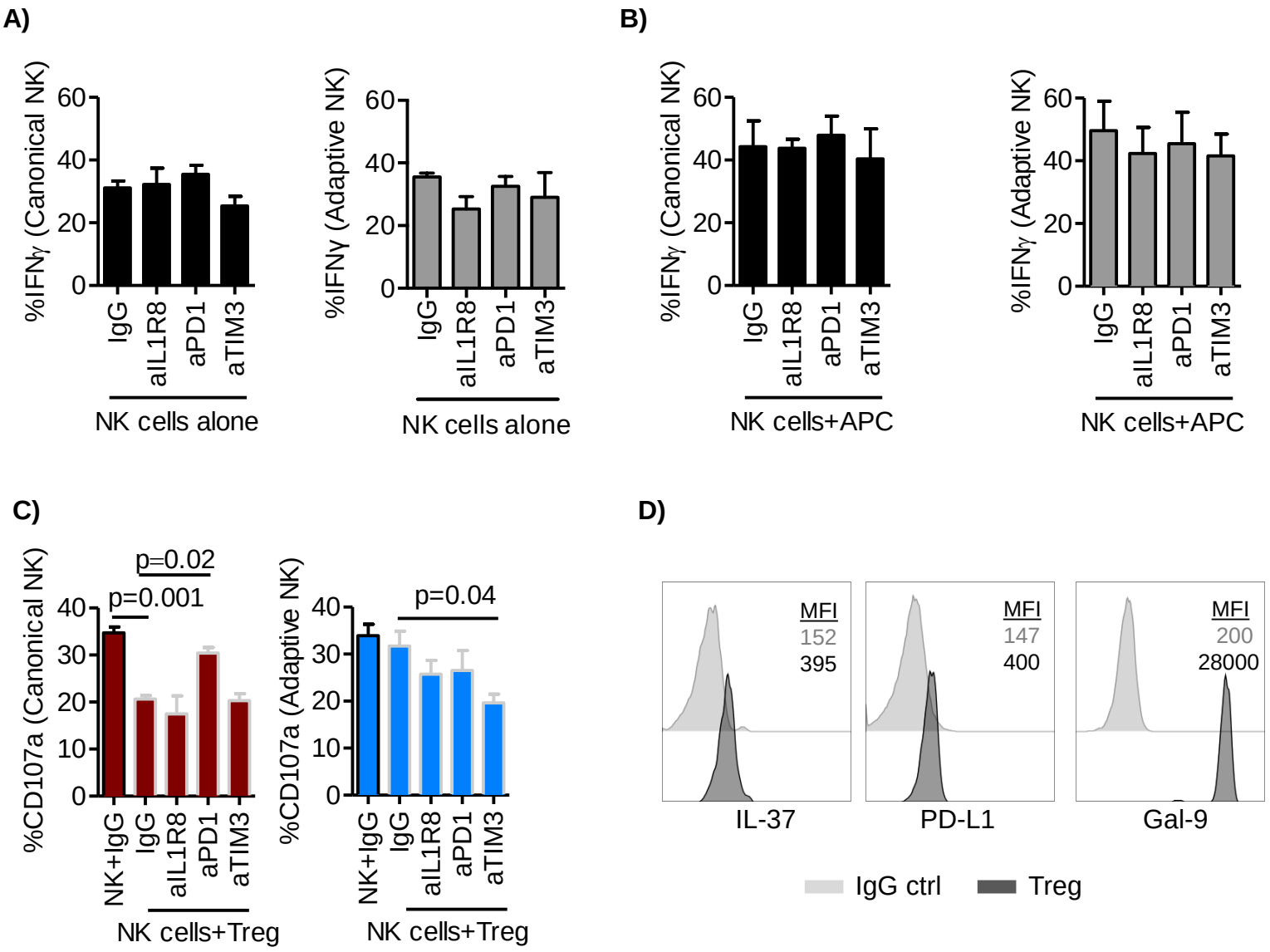
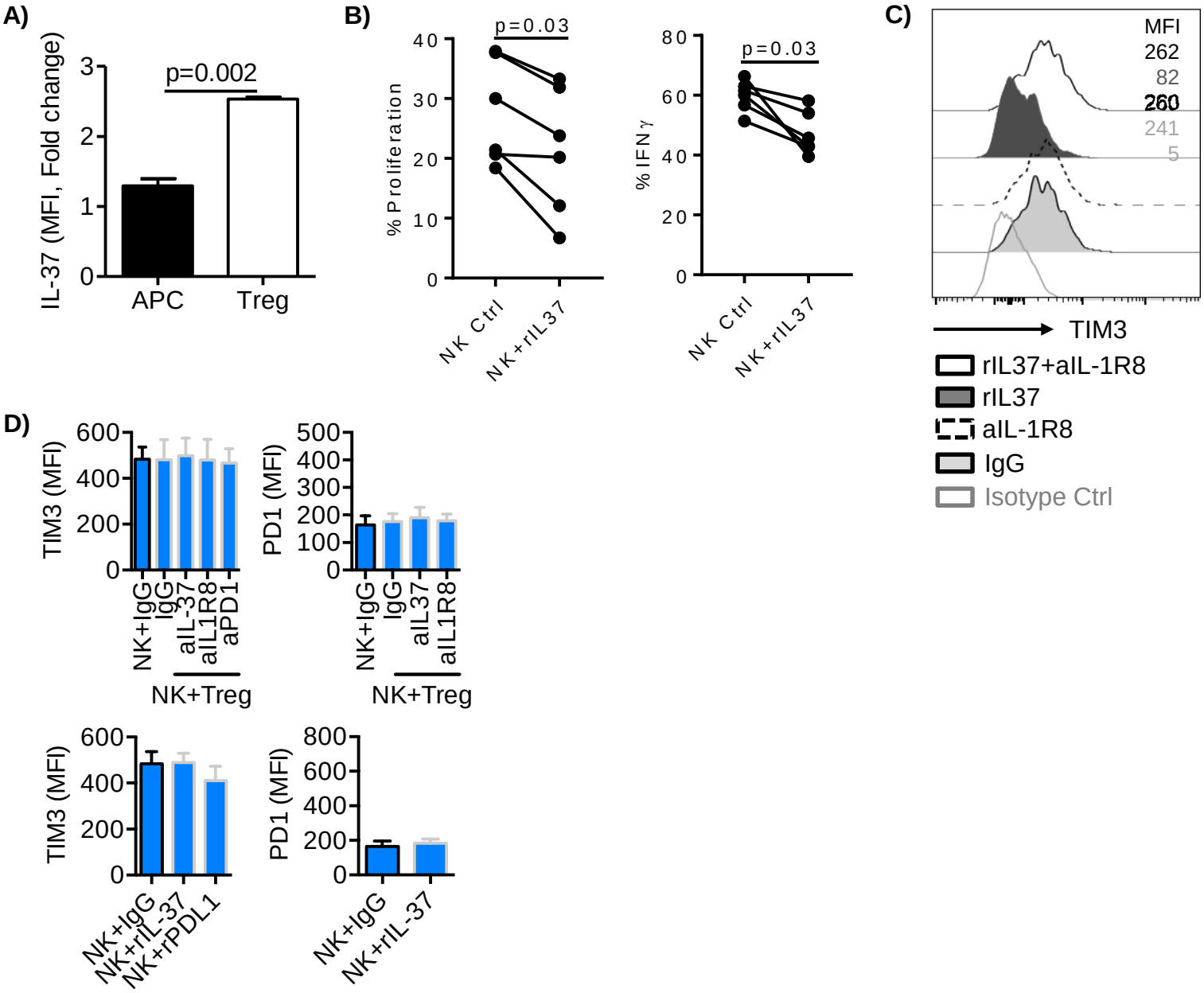
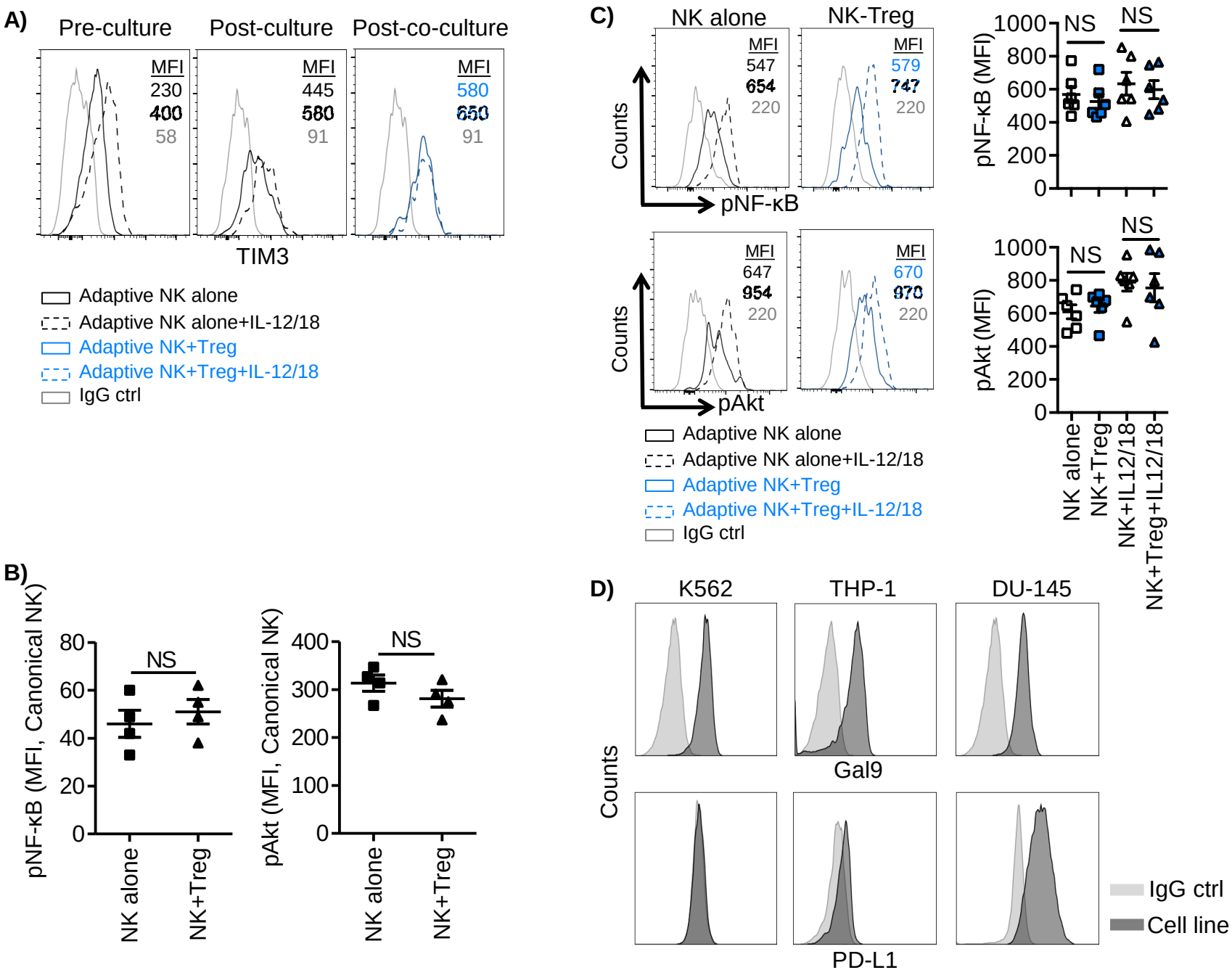
Supplementary Figure S1.



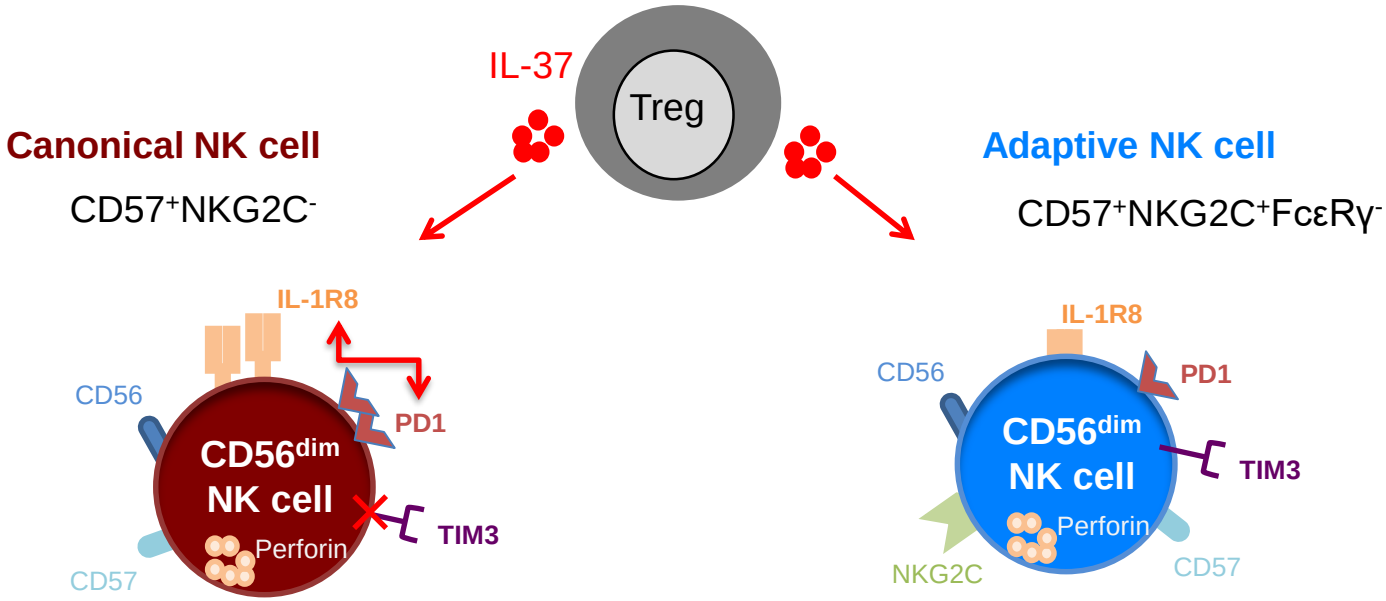
Supplementary Figure S2.



Supplementary Figure S3.



Supplementary Figure S4.



-/low pAkt/pNFκb

-/low Proliferation, Cytotoxicity, IFNγ

+/high pAkt/pNFκb

+/high Proliferation, Cytotoxicity, IFNγ

Supplementary Table S1.

Marker	Clone	Fluorochrome	Manufactory
CD3	OKT3	BV785	Biolegend
CD56	NCAM	PE/CY7	Biolegend
CD57	NK-1	BV605	BD Biosciences
CD16	3G8	AF700	Biolegend
NKp44	P44-8	APC	BD Biosciences
NKp46	9E2	PerCP-eFluor® 710	BD Biosciences
DNAM-1	11A8	APC	Biolegend
NKG2A	Z199	APC	Beckman Coulter
TIGIT	741182	APC	R&D systems
NKG2C	134591	PE	R&D systems
FCεRγ	RB Polyclonal	FITC	EMD millipore
PD-1	MIH4	APC	eBiosciences
PD-L1	29E.2A3	BV421	Biolegend
TIM-3	F38-2E2	BV421	Biolegend
TIM-3	F38-2E2	BV650	Biolegend
IL-1R8	MAB975	Primary monoclonal	R&D systems
Gal9	9M1-3	APC	Biolegend
IL-37	37D12	PE	eBiosciences
CD107a	H4A3	PerCP/Cy5.5	Biolegend
IFNγ	4S.B3	BV650	Biolegend
Ki67	B56	AF700	BD Biosciences
CellTrace		Violet	Invitrogen
Akt (pS473)	M89-61	BV421	BD Biosciences
NF-κB p65 (pS529)	K10-895.12.50	PE/CY7	BD Biosciences
Fixable dead cell marker		Near-IR	Invitrogen
Blocking antibodies	**Clone**	**Isotype control**	**Manufactory**
Anti-IL-1R8	MAB975	IgG1	R&D systems
Anti-TIM3	F38-2E2	IgG1	Biolegend
Anti-PD1	scFv anti-PD1		Beigene
Anti-IL-37	MAB19751	IgG2b	R&D systems

Supplementary Figure S1.

Canonical and adaptive NK cells were cultured with with IL-2 (50 IU/ml) **A)** alone, **B)** with APCs (1:1), or **C)** APCs + Treg (Treg:NK, 1:2) in the presence of blocking antibodies against IL1R8, PD1, TIM3, or control IgG for 6 days. NK cell cultures were then stimulated with anti-CD16 antibody, and IL-12 and IL-18 for 6 hours prior to analysis of IFN-γ production and degranulation (CD107a). Cumulative data (*n* = 4-7) are shown from 3 independent experiments as mean ± SEM. **D)** Expanded Tregs were stimulated with IL-2 (300 UI/ml) overnight and evaluated for the intracellular production of IL-37 and the expression of PD-L1 and Gal9. Representative (*n* = 5) histograms are shown from two independent experiments.

Supplementary Figure S2.

A) Purified APC (n=6) and expanded Treg (n=6) were stained for IL-37 following 6 hours treatment with transport inhibitors golgistop and golgiplug. Statistical analyses were performed on pooled MFI fold change calculated based on respective isotype control using Mann Whitney U-test. **B)** Purified NK cells (n=6) were cultured in IL-2 (50 IU/ml) and recombinant IL-37 (3 μg/ml) for 6 days. IFNγ production and proliferation of total NK cells were evaluated following stimulation with anti-CD16 antibody (1 μg/ml), IL-12 (5 ng/ml), and IL-18 (50 ng/ml) 6 hours prior to analysis. Pooled data are shown as mean ± SEM and statistical analyses were performed by nonparametric Wilcoxon test. **C)** NK cells (n=4) were co-cultured with, IL-2 (50 IU/ml) and APCs in the presence of control IgG, recombinant (r) IL-37, anti (a)-IL1R8, or rIL-37+a-IL1R8 and evaluated for TIM3

expression 6 days post-culture. One representative donor is shown. **D)** Adaptive NK cell TIM3 and PD-1 expression were analyzed following culture with APCs ± Treg and in the presence of blocking antibodies against IL-37, IL-1R8, and PD-1 or IgG (*upper panel*). Adaptive NK cells in culture with APCs were treated with recombinant IL-37 (3 μg/ml) or PD-L1 Fc chimera protein (10 μg/ml) and evaluated for the expression of TIM3 and PD-1 expression after 6 days of culture (*lower panel*). Cumulative data (*n* = 6-8) are shown from three independent experiments as mean ± SEM.

Supplementary Figure S3.

A) Purified NK (*n* = 6) cells were co-cultured with APCs (1:1) overnight and stimulated with IL-12 (5 ng/ml) and IL-18 (50 ng/ml) to increase TIM3 or left unstimulated. Following overnight stimulation, cells were washed and cultured with IL-2 (50 IU/ml) ± Treg (Treg:NK, 1:2) for 6 days. Representative histogram of TIM3 expression is shown before and after co-culture from two independent experiments. **B)** Purified NK cells were co-cultured with APCs with IL-2 (50 IU/ml) ± Treg (Treg:NK, 1:2) for 6 days prior to analysis for the phosphorylation of NF-κB (pNF-κB) and Akt (pAkt). Cumulative data (n = 4) are shown as mean ± SEM. **C)** Following co-culture, adaptive NK cells were stimulated with soluble recombinant Gal9 (50 nM) for 20 min. prior analysis for the phosphorylation of NF-κB (pNF-κB) and Akt (pAkt). Representative and cumulative data are shown from two independent experiments. Cumulative data (*n* = 6-12) are shown as mean ± SEM. **D)** Tumor cell lines K562, THP-1, and DU-145 were analyzed for the

expression of Gal9 and PD-L1. Representative histograms are shown from two independent experiments.

Supplementary Figure S4.

Schematic summary.

Supplementary Table S1. Antibodies and fluorescent dyes used in the experiments.