Fig. S1

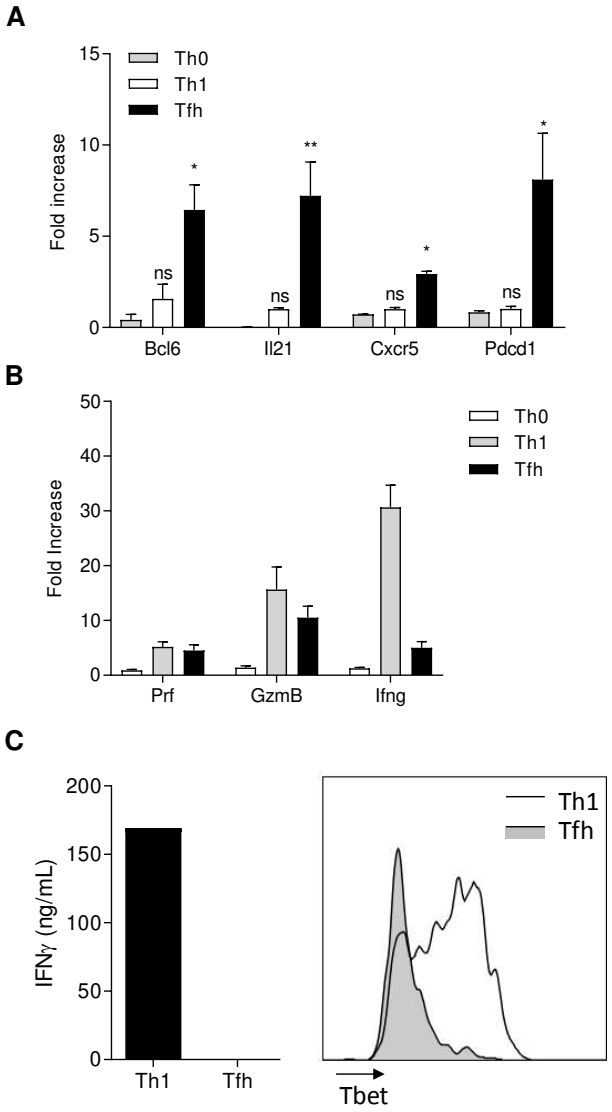


Fig.S1. Tfh phenotype. **A,** Bcl6, Il21, Cxcr5 and Pdcd1 mRNA expression in *in vitro* polarized Th0, Th1 and Tfh cells. **B**, (Perforin) Prf, (granzyme B) GzmB, and Ifng mRNA expression in *in vitro* polarized Th0, Th1 and Tfh cells. **C**, IFNγ (ELISA) and Tbet (ICS flow cytometry) expression in *in vitro* polarized Th1 and Tfh. Indicated values represent the mean ± SEM and are representative of at least three independent experiments; ns: not significant,* $p < 0.05$, ** $p < 0.01$, versus "Th0".

Fig. S2

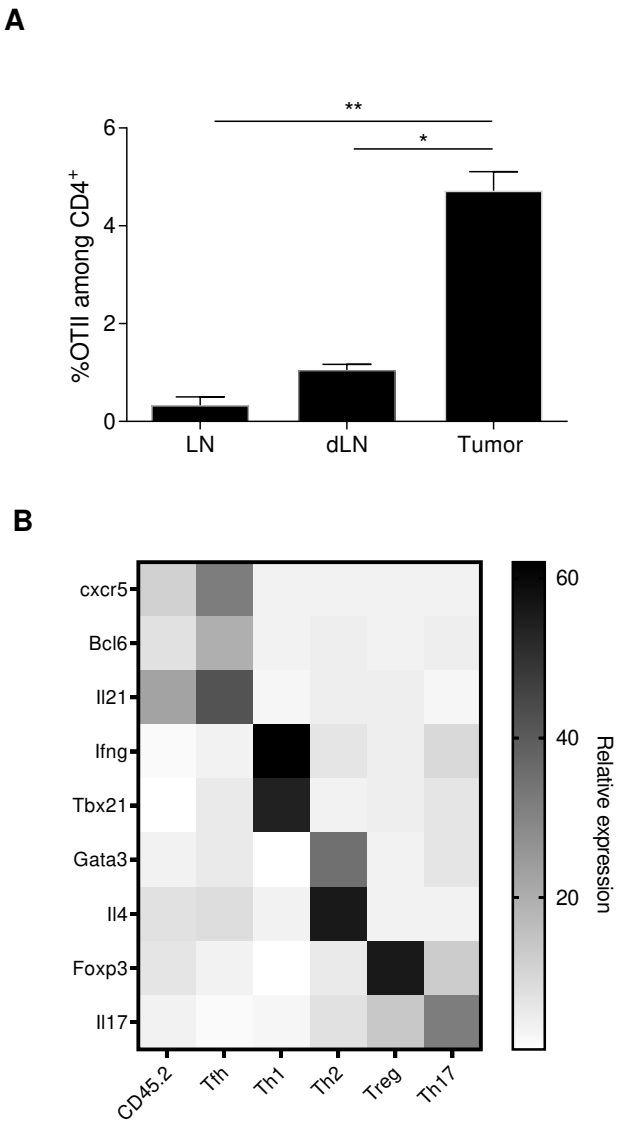


Fig. S2. T cell localization and gene expression after transfer. **A,** Percentage of CD45.2 cells among $CD4^+$ T cells measured by flow cytometry in non-draining lymph node (LN), draining lymph node (dLN) and tumor from MC38 tumor bearing mice. **B,** Cxcr5, Bcl6, Il21, Ifng, Tbx21, Gata3, Il4, Il17 and Foxp3 mRNA expression in CD45.2 sorted cells. Indicated values represent the mean ± SEM and are representative of at least three independent experiments; * $p < 0.05$, ** $p < 0.01$.

Fig. S3

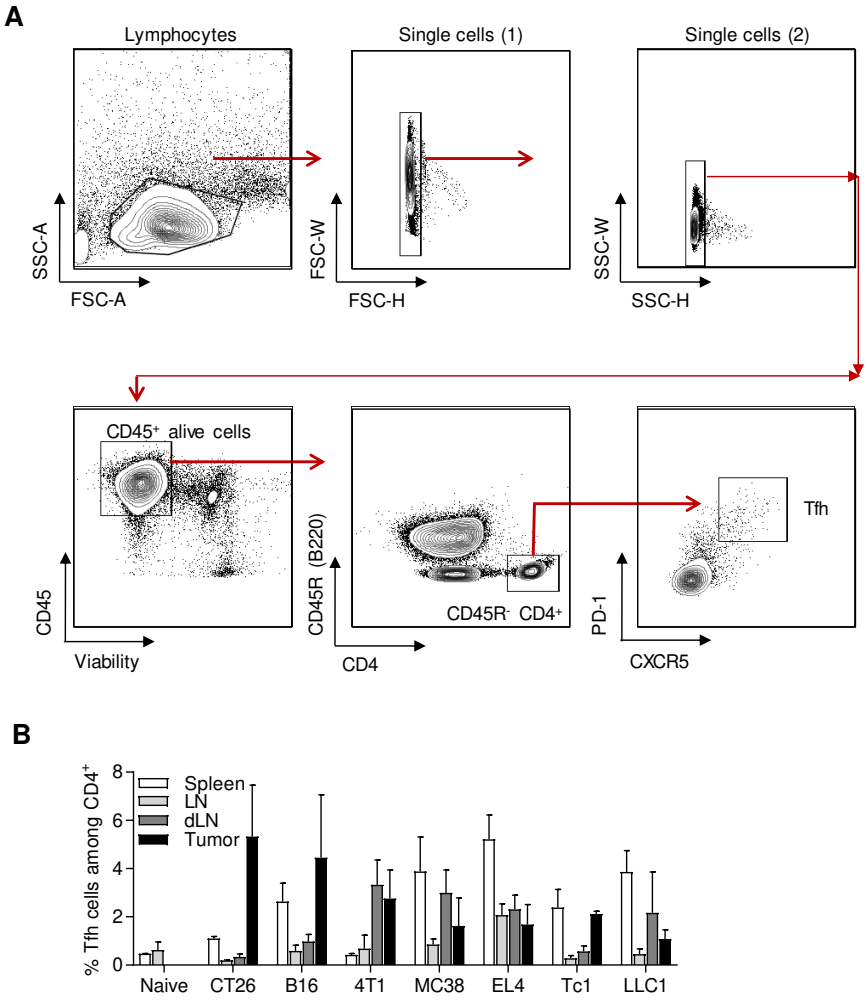


Fig. S3. Flow cytometry gating strategy to identify mouse Tfh cells. A, Flow cytometry gating strategy. **B**, Relative to figure 2B. Wild-type mice were inoculated with EL4 lymphoma, B16F-10 melanoma, LLC1 lung adenocarcinoma, Tc1 non-small cell lung cancer or MC38 colorectal carcinoma (C57BL/6 mice) or CT26 colorectal carcinoma, 4T1 triple negative breast cancer (Balb/c mice). When tumors reached 100-150 $mm^2$, the spleen, non-draining lymph node (ndLN), tumor-draining lymph node (dLN) and tumor were excised. The percentage of Tfh among $CD4^+$ T cells was analyzed by flow cytometry.

Fig. S4

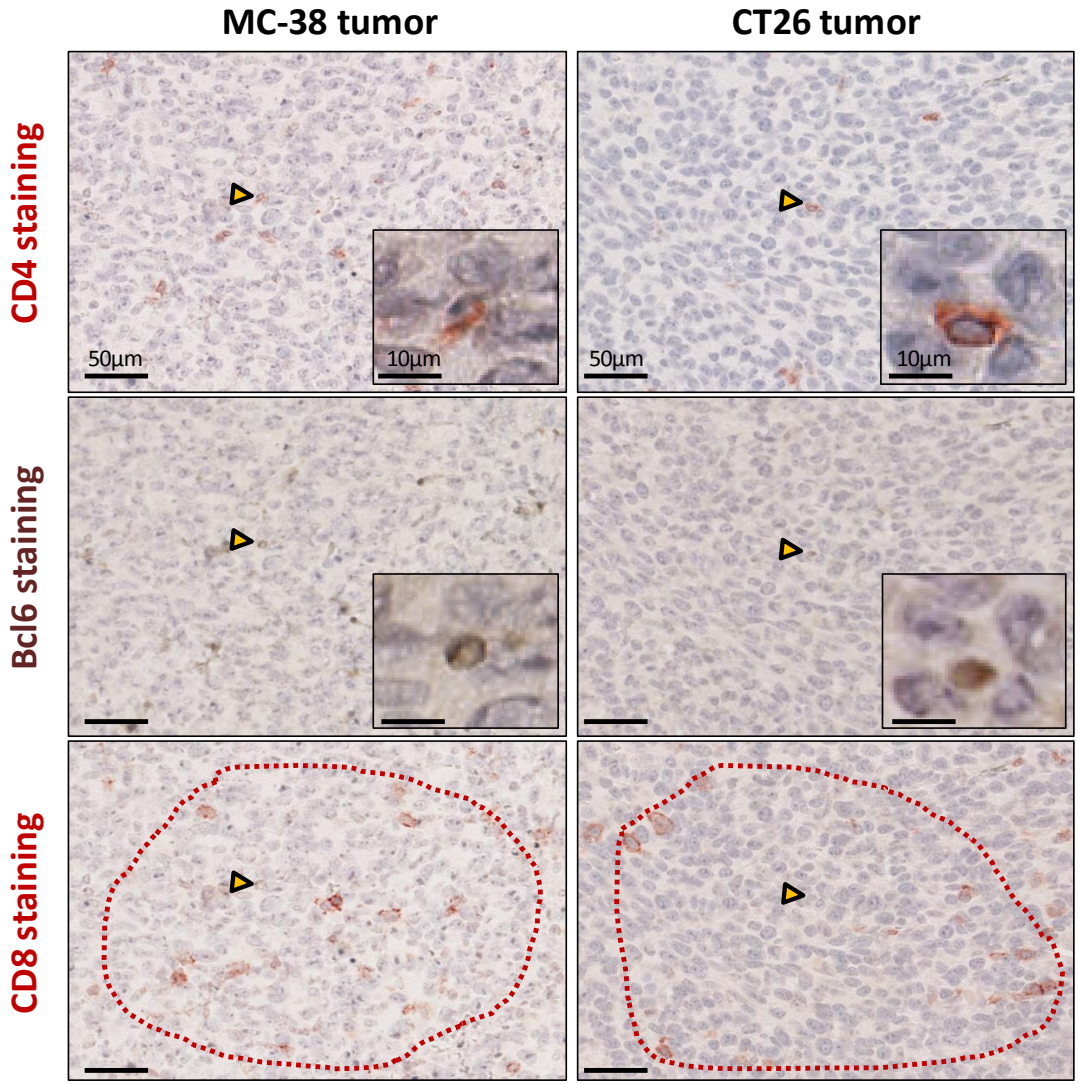


Fig. S4. Tfh localization within TLS. MC38 and CT26 tumor serial sections were stained with anti-CD4, anti-BCL6 and anti-CD8 antibodies and analyzed by immunohistochemistry. Arrow: enlarge image; dotted red line: TLS.

Fig. S5

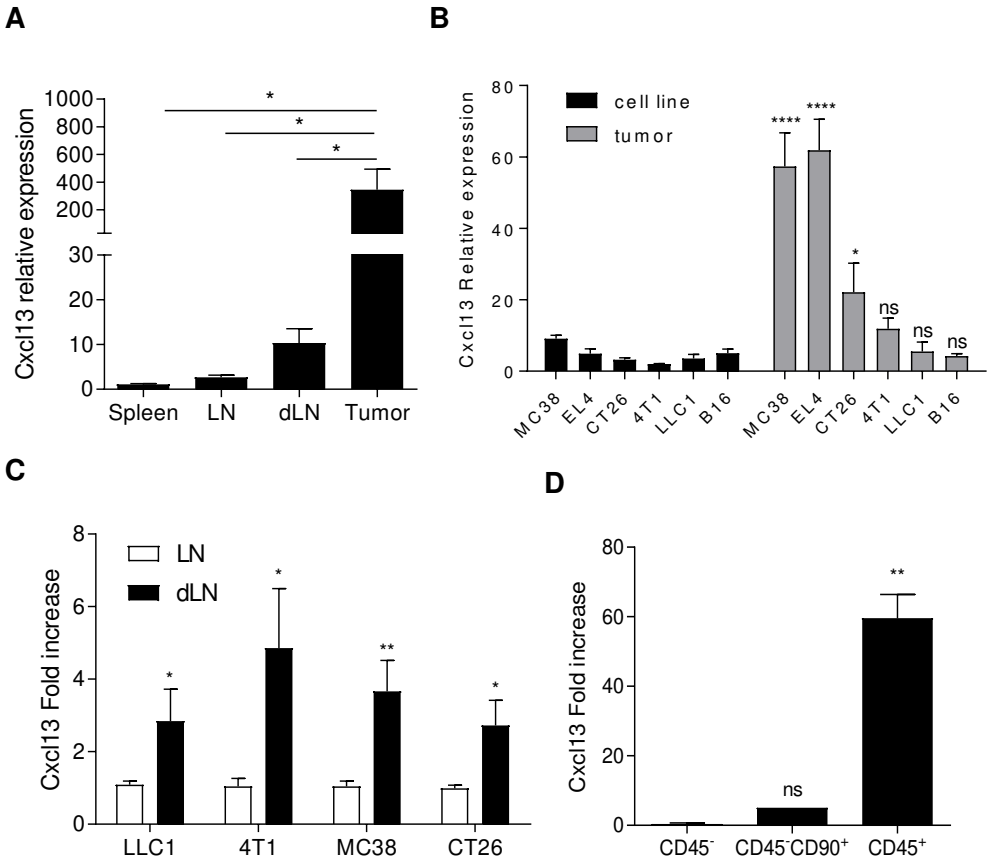


Fig. S5. Cxcl13 expression in tumor and non-tumor cells. Cxcl13 expression was analyzed by RT-PCR. **A,** Expression of Cxcl13 in $CD8^+$ cells sorted from Spleen, LN, dLN and tumor from MC38 tumor bearing mice. **B,** Expression of Cxcl13 in CT26, 4T1, B16-F10, MC38, LLC1 and EL4 cancer cell lines and in tumors from tumor bearing mice injected with CT26, 4T1, B16-F10, MC38, LLC1 and EL4 cell lines. **C,** Expression of Cxcl13 in LN and dLN from LLC1, 4T1, MC38 and CT26 tumor bearing mice. **D**, Cxcl13 expression in $CD45^-$ cells, $CD45^-$ $CD90^+$cells and $CD45^+$ cells sorted by flow cytometry from MC38 tumor bearing mice. Indicated values represent the mean ± SEM and are representative of at least three independent experiments; ns: not significant, * < 0.05, ** p < 0.01, **** p < 0.0001, versus "spleen" in **A** versus "cell line" in **B** and versus "$CD45^-$" in **D**.

Fig. S6

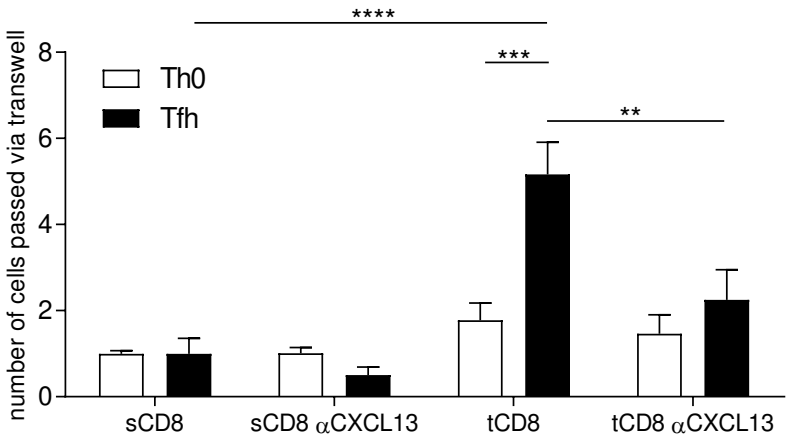


Fig. S6. Impact of CXCL13 on $CD8^+$ T cell migration. Number of Th0 or Tfh cells that have migrated through the Matrigel matrix loaded in the cell culture insert. The bottom of underneath wells was loaded with $CD8^+$ cells sorted from spleen (sCD8), tumor (tCD8) supplemented or not with anti-CXCL13. Th0 or Tfh migrated cells were stained with DAPI. Indicated values represent the mean ± SEM and are representative of at least three independent experiments; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig. S7

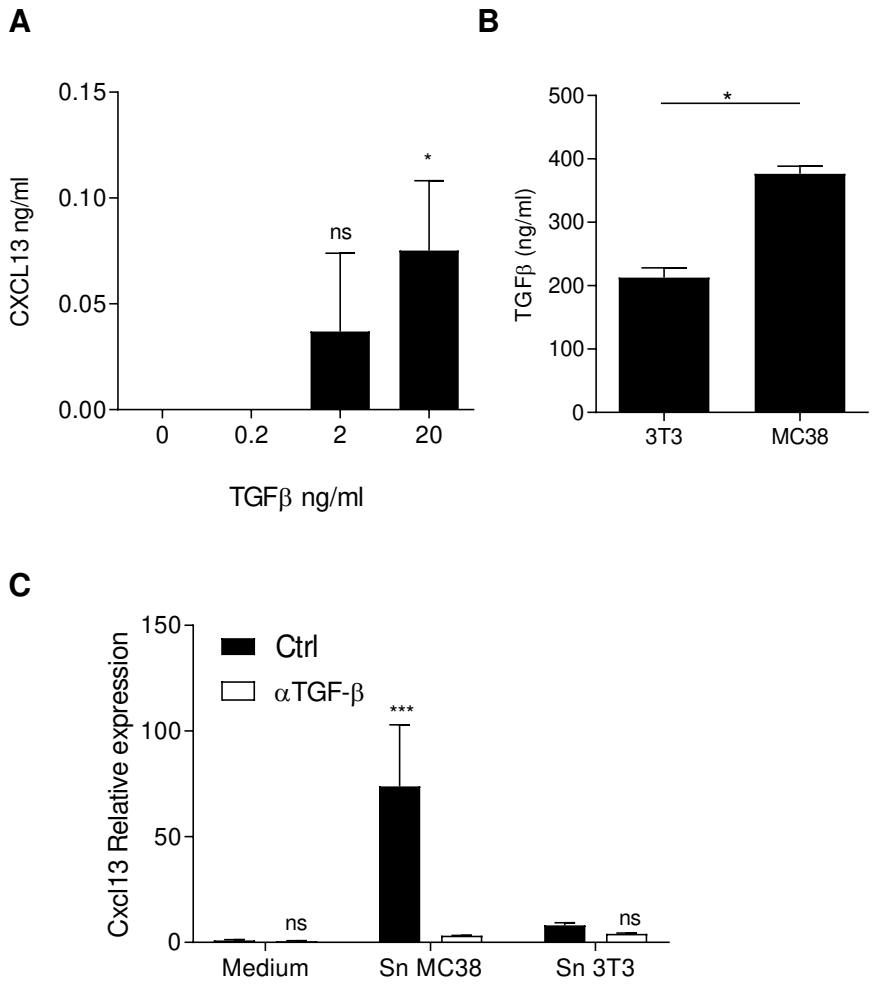


Fig. S7. Impact of TGF-β on CXCL13. **A**, The production of CXCL13 was analyzed by ELISA in supernatant of $CD8^+$ T cells activated with anti-CD3 / CD28 and treated by an increased dose of TGF-β for 72 hours. **B**, The production of TGF-β was analyzed by ELISA in MC38 cancer cells or 3T3 fibroblast-like cell supernatants. **C**, Expression of Cxcl13 was analyzed by RT-PCR in naive $CD8^+$ T cells activated with anti-CD3 / CD28 alone (medium) or with supernatant of MC38 or 3T3 cell lines for 48 hours. Indicated values represent the mean ± SEM and are representative of at least three independent experiments; ns: not significant,* $p < 0.05$, *** $p < 0.001$ versus "0" in **A** and versus Ctrl in **C**.

Fig. S8

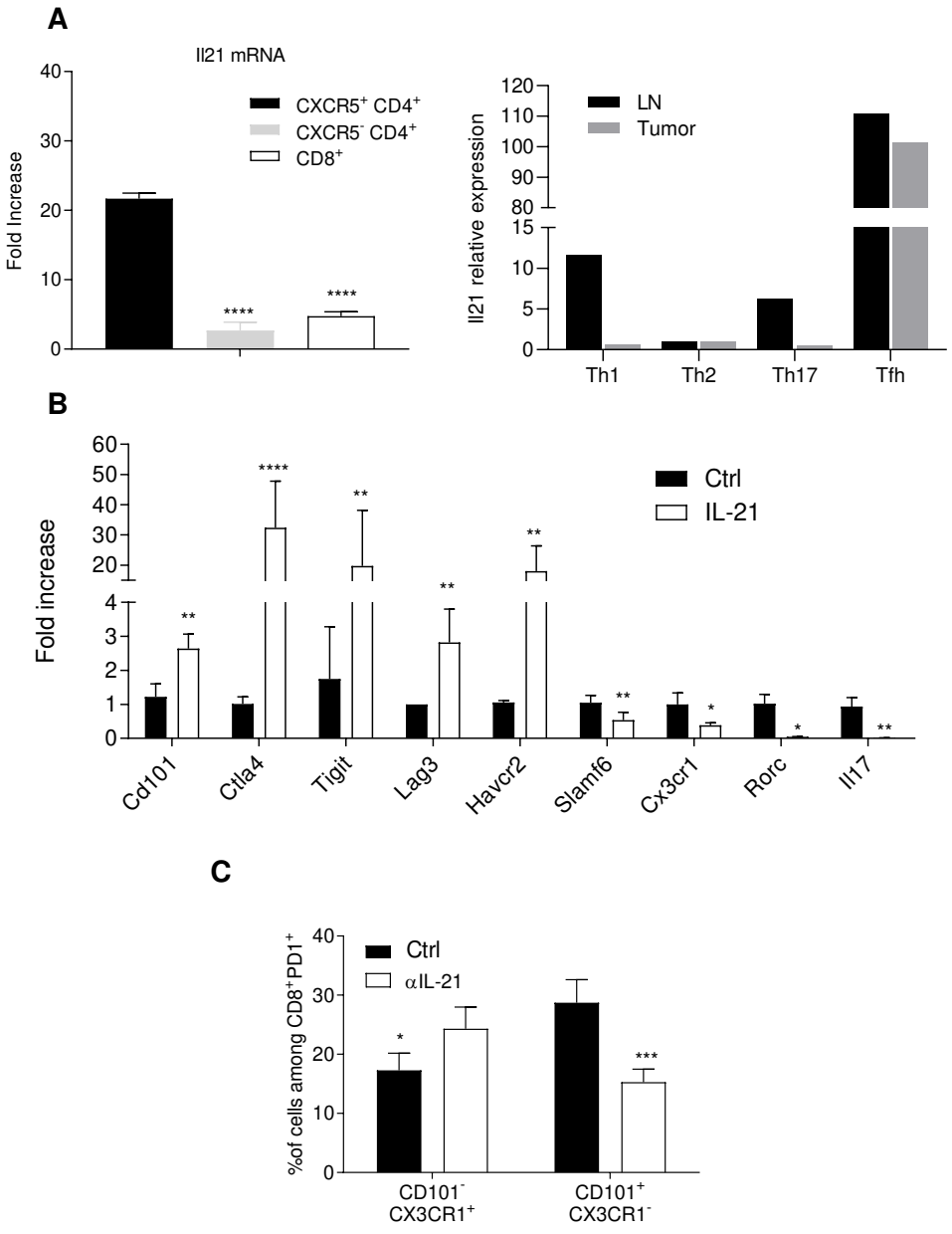


Fig. S8. IL-21 production by Tfh cells and IL-21 effect on CD8 differentiation. **A**, Expression of Il21 was analyzed by RT-PCR in Tfh ($CXCR5^+CD4^+$), $CXCR5^-CD4^+$, $CD8^+$ T cells (left panel – relative to $CXCR5^-CD4^+$) and in Th1, Th2, Th17 and Tfh cells (right panel – relative to Th2) from tumors of MC38 tumor bearing mice. **B**, Expression assessed by RT-PCR of

Cd101, Ctla4, Tigit, Lag3, Havcr2, Slamf6, Cx3cr1, Rorc and Il17 in naive $CD8^+$ T cells activated by anti-CD3 / CD28 stimulation and treated or not (Ctrl) with recombinant IL-21 (20ng/ml) for 48 hours. The relative gene expression was normalized to Actb. **C**, Analysis of CD101 and CX3CR1 markers by flow cytometry in $CD8^+PD1^+$ cells from tumor of MC38 tumor bearing mice treated or not with anti-IL-21 antibody. Indicated values represent the mean ± SEM and are representative of at least three independent experiments; ns: not significant,* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, versus "$CXCR5^+CD4^+$" in **A** and versus Ctrl in **B and C**.

Fig. S9

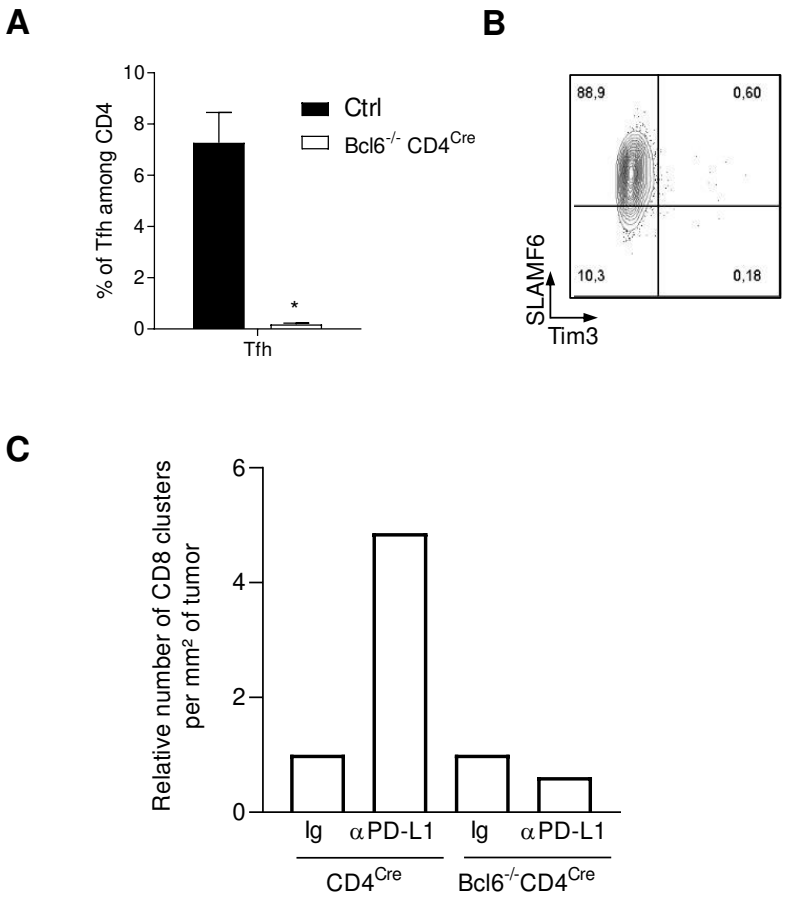


Fig. S9. Tfh cell amount in Bcl6$^{-/-}$ CD4$^{cre}$ mice and exhaustion marker expression in OTI CD8$^{+}$ T cells. **A**, Percentage of Tfh cells measured by flow cytometry in CD4$^{cre}$ mice and Bcl6$^{-/-}$ CD4$^{cre}$ mice. Indicated values represent the mean ± SEM and are representative of at least three independent experiments,* $p < 0.05$, versus Ctrl. **B**, SLAMF6, and Tim3 expression analyzed by flow cytometry in OTI CD8$^{+}$ PD-1$^{+}$ T cells activated for 3 days by anti-CD3 / CD28. **C**, MC38 tumor sections were stained with anti-CD8 antibodies and analyzed by immunohistochemistry. Values represent the relative number of CD8 T cell clusters per mm$^2$ on the tumor section.

Fig. S10

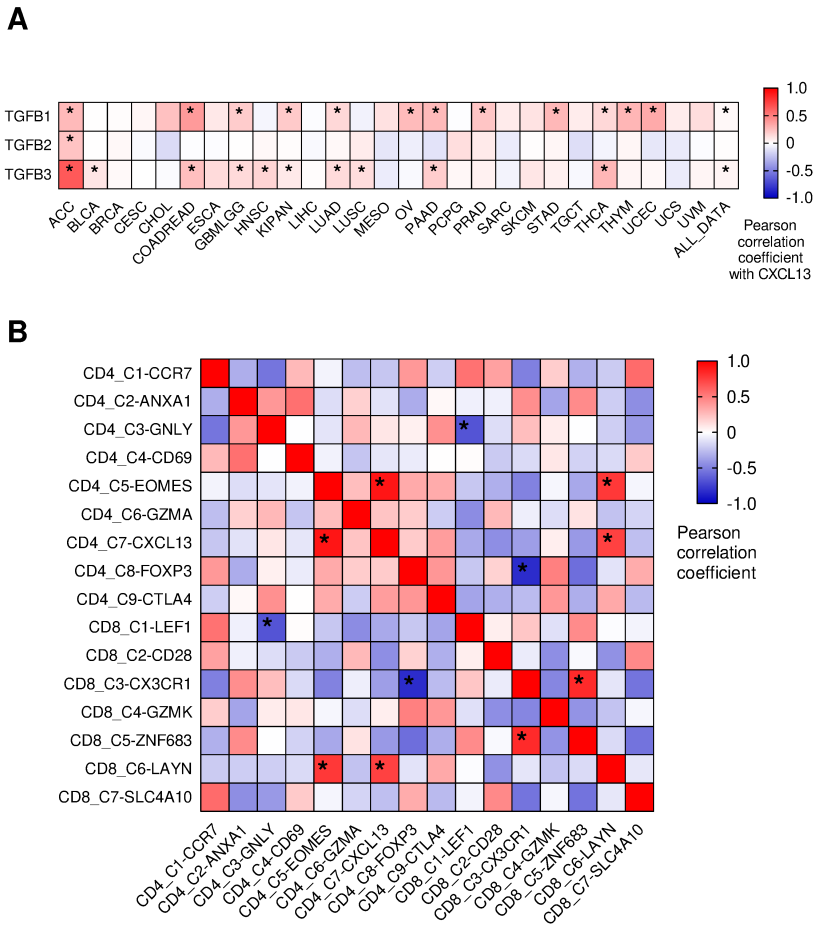


Fig. S10. Analysis of the correlation between CXCL13 and TGFB genes and between immune cell clusters. **A**. Heat map showing the Pearson correlation coefficients between CXCL13 and different genes representative of TGFB (TGFB1, TGFB2 and TGFB3) in each type of cancer provided by the TCGA. Blue cells represent a negative correlation and red cells a positive correlation between CXCL13 and each of the three genes representative of TGF$\beta$. **B.** Heat map showing the Pearson correlation coefficients between the abundance of cells in the different clusters characterized by Guo et al. from single-cell RNAseq data*: p-value < 0.05.

Fig. S11

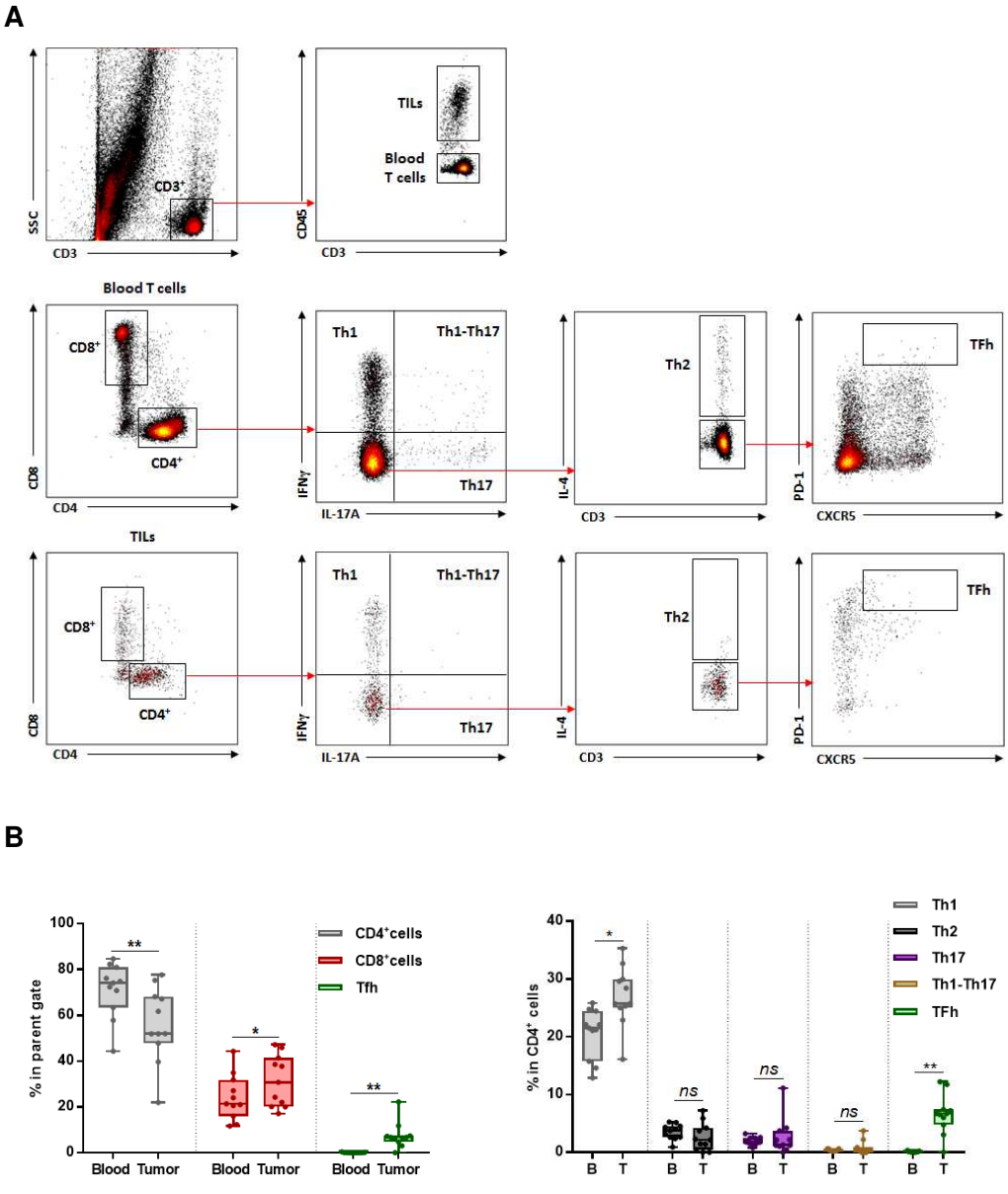


Fig. S11. Tumor samples from glioblastoma (n=2), ovarian (n=2) and breast cancer (n=7) patients were dissociated, stained with anti-CD45 and then were activated with whole blood with PMA/Iono. After activation, samples were stained with anti-IFNγ, anti-IL-21, anti-IL-4, anti-CXCL13, anti-IL-17A, anti-CD3, anti-CD4 and anti-CD8 antibodies and analysed by flow cytometry. **A.** Flow cytometry gating strategy to identify different subtypes of $CD4^+$ T

cells and $CD8^+$ T cells in blood and tumor samples. **B.** Frequency of $CD4^+$ and $CD8^+$ T cells among $CD45^+$ T cells in blood or tumor samples and frequency of Tfh cells ($CD4^+$ $CXCR5^{high}$ $PD1^{high}$) among $CD4^+$ T cells (left panel). Frequency of Th1 ($CD4^+$ $IFN\gamma^+$ $IL\text{-}17A^-$), Th17 ($CD4^+$ $IFN\gamma^-$ $IL\text{-}17A^+$), Th17-Th1 ($CD4^+$ $IFN\gamma^+$ $IL\text{-}17A^+$), Th2 ($CD4^+$ $IFN\gamma^-$ $IL\text{-}17A^-$ $IL\text{-}4^+$) and Tfh ($CD4^+$ $IFN\gamma^-$ $IL\text{-}17A^-$ $IL\text{-}4^-$ $CXCR5^{high}$ $PD1^{high}$) cells in blood and tumor (right panel).

Fig. S12

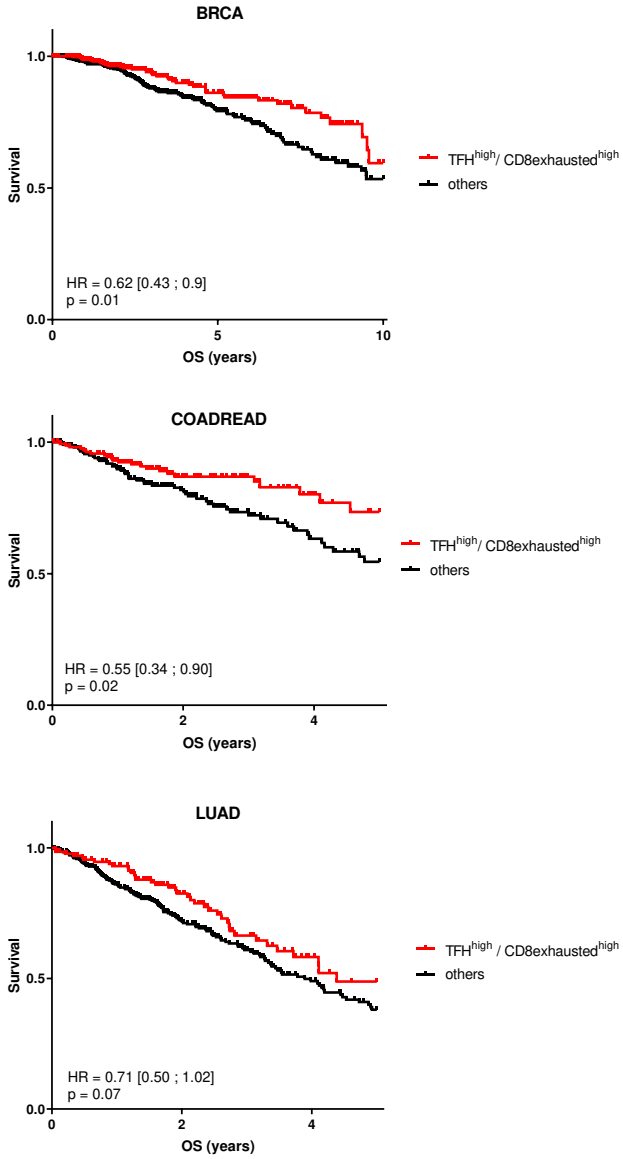


Fig. S12. Impact of Tfh/exhausted CD8 metagene on cancer patient survival. Kaplan-Meier curves of overall survival in breast invasive carcinoma (BRCA), Colon and Rectum adenocarcinoma (COADREAD) and Lung adenocarcinoma (LUAD). Red curves represent patients with high expression of Exhausted $CD8^+$ metagene and Tfh metagene and black curves patients with at least one metagene with low expression.

Fig. S13

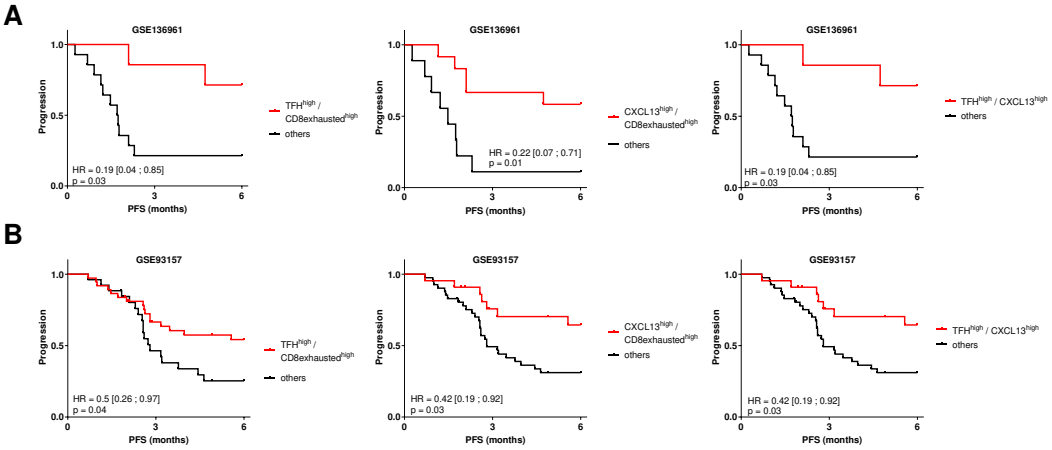


Fig. S13. Impact of Tfh/exhausted CD8 metagene and CXCL13 on cancer patient progression-free survival. Kaplan-Meier survival analysis for progression-free survival estimated for patients from GSE136961 (A) and GSE93157 (B). Red curves represent patients with high expression of two metagenes among Tfh, CXCL13 and Exhausted $CD8^+$ T cells and black curves represent other patients.

Table S1: Antibodies used in flow cytometry experiments on mice

| Target | Fluorochrome | Lot Number | Supplier |
|---|---|---|---|
| CD45 | BV395 | 30-F11 | BD Biosciences |
| CD8 | BUV805 | 53-6.7 | BD Biosciences |
| PD1 | Vioblue | HA2-7B1 | Miltenyi |
| TIM-3 | PE-Cy7 | RMT3-23 | Biolegend |
| Lag3 | BV650 | C9B7W | Biolegend |
| Tigit | APC-R700 | 1G9 | BD Horizon |
| Granzyme B | PE | REA-226 | Miltenyi |
| TNFα | BV510 | MP6-XT22 | Biolegend |
| IL-2 | FITC | JES6-5H4 | Biolegend |
| IFNγ | APC | XMG1.2 | BD Biosciences |
| Ki67 | BV510 | B56 | BD Biosciences |
| CD45 | Viogreen | REA737 | Miltenyi |
| CD4 | BUV805 | GK1.5 | BD Biosciences |
| CXCR3 | APC | REA724 | Miltenyi |
| ST2 | PE | DJ8 | MD Bioproducts |
| CCR6 | PE-Vio770 | REA277 | Miltenyi |
| CXCR5 | BV421 | L138D7 | Biolegend |
| PD1 | FITC, PE | REA802 | Miltenyi |
| B220 | APC-Cy7 | RA3-6B2 | BD |
| FoxP3 | PerCP | FJK-16S | Invitrogen |
| SLAMf6 | PE, Fitc | 13G3 | Miltenyi |
| CX3CR1 | BV711 | SA011F11 | BD Biosciences |
| CD45 | Viogreen | REA737 | Biolegend |
| BCL6 | PE-Cya7 | K112-91 | BD Biosciences |
| CD25 | Fitc | 7D4 | BD Biosciences |
| CD45r | APC-Cy7 | RA3-6B2 | BD Biosciences |
| CD278 | Alexa Fluor 6477E.17G9 | | BD Biosciences |
| CD11b Fitc | Fitc | M1/70 | BD Biosciences |
| CD11c Apc | Apc | HL3 | BD Biosciences |
| CD19 | APC-Cy7 | 1D3 | BD Biosciences |
| CD45.1 | Fitc | A20 | Biolegend |
| CD45.2 | BV510 | 104 | Biolegend |
| Fixable Viability Dye eFluor™ 780 | | | Invitrogen |
| BD Horizon™ Fixable Viability Stain 700 | | | BD |

Table S2: Primers used for RT-qPCR experiments

| | Fw | Rev |
|---|---|---|
| Ascl2 | TCCATCAAGCTTGCATTCAG | GAAGGTGCAAACGTCCACTT |
| Actb | ATGGAGGGGAATACAGCCC | TTCTTTGCAGCTCCTTCGTT |
| Bcl6 | AAAGGCCGGACACCAGTTTT | TCACGGGGAGGTTTAAGTGC |
| Blimp1 | GCAAAGAGGTTATTGGCGTGGT | CAGGCAGCCAGGTTTTGCTC |
| Cx3cr1 | CCATCTGCTCAGGACCTCAC | CACCAGACCGAACGTGAAGA |
| Cxcl13 | TTGTGTAATCGGCTTCCACA | ACGTTGAACTCCACCTCCAG |
| Cxcr5 | GCTGCAGCTATGAACTACCCA | CAGTTCCTTGTACAGGTCATCCA |
| Cxcr5 | GCTGCAGCTATGAACTACCCA | CAGTTCCTTGTACAGGTCATCCA |
| Eomes | CGGGACAACTACGATTCCATG | CTAGGGGAATCCGTGGGAGA |
| Gata3 | AGGATGTCCCTGCTCTCCTT | GCCTGCGGACTCTACCATAA |
| Granzyme B | GAAGCCAGGAGATGTGTGCT | GCACGTTTGGTCTTTGGGTC |
| Ifng | TGAGCTCATTGAATGCTTGG | ACAGCAAGGCGAAAAAGGAT |
| Il17 | TGAGCTTCCCAGATCACAGA | TCCAGAAGGCCCTCAGACTA |
| Il21 | AAAACAGGCAAAAGCTGCAT | TGACATTGTTGAACAGCTGAAA |
| Il4 | CGAGCTCACTCTCTGTGGTG | TGAACGAGGTCACAGGAGAA |
| Pdcd1 | CAGGCTGGGTAGAAGGTGAG | CATTCACTTGGGCTGTGCT |
| Perforine | TTGGTGGGACTTCAGCTTTCC | CCATACACCTGGCACGAACT |
| Rorα | CCCCTACTGTTCCTTCACCA | TGCCACATCACCTCTCTCTG |
| Slamf6 | AGTCACTCGTCCAATGCAGG | AGAGTATTCGGCCTCTCTGG |
| Tbx21 | ATCCTGTAATGGCTTGTGGG | TCAACCAGCACCAGACAGAG |
| Tcf1 | CGCAGAGACTTTTCCCGGAC | TGTTATGCAGCGGGGGTTGA |
| Tgfb | CAACCCAGGTCCTTCCTAAA | GGAGAGCCCTGGATACCAC |
| Tim3 | CCACTCCAATGTGGATAGCA | CAAGAACCCTAACCACGGAG |
| Tnfa | AGGGTCTGGGCCATAGAACT | CCACCACGCTCTTCTGTCTAC |
| Tox1 | GCCTCTCTGTTCCGTCTGAG | CTCCCCGTCAAACTTGTTGC |

Table S3: Table of metagene signatures

| Metagene | Genes |
|---|---|
| Tfh | CD200, FBLN7, ICOS, SGPP2, SH2D1A, PDCD1, TIGIT |
| Exhausted $CD8^+$ | CD244, EOMES, LAG3, PTGER4 |
| $CD8^+$ T cells | CD8A, CD8B |

Table S4: Log hazard ratio with confidence interval

| | CXCL13 | CD8$^+$ T cells | Exhausted CD8$^+$ | TfH |
|---|---|---|---|---|
| ACC | -0.767 [-1.524;-0.011] | -0.861 [-1.612;-0.109] | -0.606 [-1.366;0.153] | -1.028 [-1.805;-0.251] |
| BLCA | -0.421 [-0.757;-0.085] | -0.363 [-0.683;-0.043] | -0.598 [-0.893;-0.304] | 0.264 [-0.05;0.577] |
| BRCA | -0.515 [-0.887;-0.143] | -0.525 [-0.865;-0.185] | -0.371 [-0.715;-0.027] | -0.425 [-0.745;-0.104] |
| CESC | -0.544 [-1.019;-0.07] | -0.976 [-1.596;-0.355] | -0.887 [-1.412;-0.362] | -0.629 [-1.111;-0.148] |
| CHOL | -0.37 [-1.419;0.679] | -0.311 [-1.308;0.686] | -1.256 [-2.385;-0.127] | -0.941 [-1.882;0] |
| COADREAD | -0.586 [-1.011;-0.16] | -0.448 [-0.875;-0.022] | -0.492 [-0.923;-0.062] | -0.45 [-0.874;-0.027] |
| ESCA | -0.301 [-0.796;0.194] | 0.476 [-0.044;0.996] | -0.28 [-0.739;0.179] | -0.244 [-0.697;0.21] |
| GBMLGG | 0.438 [0.178;0.697] | 0.915 [0.663;1.167] | 1.141 [0.835;1.446] | 0.382 [0.126;0.637] |
| HNSC | -0.426 [-0.693;-0.16] | -0.373 [-0.645;-0.102] | -0.362 [-0.652;-0.071] | -0.535 [-0.806;-0.263] |
| KIPAN | 0.895 [0.634;1.155] | 0.589 [0.328;0.849] | 0.691 [0.388;0.995] | 0.418 [0.158;0.679] |
| LIHC | -0.206 [-0.552;0.139] | -0.57 [-0.926;-0.214] | -0.166 [-0.535;0.202] | 0.239 [-0.106;0.584] |
| LUAD | -0.405 [-0.739;-0.07] | -0.393 [-0.694;-0.092] | -0.325 [-0.623;-0.027] | -0.237 [-0.558;-0.085] |
| LUSC | -0.22 [-0.504;0.064] | -0.158 [-0.45;0.135] | -0.118 [-0.401;0.165] | -0.286 [-0.579;0.007] |
| MESO | -0.303 [-0.771;0.166] | 0.29 [-0.211;0.792] | -0.388 [-0.858;0.081] | -0.775 [-1.317;-0.232] |
| OV | -0.482 [-0.775;-0.189] | -0.216 [-0.525;0.092] | 0.139 [-0.154;0.433] | -0.243 [-0.548;0.061] |
| PAAD | 0.19 [-0.226;0.606] | 0.283 [-0.138;0.703] | -0.4 [-0.872;0.072] | -0.628 [-1.111;-0.145] |
| PRAD | -0.625 [-1.898;0.648] | -0.706 [-2.061;0.649] | -1.223 [-2.783;0.337] | -1.446 [-2.803;-0.09] |
| SARC | -0.441 [-0.848;-0.033] | -0.643 [-1.056;-0.229] | -0.48 [-0.887;-0.073] | -0.442 [-0.855;-0.028] |
| SKCM | -0.749 [-1.484;-0.015] | -0.853 [-1.592;-0.115] | -0.867 [-1.631;-0.103] | 0.308 [-0.472;1.087] |
| STAD | -0.346 [-0.662;-0.03] | 0.148 [-0.175;0.472] | -0.296 [-0.624;0.031] | -0.392 [-0.741;-0.044] |
| THCA | -0.518 [-1.507;0.47] | -0.745 [-1.733;0.244] | -0.794 [-1.782;0.195] | 0.725 [-0.531;1.981] |
| UCEC | -1.15 [-1.954;-0.347] | -0.74 [-1.44;-0.039] | -0.495 [-1.21;0.22] | -0.554 [-1.255;0.147] |
| UCS | -0.79 [-1.581;0.001] | -0.448 [-1.243;0.347] | 0.741 [0.049;1.433] | 0.428 [-0.297;1.154] |
| UVM | 2.069 [1.141;2.997] | 2.025 [0.901;3.15] | 1.408 [0.546;2.271] | -0.448 [-1.338;0.441] |
| ALL DATA | 0.209 [0.132;0.286] | -0.188 [-0.266;-0.111] | 0.127 [0.045;0.208] | -0.109 [-0.193;-0.026] |
| NSCL | -0.924 [-1.911;0.063] | -0.540 [-1.397;0.317] | -1.037 [-1.874;-0.200] | -0.331 [-1.180;0.518] |