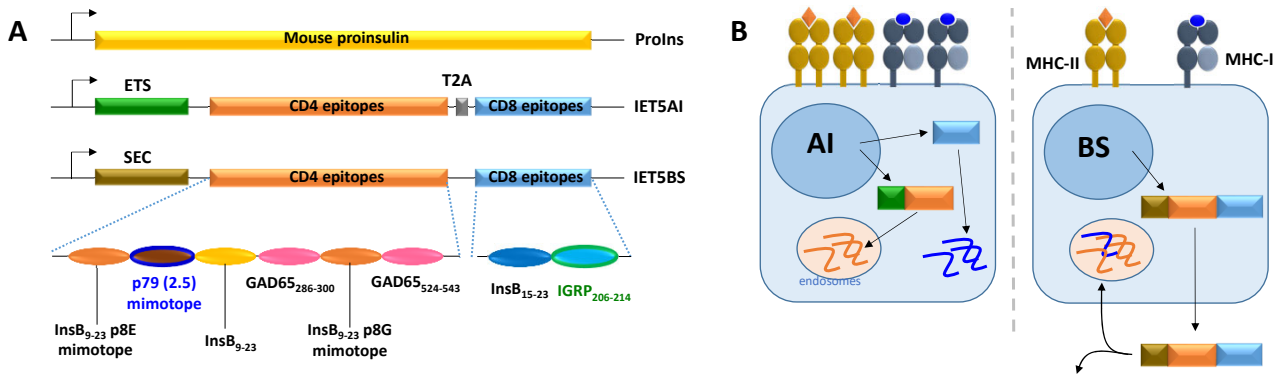

Figure S1. DNA constructs: arrangement and targeting of epitopes. (**A**) Constructs used for expression of mouse proinsulin (ProIns) or tailored epitopes (IET5AI and BS) on pDNA vectors (pBHT568 backbone). The AI variant features the invariant chain's endosomal targeting signal (ETS) Ii_{1-80}, preceding native CD4 epitopes ($InsB_{9-23}$; $GAD65_{286-300}$; $GAD65_{534-543}$) and mimotopes ($InsB_{9-23}$ R22E [p8E] and E21G/R22E [p8G]; and 2.5mi [p79]), followed by a cleavage site (T2A), separating them from native CD8 epitopes ($InsB_{15-23}$; $IGRP_{206-214}$). The BS variant features the same epitopes and mimotopes as AI but expressed them on a single polypeptide preceded by an albumin secretion signal (SEC). The epitopes recognized by the TCR-tg T cells from BDC2.5 and NY8.3 mice are indicated in blue and green, respectively. (**B**) Epitopes produced by the AI variant remain intracellular, resulting in maximal antigen loading in the transfected cells, whereas epitopes produced by the BS variant are secreted. The secreted polypeptides may then be taken up by the producing cells and by other cells in the vicinity.

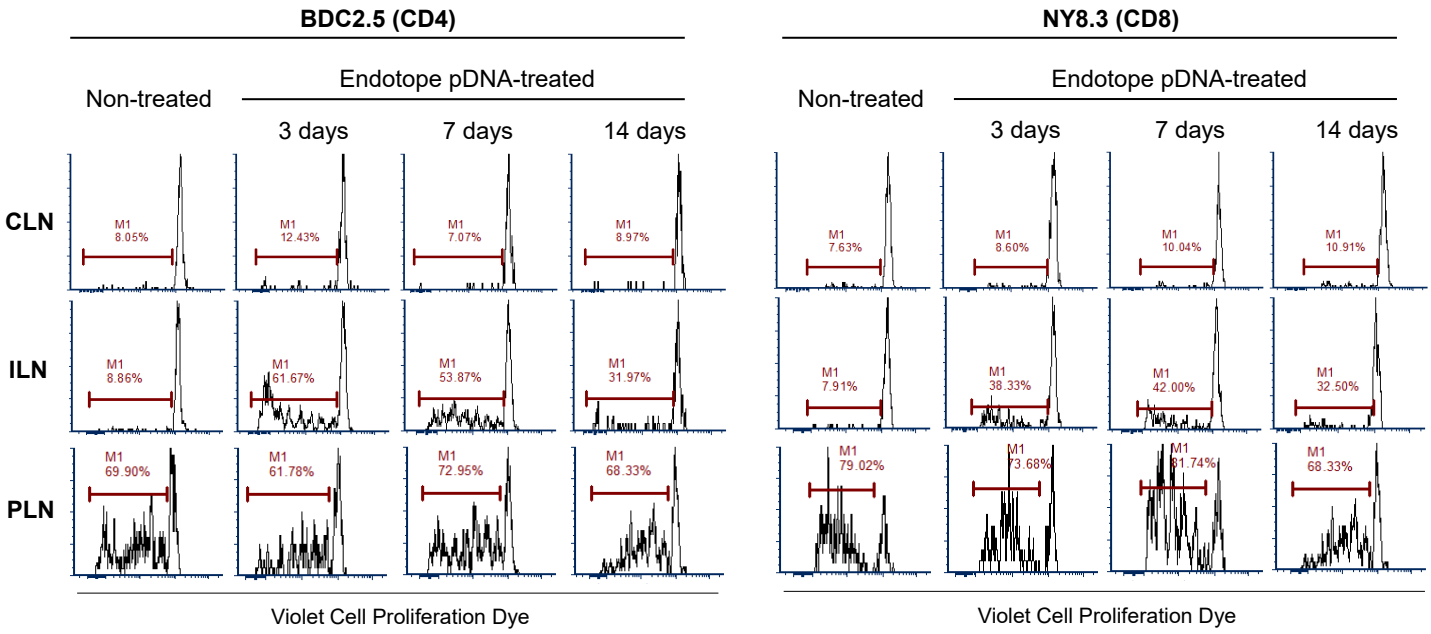

Figure S2. Persistence of Endotope's epitopes presentation in vivo after pDNA inoculation.
Representative data from one experiment out of two showing the proliferation (% T cells that have divided at least once) of TCR-tg BDC2.5 CD4+ and NY8.3 CD8+ T cells transferred into either non-treated control NOD mice or NOD mice that have been received Endotope pDNA by i.d. injection 3, 7 or 14 days earlier. Proliferation was assessed 3 days after adoptive transfer in inguinal LNs (ILN) draining the inoculation site, cervical LNs (CLN) serving as internal negative control and pancreatic LNs (PLN) serving as positive control.

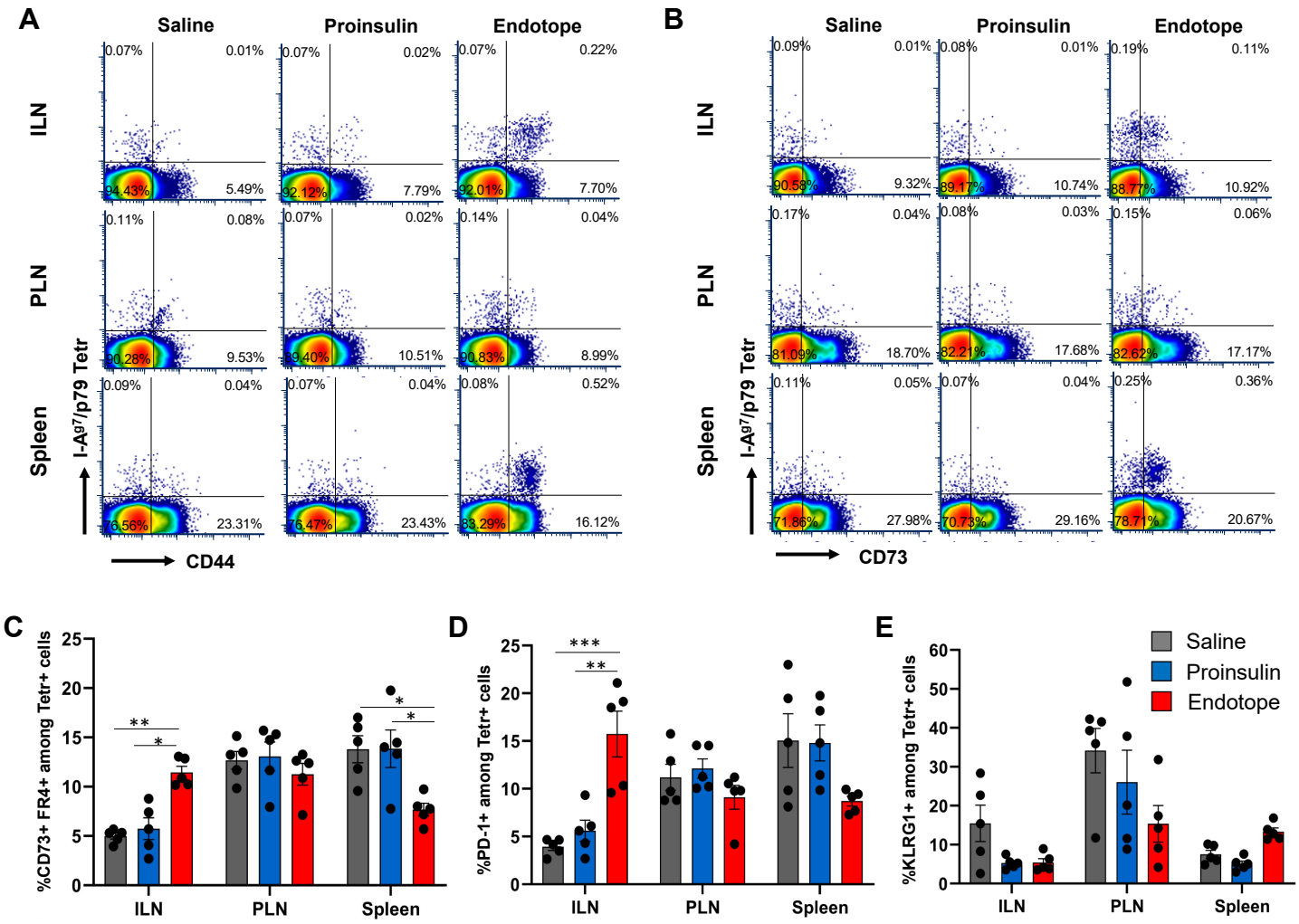

Figure S3. Effect of Endotope pDNA on the phenotype of epitope-specific CD4+ T cells. Female NOD mice (n=5 mice per group) were treated i.d. and weekly for 10 weeks. (**A,B**) Representative dot plots showing expression of CD44 (A) and CD73 (B) on p79-reactive tetramer (Tetr)+ CD4+ T cells from inguinal LN (ILN), pancreatic LN (PLN) and spleen after saline, Proinsulin or Endotope pDNA treatment. (**C-E**) Percentage (mean ±SEM) of CD73+ FR4+ cells (C), PD-1+ cells (D) and KLRG1+ cells (E) among Tetr+ CD4+ T cells.

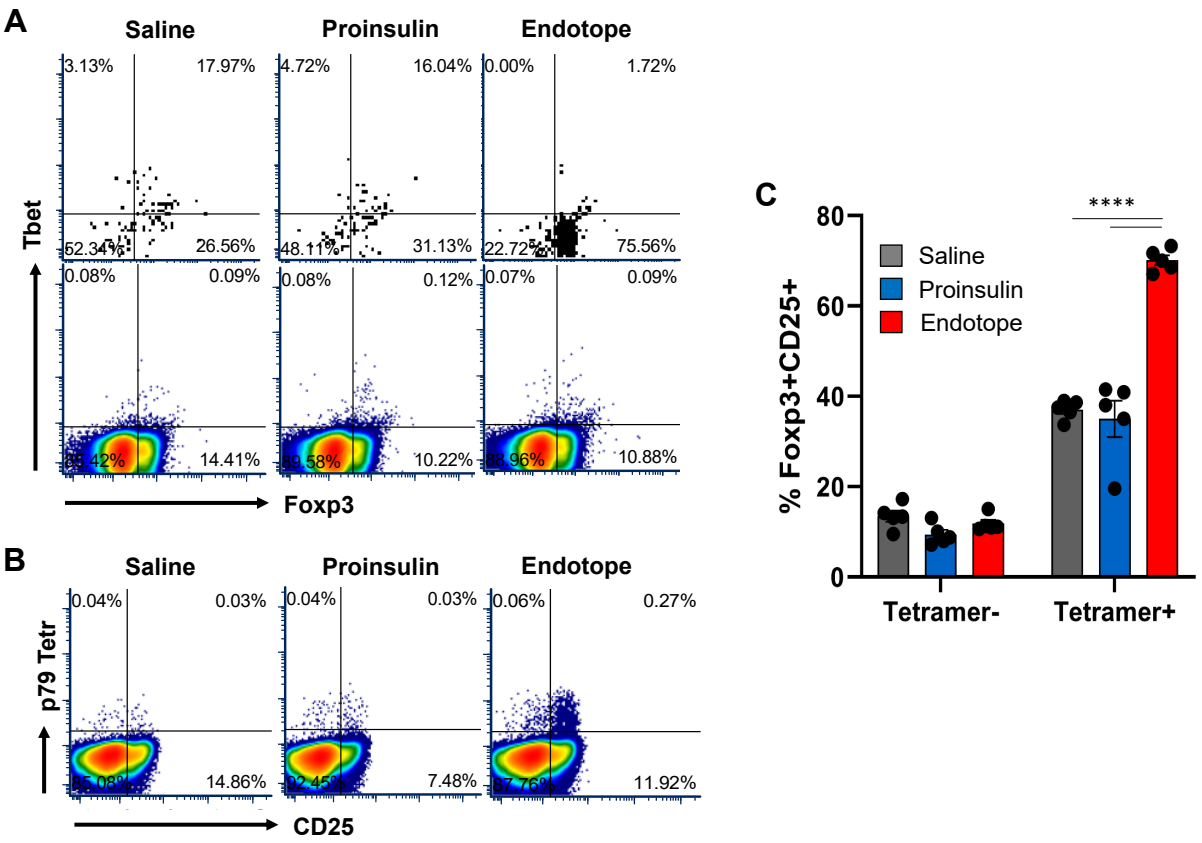

Figure S4. Effect of Endotope pDNA on the phenotype of epitope-specific CD4+ T cells. Female NOD mice (n=5 mice per group) were treated i.d. and weekly for 10 weeks. (**A,B**) Representative dot plots showing expression of Foxp3 and Tbet in Tetr+ (top) and Tetr- (bottom) CD4+ T cells (A) and expression of CD25 in Tetr+ and Tetr- cells among total CD4+ T cells (B). (**C**) Percentage (mean ±SEM) of Foxp3+ CD25+ T cells among Tetr+ and Tetr- CD4+ T cells. Significant differences were determined by two-way ANOVA with Tukey's multiple comparisons.

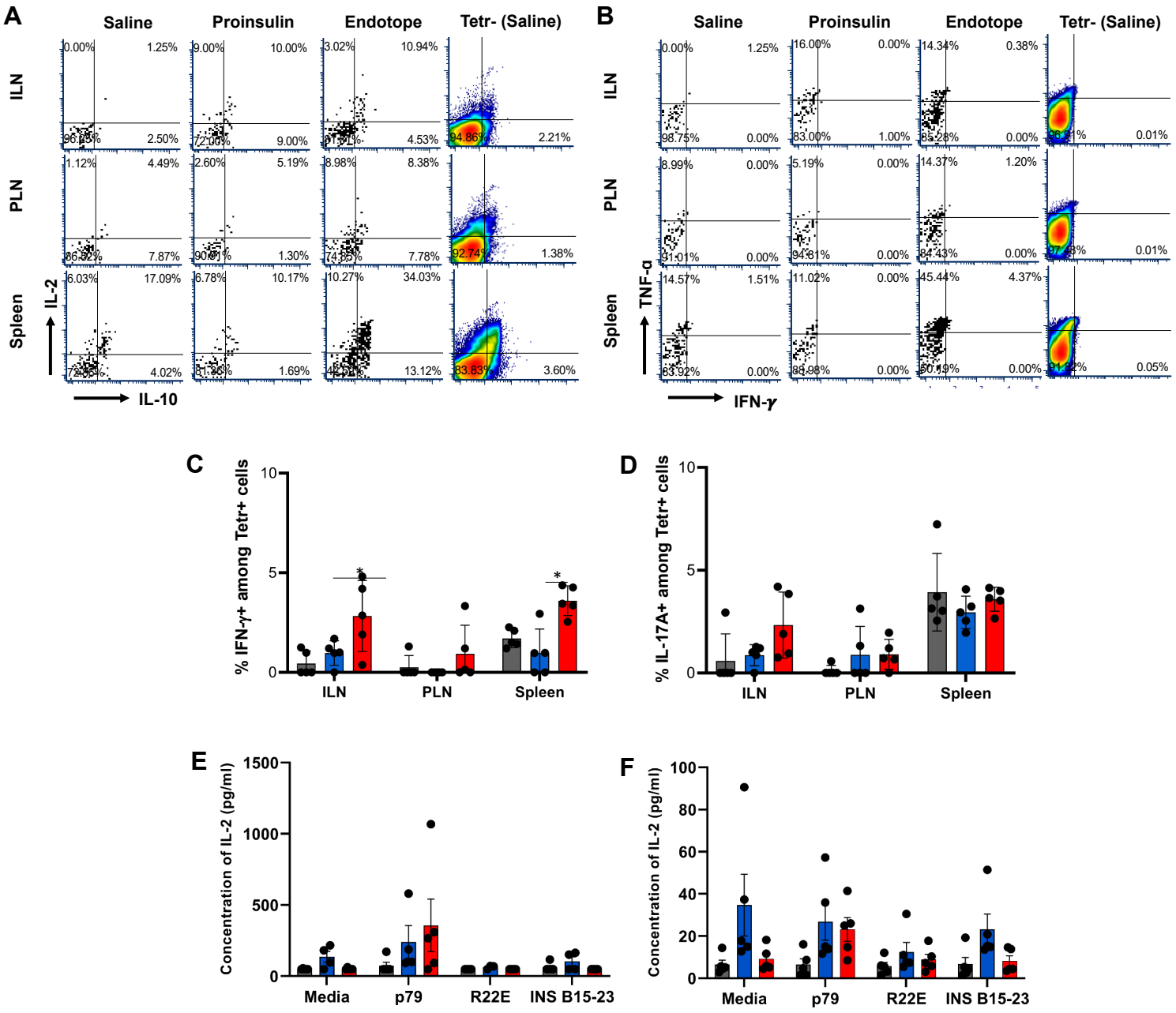

Figure S5. Effect of Endotope pDNA on the cytokine profile of epitope-specific CD4+ T cells. Female NOD mice (n=5 mice per group) were treated i.d. and weekly for 10 weeks. (**A,B**) Representative dot plots showing expression of IL-2 and IL-10 (A) and TNF-α and IFN-γ (B) on p79-reactive tetramer (Tetr)+ CD4+ T cells from inguinal LN (ILN), pancreatic LN (PLN) and spleen after saline, Proinsulin or Endotope pDNA treatment, and on Tetr- CD4+ T cells (saline group shown as example). (**C,D**) Percentage (mean ±SEM) of IFN-γ+ cells (C) and IL-17A+ cells (D) among Tetr+ CD4+ T cells, assessed by intracellular staining. (**D,E**) Levels (mean ±SEM) of IL-2 produced 3 days after restimulation of ILN cells (D) or splenocytes (E) with p79, $InsB_{9\text{-}23}$ R22E or InsB15-23 peptides. Significant differences were determined by two-way ANOVA with Tukey's multiple comparisons.

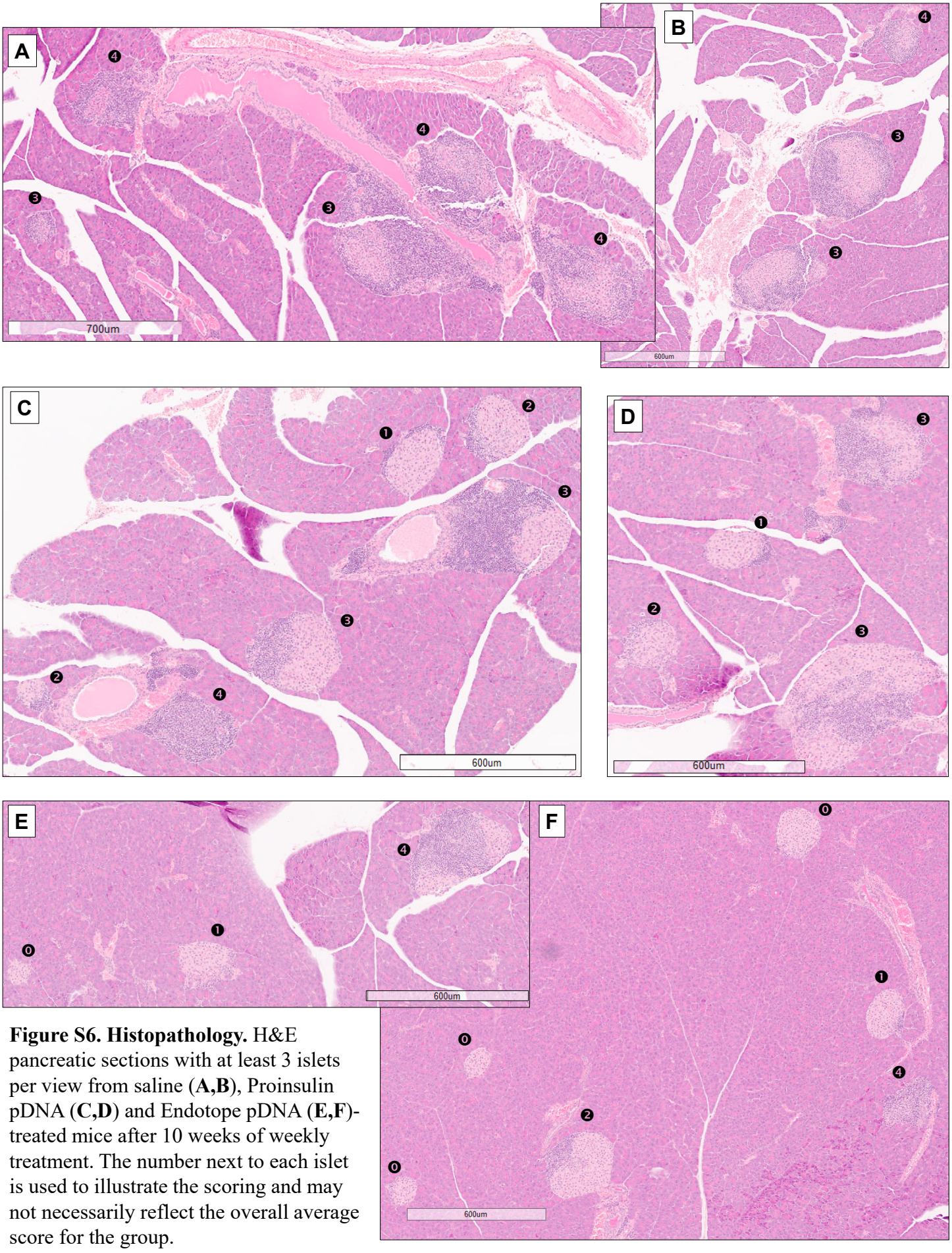

Figure S6. Histopathology. H&E pancreatic sections with at least 3 islets per view from saline (**A,B**), Proinsulin pDNA (**C,D**) and Endotope pDNA (**E,F**)-treated mice after 10 weeks of weekly treatment. The number next to each islet is used to illustrate the scoring and may not necessarily reflect the overall average score for the group.

Table S1. **List of antibodies used to characterize T cell responses**. All antibodies are anti-mouse and purchased from Biolegend except Foxp3, TIGIT and T-bet, purchased from eBioscience. The I-A^{g7}/p79 tetramer (I-A^{g7}/ AAAAVRPLWVRMEAA) was used APC-conjugated at 1:400 dilution.

Target	Clone	Conjugate	Dilution	RRID
CD4	GK1.5	APC Cy7	1:400	AB_312699
CD25 (IL-2Ra)	PC61	BV605	1:400	AB_2563059
CD44	IM7	AF700	1:400	AB_493713
CD73	TY/11.8	FITC	1:300	AB_2716076
FR4	12A5	PE	1:300	AB_1134202
CD279 (PD-1)	RMP1-30	PE-Cy7	1:400	AB_2637375
TIGIT	GIGD7	PE-Cy7	1:300	AB_572017
Foxp3	FKJ-16s	BV421	1:100	AB_1518813
T-bet	O4-46	PE	1:100	AB_10564071
IFN-γ	XMG1.2	BV785	1:100	AB_2629667
IL-10	JES5-16E3	PE-Cy7	1:100	AB_11150582
IL-2	MQ1-17H12	PE	1:100	AB_315089
IL-17A	TC11-18H10.1	BV605	1:100	AB_536018
TNF-α	MP6-XT22	PerCP/Cy5.5	1:100	AB_315427
Granzyme B	QA16A02	AF700	1:100	AB_2728389