# Figure S1

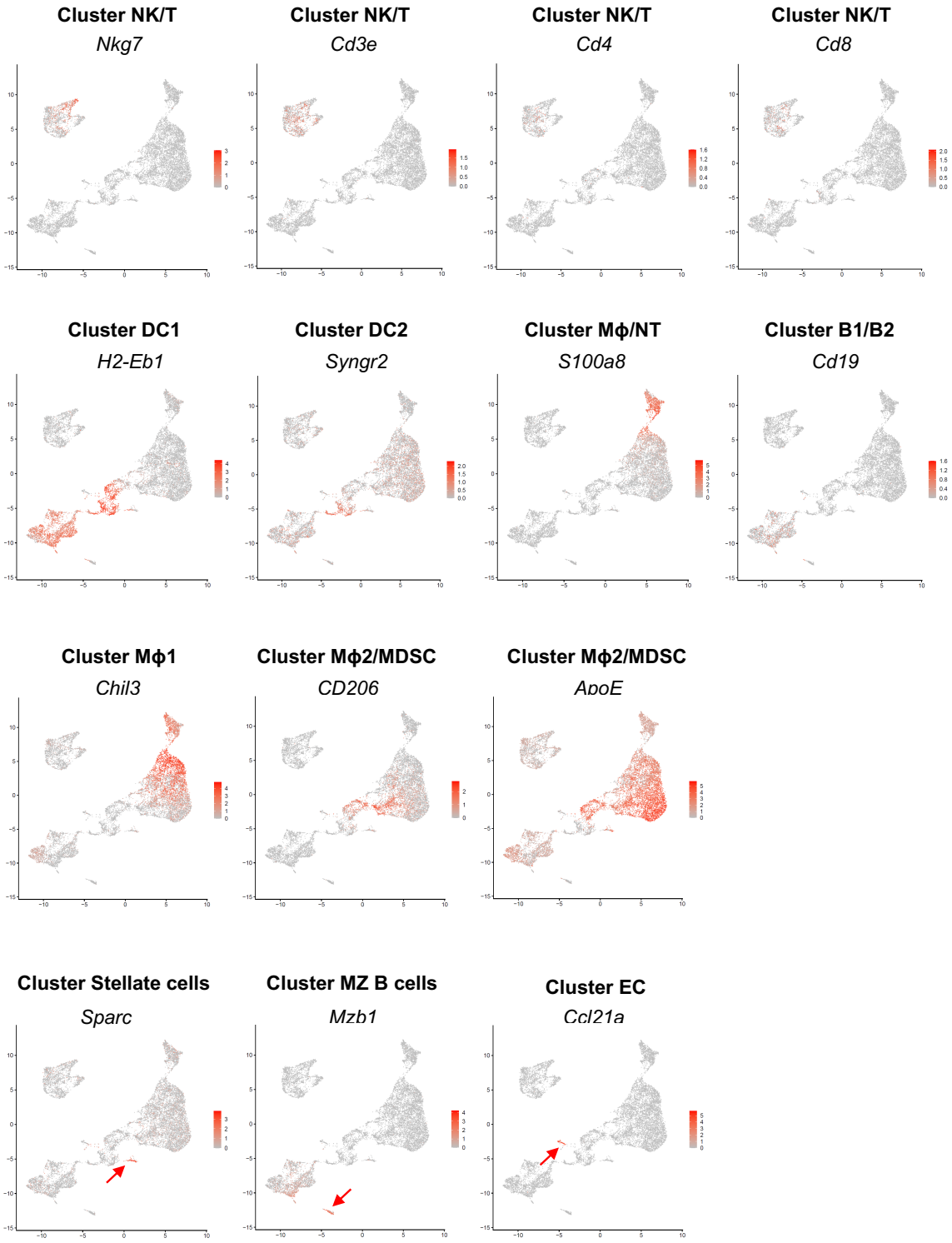


**Fig. S1. UMAP showing the expression level of representative markers for each cell type. A.** Top markers of each cluster are represented in UMAPs plots. Mϕ = macrophages, NT = neutrophils, DC = dendritic cells, NK = natural killer cells, T = T cells, B = B cells, EC = endothelial cells and MZ = marginal zone.

# Figure S2

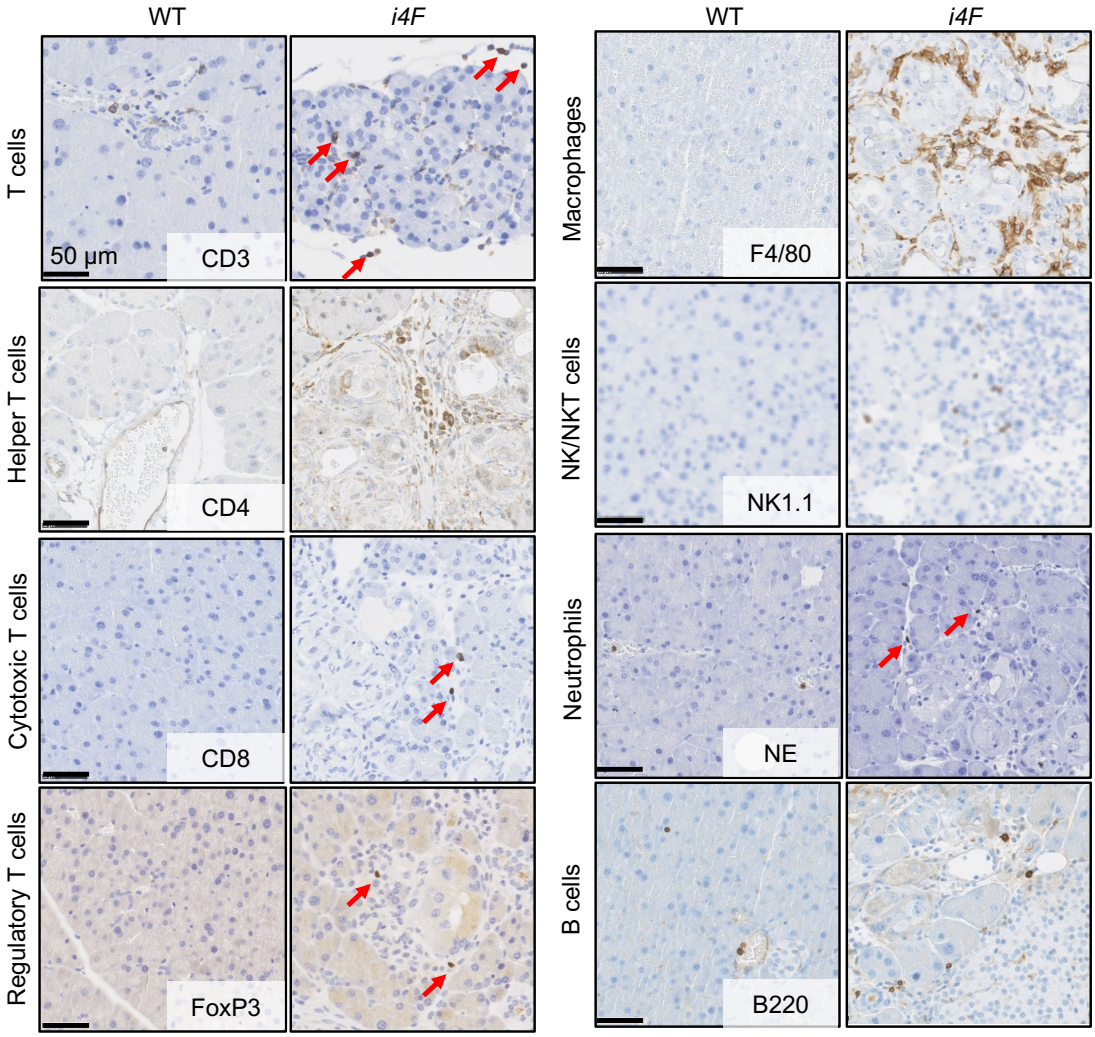


**Fig. S2. Immune cells infiltrate partially reprogrammed pancreas.** Representative images of partially reprogrammed pancreas at day 7 stained for the indicated immune cell markers (*n*=4): CD3 (T cells), CD4 (helper T cells), CD8 (cytotoxic T cells), FoxP3 (regulatory T cells), F4/80 (macrophages), NK1.1 (NK/NKT cells), NE (neutrophil elastase, neutrophils) and B220 (B cells).

# Figure S3

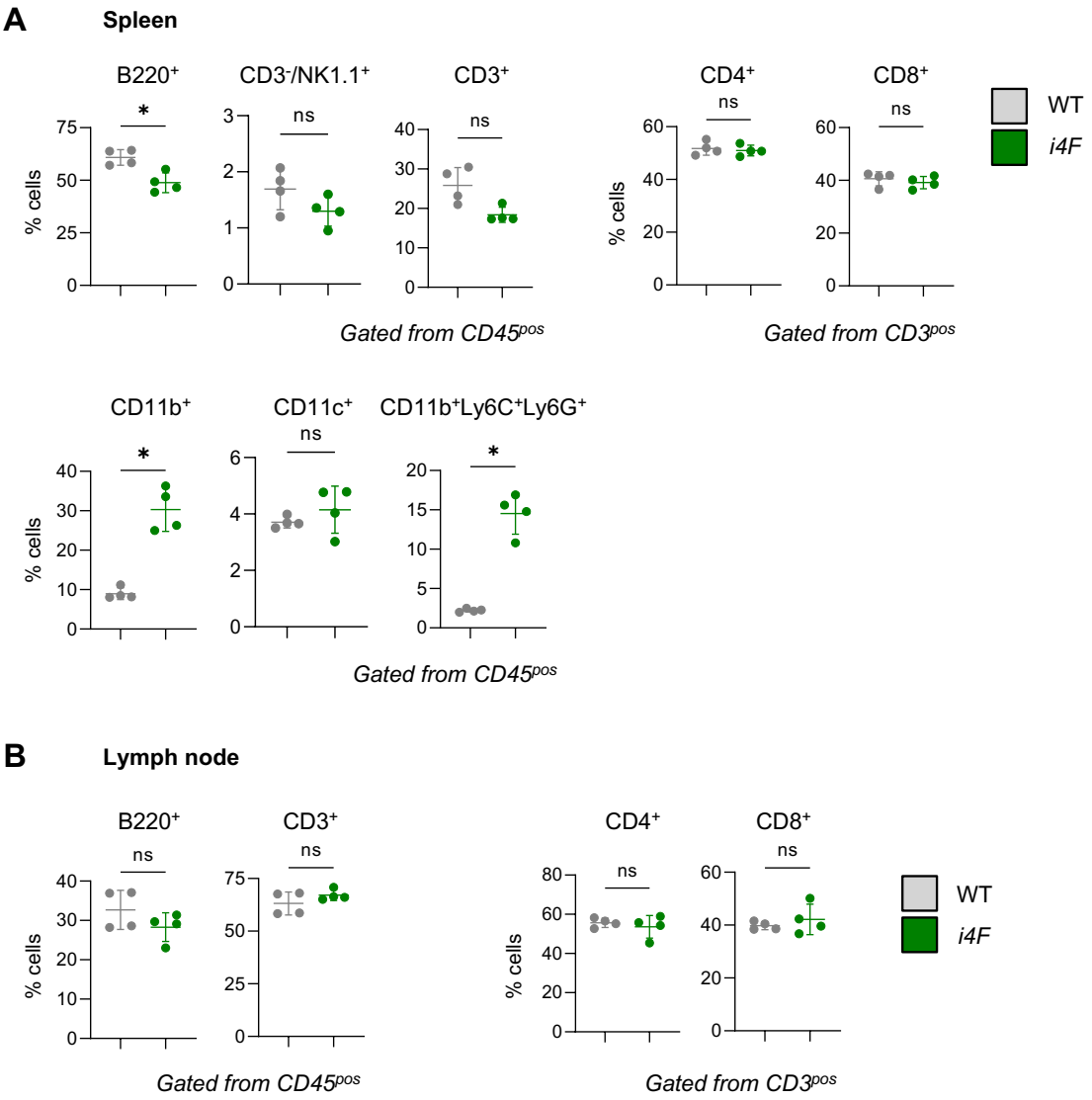


**Fig. S3. Gr1$^+$ cells and CD11b$^+$ cells are upregulated in the spleen of *i4F* mice.** Spleen and lymph nodes of *i4F* mice treated with doxycycline for 7 days (1 mg/ml) were harvested and most abundant immune populations were analysed by flow cytometry (*n*=4).

## Figure S4

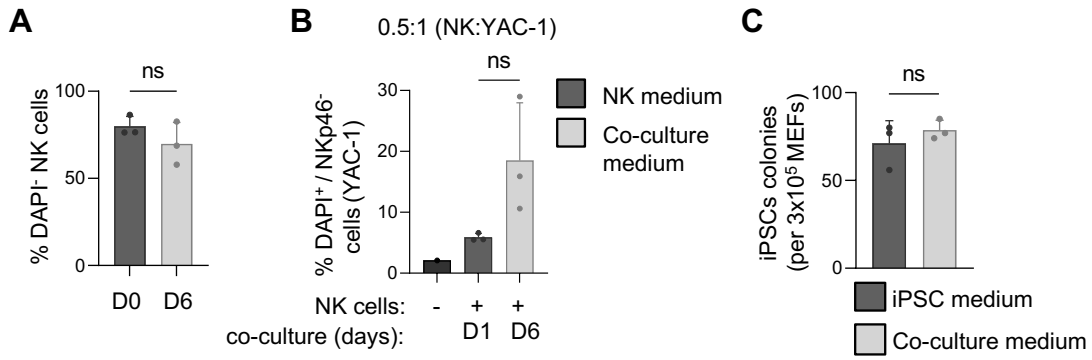


**Fig. S4. Co-culture medium maintains NK cell survival and cytotoxicity, and iPSC colony formation. A**. Viability of freshly isolated splenic WT NK cells and WT NK cells cultured in co-culture media for 6 days was analyzed. Gated from DAPI$^-$ cells (*n*=3). **B**. Splenic WT NK cells were either primed overnight in NK cell medium (D1) or maintained in co-culture medium for 5 more days (D6). Both conditions were co-cultured with YAC-1 cells for 4 hours to assess their cytotoxic capacity. Cell death was assessed using DAPI and NK cells were excluded using NKp46 antibody (*n*=3). **C**. *i4F* MEFs were reprogrammed *in vitro* with either iPSC medium for 11 days or with iPSC medium replaced by co-culture medium from days 2 to 6 of reprogramming. At day 11, iPSCs colonies were scored by Alkaline Phosphatase staining (*n*=3).

# Figure S5

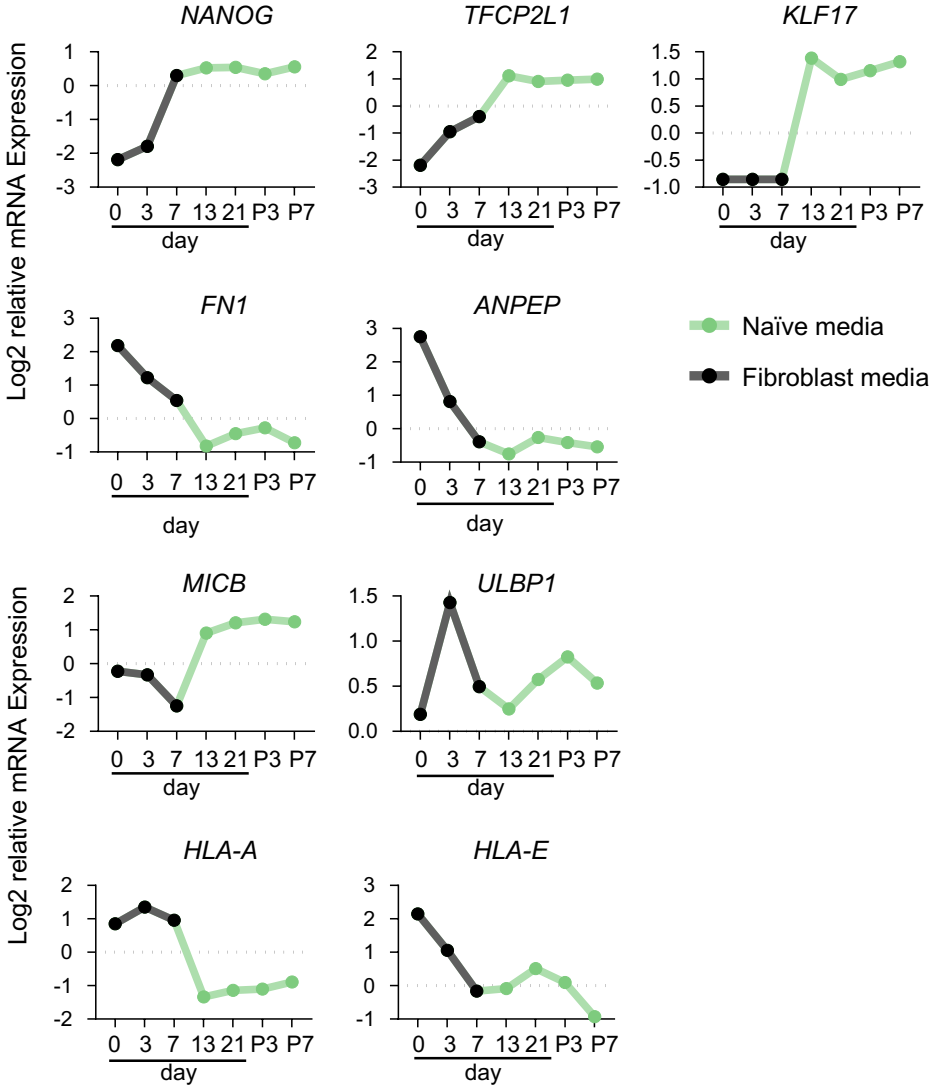


**Fig. S5. Human fibroblasts upregulate NK-activating ligand MICB and downregulate MHC-I molecules during reprogramming.** Previously published scRNAseq data from human dermal fibroblasts reprogrammed to naïve iPSCs for 21 days (Liu *et al.*, 2020). Cells were transduced with the transcription factors *OCT4*, *KLF4*, *SOX2* and *MYC*, and cultured in fibroblast medium for 7 days. Medium was changed to naïve medium at day 8 and cells were cultured until day 21. Relative mRNA expression of marker genes associated with pluripotency (*NANOG*, *TFCP2L1* and *KLF17*), human fibroblasts (*FN1* and *ANPEP*), NK-activating ligands (*MICB* and *ULBP1*) and MHC-I molecules (*HLA-A* and *HLA-E*) are represented at days 0, 3, 7, 13 and 21, and passages (P) 3 and 7.

# Figure S6

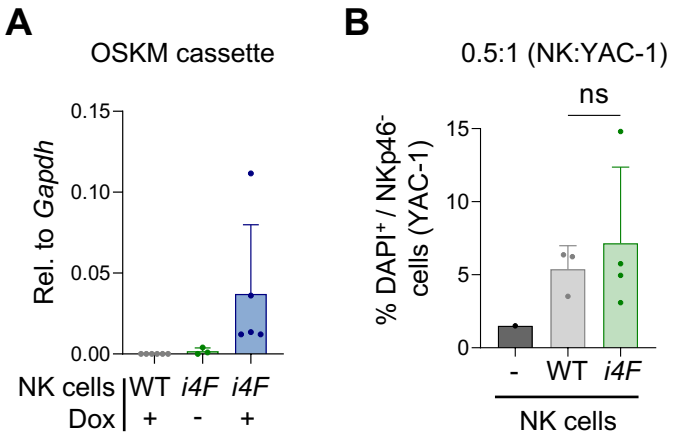


**Fig. S6. NK cells maintain their cytotoxic activity upon OSKM induction. A.** Spleens were harvested and NK cells were isolated on day 7 post-doxycycline (dox) initiation. Expression of the OSKM transgene was assessed by RT-qPCR (*n*=5 for WT+ dox and *i4F* + dox groups, and *n*=3 for *i4F* group). **B**. Percentage of DAPI$^{+}$ YAC-1 cells lysed by WT or *i4F* NK cells. Mice were reprogrammed *in vivo* for 5 days and NK cells were isolated from the spleen. NK cells were primed *in vitro* with IL-2 and IL-15 in NK media for 6 days in the presence of doxycycline (1 µg/ml). A cytotoxic assay using YAC-1 as target cells was done after 4 hours of co-culture. Cell death was assessed using DAPI and NK cells were excluded using NKp46 antibody (*n*=3 for WT and *n*=4 for *i4F* group).

# Figure S7

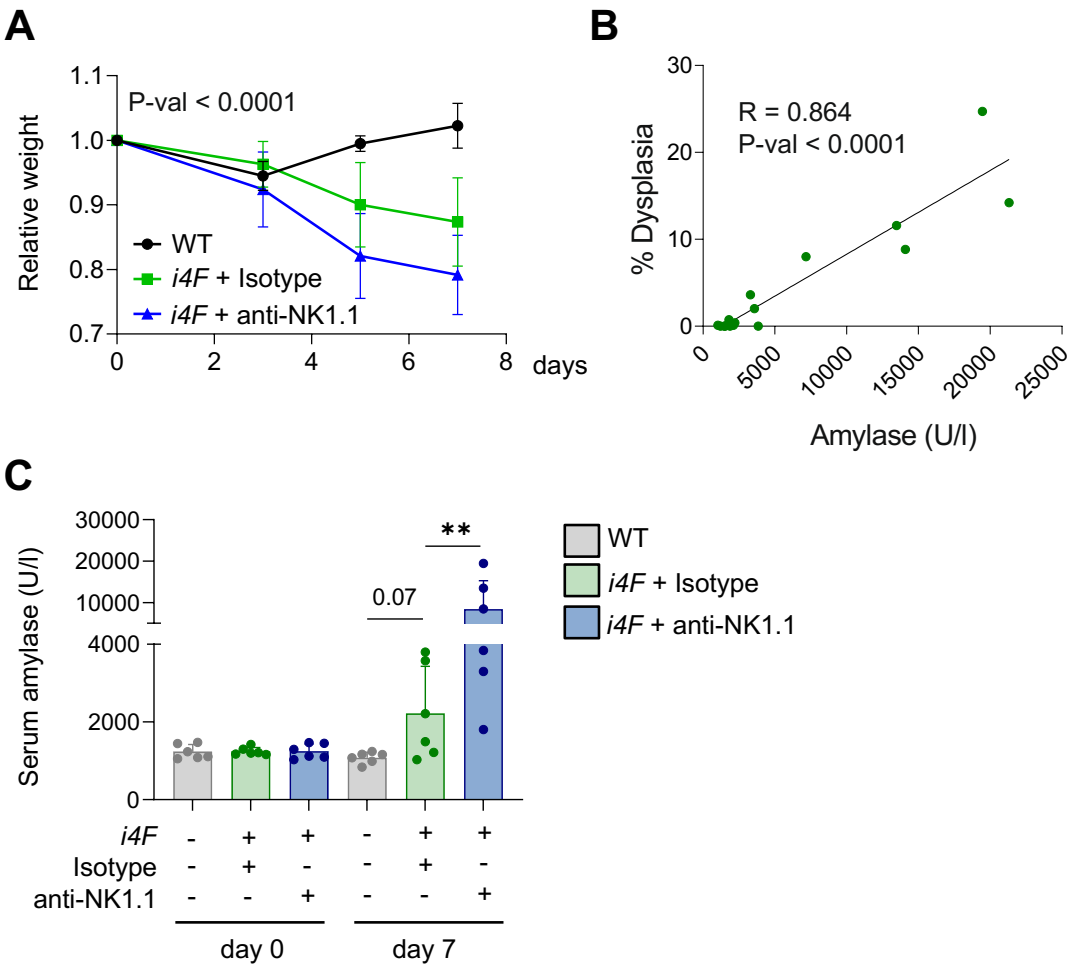


**Fig. S7. Reprogrammed *i4F* mice treated with anti-NK1.1 lose more weight and have higher levels of amylase in serum than *i4F* mice treated with isotype control antibody. A.** Relative weight loss of mice treated with doxycycline and anti-NK1.1 or isotype control antibodies for 7 days ($n$ = 6). **B**. Correlation between amylase in serum and percentage of dysplasia in pancreas of *i4F* mice at day 7 of reprogramming ($n$=12). **C**. Amylase levels in serum at days 0 and 7 from reprogrammed mice treated with anti-NK1.1 or isotype control antibodies ($n$ = 6). Graphs represent mean ± SD; **$p$<0.01 and statistical significance was evaluated using simple lineal regression (**A** and **B**) and two-tailed Student's t-test (**C**).

**Table S1**. List of primers used for mRNA expression analyses.

| Name | Forward | Reverse |
|---|---|---|
| *E2A-cMyc* | GGCTGGAGATGTTGAGAGCAA | AAAGGAAATCCAGTGGCGC |
| *Rae1* | ACCCGAATGCAGACAGGAAGTTGA | GGACCTTGAGGTTGATCTTGGCTT |
| *Mult1* | CAATGTCTCTGTCCT CGGAA | CTGAACACGTCTCAGGCACT |
| *Icam1* | CTGTTTGAGCTGAGCGAGAT | AGGGTGAGGTCCTTGCCTAC |
| *Cd155* | CAACTGGTATGTTGGCCTCA | ATTGGTGACTTCGCACACAA |
| *Gapdh* | AGGTCGGTGTGAACGGATTTG | TGTAGACCATGTAGTTGAGGTCA |

**Table S2**. List of fluorescent antibodies used for cytometry analyses.

| Antibody | Source | Identifier | Dilution |
|---|---|---|---|
| B220 PE | Biolegend | 103207 | 1:200 |
| CD107a BV711 | Biolegend | 564348 | 1:100 |
| CD11b A488 | BioLegend | 101219 | 1:200 |
| CD11b BV786 | BD Biosciences | 740861 | 1:200 |
| CD11b PECy7 | eBioscience | 25-0112-82 | 1:300 |
| CD11b PerCPCy5.5 | eBioscience | 45-0112-82 | 1:400 |
| CD11c PE-Vio 770 | Milteny Biotec | 130-110-840 | 1:200 |
| CD155 PE-Cy7 | Biolegend | 131512 | 1:200 |
| CD19-B220 APC-eF780 | eBioscience | 47-0452-80 | 1:200 |
| CD3 AF700 | eBioscience | 56-0032-82 | 1:100 |
| CD3 APC | eBiosciences | 17-0032-80 | 1:300 |
| CD3 FITC | Biolegend | 100203 | 1:100 |
| CD3ϵ PerCPCy5.5 | Biolegend | 100327 | 1:100 |
| CD4 APC-eFluor780 | eBioscience | 47-0041-80 | 1:200 |
| CD4 PE EF610 | eBioscience | 61-0042-80 | 1:400 |
| CD45 BV605 | Biolegend | 103139 | 1:400 |
| CD45 PE | BD Biosciences | 553081 | 1:400 |
| CD45 PerCP | BioLegend | 103130 | 1:200 |
| CD54/ICAM1 FITC | eBioscience | 11-0541-82 | 1:200 |
| CD8 BV786 | BD Biosciences | 563332 | 1:400 |
| CD8 FITC | eBioscience | 11-0081-82 | 1:400 |
| F4/80 AF647 | BioLegend | 123122 | 1:100 |
| F4/80 APC | BioLegend | 123115 | 1:100 |
| H60 APC | Milteny Biotec | 130-108-821 | 1:100 |
| Ly49CI BV421 | BD Biosciences | 744027 | 1:100 |
| Ly6C FITC | BD Biosciences | 561085 | 1:300 |
| Ly6G PE | BD Biosciences | 561104 | 1:300 |
| NK1.1 APCCy7 | BioLegend | 108723 | 1:400 |
| NK1.1 BV711 | Biolegend | 108745 | 1:200 |
| NKG2A/CD159A PECy7 | Biolegend | 142809 | 1:100 |
| NKG2D/CD314 PE | Biolegend | 130207 | 1:100 |
| NKp46-APC/Fire™ 750 | BD Biosciences | 137631 | 1:50 |
| Rae1 Pan FITC | Milteny Biotec | 130-111-468 | 1:50 |
| ULBP1/MULT1 PE | R&D Systems | FAB2588P | 1:100 |