routine clinical use and provides independent prognostic information with implications for stratification to novel therapeutic regimens, potentially checkpoint inhibitors LAG-3 or CTLA-4 for high and low-risk groups, respectively.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype (25-35%) of non-Hodgkin lymphoma, characterized by aggressive behaviour and a high degree of clinical and molecular heterogeneity.¹ The introduction of rituximab, a monoclonal anti-CD20 antibody, in combination with chemotherapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), marked a significant advancement in treatment and significantly improved overall survival (OS), resulting in 60-70 % of patients reaching complete remission². For relapsed or refractory patients, CD19 CAR-T cell therapy and CD3:CD20 bispecific antibodies are approved and have demonstrated encouraging clinical efficacy.³ However, other immune-targeting treatments, such as checkpoint blockade of programmed cell death 1 (PD-1), have shown limited response in DLBCL, and predictive biomarkers are lacking.⁴ To take full advantage of breakthroughs in immunotherapy, such options should be considered up front for high-risk patients. In an upcoming clinical trial, high-risk DLBCL patients will be stratified to CAR-T cells as part of frontline treatment (EU Trial number: 2025:522639-36-00), partly based on genetic classification using LymphPlex⁵ a simplified version of LymphGen.^{6, 7} Genetic classification only partially overlap with the well-established cell-of-origin (COO) DLBCL subtypes. COO defines a molecular distinction in the developmental stage of malignant B-cells⁸, and the germinal center B cell-like (GCB) subtype has been shown to have a superior prognosis to the activated B cell-like (ABC) subtype⁹, but is not currently used for patient stratification in clinical practice.

To fully take advantage of the development of immune-mediated and directed therapeutic strategies, including checkpoint inhibitors, CAR-T cells, but also emerging strategies for macrophage re-polarization, an improved understanding of the TIME cellular and molecular heterogeneity is needed. Informed strategies that integrate different types of risk parameters to enable precision medicine efforts for broader sets of DLBCL patients are still lacking.¹⁰

Advancements in digital pathology, single-cell and spatial omics, have improved the understanding of the DLBCL TIME.¹¹⁻¹⁶ A recent study using single-nucleus multiome analysis revealed microenvironmental lymphoma archetypes associated with immune cell subsets and cell states, with the potential to predict clinical outcome in CD19 CAR-T-cell-treated DLBCL patients.¹¹ Additionally, lymphoma ecosystems and microenvironments have been described, further connecting the DLBCL TIME with molecular subtypes and outcome.^{12, 16} Using image-based approaches, Colombo et al. (2022) and Autio et al. (2025) have identified distinct cellular neighbourhoods (CNs) with diverse immune activity, and pinpoint relevant therapeutic targets, such as LAG-3¹³, and connected the identified CNs with outcome and response to treatment.^{13, 14} In a study by Wright et al., three TIME categories were defined: Immune-deficient, DC-enriched, and Mac-enriched. The immune-deficient category was populated mainly by tumor-cell-rich CNs, with a mix of immune-poor, myeloid-rich, and broad inflammation CNs. The DC-enriched was populated by CD11c+ dendritic cells (DCs), while the Mac-enriched mostly contained CD163+ cells.¹⁵ Additionally, Liu et al. used the GeoMx Digital Spatial Profiler (DSP) platform to define DLBCL-associated Dark zone (DZ) and Germinal center (GC) macrophage signatures, emphasizing the plasticity of immune cells across different regions of

the malignant tissue.¹⁷ Myeloid cells, including myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), particularly CD163+ M2-like macrophages, are involved in immune suppression and associated with poor outcomes in DLBCL.^{15, 18-20} In contrast, CD11c has been suggested as an indicator of favorable prognosis and a potential biomarker for stratification for treatment prediction, and is often found on the conventional type 1 DC subtype (cDC1).^{21, 22} With increasing evidence of the importance of the myeloid compartment in DLBCL, there is a need to define strategies with independent prognostic value that can be easily implemented in routine practice, and to identify druggable molecular traits associated with DLBCL TIME heterogeneity.

This comprehensive study evaluates the independent and combined prognostic importance of CD163+ and CD11c+ cells for overall survival (OS), independent of treatment, in DLBCL, using multiplex immunofluorescence (mIF), dual IHC staining, and downstream machine learning-based image analysis in a population-based cohort of 561 DLBCL not otherwise specified (NOS) patients. To advance the biological understanding underlying the prognostic role of CD163+ and CD11c+ cells, we investigated the differences in gene expression of combined CD163/CD11c subgroups of patients using a panel-based (1800-plex) regional transcriptomic analysis of CD20+, CD3+, and CD163+ cells.

Methods

Further details of the experiments and analysis are provided in the *Online Supplementary Materials and Methods*.

Patient Material and Characteristics

Diagnostic formalin-fixed paraffin-embedded (FFPE) tissue biopsies were obtained from the population-based Biobank of Lymphomas in Southern Sweden (BLISS), consisting of 733 patients diagnosed with DLBCL between 2000 and 2014. Based on expert pathology review, tissue microarrays (TMAs) were constructed into 12 TMA receiver blocks and the final BLISS-DLBCL TMA cohort consisted of 643 patients (Figure 1). The study was approved by the Ethical Regional Committee in Lund (2014/854 (2019-04444)). All subjects gave informed consent for inclusion before participating in the study. This study was conducted following the Declaration of Helsinki.

Tumor-only Panel Sequencing

DNA was extracted from 106 FFPE samples, selected for sequencing analysis based on the availability of clinical data and DNA quality. Selected TP53 mutations for each patient are listed in *Online Supplementary Table S1*.

Multiplex Immunofluorescent (mIF) and Immunohistochemistry (IHC) staining

Staining of replicate mIF slides was performed according to standard mIF and GeoMx DSP protocols (<https://university.nanostring.com>, accessed on August 15, 2023), resulting in the mIF CD163/CD11c panel (DAPI, CD20, CD163, CD11c) (Figure 2A and *Online Supplementary*

Figure S1A) and the DSP panel (Syto13, CD20, CD3, CD163) (*Figure 2C*). Dual IHC staining of CD163 and CD11c was performed with identical antibody clones as in the mIF CD163/CD11c panel (*Figure 2B* and *Online Supplementary Figure S1B*), using published standard protocols²⁵. Scanning was performed using the GeoMx DSP instrument (mIF) and the Hamamatsu NanoZoomer (IHC). See details about the antibodies used in *Online Supplementary Table S2*.

Image analysis of mIF and dual IHC

Segmentation and classification of the mIF CD163/CD11c panel and IHC CD163/CD11c panel were performed using the open-access software QuPath in combination with Cellpose. Exclusion of low-quality cores yielded the mIF CD163/CD11c cohort (n=405) and the IHC CD163/CD11c cohort (n=371). The mIF CD163/CD11c cohort did not differ in the distribution of clinicopathologic parameters compared with the BLISS-DLBCL TMA-NOS cohort (n=561), as measured by Pearson's χ^2 test (*Online Supplementary Table S3*). The average proportion of positive cells was calculated in cases with two cores available; the CV between cores for the mIF CD20 staining is shown in *Online Supplementary Figure S1C*. The individual classification models for each mIF marker demonstrate high accuracy (83%-89%) (*Online Supplementary Figure S1D-E*).

Digital spatial profiling

The DSP panel was used to select one region of interest (ROI) per patient. Within each ROI, the morphology markers (CD3, CD163, or CD20) were used to define Areas of Illumination (AOIs) by thresholding fluorescence intensities, as described in GeoMx DSP protocols, as previously reported²³ (*Figure 2D*). Collection and quantification of the 1811 mRNA targets in the Cancer Transcriptome Atlas (CTA) panel was performed using the GeoMx DSP instrument. Gene and segment QC were performed in R using StandR workflow²⁴ (*Online Supplementary Figure S2*).

Data analysis

Data analysis was performed using R and Python.

mIF and dual IHC

Maximally selected rank statistics were used to determine a cutpoint of the mIF CD11c and CD163 proportions (%). The cell proportions from dual IHC and mIF staining of CD163 and CD11c, respectively, were compared using Pearson correlation. Patients were divided based on mIF CD163 and CD11c cutpoints and for dual IHC also rounded values of the cutpoints. For survival analysis, Kaplan-Meier plots, the Log-Rank test, and Cox proportional hazards models were used.

GeoMx DSP

In differential expression analysis and Gene Set Enrichment Analysis (GSEA), adjusted p-values < 0.05 were considered statistically significant. Cell-type associated gene lists were obtained from reference datasets (*Online Supplementary Table S4-S6*) and represent genes

associated with macrophages (CTA-CD163), T cells (CTA-CD3), B cells (CTA-CD20), and global gene signature (CTA-Global). CIBERSORTx²⁵ was used for cell deconvolution. The LymphoMapR was used to determine Lymphoma Microenvironment Archetype Profiles¹¹.

Model and gene signature construction

A GEX risk score was built on selected genes from a regularized logistic regression model trained on the gene expression data from CD163⁺ cell segments to distinguish between the CD163^{high}/CD11c^{low} and CD163^{low}/CD11c^{high} patients. The score was further used to divide patients into “Low”, “Intermediate”, and “High” (*Online Supplementary Figure S3*).

For validation of the constructed GEX risk score, DLBCL expression array datasets (GSE10846²⁶, GSE87371²⁷, and GSE31312²⁸) and whole RNA expression data set (GSE181063^{29,30}) were obtained from Gene Expression Omnibus (*Online Supplementary Table S7*).

Results

Patient characteristics

Clinical characteristics of the complete population-based BLISS-DLBCL cohort (n=733) and the BLISS-DLBCL TMA subcohort (n=643) are presented in *Online Supplementary Table S8*. An overview of available patient samples for each analysis is presented in Figure 1. Analysis was restricted to DLBCL-NOS cases (n=561). COO was determined using the Hans algorithm based on IHC staining of CD10, MUM-1, and BCL-6 (*Online Supplementary Figure S4A-S4C*)⁸. Among the BLISS-DLBCL TMA-NOS cases, 39.2% and 49% were classified as GCB and non-GCB, respectively, and 11.8% could not be classified (*Online Supplementary Table S8*). Previous studies have indicated a difference in outcome related to COO, but in this cohort, no difference in 5-year OS was seen (*Online Supplementary Figure S4D*). The median follow-up time in the BLISS-DLBCL TMA-NOS cohort was 6 years, and the 5-year OS was 55.8%.

Furthermore, cases treated with R-CHOP-like regimens accounted for 48%, other treatments accounted for 27%, and no treatment/missing treatment information accounted for 25% of DLBCL-NOS cases. The mIF CD163/CD11c and BLISS-DLBCL TMA-NOS cohorts had no significant difference in clinical characteristics, and with similar treatment variants of 48% receiving R-CHOP-like regimens and 26% with missing/no treatment information (*Online Supplementary Table S3*).

CD163⁺ and CD11c⁺ cell subsets enhance prognostic stratification beyond IPI.

To define the prognostic role of CD163 and CD11c-positive cells, for OS, independent on treatment, mIF staining and digital classification of CD20⁺, CD11c⁺, and CD163⁺ cell frequencies were performed (Figure 2A). The CD20⁺ cell frequency ranged from 25% to 98% among included cases. The CD11c⁺ and CD163⁺ cell frequencies were skewed, ranging from 0% to 67% (mean, 13%) and 47% (mean, 6%), respectively (*Online Supplementary Figure S5A-S5C*). Optimal cutpoints of 0.9% and 1.9% for CD163 and CD11c, respectively, were identified using maximum rank statistics (5-year OS). CD163 was associated with inferior 5-year OS, while CD11c was associated with beneficial prognosis (*Online Supplementary Figure*

S5D-G), but the individual markers were not independent of gender and IPI. In a multivariate model including both CD163 and CD11c, CD11c remained significantly associated with outcome (*Online Supplementary Figure S6A*). Furthermore, in a separate analysis of GCB and non-GCB cases, CD11c was significantly associated with superior survival only in the univariate analysis in the GCB group (*Online Supplementary Table S9*).

Combined stratification based on CD163⁺ and CD11c⁺ cell infiltration was evaluated using Kaplan-Meier survival analysis (Figure 3A). The CD163^{high}/CD11c^{low} subgroup had significantly worse survival than the CD163^{low}/CD11c^{high} subgroup (Figure 3B). Significantly inferior survival was observed in the CD163^{high}/CD11c^{low} subgroup, also after adjusting for sex and IPI (HR = 1.66, p=0.031) (Figure 3C). When assessing the prognostic effect in COO subgroups, only the GCB subgroup showed a significant difference in Kaplan-Meier survival analysis; tentatively due to overlapping survival curves during the first six months, although later time-points showed identical trends with inferior survival for the CD163^{high}/CD11c^{low} subgroup in the non-GCB subgroup (*Online Supplementary Figure S6B and S6C*). In univariate Cox-regression analysis, inferior survival was observed in the CD163^{high}/CD11c^{low} subgroup compared to the CD163^{low}/CD11c^{high} subgroup in both GC and non-GCB (*Online Supplementary Figure S6D*), and chi-square analysis showed that several of the established high-risk clinical characteristics were enriched in the CD163^{high}/CD11c^{low} subgroup including IPI and COO (*Online Supplementary Table S10*). The CD20⁺ (tumor) cell frequency measured by mIF did not differ significantly between the CD163/CD11c subgroups (*Online Supplementary Figure S6E*).

Data on TP53 mutational status were available in a subset of 80 patients. Chi-Square test showed no difference in TP53 mutational status among the CD163/CD11c subgroups (*Online Supplementary Figure S7A and S7B*), but the frequency of TP53 mutations was higher in the favorable prognostic subgroup, CD163^{low}/CD11c^{high} (35%), compared to the poor prognostic CD163^{high}/CD11c^{low} (21%) and the CD163^{high}/CD11c^{high} subgroup (16%).

Overall, these results suggest that the combined analysis of CD163⁺ and CD11c⁺ cells provides additive and independent prognostic information beyond established risk factors, including sex, IPI, and TP53 mutational status.

Dual staining of CD163 and CD11c using IHC confirms the possibility of identifying the prognostic DLBCL CD163/CD11c subgroups in clinical routine.

To investigate the potential of routine clinical implementation, a dual IHC staining of CD163/CD11c was performed (Figure 2B). In the investigations of the overlapping mIF/IHC cases (IHC CD163/CD11c cohort (n=371)), the CD163 and CD11c IHC staining showed overall similar proportions as the mIF CD163/CD11c staining, with correlation values (R^2) of 0.42 and 0.34, respectively (*Online Supplementary Figure S8A-S8B*). In a comparison of cell proportions of the prognostic CD163/CD11c subgroups detected with either mIF and IHC, the proportion of CD163 and CD11c positive cells remained the same in the high abundance subgroups, respectively. However, the CD163 and CD11c cell proportion were higher as measured by IHC compared to mIF, in the low abundance subgroups but with minor differences in absolute cell frequencies (*Online Supplementary Figure S8C*). Kaplan Meier survival analysis of the combined CD163/CD11c subgroups using the mIF established cutpoints of 0.9%

(CD163) and 1.9% (CD11c) was assessed alongside potentially more clinically feasible rounded cutpoints of 1% and 2%. Both sets of cutpoints showed significant survival differences among the three stratified CD163/CD11c subgroups, with the CD163^{high}/CD11c^{low} subgroup consistently associated with worse prognosis (Figure 4 and *Online Supplementary Figure S8D*). Thus, after prospective and inter-laboratory validation, this routine methodology could be a feasible approach to include as prognostically independent information in clinical decision-making to stratify DLBCL patients for alternative first-line treatment.

Prognostic CD163/CD11c subgroups show immune activation or exhaustion, and a gene signature-based risk score can be validated in independent data.

Cell segments (AOIs) were defined using mIF staining of CD20, CD3, and CD163 in selected ROIs from 406 of the 561 available DLBCL-NOS patients. The cell segments were profiled with the GeoMx DSP and the CTA panel (~1811 transcripts) (Figure 2C-D). Stratification by the identified mIF CD163/CD11c subgroups (CD163^{high}/CD11c^{low}, CD163^{high}/CD11c^{high}, and CD163^{low}/CD11c^{high}) allowed dichotomization of 325 patients (DSP-mIF cohort) with CTA gene expression data (*Online Supplementary Figure S9A*). Protein abundance stratification across the defined CD163/CD11c subgroups corresponds to differences in mRNA expression. (*Online Supplementary Figure S9B*). To identify genes associated with the prognostic subgroups (CD163^{high}/CD11c^{low} and CD163^{low}/CD11c^{high}), differential gene expression analysis (DGEA) was performed using the complete CTA gene list in the CD20⁺, CD3⁺, and CD163⁺ cell segments (*Online Supplementary Tables S11-S13*). DGEA results were visualized using cell-type associated gene lists (*Online Supplementary Table S14-S16*).

Combined CD163 and CD11c identify distinct molecular programs in CD163⁺ cells and pinpoint migration-inducing genes associated with CD163^{high}/CD11c^{low} DLBCL.

In the CD163^{high}/CD11c^{low} subgroup, CD163⁺ cells showed increased expression of common M2-like macrophage markers, including *MRC1*, *SIGLEC1* (CD169), and *MARCO* (Figure 5A-B). Additionally, *PFKFB3*, a key regulator of glycolysis contributing to the Warburg effect in cancer cells and metabolic activation in immune cells, and *CXCL10*, an IFN- γ induced chemokine involved in monocyte and macrophage chemotaxis as well as inflammation, and *CXCL16* recruiting CXCR6⁺ lymphocytes, were all upregulated in the CD163^{high}/CD11c^{low} subgroup.^{31, 32} *C1QA* and *C1QB*, initiators of the classical complement system, were upregulated and have been associated with suppressive features and specific subtypes of macrophages related to dark-zone macrophages in DLBCL.¹⁷ In contrast, the CD163^{low}/CD11c^{high} subgroup showed upregulation of *MMP9*, *IFNGR1*, *CFP*, *IL18*, and *CCL19*, along with the expected *ITGAX* (CD11c) (Figure 5A-B). *MMP9* is associated with extracellular matrix remodelling and poor outcome in DLBCL.³³ *IFNGR1* is a subunit of the IFNGR responsible for binding to IFN- γ and initiating JAK-STAT signalling. *IL18* is an activator of NK cells³⁴, and *CCL19* binds to CCR7⁺ T-cells and can activate several signalling cascades, such as the JNK/MAPK pathway.³⁵ Visualization of the top 20 pathways, sorted by p-value, confirms the results from the individual DEGs and supports that chemotaxis and migration of monocytes are associated with the CD163^{high}/CD11c^{low} subgroup, with active recruitment of suppressive myeloid cells to the TIME. In the CD163^{low}/CD11c^{high} subgroup,

enrichment of enhanced NK cell proliferation and JNK pathway activation was identified (Figure 5C).

Exhaustion marker expression in T-cells is associated explicitly with the CD163^{high}/CD11c^{low} patient subgroup.

In the CD163^{high}/CD11c^{low} subgroup, the CD3⁺ cells showed a higher presence of cytotoxic T-cell markers (*GZMB*, *GZMH*, *GZMA*, and *PRF1*), and the exhaustion marker *LAG3* (Online Supplementary Figure S10A-S10B). This is in agreement with Roeder et al., who showed that low expression of ICOS and TCF7 in combination with high expression of cytotoxic and exhausted T-cell markers (*GZMH*, *GZMA*, *GZMB*, *LAG3*) identified a terminally exhausted T-cell phenotype in DLBCL.³⁶ In contrast, the CD163^{low}/CD11c^{high} displayed a more functional and active T helper response (*TNFRSF4* (OX40), *LTB*, *CD3*, *CD4*, *ICOS*, *TCF7*) but with the presence of Tregs and immune regulation/inhibition (*FOXP3*, *TIGIT*, and *CTLA4*). This supports previous observations where OX40, expressed on activated T-cells, was associated with co-expression of immune checkpoint inhibitors, favorable DLBCL clinical characteristics, and improved response to chemoimmunotherapy.³⁷

Level of CD163⁺ infiltration is associated with proliferative malignant cells of non-GCB origin.

In the CD163^{high}/CD11c^{low} subgroup, CD20⁺ cells showed relative upregulation of the proliferation-related *MKI67*, *MYC*, and *CDK1* genes. Several upregulated genes indicate active NK-kB signalling, which is representative of the non-GCB subtype³⁸, including *BATF*, *IRF4*, as well as *POU2F2* (OCT2), a transcription factor critical for B-cell development and lymphomagenesis.^{39, 40} In contrast, the CD163^{low}/CD11c^{high} subgroup showed higher levels of MHC class II-related HLA genes, e.g., *HLA-DRA*, *HLA-DOB*, *HLA-DQB1*, *HLA-DPA1*, and *CD74*, indicative of active antigen presentation (Online Supplementary Figure S10C-S10D). Upregulation of *FCER2*, *CR2*, *IL4R*, and *CD81* suggests an enrichment of cases of the GCB subtype, in line with IHC data.

MIF and *PLK1* (CTA-Global, no cell-type label) was upregulated in the CD163^{high}/CD11c^{low} CD20⁺ segments and is associated with tumor progression and worse survival in multiple cancer types.^{41, 42} In the CD163^{low}/CD11c^{high} subgroup, upregulation of *HLA-A* and *HLA-F* suggests expression of MHC-I, which can also be interpreted as a downregulation of MHC-I in the CD163^{high}/CD11c^{low} subgroup and thus impaired tumor neoantigen presentation⁴³ (Online Supplementary Figure S10E-S10F).

Pathway analysis in the CD20⁺ and CD3⁺ segments showed that the CD163^{high}/CD11c^{low} subgroup had upregulation of genes associated with DNA replication, chromosomal organization, cell cycle regulation, and apoptosis. In contrast, the CD163^{low}/CD11c^{high} subgroup displayed enrichment of pathways related to T-cell activation, antigen presentation, positive regulation of cell adhesion, and T-cell receptor signalling (Online Supplementary Figure S10G-S10H).

In summary, gene expression analysis showed that the poor prognostic CD163^{high}/CD11c^{low} subgroup was dominated by immunosuppressive TAMs with M2-and dark-zone-associated genes (*MRC1*, *SIGLEC1*, *MARCO*, *C1QA*, and *C1QB*), cytotoxic/exhausted T-cells (*GZMA*, *GZMB*, *PRF1*, *LAG3*), and tumor cells with a proliferative, pro-tumorigenic, and non-GCB-associated molecular profile (*MYC*, *CDK1*, *IRF4*). Patients with CD163^{low}/CD11c^{high} TIME, on the other hand, were associated with improved outcome, active antigen-presenting and immune-response molecular profile (*HLA-A*, *HLA-F*, *CD3*, *CD4*, *LTB*, *TCF7*, *ITGAX*), yet with a regulatory phenotype (*CTLA4*, *TIGIT*, *FOXP3*, *VSIR*).

Supervised feature selection identifies CD163/CD11c-associated gene signatures that predict survival in independent DLBCL cohorts

To explore the gene expression programs differentiating the prognostic mIF CD163/CD11c subgroups, a regularized logistic regression was applied to the transcriptional data. This data was collected from CD163⁺ cell segments (CD163⁺ DSP-mIF cohort: n=208). The model was trained to separate the prognostic subgroups using a repeated nested cross-validation approach and resulted in a test accuracy of 95.3% (*Online Supplementary Figure S3*). The final selection consisted of 16 genes (*Figure 6A*), and a combined GEX risk score using a weighted sum of model coefficients across the genes was created. The GEX risk score was associated with inferior OS in the discovery cohort (CD163⁺ DSP-mIF cohort) (*Figure 6B*). To validate the GEX risk score, external bulk RNA-seq datasets (GSE10846, GSE87371, GSE31312, and GSE181063) were used, and in all four, the signature was associated with inferior OS (*Figure 6B*). The GEX risk score was used to order, and stratify the patients into low, intermediate, and high risk (*Figure 6C*). In the discovery and all validation cohorts, a significant difference in OS was seen between the high and low groups. A significant difference between the intermediate and low groups was seen in three out of five cohorts (GSE10846, GSE87371, and GSE181063), and between the high and intermediate groups in four out of five cohorts (CD163⁺ DSP-mIF, GSE31312, GSE10846, and GSE181063) (*Online Supplementary Figure S11*). Kaplan-Meier survival analysis was used to visualize the difference in outcome between the low, intermediate, and high subgroups (*Figure 6D-H*).

Among the validation cohorts, only the GSE31312 cohort was uniformly treated with R-CHOP. In a sensitivity analysis, the GEX risk score was investigated in R-CHOP-treated patients from the other three cohorts with mixed treatment (GSE10846, GSE87371, and GSE181063). In this sensitivity analysis, two of the three validation cohorts had GEX risk score significantly associated with inferior OS, both as a continuous and as a categorical variable (*Online Supplementary Figure S12A and S12B*). Kaplan Meier survival analysis confirmed the observation that the risk score is significantly associated with outcome in R-CHOP selected cohorts (*Online Supplementary Figure S12C-S12E*).

Specific macrophage subtypes and DLBCL TME archetypes are associated with the prognostic CD163/CD11c subgroups.

Immune cell proportions beyond the investigated cell types were predicted using several methods, and association to the prognostic CD163/CD11c subgroups was determined. Both

subgroups showed a high proportion of M2 macrophages. The CD163^{high}/CD11c^{low} subgroup had a significantly higher predicted proportion of M1 macrophages, while the CD163^{low}/CD11c^{high} subgroup was predicted to be composed mainly of M0 macrophages (*Online supplementary Figure S13A-S13B*). Comparing MoMac-VERSE cell types, few cell types showed a significant difference in predicted frequency related to the CD11c/CD163 subgroups (*Online Supplementary Figure S13C-S13D*). Furthermore, using the LymphoMap archetypes, we identified the TEX archetype to be more abundant in the CD163^{high}/CD11c^{low} subgroup (*Online Supplementary Figure S13E*). Key markers for the TEX archetype¹¹ and the CD163^{high}/CD11c^{low} subgroup overlap and include *MRC1*, *SIGLEC1*, and *CXCL16*. The TEX archetype has been described to contain exhausted CD8⁺ T-cells and a super-activated macrophage population¹¹, in line with the present study.

Discussion

Targeted and immune-related therapeutics, including checkpoint inhibitors and CAR-T, have become more widely available for the treatment of DLBCL. Still, biologically informed selection tools to stratify DLBCL patients into optimal treatment protocols are lacking. Such tools could improve outcomes for high-risk patient groups. The relative composition of M1 and M2 macrophages has recently been highlighted as critical cell types in the DLBCL TIME.^{14, 17, 44} However, the definition of macrophages along the M1-to-M2 continuum is a simplification, and a wide range of suppressive cells are present in DLBCL TIME, including MDSCs and numerous TAM populations. Stratification based on either CD163 or CD11c alone has previously been associated with DLBCL outcomes¹⁵, but the combination of these markers and the molecular investigation of the cell populations they represent has not been described. Thus, based on recent scientific insights on the importance of CD11c-enriched or CD163-enriched DLBCL microenvironments¹⁵, our study demonstrates that the combined imaging of CD163 and CD11c enables the identification of superior- and inferior-prognosis subgroups of patients with distinct TIME DLBCL biology, independent of IPI. The high-risk group was enriched in non-GCB cases, but had a trend towards lower frequency of TP53 mutation, consistent with a reduced dependency on the cell neighbourhood and more intrinsically driven, but emphasizing that the inferior outcome is not driven primarily by TP53. We conclude that, up to five years after diagnosis, differences in outcome that are prominent early on also persist, indicating that these subgroups pinpoint inherited differences in tumor biology and/or interplay with host immune factors that also impact outcome in subsequent lines of treatment.

To enable relative comparisons, cell frequencies were determined using digital pathology tools, enabling high-throughput digital quantification of multiple immune cell subsets across large patient cohorts, an approach that until recently has been technically challenging. The difference in outcome between the CD163 and CD11c subgroups is distinct, despite the generally low frequencies of infiltrating positive cells. The cutpoints (~1 and 2%) used in the present study should not be interpreted as definitive biological thresholds, but as a tool to predict outcome, as confirmed by dual routine pathology IHC staining although requiring inter-laboratory validation in prospective studies before implementation.

To further understand the biology of these inferior (CD163^{high}/CD11c^{low}) and superior (CD163^{low}/CD11c^{high}) patient subgroups, we applied targeted spatial transcriptomics to ROIs enriched for CD20⁺, CD3⁺, and CD163⁺ cells. The CD163^{high}/CD11c^{low} subgroup was associated with classical M2-associated genes such as *MRC1*, *SIGLEC1*, and *MARCO*⁴⁵⁻⁴⁷, but using cell deconvolution analysis, pure M1/M2 phenotypes could not be distinguished within any of the prognostic CD163/CD11c subgroups. Instead, other molecular and cellular features indicate the presence of other macrophage subtypes, such as DZ macrophages¹⁷ and super-activated macrophages¹¹, in the high-risk CD163^{high}/CD11c^{low} subgroup. Of note, *PFKFB3*, a key factor in glycolysis, and reported to be important in cell migration and thus metastasis³¹, was strongly associated with the high-risk group. Small molecule inhibitors have been evaluated in other cancer types and show reduced glycolysis and suppressed tumor progression.^{48, 49} Furthermore, reprogramming the suppressive macrophage population, such as by inhibiting *MARCO*⁵⁰, in the high-risk CD163/CD11c subgroup could be a potential therapeutic approach.

The proportions of infiltrating CD163⁺ and CD11c⁺ cells are generally low, and polarization of the myeloid compartment is likely one of several TIME properties that govern outcome in the highly variable DLBCL TIME. In support of this interpretation, we show that the immunosuppressive marker *LAG3* is relatively upregulated, along with classical markers of cytotoxic T cells in the CD163^{high}/CD11c^{low} subgroup. This is in line with the original report on the TEX archetype in DLBCL¹¹, in which an exhausted T-cell phenotype is identified alongside suppressive macrophages. In the LymphoMap study by Li et al., TEX was the only archetype where patients had no benefit of CAR-T compared to the standard of care but was not directly associated with inferior survival. Furthermore, Wright et al.¹⁵ reported that CD163⁺ macrophages, compared to CD11c⁺ DC cells, had differential regulation of genes with similar functions (↑ IDO-1⁺, ↑ LAG-3⁺, ↑ CD8⁺ T-cells, ↓ HLA-DR).¹⁵

Compared with CAR-T cells and bispecific antibodies, PD-1/PD-L1, and CTLA-4 checkpoint inhibitors have shown surprisingly poor efficiency in DLBCL patients.⁴ However, new alternative checkpoint molecules, such as LAG-3, have recently been evaluated in a phase 1/2a study in combination with PD-1, in relapsed or progressed DLBCL.⁵¹ Thus, we propose that stratification by the presence of CD163^{high}/CD11c^{low} TIME may identify patient subgroups that could benefit from LAG3-directed treatment.

The beneficial CD163^{low}/CD11c^{high} subgroup of patients was characterized by increased expression of HLA genes, suggesting more active antigen presentation, a finding confirmed by pathway analysis. Furthermore, in the CD163^{low}/CD11c^{high}, higher expression of *TIGIT*, *CTLA4*, and *TCF7* was observed. This supports the need for patient stratification to select optimal checkpoint inhibitor targets in subgroups of patients with distinct TIMEs. Beyond CTLA-4 inhibition, recent studies focus on how additional checkpoint targets, such as *TIGIT*, can benefit DLBCL patients.⁵² Thus, both strategies should be explored and might provide alternatives for elderly/frail patients with low tolerance for chemotherapy, specifically in the low-risk CD163/CD11c subgroup.

Importantly, the prognostic role of the distinct molecular CD163/CD11c subgroups was validated in four independent DLBCL cohorts using a defined 16 plex weighted GEX risk score. As external mIF and IHC DLBCL data sets were unavailable to us, the defined GEX risk score was used to demonstrate that the underlying biology associated with the CD163/CD11c prognostic subgroups is predictive of outcome across cohorts. In a sensitivity analysis of the external cohorts, R-CHOP treated patients were selected, and a significant prognostic association with outcome could be confirmed in three of the four data sets. The R-CHOP treated patients in GSE87371 were few (n=109), which might explain the lack of statistical significance.

Overall, our study contributes to understanding the relationship between outcome and TIME biology in DLBCL. We conclude that routine pathology staining for CD163 and CD11c would allow stratification of DLBCL into distinct prognostic groups with fundamentally different TIME properties. The beneficial prognostic patient subgroup with CD163^{low}/CD11c^{high} TIME will potentially derive greater benefit from checkpoint-targeting inhibitors such as CTLA-4 or TIGIT and CAR-T cells. In contrast, the poor-prognostic subgroup, dominated by exhausted T-cells, highly proliferative tumor cells, and an inflammatory profile with high levels of CD163⁺ cells, might require more exploratory approaches, including targeting tumor metabolism, LAG-3 inhibition, or macrophage reprogramming.

Limitations of the Study

The study has a translational focus on the prognostic role of the CD163^{high}/CD11c^{low} patient sub-group, and full characterization of the immune compartment and functional investigation of cells are outside the scope. On the methodological side, a limitation of spatially guided transcriptomic analysis is lateral diffusion and the inevitable capture of mRNA from neighbouring cells beyond the selected cell segment. Our study observed that mRNAs related to other cell types, particularly the highly abundant malignant B-cells, were also detected within the CD3 and CD163 segments. Furthermore, because this study was limited to a selected panel of 1811 mRNAs, the cell deconvolution analysis was not fully compatible with the reference data and may not accurately distinguish specific cell populations. It is also worth noting that the study was based on TMAs with 1 mm² cores as well as even smaller regions, ROIs, for the transcriptomic analysis. The representation of the myeloid and T-cell heterogeneity remains a crucial limitation in analyzing such small regions. However, CD20 expression was consistent between cores, with reasonably low intra-patient heterogeneity. Additionally, digital pathology tools may have limitations for quantifying cells in mIF and IHC images, particularly sensitive to varying staining intensity and imaging conditions. Furthermore, the mutational and translocation status of *MYC* and *BCL2* was not available for this patient cohort, thereby precluding stratification of double-hit high-grade B-cell lymphoma. Finally, the COO classification was based on a manual pathology review of IHC staining using the Hans algorithm, not on gene expression analysis.

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Figure legends

Figure 1. Study overview. Workflow including the number of patients for which tissue and data were available. The number of collected cell segments is provided in total and for each specific analysis.

Figure 2. Overview of laboratory procedures and methods used for patient characterization. (A) Detection of CD11c⁺ and CD163⁺ cells using multiplex immunofluorescence (mIF) staining, (B) Dual IHC for technical verification of CD163/CD11c subgroup stratification, (C) the cancer transcriptome atlas (CTA) panel of mRNA probes and segmented cell types, and (D) the schematic overview of the GeoMx Digital Spatial Profiler workflow (DSP).

Figure 3. Multiplex IF analysis of CD163 and CD11c defines a combined independent subgroup of high-risk DLBCL patients beyond IPI. (A) Representative DLBCL patient cores classified as CD163^{high}/CD11c^{low} or CD163^{low}/CD11c^{high}. (B) Kaplan-Meier survival analysis curve and log-rank test comparing survival probability between CD163^{high}/CD11c^{low}, CD163^{high}/CD11c^{high}, and CD163^{low}/CD11c^{high} IF subgroups, and (C) Cox regression analysis comparing CD163^{high}/CD11c^{low} with CD163^{low}/CD11c^{high} in univariate analysis, and in multivariate analysis with gender and IP as covariates. The CD163^{low}/CD11c^{low} subgroup had only three patients and was excluded from downstream analyses.

Figure 4. Dual IHC staining confirms the prognostic CD163/CD11c subgroups. For more feasible routine pathology use, stratification based on the rounded cutpoints of 1% and 2% for CD163 and CD11c, respectively.

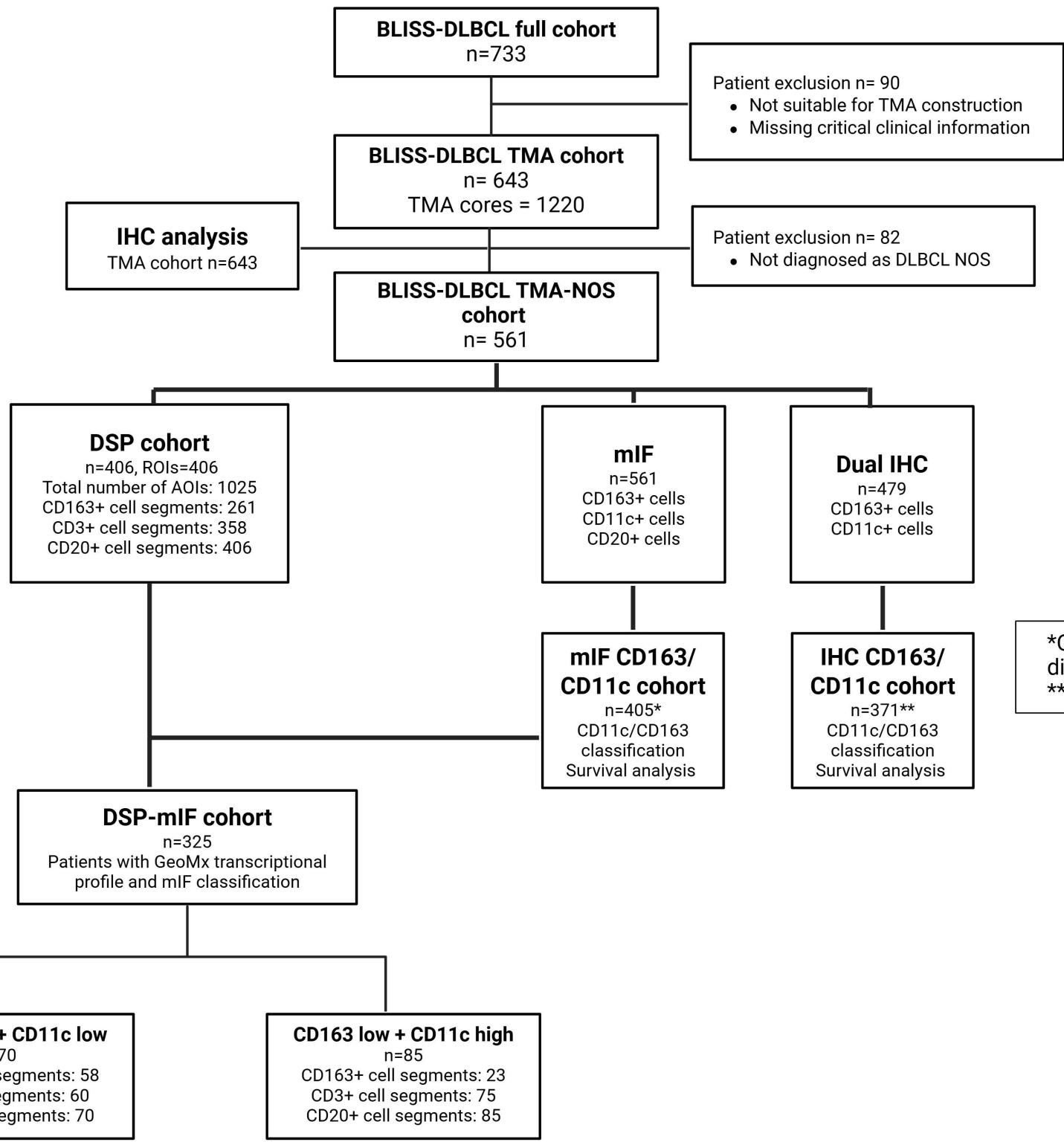
Figure 5. Characterization of the transcriptome comparing CD163^{low}/CD11c^{high} and CD163^{high}/CD11c^{low} subgroups. DEGs (adjusted p-value <0.05) in the CD163⁺ segments are shown in (A) a volcano plot where genes with logFC >0 (orange) are upregulated in the CD163^{low}/CD11c^{high} subgroup, while genes with logFC <0 (blue) are upregulated in the CD163^{high}/CD11c^{low} subgroup. (B) Heatmap with normalized gene expression represented on a red-to-blue scale. The CD163/CD11c subgroups and cell of origin (COO) are annotated for each patient, i.e., CD163⁺ segment. (C) Top 20 up- and down-regulated pathways comparing CD163^{low}/CD11c^{high} with CD163^{high}/CD11c^{low} in the CD163⁺ segments. Pathways positively associated with CD163^{low}/CD11c^{high} are shown in orange and have NES >0. Pathways positively associated with CD163^{high}/CD11c^{low} are shown in blue and have NES <0.

Figure 6. GEX risk score. A high-risk gene signature associated with the CD163^{high}CD11c^{low} subgroup was constructed from a regularized logistic regression. A) The 16-plex gene signature and corresponding weights. B) Forest plot showing Cox regression results comparing the discovery (CD163⁺ DSP-mIF) and validation cohorts. C) Scatter plot showing the distribution of the GEX risk score and group division in color across ordered patients, where the dashed lines indicate threshold values and group division. Kaplan-Meier curves of high, intermediate,

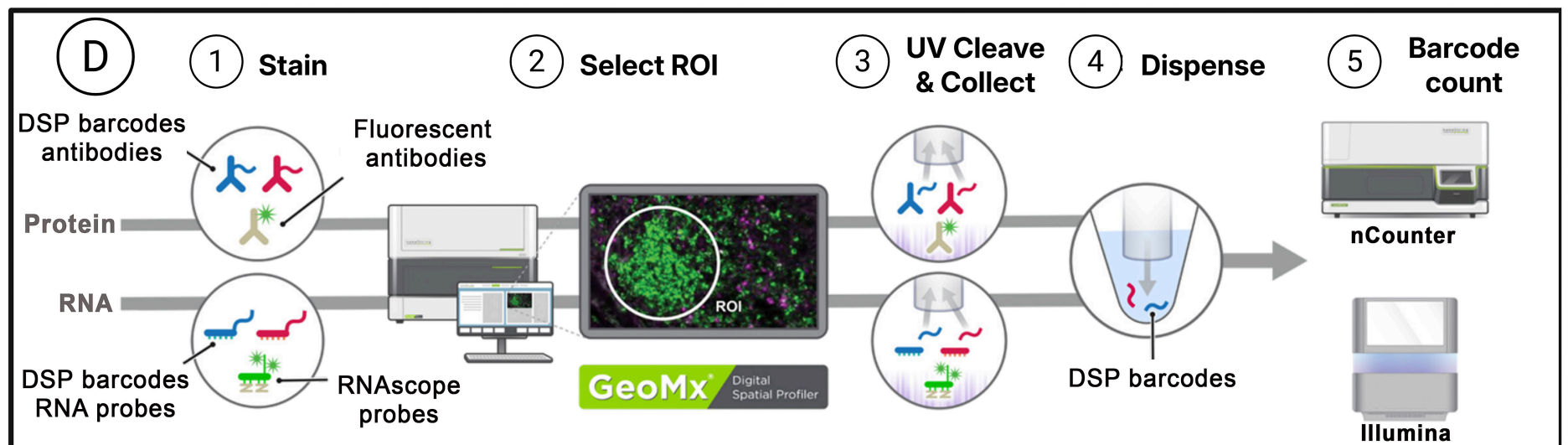
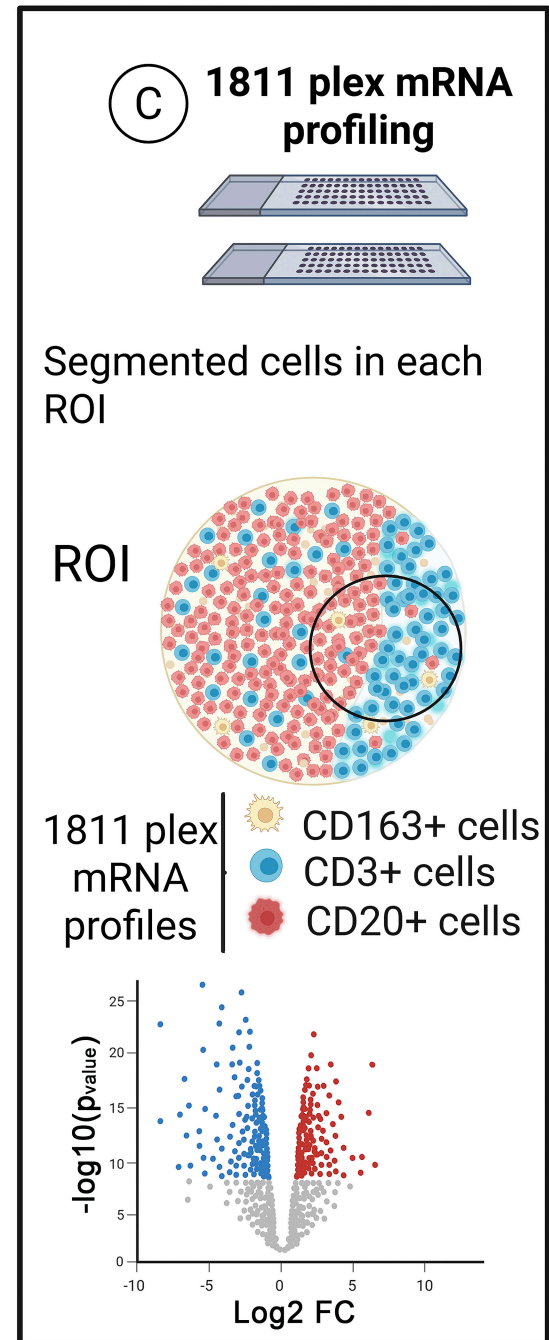
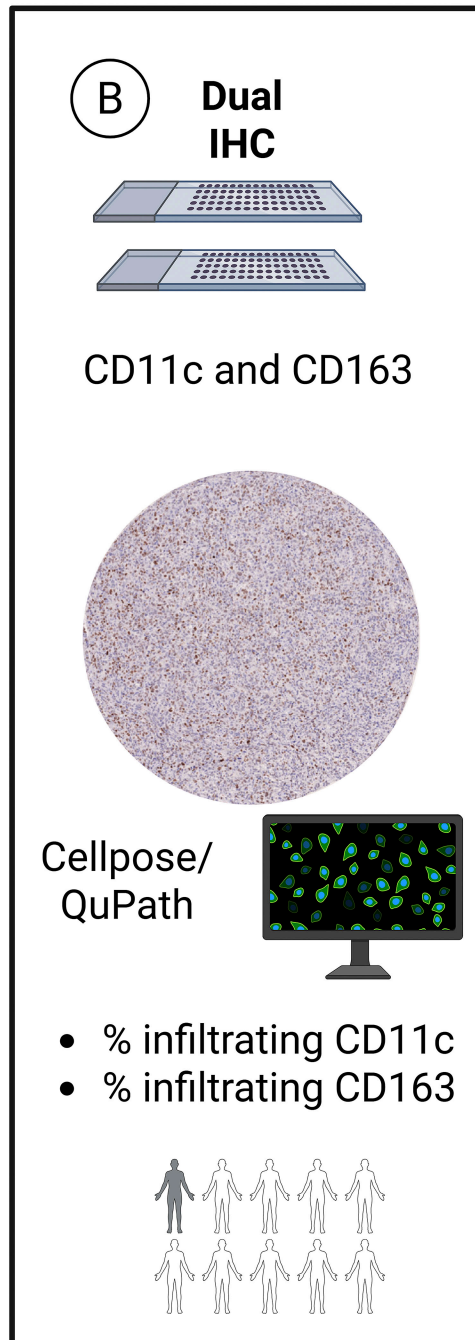
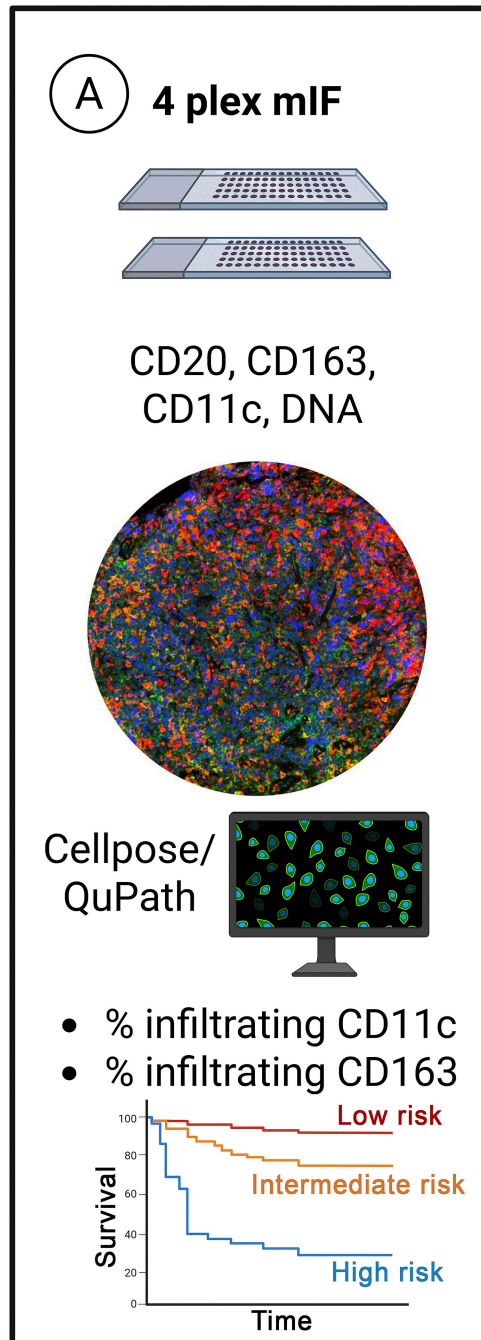
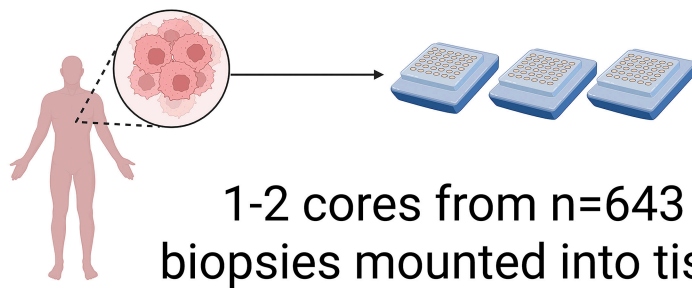
Multi-Modal Investigation of High-Risk CD163+/CD11c- DLBCL

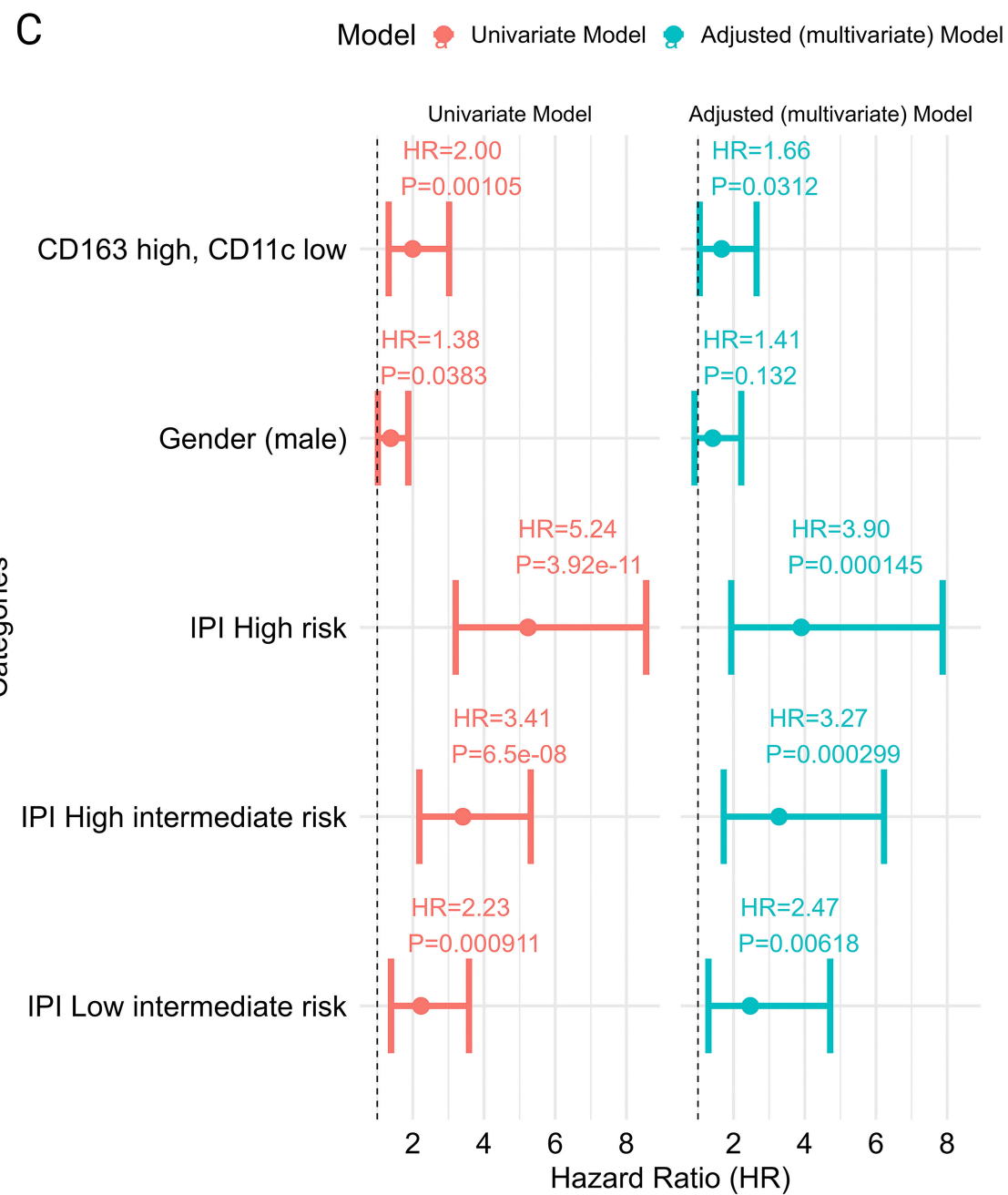
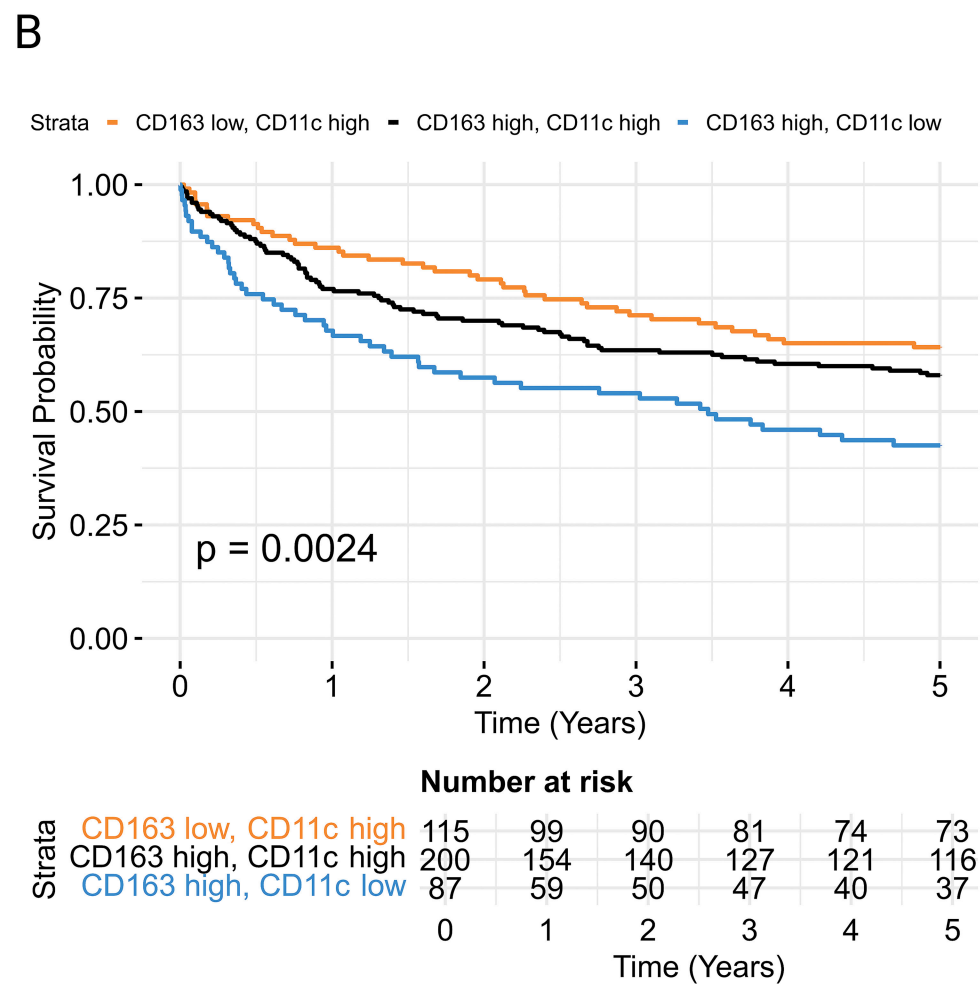
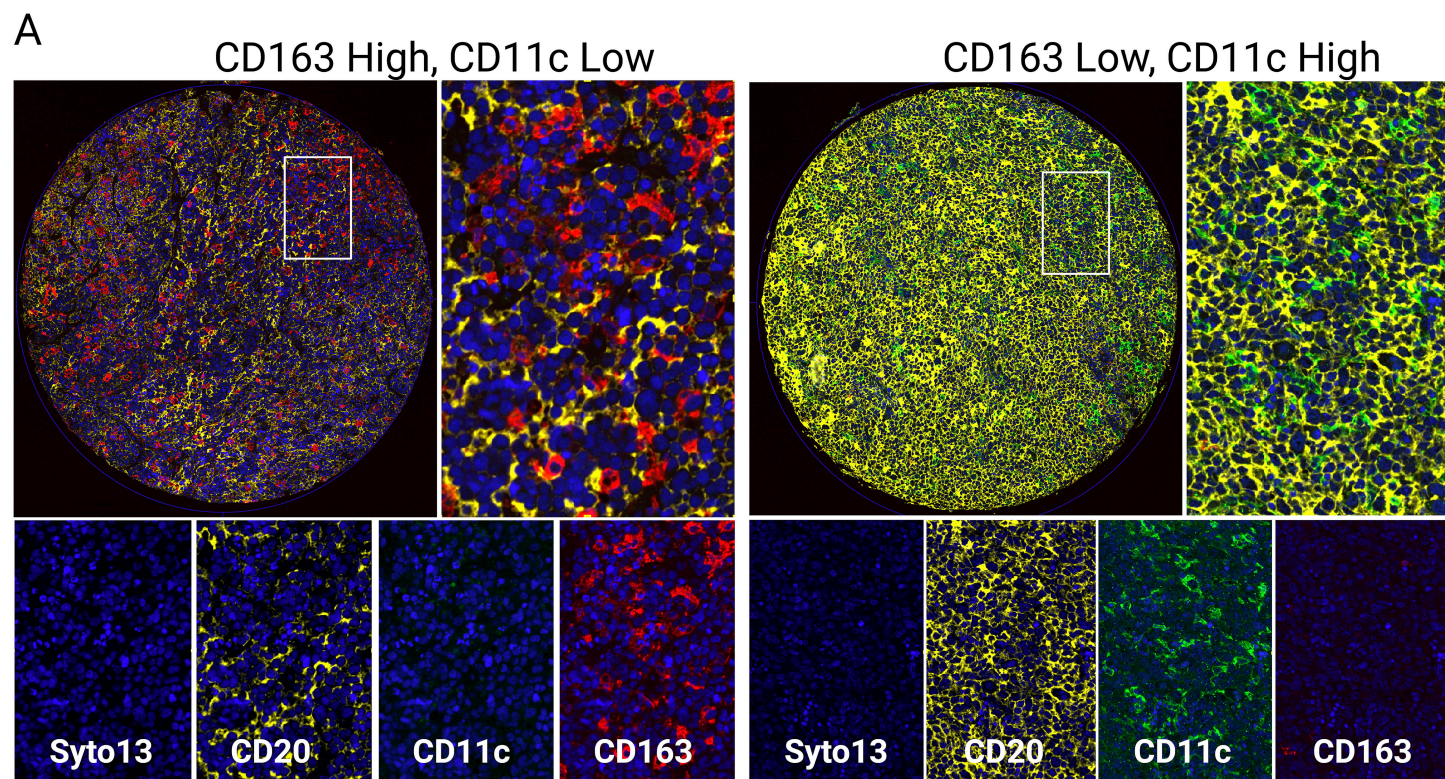
and low GEX risk groups for the D) discovery cohort (CD163+ DSP-mIF), and external validation cohorts E) GSE87371, F) GSE10846, G) GSE31312, and H) GSE181063.

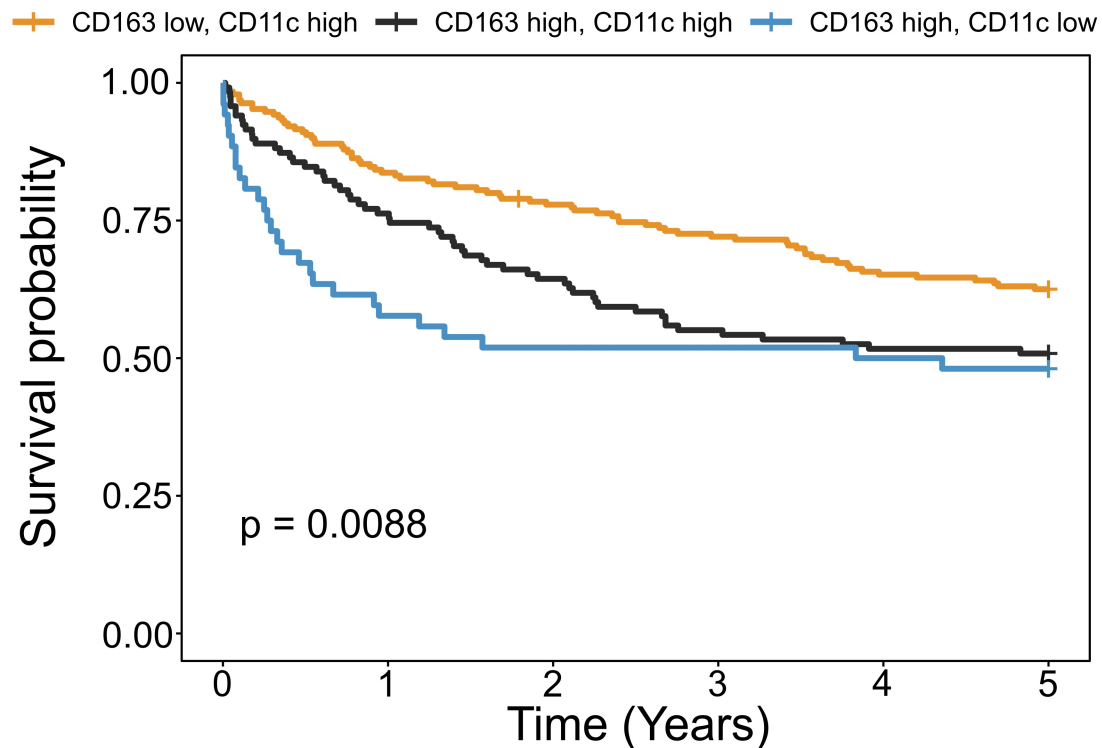
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*QC exclusion: poor tissue quality, insufficient digital quantification, <25% CD20+ cells
** QC exclusion and overlap with mIF cohort



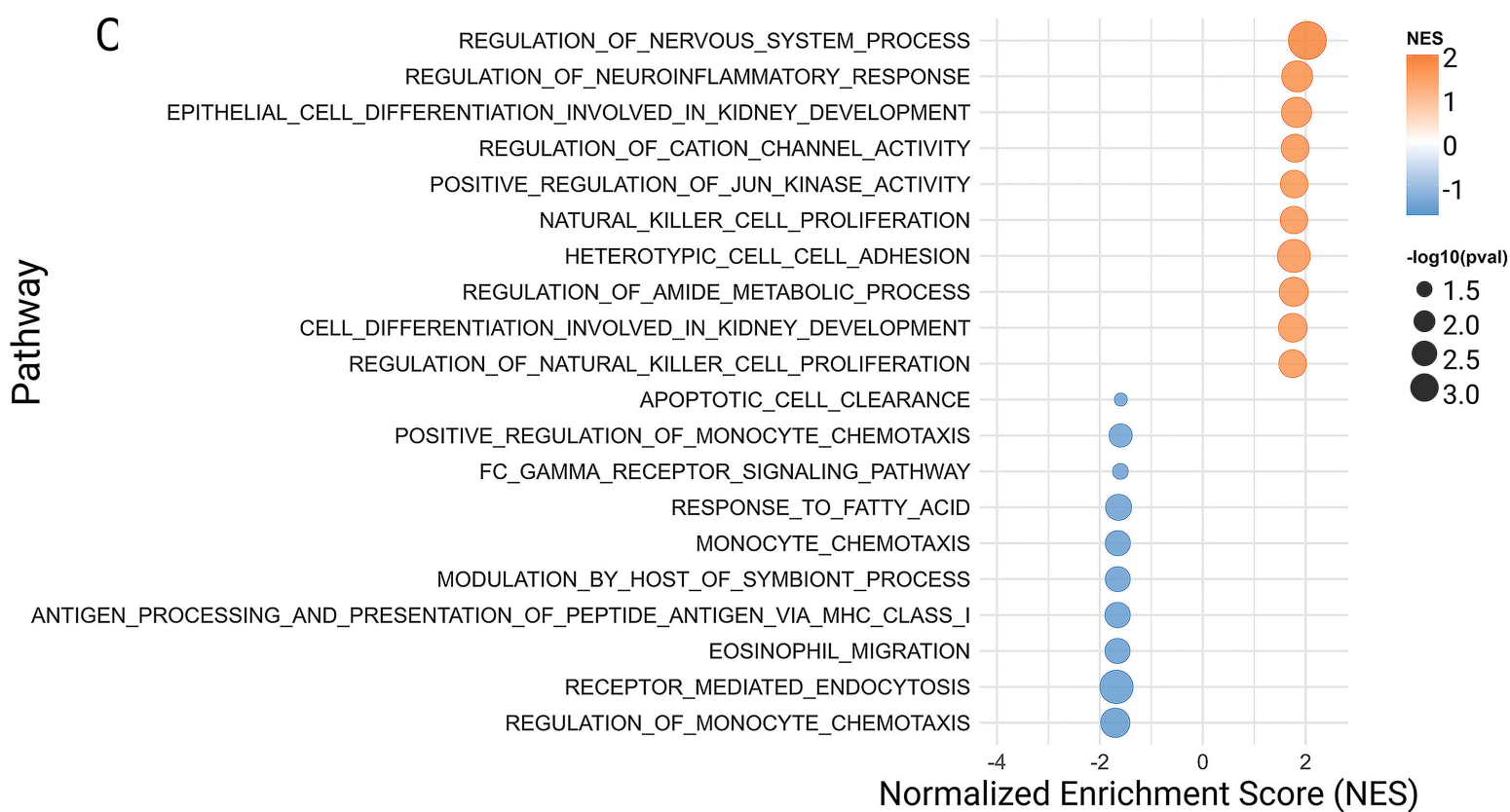
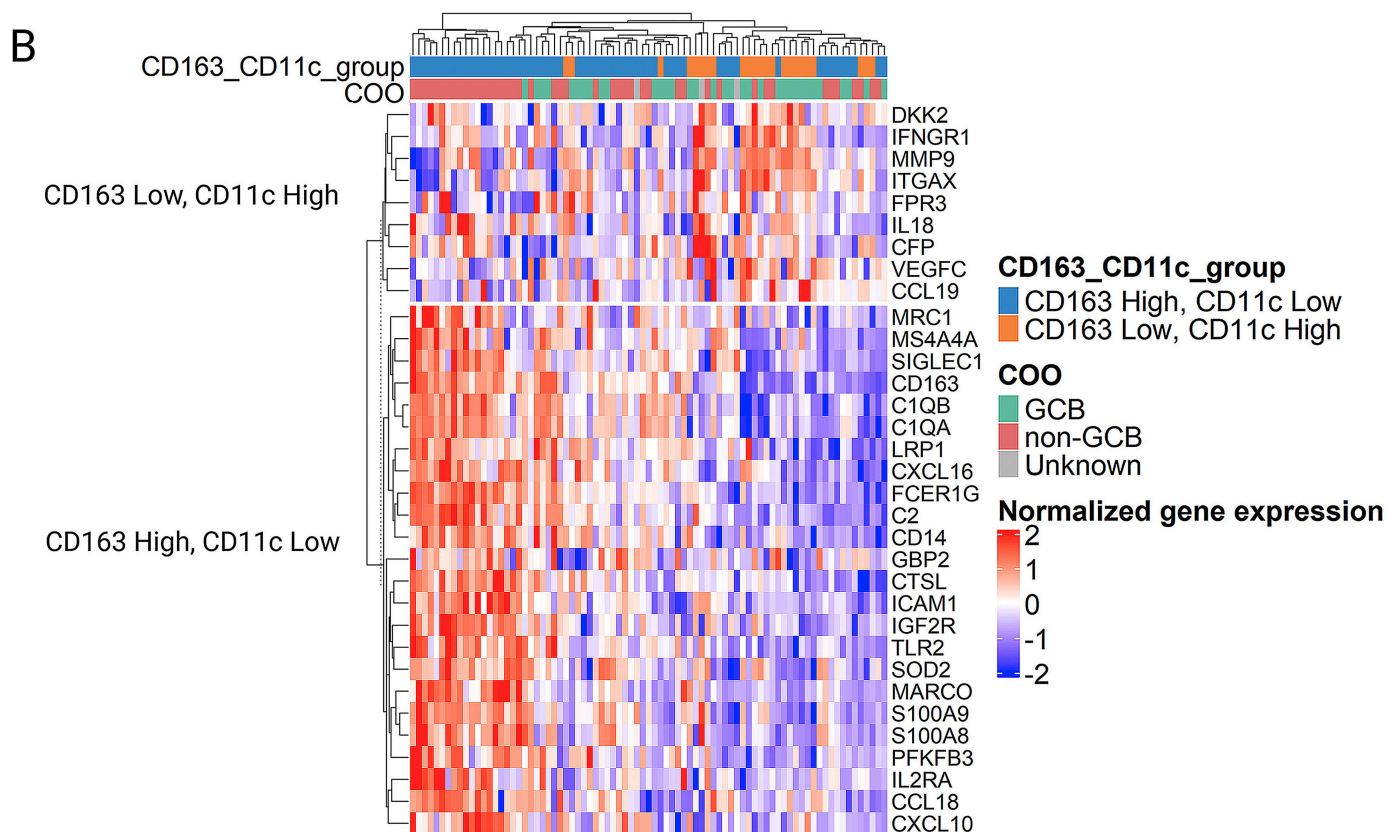
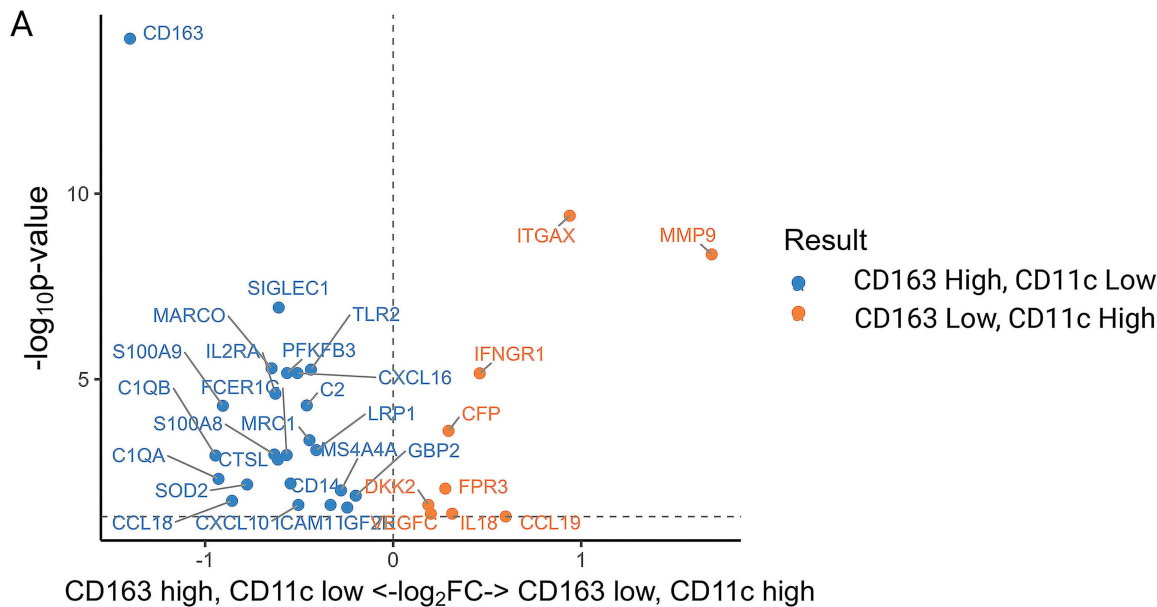




Number at risk

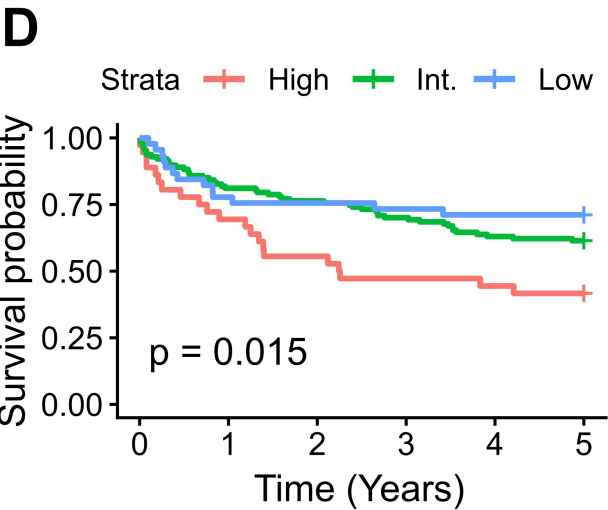
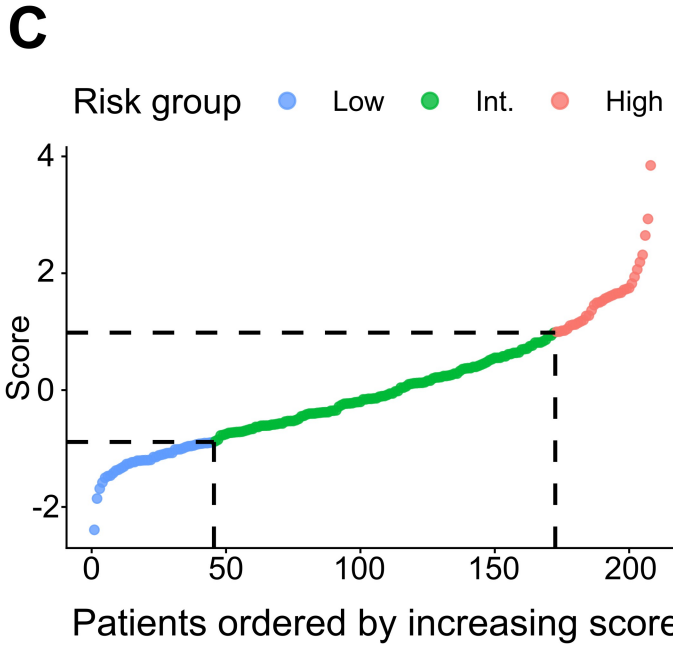
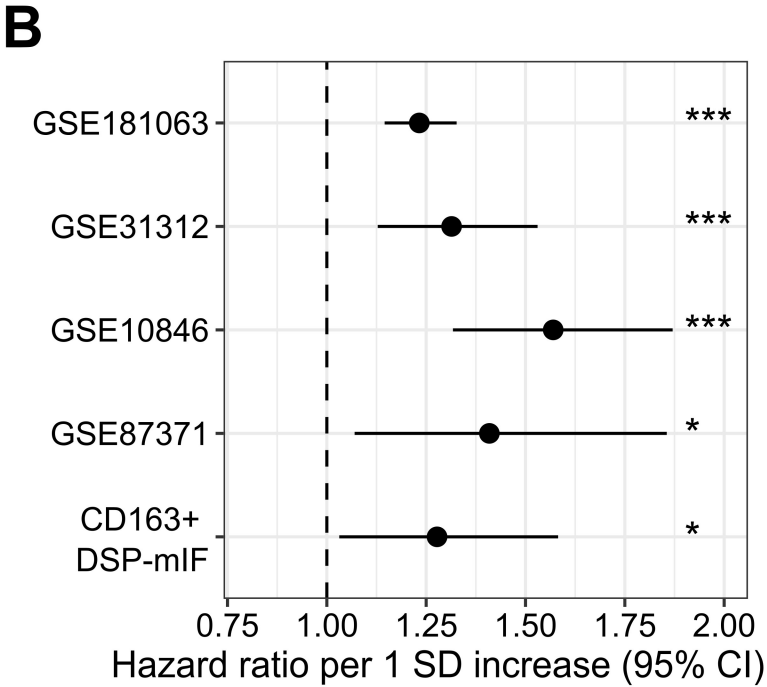
	0	1	2	3	4	5
CD163 low, CD11c high	190	159	147	136	123	118
CD163 high, CD11c high	118	90	76	65	61	60
CD163 high, CD11c low	52	30	27	27	26	25

Time (Years)



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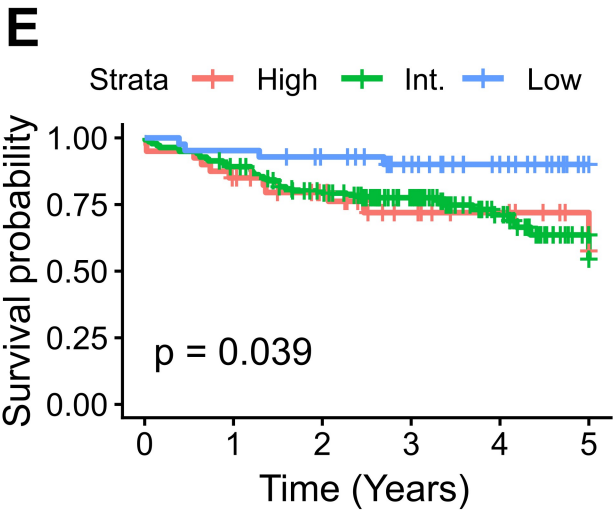
Gene	Weight
ITGAX	-1.418
TNFRSF1B	-1.011
TNFSF15	0.878
PFKFB3	0.732
C1QA	0.721
COL27A1	0.502
PPBP	0.498
IL2RA	0.370
IL6ST	-0.350
CD163	0.317
IL6	0.257
BRIP1	-0.226
PPARG	0.207
CLEC7A	-0.047
IFNGR1	-0.036
MMP9	-0.022



Number at risk

Strata	High	Int.	Low
0	36	127	45
1	25	103	35
2	20	97	34
3	17	89	33
4	16	80	32
5	0	0	0

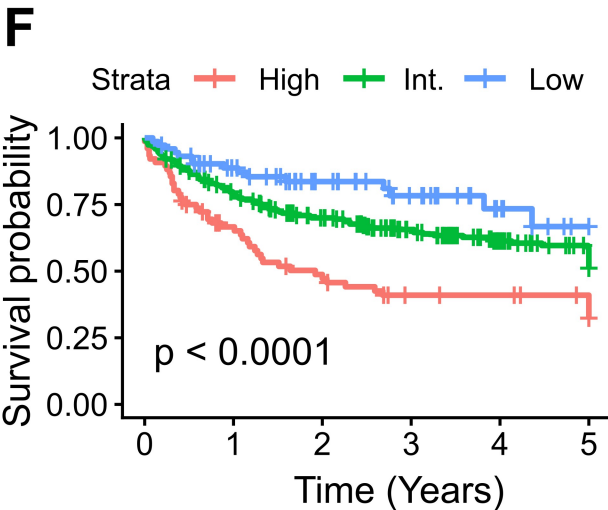
Time (Years)



Number at risk

Strata	High	Int.	Low
0	40	139	42
1	33	122	40
2	25	98	36
3	14	69	28
4	10	35	17
5	5	7	4

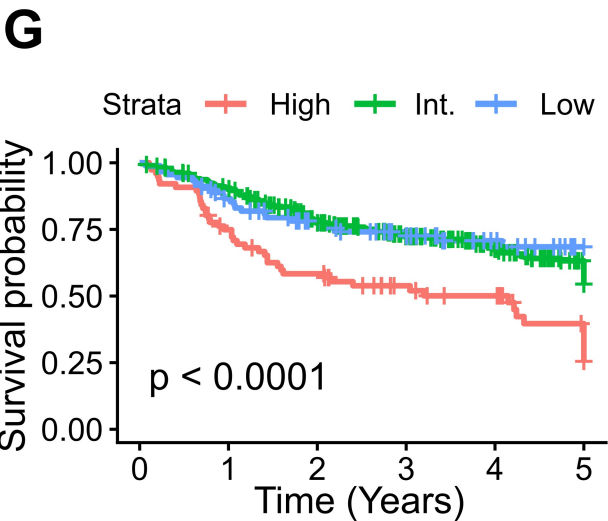
Time (Years)



Number at risk

Strata	High	Int.	Low
0	76	265	73
1	45	202	55
2	32	156	38
3	23	116	25
4	22	83	13
5	19	62	6

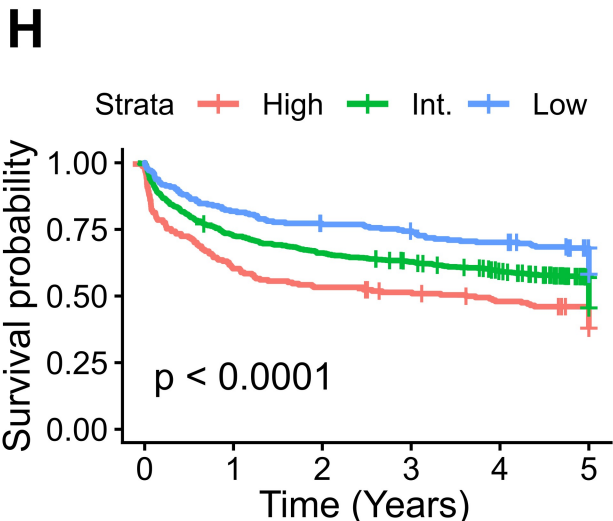
Time (Years)



Number at risk

Strata	High	Int.	Low
0	76	304	90
1	55	267	74
2	42	205	58
3	29	152	47
4	24	104	32
5	14	65	20

Time (Years)



Number at risk

Strata	High	Int.	Low
0	210	852	241
1	129	619	198
2	114	564	184
3	107	531	177
4	98	491	167
5	91	435	152

Time (Years)

Supplementary Materials and Methods

Patient Material and Characteristics

Diagnostic FFPE blocks from 733 DLBCL patients were considered, and based on expert pathology review, tissue microarrays (TMAs) were constructed with 1 mm cores and transferred via an automated device (ATA-27, Beecher Instruments, Sun Prairie, WI, USA) into 12 TMA receiver blocks, from a total of 650 patients.

Tumor-only Panel Sequencing

DNA was extracted from FFPE samples using Maxwell RSC FFPE DNA kit (Promega Corporation, Madison, USA). TP53 mutation status was assessed in the Scout Software (v.4.108.2) and validated using the Integrative Genomic Viewer (IGV) platform (v.2.19.7). DNA quality of the FFPE extracted DNA was assessed by quantitative PCR dCT values and only samples with dCT < 6 were sequenced. 110 patient samples from the BLISS-DLBCL cohort were selected for sequencing analysis based on the availability of clinical data, DNA, and DNA quality. Library prep control was conducted using Qubit/Quant-iT and TapeStation. Library prep was done using KAPA HyperPlus kit (Roche Molecular Systems, Inc;). Twist Target Enrichment Standard Hybridization was used. Samples were sequenced with GMS lymphoid panel (v.7.4). Sequencing results were mapped against GRCh37 as the reference genome and analyzed with the Bioinformatic analysis pipeline for somatic mutations in cancer (BALSAMIC). TNScope and VarDict were used for variant calling. Protein-altering exonic and canonical splice site variants passing the caller filters were retained for further analysis. Additional filtering criteria were included: a variant allele frequency (VAF) > 10%, gnomAD population frequency < 0.1%, a minimum of 5 supporting alternative reads, and depth >250X were kept. TP53 mutation status was assessed in the Scout Software and validated using the Integrative Genomic Viewer (IGV) platform. *Online Supplementary Table S1* lists selected TP53 mutations for each case.

IHC staining

FFPE TMA tissue sections (4 µm) were prepared on glass slides (Superfrost® Plus, Epredia, Portsmouth, NH, USA, and BOND Plus, Leica Biosystems, IL, United States). The IHC slides were baked at 60°C for one hour and stained with anti-CD10, anti-CD20, anti-BCL6, and anti-MUM1 using Dako's AutostainerLink 48 with EnVisioFLEX High Kit (Agilent Dako, Santa Clara, USA). The NanoZoomer S60 (Hamamatsu Photonics, Hamamatsu, Shizuoka, Japan) was used for 40x scanning of the slides. EBER (Epstein-Barr Virus Early RNA) in situ hybridization was performed using automated protocols (Ventana BenchMark ULTRA, Roche Diagnostics) and Ventana ISH iViewBlue Detection Kit (Ventana, #800-092) with Inform EBER Probe according to the manufacturer's instructions. The tissue was classified as EBV-positive when more than 10% of cells stained, as assessed by visual inspection. Patients classified as EBV+ were excluded from this study, and only patients diagnosed as DLBCL NOS were used in the downstream analysis. See *Online Supplementary Table S2* for details of antibodies used.

Dual CD163/CD11c IHC staining

The IHC slides were baked as described above and dewaxed at 70°C. The Ventana Discovery Ultra platform was used. A CC1 antigen retrieval was performed at 95°C for 64 minutes at pH 8.5. The CD11c antibody was added at a 1:300 dilution, and a multimer OmniMap Rabbit was incubated for 16 minutes. The detection probe ChromoMap DAB was incubated. A second antigen retrieval with CC2 at 100°C was performed before the incubation of the CD163 antibody at a 1:200 dilution. OmniMap Rabbit was added once again for 16 minutes, and Discovery Purple was incubated for 32 minutes. A counterstain HTX II was added for 8 minutes. The slides were scanned using the NanoZoomer S60 (Hamamatsu Photonics, Hamamatsu, Shizuoka, Japan).

Image-based analysis of the mIF CD163/CD11c panel using digital classification tools

The Cellpose cyto3^{1,2} model was trained and fine-tuned on 32 representative regions from 4 of the 23 TMA images. A validation of the segmentation model was performed by manually annotating 4000 cells for comparison, with ~90% of the cells accurately detected. The resulting segmentation model was loaded into QuPath (v 0.5.1)³ for 19 TMA images. An object classifier for each antibody was created in QuPath using a random forest and trained on ~200 detections from seven different TMA images. After training, the classifiers were evaluated using one of the eight TMA images. A representative region containing roughly 100 cells was manually annotated for each slide within a randomly chosen core using QuPath's rectangle annotation tool. Manual cell classification in this region was then performed to derive a reference value, defined as the ground truth. Each classifier was then applied to the validation regions, and its output was compared with the ground truth. All three models demonstrate high accuracy (83%-89%) (*Online Supplementary Figure S1*). Furthermore, the classifiers were applied to all 23 TMA images to make a combined classifier, and the results were exported for further downstream analysis. Additionally, due to poor tissue quality, staining issues, low CD20 frequency (<25%), and insufficient digital quantification, 156 patients were excluded from downstream analysis, leaving 405 patients for whom the final classifier could be exported. However, the exclusion did not affect the distribution of clinicopathologic parameters compared with the BLISS-DLBCL TMA-NOS cohort (n=561), as assessed by Pearson's χ^2 test (*Online Supplementary Table S3*). Of note, cells classified as double-positive, such as CD20/CD11c, were reclassified as CD20 due to high background in the CD11c channel. CD11c and CD163 double-positive cells accounted for less than 10% of cells across all patients and were not included in downstream analysis.

Image-based analysis of the dual IHC staining on the IHC CD163/CD11c cohort

QuPath (v.0.6.0) was used to analyze the dual CD163/CD11c IHC staining where first 100 small image pages were cropped out to finetune cellpose^{1,4} (v.4.0.1) using the weights from cellpose-sam as start point. The final model was applied. A pixel classifier was used to segment CD163+, CD11c+ and CD163+/CD11c+ positive staining. Cells were assigned to be positive for a marker if the staining covered at least 50% over the cell's body. If multiple staining's covered a cell, the staining with the highest overlap was chosen. Cores with a cell count under the 2.5% of the cell

count distribution over all cores was removed. Cores were visually inspected for folds and other artifacts and determined to be kept or removed. Only patients overlapping the mIF data were kept.

Digital spatial profiling

Selection of Region of Interest (ROI)

IHC staining for CD20 was used to guide the selection of relevant regions and cores containing tumor-rich areas. The cell-type-enriched AOIs enabled the collection of UV-cleavable probes in masked areas (AOIs). A summary of the number of patients, ROIs, and cell-type-enriched segments (AOIs) analyzed is provided in Figure 1. The number of CD3+ and CD163+ cells infiltrating the CD20+ DLBCL tissues varied across patients. Although selection of ROIs was performed to enable the collection of the three (CD20+, CD3+, and CD163+) cell segments from all patients, this was not always possible due to a low number of infiltrating CD3+ and/or CD163+ cells.

Transcriptional analyses

The oligos from each AOI were cleaved using ultraviolet light and collected into individual wells of a microtiter plate for separate profiling of each segment. The collected oligos' library was prepared using GeoMx DSP reagents (Bruker Spatial Biology). The NextSeq2000 instrument (Illumina, San Diego, CA) with the High Output Kit v2.5 (75 Cycles) (Illumina) was used to sequence the prepared library. Counts were generated by passing the sequencing reads through the GeoMx NGS pipeline.

Pre-processing of GeoMx™ data

Gene filtering was performed using the addPerROIQC function in StandR (v.1.8.0), resulting in the use of all 1811 expressed genes for downstream analysis. Segments were collected within a predefined area range (~3000-30000 μm^2); however, out of the total 1025 segments, 10 segments were >30000 μm^2 and 27 segments were <3000 μm^2 (*Online Supplementary Figure S2A-2B*). A quality control considering library size and segment area, as suggested in the StandR (v.1.8.0) workflow, concluded that all segments could be included in the analysis (*Online Supplementary Figure S2C-2D*). Cyclic loess normalization was applied using limma (v.30.6.4) to correct for potential technical variation. This method provided robust normalization and good separation of the cell-type-enriched segments, as observed in the PCA (*Online Supplementary Figure S2E*).

Data analysis

Data analysis was performed using R (v.4.4.0 and v.4.5.2) and R Studio (RStudio 2024.12.0+467, R Foundation for Statistical Computing, Vienna, Austria, RRID:SCR_000432).

Image and Survival Analysis

Maximally selected rank statistics (maxstat v.0.7-25, RRID:SCR_025679) were used in R to define categorical groups and to identify cut-point values to dichotomize patients based on CD11c and/or CD163 expression. The method allows identification of the optimal cut point that

maximizes the difference in outcome, which is defined here as 5-year overall survival (OS). Survival analysis and visualization were performed with the survival package (v.3.8-3, RRID:SCR_021137), using survfit and the log-rank test to visualize and compare survival distributions in Kaplan-Meier plots. The coxph function was used to fit Cox proportional hazard models and adjust for covariates. The package emmeans (v.2.0.2, RRID:SCR_018734) was used to extract the cox regression result between categorical comparisons.

IHC and mIF validation

The CD163⁺ and CD11c⁺ cells from the IHC and mIF, respectively, were correlated using Pearson correlation. The cell type distribution in the IHC was checked against the assigned groups based on the mIF staining to compare whatever there was a difference between the cell type distribution from the mIF assignment and the IHC assignment. The IHC cell type frequency was further divided based on the determined mIF cut-points and rounded cut-points for high CD163 and high CD11c levels and checked for significance in survival using Kaplan-Meier estimate between the survival curves.

Cell-type-specific gene lists

To enable visualization (DGEA) and analysis of genes associated with specific cell types, gene lists of well-characterized genes for CD3⁺ (T cells), CD20⁺ (B cells), and CD163⁺ (macrophages) cells were created using several resources (*Online Supplementary Table S4-S6*). The references include LM22⁵ and LM7⁵, signature matrices from CIBERSORTx using mastR (v.1.8.0) package⁶, and the signature matrix safeMatrix from SpatialDecon.⁷ Genes from differential expression analysis (using limma) with a log2 fold change >2 were used to define each cell type. Furthermore, the Database of Immune Cell Expression (DICE)⁸, monacoimmune⁹, and Human Primary Cell Atlas (HPCA)¹⁰ from celldex (v.1.18.0) were used. The top 50 genes, based on FDR, were selected to define each cell type filter, with genes having a log2 fold change >2 and FDR <0.05. In addition, studies with scRNAseq data identifying the different cell types were used.¹¹⁻²⁰ Genes not listed in any of the cell-type-associated lists are referred to as CTA-Global.

For cell deconvolution and pathway analysis, all CTA genes were used.

GeoMx transcriptional data analysis

For analysis of the GeoMx data, the SpatialExperiment package (v.1.14.0) and the StandR (v.1.8.0) workflow in R²¹ was used. Differential expression analysis was performed using the limma voom package (v3.60.4, RRID:SCR_010943), with an adjusted p-value < 0.05 and log2 fold change (logFC) > 0 as cut-offs. Gene set enrichment analysis (GSEA) was conducted using the KEGG_medicus and Gene Ontology (GO) Biological Process databases via the fgsea package (v1.30.0, RRID:SCR_020938).

For data visualization, the following R packages were used: ggplot2 (v3.5.1, RRID:SCR_014601), ggvenn (v0.1.10, RRID:SCR_025300), and ComplexHeatmap (v2.20.0, RRID:SCR_017270).

The stats package (v.4.4.0 and v.4.5.2) was used to compare differences between two or more independent groups. The Wilcoxon rank-sum test (Mann-Whitney U test) was used via the

wilcox.test() function and the Kruskal–Wallis rank-sum test was applied using the kruskal.test() function. The Fisher’s Exact test using the Fisher.test() function, and Pearson’s χ^2 test using the chisq.test() were used for comparison between categorical groups.

Cell deconvolution

For cell deconvolution of the CD163⁺ segments, two different reference data sets were used. Expression matrices from LM22⁵ and the MoMac-verse reference atlas²² were filtered to match genes available in CTA. The filtered expression matrices were then uploaded to the CIBERSORTx website, and signature matrices were constructed and further used in CIBERSORTx cell deconvolution.⁶ The MoMac-VERSE integrates 41 single-cell RNA-sequencing (scRNA-seq) datasets from healthy and pathological tissues, including 17 distinct monocyte/macrophage subtypes. Furthermore, normalized expression values from each CD163⁺ segment were analyzed using the LymphoMapR (v.1.0) package to assess the proportion of lymphoma archetypes in each sample.¹³

Risk model construction

A regularized logistic regression model was built on the CD163⁺ DSP-mIF cohort using a nested cross-validation approach of the gene-expression from the CD163⁺ segments using programming language Python (v.3.12.10) and the package scikit-learn (v.1.8.0, RRID:SCR_002577). The model was trained to distinguish between the CD163^{high}/CD11c^{low} and CD163^{low}/CD11c^{high} samples (*Online Supplementary Figure S3*). The CD163^{high}/CD11c^{low} was set as the positive class. The outer loop used repeated stratified 5-fold cross-validation, repeated 30 times, to generate unbiased out-of-fold predicted probabilities for every CD163^{high}/CD11c^{low} and CD163^{low}/CD11c^{high} sample. Within each outer split, model selection and calibration were performed on the training data to prevent information leakage. The predictive model consisted of standardization followed by regularized logistic regression, with probability calibration applied using sigmoid calibration (Platt scaling) inside the training pipeline. The inner loop used repeated stratified 5-fold cross-validation, repeated 10 times, for hyperparameter tuning. Hyperparameters were tuned by grid search over the regularization strength C and the elastic-net mixing parameter l1_ratio, using the ROC AUC as the selection metric. The final out-of-fold ROC AUC was computed from the aggregated outer-loop predictions. The frequency on how often each gene received a nonzero logistic regression coefficient across outer folds was tracked to assess the stability of each gene. Genes selected in at least 50% of outer fits were defined as stable features. After cross-validation, a final model was fit on all CD163^{high}/CD11c^{low} and CD163^{low}/CD11c^{high} samples using only the stable genes and the most frequently selected hyperparameters from the nested search. The resulting coefficients were retained as signed feature weights, where positive coefficients indicated stronger association with class CD163^{high}/CD11c^{low}.

GEX risk score construction and cohort-specific normalization

Using R (v.4.5.2), the final selected genes and their corresponding weights was used to derive a continuous GEX risk score. For each sample, genes were ranked by expression across all genes in the signature, to ensure robustness to outliers and reduce sensitivity to between-sample

normalization differences. A weighted sum of these ranks was then computed using the model coefficients as weights and normalized by the sum of absolute weights to ensure comparability across samples. Higher scores indicated a more CD163^{high}/CD11c^{low} expression profile (high risk). Lastly, the risk score was standardized (z-scored) separately within each cohort prior to downstream analyses to create an interpretable unit scale (+/- SD from cohort mean).

Survival-based cutoff selection

In the discovery (CD163+ DSP-mIF cohort) cohort, two cutoffs on the standardized GEX risk score were determined using survival data. Candidate lower and upper thresholds were evaluated across predefined quantile ranges of the score distribution (0.05-0.45). For each candidate pair, samples were assigned to three groups: high, intermediate, and low. Only threshold combinations yielding at least 15 samples per group were considered. For each valid combination, pairwise survival differences were assessed using log-rank tests (survdiff from the R package survival) for high versus intermediate, intermediate versus low, and low versus high groups with 5-year OS as the outcome. The optimal cutoffs were selected by maximizing the summed chi-square statistic across these comparisons, with preference for solutions in which all pairwise comparisons were statistically significant. The lower bound was found to be -0.887 and upper bound 0.984.

Validation in independent cohorts.

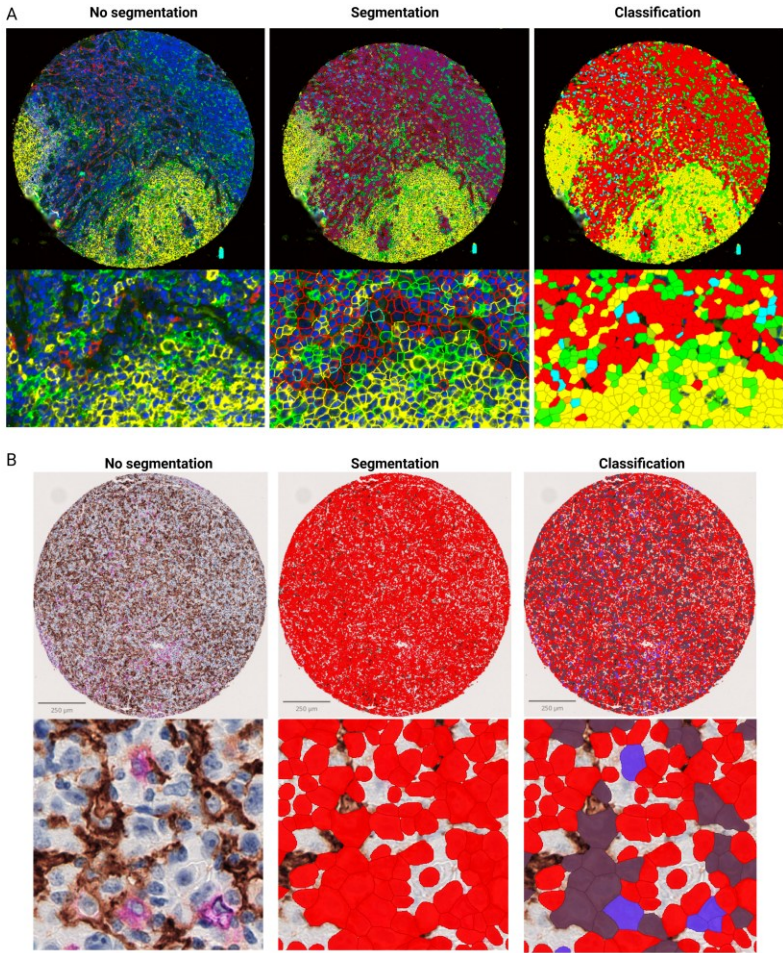
The final gene weights and discovery-derived cutoffs were applied unchanged to independent validation datasets. For each cohort, the GEX risk score was computed using the same weighted rank-based approach and standardized within that cohort. Samples were then assigned to high, intermediate or low groups using the fixed thresholds derived from the CD163+ DSP-mIF cohort. Three different CHOP and R-CHOP-treated DLBCL patient cohorts with DLBCL expression microarray datasets were used for validation (GSE10846²³, GSE87371²⁴, GSE31312²⁵). The microarray expression datasets were downloaded using getGEO() from the R package GEOquery (v.2.76.0, RRID:SCR_000146), and each probe was annotated to gene name using the library hgu133plus2.db (v. 3.13.0). Additionally, an Illumina-based microarray expression data set (GSE181063^{26, 27}) were obtained from Gene Expression Omnibus and annotated with the library illuminaHumanv4.db (v 1.26.0). Clinical characteristics and 5-year OS data from the downloaded objects were used for survival analysis

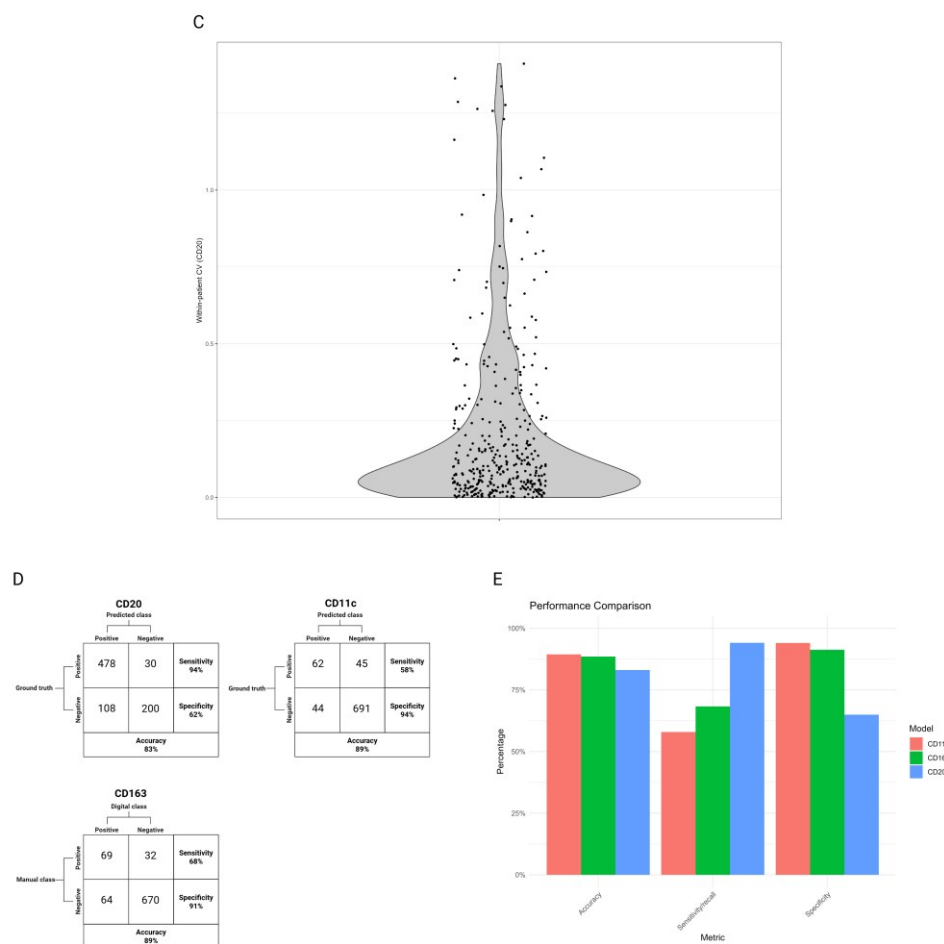
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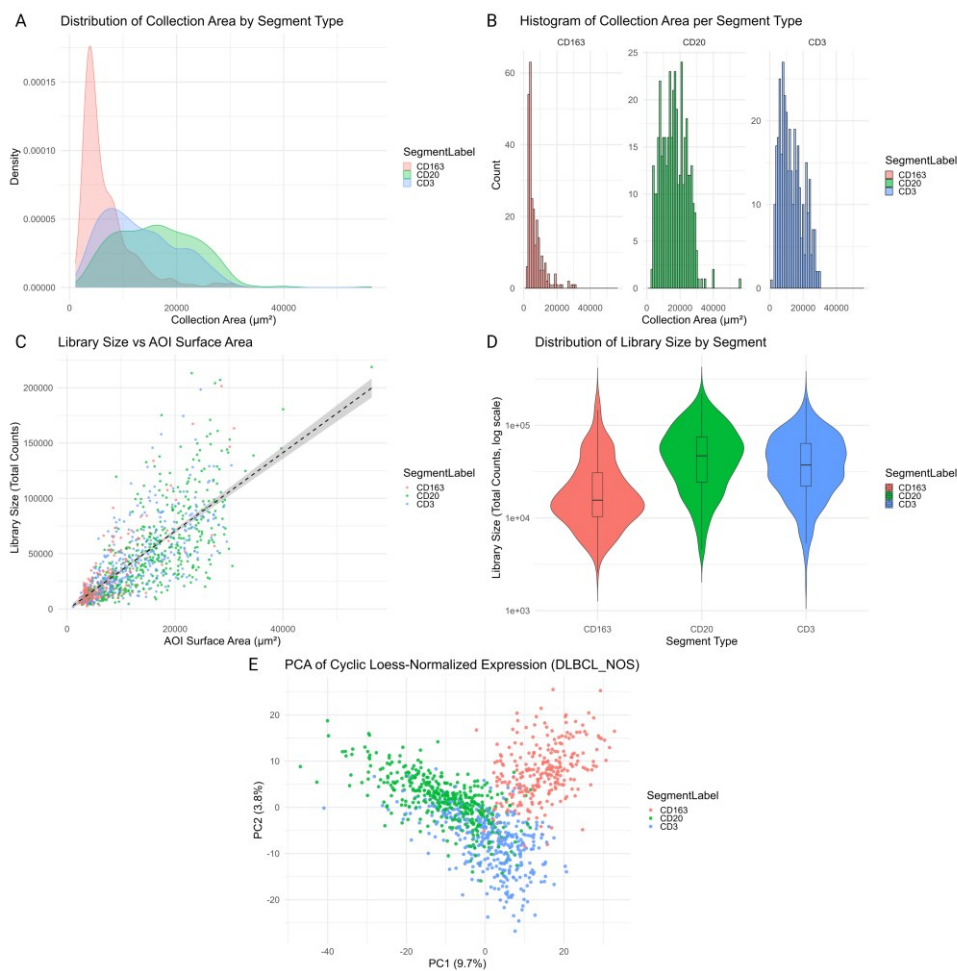
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Supplementary Figures

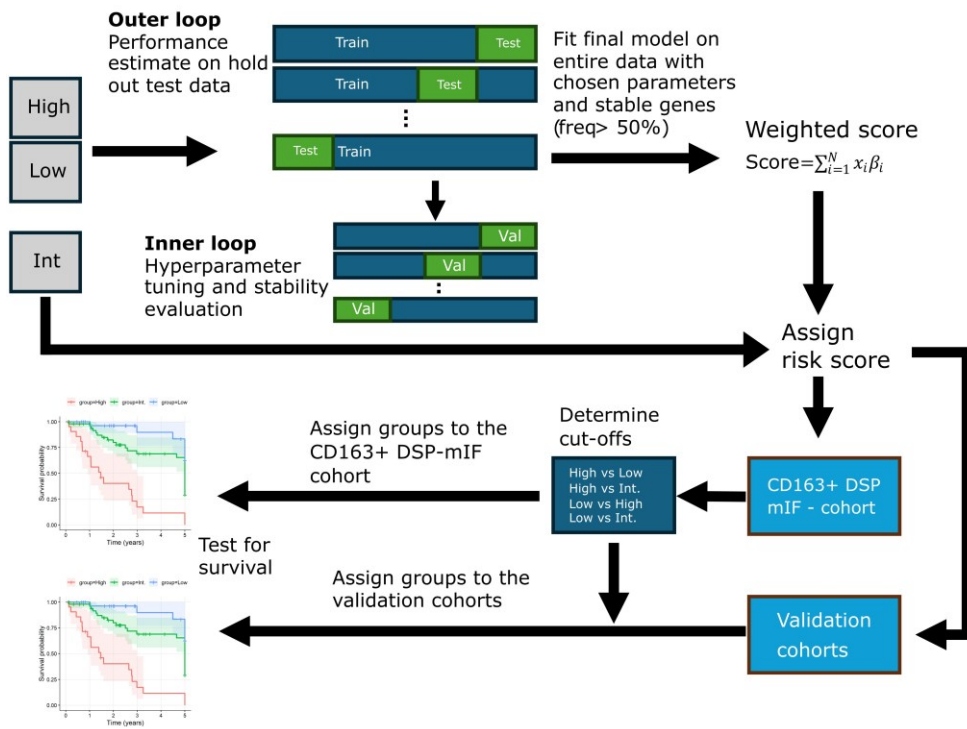




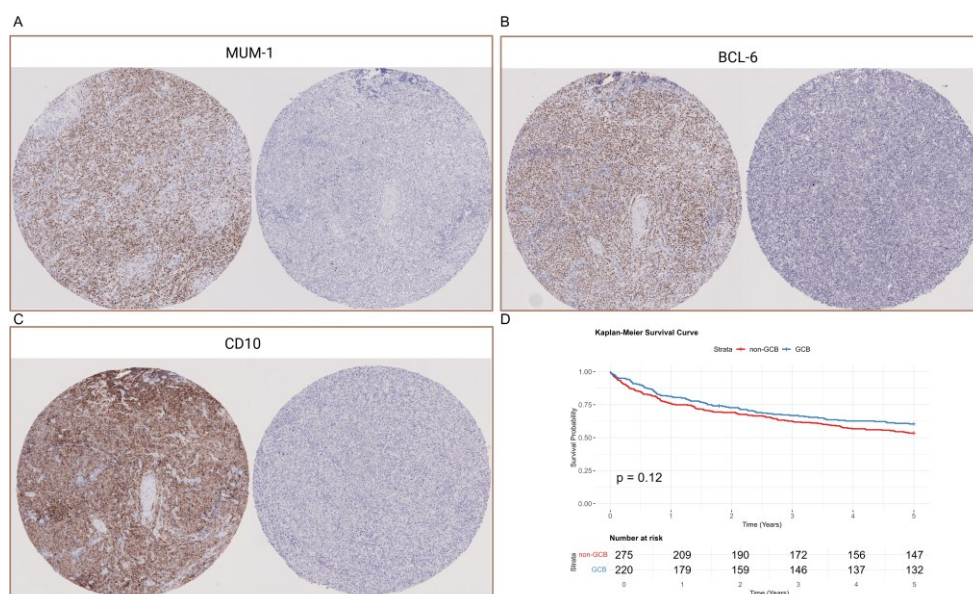
Supplementary Figure S1 mIF image-based cell type classification models and dual IHC staining. (A) Representative core showing original mIF image (far left), segmentation using a fine-tuned Cellpose segmentation model (middle), and classification using Qupath random forest model for each morphology marker marked as CD20+ (yellow), CD11c+ (green), and CD163+ (blue) (far right). (B) Representative core showing original dual IHC staining detecting of CD163+ and CD11c+ cells using ChromoMap DAB (CD11c) and Discovery Purple (CD163). (far left), segmentation using a fine-tuned Cellpose segmentation model (middle), and classification using Qupath pixel classification model for each marker marked as CD163 (blue) and CD11c+ (brown) (far right). (C) CV between cores from the same patients of the proportion (%) of CD20+ cells. (D) Number of predicted positive and negative classifications compared to ground truth classifications, used in the validation for each classification model. (E) Comparison of accuracy, sensitivity/recall, and specificity for each classification model. The specificity is low for CD20+ cells present at very high frequencies, increasing the risk of false-positive detection. The sensitivity is low in the CD11c and CD163 models, where the cell frequencies are generally low, suggesting challenges in accurately segmenting and classifying CD11c and CD163-positive cells. However, because the classification is a relative measure of CD11c- and CD163-positive cells, absolute quantification and precision are not critical for ranking patients from high to low based on these two parameters.



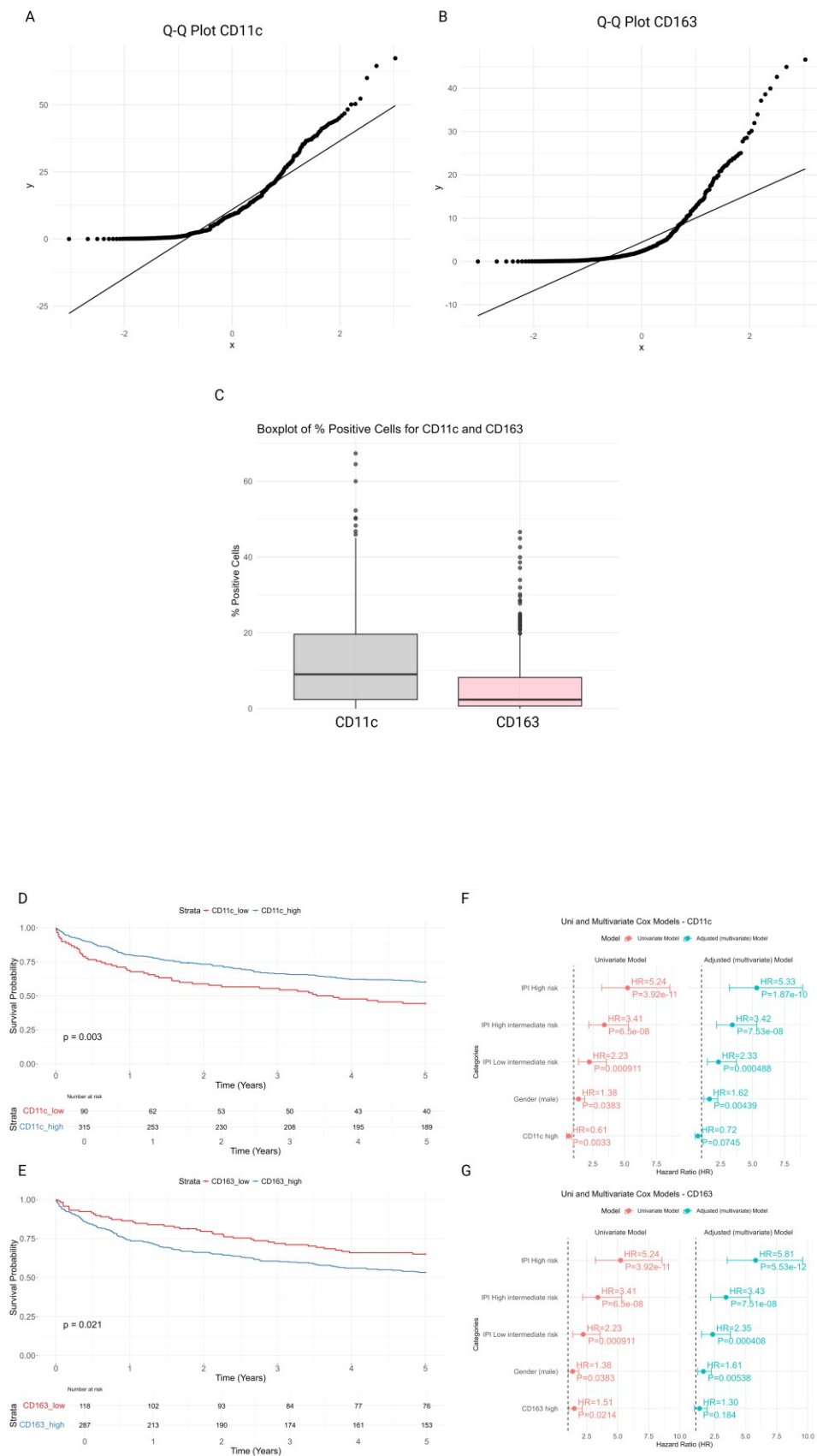
Supplementary Figure S2. Overview of the collection area and Library size in each cell segment. (A) and (B) Distribution of collection area (μm^2) in each cell segment and visualized in a density plot (A) and as a histogram separated by cell segment (B). C, Collection area (μm^2) and Library size (total counts) in each cell segment. (D) Distribution of library size in each cell segment. (E) PCA plot of cyclic-loess normalized expression of all segments, with labels for respective cell annotation.



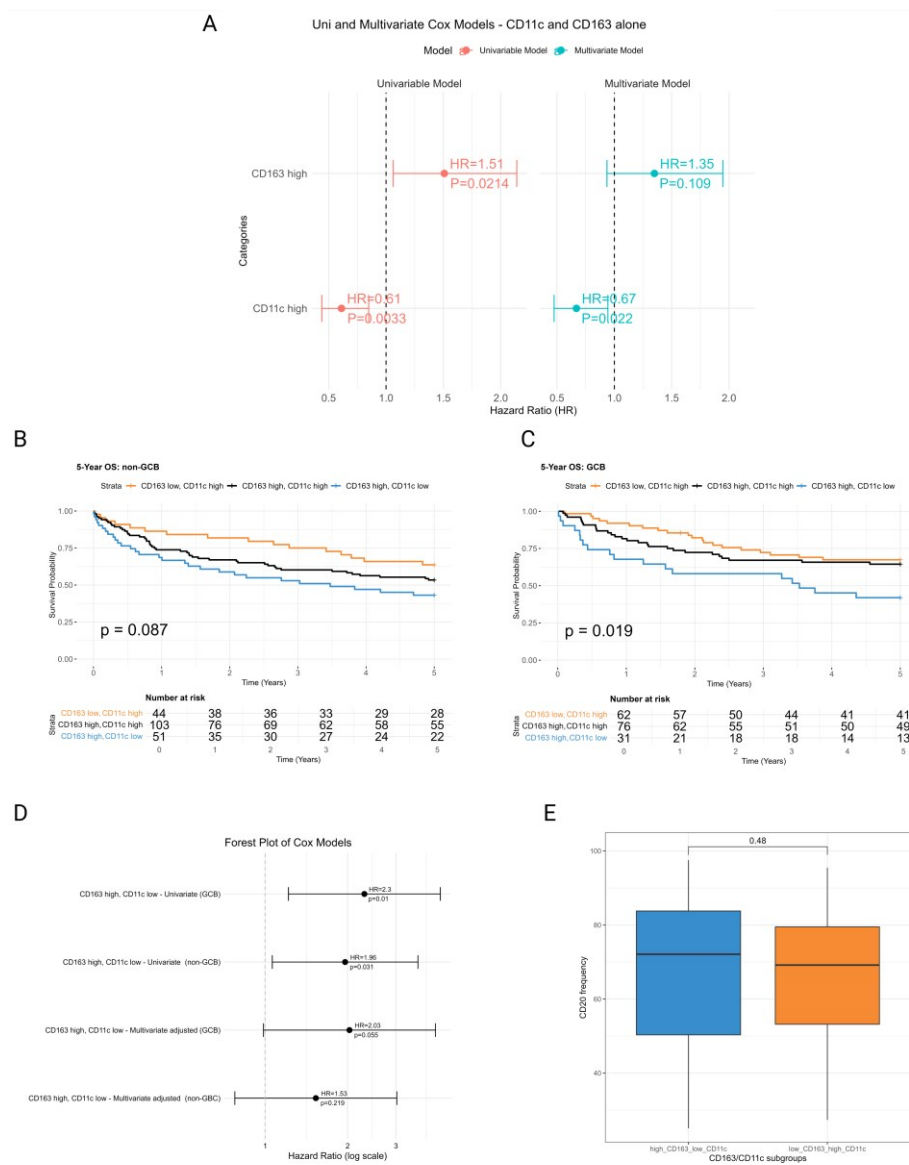
Supplementary Figure S3. Schematic figure over pipeline for gene signature construction. The regularized logistic regression model was trained to distinguish between the two extreme risk groups: CD163^{high}/CD11^{low} (high) and CD163^{low}/CD11^{high} (low) samples using gene expression from the CD163 segments. A repeated nested cross-validation was used to tune model hyperparameters using the inner loop while estimating the performance was done on the hold out data from the outer loop. A final model was trained on the entire CD163+ DSP-mIF data with genes with a non-zero coefficient frequency > 0.5 from the model construction in the inner loop and the final genes and corresponding coefficients were extracted. Using the final selected genes and their corresponding weights, a continuous GEX risk score was derived for each sample. For each sample, genes were ranked by expression across all genes in the signature. A weighted sum of these ranks was then computed using the model coefficients as weights, and normalized by the sum of absolute weights and the derived score was z-normalized separately within each cohort. In the CD163+ DSP-mIF cohort, two cutoffs on the standardized risk score were determined using survival data. Candidate lower and upper thresholds were evaluated across predefined quantile ranges of the score distribution (0.05-0.45). For each candidate pair, samples were assigned to three groups: low, intermediate, and high. The optimal cutoffs were selected by maximizing the summed chi-square statistic across comparisons between low, intermediate, high. The final gene weights and CD163+ DSP-mIF-derived cut-offs were applied unchanged to independent validation datasets. For each cohort, the risk score was computed using the same weighted rank-based approach and standardized within that cohort. Samples were then assigned to low, intermediate or high. The survival was then visualized using Kaplan Meier curves.



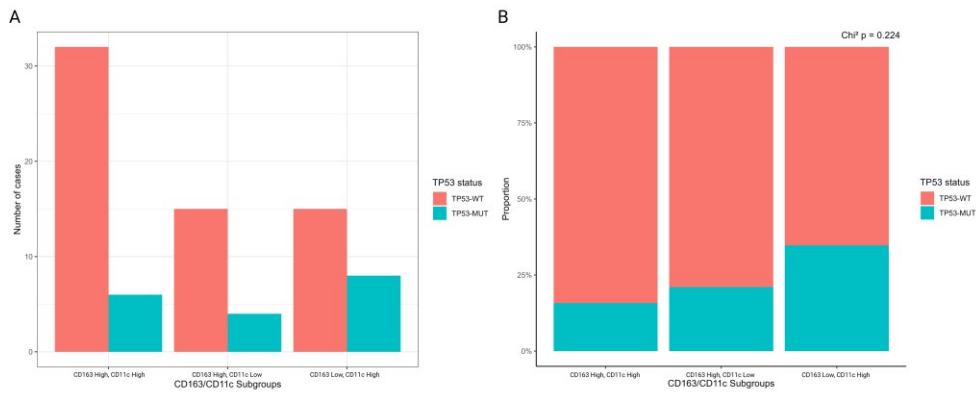
Supplementary Figure S4. (A-C) IHC staining of MUM-1 (A), BCL-6 (B), and CD10 (C). Exemplified with a positive (left) and negative (right) core of each marker. D) Kaplan-Meier survival analysis and log-rank test using 5-year overall survival (OS) stratifying patients by GCB or non-GCB.



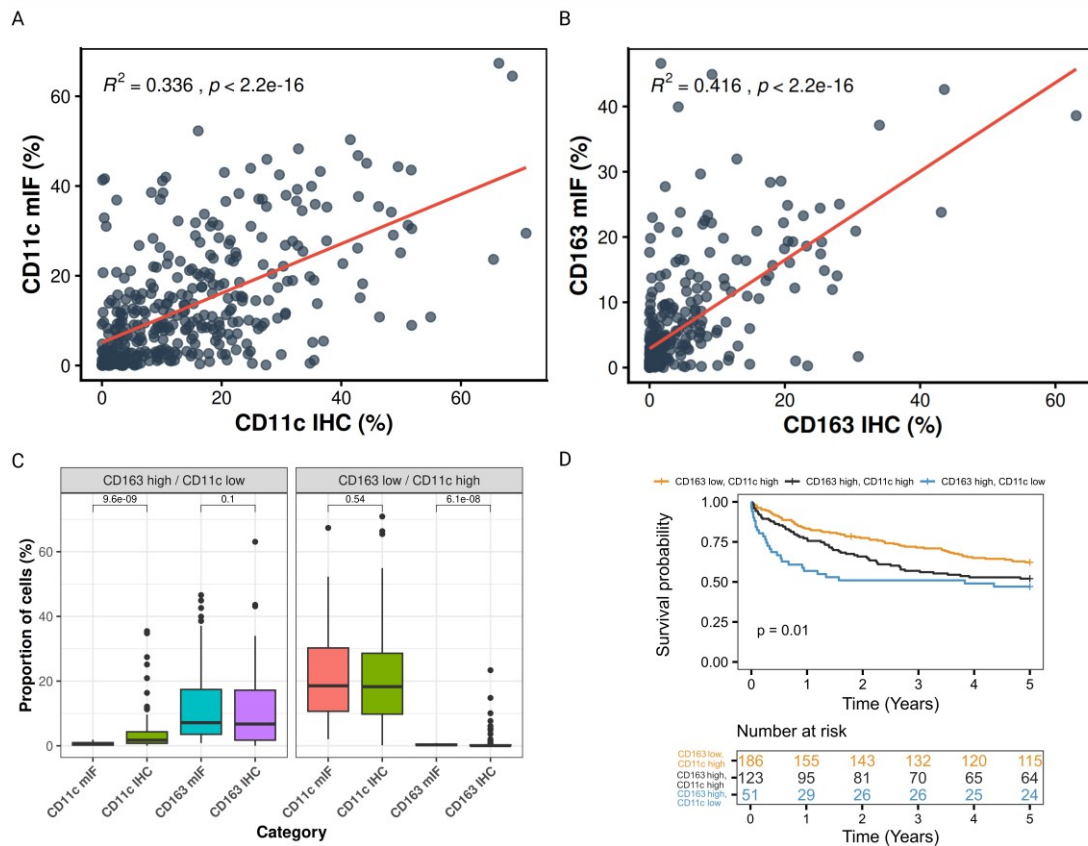
Supplementary Figure S5. Distribution of CD11c and CD163 frequencies and survival analysis of CD11c and CD163. (A) and (B) Assessment of normal distribution using Quantile-quantile (QQ) plots shows deviations in the upper quantiles, indicating a right-skewed distribution for CD11c (A) and CD163 (B). (C) Box plots showing the distribution of CD11c and CD163 frequencies across all patients. (D) and (E) Kaplan-Meier survival analysis and log-rank test were performed for CD11c (D) and CD163 (E) as individual markers. (F) and (G) Univariate and multivariate (with gender and IPI as covariates) Cox regression analysis comparing high versus low expression of CD11c (F) and CD163 (G).



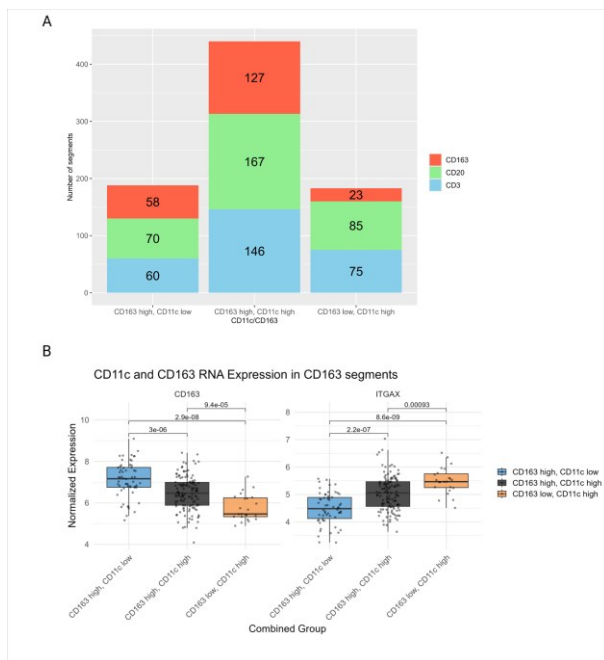
Supplementary Figure S6. Survival analysis. (A) Uni- and multivariate Cox regression analysis comparing high versus low expression of CD11c and CD163. (B) and (C) Kaplan-Meier survival analysis and log-rank test were performed for non-GCB (B) and GCB (C) subgroups, comparing survival probabilities between the CD163^{high}/CD11c^{low}, CD163^{high}/CD11c^{high}, and CD163^{low}/CD11c^{high} subgroups. (D) Cox regression analysis comparing CD163^{high}/CD11c^{low} with CD163^{low}/CD11c^{high} in univariate and multivariate analysis (with gender and IPI covariates) in non-GCB and GCB patients separately. The CD163^{low}/CD11c^{low} subgroup had only three patients and was excluded from downstream analyses. (E) Comparing frequency of CD20+ cells between the CD163/CD11c subgroups (CD163^{high}/CD11c^{low} and CD163^{low}/CD11c^{high}).



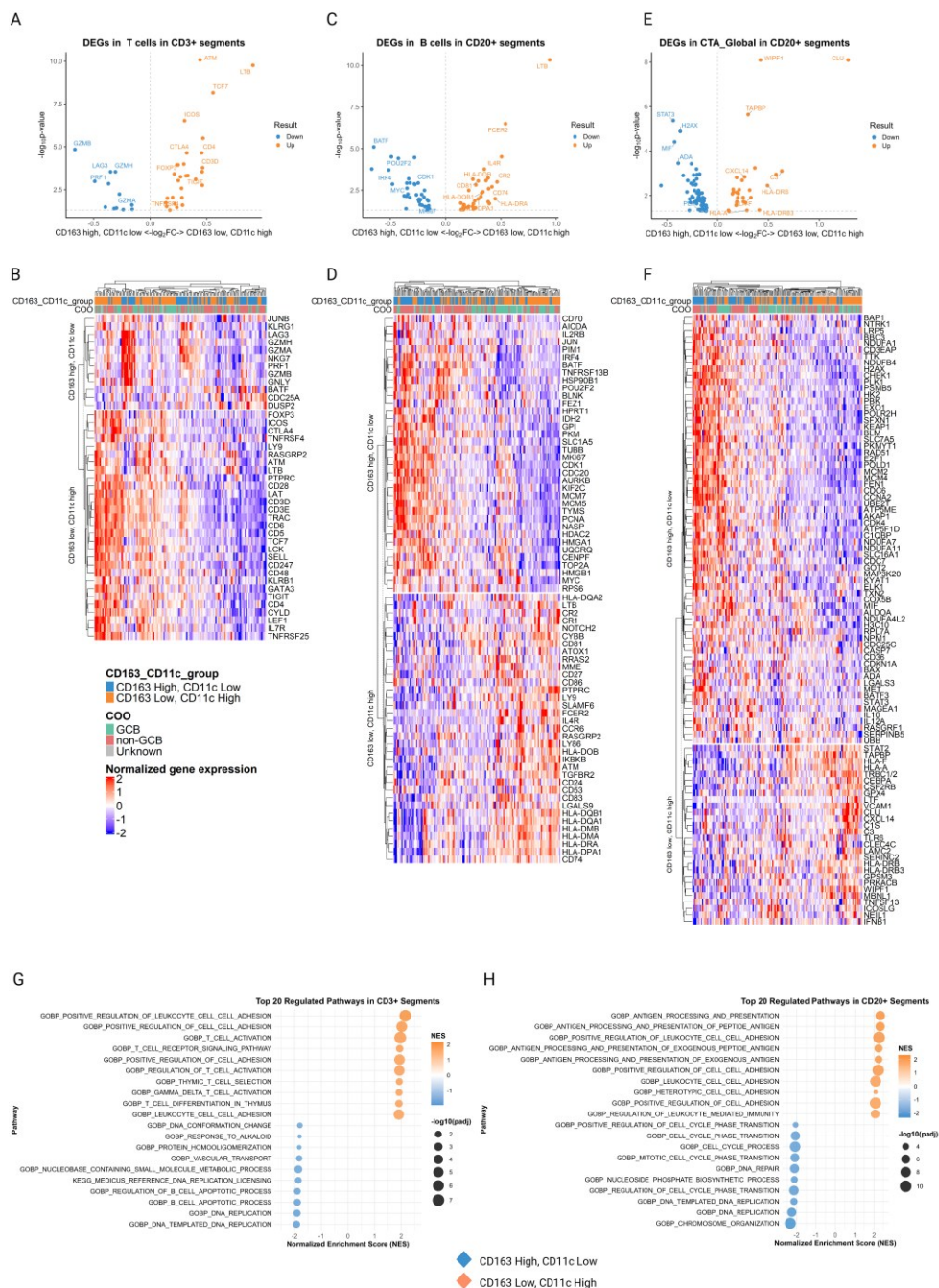
Supplementary Figure S7. TP53 mutational status. (A) Number of cases as either TP53-wild type or TP53-mutated in each CD163/CD11c subgroups, of the analyzed patients in the mIF CD163/CD11c cohort (n=80). (B) Proportion of cases classified as TP53-WT or TP53-Mut in each CD163/CD11c subgroup, showing no significant difference between all three subgroups when analyzed using Chi-square test.



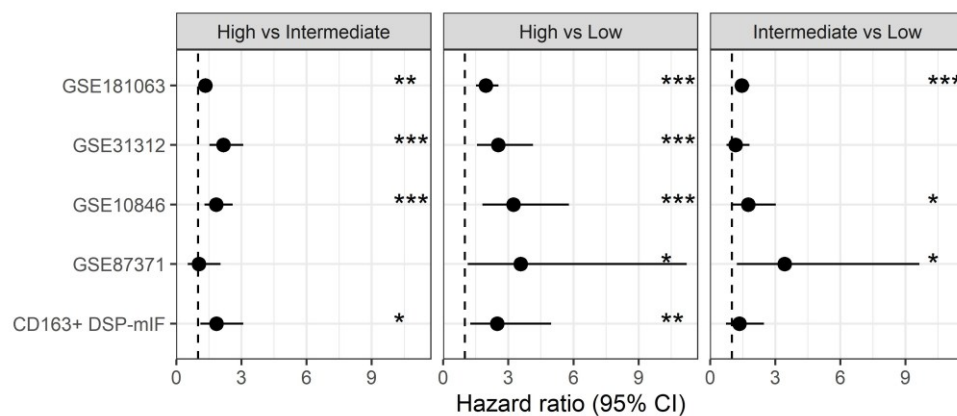
Supplementary Figure S8. Dual IHC and mIF correlations. (A) Correlation plot between CD11c mIF (%) and CD11c IHC (%). (B) Correlation plot between CD163 mIF (%) and CD163 IHC (%). (C) Comparison of CD11c and CD163 cell proportions (%) when grouped as either CD163^{high}/CD11c^{low} or CD163^{low}/CD11c^{high} (from mIF stratification) using mIF or IHC staining. (D) Stratification based on the mIF CD163/CD11c identified cutpoints of 0.9% and 1.9% for CD163 and CD11c.



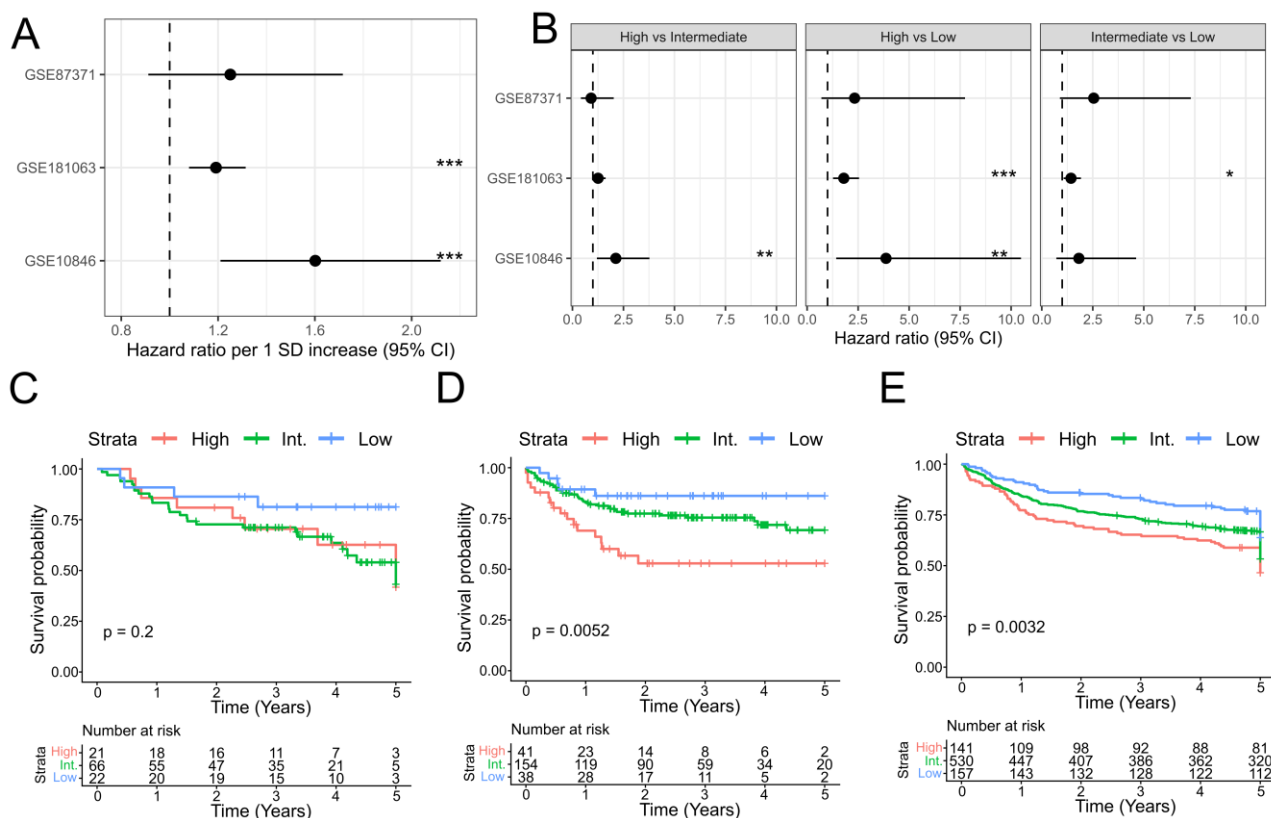
Supplementary Figure S9. Overview of segment distribution and RNA expression in each CD163/CD11c combined group. (A) Number of collected CD20+, CD3+, and CD163+ segments in each of the defined CD163/CD11c subgroups. (B) Gene expression of CD163 and ITGAX comparing CD163/CD11c subgroups in the CD163+ cell segment.



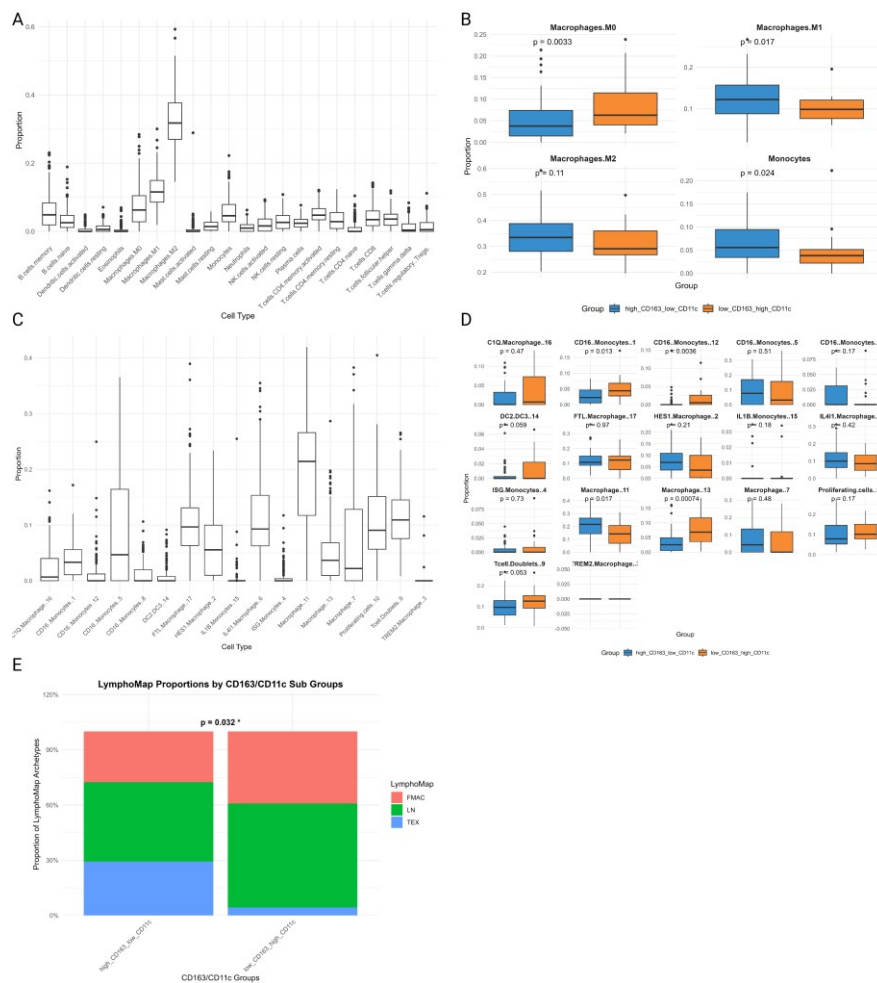
Supplementary Figure S10. Differential expression analysis and Gene set enrichment analysis in CD3+ and CD20+ cell segments. Differentially expressed genes (DEGs; adjusted $p < 0.05$) are displayed in volcano plots, where genes with $\log_2FC > 0$ (orange) are upregulated in the CD163^{low}/CD11c^{high} subgroup and genes with $\log_2FC < 0$ (blue) are upregulated in the CD163^{high}/CD11c^{low} subgroup for each segment. DEGs are also visualized in a heatmap, with normalized gene expression shown on a red-to-blue scale. CD163/CD11c subgroup assignments and cell of origin (COO) classifications are annotated for each patient. (A) and (B) Differential gene expression analysis (DGEA) for CD3+ segments using the CTA-CD3 cell-type-associated gene list. (C) and (D) DGEA for CD20+ segments using the CTA-CD20 cell-type-associated gene list. (E) and (F) DGEA for CD20+ segments using the CTA-Global gene list. (G) and (H) Top 20 upregulated and downregulated pathways comparing CD163^{low}/CD11c^{high} vs. CD163^{high}/CD11c^{low} in CD3+ (G) and CD20+ (H) segments. Pathways positively associated with CD163^{low}/CD11c^{high} (NES > 0) are shown in orange, and pathways positively associated with CD163^{high}/CD11c^{low} (NES < 0) are shown in blue.



Supplementary Figure S11. Forest plot displaying the result from the CD163+ DSP-mIF cohort and validation cohorts from cox regression survival analysis using the categorical risk group division “Low”, Intermediate”, “High” score, where the “Low” risk group is set as the reference. *p-value<0.05, **p-value<0.01, ***p-value<0.001.



Supplementary Figure S12. GEX risk score survival analysis on external cohorts with R-CHOP treatment regimen. A) Forest plot displaying the result from the validation cohorts from Cox regression using the GEX risk score. B) Forest plot displaying the result from the validation cohorts from Cox regression using the categorical risk group division “Low”, Intermediate”, “High” score, where the “Low” risk group is set as the reference. Plots C-E) Display Kaplan Meier curves between the risk groups where C) GSE87371, D) GSE10846, and E) GSE181063. *p-value<0.05, **p-value<0.01, ***p-value<0.001.



Supplementary Figure S13. Cell deconvolution reveals a distinct cellular composition in CD163^{high}/CD11c^{low} samples compared to CD163^{low}/CD11c^{high} samples. (A) Predicted cell proportions in CD163⁺ segments using the LM22 signature matrix with Cibersortx deconvolution framework. (B) Predicted macrophage subtype proportions comparing CD163/CD11c subgroups using the LM22 signature matrix. (C) Predicted monocyte and macrophage cell proportions in CD163⁺ segments using the MoMac-VERSE signature matrix with Cibersortx deconvolution framework. (D) Predicted cell proportions comparing CD163/CD11c subgroups using the MoMac-VERSE signature matrix. (E) Predicted LymphoMap archetypes comparing CD163/CD11c subgroups.

Supplementary Tables

Supplementary Table 1. Validated TP53 Mutations.

ID	Type	Callers	Chromosome	Position	Change	HGN_C_id	Gene_name	Canonical_transcript.HGV S.protein_change	Primary_transcript.HGV S.protein_change	Consequence	CA DD	Gnom AD.AF	VAF.T UMOR	COSMIC.ID
142	CANCER	TNScore:Pass VarDict:Pass	17	7578177	C>T	11998	TP53	NM_000546/c.672G>A/p.Glu224=	NM_000546/c.672G>A/p.Glu224=	splice region variant	27.5	N/A	0.4896 (1083 128)	COSV52681634 COSV52721244 COSV105016529 COSV52678333
177	CANCER	TNScore:Pass VarDict:Pass	17	7578478	G>C	11998	TP53	NM_000546/c.452C>G/p.Pro151Arg	NM_000546/c.452C>G/p.Pro151Arg	missense variant	23.6	N/A	0.1951 (1011 460)	COSV52677206 COSV52811105 COSV52707835
238	CANCER	TNScore:Pass VarDict:Pass	17	7577130	A>G	11998	TP53	NM_000546/c.808T>C/p.Phe270Leu	NM_000546/c.808T>C/p.Phe270Leu	missense variant	29.1	N/A	0.4168 (571 795)	COSV52697968 COSV52691720 COSV106055487 COSV52744290
238	CANCER	TNScore:Pass VarDict:Pass	17	7578190	T>C	11998	TP53	NM_000546/c.659A>G/p.Tyr220Cys	NM_000546/c.659A>G/p.Tyr220Cys	missense variant	29.3	N/A	0.4296 (839 111)	COSV52677517 COSV52661282
238	CANCER	TNScore:Pass VarDict:Pass	17	7578202	A>T	11998	TP53	NM_000546/c.647T>A/p.Val216Glu	NM_000546/c.647T>A/p.Val216Glu	missense variant	29.9	N/A	0.4213 (765 1049)	COSV52856938 COSV52866969 COSV52676908 COSV53036902
286	CANCER	TNScore:Pass VarDict:Pass	17	7577539	G>A	11998	TP53	NM_000546/c.742C>T/p.Arg248Trp	NM_000546/c.742C>T/p.Arg248Trp	missense variant	27.2	N/A	0.6645 (1022 514)	COSV53097881 COSV52662035 COSV52797251
289	CANCER	TNScore:Pass VarDict:Pass	17	7577550	C>A	11998	TP53	NM_000546/c.731G>T/p.Gly244Val	NM_000546/c.731G>T/p.Gly244Val	missense variant	27.6	N/A	0.5479 (675 551)	COSV52724858 COSV52661058

														COSV528 39584
3 0 1	CAN CER	TNScope:Pass VarDict: Pass	17	7577 539	G>A	1199 8	TP53	NM_000546/c.742C>T/p.Arg248Trp	NM_000546/c.742C>T/p.Arg248Trp	missense variant	27. 2	N/A	0.4476 (1336 1646)	COSV530 97881 COSV527 97251 COSV526 62035
4 2	CAN CER	TNScope:Pass VarDict: Pass	17	7577 512	G>C	1199 8	TP53	NM_000546/c.769C>G/p.Leu257Val	NM_000546/c.769C>G/p.Leu257Val	missense variant	23. 6	N/A	0.1854 (441 1937)	COSV531 20630 COSV527 17368
4 3 2	CAN CER	TNScope:Pass VarDict: Pass	17	7577 580	T>C	1199 8	TP53	NM_000546/c.701A>G/p.Tyr234Cys	NM_000546/c.701A>G/p.Tyr234Cys	missense variant	25. 2	N/A	0.16 (256 1344)	COSV526 86167 COSV531 42556 COSV526 61201
4 3 2	CAN CER	TNScope:Pass VarDict: Pass	17	7578 530	A>G	1199 8	TP53	NM_000546/c.400T>C/p.Phe134Leu	NM_000546/c.400T>C/p.Phe134Leu	missense variant	28. 2	N/A	0.1499 (409 2320)	COSV526 97695 COSV529 23862 COSV526 60909 COSV526 76112
4 7	CAN CER	TNScope:Pass VarDict: Pass	17	7577 082	C>T	1199 8	TP53	NM_000546/c.856G>A/p.Glu286Lys	NM_000546/c.856G>A/p.Glu286Lys	missense variant	27. 8	N/A	0.5586 (758 595)	COSV526 88214 COSV526 87201 COSV526 64318
4 8 0	CAN CER	TNScope:Pass VarDict: Pass	17	7574 034	C>T	1199 8	TP53	NM_000546/c.994-1G>A/-	NM_000546/c.994-1G>A/-	splice acceptor variant	34	N/A	0.2531 (352 1037)	COSV527 66192 COSV527 46625 COSV526 68116
5 5 8	CAN CER	TNScope:Pass VarDict: Pass	17	7577 568	C>T	1199 8	TP53	NM_000546/c.713G>A/p.Cys238Tyr	NM_000546/c.713G>A/p.Cys238Tyr	missense variant	29	N/A	0.4207 (260 357)	COSV528 04264 COSV526 61646 COSV527 06816
5 7 2	CAN CER	TNScope:Pass VarDict: Pass	17	7577 548	C>T	1199 8	TP53	NM_000546/c.733G>A/p.Gly245Ser	NM_000546/c.733G>A/p.Gly245Ser	missense variant	28. 9	3,00E-05	0.0555 (106 1800)	COSV526 61877 COSV528 39866 COSV526

														61744 COSV527 13951
572	CAN CER	TNScope:Pass VarDict:Pass	17	7578406	C>T	11998	TP53	NM_000546/c.524G>A/p.Arg175His	NM_000546/c.524G>A/p.Arg175His	missense variant	24.2	N/A	0.0626 (220 3292)	COSV526 77601 COSV527 31306 COSV526 61038 COSV538 01286
572	CAN CER	TNScope:Pass VarDict:Pass	17	7578502	A>G	11998	TP53	NM_000546/c.428T>C/p.Val143Ala	NM_000546/c.428T>C/p.Val143Ala	missense variant	21.7	N/A	0.278 (886 2295)	COSV527 37174 COSV527 60297 COSV528 68891
580	CAN CER	TNScope:Pass VarDict:Pass	17	7577069	C>T	11998	TP53	NM_000546/c.869G>A/p.Arg290His	NM_000546/c.869G>A/p.Arg290His	missense variant	14.65	0.00013	0.6985 (695 299)	COSV526 83585 COSV532 96796
580	CAN CER	TNScope:Pass VarDict:Pass	17	7578406	C>T	11998	TP53	NM_000546/c.524G>A/p.Arg175His	NM_000546/c.524G>A/p.Arg175His	missense variant	24.2	N/A	0.5391 (1123 950)	COSV538 01286 COSV526 61038 COSV527 31306 COSV526 77601
587	CAN CER	TNScope:Pass VarDict:Pass	17	7577557	A>T	11998	TP53	NM_000546/c.724T>A/p.Cys242Ser	NM_000546/c.724T>A/p.Cys242Ser	missense variant	26.7	N/A	0.7395 (1059 368)	COSV526 77021 COSV528 39973 COSV526 60956 COSV527 60397
596	CAN CER	TNScope:Pass VarDict:Pass	17	7578235	T>C	11998	TP53	NM_000546/c.614A>G/p.Tyr205Cys	NM_000546/c.614A>G/p.Tyr205Cys	missense variant	22.9	N/A	0.552 (818 663)	COSV526 88506 COSV526 77268 COSV526 65440
606	CAN CER	TNScope:Pass VarDict:Pass	17	7577539	G>A	11998	TP53	NM_000546/c.742C>T/p.Arg248Trp	NM_000546/c.742C>T/p.Arg248Trp	missense variant	27.2	N/A	0.3796 (238 388)	COSV527 97251 COSV530 97881 COSV526 62035

6 2 7	CAN CER	TNScope:Pass VarDict: Pass	17	7578 400	G>A	1199 8	TP53	NM_000546/c.530C>T/p.Pro177Leu	NM_000546/c.530C>T/p.Pro177Leu	missense variant	26. 8	N/A	0.2887 (623 1533)	COSV527 83879 COSV526 61381 COSV527 21872
6 8 3	CAN CER	TNScope:Pass VarDict: Pass	17	7577 559	G>A	1199 8	TP53	NM_000546/c.722C>T/p.Ser241Phe	NM_000546/c.722C>T/p.Ser241Phe	missense variant	25. 7	N/A	0.4937 (789 807)	COSV527 60886 COSV526 62386 COSV527 13934 COSV526 61688
6 8 8	CAN CER	TNScope:Pass VarDict: Pass	17	7577 548	C>T	1199 8	TP53	NM_000546/c.733G>A/p.Gly245Ser	NM_000546/c.733G>A/p.Gly245Ser	missense variant	28. 9	3,00E-05	0.7487 (983 328)	COSV527 13951 COSV526 61744 COSV528 39866 COSV526 61877
7 2	CAN CER	TNScope:Pass VarDict: Pass	17	7578 266	T>A	1199 8	TP53	NM_000546/c.583A>T/p.Ile195Phe	NM_000546/c.583A>T/p.Ile195Phe	missense variant	24. 6	N/A	0.2024 (382 1504)	COSV528 09310 COSV526 77568 COSV532 33300
7 2	CAN CER	TNScope:Pass VarDict: Pass	17	7578 508	C>T	1199 8	TP53	NM_000546/c.422G>A/p.Cys141Tyr	NM_000546/c.422G>A/p.Cys141Tyr	missense variant	23. 8	N/A	0.1772 (359 1660)	COSV526 64953 COSV529 26626 COSV531 55598
7 5	CAN CER	TNScope:Pass VarDict: Pass	17	7577 550	C>A	1199 8	TP53	NM_000546/c.731G>T/p.Gly244Val	NM_000546/c.731G>T/p.Gly244Val	missense variant	27. 6	N/A	0.1711 (242 1170)	COSV526 61058 COSV527 24858 COSV528 39584
8 4	CAN CER	TNScope:Pass VarDict: Pass	17	7577 106	G>A	1199 8	TP53	NM_000546/c.832C>T/p.Pro278Ser	NM_000546/c.832C>T/p.Pro278Ser	missense variant	28. 5	N/A	0.6476 (669 362)	COSV526 68132 COSV529 50563 COSV526 84662 COSV526 79740

94	CANCER	TNScore:Pass VarDict:Pass	17	7578268	A>C	11998	TP53	NM_000546/c.581T>G/p.Leu194Arg	NM_000546/c.581T>G/p.Leu194Arg	missense variant	24.7	N/A	0.8845 (3523 450)	COSV52713187 COSV52677924 COSV52679257 COSV52663681
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Supplementary Table S2. Antibodies used in IHC and mIF staining.

Antibody	Supplier	Product number	Clone	Koncentration	Flouorochrome	Panel
CD20	Novus	NBP2-47840AF594	IGEL/773	8 µg/ml	AF594	DSP and mIF CD163/CD11c
CD3e	Bio-Techne (Minneapolis, Minnesota, USA)	UM500048CF	UMAB54	4 µg/ml	AF532	DSP
CD163	Abcam	AB313666	EPR19518	2 µg/ml (mIF), 1:200 (IHC)	AF647	DSP, mIF CD163/CD11c, IHC CD163/CD11c
CD11c	Abcam	ab216655	EP1347Y	5 µg/ml (mIF), 1:300 (IHC)	AF532	mIF CD163/CD11c, IHC CD163/CD11c
CD20 (IHC)	Dako	IR604	L26	RTU	Not applicable	IHC
CD10	Dako	IR648	56C6	RTU	Not applicable	IHC
BCL-6	Dako	IR625	PG-B6p	RTU	Not applicable	IHC
MUM-1	Dako	IR644	MUM1p	RTU	Not applicable	IHC
Inform EBER Probe	Ventana	800-2842	Not applicable		Not applicable	In-situ hybr.
DAPI	Thermo Fisher Scientific (Waltham, Massachusetts, USA)	62248	N/A	300 nM		mIF CD63/CD11c
Syto13	Invitrogen™, Thermo Fisher Scientific	S7575	N/A	500 nM	N/A	mIF CD63/CD11c
Discovery Purple	Ventana Medical Systems Inc, Tucson, AZ)	NA	N/A			IHC CD163/CD11c
ChromoMap DAB	Ventana Medical Systems Inc, Tucson, AZ)	NA	N/A			IHC CD163/CD11c

Supplementary Table S3. Patient characteristics of the BLISS-DLBCL TMA-NOS cohort and in the mIF CD163/CD11c cohort. Chi-squared p-value for comparison of patients in each category of each patient characteristics, missing values are excluded from the comparison.

Characteristic	Category	BLISS-DLBCL TMA-NOS cohort (n, %)	mIF CD163/CD11c cohort (n, %)	Chi-squared p value
Total		561 (100%)	405 (100%)	
Gender	F	251 (44.7%)	178 (44%)	0.858
	M	310 (55.3%)	227 (56%)	
Cell of origin	ABC	275 (49%)	198 (48.9%)	0.598
	GCB	220 (39.2%)	172 (42.5%)	
	Unknown	66 (11.8%)	35 (8.6%)	
LDH	High	294 (52.4%)	202 (49.9%)	0.466
	Low	234 (41.7%)	179 (44.2%)	
	Missing	33 (5.9%)	24 (5.9%)	
Age at diagnosis	<=60	143 (25.5%)	104 (25.7%)	1.000
	>60	418 (74.5%)	301 (74.3%)	
WHO	0-1	447 (79.7%)	319 (78.8%)	0.752
	>=2	109 (19.4%)	83 (20.5%)	
	Missing	5 (0.9%)	3 (0.7%)	
Stage	I-II	281 (50.1%)	203 (50.1%)	1.000
	III-IV	257 (45.8%)	187 (46.2%)	
	Missing	23 (4.1%)	15 (3.7%)	
IPI	low risk	198 (35.3%)	147 (36.3%)	0.983
	low intermediate risk	123 (21.9%)	86 (21.2%)	
	high intermediate risk	123 (21.9%)	90 (22.2%)	
	high risk	69 (12.3%)	48 (11.9%)	
	Missing	48 (8.6%)	34 (8.4%)	
Treatment	Ann Rituximab	12 (2.1%)	11 (2.7%)	0.993
	CHOEP	16 (2.9%)	13 (3.2%)	
	CHOP	64 (11.4%)	49 (12.1%)	
	COP	2 (0.4%)	2 (0.5%)	
	Other	39 (7%)	27 (6.7%)	
	R-CHOEP	16 (2.9%)	12 (3%)	
	R-CHOP	255 (45.5%)	173 (42.7%)	
	R-COP	5 (0.9%)	5 (1.2%)	
	Radiotherapy	12 (2.1%)	7 (1.7%)	
	Missing	140 (25%)	106 (26.2%)	

Supplementary Table S4. CD3 cell-type-specific gene list (CTA-CD3) with references.

Gene	References
BCOR	LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
BTLA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CCL20	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCR4	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CCR5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCR6	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCR7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CD160	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD244	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD247	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD27	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD28	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD300A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD3D	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD3E	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD3G	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD40LG	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CD48	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD53	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD6	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD69	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD70	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/

CD8A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD8B	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD96	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CDC25A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CSF2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CTLA4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CTSW	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCL13	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCR3	LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCR5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCR6	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CYLD	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
DPP4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
DUSP2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
EFNA5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
ETS1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
FLT3LG	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
FOXP3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
FZD3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
GATA3	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
GIMAP4	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
GIMAP6	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
GNLY	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
GZMA	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
GZMB	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
GZMH	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
GZMK	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
GZMM	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
ICOS	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IFNG	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IL10RA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL12RB2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IL16	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL17A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IL18RAP	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/

IL21	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IL26	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IL2RA	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IL2RB	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL2RG	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IL32	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IL4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IL7R	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IL9	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
ITGAL	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
ITGB7	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
ITK	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
KLRB1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
KLRD1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
KLRG1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
KLRK1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LAG3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LAIR2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
LAT	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LCK	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LEF1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LILRA4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LRRN3	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
LTA	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
LTB	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LY9	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
MAP4K2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
MBL2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
NEFL	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
NKG7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
NOG	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
NR4A3	LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/

OASL	LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
PDCD1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; https://www.nature.com/articles/s41467-022-28020-5
PMCH	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; https://www.nature.com/articles/s41467-022-28020-5
PRF1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
PTPRC	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
PVRIG	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
RASGRP1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
RASGRP2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
RORA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
RUNX3	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
SH2D1A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
SLAMF6	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
SOCS1	LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
SSX1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
TCF7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TIGIT	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TNFRSF25	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TNFRSF4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
TNFSF8	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TRAC	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TRAT1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
TRDC	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
TSHR	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
TXK	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
WNT7A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
ZAP70	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
ABCB1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
ACTB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ANXA1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ATM	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
B2M	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
BATF	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
BIRC3	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CASP8	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CCL4	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/

CCND3	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CD44	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CD99	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CX3CR1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
EOMES	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
FLNA	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
FYN	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HLA-C	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HLA-E	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ID2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ITGB1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ITGB2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
JUNB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
KLRF1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LCP1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
LDHB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
LY6E	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
PPP2R2B	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
RAC2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
RPLP0	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
RPS27A	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
RPS6	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
S100B	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
SELL	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
SPN	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
TBX21	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
TNFAIP3	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ZEB2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/

Supplementary Table S5. CD20 cell-type-specific gene list (CTA-20) with references.

gene	reference
ACTB	Reddy et al. 2017; Ye et al. 2022
ADGRE5	Steen et al. 2022
AICDA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
ANP32B	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ATM	https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1;NA;NA;NA
ATOX1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
AURKB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
BATF	Steen et al. 2022; Ye et al. 2022
BCL2	Reddy et al. 2017; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1;NA;NA;NA
BCL2L1	Steen et al. 2022
BCL6	Reddy et al. 2017; Steen et al. 2022
BIRC3	https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1;NA;NA;NA
BIRC5	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
BLK	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025
BLNK	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025
BLVRA	Steen et al. 2022
BRAF	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
BRCA1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
BRIP1	Li et al. 2025
BTK	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017; Li et al. 2025; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
BTLA	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CAMP	Steen et al. 2022
CARD11	Reddy et al. 2017; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1;NA;NA;NA
CCND1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1;NA ; https://www.nature.com/articles/s41598-021-98560-1 ; https://www.nature.com/articles/s41408-024-01146-z#Sec2
CCR6	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCR7	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CD180	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD19	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;

	https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://www.nature.com/articles/s41598-021-98560-1 ; NA; NA; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD1C	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD1D	Steen et al. 2022
CD200	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Steen et al. 2022
CD22	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017; Li et al. 2025; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD24	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; NA; NA; NA
CD27	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022
CD37	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; Li et al. 2025
CD38	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CD40	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CD48	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ; NA; NA; NA
CD53	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD55	Steen et al. 2022; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ; NA; NA; NA
CD69	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
CD70	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CD74	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; NA; NA
CD79A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; NA; NA; NA; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD79B	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017; Ye et al. 2022; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; NA; NA; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD81	https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ; NA; NA; NA
CD83	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; Li et al. 2025
CD86	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CD9	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CDC20	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://link.springer.com/article/10.1007/s12308-020-00418-4 ; NA; NA; NA

CDK1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CDKN2A	https://www.nature.com/articles/s41408-024-01146-z#Sec2 ;NA;NA;NA
CDKN2B	https://www.nature.com/articles/s41408-024-01146-z#Sec2 ;NA;NA;NA
CENPF	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CHAD	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CLECL1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;NA;NA;NA
COL4A3	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
COL4A4	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CR1	LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CR2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CTSH	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CXCR4	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ;NA;NA;NA
CXCR5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CXXC5	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CYBB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
CYLD	Steen et al. 2022
DNMT1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
DTX1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ;NA;NA;NA
DUSP1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
DUSP2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
E2F5	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
EBI3	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Steen et al. 2022
EGR1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ENO1	Ye et al. 2022
ESR2	Li et al. 2025
EWSR1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
EZH2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
FAM30A	LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
FANCA	Li et al. 2025
FCER2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Steen et al. 2022
FCGRT	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
FCRL2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
FEZ1	Steen et al. 2022
FOS	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022

FOXM1	https://link.springer.com/article/10.1007/s12308-020-00418-4 ;NA;NA;NA
GBP1	Steen et al. 2022
GBP4	Steen et al. 2022
GLUL	Steen et al. 2022
GNG7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
GPI	Steen et al. 2022
GPX1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
GUSB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HCK	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HDAC2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HELLS	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HHEX	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HIF1A	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HLA-B	Ye et al. 2022
HLA-C	Ye et al. 2022
HLA-DMA	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;NA;NA;NA
HLA-DMB	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;NA;NA;NA
HLA-DOA	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HLA-DOB	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
HLA-DPA1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
HLA-DPB1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
HLA-DQA1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;NA;NA;NA
HLA-DQA2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HLA-DQB1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
HLA-DRA	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
HMGA1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HMGB1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
HPRT1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
HSP90B1	Ye et al. 2022
HSPB1	Ye et al. 2022
IDH2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
IGF1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5

IGLL1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IKBKB	Reddy et al. 2017
IL10RA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL16	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL21R	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL26	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IL2RB	Steen et al. 2022
IL4R	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
ILF3	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
IRF1	Steen et al. 2022
IRF4	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Reddy et al. 2017
IRF8	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017
IRF9	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ITGA4	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
ITGAE	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ITGB7	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
JUN	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
JUNB	Ye et al. 2022
KBTBD8	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
KIF2C	https://link.springer.com/article/10.1007/s12308-020-00418-4 ;NA;NA;NA
LDHA	Steen et al. 2022; Ye et al. 2022
LEF1	Steen et al. 2022
LGALS9	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
LTA	Steen et al. 2022
LTB	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022
LTK	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
LY86	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
LY9	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LYN	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025
MAD2L2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
MBL2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
MCL1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017
MCM5	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
MCM7	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
MDM4	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
MEF2C	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025
MKI67	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://www.nature.com/articles/s41598-021-98560-1 ; https://link.springer.com/article/10.1007/s12308-020-00418-4 ;NA;NA
MME	Li et al. 2025

MS4A1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; NA;NA;NA; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
MSH6	Li et al. 2025
MTF2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
MTOR	Reddy et al. 2017
MYBL2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
MYC	Reddy et al. 2017; https://www.nature.com/articles/s41408-024-01146-z#Sec2 ;NA;NA;NA
MYD88	Reddy et al. 2017
NASP	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
NCF4	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
NFKBIA	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Steen et al. 2022; Ye et al. 2022
NFKBIZ	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
NOTCH1	https://www.nature.com/articles/s41408-024-01146-z#Sec2 ;NA;NA;NA
NOTCH2	Steen et al. 2022; https://www.nature.com/articles/s41408-024-01146-z#Sec2 ;NA;NA;NA
NSD2	https://www.nature.com/articles/s41408-024-01146-z#Sec2 ;NA;NA;NA
OAS1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Steen et al. 2022
OAZ1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ORC6	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
PARP9	Steen et al. 2022
PAX5	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017; Li et al. 2025; https://www.nature.com/articles/s41598-021-98560-1 ;NA;NA;NA
PCNA	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
PDGFD	Li et al. 2025
PDK1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
PDZK1IP1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
PEBP1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
PIK3R1	Reddy et al. 2017
PIM1	Steen et al. 2022
PKM	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
PLCG2	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ;NA;NA;NA
PMAIP1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
PNOC	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
POU2AF1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/

POU2F2	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;NA;NA
PPBP	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
PRDM1	Steen et al. 2022
PRKCB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ;NA;NA;NA
PRKCE	Li et al. 2025
PRKX	Steen et al. 2022
PSMB7	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
PTGER4	Steen et al. 2022
PTPRC	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
PTTG1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
PVRIG	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
RAD21	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
RASGRP2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
RBX1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
REL	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
REN	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
RHOA	Reddy et al. 2017
RHOB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
RPA3	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
RPLP0	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
RPS6	Ye et al. 2022
RRAS2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Li et al. 2025
RRM2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
SELL	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
SF3B1	Reddy et al. 2017
SH2B2	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
SLAMF1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM7 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
SLAMF6	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Steen et al. 2022
SLC1A5	Steen et al. 2022
SMARCB1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
SMC1A	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
SMC3	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
SOCS1	https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ;NA;NA;NA
SOX11	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://www.nature.com/articles/s41598-021-98560-1 ;NA;NA;NA
SPIB	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;NA;NA
SRSF2	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/

SSX1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
STMN1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
SYK	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Reddy et al. 2017; Li et al. 2025; https://pmc.ncbi.nlm.nih.gov/articles/PMC12490240/#mmc1 ;NA;NA;NA
TAP1	Steen et al. 2022
TCL1A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
TCL1B	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
TFDP1	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
TFEB	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
TGFR2	Reddy et al. 2017
TLR1	Steen et al. 2022
TLR10	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TLR9	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TNFRSF13B	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
TNFRSF13C	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ;NA;NA;NA
TNFRSF17	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TOP2A	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022; https://link.springer.com/article/10.1007/s12308-020-00418-4 ;NA;NA;NA
TP53	https://www.nature.com/articles/s41408-024-01146-z#Sec2 ;NA;NA;NA
TPM4	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
TSHR	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
TUBB	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
TYMS	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
UBA7	Steen et al. 2022
UBC	Ye et al. 2022
UBE2C	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/ ; Ye et al. 2022
UQCRCQ	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
WEE1	Li et al. 2025
WNT16	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
ZBTB20	DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ZBTB32	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; DE MCL - https://pmc.ncbi.nlm.nih.gov/articles/PMC7476085/
ZC3H12A	Steen et al. 2022

Supplementary Table S6. CD163 cell-type-specific gene list (CTA-CD163) with references.

gene	reference
ANLN	Li et al. 2025
APOE	Ye et al. 2022; Li et al. 2025
APOL6	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
APP	Li et al. 2025
AQP9	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
ATG7	Li et al. 2025
BCAT1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Li et al. 2025
BRCA2	Li et al. 2025
BRIP1	Li et al. 2025
C1QA	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022; Li et al. 2025
C1QB	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022; Li et al. 2025
C2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
C5AR1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CCL13	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CCL14	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL17	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
CCL18	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CCL19	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL20	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
CCL22	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Cheng et al. 2021
CCL23	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL24	Cheng et al. 2021
CCL4	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
CCL5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CCL7	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL8	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCR1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CCR7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CCRL2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD14	Ye et al. 2022
CD163	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Li et al. 2025
CD209	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD274	Li et al. 2025
CD276	Cheng et al. 2021

CD38	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Li et al. 2025
CD4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Li et al. 2025
CD40	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CD44	Li et al. 2025
CD48	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD53	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD68	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022
CD74	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD80	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CD83	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD84	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
CD86	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Cheng et al. 2021; Li et al. 2025
CDC14B	Li et al. 2025
CFP	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CHIT1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CLEC4A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CLEC5A	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CLEC7A	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Cheng et al. 2021; Li et al. 2025
CMKLR1	Li et al. 2025
COL27A1	Li et al. 2025
COLEC12	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Li et al. 2025
CR1	Li et al. 2025
CSF1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CSF1R	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
CTSH	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CTSL	Li et al. 2025
CTSS	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
CXCL10	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CXCL11	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CXCL13	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCL16	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CXCL3	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCL5	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCL8	Ye et al. 2022
CXCL9	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CYBB	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
DAB2	Li et al. 2025
DEFB1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
DKK2	Li et al. 2025
DPP4	Li et al. 2025
DST	Li et al. 2025

DUSP1	Li et al. 2025
EBI3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
EGF	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
ELANE	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
ESR1	Li et al. 2025
FBP1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
FCER1G	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
FN1	Cheng et al. 2021
FOS	Li et al. 2025
FPR3	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
FZD2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
GBP1	Li et al. 2025
GBP2	Li et al. 2025
GLUL	Li et al. 2025
GNAQ	Li et al. 2025
GPC4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
HAVCR2	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
HCK	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
HIF1A	Li et al. 2025
HLA-DMB	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
HMGA2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
ICAM1	Li et al. 2025
IDO1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
IFNGR1	Li et al. 2025
IGF2R	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
IL10RA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL13RA1	Li et al. 2025
IL15	Li et al. 2025
IL17RA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
IL18	Li et al. 2025
IL1A	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
IL1B	Ye et al. 2022
IL1RN	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
IL21R	Li et al. 2025
IL22RA2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IL23R	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IL2RA	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
IL4R	Cheng et al. 2021
IL6	Cheng et al. 2021
IL6R	Li et al. 2025
IL6ST	Li et al. 2025
INHBA	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
IRAK3	Li et al. 2025
IRF1	Cheng et al. 2021

IRF4	Cheng et al. 2021
IRF5	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Cheng et al. 2021
ITGAM	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
ITGAV	Li et al. 2025
ITGAX	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
ITGB2	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
ITGB3	Li et al. 2025
JAK2	Li et al. 2025
LAG3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LAIR1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LAMP3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LCP1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LEP	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
LGALS9	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LILRA3	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LILRB1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
LILRB2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
LILRB4	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
LRP1	Li et al. 2025
LY96	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
LYZ	Li et al. 2025
MAML2	Li et al. 2025
MAP3K8	Li et al. 2025
MARCO	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
MBL2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
MCL1	Li et al. 2025
MELK	Li et al. 2025
MERTK	Li et al. 2025
MKI67	Li et al. 2025
MMP9	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Ye et al. 2022; Li et al. 2025
MRC1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
MS4A4A	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
MS4A6A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Li et al. 2025
MSR1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021; Li et al. 2025
NFATC1	Li et al. 2025
NFE2L2	Li et al. 2025
NFKBIA	Li et al. 2025
NFKBIE	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
NOD2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
NOTCH2	Li et al. 2025
NRP1	Li et al. 2025
OTOA	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
P2RY13	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/

PDCD1LG2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Li et al. 2025
PDGFC	Li et al. 2025
PFKFB3	Li et al. 2025
PIK3CB	Li et al. 2025
PIK3R5	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
PLA1A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
PLAUR	Li et al. 2025
PLD1	Li et al. 2025
PPARG	Li et al. 2025
PPARGC1B	Li et al. 2025
PPBP	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
PRG2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
PRKCA	Li et al. 2025
PRKCD	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
PTGER4	Li et al. 2025
RIPK2	Li et al. 2025
RSAD2	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
S100A8	Ye et al. 2022
S100A9	Ye et al. 2022
SAMSN1	Li et al. 2025
SGK1	Li et al. 2025
SIGLEC1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Li et al. 2025
SIRPA	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
SIRPB2	Li et al. 2025
SLAMF1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
SLAMF7	Li et al. 2025
SLC11A1	Li et al. 2025
SOCS1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
SOD2	Li et al. 2025
SOST	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
SPP1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Li et al. 2025
SPRED1	Li et al. 2025
STAT1	Li et al. 2025
TBXAS1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
TFRC	Li et al. 2025
TGFB1	Cheng et al. 2021
TGFB2	Cheng et al. 2021
TGFB3	Cheng et al. 2021
THBD	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
TIAM1	Li et al. 2025
TLR2	Li et al. 2025
TLR4	Li et al. 2025
TLR7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
TLR8	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TNF	Cheng et al. 2021

TNFAIP3	Li et al. 2025
TNFAIP6	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
TNFRSF11A	Li et al. 2025
TNFRSF1B	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TNFSF12	Cheng et al. 2021
TNFSF13B	Li et al. 2025
TNFSF14	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
TNFSF15	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
TNFSF8	Cheng et al. 2021
TRAF3	Li et al. 2025
TREM2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
TYMP	Li et al. 2025
VEGFA	Cheng et al. 2021
VEGFB	Cheng et al. 2021
VEGFC	Cheng et al. 2021
VEGFD	Cheng et al. 2021
VTCN1	Cheng et al. 2021
WIF1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
WNT5B	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
WNT7B	Cheng et al. 2021
ZEB2	Li et al. 2025
gene	reference
ANLN	Li et al. 2025
APOE	Ye et al. 2022; Li et al. 2025
APOL6	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
APP	Li et al. 2025
AQP9	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
ATG7	Li et al. 2025
BCAT1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Li et al. 2025
BRCA2	Li et al. 2025
BRIP1	Li et al. 2025
C1QA	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022; Li et al. 2025
C1QB	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022; Li et al. 2025
C2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
C5AR1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CCL13	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CCL14	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL17	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
CCL18	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021

CCL19	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL20	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
CCL22	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Cheng et al. 2021
CCL23	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL24	Cheng et al. 2021
CCL4	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Cheng et al. 2021
CCL5	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CCL7	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCL8	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CCR1	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CCR7	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CCRL2	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD14	Ye et al. 2022
CD163	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Li et al. 2025
CD209	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CD274	Li et al. 2025
CD276	Cheng et al. 2021
CD38	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Li et al. 2025
CD4	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Li et al. 2025
CD40	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CD44	Li et al. 2025
CD48	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD53	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD68	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Ye et al. 2022
CD74	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD80	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CD83	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CD84	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
CD86	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Cheng et al. 2021; Li et al. 2025
CDC14B	Li et al. 2025
CFP	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CHIT1	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CLEC4A	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CLEC5A	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5
CLEC7A	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Cheng et al. 2021; Li et al. 2025
CMKLR1	Li et al. 2025
COL27A1	Li et al. 2025
COLEC12	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; Li et al. 2025

CR1	Li et al. 2025
CSF1	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CSF1R	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
CTSH	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CTSL	Li et al. 2025
CTSS	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/ ; Li et al. 2025
CXCL10	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CXCL11	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/ ; Cheng et al. 2021
CXCL13	LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCL16	HPCA - https://pmc.ncbi.nlm.nih.gov/articles/PMC3849585/
CXCL3	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/
CXCL5	spatialdecon - https://www.nature.com/articles/s41467-022-28020-5 ; LM22 - https://pmc.ncbi.nlm.nih.gov/articles/PMC4739640/

Supplementary Table S7. Clinical characteristics of independent DLBCL cohorts.

Characteristic	GSE10846 N = 414 ¹	GSE181063 N = 1,310 ¹	GSE31312 N = 470 ¹	GSE87371 N = 223 ¹
RCHOP-treated (n)	231	825	470	109
Age, mean (SD)	61.14 (15.45)	63.37 (18.23)	61.83 (14.91)	56.72 (16.05)
Gender, n (%)				
F	190 (46%)	583 (45%)	199 (42%)	107 (48%)
M	224 (54%)	727 (55%)	271 (58%)	116 (52%)

¹Mean; Mean (SD); n (%)

Supplementary Table S8. Patient characteristics of all patients in the BLISS-DLBCL patient cohort and for the selected patient groups based on TMA core availability (BLISS-DLBCL TMA) and diagnosed with DLBCL-NOS (BLISS-DLBCL TMA-NOS).

Characteristic	Variable	BLISS-DLBCL Cohort (n, %)	BLISS-DLBCL TMA Cohort (n, %)	BLISS-DLBCL TMA-NOS Cohort (n, %)
Total		733 (100%)	643 (100%)	561 (100%)
Follow-up time (years)		-	5.9	6.0
5-year survival (%)		-	54.9	55.8
Gender	F	327 (44.6%)	284 (44.2%)	251 (44.7%)
	M	399 (54.4%)	359 (55.8%)	310 (55.3%)
	Missing	7 (1%)	0 (0%)	0 (0%)
Cell of origin	ABC	-	-	275 (49%)
	GCB	-	-	220 (39.2%)
	Unknown	-	-	66 (11.8%)
	Missing	-	-	0 (0%)
Treatment	Ann Rituximab	14 (1.9%)	13 (2%)	12 (2.1%)
	CHOEP	23 (3.1%)	20 (3.1%)	16 (2.9%)
	CHOP	80 (10.9%)	72 (11.2%)	64 (11.4%)
	COP	2 (0.3%)	2 (0.3%)	2 (0.4%)
	Other	58 (7.9%)	50 (7.8%)	39 (7%)
	R-CHOEP	19 (2.6%)	18 (2.8%)	16 (2.9%)
	R-CHOP	325 (44.3%)	287 (44.6%)	255 (45.5%)
	R-COP	6 (0.8%)	6 (0.9%)	5 (0.9%)
	Radiotherapy	19 (2.6%)	14 (2.2%)	12 (2.1%)
	Missing	187 (25.5%)	161 (25%)	140 (25%)
Year of diagnosis	2000-2007	393 (53.6%)	345 (53.7%)	302 (53.8%)
	2008-2014	333 (45.4%)	298 (46.3%)	259 (46.2%)
	Missing	7 (1%)	0 (0%)	0 (0%)
LDH	High	381 (52%)	339 (52.7%)	294 (52.4%)
	Low	297 (40.5%)	265 (41.2%)	234 (41.7%)
	Missing	55 (7.5%)	39 (6.1%)	33 (5.9%)
Diagnosis	BCL UNS	25 (3.4%)	21 (3.3%)	0 (0%)
	DLBCL EBV	16 (2.2%)	16 (2.5%)	0 (0%)
	DLBCL_NOS	638 (87%)	561 (87.2%)	561 (100%)
	FL12	2 (0.3%)	2 (0.3%)	0 (0%)
	FL3A	2 (0.3%)	2 (0.3%)	0 (0%)
	Indolent BCL	1 (0.1%)	1 (0.2%)	0 (0%)
	MZL	2 (0.3%)	2 (0.3%)	0 (0%)
	PBL	2 (0.3%)	2 (0.3%)	0 (0%)
	PCLBCL-LT	4 (0.5%)	4 (0.6%)	0 (0%)
	PCNSL	4 (0.5%)	3 (0.5%)	0 (0%)
	TCRBCL	14 (1.9%)	14 (2.2%)	0 (0%)
	tFL	16 (2.2%)	15 (2.3%)	0 (0%)
	Missing	7 (1%)	0 (0%)	0 (0%)

Age diagnosis	<=60	190 (25.9%)	166 (25.8%)	143 (25.5%)
	>60	536 (73.1%)	477 (74.2%)	418 (74.5%)
	Missing	7 (1%)	0 (0%)	0 (0%)
WHO	0-1	565 (77.1%)	504 (78.4%)	447 (79.7%)
	>=2	155 (21.1%)	133 (20.7%)	109 (19.4%)
	Missing	13 (1.8%)	6 (0.9%)	5 (0.9%)
Stage	I-II	341 (46.5%)	310 (48.2%)	281 (50.1%)
	III-IV	356 (48.6%)	307 (47.7%)	257 (45.8%)
	Missing	36 (4.9%)	26 (4%)	23 (4.1%)
EBV status	N/A	37 (5%)	37 (5.8%)	31 (5.5%)
	Negative	593 (80.9%)	589 (91.6%)	530 (94.5%)
	Positive	17 (2.3%)	17 (2.6%)	0 (0%)
	Missing	86 (11.7%)	0 (0%)	0 (0%)
IPI	Low risk	238 (32.5%)	216 (33.6%)	198 (35.3%)
	Low intermediate risk	159 (21.7%)	144 (22.4%)	123 (21.9%)
	High intermediate risk	168 (22.9%)	146 (22.7%)	123 (21.9%)
	High risk	96 (13.1%)	81 (12.6%)	69 (12.3%)
	Missing	72 (9.8%)	56 (8.7%)	48 (8.6%)

Supplementary Table S9. Cox regression analysis of CD11c and CD163 as univariate and multivariate (adjusted for gender and IPI) in non-GCB and GCB patient groups.

COO	Marker	Model	HR	p-value	Significant (p-value<0.05)
non-GCB	CD11c High	Univariate	0.66 (0.43-1.03)	0.065	
non-GCB	CD11c High	Multivariate	0.89 (0.54-1.48)	0.657	
GCB	CD11c High	Univariate	0.54 (0.32-0.94)	0.028	*
GCB	CD11c High	Multivariate	0.62 (0.34-1.13)	0.119	
non-GCB	CD163 High	Univariate	1.60 (0.93-2.74)	0.088	
non-GCB	CD163 High	Multivariate	1.33 (0.74-2.38)	0.334	
GCB	CD163 High	Univariate	1.55 (0.92-2.63)	0.101	
GCB	CD163 High	Multivariate	1.39 (0.78-2.46)	0.259	

Supplementary Table S10. Patient characteristics of the BLISS-DLBCL TMA-NOS cohort and in the CD163^{high}/CD11c^{low} and CD163^{low}/CD11c^{high} subgroups. Chi-squared test was used to compare patient characteristics between the CD163/CD11c defined groups. Missing values are excluded from the comparison.

Characteristic	Variable	BLISS-DLBCL NOS TMA cohort (n, %)	CD163 ^{high} /CD11c ^{low} (n, %)	CD163 ^{low} /CD11c ^{high} (n, %)	Chi-squared p value
Total		561 (100%)	87 (100%)	115 (100%)	
Gender	F	251 (44.7%)	39 (44.8%)	57 (49.6%)	0.599
	M	310 (55.3%)	48 (55.2%)	58 (50.4%)	
Cell of origin	non-GCB	275 (49%)	51 (58.6%)	44 (38.3%)	0.008
	GCB	220 (39.2%)	31 (35.6%)	62 (53.9%)	
	Unknown	66 (11.8%)	5 (5.7%)	9 (7.8%)	
LDH	High	294 (52.4%)	47 (54%)	52 (45.2%)	0.242
	Low	234 (41.7%)	35 (40.2%)	57 (49.6%)	
	Missing	33 (5.9%)	5 (5.7%)	6 (5.2%)	
Age at diagnosis	<=60	143 (25.5%)	17 (19.5%)	27 (23.5%)	0.618
	>60	418 (74.5%)	70 (80.5%)	88 (76.5%)	
WHO	0-1	447 (79.7%)	56 (64.4%)	100 (87%)	<0.001
	>=2	109 (19.4%)	30 (34.5%)	14 (12.2%)	
	Missing	5 (0.9%)	1 (1.1%)	1 (0.9%)	
Stage	I-II	281 (50.1%)	35 (40.2%)	69 (60%)	0.006
	III-IV	257 (45.8%)	49 (56.3%)	41 (35.7%)	
	Missing	23 (4.1%)	3 (3.4%)	5 (4.3%)	
IPI	low risk	198 (35.3%)	21 (24.1%)	50 (43.5%)	0.001
	low intermediate risk	123 (21.9%)	17 (19.5%)	30 (26.1%)	
	high intermediate risk	123 (21.9%)	24 (27.6%)	18 (15.7%)	

	high risk	69 (12.3%)	19 (21.8%)	9 (7.8%)	
	Missing	48 (8.6%)	6 (6.9%)	8 (7%)	

Supplementary Table S11. CD20+ segments. Differentially expressed genes in the DGEA of the complete CTA panel. Up represents upregulation in the CD163^{low}/CD11c^{high} subgroup compared to the CD163^{high}/CD11c^{low} (Down). All values are rounded to four decimal places.

Gene	logFC	P.Value	adj.P.Val	Result
LTB	0,9407	0,0000	0,0000	Up
CLU	1,2834	0,0000	0,0000	Up
WIPF1	0,4196	0,0000	0,0000	Up
LCK	0,4539	0,0000	0,0000	Up
MMP9	0,8835	0,0000	0,0000	Up
FCER2	0,5411	0,0000	0,0000	Up
TAPBP	0,2996	0,0000	0,0000	Up
STAT3	-0,4377	0,0000	0,0000	Down
BATF	-0,6501	0,0000	0,0000	Down
H2AX	-0,3687	0,0000	0,0000	Down
IL4R	0,5052	0,0000	0,0000	Up
POU2F2	-0,4907	0,0000	0,0000	Down
SLC1A5	-0,2815	0,0000	0,0000	Down
PKM	-0,4280	0,0000	0,0000	Down
MIF	-0,4241	0,0000	0,0000	Down
LDHB	-0,4130	0,0000	0,0001	Down
TNFRSF13B	-0,6686	0,0000	0,0002	Down
PTPRC	0,3494	0,0000	0,0002	Up
HSP90B1	-0,5142	0,0000	0,0002	Down
CD4	0,3704	0,0000	0,0003	Up
ADA	-0,3876	0,0000	0,0004	Down
TNF	0,2661	0,0000	0,0004	Up
BBC3	-0,2595	0,0000	0,0004	Down
CYBB	0,3833	0,0000	0,0006	Up
VCAM1	0,3651	0,0000	0,0006	Up
MCM7	-0,3343	0,0000	0,0006	Down
NDUFA11	-0,2086	0,0000	0,0006	Down
ATM	0,2452	0,0000	0,0007	Up
C3	0,6302	0,0000	0,0008	Up
HLA-DOB	0,3651	0,0000	0,0008	Up
CD81	0,2943	0,0000	0,0009	Up
CR2	0,4643	0,0000	0,0010	Up
TXN2	-0,1778	0,0000	0,0011	Down
TRBC1/2	0,5739	0,0000	0,0011	Up
LYZ	0,7013	0,0000	0,0011	Up
NDUFA7	-0,2017	0,0000	0,0011	Down
PCNA	-0,3214	0,0000	0,0012	Down
CDK1	-0,2487	0,0000	0,0012	Down
TYMS	-0,3515	0,0000	0,0012	Down
NDUFB4	-0,2376	0,0000	0,0012	Down
NPM1	-0,3400	0,0000	0,0012	Down
GPI	-0,2822	0,0000	0,0013	Down

CCL19	0,6709	0,0000	0,0014	Up
IRF4	-0,4813	0,0000	0,0014	Down
AURKB	-0,2784	0,0000	0,0014	Down
CXCL14	0,2655	0,0000	0,0015	Up
ATOX1	0,2727	0,0000	0,0015	Up
LAMC2	0,1857	0,0000	0,0015	Up
EXO1	-0,2053	0,0000	0,0018	Down
ITGB2	0,3995	0,0000	0,0018	Up
HLA-DQA1	0,4179	0,0001	0,0020	Up
GPSM3	0,2404	0,0001	0,0021	Up
C1QBP	-0,2962	0,0001	0,0021	Down
CDK4	-0,2328	0,0001	0,0022	Down
CSF1R	0,3262	0,0001	0,0023	Up
PIM1	-0,3498	0,0001	0,0024	Down
HLA-E	0,3247	0,0001	0,0025	Up
CD74	0,3876	0,0001	0,0026	Up
CDKN1A	-0,2631	0,0001	0,0028	Down
NDUFA1	-0,2132	0,0001	0,0032	Down
CCR6	0,2083	0,0001	0,0032	Up
SAMSN1	0,2983	0,0001	0,0032	Up
CCNA2	-0,2469	0,0001	0,0032	Down
HDAC2	-0,1916	0,0001	0,0032	Down
HK2	-0,2181	0,0001	0,0033	Down
H3C10	-0,5584	0,0001	0,0036	Down
HLA-DRB	0,4902	0,0001	0,0036	Up
IL18	0,2832	0,0001	0,0038	Up
CD27	0,3371	0,0002	0,0039	Up
KLRK1	0,2498	0,0002	0,0041	Up
HLA-DQB1	0,3266	0,0002	0,0046	Up
CD163	-0,3441	0,0002	0,0052	Down
TNFSF13	0,1520	0,0002	0,0053	Up
MBNL1	0,2112	0,0002	0,0055	Up
BLNK	-0,3419	0,0002	0,0055	Down
TIGIT	0,2623	0,0002	0,0056	Up
LTF	0,3146	0,0002	0,0057	Up
CD70	-0,2168	0,0002	0,0057	Down
UBE2T	-0,1886	0,0003	0,0059	Down
FEN1	-0,2273	0,0003	0,0059	Down
CD84	0,2153	0,0003	0,0060	Up
IL2RB	-0,2644	0,0003	0,0060	Down
TLR6	0,1543	0,0003	0,0069	Up
MYC	-0,3759	0,0003	0,0069	Down
ALDOA	-0,3030	0,0003	0,0069	Down
BATF3	-0,1844	0,0003	0,0069	Down
PRKACB	0,1868	0,0003	0,0072	Up
AICDA	-0,3537	0,0004	0,0072	Down

S100A9	-0,4587	0,0004	0,0075	Down
LILRB4	0,3453	0,0004	0,0075	Up
HLA-DMB	0,3189	0,0004	0,0077	Up
E2F1	-0,2036	0,0004	0,0077	Down
MAGEA1	-0,1535	0,0004	0,0077	Down
CEBPA	0,2020	0,0004	0,0082	Up
CENPF	-0,1960	0,0004	0,0083	Down
SFXN1	-0,1783	0,0004	0,0084	Down
CLEC4C	0,1445	0,0004	0,0084	Up
UBB	-0,1858	0,0005	0,0084	Down
HMGA1	-0,3232	0,0005	0,0088	Down
HLA-DRA	0,4473	0,0006	0,0103	Up
HLA-DPA1	0,2940	0,0006	0,0107	Up
TUBB	-0,2401	0,0006	0,0109	Down
SLC7A5	-0,2531	0,0006	0,0109	Down
ATP5ME	-0,1848	0,0006	0,0109	Down
TOP2A	-0,2284	0,0007	0,0117	Down
UQCRCQ	-0,1662	0,0007	0,0119	Down
CDC20	-0,2466	0,0007	0,0120	Down
ATP5F1D	-0,1912	0,0007	0,0122	Down
NEIL1	0,2503	0,0007	0,0124	Up
MCM4	-0,2423	0,0008	0,0124	Down
HLA-F	0,3266	0,0008	0,0124	Up
CDC7	-0,1456	0,0008	0,0124	Down
STAT2	0,1962	0,0008	0,0126	Up
CR1	0,2628	0,0009	0,0136	Up
CASP7	-0,1313	0,0009	0,0136	Down
AKAP1	-0,1752	0,0009	0,0137	Down
FEZ1	-0,1582	0,0009	0,0138	Down
LGALS3	-0,2766	0,0009	0,0144	Down
PKMYT1	-0,1963	0,0009	0,0144	Down
KEAP1	-0,1577	0,0010	0,0144	Down
MET	-0,1588	0,0010	0,0146	Down
RAD51	-0,1547	0,0010	0,0151	Down
MCM5	-0,2405	0,0011	0,0155	Down
CD24	0,3842	0,0011	0,0158	Up
BAX	-0,2065	0,0011	0,0163	Down
PBK	-0,1579	0,0012	0,0166	Down
CHEK1	-0,1925	0,0012	0,0171	Down
CDC6	-0,1688	0,0012	0,0172	Down
BAP1	-0,1356	0,0013	0,0176	Down
IKBKB	0,1376	0,0014	0,0189	Up
C1QB	-0,3713	0,0014	0,0189	Down
CSF2RB	0,2544	0,0014	0,0189	Up
GPX4	0,1889	0,0014	0,0189	Up
KYAT1	-0,1596	0,0014	0,0189	Down

BLM	-0,1570	0,0014	0,0189	Down
MCM2	-0,2298	0,0015	0,0197	Down
IL13RA1	0,1960	0,0015	0,0199	Up
CD83	0,3942	0,0015	0,0203	Up
RASGRP2	0,2503	0,0016	0,0206	Up
GOT2	-0,2697	0,0016	0,0206	Down
C1S	0,2747	0,0016	0,0211	Up
IL10	-0,2065	0,0018	0,0233	Down
RRAS2	0,1662	0,0019	0,0239	Up
MKI67	-0,2310	0,0019	0,0239	Down
COX5B	-0,1415	0,0020	0,0246	Down
MELK	-0,1671	0,0020	0,0248	Down
IDH2	-0,2139	0,0021	0,0253	Down
HPRT1	-0,1532	0,0022	0,0274	Down
NOTCH2	0,1639	0,0023	0,0277	Up
ICOSLG	0,1807	0,0023	0,0277	Up
ELK1	-0,1598	0,0023	0,0277	Down
POLR2H	-0,1482	0,0023	0,0277	Down
SERPINB5	-0,1150	0,0024	0,0281	Down
CXCL13	0,4554	0,0024	0,0281	Up
MME	0,2428	0,0026	0,0300	Up
CD53	0,2074	0,0026	0,0300	Up
JUN	-0,1876	0,0027	0,0308	Down
KIF2C	-0,1655	0,0027	0,0309	Down
CD99	0,2360	0,0027	0,0309	Up
CD3D	0,2583	0,0027	0,0311	Up
ITGAX	0,2877	0,0028	0,0313	Up
MAP3K20	-0,1464	0,0028	0,0314	Down
TGFBR2	0,2039	0,0031	0,0344	Up
LY9	0,1804	0,0032	0,0349	Up
IL12A	-0,1106	0,0033	0,0356	Down
SLAMF6	0,1608	0,0033	0,0356	Up
HLA-DMA	0,2693	0,0033	0,0363	Up
RASGRF1	-0,1493	0,0034	0,0368	Down
HMGB1	-0,1497	0,0037	0,0400	Down
LRP5	-0,1485	0,0038	0,0408	Down
RPS6	-0,3585	0,0039	0,0412	Down
HLA-DQA2	0,1588	0,0040	0,0418	Up
C1QA	-0,3293	0,0040	0,0421	Down
NDUFA4L2	-0,1409	0,0041	0,0427	Down
CD36	-0,1744	0,0042	0,0430	Down
PLK1	-0,1895	0,0042	0,0433	Down
CD68	0,2591	0,0042	0,0433	Up
LGALS9	0,2507	0,0043	0,0434	Up
CD6	0,1866	0,0043	0,0438	Up
HLA-DRB3	0,4084	0,0045	0,0452	Up

NTRK1	-0,1155	0,0045	0,0453	Down
HLA-A	0,2880	0,0047	0,0463	Up
IFNB1	0,1059	0,0047	0,0463	Up
LY86	0,1413	0,0048	0,0463	Up
NASP	-0,1658	0,0048	0,0463	Down
CD86	0,1607	0,0048	0,0463	Up
SIRPB2	0,1309	0,0048	0,0463	Up
RPL7A	-0,2799	0,0048	0,0463	Down
SLC16A1	-0,1532	0,0049	0,0464	Down
PSMB5	-0,1306	0,0049	0,0464	Down
TTK	-0,1552	0,0049	0,0464	Down
POLD1	-0,1716	0,0050	0,0471	Down
TRAC	0,2788	0,0050	0,0471	Up
CD3EAP	-0,1239	0,0052	0,0484	Down
CDC25C	-0,1144	0,0053	0,0496	Down
IFNGR1	0,1786	0,0054	0,0498	Up
SERINC2	0,1098	0,0054	0,0498	Up

Supplementary Table S12. CD3+ segments. Differentially expressed genes in the DGEA of the complete CTA panel. Up represents upregulation in the CD163low/CD11chigh subgroup compared to the CD163high/CD11clow (Down). All values are rounded to four decimal places.

Gene	logFC	P.Value	adj.P.Val	Result
ATM	0,4408	0,0000	0,0000	Up
LTB	0,9085	0,0000	0,0000	Up
TCF7	0,5556	0,0000	0,0000	Up
CD163	-0,6420	0,0000	0,0000	Down
ICOS	0,3039	0,0000	0,0000	Up
RASGRP2	0,4668	0,0000	0,0000	Up
FCER2	0,4965	0,0000	0,0000	Up
GZMB	-0,6654	0,0000	0,0000	Down
CTLA4	0,3233	0,0000	0,0000	Up
CD4	0,4559	0,0000	0,0000	Up
IL6ST	0,3557	0,0000	0,0000	Up
WIPF1	0,3348	0,0000	0,0000	Up
CXCL14	0,3376	0,0000	0,0000	Up
GPX4	0,3009	0,0000	0,0001	Up
MBNL1	0,2950	0,0000	0,0001	Up
CCL18	-0,7392	0,0000	0,0001	Down
AURKB	-0,3297	0,0000	0,0001	Down
MIF	-0,3839	0,0000	0,0001	Down
MMP9	0,7243	0,0000	0,0001	Up
MAF	0,3132	0,0000	0,0001	Up
LEF1	0,2974	0,0000	0,0001	Up
SLC1A5	-0,2654	0,0000	0,0001	Down
TNFRSF25	0,2468	0,0000	0,0001	Up
CYLD	0,2359	0,0000	0,0001	Up
STAT3	-0,3799	0,0000	0,0001	Down
TXNIP	0,6714	0,0000	0,0001	Up
CD3D	0,4635	0,0000	0,0002	Up
FCGR3A/B	-0,4305	0,0000	0,0002	Down
VEGFA	-0,3499	0,0000	0,0003	Down
GZMH	-0,3070	0,0000	0,0003	Down
IFNGR1	0,3019	0,0000	0,0003	Up
LAG3	-0,3506	0,0000	0,0003	Down
IL7R	0,4593	0,0000	0,0003	Up
FOXP3	0,2129	0,0000	0,0004	Up
H2AX	-0,3002	0,0000	0,0005	Down
TIGIT	0,3330	0,0000	0,0005	Up
C1QB	-0,5567	0,0000	0,0005	Down
LCK	0,3168	0,0000	0,0005	Up
ATOX1	0,2892	0,0000	0,0005	Up
LFNG	0,2219	0,0000	0,0005	Up
POU2F2	-0,3934	0,0000	0,0005	Down
JUN	-0,2830	0,0000	0,0006	Down

ITGAX	0,4489	0,0000	0,0006	Up
LY9	0,2687	0,0000	0,0006	Up
TNFRSF13B	-0,6033	0,0000	0,0006	Down
RBL2	0,2268	0,0000	0,0006	Up
ADA	-0,3579	0,0000	0,0006	Down
SELL	0,4021	0,0000	0,0008	Up
S100A9	-0,5880	0,0000	0,0008	Down
CXCL11	-0,2846	0,0000	0,0008	Down
SLC7A5	-0,3165	0,0000	0,0008	Down
PKM	-0,3456	0,0000	0,0009	Down
CEBPA	0,2489	0,0000	0,0009	Up
CD5	0,2492	0,0000	0,0009	Up
CASP7	-0,1656	0,0000	0,0010	Down
BATF	-0,4895	0,0000	0,0010	Down
CDK2	-0,2035	0,0000	0,0010	Down
NSD2	-0,2291	0,0000	0,0012	Down
MKI67	-0,3014	0,0000	0,0012	Down
PRF1	-0,3678	0,0000	0,0014	Down
CD84	0,2498	0,0000	0,0014	Up
IFNGR2	0,2251	0,0001	0,0015	Up
LOXL2	-0,2660	0,0001	0,0017	Down
TRAC	0,4605	0,0001	0,0018	Up
CD24	0,4475	0,0001	0,0019	Up
SERINC5	0,2197	0,0001	0,0019	Up
SF3B1	0,2018	0,0001	0,0020	Up
C3	0,5921	0,0001	0,0024	Up
C1QA	-0,4967	0,0001	0,0025	Down
IRAK4	0,1578	0,0001	0,0025	Up
CCL21	0,6233	0,0001	0,0026	Up
TNFRSF11B	0,1618	0,0001	0,0026	Up
CD6	0,2768	0,0001	0,0027	Up
SERINC1	0,1918	0,0001	0,0028	Up
ICAM4	-0,1495	0,0001	0,0028	Down
RRM2	-0,2743	0,0001	0,0030	Down
S100A8	-0,4268	0,0001	0,0035	Down
CLU	0,6887	0,0002	0,0040	Up
PRKACB	0,1951	0,0002	0,0041	Up
HLA-DMB	0,3399	0,0002	0,0043	Up
GPSM3	0,2242	0,0002	0,0043	Up
ROCK1	0,1746	0,0002	0,0046	Up
SLC16A1	-0,1962	0,0002	0,0052	Down
HLA-DOB	0,3005	0,0002	0,0052	Up
TRBC1/2	0,6278	0,0002	0,0052	Up
CD59	-0,1968	0,0003	0,0057	Down
GZMA	-0,2719	0,0003	0,0058	Down
MCM7	-0,2609	0,0003	0,0061	Down

PKMYT1	-0,2139	0,0003	0,0064	Down
PRKCB	0,1966	0,0004	0,0076	Up
TAPBP	0,1980	0,0004	0,0078	Up
ORC6	-0,1797	0,0004	0,0084	Down
IL4R	0,3485	0,0004	0,0084	Up
GPI	-0,2290	0,0004	0,0085	Down
PRC1	-0,1955	0,0005	0,0087	Down
TNFRSF4	0,1982	0,0005	0,0091	Up
PTPRC	0,2806	0,0005	0,0094	Up
RRAS2	0,1826	0,0005	0,0096	Up
UBC	-0,2000	0,0005	0,0096	Down
KLRB1	0,1520	0,0006	0,0100	Up
SYK	0,2378	0,0006	0,0105	Up
ALDOA	-0,2818	0,0006	0,0111	Down
KIF2C	-0,1859	0,0006	0,0113	Down
GBP1	-0,3389	0,0007	0,0115	Down
KAT2B	0,1550	0,0007	0,0122	Up
THY1	0,2428	0,0008	0,0134	Up
ENO1	-0,1710	0,0008	0,0140	Down
TERT	-0,1708	0,0008	0,0140	Down
JAML	0,1907	0,0008	0,0140	Up
IRF4	-0,3829	0,0009	0,0140	Down
CCNA2	-0,2054	0,0010	0,0165	Down
BBC3	-0,1856	0,0010	0,0165	Down
TFRC	-0,3999	0,0011	0,0179	Down
GATA3	0,1411	0,0012	0,0187	Up
ESR2	0,1291	0,0013	0,0198	Up
BCL2A1	-0,3027	0,0013	0,0202	Down
MCM4	-0,2174	0,0013	0,0202	Down
RHOA	0,1812	0,0014	0,0208	Up
XPA	0,1377	0,0014	0,0217	Up
ITGA2B	-0,1324	0,0014	0,0218	Down
CD247	0,2193	0,0015	0,0219	Up
AURKA	-0,1658	0,0015	0,0222	Down
TOP2A	-0,2088	0,0015	0,0224	Down
CHEK1	-0,1836	0,0015	0,0224	Down
HLA-DQA1	0,3245	0,0017	0,0244	Up
FN1	-0,6915	0,0017	0,0244	Down
CCL19	0,5565	0,0017	0,0244	Up
CDC25A	-0,1613	0,0018	0,0248	Down
RICTOR	0,1352	0,0018	0,0254	Up
CD3E	0,2859	0,0018	0,0256	Up
IL10	-0,2077	0,0019	0,0259	Down
COL5A1	-0,2750	0,0020	0,0280	Down
FANCA	-0,2180	0,0022	0,0299	Down
IL18	0,2305	0,0022	0,0299	Up

BLVRA	0,1553	0,0022	0,0300	Up
BRCA1	-0,1543	0,0023	0,0302	Down
CD28	0,1456	0,0023	0,0305	Up
SPP1	-0,4766	0,0025	0,0328	Down
PBK	-0,1477	0,0025	0,0328	Down
BMI1	0,2018	0,0026	0,0329	Up
NKG7	-0,3965	0,0026	0,0329	Down
CR2	0,3088	0,0026	0,0331	Up
CD48	0,2363	0,0027	0,0345	Up
PLK1	-0,1946	0,0028	0,0356	Down
MUC4	-0,1319	0,0029	0,0368	Down
NDUFB1	0,1369	0,0030	0,0368	Up
CYBB	0,2607	0,0030	0,0371	Up
ATP2A2	-0,1469	0,0030	0,0372	Down
BAX	-0,1863	0,0031	0,0375	Down
PLCE1	-0,1140	0,0031	0,0375	Down
DUSP2	-0,2978	0,0031	0,0375	Down
ELMO1	0,1379	0,0032	0,0384	Up
SMAD3	0,1226	0,0032	0,0384	Up
FOXA2	-0,1224	0,0033	0,0387	Down
MDM4	0,1804	0,0035	0,0401	Up
GNLY	-0,3191	0,0035	0,0401	Down
IDO1	-0,2664	0,0035	0,0405	Down
SERPINH1	-0,1681	0,0037	0,0417	Down
PDGFRB	-0,1927	0,0037	0,0417	Down
LAMP1	0,1831	0,0037	0,0417	Up
FGFR1	0,1744	0,0037	0,0417	Up
MYBL2	-0,2871	0,0037	0,0417	Down
KLRG1	-0,1587	0,0040	0,0443	Down
LRRC32	-0,1865	0,0041	0,0453	Down
IFIT3	-0,1838	0,0041	0,0453	Down
CDKN1B	0,1614	0,0042	0,0460	Up
CENPF	-0,1563	0,0042	0,0460	Down
JUNB	-0,2377	0,0043	0,0463	Down
ICAM2	0,1403	0,0044	0,0468	Up
COL6A6	0,1281	0,0044	0,0472	Up
AICDA	-0,2731	0,0045	0,0475	Down
CEACAM3	-0,2346	0,0045	0,0475	Down
UBB	-0,1532	0,0046	0,0485	Down
LYZ	0,5472	0,0047	0,0494	Up
MUC1	-0,1780	0,0048	0,0498	Down
PIM1	-0,2523	0,0048	0,0498	Down
H3C10	-0,4092	0,0049	0,0498	Down
LAT	0,1745	0,0049	0,0499	Up

Supplementary Table S13. CD163+ segments. Differentially expressed genes in the DGEA of the complete CTA panel. Up represents upregulation in the CD163low/CD11chigh subgroup compared to the CD163high/CD11clow (Down). All values are rounded to four decimal places.

Gene	logFC	P.Value	adj.P.Val	Result
FCGR3A/B	-1,3606	0,0000	0,0000	Down
CD163	-1,3998	0,0000	0,0000	Down
FCGR1A	-0,8231	0,0000	0,0000	Down
ITGAX	0,9391	0,0000	0,0000	Up
FGCR2A/B	-1,0190	0,0000	0,0000	Down
MMP9	1,6941	0,0000	0,0000	Up
CXCL14	0,5596	0,0000	0,0000	Up
SIGLEC1	-0,6088	0,0000	0,0000	Down
MARCO	-0,6468	0,0000	0,0000	Down
TLR2	-0,4374	0,0000	0,0000	Down
CXCL16	-0,5096	0,0000	0,0000	Down
PFKFB3	-0,5642	0,0000	0,0000	Down
IFNGR1	0,4604	0,0000	0,0000	Up
OLFML2B	-0,3727	0,0000	0,0000	Down
CEBPA	0,4193	0,0000	0,0000	Up
IL2RA	-0,6264	0,0000	0,0000	Down
C2	-0,4595	0,0000	0,0001	Down
S100A9	-0,9059	0,0000	0,0001	Down
IDH1	-0,2928	0,0000	0,0002	Down
LTB	0,6580	0,0000	0,0002	Up
CFP	0,2947	0,0000	0,0002	Up
MRC1	-0,4452	0,0000	0,0004	Down
F13A1	-0,4933	0,0000	0,0007	Down
FLNA	0,4761	0,0000	0,0008	Up
LRP1	-0,4089	0,0000	0,0008	Down
S100A8	-0,6321	0,0000	0,0011	Down
NFAM1	-0,2834	0,0000	0,0011	Down
FCER1G	-0,5663	0,0000	0,0011	Down
LTBR	-0,2667	0,0000	0,0011	Down
C1QB	-0,9453	0,0000	0,0011	Down
CTSL	-0,6130	0,0000	0,0015	Down
CEBPB	-0,3119	0,0000	0,0022	Down
IFI27	-0,5405	0,0000	0,0023	Down
IRF2	-0,2347	0,0000	0,0026	Down
EFNA2	-0,2369	0,0001	0,0046	Down
C1QA	-0,9289	0,0001	0,0048	Down
CD14	-0,5457	0,0001	0,0064	Down
TCF7	0,3913	0,0001	0,0064	Up
SOD2	-0,7768	0,0001	0,0068	Down
TNR	0,2069	0,0002	0,0077	Up
POLD4	0,2095	0,0002	0,0077	Up
BCL2A1	-0,4196	0,0002	0,0079	Down

FGFR1	0,2904	0,0002	0,0079	Up
KDM5C	0,2023	0,0002	0,0088	Up
FPR3	0,2773	0,0002	0,0088	Up
MS4A4A	-0,2776	0,0003	0,0099	Down
MTF1	-0,2003	0,0003	0,0106	Down
MIF	-0,2890	0,0003	0,0120	Down
C3	0,6130	0,0004	0,0133	Up
TYK2	0,1925	0,0004	0,0133	Up
PBX3	-0,1984	0,0004	0,0133	Down
GBP2	-0,1992	0,0004	0,0137	Down
CCL18	-0,8569	0,0006	0,0188	Down
DDIT3	-0,2108	0,0006	0,0205	Down
RXRG	0,1823	0,0007	0,0219	Up
POU2F2	-0,3229	0,0007	0,0237	Down
BLVRA	0,2191	0,0008	0,0243	Up
IL2RG	0,2521	0,0008	0,0243	Up
CXCL10	-0,5040	0,0008	0,0243	Down
DKK2	0,1873	0,0008	0,0243	Up
ICAM1	-0,3330	0,0008	0,0243	Down
PPP3CB	0,1821	0,0009	0,0251	Up
CCL3/L1	-0,3405	0,0009	0,0251	Down
NECTIN2	-0,2073	0,0009	0,0259	Down
CXCL12	-0,3031	0,0009	0,0259	Down
NKG7	-0,4840	0,0009	0,0259	Down
C7	0,3184	0,0010	0,0266	Up
NUPR1	-0,4143	0,0010	0,0277	Down
IGF2R	-0,2442	0,0011	0,0285	Down
NDC80	-0,2100	0,0013	0,0327	Down
TLR6	0,1870	0,0013	0,0338	Up
AR	-0,1828	0,0014	0,0362	Down
ASXL1	0,3522	0,0015	0,0373	Up
PBRM1	-0,2060	0,0015	0,0376	Down
IL18	0,3143	0,0017	0,0417	Up
FCAR	0,1975	0,0018	0,0418	Up
PLAU	0,3351	0,0018	0,0418	Up
VEGFC	0,2001	0,0018	0,0418	Up
MEFV	-0,1938	0,0020	0,0448	Down
CD160	-0,1722	0,0021	0,0469	Down
ERO1A	-0,1873	0,0021	0,0472	Down
CD63	-0,3535	0,0022	0,0478	Down
CCL19	0,5983	0,0023	0,0498	Up

Supplementary Table S14. CD20+ segments. Differentially expressed genes in the DGEA of the CTA-CD20 gene list. Up represents upregulation in the CD163low/CD11chigh subgroup compared to the CD163high/CD11clow (Down). All values are rounded to four decimal places.

Gene	logFC	adj.P.Val	Result
LTB	0,9407	0,0000	Up
FCER2	0,5411	0,0000	Up
BATF	-0,6501	0,0000	Down
IL4R	0,5052	0,0000	Up
POU2F2	-0,4907	0,0000	Down
SLC1A5	-0,2815	0,0000	Down
PKM	-0,4280	0,0000	Down
TNFRSF13B	-0,6686	0,0002	Down
PTPRC	0,3494	0,0002	Up
HSP90B1	-0,5142	0,0002	Down
CYBB	0,3833	0,0006	Up
MCM7	-0,3343	0,0006	Down
ATM	0,2452	0,0007	Up
HLA-DOB	0,3651	0,0008	Up
CD81	0,2943	0,0009	Up
CR2	0,4643	0,0010	Up
PCNA	-0,3214	0,0012	Down
CDK1	-0,2487	0,0012	Down
TYMS	-0,3515	0,0012	Down
GPI	-0,2822	0,0013	Down
IRF4	-0,4813	0,0014	Down
AURKB	-0,2784	0,0014	Down
ATOX1	0,2727	0,0015	Up
HLA-DQA1	0,4179	0,0020	Up
PIM1	-0,3498	0,0024	Down
CD74	0,3876	0,0026	Up
CCR6	0,2083	0,0032	Up
HDAC2	-0,1916	0,0032	Down
CD27	0,3371	0,0039	Up
HLA-DQB1	0,3266	0,0046	Up
BLNK	-0,3419	0,0055	Down
CD70	-0,2168	0,0057	Down
IL2RB	-0,2644	0,0060	Down
MYC	-0,3759	0,0069	Down
AICDA	-0,3537	0,0072	Down
HLA-DMB	0,3189	0,0077	Up
CENPF	-0,1960	0,0083	Down
HMGA1	-0,3232	0,0088	Down
HLA-DRA	0,4473	0,0103	Up
HLA-DPA1	0,2940	0,0107	Up
TUBB	-0,2401	0,0109	Down
TOP2A	-0,2284	0,0117	Down

UQCRQ	-0,1662	0,0119	Down
CDC20	-0,2466	0,0120	Down
CR1	0,2628	0,0136	Up
FEZ1	-0,1582	0,0138	Down
MCM5	-0,2405	0,0155	Down
CD24	0,3842	0,0158	Up
IKBKB	0,1376	0,0189	Up
CD83	0,3942	0,0203	Up
RASGRP2	0,2503	0,0206	Up
RRAS2	0,1662	0,0239	Up
MKI67	-0,2310	0,0239	Down
IDH2	-0,2139	0,0253	Down
HPRT1	-0,1532	0,0274	Down
NOTCH2	0,1639	0,0277	Up
MME	0,2428	0,0300	Up
CD53	0,2074	0,0300	Up
JUN	-0,1876	0,0308	Down
KIF2C	-0,1655	0,0309	Down
TGFBR2	0,2039	0,0344	Up
LY9	0,1804	0,0349	Up
SLAMF6	0,1608	0,0356	Up
HLA-DMA	0,2693	0,0363	Up
HMGB1	-0,1497	0,0400	Down
RPS6	-0,3585	0,0412	Down
HLA-DQA2	0,1588	0,0418	Up
LGALS9	0,2507	0,0434	Up
LY86	0,1413	0,0463	Up
NASP	-0,1658	0,0463	Down
CD86	0,1607	0,0463	Up

Supplementary Table S15. CD3+ segments. Differentially expressed genes in the DGEA of the CTA-CD3 gene list. Up represents upregulation in the CD163low/CD11chigh subgroup compared to the CD163high/CD11clow (Down). All values are rounded to four decimal places.

Gene	logFC	adj.P.Val	Result
ATM	0,4408	0,0000	Up
LTB	0,9085	0,0000	Up
TCF7	0,5556	0,0000	Up
ICOS	0,3039	0,0000	Up
RASGRP2	0,4668	0,0000	Up
GZMB	-0,6654	0,0000	Down
CTLA4	0,3233	0,0000	Up
CD4	0,4559	0,0000	Up
LEF1	0,2974	0,0001	Up
TNFRSF25	0,2468	0,0001	Up
CYLD	0,2359	0,0001	Up
CD3D	0,4635	0,0002	Up
GZMH	-0,3070	0,0003	Down
LAG3	-0,3506	0,0003	Down
IL7R	0,4593	0,0003	Up
FOXP3	0,2129	0,0004	Up
TIGIT	0,3330	0,0005	Up
LCK	0,3168	0,0005	Up
LY9	0,2687	0,0006	Up
SELL	0,4021	0,0008	Up
CD5	0,2492	0,0009	Up
BATF	-0,4895	0,0010	Down
PRF1	-0,3678	0,0014	Down
TRAC	0,4605	0,0018	Up
CD6	0,2768	0,0027	Up
GZMA	-0,2719	0,0058	Down
TNFRSF4	0,1982	0,0091	Up
PTPRC	0,2806	0,0094	Up
KLRB1	0,1520	0,0100	Up
GATA3	0,1411	0,0187	Up
CD247	0,2193	0,0219	Up
CDC25A	-0,1613	0,0248	Down
CD3E	0,2859	0,0256	Up
CD28	0,1456	0,0305	Up
NKG7	-0,3965	0,0329	Down
CD48	0,2363	0,0345	Up
DUSP2	-0,2978	0,0375	Down
GNLY	-0,3191	0,0401	Down
KLRG1	-0,1587	0,0443	Down
JUNB	-0,2377	0,0463	Down
LAT	0,1745	0,0499	Up

Supplementary Table S16. CD163+ segments. Differentially expressed genes in the DGEA of the CTA-CD163 gene list. Up represents upregulation in the CD163low/CD11high subgroup compared to the CD163high/CD11clow (Down). All values are rounded to four decimal places.

Gene	logFC	adj.P.Val	Result
CD163	-1,3998	0,0000	Down
ITGAX	0,9391	0,0000	Up
MMP9	1,6941	0,0000	Up
SIGLEC1	-0,6088	0,0000	Down
MARCO	-0,6468	0,0000	Down
TLR2	-0,4374	0,0000	Down
CXCL16	-0,5096	0,0000	Down
PFKFB3	-0,5642	0,0000	Down
IFNGR1	0,4604	0,0000	Up
IL2RA	-0,6264	0,0000	Down
C2	-0,4595	0,0001	Down
S100A9	-0,9059	0,0001	Down
CFP	0,2947	0,0002	Up
MRC1	-0,4452	0,0004	Down
LRP1	-0,4089	0,0008	Down
S100A8	-0,6321	0,0011	Down
FCER1G	-0,5663	0,0011	Down
C1QB	-0,9453	0,0011	Down
CTSL	-0,6130	0,0015	Down
C1QA	-0,9289	0,0048	Down
CD14	-0,5457	0,0064	Down
SOD2	-0,7768	0,0068	Down
FPR3	0,2773	0,0088	Up
MS4A4A	-0,2776	0,0099	Down
GBP2	-0,1992	0,0137	Down
CCL18	-0,8569	0,0188	Down
CXCL10	-0,5040	0,0243	Down
DKK2	0,1873	0,0243	Up
ICAM1	-0,3330	0,0243	Down
IGF2R	-0,2442	0,0285	Down
IL18	0,3143	0,0417	Up
VEGFC	0,2001	0,0418	Up
CCL19	0,5983	0,0498	Up