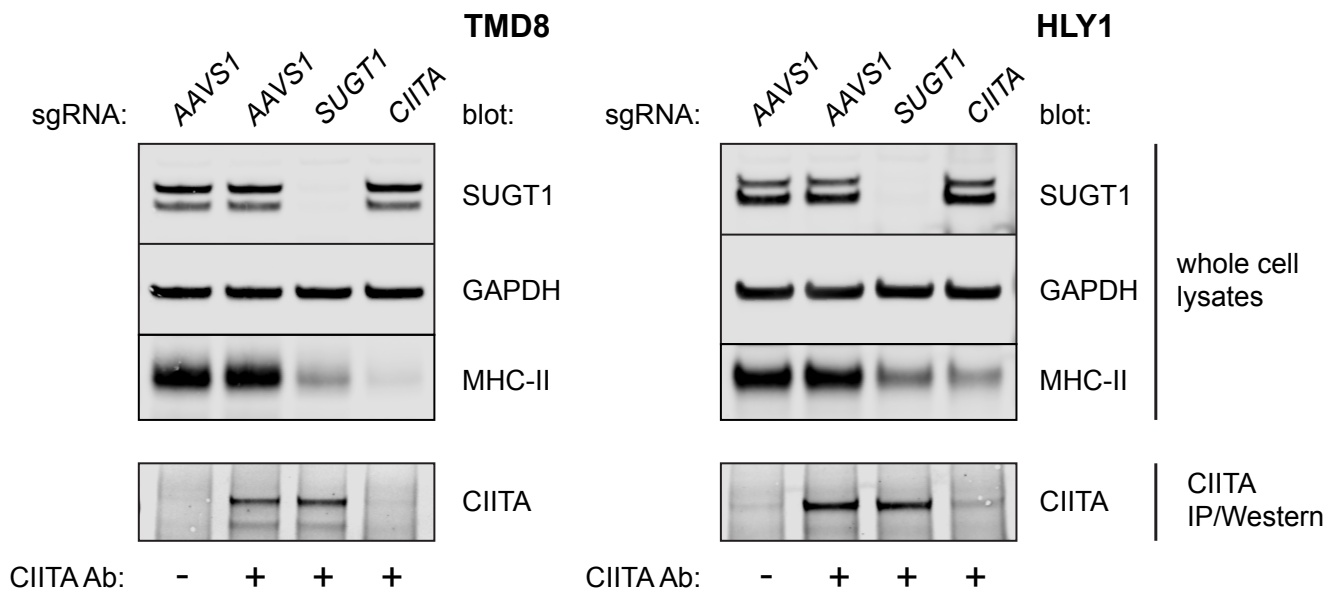


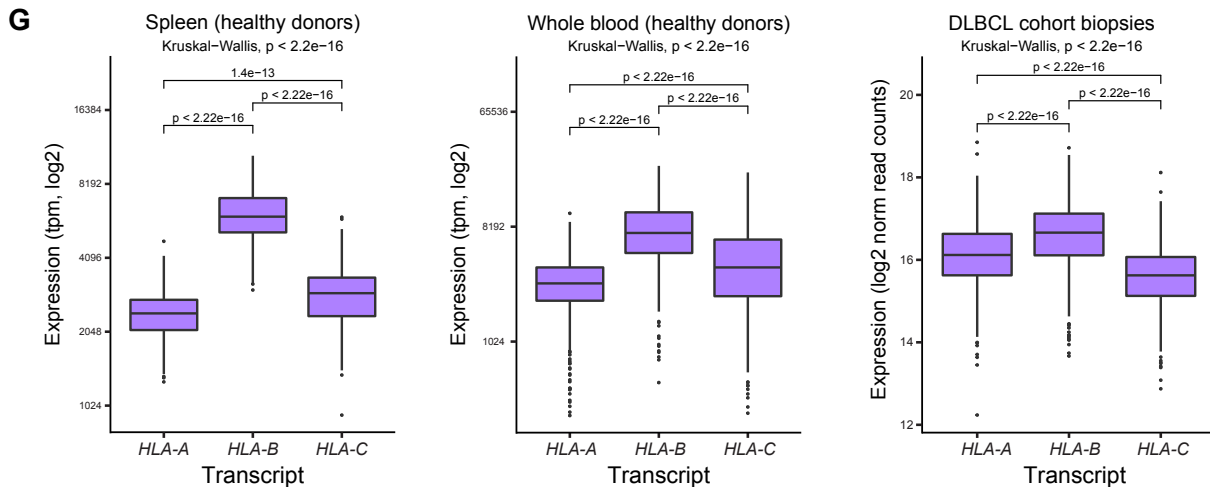
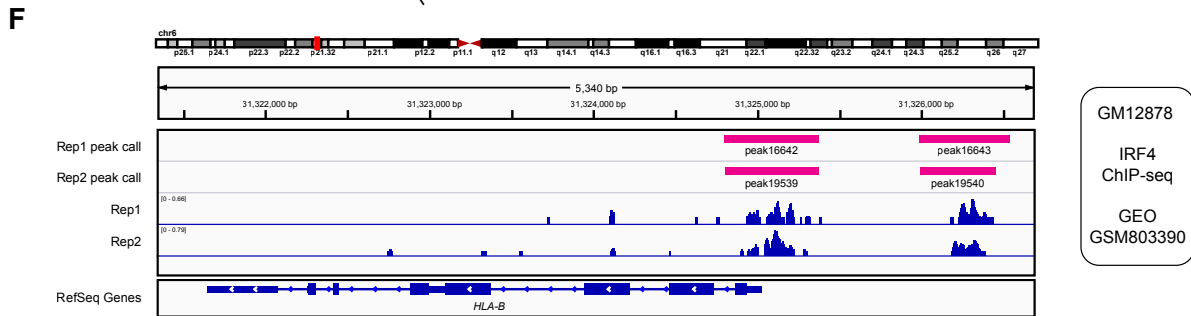
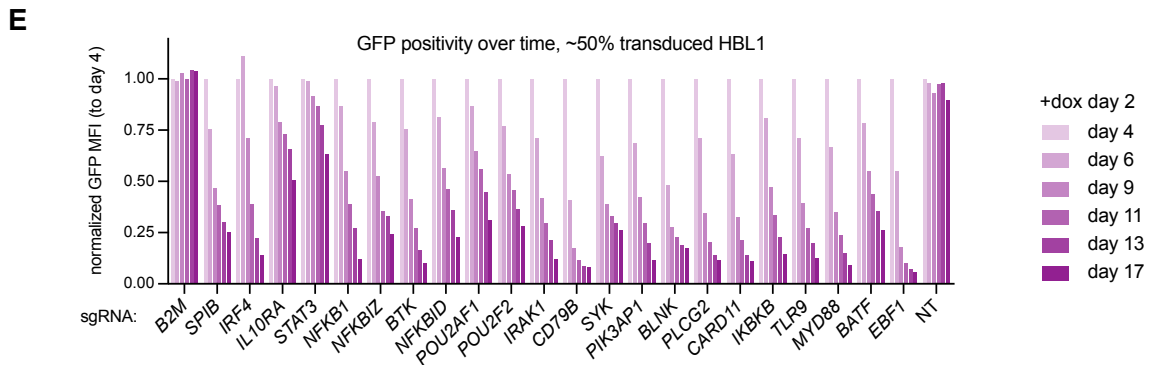
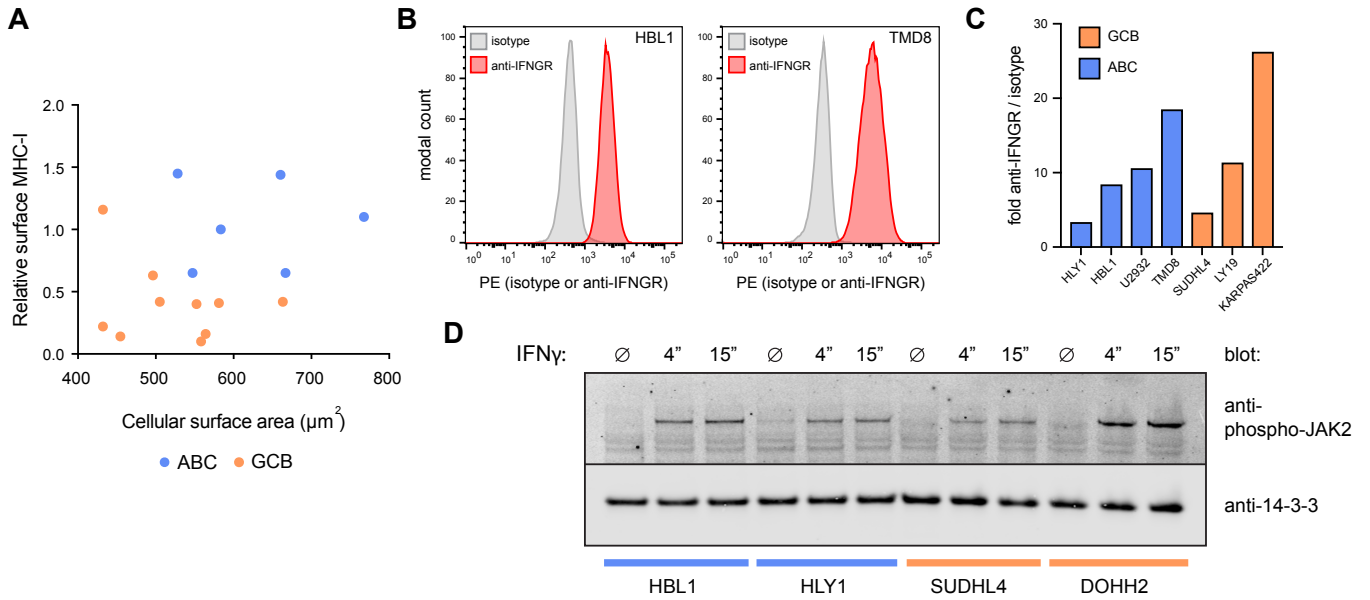
Supplemental Figure 1. HLA-A2 correlation with pan-MHC-I measurements and screen correlation with validation cell lines (related to Figures 1-3).

(A) HLA-A2 per CD147 measurements were plotted against W6/32 per CD147 staining across a number of genetically modified HBL1 cell lines; linear regression is depicted. (B) Individual sgRNA-expressing cell lines were measured for surface MHC-I per CD147 and plotted against the CRISPR screen segregation score for the same gene. p-values represent likelihood of non-zero slope. (C) Surface MHC-I from individual deletion cell lines were plotted against the $-\log(p\text{-value})$ of the same gene from STARS analysis of the CRISPR screens. p-values represent likelihood of a non-zero slope.



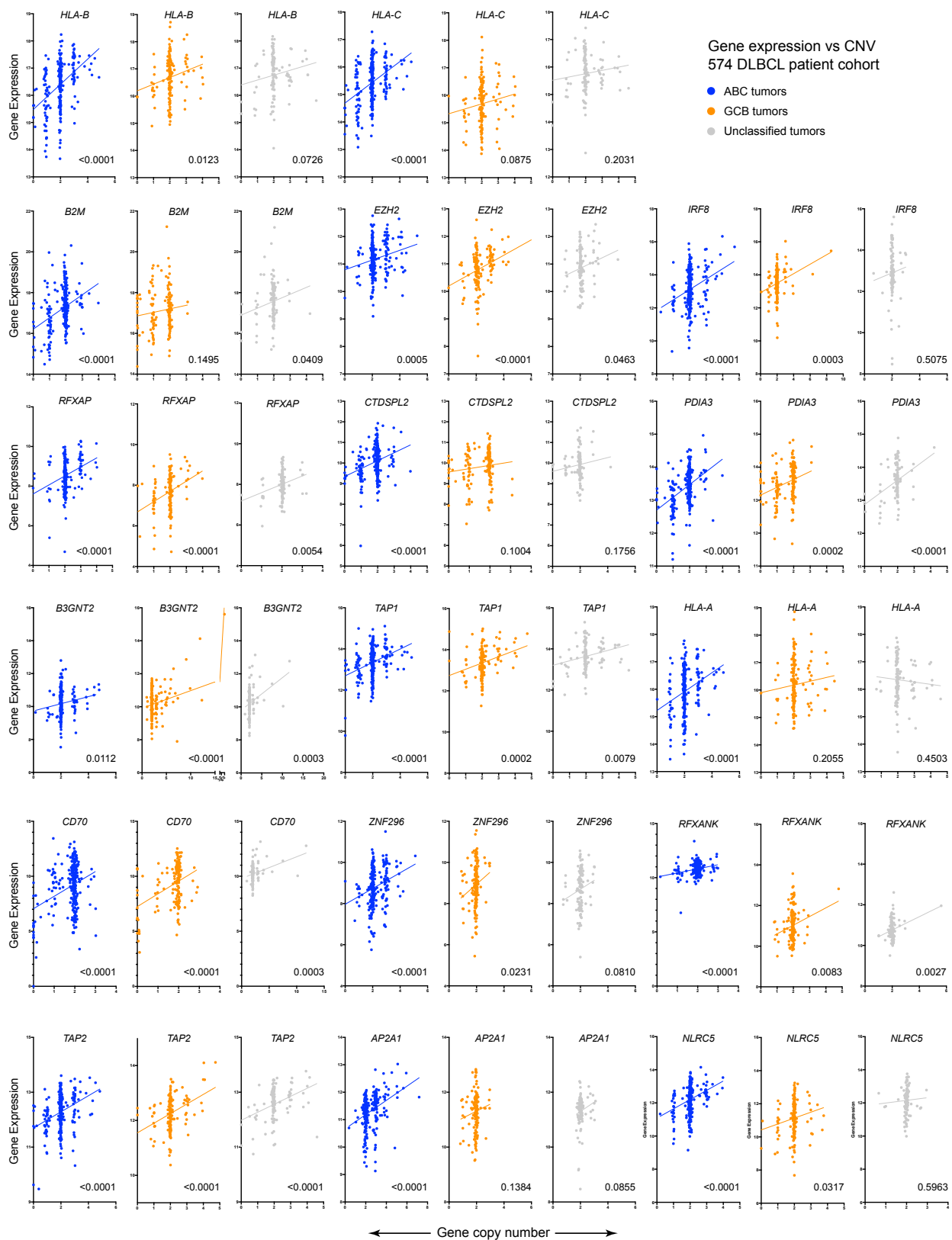
Supplemental Figure 2. SUGT1 controls steady state expression of MHC-II (related to Figure 4).

TMD8 and HLY1 cells were infected with sgRNA against *AAVS1* (negative control), *SUGT1*, or *CIITA*, and lysates were prepared for immunoblotting. For detection of *CIITA*, IP/western was required – unique antibodies were used for IP and blotting to confirm specificity.



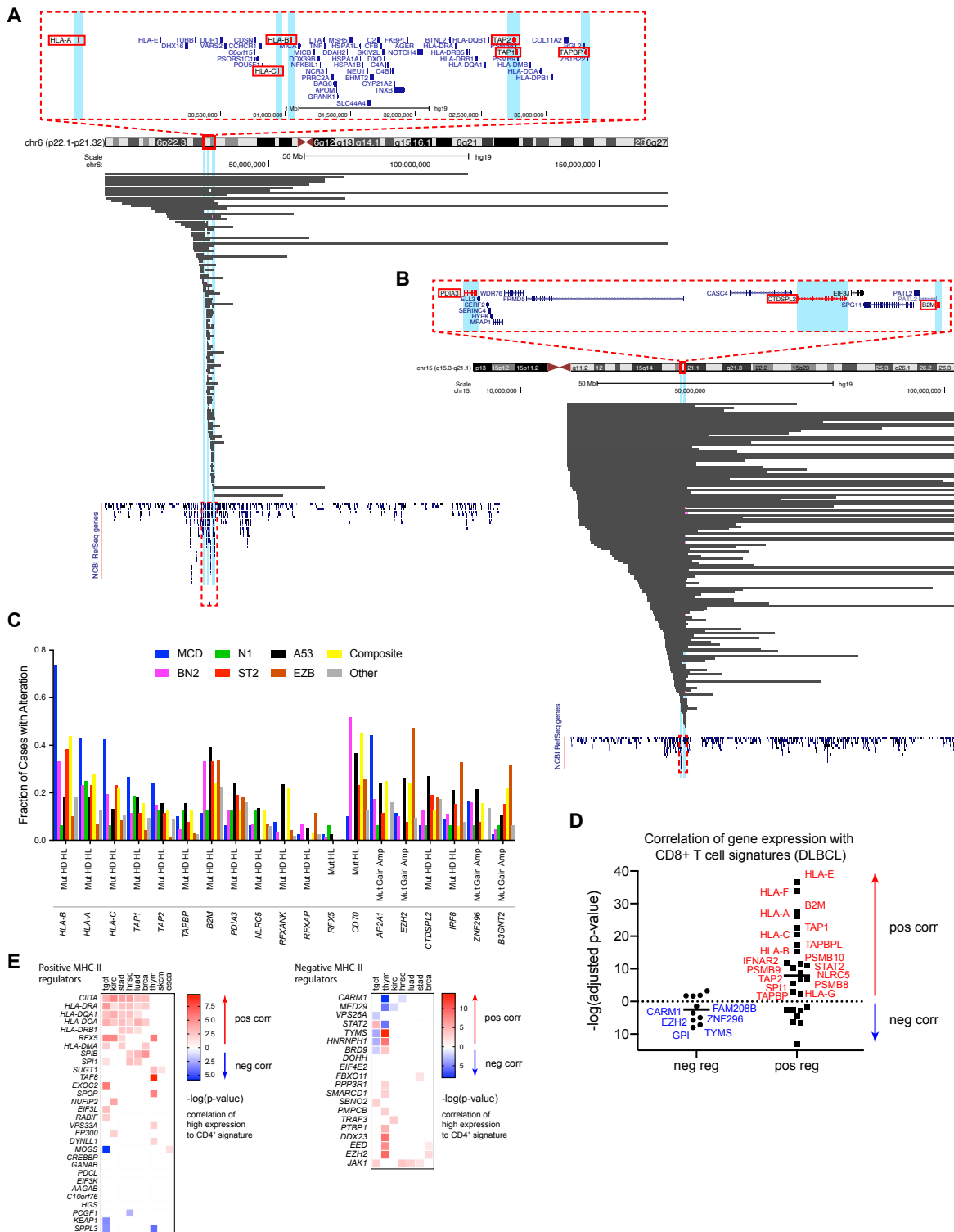
Supplemental Figure 3. ABC DLBCLs are not impaired for interferon signaling; sgRNA validation; *HLA-B* as a dominant class I gene in B cells (related to Figure 5).

(A) Cell surface area was estimated by diameter measurements made by an automated cell counter and plotted against relative surface MHC-I expression (normalized to HBL1 cells). GCBs orange; ABCs blue. **(B)** Representative staining of IFN γ receptor is shown for HBL1 and TMD8 relative to isotype control. **(C)** A panel of 7 DLBCLs all show IFN γ receptor expression over isotype control staining, regardless of ABC/GCB classification. **(D)** The indicated cells were treated with 500U/mL of recombinant IFN γ for 4 minutes, 15 minutes, or left untreated prior to cell lysate preparation and western blotting. **(E)** Genes previously identified as essential for ABC DLBCL (Phelan et al., 2018) were deleted in ~50% of HBL1 cells using a GFP⁺ sgRNA backbone. GFP MFI of the unselected population was monitored for 17 days. Normalized to day 4, all sgRNAs (except B2M and non-targeting controls) led to impaired GFP⁺ cell growth, indicating validation of the sgRNA. **(F)** *HLA-B* gene and promoter region from published IRF4 ChIP-seq datasets of lymphoblastoid GM12878 (Gene Expression Omnibus, GSM803390). **(G)** Boxplots of gene expression of *HLA-A*, *HLA-B*, and *HLA-C* across healthy donor spleen (GTEx), healthy donor whole blood (GTEx), and the DLBCL cohort, highlighting the relative dominance of *HLA-B* in these tissues.



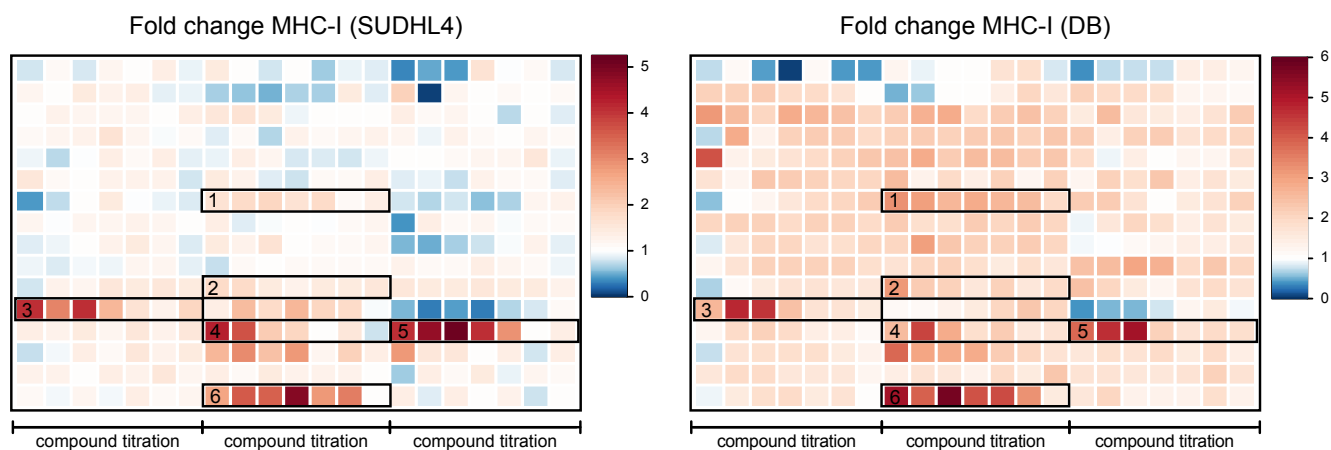
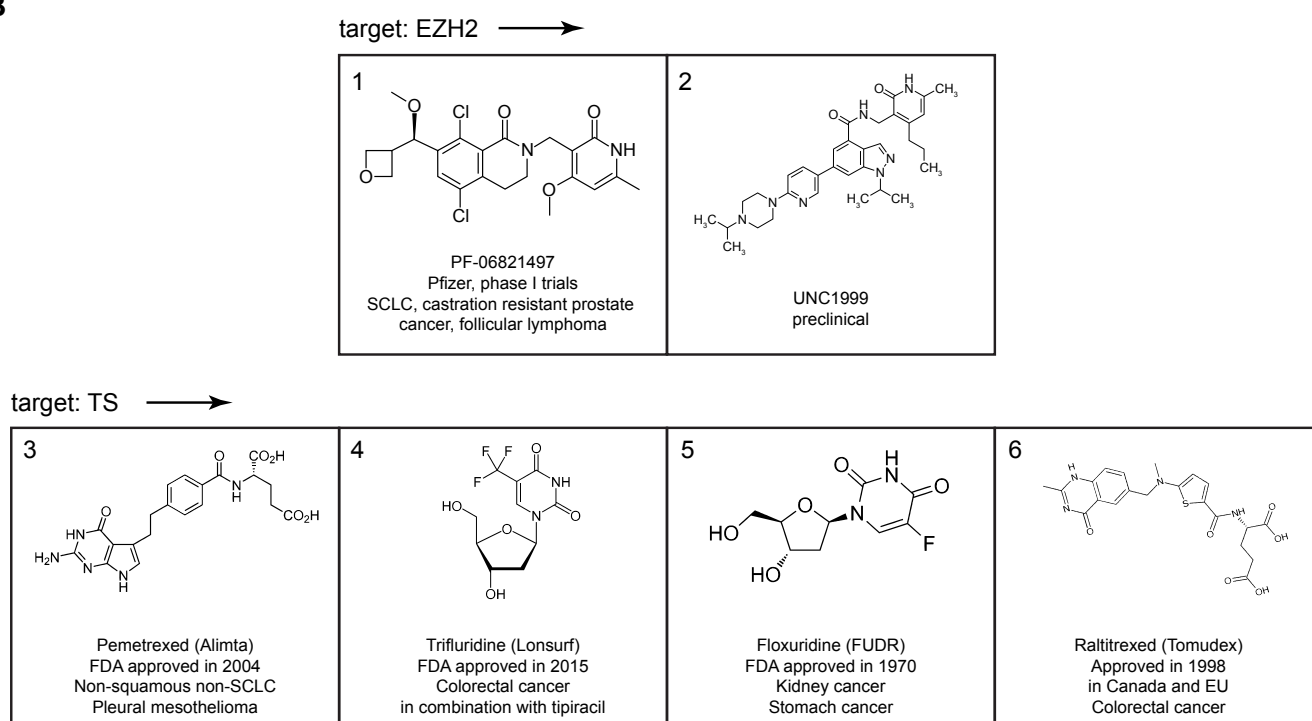
Supplemental Figure 4. Copy number variation correlation with gene expression in DLBCL patient tumors (related to Figure 6).

Gene copy number variation is plotted versus gene expression for DLBCL patient tumor samples, indicating significant mRNA alterations upon genetic copy number changes across most samples and genes. p-values represent likelihood of positive correlation.



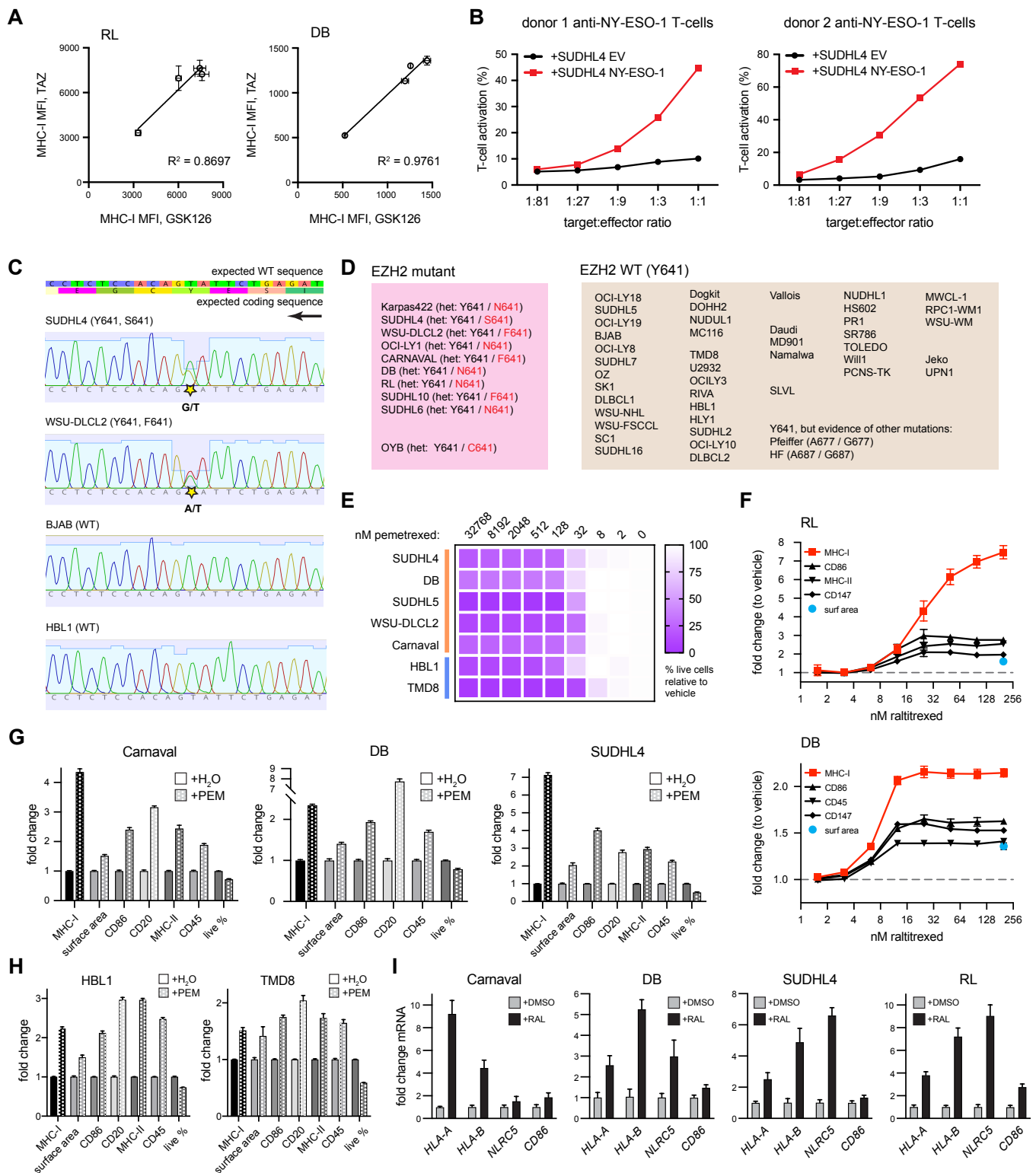
Supplemental Figure 5. Patient chromosomal deletions; subtype classifications of mutations; additional T cell signatures (related to Figure 6).

(A) Summary of chromosomal losses in patient tumors at the MHC locus, showing clear selection of losses in APP machinery. Each grey bar indicates a deleted section of chromosome 6 in a patient tumor sample. **(B)** Same as **A**, but with chromosome 15. **(C)** Frequency of mutation in indicated genes across DLBCL patient cohort, separated by LymphGen subclassification (Wright et al., 2020). Mut, mutation; HD, homozygous deletion; HL, heterozygous loss; gain, single copy gain; amp, multiple copy gain. **(D)** Correlation of CD8⁺ T cell signatures in the DLBCL cohort, split between validated positive and negative regulators of MHC-I. **(E)** Correlation of CD4⁺ T cell signatures with MHC-II regulators across TCGA cohorts.

A**B**

Supplemental Figure 6. Targeted drug screen for inhibitors of negative MHC-I regulators (related to Figure 7).

(A) Small molecules were selected based on consensus gene targets, cross referenced to a list of validated MHC-I negative regulators. 48 selected small molecules were dry-spotted into wells of 384-well plates in a 7-dose titration series, spanning 5.7nM – 23.5 μ M final concentrations upon cell plating. Cells were grown for 2 days prior to flow cytometry analysis of MHC-I surface expression. Fold change in surface MHC-I relative to vehicle controls is plotted by heatmap. Compounds 1-6, highlighted in black boxes, showed consistent, dose-dependent upregulation of MHC-I in both cell lines tested. (B) Chemical structures and clinical information related to compounds 1-6 above.



Supplemental Figure 7. Inhibition of EZH2 and TS (related to Figure 7).

(A) Treatment of DB or RL cells with increasing doses of tazemetostat or GSK126 for 7 days (DMSO, 0.4, 1.5, and 4 μ M) yields similar MHC-I inductions. (B) Confirmation of canonical NY-ESO-1 antigen presentation in transduced SUDHL4 lines. NY-ESO-1 specific primary human T cells were stained for 4-1BB upregulation after co-culture with SUDHL4 cells transduced with either empty vector (EV) or NY-ESO-1 at the indicated target:effector ratios. (C) Example chromatograms of targeted sequencing of EZH2 gDNA near Y641.

Homozygous Y641 lines and heterozygous Y641 with Y641N/S/F are clearly distinguished. **(D)** Summary of EZH2 mutational status at Y641 across a number of lymphoma tumor lines. **(E)** The indicated DLBCLs were cultured with serial dilutions of the TS inhibitor pemetrexed to determine growth inhibition after 48 hours. **(F)** RL and DB cells were treated with DMSO or serial dilutions of raltitrexed and stained for the indicated surface markers after 48 hours. **(G)** Cells were treated with pemetrexed (PEM) or vehicle control and stained for various surface markers after 48 hours (Carnaval, 500nM; DB, 100nM; SUDHL4, 500nM). Surface areas were calculated by automated diameter measurements. **(H)** Same as **G** but with ABC DLBCL lines HBL1 (100nM PEM) and TMD8 (30nM PEM). **(I)** Cells were treated with raltitrexed (RAL) or DMSO for 48 hours (Carnaval, 30nM; DB, 200nM; SUDHL4, 75nM; RL, 200nM), followed by RNA purification and qPCR. For entire figure, bar graphs represent mean with standard deviations, minimum n = 3.