**Supplemental Figures**

**Figure S1. B3 binds to PD-L1 on multiple tumor types.** (**A**) flow cytometry using B3 or commercial αPD-L1 on IFNγ treated and untreated tumor cell lines. B16 (melanoma), CT26 (colon adenocarcinoma), MDAC8 (pulmonary adenocarcinoma), Panc02 (pancreatic adenocarcinoma). (**B**) flow cytometry on IFNγ treated B16 melanoma using the indicated detection and blocking VHH or antibody as indicated. (**C**) B3 and αPD-L1 dose-response binding by flow cytometry on IFNγ treated and untreated B16 melanoma.

**Figure S2. In vitro killing of IFNγ treated B16-ova cells by activated OT-I T cells is inhibited by PD-L1.** (**A-B**) B16 or B16-ova cells treated for 18 hours with IFNγ (20 ng/mL) were washed to remove the IFNγ and were incubated with CD3/CD28 activated OT-I T cells and cultured for 48 hours in the presence of B3 or αPD-L1 as indicated. (**A**) Comparison of OT-I mediated killing of wild-type (WT) and ovalbumin-expressing B16 cells (ova). B16 survival was assessed using the CellTiterGlo (CTG) bioluminescent assay, and values were normalized to untreated B16 cells. (**B**) B16 ova cells were labelled with CFSE and cultured with unlabelled B16 WT cells. Survival was assessed by flow cytometry using the ratio of CSFE positive to CSFE negative cells normalized to untreated cells. (A-B) Error bars show SEM. (**C**) Flow cytometry using the indicated antibodies on B16-ova cells treated as in (A) or left untreated. (**D**) Flow cytometry with the indicated VHH or antibody on OT-I T cells activated for 48 hours with αCD3/CD28 beads and then incubated for an additional 24 hours in culture supernatant in the absence of stimulation. (A-D) Results represent 2-3 independent experiments.

**Figure S3. Single agent treatment with B3 does not alter B16 growth in vivo**. (**A**) C57BL/6 mice were inoculated with 5x105 B16 cells subcutaneously on day 0, and vaccinated on day 0 with 5x105 B16 cells engineered to secrete GM-CSF (GVAX). Starting on day 0, mice were treated every other day with 250 μg of VHH CTR in PBS by intraperitoneal injection (VHH CTR) or were left untreated (PBS). (**B**) C57BL/6 mice were inoculated B16 as in (A), and were treated as in (A) with B3 or VHH CTR. (A-B) Tumor size was measured by precision calipers. Error bars represent SEM. N=5 for each group.

**Figure S4. Lack of efficacy of B3-IL2 in KPC model and A12-GMCSF in Panc02 model.** (**A-B**) 100,000 KPC cells were orthotopically implanted into C57BL/6 mice. Mice were treated IP with VHHCTR or B3-IL2 at 1 g/mouse daily for 18 days. Tumors were harvested at day 21 post-implantation, weighed, digested and infiltrates analyzed by flow cytometry. N=5 mice per group. (**C**) A fusion of A12 and GM-CSF was purified from mammalian cell culture. To confirm that the cytokine element retained functionality, A12-GMCSF or recombinant GM-CSF was added at the indicated concentrations to mouse bone marrow cells. Dendritic cell differentiation was confirmed by flow cytometry analysis of % CD11c+ cells at day 3 of culture. Similar results were observed at culture day 8. (**D**) 100,000 Panc02 cells were orthotopically implanted into C57BL/6 mice. Mice were treated IP with VHHCTR or A12-GMCSF at 10 g/mouse daily for 18 days. Tumors were harvested at day 21 post-implantation. N=5 mice per group.

**Figure S5. Combination B3-IL2 and A12-IFN has additive benefit over either agent alone.** (**A**) C57BL/6 mice were inoculated with 100,000 Panc02 cells orthotopically and treated with VHHCTR, A12, B3 admixed with IFN, B3-IL2, A12-IFN, or combination B3-IL2 and A12-IFN. Compounds were administered daily for 18 days at 5 g per mouse IP. (**B**) Draining lymph node cells from mice treated in (A) were fixed, permeablized, and stained with antibodies to CD4 and Foxp3. Tregs as a percent of CD4 cells were quantified by flow cytometry. \* p<0.05. Error bars are SEM.

**Figure S6. A12-IFN alters the tumor microenvironment in KPC organoid model of pancreatic cancer.** (**A**) Organoids derived from KPC mice (line M19, gift of D. Tuveson) were inoculated orthotopically into C57BL/6 mice and treated with the indicated VHH constructs 5 g/mouse IP daily. Five weeks post-implantation, tumors were harvested and analyzed by flow cytometry for the indicated populations. N=4 mice per group. Results representative of two independent experiments. (**B**) Organoid tumor cell suspensions from (A) were gated on CD45- FSChigh tumor cells. Mean fluorescence intensity of MHC class II is shown. Results representative of 3 independent experiments.