SUPPLEMENTAL METHODS

FL cell lines and primary cells

FL cells were isolated from lymph nodes, peripheral blood, tonsil or paravertebral mass from a cohort of 19 patients, and serum from 17 patients diagnosed according to the World Health Organization (WHO) classification criteria at the Hospital Clinic of Barcelona (Table S1). The Ethics Committee of Hospital Clínic approved this study (IRB# HCB/2018/0397) and patients signed written informed consent.

FL cell lines DOHH-2, RL, SC-1 and WSU-FSCCL were obtained from DSMZ (Braunschweig, Germany). RL and WSU-FSCCL cell lines expressing luciferase (RL-luc, WSU-FSCCL-luc) were generated *via* retroviral transduction. Retroviral vectors containing full-length pLHCX-luc were kindly provided by Dr. Bofill-De Ros (IDIBAPS, Barcelona, Spain) (see below method description).

Cell lines and patient derived cells were cultured in RPMI-1640 supplemented with 10% FBS, 2mmol/L L-glutamine, 50 µg/mL penicillin/streptomycin (Thermo Fisher Scientific) and were maintained in a humidified atmosphere at 37ºC containing 5% CO_2. Normocin (100 µg/mL; InvivoGen) was added to the cell line cultures to prevent mycoplasma contamination. Cell lines were routinely tested for mycoplasma infection by PCR and cell line identity was verified by using the AmpFISTR identifier kit (Thermo Fisher Scientific).

Retroviral transfection of FL cells

Supernatants of Phoenix cells containing retroviral particles[1] were used to transduce WSU-FSCCL or RL cells by centrifugation (2500 rpm for 90 minutes) in the presence of polybrene (Sigma Aldrich). Selection of transfected cells was started 2 days after infection with 200 µg/mL of hygromycin B (Sigma Aldrich). The Luciferase Assay System kit (Promega) was used to confirm expression of the luciferase gene, following the manufacturer's instructions.

Monocyte migration assay

Monocytes were isolated from freshly isolated PBMCs as described in main methods by RosetteSep. Monocytes were challenged to migrate for 1.5 hours towards cell culture supernatants. LIVE/DEAD® fixable Aqua dead cell stain (Thermo Fisher Scientific) was added 1:100 in PBS to exclude dead cells. The number of viable monocytes ($CD14^+$, $Aqua^-$) was counted in a flow cytometer.

RNA isolation and quantitative real-time PCR

For total RNA isolation, 3–5 × 10^6 cells were homogenized with TRIzol reagent (Thermo Fisher Scientific), following the manufacturer's protocol. cDNA was synthesized using PrimeScript™ RT Master Mix (Takara, Saint- Germain-en-Laye, France) and quantitative real-time PCR (qPCR) was then performed on a StepOne Real-Time PCR System (Thermo Fisher Scientific). Premix Ex Taq (Probe qPCR) Master Mix (Takara) and pre-designed TaqMan® Probes (Thermo Fisher Scientific) for *PPARG, TGFB, MRC1, CCL5, CCR7* and *CXCL11* genes were used. The comparative cycle threshold method (ΔΔCt) was used to quantify the relative expression of each gene. *GUS* was used as endogenous control and samples were analyzed in duplicates.

Gene expression profiling (GEP) and data analysis

FL cells from monocultures or co-cultures were purified using CD20 magnetic beads (Miltenyi, Bergisch Gladbach, Germany). Then, total RNA was obtained using the TRIzol reagent (Thermo Fisher Scientific) followed by a cleaning step with the RNAeasy kit (Thermo Fisher Scientific). RNA integrity was examined with the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara CA, USA). Only high-quality RNA was then retrotranscribed to cDNA and hybridized on HG-U219 microarray. All samples were simultaneously run in a GeneTITAN platform (Thermo Fisher Scientific). Data was normalized to RMA using Expression Console software (Thermo Fisher Scientific). GeneChip Command Console Software was used for the scanning of the

results. Raw data were normalized using Expression Console™ Software v1.4.1.46 (Affymetrix). Data has been deposited at the Gene Expression Omnibus (GEO) of the National Center for Biotechnology Information (GSE147211).

Gene signatures were determined with GSEA version 4.0.1 (Broad Institute, Cambridge, MA, USA) using the hallmark gene sets, the C2 curated gene sets, the C3 motif gene sets, the C5 gene ontology gene sets, the C6 oncogenic signatures (Molecular Signature Database v2.5), and custom gene sets (www.lymphochip.com). A two-class analysis with 1000 permutations of gene sets and a weighted metric was used. Expression heatmaps of angiogenesis, integrin pathways, invasion, migration and cytokine genes were created using Morpheus software (https://software.broadinstitute.org/morpheus/, Broad Institute)

Fold-changes of FL-M2 co-cultures *vs* FL monocultures and P-value criteria were represented in a volcano plot. Data were visualized with the Multiplot Studio V1.5.20 Software from GenePattern archive (http://gparc.org/). Top 177 overexpressed genes selected from volcano plot were uploaded to PANTHER (http://www.pantherdb.org/) and subjected to a Mann–Whitney U-test to identify enrichment of PANTHER pathways.

Bioinformatics analysis

mRNA relative expression levels of *CSF1* and *CSF1R* in Follicular lymphoma lymph nodes (FL-LN = 362) was compared with normal tonsils (NTS = 75) according to GEP public databases (GSE55267, GSE65135, GSE65136, GSE7307, GSE71810, GSE12195, GSE12366, GSE12453, GSE99316, GSE39503, GSE38712, GSE31311, GSE15271, GSE10831, GSE3526, GSE21554, GSE53820, GSE12453, GSE93261). These selected data were all generated with Affymetrix Human Genome U133 Plus 2.0. Briefly, CEL files were normalized using the Expression Console ™ Software v1.4.1.46 (Affymetrix). To take in consideration the batch effect, join data were normalized using the Limma package included in Transcriptome Analysis console (Applied Biosystems).

CIBERSORT algorithm was used to estimate the proportion of infiltrating immune cell types in gene expression data.[2] This is a robust and accurate algorithm web tool to calculate the cell composition of a given sample. Gene expression data was uploaded to the CIBERSORT website (http://cibersort.stanford.edu/), applying the LM22 signature and 1000 permutations. For each sample, CIBERSORT output was normalized to 100 for each cell type.

Flow cytometry

Surface marker analysis was performed on an Attune flow cytometer and the data were analyzed using Attune software (Thermo Fisher Scientific) and FlowJo V10 (FlowJo, LLC, Ashland, OR). The following antibodies were used: CD19-FITC, CD14-PE, CD20-FITC, CD3-PE-Cy5, CD163-FITC, CSF-1R-BV421 and CD49d-PE-Cy5 from BD biosciences, and CD19-eFluor450, CD20-eFluor450, CD3-FITC, CD11b-PE-Cy5, CD18-PE, CD29-FITC and CD86-PE from Thermo Fisher Scientific.

For CSF-1R intracellular staining, cells were fix with 4% paraformaldehyde for 10 min and permeabilized with 0.1% saponin in 0.5% bovine serum albumin/phosphate-buffered saline (PBS) buffer for 5 min.

Viability of FL cell lines and patient samples in monocultures, co-cultures or after treatment with PLX3397 (Selleckchem), was assessed either by CD20 or CD19/Annexin-FITC/7AAD staining or by CD19/CD20, AQUA staining. FL viable cells were identified as $CD19^+/CD20^+$, and $AQUA^-$ or $Annexin\text{-}FITC^-/7AAD^-$.

Monocyte and macrophages were identified with CD11b or CD14 and the expression of specific markers CD86, CD163, CSF-1R, CD18, CD29, CD49d was analyzed. Prior to antibody addition, monocyte/macrophages were treated with FcR Blocking Reagent (Milteny).

MFIR (mean fluorescence intensity ratio) was calculated as follows:

$$MFIR\ (mean\ fluorescence\ intensity) = \frac{MFI\ (marker)}{MFI\ (isotype)}$$

MTT assay

FL cell lines (5 x 10^4) or macrophages (2.5 x 10^4) were incubated for 72 hours with 50nM PLX3397. MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) reagent (Sigma) was added for 2 to 5 additional hours before spectrophotometric measurement. Each measurement was made in triplicate, and the mean value was calculated. Results were represented using untreated control cells as a reference.

Cytokine secretion

CCL2 expression from FL and FL+HK culture supernatants was assessed by Human MCP-1 (CCL2) ELISA kit (ELH-MCP1-1, RayBiotech) following manufacturer´s instructions.

VEGF-A, Angiogenin, MMP9, SDF1-beta, CCL2, CCL3, CCL18, IL-10 and IL-8 secretion were evaluated in culture supernatants (SUPS) from FL and FL+M2 primary co-cultures using a Custom Quantibody® Multiplex ELISA Array (Raybiotech).

CSF-1 expression was evaluated in patient's serum and cell culture supernatants from FL+M2 co-cultures w/wo PLX3397 using RayBio® Human M-CSF ELISA Kit (ELH-MCSF-1, RayBiotech) and following manufacturer´s instructions. IL-10 and IL-34 were also tested in those cell culture supernatants using ABTS ELISA Buffer Kit with IL-10 (#200-10) IL-34 (#200-34) antibodies from Peprotech and following manufacturer´s instructions.

HUVEC tube formation assay

Human umbilical vein endothelial cells (HUVEC) were kindly provided by Dr Maria C. Cid and were cultured as previously described.[3] Supernatants from FL primary cells (2x10^6 cells/mL) were harvested after 48 hours from FL monocultures or FL+M2 macrophages co-cultures. 24-well plates were coated with Matrigel (BD Biosciences, San Jose, CA, USA) and allowed to polymerize for 45 minutes at 37ºC. Afterwards, the supernatants of interest were mixed (1:1) with HUVEC cells (4x10^4 cells) in HUVEC medium (RPMI 1640 medium that contains 25% of

Bovine Calf Serum (HyClone, Thermo Fisher Scientific, Waltham, MA, USA), 150 µg/ml medium endothelial cell growth supplement (ECGS) (BD Bioscience), and 4U/ml medium of sodium heparin salt (AppliChem, Darmstadt, Germany) and incubated for 24 hours. Pictures were taken at 400x magnification in a DMIL LED Leica microscope coupled to a DFC295 camera and analyzed with Suite v 3.7 software (Leica, Wetzlar, Germany). Then, the number of nodes and junctions was quantified in 5 randomly chosen fields using the Image J software (angiogenesis analyzer plugin).

Adhesion assay to extracellular matrix proteins

FL cells cultured w/wo M2 macrophages for 48 hours were recovered, counted and labeled with 1 µM Calcein AM (Thermo Fisher Scientific) for 30 minutes at 37ºC. After washing twice with PBS, $1x10^5$ cells/well were seeded in a plate previously coated with 500 ng/mL VCAM-1 (R&D Systems), 10 mg/mL fibronectin (Millipore) or BSA 1% (nonspecific adhesion) and incubated overnight at 4C. Then, the plate was washed repeatedly washed to remove non-adhered cells. Adhered cells were lysed with 1% Triton X-100, supernatant was transferred into black plates and fluorescence was measured in a spectrophotometer (Synergy Bio-Tek Instrument) (excitation filter: 485 ± 20 nm; band-pass filter: 530 ± 20 nm). Data were expressed as arbitrary fluorescent units after subtraction of nonspecific adhesion from VCAM1/fibronectin adhesion and normalized to the untreated control.

Invasion assay

FL cells co-cultured w/wo macrophages in a ratio (1:4) for 48 hours, were seeded ($0.5x10^6$cells/well) on Matrigel Invasion Chambers 8µm (BD Biosciences) in RPMI 10% FBS, and were allowed to migrate in a gradient of FBS (20%) for 24 hours. Cells crossing the barrier were labeled with anti-CD20-FITC and counted by flow cytometry. Migration ratio was calculated as the ratio between the number of $CD20^+$ in each condition and the corresponding input.

***In vivo* studies**

An FL-HK mouse model was generated by subcutaneous inoculation of the FL cell lines WSU-FSCCL or RL (10 x 10^6 cells per mouse) with/without HK cells (1x10^6 cells per mouse, ratio HK:FL 1:10) in severe combined immunodeficient (SCID) mice. Tumors were measured twice weekly with external calipers. Tumor volumes were calculated by the formula:

$$Tumor\ volume = (Tumor\ width^2 x\ Tumor\ length)/2$$

Each graph shows mean ± SEM. At the endpoint, tumors were extirpated, weighed, formalin-fixed and included in paraffin (FFPE). Animals who did not develop tumor were excluded.

For macrophage depletion studies two types of experiments were done

1) WSU–FSCCL cells (10x10^6 cells per mouse) were admixed with the FDC non-immortalized cell line HK (1x10^6 cells per mouse) and subcutaneously inoculated into the right flank of SCID mice. Tumor-bearing animals were randomized by tumor size into two groups (n = 10/group) for intratumoral injection of 50 µL of clodronate liposomes (Liposome concentration = 5mg/mL) or an equal volume of empty control liposomes, 2 days per week for 14 days. Tumor follow-up and volume calculation were done described in the main methods.

2) WSU–FSCCL cells (10x10^6 cells per mouse) were intravenously inoculated into NOD SCID NSG (NOD SCID gamma null) mice *via* tail vein. Six days later, they were randomized by mouse weight into two groups by weight (n = 6-7/group) and treated *i.v.* with 25 µL of clodronate liposomes (Liposome concentration = 5mg/mL) or an equal volume of control empty liposomes, once a week, during 20 days (ClodronateLiposomes.org, Haarlem, the Netherlands). Luciferase activity, reported as Relative Luminescence Units (RLU), was measured and monitored on a Hamamatsu ORCA II digital camera before treatment (Day 18) and one day before the end point (Day 28). At the end point spleens were extirpated, weighed, formalin-fixed and included in paraffin (FFPE).

For the combo experiments, a FL-HK mouse model was generated by subcutaneous inoculation of the FL cell line RL-luciferase (10 x 10^6 cells per mouse) with HK cells (1x10^6 cells per mouse,

ratio FDC:FL 1:10) in SCID mice (n=6 mice per group). Treatments started when tumor volumes reached 200 mm^3 (Day 16)**.** Mice were treated for 14 days w/wo PLX3397 (50 mg/kg/day, p.o.), and/or Rituximab (20-10-10 mg/kg mouse, i.p.) once a week.

Animal experiments were performed in compliance with the Animal Ethics Committee of the University of Barcelona (agreements #89/18 and 90/18).

Immunohistochemistry

FFPE sections from representative FL and FL+HK tumors w/wo treatments, and spleens from clodronate experiments were stained with the following antibodies: the pan-macrophage marker F4/80 (clone Cl:A3-1, Bio-Rad), the M2-marker CD206 (clone MMR, R&DSystems), the M1-marker iNOS (ab15323, Abcam), Phospho-histone H3 (pH3) (phospho S10 + T11 antibody [E173], ab32107, Abcam), CD10 (clone SP67, Roche) and CD20 (clone L26, Roche) and PECAM-1 (clone M-20, Santa Cruz Biotechnology). Automatic immunostaining was performed using the Leica Microsystems' Bond-max™ together with the Bond Polymer Refine Detection System (Leica Microsystems, Spain). Slides were scanned and image processing was done using Pannoramic Viewer (3DHISTECH Ltd) and Olympus CellSens 1.17 (Olympus America Inc.) software. Quantification and analysis were done in the using ImageJ software (magnification 200x). % of mitotic cells was calculated on a percentage basis according to the following equation:

$$\%\ of\ mitotic\ cells = \frac{pH3\ positive\ cells\ per\ field}{Blue\ nuclei\ (Hematoxylin)\ per\ field} \times 100$$

FFPE sections of FL patients from Hospital Clínic were probed for CSF-1R expression using the CSF-1R antibody clone FER216 developed at the Monoclonal Antibodies Unit of CNIO and kindly provided by Dra. Giovanna Roncador, using the Leica automatic immunostainer as above. The staining was visualized using an upright optical microscope (Olympus BX63) and after digitalization with a slide scanner (Nanozoomer S360, Hamamatsu), the digital

quantification of CSF-1R expression was done with Fiji-Image J software as previously described.[4]

Statistical analysis

Depending on the assay, paired t test or Mann-Whitney test were used. For *in vivo* tumor growth experiments the multiple t-Tests (Holm-Sidak method) was used to correct for multiple comparisons. Outliers were identified with the ROUT method with Q=1%. These analyses were performed using Prism software 7.0. Standard deviation (SD) or Standard Error of Mean (SEM) was calculated among experimental replicates in each case. Shapiro-Wilk test was used to estimate groups variance. Differences between the results of comparative tests were considered significant if the two-sided P value was less than 0.05. The statistical significance convention used along the manuscript was as follows: * $p<0.05$, ** $p<0.01$ and *** $p<0.001$.

Kaplan-Meier plot of Progression-Free Survival (PFS) and overall survival (OS) were performed of FL patients grouped on the basis of CSF-1R expression (n = 78). An optimum threshold on the score to separate patients into low and high-expression groups was determined using the MaxStat software to select the cutoff value producing the maximum log-rank score in the training cohort. Cutoff value = 8.335 for follicular Compartment, and 21.379 for interfollicular. P-value was obtained by the overall log-rank test.

The correlation of CSF-1R with clinical variables (Categorical data) was done using Chi square or Fisher's exact test with two-sided p values using SPSS 22. Non-parametric tests were used when necessary. To estimate the risk of HT, where competitive events are possible, cumulative incidence was calculated (cmprsk R package) and compared with Gray's test. Actuarial survival analysis was performed using Kaplan–Meier, and survival curves were compared using the log-rank test. p values<0.05 were considered statistically significant.

Figure S1

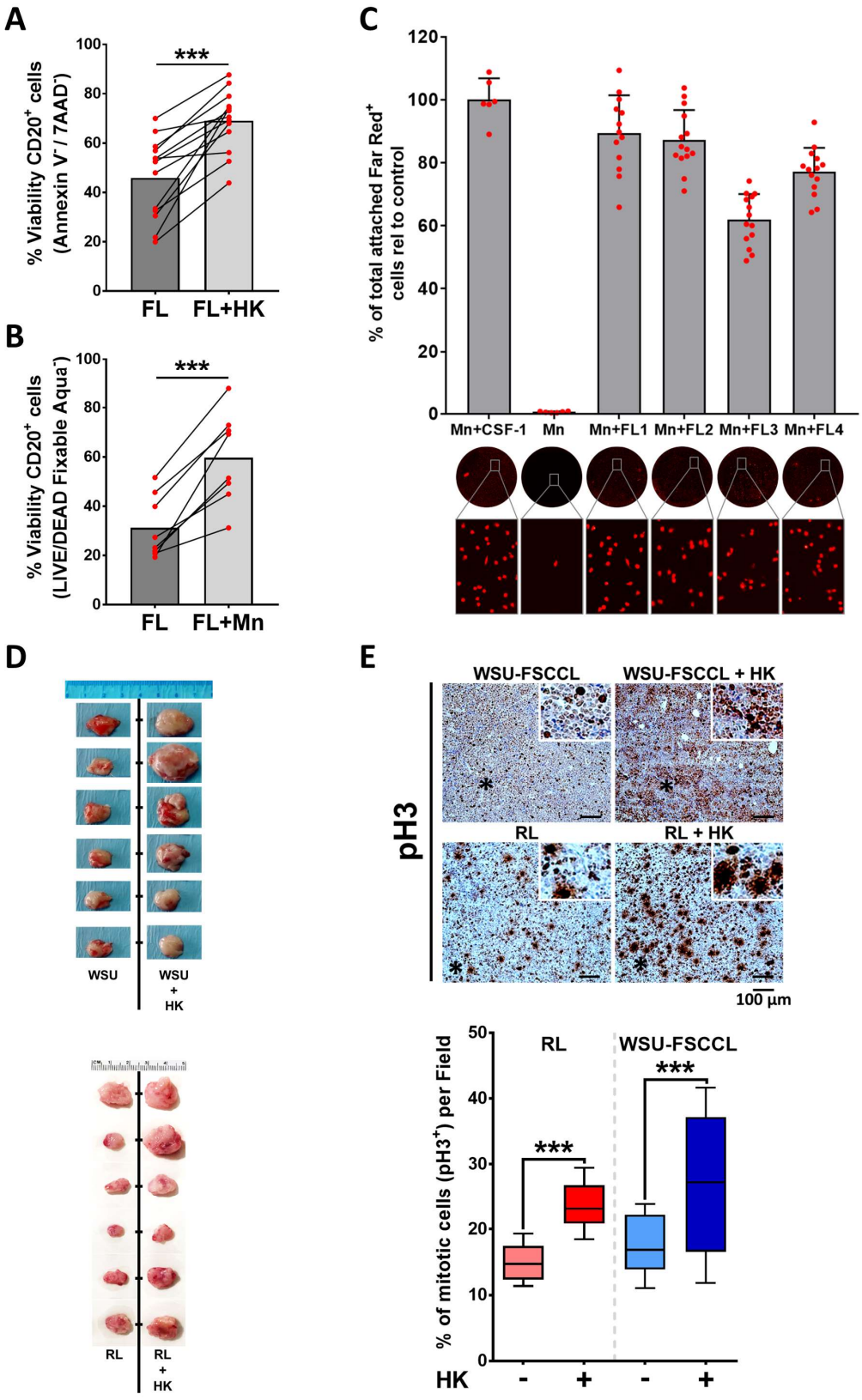
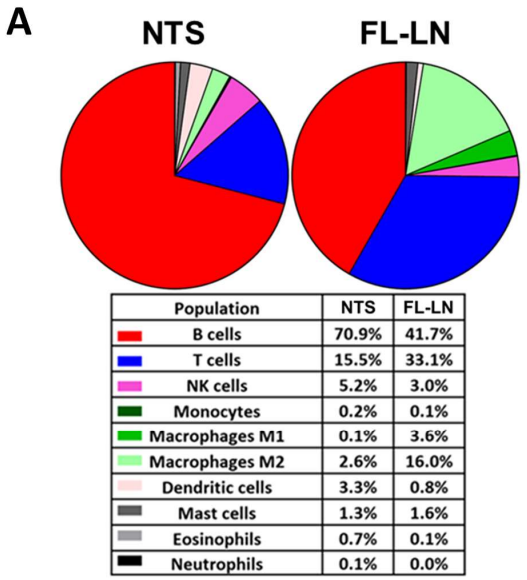
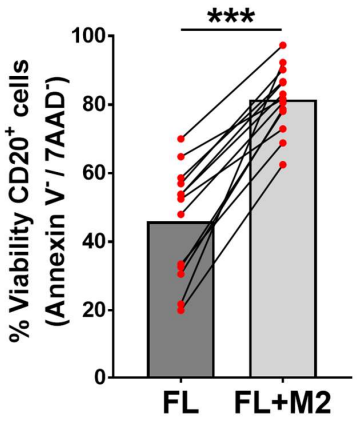


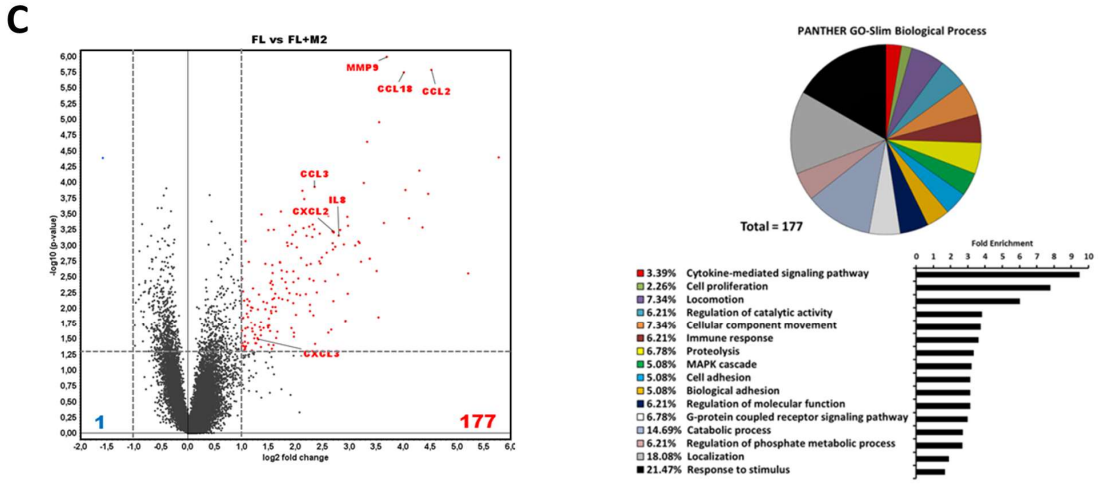
Figure S1. FL-FDC and FL-monocyte crosstalk. (A) Viability of FL cells (CD20+/Annexin V-/7AAD-) in monocultures and in FL-FDC co-cultures (48h, n=13) Paired *t* test. **(B)** Viability of FL cells (CD20+/AQUA-) in monocultures and FL-monocytes (Mn) co-cultures (n=13) after 48h assessed by flow cytometry cells. Paired *t* test. **(C)** Monocyte differentiation assay was assessed co-culturing FL primary cells (n = 4) with monocytes from PBMC (ratio 4:1) labeled with CellTrace™ Far Red for 7 days. Number of attached macrophages (Far Red+) was analyzed by cell counting using Cytation™ 1 Cell Imaging Multi-Mode Reader (BioTek). **(D)** Pictures from FL-FDC co-xenografts shown in figure 1D. **(E)** Phospho-histone H3 (pH3) staining by IHC in tumors from S1D. Representative images are shown. Quantification and analysis were done using ImageJ software (magnification 200x) as detailed in the supplemental methods section. Mann-Whitney test.

Figure S2



Population	NTS	FL-LN
B cells	70.9%	41.7%
T cells	15.5%	33.1%
NK cells	5.2%	3.0%
Monocytes	0.2%	0.1%
Macrophages M1	0.1%	3.6%
Macrophages M2	2.6%	16.0%
Dendritic cells	3.3%	0.8%
Mast cells	1.3%	1.6%
Eosinophils	0.7%	0.1%
Neutrophils	0.1%	0.0%





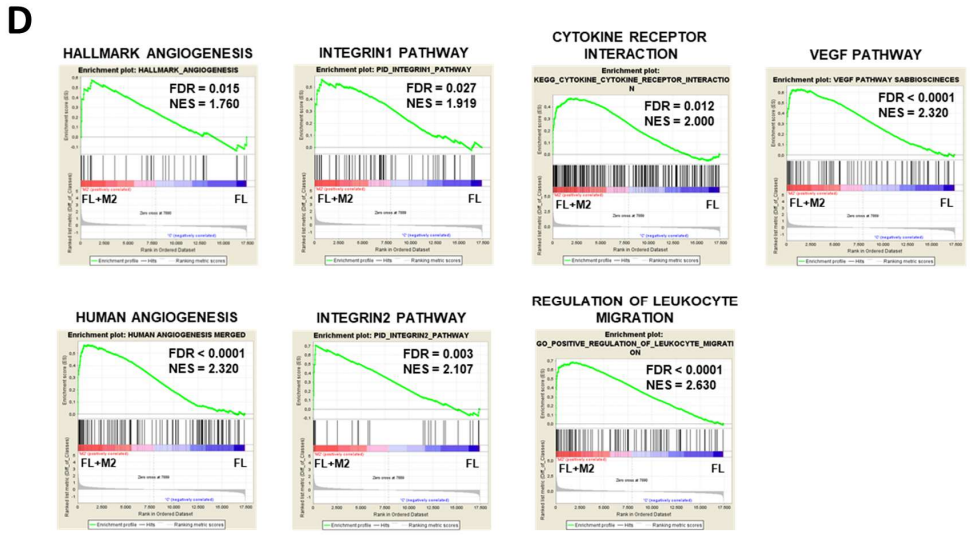


Figure S2. FL-LN are enriched in M2 macrophages and contribute to FL tumorigenesis. (A) Composition of infiltrating immune cells in Normal Tonsils (NTS, n = 75) or Follicular Lymphoma Lymph nodes (FL-LN, n = 362) evaluated by CIBERSORT in Affymetrix datasets and summarized from calculated mean values for each group. **(B)** Viability of FL cells ($CD20^+$/Annexin V^-/$7AAD^-$) in monocultures and FL-M2 co-cultures (48h, n=13) Paired *t* test. Bars represent the SD. **(C)** Volcano plot for FL monocultures vs FL-M2 co-cultures comparison (Left panel). -log10 P-value is plotted against the fold change (log2 scale). Black horizontal discontinuous line corresponds to a P-value of 0.05. 177 genes with a P-value < 0.05 and fold change>2 in either direction are labeled (Red (177 upregulated) and blue (1 downregulated)). Enrichment of biological processes found by PANTHER gene ontology analysis of the 177 volcano-filtered genes overexpressed in FL-M2 co-cultures (Right panel). **(D)** Representative enrichment plots of adhesion, invasion, angiogenesis and cytokine secretion gene sets are shown. FDR: false discovery rate. NES: normalized enrichment score.

Figure S3

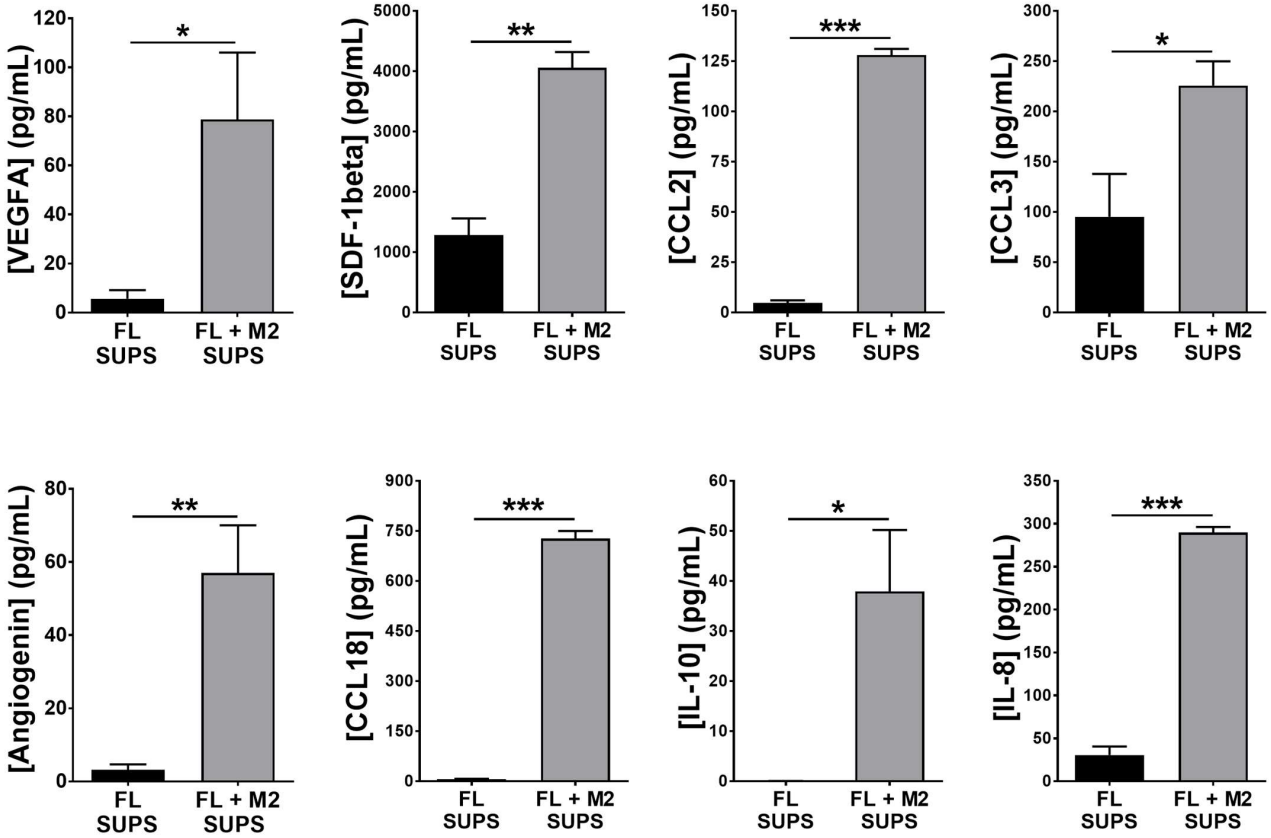


Figure S3. M2 macrophages increase FL cells cytokine secretion. Supernatants from the FL or FL-M2 co-cultures described in Figure 2 were assayed for the cytokines indicated related to the processes identified by GEP. Statistical significance was analyzed by paired t test. Bars represent the SD.

Figure S4

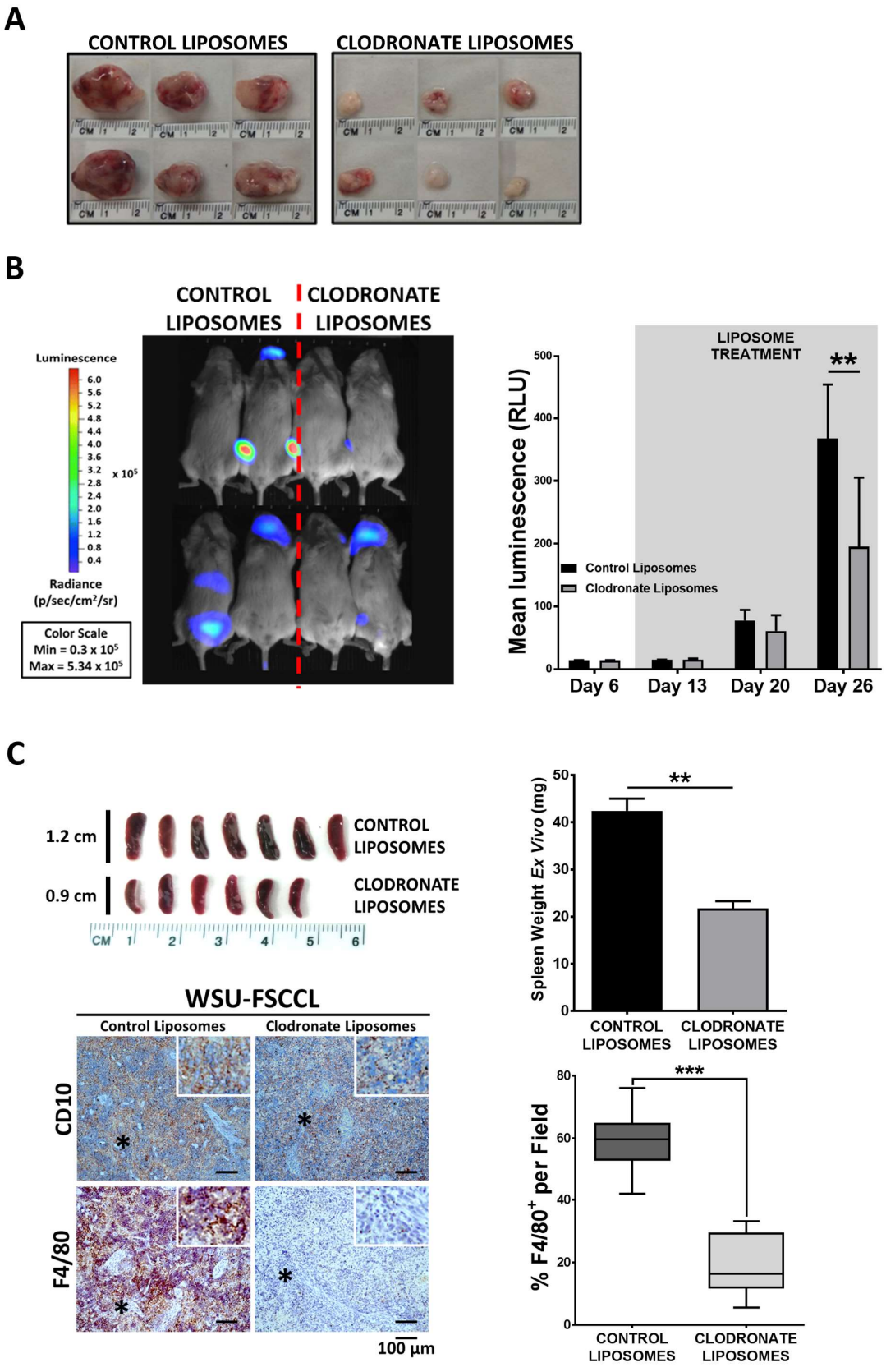


Figure S4. Macrophage depletion with liposomal clodronate in an intravenous mouse model of FL. (A) Representative images of the collected tumors from the subcutaneous model are shown of each treatment group. **(B)** WSU–FSCCL cells ($10x10^6$ cells per mouse) were intravenously inoculated into NSG mice at day 0, and then randomized and treated at day 7 for clodronate liposomes or an equal volume of control empty liposomes, once a week, during 19 days. Luciferase activity, reported as Relative Luminescence Units (RLU), was measured and monitored weekly. Bar-graph shows mean ± SEM. Statistical significance was analyzed by multiple t-Tests (Holm-Sidak method). **(C)** Spleens from S4B were extirpated, weighed and measured at the end point. Mann-Whitney test was applied. FFPE sections from spleens were stained with the germinal center marker CD10 and the pan-macrophage marker F4/80 (magnification 200x). Representative images are shown (left panel). Quantification was done using ImageJ software (right panel). Mann-Whitney test. Bars represent the SD.

Figure S5

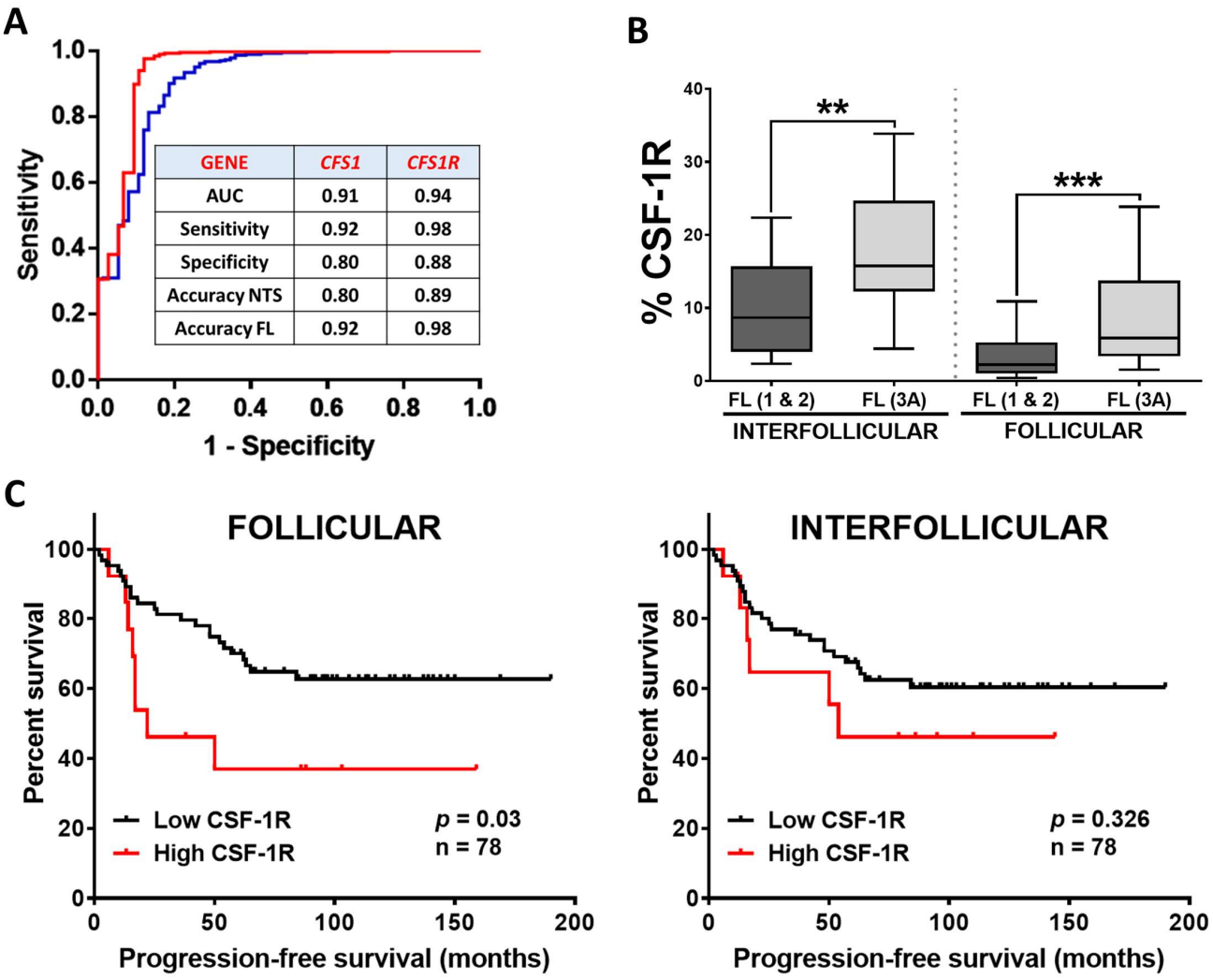


Figure S5. CSF-1 and CSF-1R expression in FL and prognostic value. (A) ROC curves of *CSF1* and *CSF1R* mRNA expression with the significantly highest AUC (Area Under Curve) calculated from the comparison between NTS and FL-LN groups of Figure 5A. **(B)** Comparison of follicular and interfollicular CSF-1R expression (FL series from Figure 5C, n=78) between grade 1-2 (56) and Grade 3A (22) FL patients. Statistical significance was analyzed by Mann-Whitney test. **(C)** Kaplan-Meier plot of Progression-free survival of FL patients grouped on the basis of CSF-1R expression. An optimum threshold on the score to separate patients into low and high-expression groups was determined using the MaxStat software to select the cutoff value producing the maximum log-rank score in the training cohort. Cutoff value = 8.335 for follicular Compartment (left panel), and 21.379 for interfollicular (right panel). *P*-value was obtained using the overall log-rank test.

Figure S6

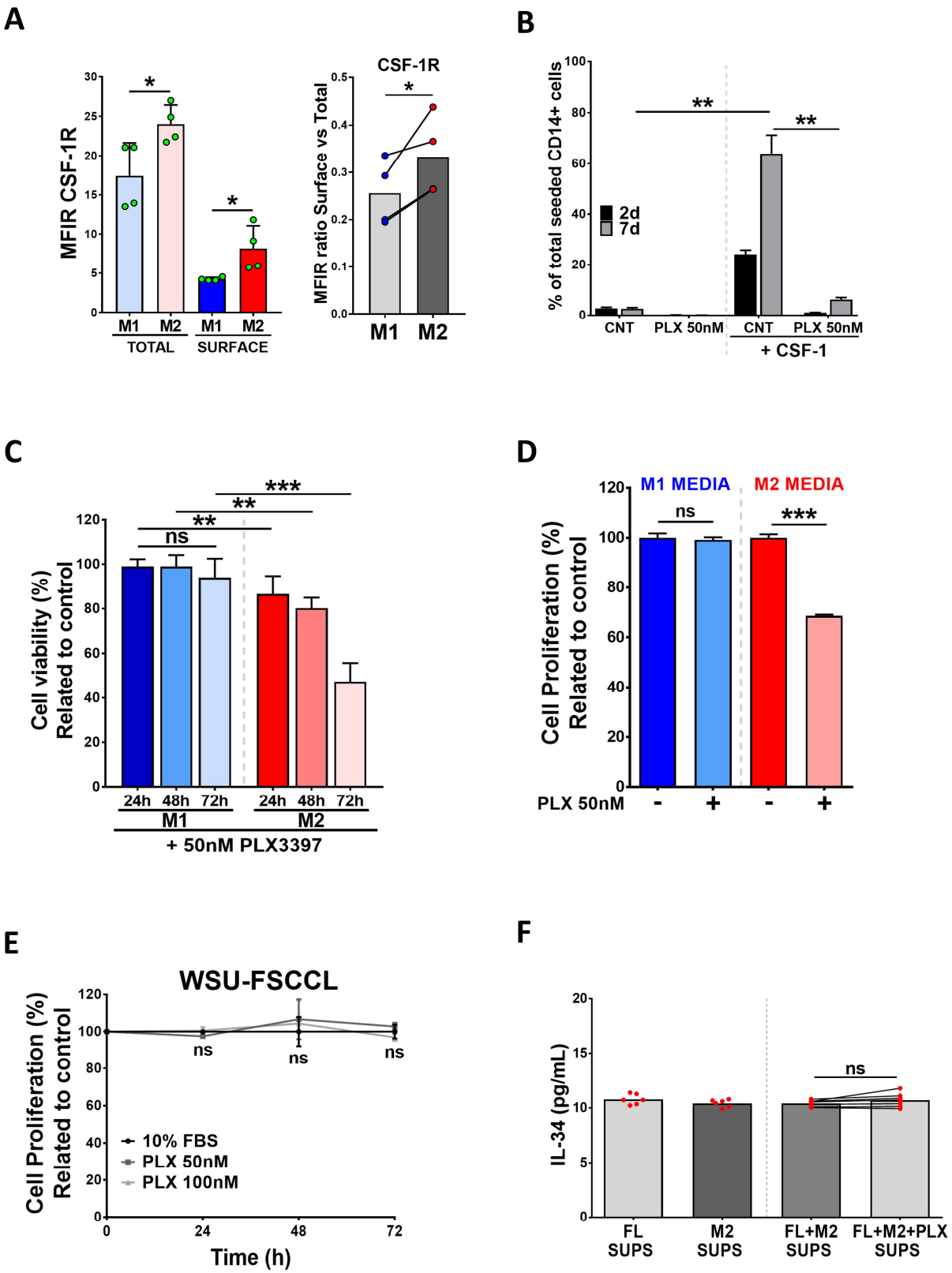


Figure S6. Effect of CSF-1R targeting with PLX3397 in macrophages and FL cells. (A) Surface and total CSF-1R expression was analyzed by flow cytometry in M1 (CSF-1 + IFNγ + LPS) and M2 (CSF-1 + IL4)-polarized macrophages. MFIR was calculated as follows: MFIR (mean fluorescence intensity ratio) = MFI (marker)/MFI (isotype). MFIR ratio between CSF-1R surface and total expression from Figure S6A was calculated as MFIR (surface)/ MFIR (total). Paired t test **(B)** Human monocytes ($5x10^5$ cells) from PBMCs were pre-treated for 1h with 50nM PLX3397 and then seeded in the presence or absence of CSF-1. Macrophage count was assessed by flow cytometry (CD14+, AQUA- cells) at day 2 and 7 of treatment. Paired t test **(C)** MTT assay of M1 or M2 macrophages in the presence or absence of the CSF-1R inhibitor PLX3397 for the times indicated. **(D)** WSU-FSCCL cells were plated with medium from M1 or M2 macrophage cultures (n=6) treated or not with PLX3397 (50nM). Viability was assessed by MTT assay. Results are expressed as % of control and represent the mean ±SD of 6 donors. Paired t test. **(E)** WSU-FSCLL was treated with PLX3397 and viability was assessed by MTT assay at the times indicated. Multiple t-Tests (Holm-Sidak method). **(F)** IL-34 was detected by ELISA in supernatants from Figure 6E. Paired t test.

Figure S7

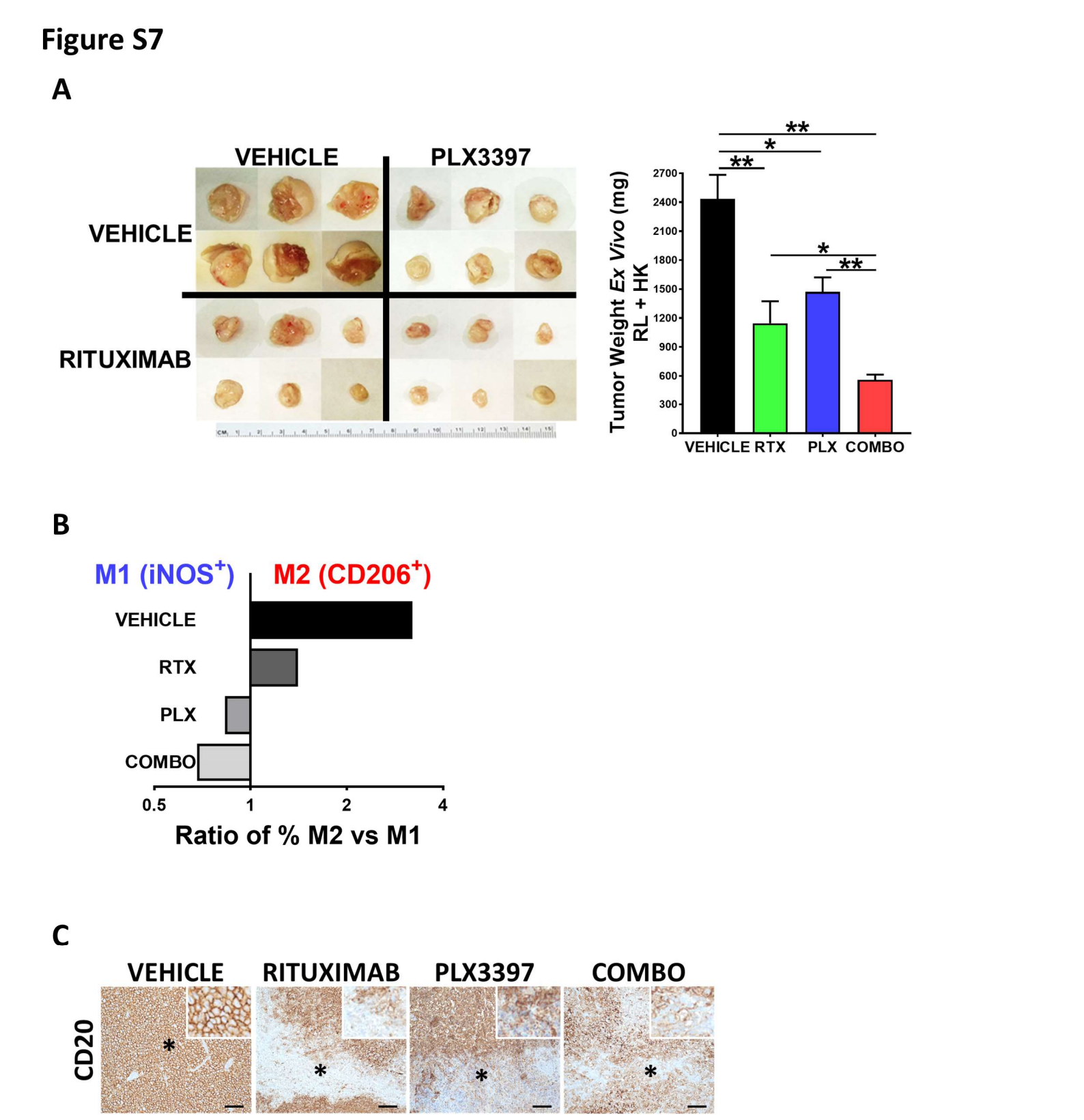


Figure S7. ***In vivo*** **PLX3397 and rituximab combo complementary results. (A)** Tumor were excised and weighted at the endpoint. Representative images are shown and graph shows tumor and weight at the endpoint where mean ± SEM are plotted the multiple t-Tests (Holm-Sidak method). **(B)** Effect of PLX3397 on M2/M1 ratio from figure 7B. **(C)** CD20 expression from Figure 7B.

SUPPLEMENTAL TABLES

Table S1. FL patients (*in vitro + serums*)

STUDY LABEL	GENDER[1]	AGE	SAMPLE TYPE[2]	% TUMOR CELLS[3]	HISTOLOGIC GRADE[4]	STAGE[5]	FLIPI[6]	DISEASE STATUS[7]
FL01	M	71	LN	49	2	II	2	D
FL02	M	77	LN	30	NA	NA	NA	NA
FL03	F	83	LN	75	2	III	2	D
FL04	M	65	LN	75	2	I	1	D
FL05	F	73	LN	73	2	IV	5	D
FL06	M	80	LN	85	2	IV	3	D
FL07	F	52	LN	85	1	IV	3	D
FL08	F	78	TS	36	3B	III	2	D
FL09	F	75	PB	78	2	IV	4	D
FL10	M	56	LN	33	3B	IV	2	D
FL11	M	50	LN	68	1	IV	2	D
FL12	M	65	LN	37	2	IV	2	D
FL13	M	52	LN	78	2	IV	3	D
FL14	F	66	PM	52	1	IV	2	D
FL15	M	63	PB	NA	2	IV	2	D
FL16	F	NA	LN	75	NA	NA	NA	NA
FL17	F	52	LN	85	1	IV	2	D
FL18	M	75	LN	75	2	I	2	D
FL19	M	70	PB	79	2	IV	3	D
FL20	M	64	S	N/A	1	IV	2	D
FL21	F	56	S	N/A	1	IV	1	D
FL22	M	45	S	N/A	2	I	0	D
FL23	F	54	S	N/A	2	IV	2	D
FL24	F	54	S	N/A	2	II	0	D
FL25	F	61	S	N/A	2	III	2	D
FL26	M	35	S	N/A	2	IV	3	D
FL27	F	65	S	N/A	2	IV	3	D
FL28	F	51	S	N/A	2	IV	3	D
FL29	F	52	S	N/A	2	I	0	D
FL30	M	56	S	N/A	2	IV	2	D
FL31	M	42	S	N/A	2/3	IV	2	D
FL32	M	74	S	N/A	3A	III	2	D
FL33	M	42	S	N/A	3A	IV	3	D
FL34	F	65	S	N/A	3A	IV	3	D
FL35	M	54	S	N/A	3A	IV	2	D
FL36	M	72	S	N/A	3A	III	2	D

[1] F:Female; M:Male; [2] PB: Peripheral Blood, LN: Lymph Node, TS: Tonsil, PM: Paravertebral Mass, S: serum; [3] % of cells positive for CD20, CD10 and showing light chain restriction; [4] Grade was evaluated by two different pathologists; [5]Ann Arbor stage; [6]FLIPI: Follicular Lymphoma International Prognostic Index; [7]Samples were obtained at D: diagnosis, R: relapse, NA: Not Available, N/A: Not Applicable

Table S2. Gene sets overrepresented in FL cells after co-culture with M2 macrophages

GENE SET NAME	# of enriched gene sets	NES (max)	FDR, q value (min)
Custom gene sets			
Immune response 2 FL bad prognosis	1	2.40	<0.0001
Angiogenesis	3	2.32	<0.0001
Serum response	1	2.17	0.0001
NF-kB pathway	2	1.99	0.0001
Toll Like Receptors (TLRs)	1	1.87	0.0130
Canonical pathways gene sets (C2CP)			
Toll Like Receptors (TLRs)	3	2.32	<0.0001
Antigen presentation	2	2.28	0.0002
Chemokines and chemokine receptors	3	2.26	0.0002
IL8 pathway	2	2.14	0.0022
Interferon gamma signaling	1	2.13	0.0022
Integrin pathway	4	2.11	0.0032
Extracellular matrix (ECM) regulation	3	2.09	0.0039
Cytokines and cytokine receptors	2	2.00	0.0120
CCR5 pathway	1	1.98	0.0147
Syndecan 2,4 pathway	2	1.97	0.0185
Motif gene sets (C3)			
V$STAT3_01	1	1.97	0.0203
Hallmark gene sets (H)			
KRAS signaling	1	2.47	<0.0001
IL6 -JAK-STAT3 signaling	1	2.39	<0.0001
Inflammatory response	1	2.27	<0.0001
TNFalpha-NF-kB signaling	1	2.21	0.0002
Interferon gamma response	1	2.00	0.0009
Epithelial mesenchymal transition	1	1.98	0.0013
IL2-STAT5 signaling	1	1.89	0.0021
Angiogenesis	1	1.77	0.0149
GO gene sets (C5)			
Leukocyte chemotaxis	23	2.63	<0.0001
Interferon gamma response	3	2.49	<0.0001
Toll Like Receptors (TLRs)	5	2.46	<0.0001
TNFalpha	4	2.45	<0.0001
Inflammatory response	4	2.45	<0.0001
Chemokine signaling	7	2.41	<0.0001
Regulation of endocytosis	4	2.35	<0.0001
Extracellular matrix disassembly	2	2.39	<0.0001
IL6 synthesis	2	2.16	0.0013
VEGF-VEGFR pathway	3	2.12	0.0025
Integrin-mediated cell adhesion	2	2.07	0.0043
Antigen processing and presentation	5	2.09	0.0034
Angiogenesis-vasculature development	2	1.93	0.0193
Oncogenic gene sets (C6)			
KRAS	10	2.260	<0.0001

GSEA was used to test for significant enrichment of defined gene signatures. NES indicates Normalized Enriched Score; FDR, False Discovery Rate. Threshold FDR<0.05 and NES>1.5. Custom genes set were experimentally derived and downloaded from http://lymphochip.nih.gov/signaturedb/index.html. C2CP, C3, C5, C6 and H gene sets were obtained from the Molecular Signature Database (v2.5).

Table S3. Complete GSEA results

CUSTOM GENE SETS				
Biological process	**Gene set name**	**Size**	**NES**	**FDR q-val**
Immune response 2 FL bad prognosis	IMMUNE RESPONSE2 FL STAUDTBADPROGNOSIS	20	2.4	0
Angiogenesis	VEGF PATHWAY SABBIOSCINECES	80	2.32	0
	HUMAN ANGIOGENESIS MERGED	120	2.22	0.00019
	VEGF PATHWAY TAQMANMICROFLUIDICS	89	1.73	0.03165
Serum response	SERUM_RESPONSE_FB_UP	158	2.17	0.00016
NF-KB pathway	NFKB_ALL_OCILY3_LY10	54	1.99	0.00423
	NFKB_OCILY10_ONLY	15	1.72	0.03222
Toll Like Receptors (TLRs)	TOLLPATHWAY	30	1.87	0.01301
CANONICAL PATHWAYS (C2CP)				
Biological process	**Gene set name**	**Size**	**NES**	**FDR q-val**
Toll Like Receptors (TLRs)	REACTOME_TOLL_RECEPTOR_CASCADES	104	2.32	0
	KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	90	2.13	0.00263
	BIOCARTA_TOLL_PATHWAY	34	1.91	0.02556
Antigen presentation	REACTOME_MHC_CLASS_II_ANTIGEN_PRESENTATION	78	2.28	0.00022
	KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	63	2.1	0.00316
Chemokines and chemokine receptors	REACTOME_CHEMOKINE_RECEPTORS_BIND_CHEMOKINES	51	2.26	0.00018
	KEGG_CHEMOKINE_SIGNALING_PATHWAY	169	2.07	0.0055
	PID_CXCR4_PATHWAY	97	1.88	0.03381
IL8 pathway	PID_IL8_CXCR1_PATHWAY	28	2.14	0.00225
	PID_IL8_CXCR2_PATHWAY	32	2.14	0.00216
Interferon gamma signaling	REACTOME_INTERFERON_GAMMA_SIGNALING	51	2.13	0.00253
Integrin pathway	PID_INTEGRIN2_PATHWAY	27	2.11	0.00322
	PID_INTEGRIN1_PATHWAY	61	1.92	0.02677
	PID_INTEGRIN_A4B1_PATHWAY	30	1.92	0.02686
	PID_INTEGRIN_A9B1_PATHWAY	24	1.87	0.03587
Extracellular matrix (ECM) regulation	NABA_ECM_REGULATORS	214	2.09	0.00397
	REACTOME_DEGRADATION_OF_THE_EXTRACELLULAR_MATRIX	26	2.05	0.00614
	NABA_ECM_AFFILIATED	142	1.92	0.02633
Cytokines and cytokine receptors	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	243	2	0.01204
	PID_IL23_PATHWAY	35	1.87	0.03424
CCR5 pathway	BIOCARTA_CCR5_PATHWAY	16	1.98	0.01478
Syndecan 2,4 pathway	PID_SYNDECAN_4_PATHWAY	32	1.97	0.01858
	PID_SYNDECAN_2_PATHWAY	31	1.94	0.02341
MOTIF GENE SETS (C3TFT)				
Biological process	**Gene set name**	**Size**	**NES**	**FDR q-val**
STATs	V$STAT3_01	20	1.97	0.02028
HALLMARKS (H)				
Biological process	**Gene set name**	**Size**	**NES**	**FDR q-val**
KRAS signaling	HALLMARK_KRAS_SIGNALING_UP	190	2.47	0
IL6 -JAK-STAT3 signaling	HALLMARK_IL6_JAK_STAT3_SIGNALING	85	2.39	0
Inflammatory response	HALLMARK_INFLAMMATORY_RESPONSE	192	2.27	0
TNFalpha-NF-kB signaling	HALLMARK_TNFA_SIGNALING_VIA_NFKB	192	2.21	0.00017
Interferon gamma response	HALLMARK_INTERFERON_GAMMA_RESPONSE	178	2	0.00093
Epithelial mesenchymal transition	HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	189	1.98	0.00127
IL2-STAT5 signaling	HALLMARK_IL2_STAT5_SIGNALING	184	1.89	0.00218

Angiogenesis	HALLMARK_ANGIOGENESIS	35	1.77	0.00548
GO GENESETS (C5)				
Biological process	**Gene set name**	**Size**	**NES**	**FDR q-val**
Leukocyte chemotaxis	GO_POSITIVE_REGULATION_OF_LEUKOCYTE_MIGRATION	102	2.63	0
	GO_REGULATION_OF_LEUKOCYTE_MIGRATION	139	2.63	0
	GO_REGULATION_OF_LEUKOCYTE_CHEMOTAXIS	89	2.59	0
	GO_POSITIVE_REGULATION_OF_LEUKOCYTE_CHEMOTAXIS	75	2.58	0
	GO_LEUKOCYTE_CHEMOTAXIS	105	2.46	0
	GO_MONOCYTE_CHEMOTAXIS	33	2.41	0
	GO_REGULATION_OF_GRANULOCYTE_CHEMOTAXIS	36	2.36	0
	GO_REGULATION_OF_MONOCYTE_CHEMOTAXIS	20	2.31	0.00017
	GO_POSITIVE_REGULATION_OF_CHEMOTAXIS	112	2.31	0.00018
	GO_POSITIVE_REGULATION_OF_MONOCYTE_CHEMOTAXIS	15	2.25	0.00052
	GO_REGULATION_OF_CHEMOTAXIS	168	2.23	0.00068
	GO_REGULATION_OF_MONONUCLEAR_CELL_MIGRATION	15	2.22	0.00071
	GO_REGULATION_OF_MACROPHAGE_CHEMOTAXIS	15	2.21	0.0008
	GO_REGULATION_OF_NEUTROPHIL_CHEMOTAXIS	25	2.2	0.00094
	GO_REGULATION_OF_NEUTROPHIL_MIGRATION	30	2.14	0.00203
	GO_LYMPHOCYTE_CHEMOTAXIS	32	2.12	0.00264
	GO_POSITIVE_REGULATION_OF_NEUTROPHIL_MIGRATION	25	2.07	0.00466
	GO_REGULATION_OF_LYMPHOCYTE_MIGRATION	35	2.05	0.00649
	GO_LYMPHOCYTE_MIGRATION	42	1.87	0.03222
	GO_NEGATIVE_REGULATION_OF_CHEMOTAXIS	48	1.9	0.02575
	GO_POSITIVE_REGULATION_OF_LYMPHOCYTE_MIGRATION	25	1.86	0.03391
	GO_REGULATION_OF_LYMPHOCYTE_CHEMOTAXIS	18	1.86	0.03401
	GO_NEGATIVE_REGULATION_OF_LEUKOCYTE_MIGRATION	31	1.86	0.03553
Interferon gamma response	GO_CELLULAR_RESPONSE_TO_INTERFERON_GAMMA	97	2.49	0
	GO_RESPONSE_TO_INTERFERON_GAMMA	115	2.41	0
	GO_INTERFERON_GAMMA_MEDIATED_SIGNALING_PATHWAY	56	2.02	0.00867
Toll Like Receptors (TLRs)	GO_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	78	2.46	0
	GO_REGULATION_OF_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	43	2.12	0.00266
	GO_TOLL_LIKE_RECEPTOR_4_SIGNALING_PATHWAY	16	1.99	0.01138
	GO_NEGATIVE_REGULATION_OF_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	23	1.96	0.01548
	GO_MYD88_DEPENDENT_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	30	1.86	0.03518
TNFalpha	GO_POSITIVE_REGULATION_OF_TUMOR_NECROSIS_FACTOR_SUPERFAMILY_CYTOKINE_PRODUCTION	54	2.45	0
	GO_REGULATION_OF_TUMOR_NECROSIS_FACTOR_SUPERFAMILY_CYTOKINE_PRODUCTION	93	2.4	0
	GO_NEGATIVE_REGULATION_OF_TUMOR_NECROSIS_FACTOR_SUPERFAMILY_CYTOKINE_PRODUCTION	39	1.96	0.01479
	GO_REGULATION_OF_TUMOR_NECROSIS_FACTOR_BIOSYNTHETIC_PROCESS	15	1.81	0.04811
Inflammatory response	GO_INFLAMMATORY_RESPONSE	397	2.46	0
	GO_POSITIVE_REGULATION_OF_INFLAMMATORY_RESPONSE	98	2.38	0
	GO_REGULATION_OF_INFLAMMATORY_RESPONSE	266	2.21	0.00076
	GO_REGULATION_OF_ACUTE_INFLAMMATORY_RESPONSE	66	1.94	0.01855
Chemokine signaling	GO_CHEMOKINE_RECEPTOR_BINDING	48	2.41	0
	GO_CHEMOKINE_ACTIVITY	41	2.4	0
	GO_CHEMOKINE_MEDIATED_SIGNALING_PATHWAY	62	2.4	0
	GO_CCR_CHEMOKINE_RECEPTOR_BINDING	27	2.29	0.00034
	GO_CXCR_CHEMOKINE_RECEPTOR_BINDING	15	2.08	0.00426

	GO_POSITIVE_REGULATION_OF_CHEMOKINE_PRODUCTION	47	2.04	0.00706
	GO_REGULATION_OF_CHEMOKINE_PRODUCTION	62	1.95	0.01722
Regulation of endocytosis	GO_RECEPTOR_MEDIATED_ENDOCYTOSIS	196	2.35	0
	GO_REGULATION_OF_ENDOCYTOSIS	181	2.22	0.00076
	GO_ENDOCYTOSIS	437	2.21	0.00081
	GO_POSITIVE_REGULATION_OF_ENDOCYTOSIS	104	2.16	0.00151
Extracellular matrix disassembly	GO_EXTRACELLULAR_MATRIX_DISASSEMBLY	68	2.4	0
	GO_EXTRACELLULAR_MATRIX_BINDING	48	2.01	0.00936
IL6 synthesis	GO_REGULATION_OF_INTERLEUKIN_6_PRODUCTION	96	2.17	0.00137
	GO_POSITIVE_REGULATION_OF_INTERLEUKIN_6_PRODUCTION	63	2.14	0.00196
VEGF-VEGFR pathway	GO_REGULATION_OF_VASCULAR_ENDOTHELIAL_GROWTH_FACTOR_PRODUCTION	29	2.12	0.00259
	GO_VASCULAR_ENDOTHELIAL_GROWTH_FACTOR_RECEPTOR_SIGNALING_PATHWAY	65	1.84	0.03939
	GO_POSITIVE_REGULATION_OF_VASCULAR_ENDOTHELIAL_GROWTH_FACTOR_PRODUCTION	25	1.83	0.04149
Integrin-mediated cell adhesion	GO_INTEGRIN_MEDIATED_SIGNALING_PATHWAY	73	2.08	0.00432
	GO_INTEGRIN_BINDING	96	2.05	0.00646
Antigen processing and presentation	GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_OR_POLYSACCHARIDE_ANTIGEN_VIA_MHC_CLASS_II	77	2.1	0.00348
	GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_ANTIGEN_VIA_MHC_CLASS_II	77	2.08	0.00431
	GO_ANTIGEN_BINDING	67	1.99	0.01098
	GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_ANTIGEN	146	1.89	0.02782
	GO_ANTIGEN_PROCESSING_AND_PRESENTATION	180	1.89	0.02819
Angiogenesis-vasculature development	GO_POSITIVE_REGULATION_OF_VASCULATURE_DEVELOPMENT	124	1.93	0.01933
	GO_ANGIOGENESIS	276	1.82	0.04686
ONCOGENIC GENE SETS (C6)				
Biological process	**Gene set name**	**Size**	**NES**	**FDR q-val**
KRAS	KRAS.LUNG.BREAST_UP.V1_UP	127	2.26	0
	KRAS.50_UP.V1_UP	45	2.09	0.00015
	KRAS.KIDNEY_UP.V1_UP	133	2.09	0.00013
	KRAS.300_UP.V1_UP	133	2.09	0.00012
	KRAS.600.LUNG.BREAST_UP.V1_UP	248	1.91	0.00143
	KRAS.600_UP.V1_UP	253	1.86	0.00235
	KRAS.KIDNEY_UP.V1_DN	121	1.8	0.00469
	KRAS.BREAST_UP.V1_UP	126	1.73	0.00864
	KRAS.LUNG_UP.V1_UP	123	1.71	0.009
	KRAS.DF.V1_UP	160	1.52	0.04356

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