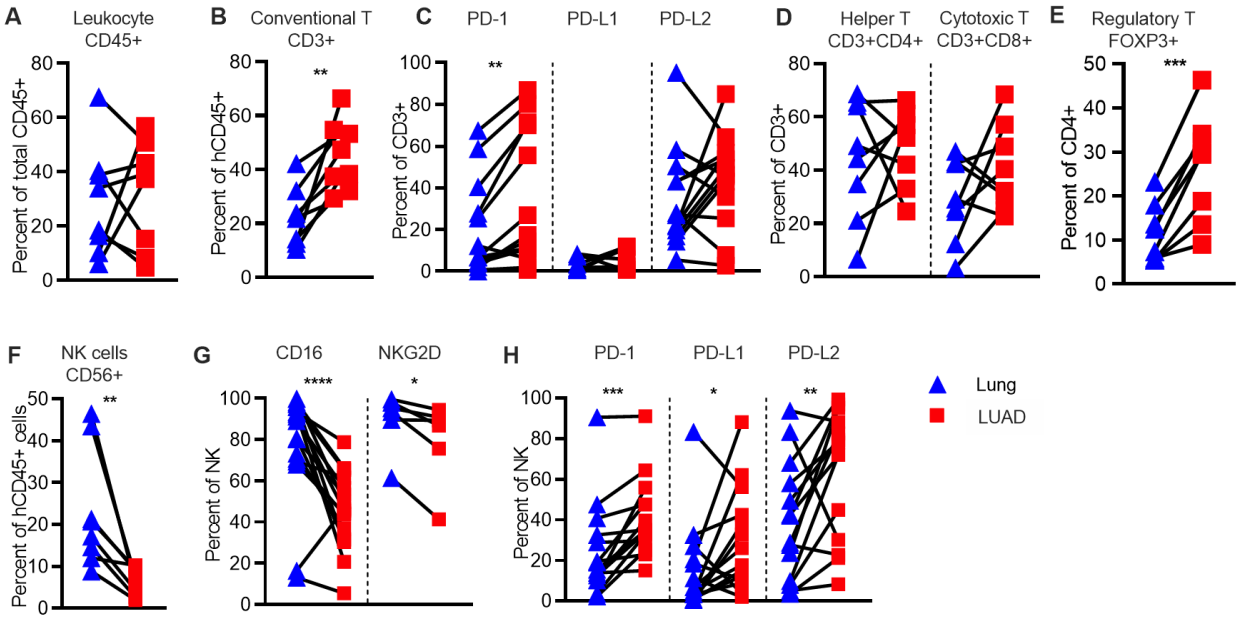
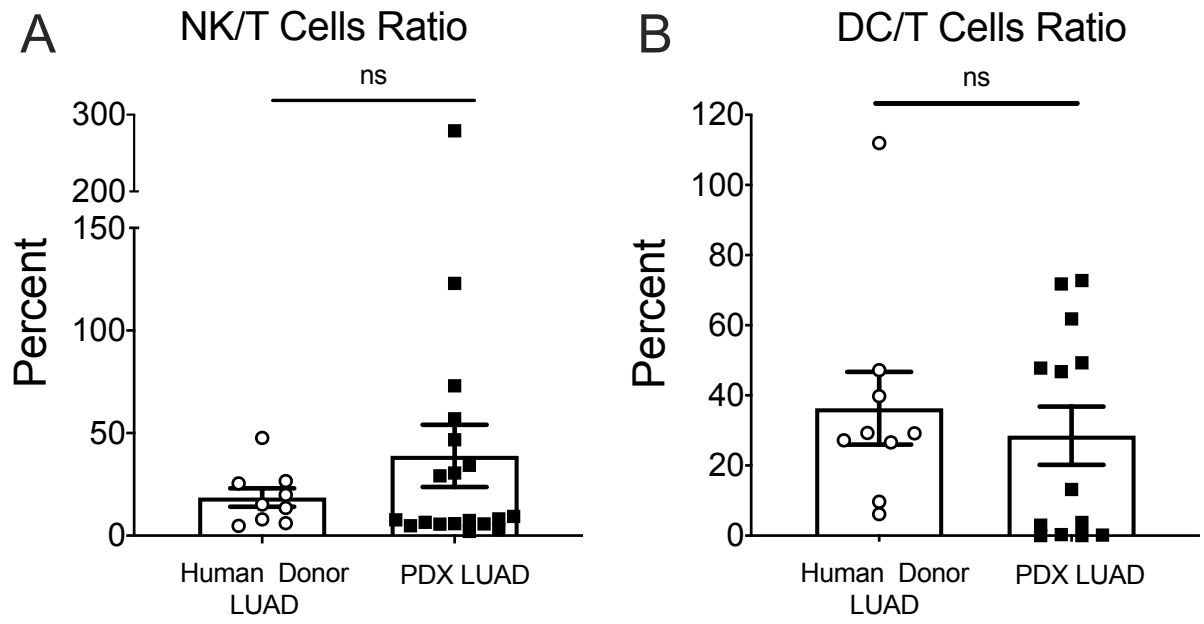
Supplemental Figure 1



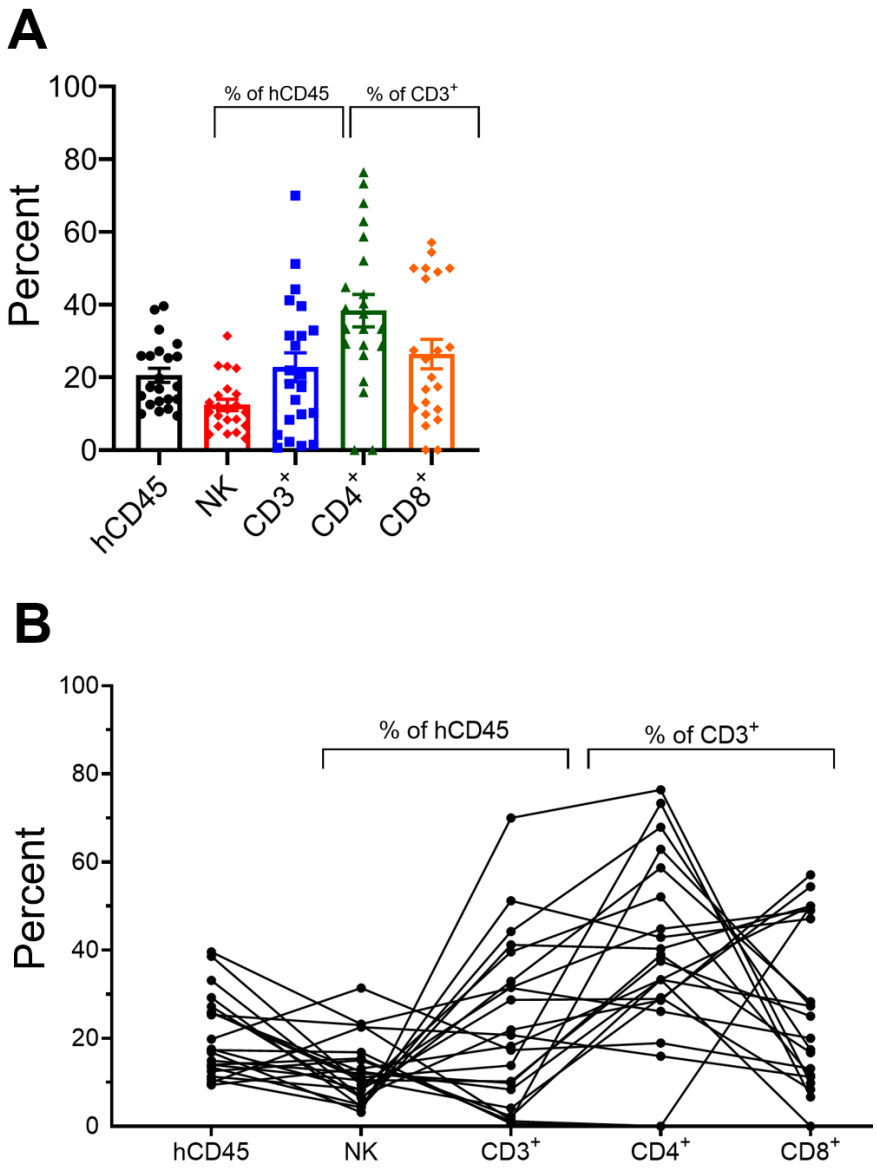
Supplemental Figure 1. Higher proportions of NK and T-cells express PD-molecules in LUAD compared to normal lung across genetically unrelated human donors. Flow cytometry staining of freshly excised human donor LUAD compared donor-matched normal lung tissue. (**A**) Percent of human CD45 cells, (B) percent of CD3 T-cells, as well as their expression of (C) PD-1, PD-L1, and PD-L2. (D) Frequencies of CD4 and CD8 T-cells as prevent of CD3 T-cells. (E) Frequencies of T-regs as a percent of CD4 cells. (F) Frequency of NK cells as a percent of human CD45 cells, their expression of (G) CD16, NKG2D, and (H) PD-1, PD-L1, PD-L2. Each paired data are from a genetically unrelated human donor. Paired t-test, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Supplemental Figure 2



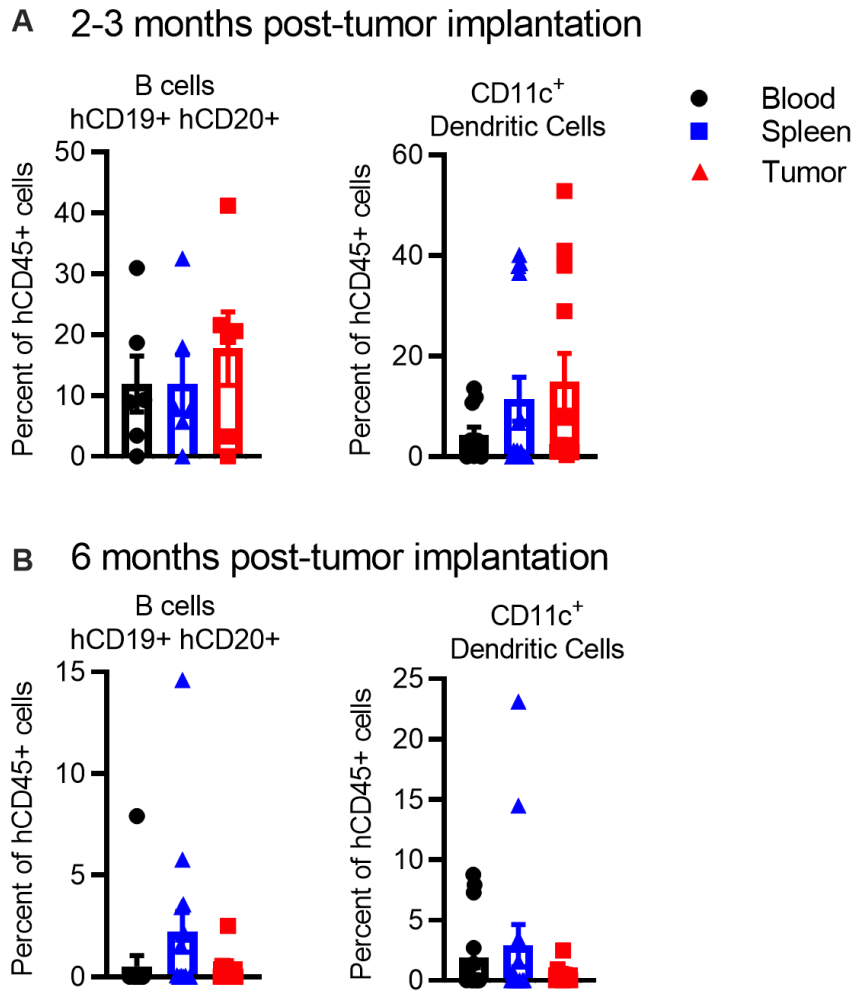
Supplemental Figure 2: Immune cell ratios are preserved in TIL-PDX-LUAD. The ratio of NK to T-cells **(A)** and DC to T-cells **(B)** in input human donor LUAD versus TIL-PDX-excised LUAD status-post implantation showing no statistically significant difference. Each data point represents a human donor (blue) or a TIL-PDX animal's tumor. Unpaired t-test; n.s. not significant ($p>0.05$).

Supplemental Figure 3



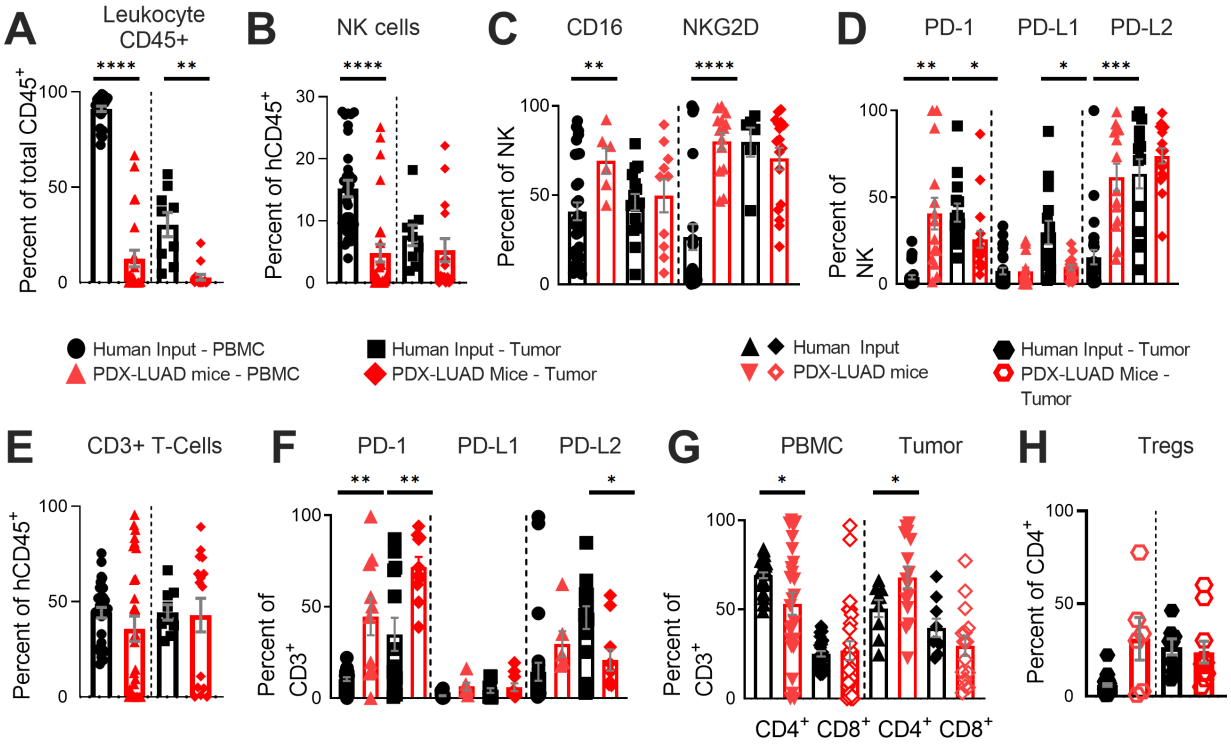
Supplemental Figure 3. Immune cell reconstitution across a cohort of PDX-LUAD mice 4-months post-implant. Flow cytometry of human immune cells from PBMC of a single TIL-PDX-LUAD cohort of 22 mice analyzed 4-months post-transplant. Frequency of human hematopoietic cells (human $CD45^+$ of total $CD45^+$), NK cells ($CD45^+CD56^+CD3^-$), conventional T cells ($CD45^+CD56^-CD3^+$), T helper cells ($CD45^+CD56^-CD3^+CD4^+$ $CD8^-$), and CTL ($CD45^+CD56^-CD3^+CD8^+CD4^-$). Each data point represents one TIL-PDX-LUAD mouse from a single human tumor-donor, N=22.

Supplemental Figure 4



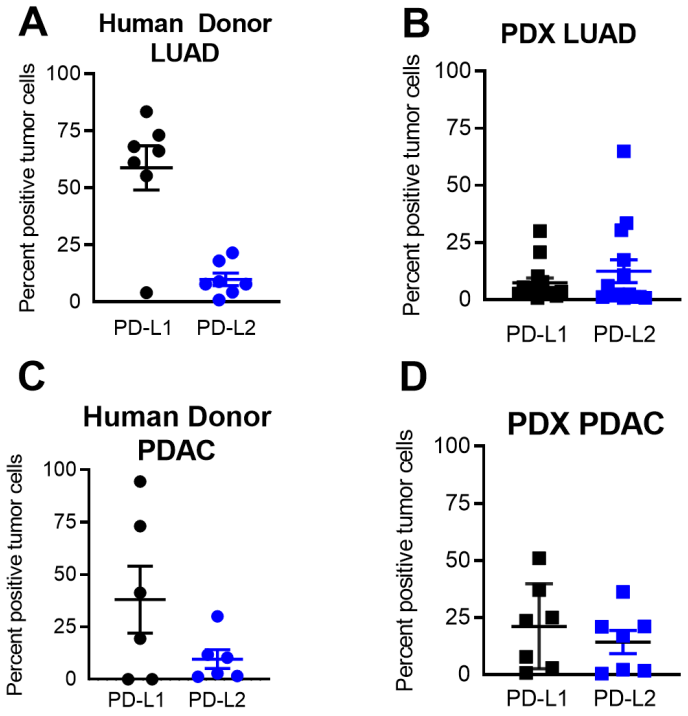
Supplemental Figure 4: Long-term reconstitution of TIL-PDX-LUAD mice with human B cells and dendritic cells (DC). Frequencies of Human B cells ($CD45^+CD3^-CD56^-CD19^+CD20^+$) and DC ($CD45^+CD3^-CD56^-CD19^-CD11c^+$) in PBMC, spleen, and excised tumor of TIL-PDX-LUAD mice (**A**) 2-3- and (**B**) 6-months post-tumor implantation, as determined by flow cytometry. Three genetically unrelated donor-cohorts were analyzed. Depending on cohort size, three to six TIL-PDX-LUAD mice of each cohort were analyzed at each time point, resulting in N= 11-15 data points per tissue.

Supplemental Figure 5



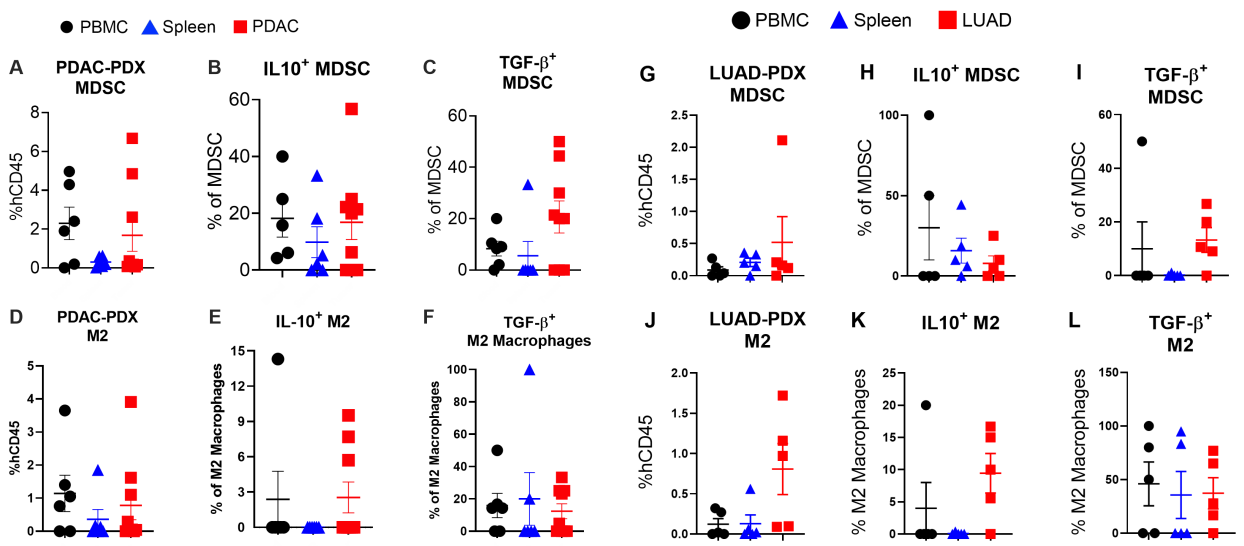
Supplemental Figure 5. Reconstituted TILs in TIL-PDX-LUAD retain human donor LUAD immune phenotypes. (**A-H**) Flow cytometry of human immune cells from LUAD tumor and PBMC of human donor compared to LUAD tumor and PBMC of implanted TIL-PDX-LUAD mice 2-months post-transplant. (**A**) Frequency of human hematopoietic cells ($CD45^+$), (**B**) NK cells ($CD45^+CD3^-CD56^+$), (**C**) expression of activating receptors CD16 and NKG2D, and (**D**) PD-1, PD-L1 and PD-L2 on NK cells. (**E**) Frequency of conventional T cells ($CD45^+CD3^+CD56^-$), and (**F**) expression of PD-1, PD-L1 and PD-L2 on conventional T cells. (**G**) Frequencies of T helper ($CD45^+CD3^+CD4^+CD8^-CD56^-$) and CTL ($CD45^+CD3^+CD4^-CD8^+CD56^-$), and (**H**) T-reg ($CD45^+ CD3^+CD4^+Foxp\text{-}3^+CD8^-CD56^-$) subsets. Human input PBMC or Tumor: Each data point represents one genetically unrelated human donor. TIL-PDX-LUAD mice: Five genetically unrelated donor-cohorts were analyzed. Depending on cohort size, three to six TIL-PDX mice of each cohort were analyzed at each time point, resulting in 15-30 data points total per cell type/marker and time point. Data are represented as mean SEM; one-way ANOVA with post-hoc Tukey test *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Supplemental Figure 6



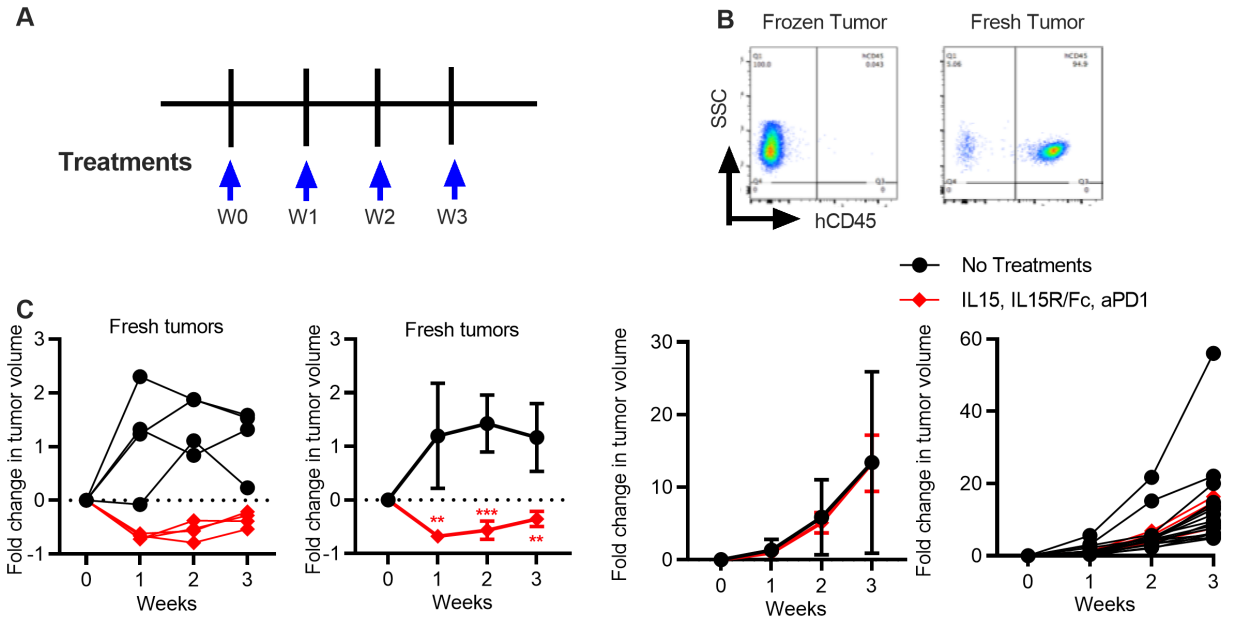
Supplemental Figure 6: PD-L1 and PD-L2-expression in freshly resected human donor LUAD and PDAC compared to TIL-PDX-LUAD and TIL-PDX-PDAC. Frequency of PD-L1 and PD-L2 expressing non-hematopoietic cells ($CD45^-$) in freshly dissected human tumors or TIL-PDX-LUAD or TIL-PDX-PDAC tumors four months post-transplant as determined by flow cytometry. N = 7 (LUAD) and N = 6 (PDAC) freshly excised tumor tissues were obtained from genetically unrelated human donors and analyzed by flow cytometry. Three genetically unrelated tumor donor cohorts were analyzed. Depending on cohort size, two to four TIL-PDX mice were analyzed per cohort for N = 7 PDX-PDAC and N = 10 TIL-PDX-LUAD mice. Unpaired t-test, p=0.0001 for PD-L1 freshly excised LUAD vs. TIL-PDX LUAD and not significant for all other comparisons. Freshly excised and TIL-PDX derived tumor tissues were not donor matched.

Supplemental Figure 7



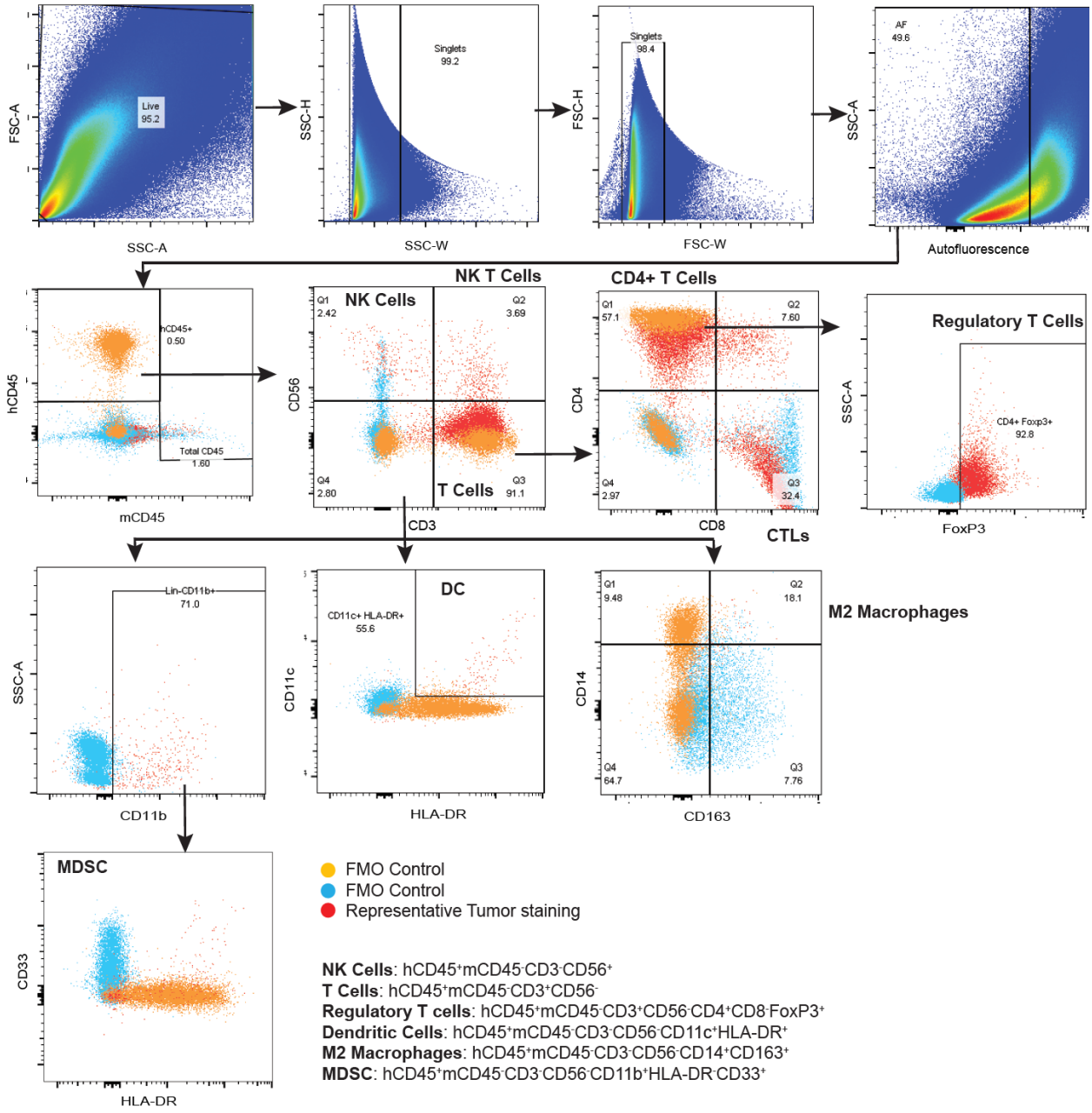
Supplemental Figure 7. Immuno-suppressive MDSC and M2 persistence in TIL-PDX-PDAC and TIL-PDX-LUAD mice. Frequency of (**A&G**) MDSC (human $CD45^{+}CD3^{-}CD56^{-}CD16^{-}HLADR^{low/-}CD11b^{+}CD33^{+}$), (**B&H**) IL-10 producing MDSC and (**C&I**) TGF-beta-producing MDSC, as well as (**D&J**) M2 macrophages ($CD45^{+}CD3^{-}CD56^{-}CD14^{+}CD163^{+}$), (**E&K**) IL-10 producing M2 macrophages and (**F&L**) TGF-beta-producing M2 macrophages in PBMC, spleens and tumors of TIL-PDX-PDAC and TIL-PDX-LUAD mice 4-months post-transplant as determined by flow cytometry. Three (PADC) or two (LUAD) genetically unrelated tumor donor cohorts were analyzed. Depending on cohort size, two to three TIL-PDX-PDAC or mice were analyzed per cohort for N = 6-7 PDX-PDAC and N = 5 TIL-PDX-LUAD mice .

Supplemental Figure 8



Supplemental Figure 8. Human immune cells are required for successful PD-1 blockade + IL-15/ IL15RaFc therapy. (**A**) Freshly harvested LUAD tumor tissue was transplanted into NSG mice (**B**), while the other half was frozen at -80°C for two weeks before being transplanted into NSG mice. Flow cytometry of TIL-PDX-LUAD mice demonstrating (**A**) the presence of human immune cells (human $CD45^+$) in recipients of fresh tumor tissue, compared to (**B**) the absence of human immune cells in recipients of frozen tumor tissue. TIL-PDX-LUAD mice were treated with either human IL-15 + human IL-15Ra Fc + PD-1 blocking antibody or left untreated, and tumor volumes were recorded weekly. N = 4 – 16 TIL-PDX-LUAD mice per group from two genetically unrelated donor cohorts, thus N= 8-32 mice total per group. Data are represented as mean SEM; Multiple t-test, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Supplemental Figure 9



Supplemental Figure 9. Gating Strategy. Fluorescence minus one (FMO) controls for each fluorophore in each respective panel displayed in orange and teal. Representative TIL-PDX-LUAD staining in red. Markers of different cell types as detailed in the figure.

Supplemental Table 1

Antibody specificity	Fluorophore	Clone	Source	Identifier
CD45	Brilliant Violet 605™	HI30	Biolegend	304042
CD3	Brilliant Violet 711™	OKT3	Biolegend	317328
CD3	APC/Fire 750	UCHT1	Biolegend	300470
CD56	Brilliant Violet 421™	HCD56	Biolegend	318328
CD56	Brilliant Violet 570™	HCD56	Biolegend	318330
CD4	Brilliant Violet 650™	OKT4	Biolegend	317436
CD4	Brilliant Violet 750™	SK3	Biolegend	344644
CD8a	Brilliant Violet 785™	RPA-T8	Biolegend	301046
CD11c	PE/Cy7	3.9	Biolegend	301608
CD11b	PE/Dazzle™	ICRF44	Biolegend	301348
CD16	Brilliant Violet 510™	3G8	Biolegend	302048
CD16	PE/Cy7	3G8	Biolegend	302010
CD19	Alexa Fluor® 700	HIB19	Biolegend	302226
CD20	APC/Cy7	2H7	Biolegend	302314
CD33	FITC	HIM3-4	Biolegend	303304
CD33	BUV737	HIM3-4	BD	749230
CD94	PerCP Cy5.5	DX22	Biolegend	305514
CD163	Brilliant Violet 711™	GHI/61	Biolegend	333630
PD-1	Brilliant Violet 785™	EH12.2H7	Biolegend	329930
PD-1	Brilliant Violet 480™	EH12.1	BD Biosciences	566112
PD-L2	Alexa Fluor® 488	176611	R & D	FAB1224G
PD-L2	APC	MIH18	Biolegend	345508
PD-L1	Alexa Fluor® 700	130021	R & D	FAB1561N
NKG2D	Brilliant Violet 510™	1D11	Biolegend	320816
NKG2D	Super Bright 436	1D11	ThermoFisher	62-5878-42
FOXP3	Alexa Fluor® 647	150D	Biolegend	320014
FOXP3	Alexa Fluor® 532	PCH101	ThermoFisher	58-4776-42
HLA-DR	Brilliant Violet 650™	L243	Biolegend	307650
IL-10	Alexa Fluor® 647	JES3-9D7	Biolegend	501412
TGF-beta	PerCP/eFluor 710	FNLAP	Thermofisher	46-9829-42
CD45	PE/Cy5	30-F11	Biolegend	103110
CD45*	PE	30-F11	Biolegend	103106
CD45*	PerCP/Cy5.5	30-F11	Biolegend	103132
Fc Block ™	N/A	N/A	BD Biosciences	564220
Mouse Fc Block ™*	N/A	2.4G2	BD Biosciences	553142

*** murine specific antibodies, all others are specific to human antigen**