Figure S1: Anti-HVEM therapy in humanized mice. (A) Mean tumor volume (± SEM) of the PC3 prostate cancer cell line in non-humanized NSG mice at the indicated time after treatment initiation. Arrows indicates days of the injection of the anti-HVEM mAb. Number of mice are indicated in brackets. The p value is the result of a linear regression analysis testing the null hypothesis that the two slopes are identical. Results are compiled from 3 independent experiments. **(B)** Expression of HVEM on the MDA-MB-231 breast cancer cell line (MDA) by flow cytometry. Pale grey histogram is from the FMO control. Mean tumor volume (± SEM) of MDA-MB-231 cells in humanized mice treated at the indicated times with the anti-HVEM mAb (arrows). Number of mice included in the study are indicated in brackets. Results are compiled from 2 independent experiments. **(C)** Expression of HVEM on the Gerlach melanoma cell line by flow cytometry. Pale grey histogram is from the FMO control. Mean tumor volume (± SEM) of Gerlach cells in humanized mice treated at the indicated times with the anti-HVEM mAb (arrows). Number of mice included in the study are indicated in brackets. Results are compiled from 2 independent experiments.

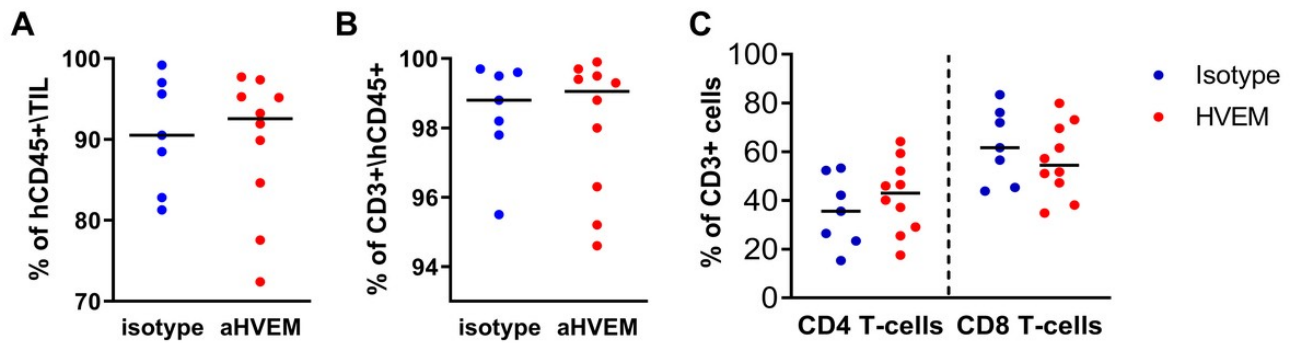**Figure S2: T cell landscape in PC3 tumor of humanized mice.** (A) Frequencies of human CD45+ cells among all TILs collected from PC3 tumors of humanized mice at D21 post treatment initiation. (B) Frequencies of CD3+ cells among human CD45+ TILs (B) and of CD4+ or CD8+ cells in CD3+CD45+ cells (C) in the same conditions. Each dot is a mouse. Results are cumulative of 2 independent experiments.
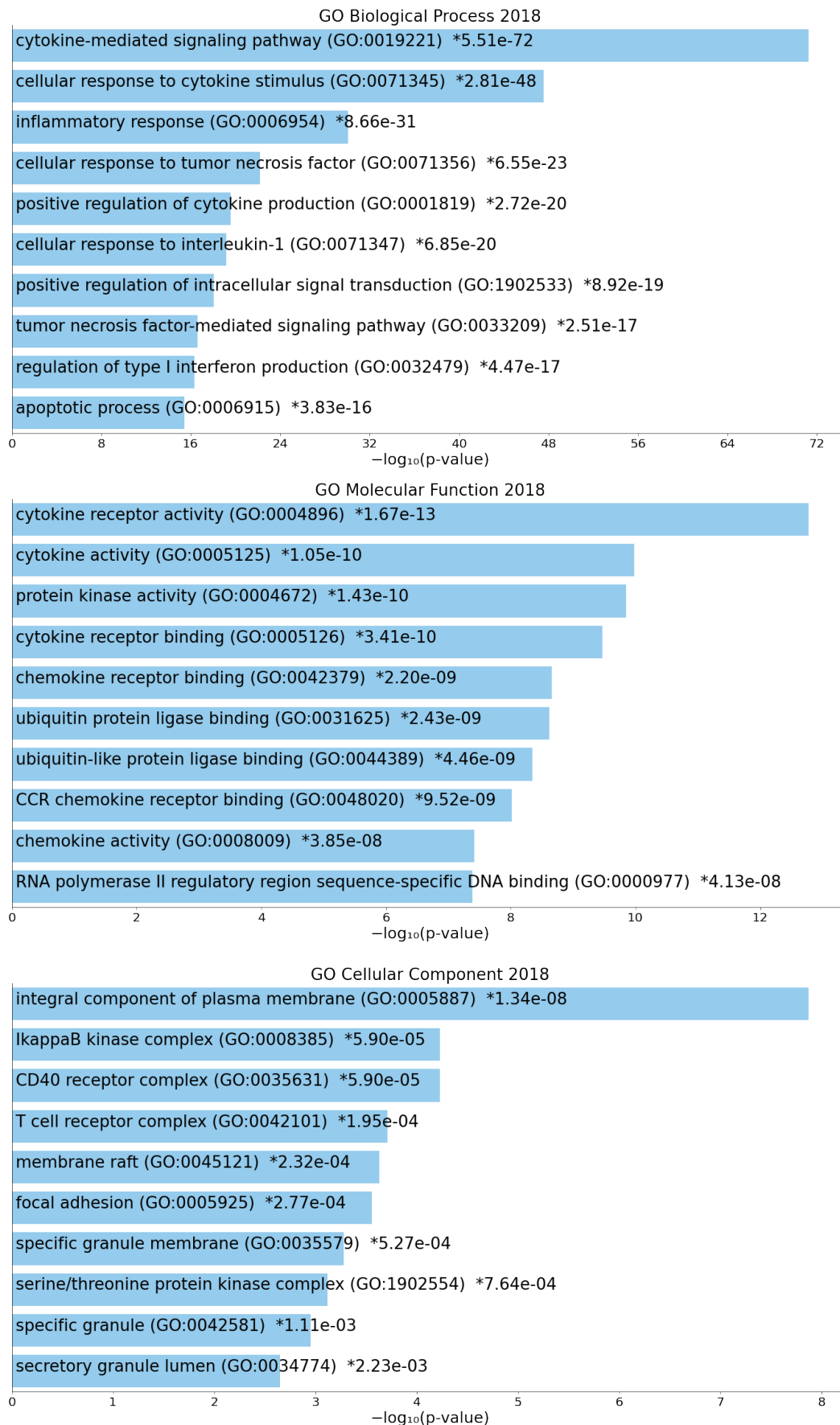
GO Biological Process 2018

- cytokine-mediated signaling pathway (GO:0019221) *5.51e-72
- cellular response to cytokine stimulus (GO:0071345) *2.81e-48
- inflammatory response (GO:0006954) *8.66e-31
- cellular response to tumor necrosis factor (GO:0071356) *6.55e-23
- positive regulation of cytokine production (GO:0001819) *2.72e-20
- cellular response to interleukin-1 (GO:0071347) *6.85e-20
- positive regulation of intracellular signal transduction (GO:1902533) *8.92e-19
- tumor necrosis factor-mediated signaling pathway (GO:0033209) *2.51e-17
- regulation of type I interferon production (GO:0032479) *4.47e-17
- apoptotic process (GO:0006915) *3.83e-16

$-\log_{10}$(p-value)

GO Molecular Function 2018

- cytokine receptor activity (GO:0004896) *1.67e-13
- cytokine activity (GO:0005125) *1.05e-10
- protein kinase activity (GO:0004672) *1.43e-10
- cytokine receptor binding (GO:0005126) *3.41e-10
- chemokine receptor binding (GO:0042379) *2.20e-09
- ubiquitin protein ligase binding (GO:0031625) *2.43e-09
- ubiquitin-like protein ligase binding (GO:0044389) *4.46e-09
- CCR chemokine receptor binding (GO:0048020) *9.52e-09
- chemokine activity (GO:0008009) *3.85e-08
- RNA polymerase II regulatory region sequence-specific DNA binding (GO:0000977) *4.13e-08

$-\log_{10}$(p-value)

GO Cellular Component 2018

- integral component of plasma membrane (GO:0005887) *1.34e-08
- IkappaB kinase complex (GO:0008385) *5.90e-05
- CD40 receptor complex (GO:0035631) *5.90e-05
- T cell receptor complex (GO:0042101) *1.95e-04
- membrane raft (GO:0045121) *2.32e-04
- focal adhesion (GO:0005925) *2.77e-04
- specific granule membrane (GO:0035579) *5.27e-04
- serine/threonine protein kinase complex (GO:1902554) *7.64e-04
- specific granule (GO:0042581) *1.11e-03
- secretory granule lumen (GO:0034774) *2.23e-03

$-\log_{10}$(p-value)

Figure S3: Enrichment analysis in TILs of anti-HVEM-treated mice. A list of DEG up regulated by the anti-HVEM treatment in CD45+ TILs was entered in Enrichr and analyzed with Appyter. The top 10 ontologies in each of the indicated categories (Biological process, Molecular function and Cellular component) are represented according to their p value from an exact Fisher test embedded in the application. A star denotes an adjusted p value inferior to 0.05.