A
Go Term - B3
response to topologically incorrect protein
response to organic substance
regulation of immune system process
mononuclear cell proliferation
lymphocyte homeostasis
establishment of localization in cell
ER−nucleus signaling pathway
endoplasmic reticulum unfolded protein response
cellular response to chemical stimulus
cell surface receptor signaling pathway
cell redox homeostasis
Average Fold Change (ln)
1
5
10
20
Localization
Intracellular
Secreted
Surface
Unknown
ACY3
AIM2
AMPD1
ARID5B
BACH2
BANK1
BHLHE41
BLK
BMP8B
BRSK1
CADM1
CADPS2
CAV1
CCR10
CD19
CD22
CD24
CD38
CD40
CD79A
CD79B
CDK14
CHD7
CPNE5
CTHRC1
CXXC4
DCC
DERL1
DERL3
DKK1
DNAJB9
DPEP1
DST
EDNRB
EIF2AK3
FBXW7
FCER2
FICD
FRZB
HERPUD1
HID1
HLA−DOB
HM13
HSP90B1
HVCN1
IFT57
IL5RA
ITGA8
JSRP1
KDELR3
LAX1
LMAN1
LMF1
MEI1
MEIS2
MS4A1
MYDGF
MYO6
MZB1
P2RX5
PARD3
PAX5
PDIA4
PDIA5
PDK1
PERP
PHGDH
PMEPA1
PRDX4
PTP4A3
RAB30
RAPGEF1
SDC1
SDF2L1
SEL1L
SH2B2
SLAMF7
SPCS2
SRPRB
SWAP70
SYT1
SYVN1
TCL1A
TIFA
TNFRSF13B
TNFRSF13C
TNFRSF17
TP53INP1
TRAM2
B
PIM2
POU2AF1
TNFRSF17
FCRL5
SLAMF7
CD79B
LAX1
HVCN1
CD19
CD22
FCRL1
SDC1
TNFRSF13B
CADM1
SLC1A4
PERP
CCR10
ITGA8
DPEP1
MZB1
EAF2
HLA−DOB
BANK1
PAX5
TCL1A
localization
Tissue-Specific Intracellular
Tissue-Nonspecific Surface
Tissue-Specific Surface
Dependency
1
0.5
0
−0.5
−1
C
MMRF Pilot
WashU Cohort 1
WashU Cohort 2
expression
CCL3
CXCL10
CXCL12
CXCR6
CCR4
Cell type

**Figure S1. Related to Figure 2**

**A**, Gene ontology (GO) gene-set enrichment analysis of plasma and B-cell marker genes. GO terms from “Biological Function”. level 3 with enrichment FDR (q) <0.05 are shown for individual genes. Bubble size indicates fold change (ln) of plasma and B-cell expression relative to that of other BM cells; color indicates predicted cellular localization of gene products. **B**, Heatmap showing DepMap dependency scores, as assessed by CRISPR-Cas9 knockout, of myeloma markers across 21 plasma cell lines. As described by DepMap, a score of 0 indicates a non-essential gene, and -1 is the median dependency score of common essential genes. **C**, Bubble plots showing the normalized expression of chemokine and chemokine receptors, averaged by sample and cell type. Column corresponds to samples, colored by cohorts.

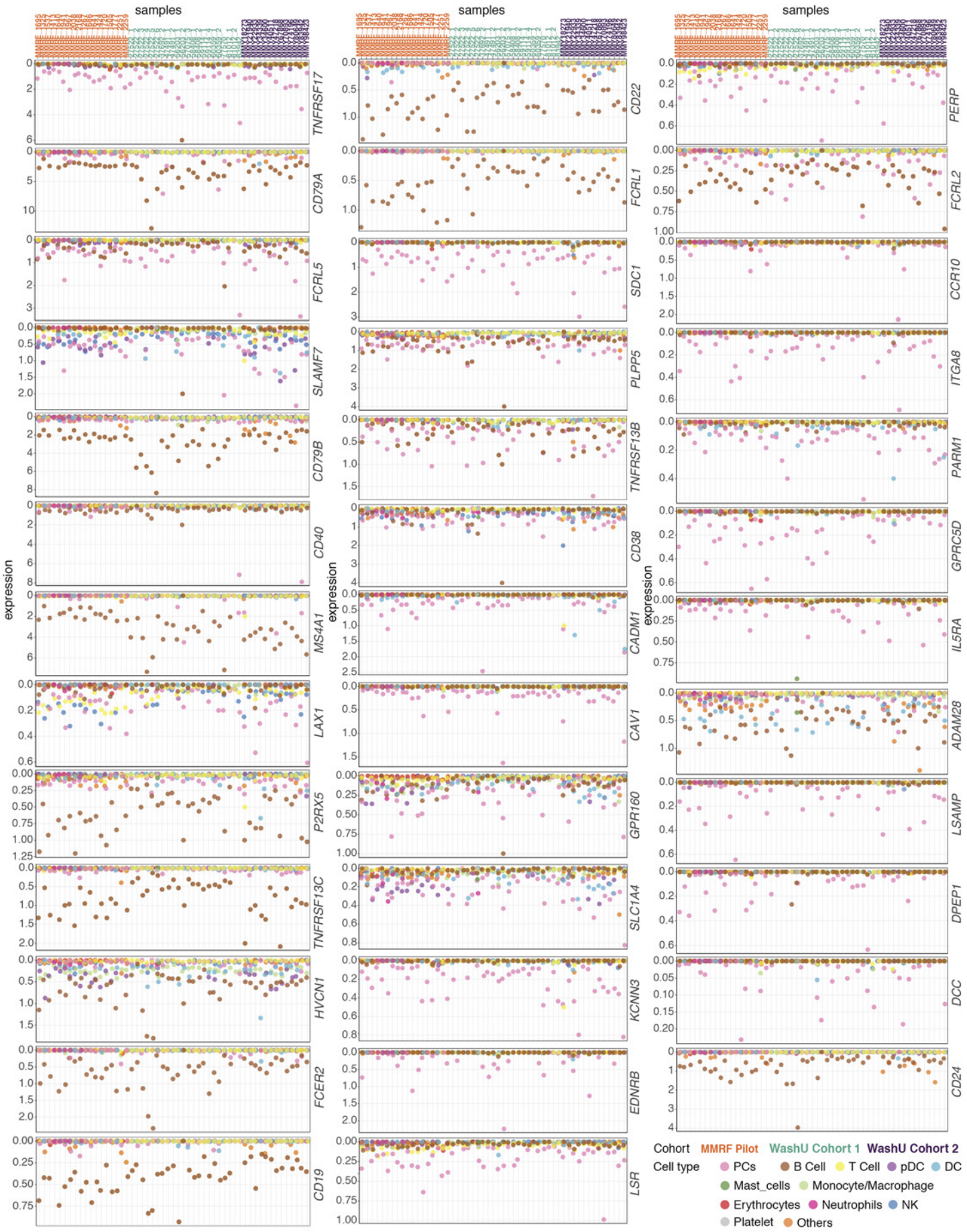

samples
expression
TNFRSF17
CD79A
FCRL5
SLAMF7
CD79B
CD40
MS4A1
LAX1
P2RX5
TNFRSF13C
HVCN1
FCER2
CD19
CD22
FCRL1
SDC1
PLP5
TNFRSF13B
CD38
CADM1
CAV1
GPR160
SLC1A4
KCNN3
EDNRB
LSR
PERP
FCRL2
CCR10
ITGA8
PARM1
GPRC5D
IL5RA
ADAM28
LSAMP
DPEP1
DCC
CD24
Cohort MMRF Pilot WashU Cohort 1 WashU Cohort 2
Cell type PCs B Cell T Cell pDC DC
Mast_cells Monocyte/Macrophage
Erythrocytes Neutrophils NK
Platelet Others

**Figure S2. Related to Figure 3**
Bubble plots showing the normalized expression of target candidates, averaged by sample and cell type. Column corresponds to samples, colored by cohorts. All genes are annotated as having cell surface expression.

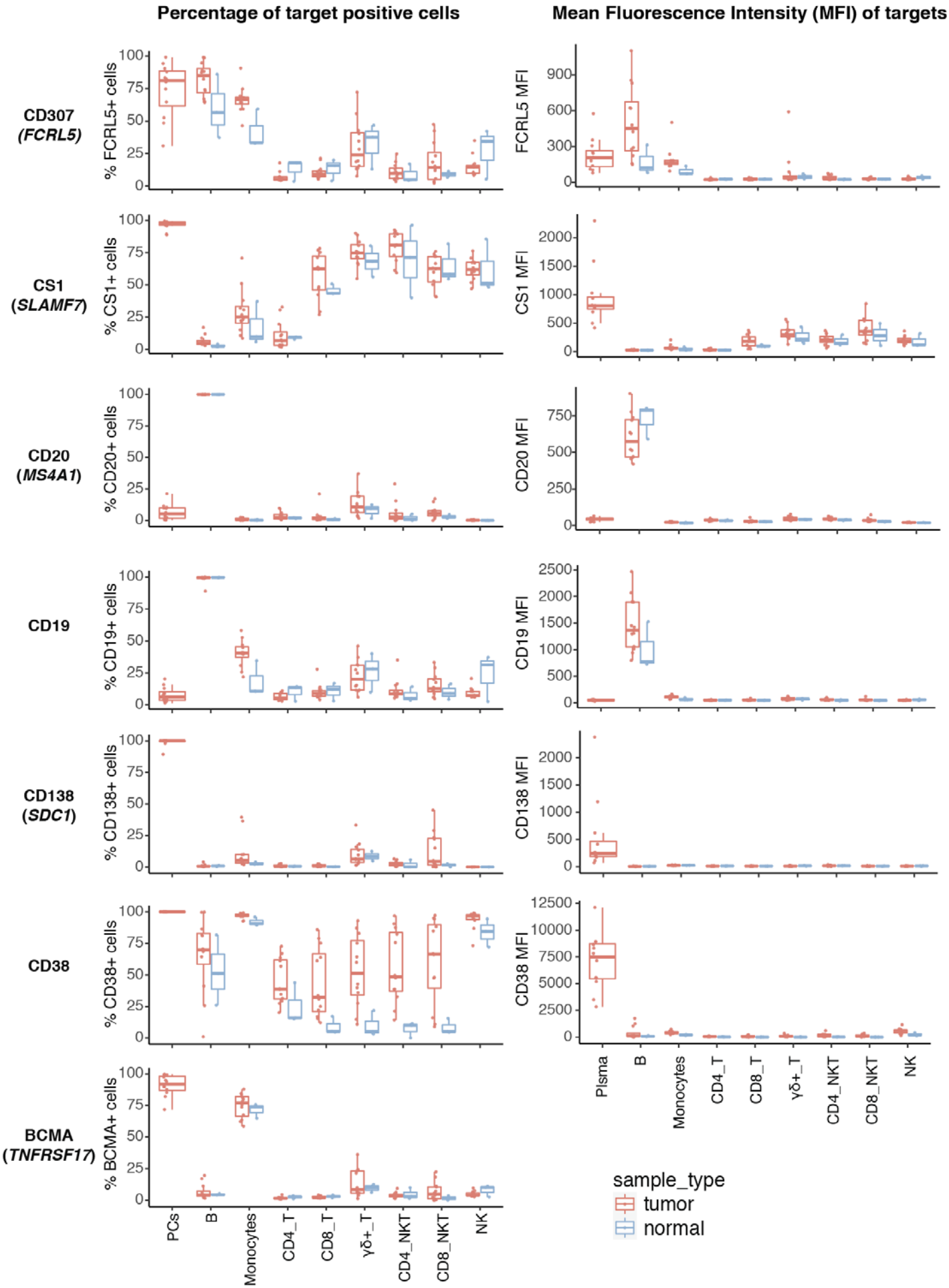

Percentage of target positive cells
Mean Fluorescence Intensity (MFI) of targets
CD307 (FCRL5)
% FCRL5+ cells
FCRL5 MFI
CS1 (SLAMF7)
% CS1+ cells
CS1 MFI
CD20 (MS4A1)
% CD20+ cells
CD20 MFI
CD19
% CD19+ cells
CD19 MFI
CD138 (SDC1)
% CD138+ cells
CD138 MFI
CD38
% CD38+ cells
CD38 MFI
BCMA (TNFRSF17)
% BCMA+ cells
PCs
Plsma
B
Monocytes
CD4_T
CD8_T
γδ+_T
CD4_NKT
CD8_NKT
NK
sample_type
tumor
normal

**Figure S3. Related to Figure 3**

Box plots showing percentage of target positive cells (left) and MFI of targets (right) in MM BMMC or PBMC from healthy donors across cell populations in flow cytometry. Viable cell populations were gated on the following: CD45loCD319+CD38+CD138+ PCs; CD45+CD20+CD19+ B cells; CD45+CD14+CD33+ Monocytes; CD45+CD3+ T cells; CD45+CD3+gdTCR+ gdT; CD45+CD56+CD3+ NKTs; CD45+CD56+CD3- NK cells. Plasma cells were not detected in sufficient quantity for comparison in healthy donor PBMCs.

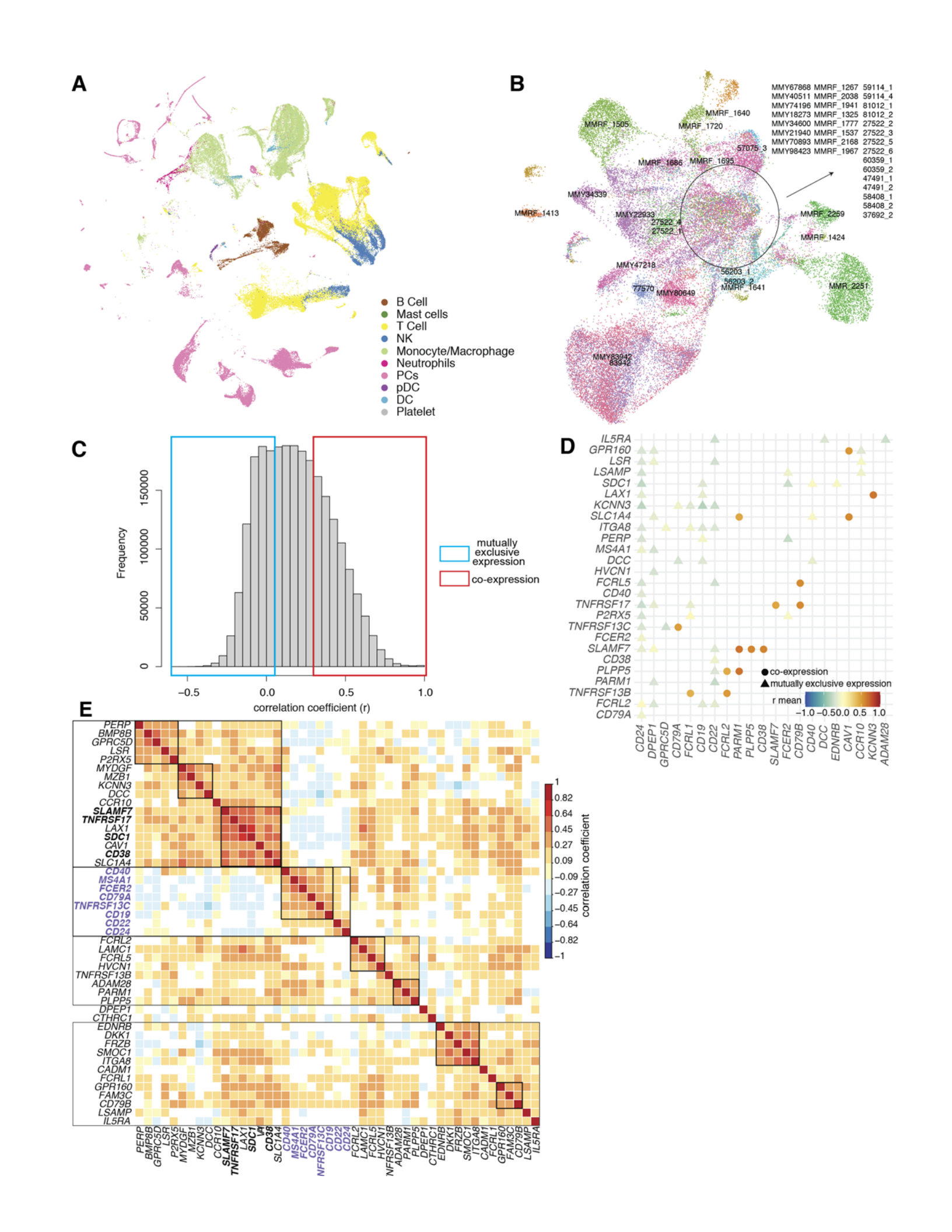

A
B Cell
Mast cells
T Cell
NK
Monocyte/Macrophage
Neutrophils
PCs
pDC
DC
Platelet
B
MMY67868 MMRF_1267 59114_1
MMY40511 MMRF_2038 59114_4
MMY74196 MMRF_1941 81012_1
MMY18273 MMRF_1325 81012_2
MMY34600 MMRF_1777 27522_2
MMY21940 MMRF_1537 27522_3
MMY70893 MMRF_2168 27522_5
MMY98423 MMRF_1967 27522_6
60359_1
60359_2
47491_1
47491_2
58408_1
58408_2
37692_2
MMRF_1640
MMRF_1505
MMRF_1720
57075_3
MMRF_1686
MMRF_1695
MMY34339
MMRF_1413
MMY22933
27522_4
27522_1
MMRF_2259
MMRF_1424
MMY47218
56203_1
56203_2
MMRF_1641
77570
MMY80649
MMRF_2251
MMY83942
83942
C
Frequency
0
50000
100000
150000
−0.5
0.0
0.5
1.0
correlation coefficient (r)
mutually exclusive expression
co-expression
D
IL5RA
GPR160
LSR
LSAMP
SDC1
LAX1
KCNN3
SLC1A4
ITGA8
PERP
MS4A1
DCC
HVCN1
FCRL5
CD40
TNFRSF17
P2RX5
TNFRSF13C
FCER2
SLAMF7
CD38
PLPP5
PARM1
TNFRSF13B
FCRL2
CD79A
co-expression
mutually exclusive expression
r mean
−1.0 −0.5 0.0 0.5 1.0
CD24
DPEP1
GPRC5D
CD79A
FCRL1
CD19
CD22
FCRL2
PARM1
PLPP5
CD38
SLAMF7
FCER2
CD79B
CD40
DCC
EDNRB
CAV1
CCR10
KCNN3
ADAM28
E
PERP
BMP8B
GPRC5D
LSR
P2RX5
MYDGF
MZB1
KCNN3
DCC
CCR10
SLAMF7
TNFRSF17
LAX1
SDC1
CAV1
CD38
SLC1A4
CD40
MS4A1
FCER2
CD79A
TNFRSF13C
CD19
CD22
CD24
FCRL2
LAMC1
FCRL5
HVCN1
TNFRSF13B
ADAM28
PARM1
PLPP5
DPEP1
CTHRC1
EDNRB
DKK1
FRZB
SMOC1
ITGA8
CADM1
FCRL1
GPR160
FAM3C
CD79B
LSAMP
IL5RA
1
0.82
0.64
0.45
0.27
0.09
−0.09
−0.27
−0.45
−0.64
−0.82
−1
correlation coefficient

**Figure S4. Related to Figure 4**

**A**, UMAP showing all cells from 53 samples, colored by cell type. Compared to immune populations, plasma populations formed much more dispersed clusters, indicating the transcriptomic heterogeneity of tumor cells across patients. **B**, UMAP showing plasma cells from 53 patients, clustered by candidate targets, colored by samples. Most samples are clustered around the center while some samples form their individual clusters. **C**, Distribution of correlation coefficient of 2000 random genes and candidate targets. Red box shows the cutoff of identification of co-expressions and the blue box shows the cutoff of identification of mutually exclusive expressions. **D**, Co-expressed or mutually exclusively expressed gene pairs found in all three cohorts. Gene pairs with $0.05 < r < 0.3$ were not shown. **E**, Pearson correlation heatmap of CoMMpass study bulk RNA-seq expression values. Gene groups with prominent positive correlation are boxed. Notable gene group containing canonical tumor markers have bolded names; a second group containing B-cell markers is labeled in purple.

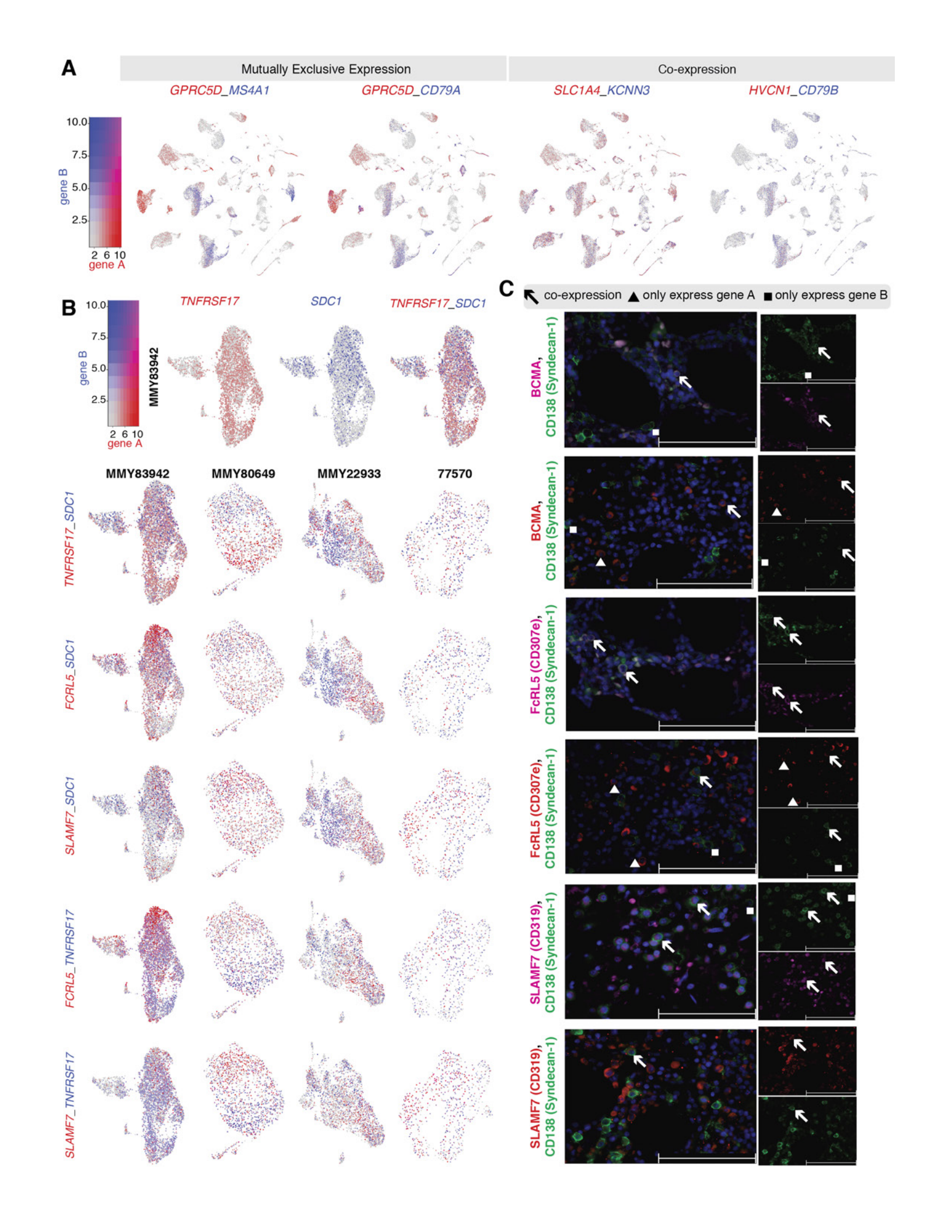

A
Mutually Exclusive Expression
Co-expression
GPRC5D_MS4A1
GPRC5D_CD79A
SLC1A4_KCNN3
HVCN1_CD79B
gene B
gene A
B
TNFRSF17
SDC1
TNFRSF17_SDC1
MMY83942
MMY80649
MMY22933
77570
TNFRSF17_SDC1
FCRL5_SDC1
SLAMF7_SDC1
FCRL5_TNFRSF17
SLAMF7_TNFRSF17
C
co-expression
only express gene A
only express gene B
BCMA, CD138 (Syndecan-1)
FcRL5 (CD307e), CD138 (Syndecan-1)
SLAMF7 (CD319), CD138 (Syndecan-1)

**Figure S5. Related to Figure 4**

**A**, In addition to Fig. 4C, more examples of gene pairs showing mutually exclusive expressions (left two) or co-expressions (right two). **B**, UMAPs of PCs from 4 patients colored by dual expression of gene pairs. **C**, Representative immunofluorescence (IF) co-staining of target pairs in bone marrow biopsies from patient s10-10686; 63x magnification; scale bar 100μm. Three channel overlay (Hoescht staining of nuclei in blue) enlarged, single channel violet/red and green images shown on right.

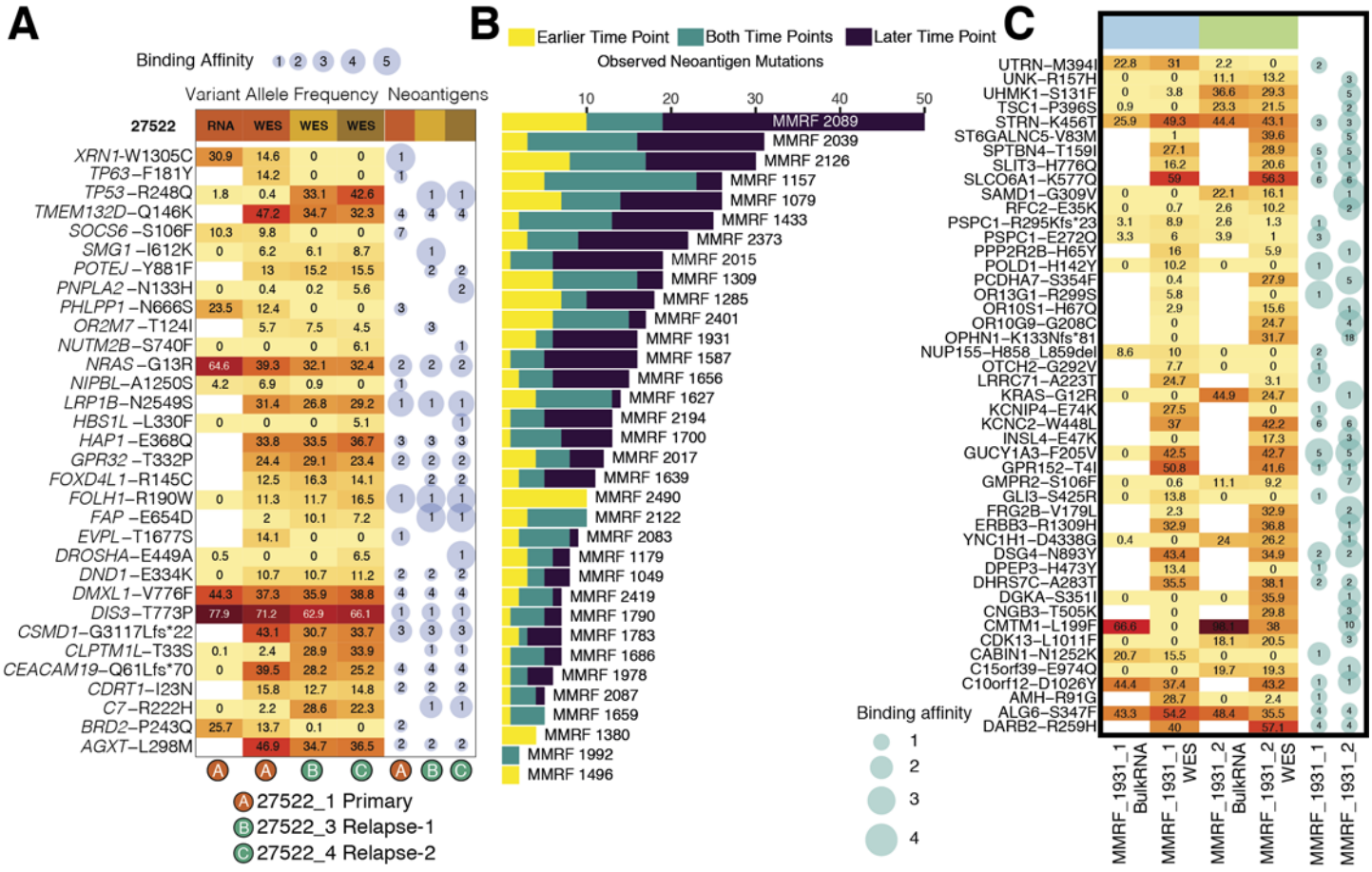
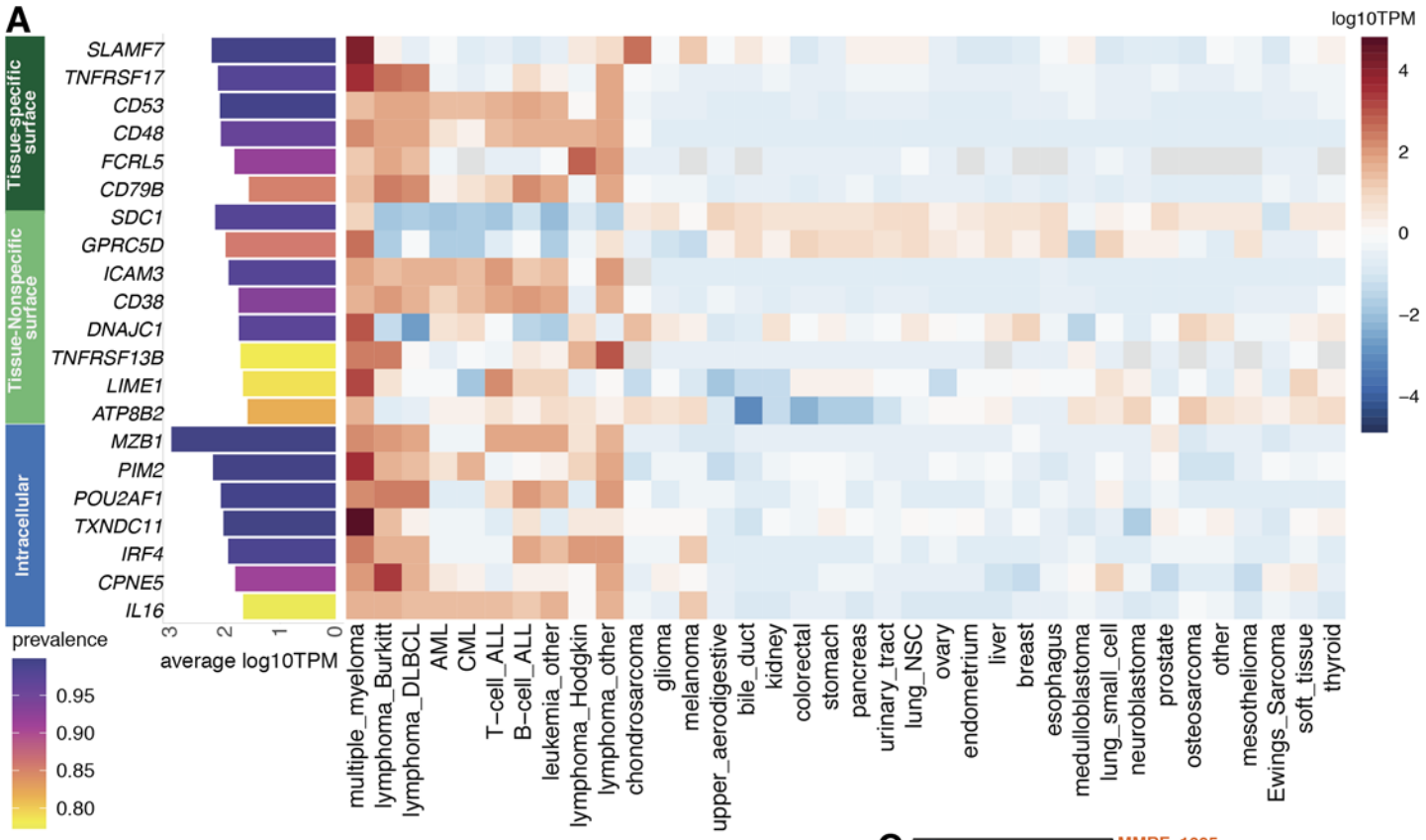
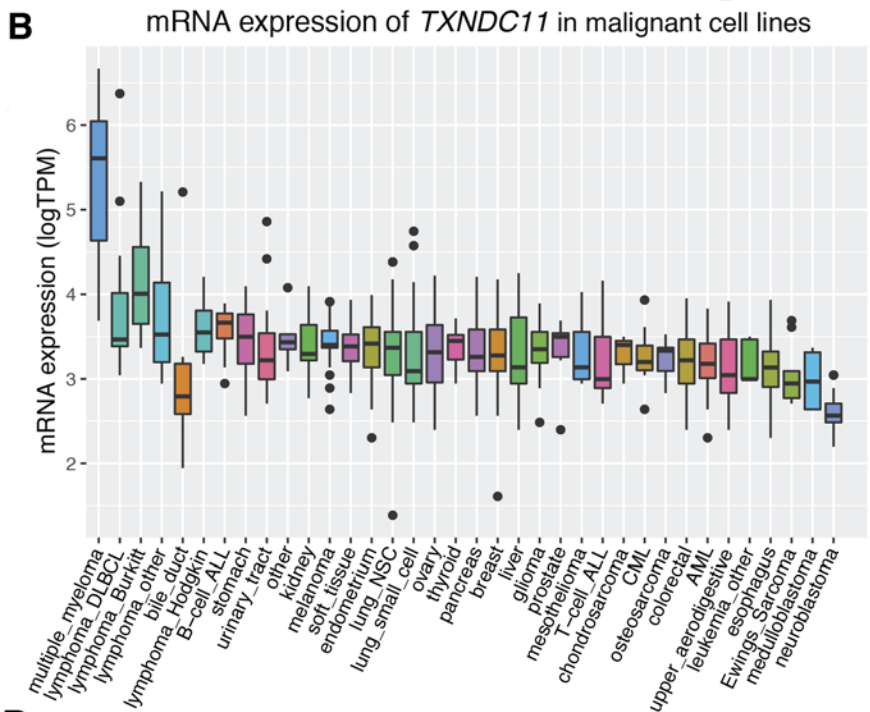
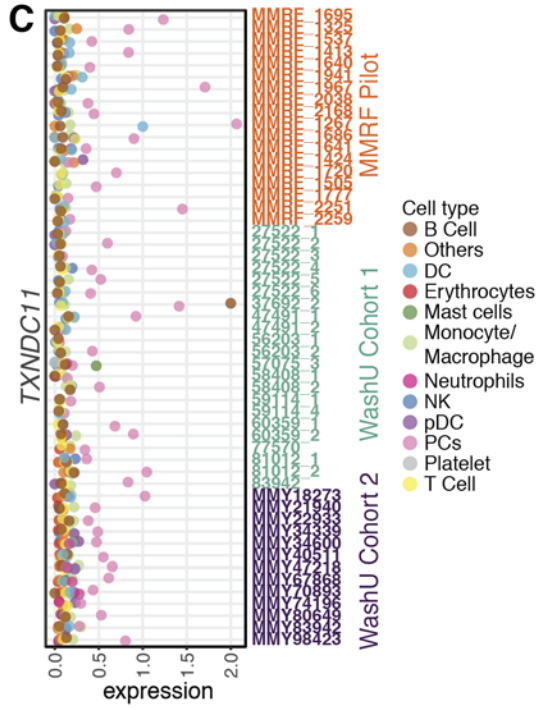

A
Binding Affinity 1 2 3 4 5
Variant Allele Frequency
Neoantigens
27522
RNA
WES
WES
WES
XRN1–W1305C 30.9 14.6 0 0
TP63–F181Y 14.2 0 0
TP53–R248Q 1.8 0.4 33.1 42.6
TMEM132D–Q146K 47.2 34.7 32.3
SOCS6–S106F 10.3 9.8 0 0
SMG1–I612K 0 6.2 6.1 8.7
POTEJ–Y881F 13 15.2 15.5
PNPLA2–N133H 0 0.4 0.2 5.6
PHLPP1–N666S 23.5 12.4 0 0
OR2M7–T124I 5.7 7.5 4.5
NUTM2B–S740F 0 0 0 6.1
NRAS–G13R 64.6 39.3 32.1 32.4
NIPBL–A1250S 4.2 6.9 0.9 0
LRP1B–N2549S 31.4 26.8 29.2
HBS1L–L330F 0 0 0 5.1
HAP1–E368Q 33.8 33.5 36.7
GPR32–T332P 24.4 29.1 23.4
FOXD4L1–R145C 12.5 16.3 14.1
FOLH1–R190W 0 11.3 11.7 16.5
FAP–E654D 2 10.1 7.2
EVPL–T1677S 14.1 0 0
DROSHA–E449A 0.5 0 0 6.5
DND1–E334K 0 10.7 10.7 11.2
DMXL1–V776F 44.3 37.3 35.9 38.8
DIS3–T773P 77.9 71.2 62.9 66.1
CSMD1–G3117Lfs*22 43.1 30.7 33.7
CLPTM1L–T33S 0.1 2.4 28.9 33.9
CEACAM19–Q61Lfs*70 0 39.5 28.2 25.2
CDRT1–I23N 15.8 12.7 14.8
C7–R222H 0 2.2 28.6 22.3
BRD2–P243Q 25.7 13.7 0.1 0
AGXT–L298M 46.9 34.7 36.5
A A B C A B C
A 27522_1 Primary
B 27522_3 Relapse-1
C 27522_4 Relapse-2
B
Earlier Time Point
Both Time Points
Later Time Point
Observed Neoantigen Mutations
10 20 30 40 50
MMRF 2089
MMRF 2039
MMRF 2126
MMRF 1157
MMRF 1079
MMRF 1433
MMRF 2373
MMRF 2015
MMRF 1309
MMRF 1285
MMRF 2401
MMRF 1931
MMRF 1587
MMRF 1656
MMRF 1627
MMRF 2194
MMRF 1700
MMRF 2017
MMRF 1639
MMRF 2490
MMRF 2122
MMRF 2083
MMRF 1179
MMRF 1049
MMRF 2419
MMRF 1790
MMRF 1783
MMRF 1686
MMRF 1978
MMRF 2087
MMRF 1659
MMRF 1380
MMRF 1992
MMRF 1496
C
UTRN–M394I 22.8 31 2.2 0
UNK–R157H 0 0 11.1 13.2
UHMK1–S131F 0 3.8 36.6 29.3
TSC1–P396S 0.9 0 23.3 21.5
STRN–K456T 25.9 49.3 44.4 43.1
ST6GALNC5–V83M 1 39.6
SPTBN4–T159I 27.1 28.9
SLIT3–H776Q 16.2 20.6
SLCO6A1–K577Q 59 56.3
SAMD1–G309V 0 0 22.1 16.1
RFC2–E35K 0 0.7 2.6 10.2
PSPC1–R295Kfs*23 3.1 8.9 2.6 1.3
PSPC1–E272Q 3.3 6 3.9 1
PPP2R2B–H65Y 16 5.9
POLD1–H142Y 0 10.2 0 0
PCDHA7–S354F 0.4 27.9
OR13G1–R299S 5.8 0
OR10S1–H67Q 2.9 15.6
OR10G9–G208C 0 24.7
OPHN1–K133Nfs*81 0 31.7
NUP155–H858_L859del 8.6 10 0 0
OTCH2–G292V 7.7 0 0
LRRC71–A223T 24.7 3.1
KRAS–G12R 0 0 44.9 24.7
KCNIP4–E74K 27.5 0
KCNC2–W448L 37 42.2
INSL4–E47K 0 17.3
GUCY1A3–F205V 0 42.5 42.7
GPR152–T4I 50.8 41.6
GMPR2–S106F 0 0.6 11.1 9.2
GLI3–S425R 0 13.8 0 0
FRG2B–V179L 2.3 32.9
ERBB3–R1309H 32.9 36.8
YNC1H1–D4338G 0.4 0 24 26.2
DSG4–N893Y 43.4 34.9
DPEP3–H473Y 13.4 0
DHRS7C–A283T 35.5 38.1
DGKA–S351I 0 0 0 35.9
CNGB3–T505K 0 29.8
CMTM1–L199F 66.6 0 38.1 38
CDK13–L1011F 0 0 18.1 20.5
CABIN1–N1252K 20.7 15.5 0 0
C15orf39–E974Q 0 0 19.7 19.3
C10orf12–D1026Y 44.4 37.4 43.2
AMH–R91G 28.7 0 2.4
ALG6–S347F 43.3 54.2 48.4 35.5
DARB2–R259H 40 57.1
Binding affinity
1
2
3
4
MMRF_1931_1 BulkRNA
MMRF_1931_1 WES
MMRF_1931_2 BulkRNA
MMRF_1931_2 WES
MMRF_1931_1
MMRF_1931_2

**Figure S6. Related to Figure 6**

**A**, Variant allele frequency (VAF) and expression pattern of neoantigens from patient 27522 across three time points. **B**, Expressed immunogenic peptides across timepoints along with disease progression. WES, Whole Exome sequencing. **C**, Predicted neoantigens for MMRF 1931 and the associated RNA and WES VAF from two time points.


A
log10TPM
Tissue-specific surface
Tissue-Nonspecific surface
Intracellular
SLAMF7
TNFRSF17
CD53
CD48
FCRL5
CD79B
SDC1
GPRC5D
ICAM3
CD38
DNAJC1
TNFRSF13B
LIME1
ATP8B2
MZB1
PIM2
POU2AF1
TXNDC11
IRF4
CPNE5
IL16
prevalence
average log10TPM
multiple_myeloma
lymphoma_Burkitt
lymphoma_DLBCL
AML
CML
T−cell_ALL
B−cell_ALL
leukemia_other
lymphoma_Hodgkin
lymphoma_other
chondrosarcoma
glioma
melanoma
upper_aerodigestive
bile_duct
kidney
colorectal
stomach
pancreas
urinary_tract
lung_NSC
ovary
endometrium
liver
breast
esophagus
medulloblastoma
lung_small_cell
neuroblastoma
prostate
osteosarcoma
other
mesothelioma
Ewings_Sarcoma
soft_tissue
thyroid


B
mRNA expression of TXNDC11 in malignant cell lines
mRNA expression (logTPM)


C
TXNDC11
expression
MMRF Pilot
WashU Cohort 1
WashU Cohort 2
Cell type
B Cell
Others
DC
Erythrocytes
Mast cells
Monocyte/ Macrophage
Neutrophils
NK
pDC
PCs
Platelet
T Cell

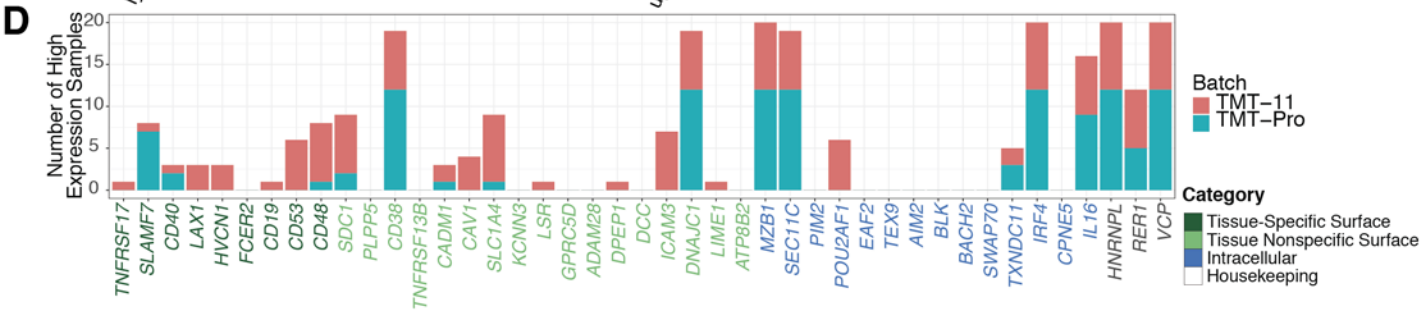

D
Number of High Expression Samples
Batch
TMT−11
TMT−Pro
Category
Tissue-Specific Surface
Tissue Nonspecific Surface
Intracellular
Housekeeping

**Figure S7. Related to Figure 7**

**A**, Bar chart showing average expression of candidate markers in CD138+ sorted MM BM samples in the MMRF CoMMpass study. Color of bars indicates the proportion of samples having genes with expression above 95 percentile across all genes. Heatmap showing averaged mRNA expression of candidate markers across all profiled cell lines for each tissue type (n=1061; CCLE accessed March 23rd, 2021). DLBCL, diffuse large B cell lymphoma; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; NSC, non–small cell. **B**, mRNA expression of TXNDC11 in malignant cell lines in CCLE. **C**, Bubble plot showing the normalized expression of TXNDC11 averaged by sample and cell type. Row corresponds to samples, colored by cohorts. **D**, Bar plot showing number of samples in which target protein expression surpasses the detected global median in that sample. Bars are colored by batch chemistry.