SUPPLEMENTAL METHODS

HERV-W-Env staining using GN_mAb_Env04 antibody: A preliminary IHC study was performed on pancreata from a pilot cohort of 6 non-T1D controls and 11 T1D donors. For this study, one pancreas section was obtained for each donor and the staining was performed using GN_mAb_Env04 antibody and with Dako HRP system (K0679). Slides were deparaffinized and rehydrated. Peroxidases and avidines (Dako X0590) were blocked 10 and 5 minutes respectively. GN_mAb_Env04 was diluted in 10% human serum at 5µg/mL and incubated 1 hour at room temperature before incubating for 30 minutes Polyclonal Rabbit anti Mouse IgG biotinylated 10 µg/mL in PBS. After Streptavidin and DAB steps, hematoxylin counterstaining was applied. The slides were digitalized with the slide scanner NANOZOOMER 2.0RS/C10730-12 (Hamamatsu), objective x40.

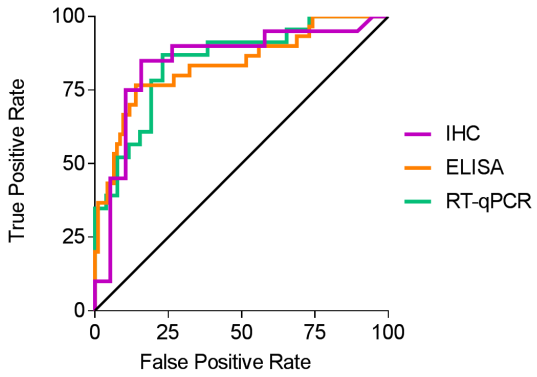
CD68 immunostaining: Slides adjacent to the ones stained with GN_mAb_Env04 were dewaxed, rehydrated, and antigenic site retrieval was carried out by 12 minutes microwaving in 10mM Tris-1mM EDTA (pH 9). Samples were washed in PBS, and incubated with the primary antibody (monoclonal anti-human CD68, M087629-2 Dako), diluted 1/100 in PBS-3% BSA, overnight at 4°C. Endogenous peroxidase activity was blocked for 20 min with 0.5% hydrogen peroxide at room temperature and samples were incubated with the HRP mouse EnvisionTM System (Dako, K4000) for 45 minutes at room temperature. Antigen-antibody complexes were revealed by DAB (Dako, K3468) and cells were slightly counterstained with Mayer's hematoxylin (Diapath, ref. C0303). Sections were mounted with aqueous medium for microscopic observation.

Supplemental Table 1: Antibodies

Antibody	Supplier	Reference	Type	Working Concentration
ELISA				
GN_mAb_Env04	Geneuro-Innovation	GN_mAb_Env04	Monoclonal mouse IgG1	2.5µg/ml
GN_mAb_Env16	Geneuro-Innovation	GN_mAb_Env16	Monoclonal mouse IgG2a	2.5µg/ml
GN_mAb_Env01-HRP	Geneuro-Innovation	GN_mAb_Env01-HRP	Monoclonal mouse IgG1	0.5µg/ml
IHC				
Isotype mouse IgG2a	Abcam	Ab18415	Monoclonal mouse IgG2a	0.5 mg/mL
GN_mAb_Env03	Geneuro-Innovation	GN_mAb_Env03	Monoclonal mouse IgG2a	5 µg/mL
Anti-insulin	Cell Signaling	3014	Rabbit monoclonal	1/400
Rabbit IgG isotype	Abcam	ab172730	Rabbit monoclonal EPR25A	10 µg/mL
Anti-glucagon	Sigma	G2654	Mouse IgG1 clone K79bB10	1/64000
Mouse IgG1 isotype	Abcam	ab18447	Mouse IgG1, kappa monoclonal [MG1-45]	1.16 µg/mL
GN_mAb_Env04	Geneuro-Innovation	GN_mAb_Env04	Monoclonal mouse IgG1	5 µg/mL
Monoclonal mouse IgG1	Abcam	ab18448	Mouse IgG1 kappa monoclonal MG1-45	5 µg/mL
Anti-Mouse IgG biotinilated	Dako	E0464	Polyclonal Rabbit anti Mouse IgG biotinylated	10 µg/mL
Immunofluorescence				
Anti-CD68	Dako	M0876	Mouse Monoclonal IgG3 PG-M1	3 µg/mL
Anti-CD3	Dako	A0452	Rabbit Polyclonal	12 µg/mL
Donkey anti-rabbit 547	Interchim	FP-SB 5110	Donkey Polyclonal	4 µg/mL
Donkey anti-mouse 647	Interchim	FP-SC 4110	Donkey Polyclonal	20 µg/mL
Anti-Glucagon-AF488	Interchim	BS-3796R-A488	Rabbit Polyclonal conjugated AF488	10 µg/mL
Cell Culture				
GNbAC1	Geneuro	GNbAC1	Humanized monoclonal antibody IgG4	3µg/mL

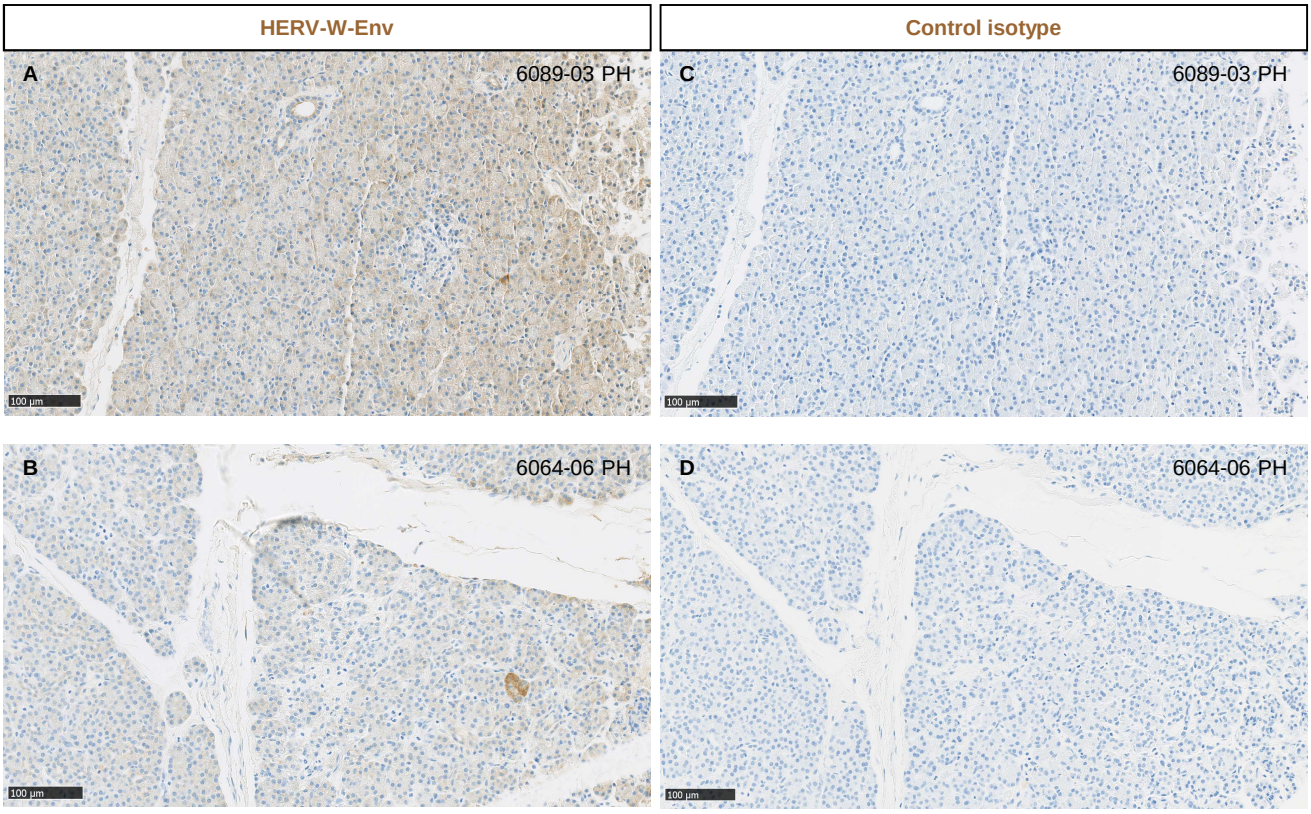
Supplemental Table 2: Primers

Description	Primers name	Forward primer	Reverse primer
Mouse genotyping, detection of the transgene	CAG-Env	ACGTCAGTAGTCATAGGAACTGCG GTCG	TACAGGCGTGAACCACTGCTC CCT
Mouse genotyping, detection of WT HPRT locus	WT-HPRT	TGTCCTTAGAAAACACATATCCAG GGTTTAGG	CTGGCTTAAAGACAACATCTG GGAGAAAAA
HERV-W-env detection in human PBMC	UNO	GTATGTCTGATGGGGGTGGAG	CTAGTCCTTTGTAGGGGCTAG AG
Housekeeping gene *B2M*	B2M	TTACTCACGTCATTCAGCAG	GATGGATGAAACCCAGACAC
Housekeeping gene *YWHAZ*	YWHAZ	TCTCATAATAGAACACAGAGAAGT	TCAGTCACAACAAGCATACC



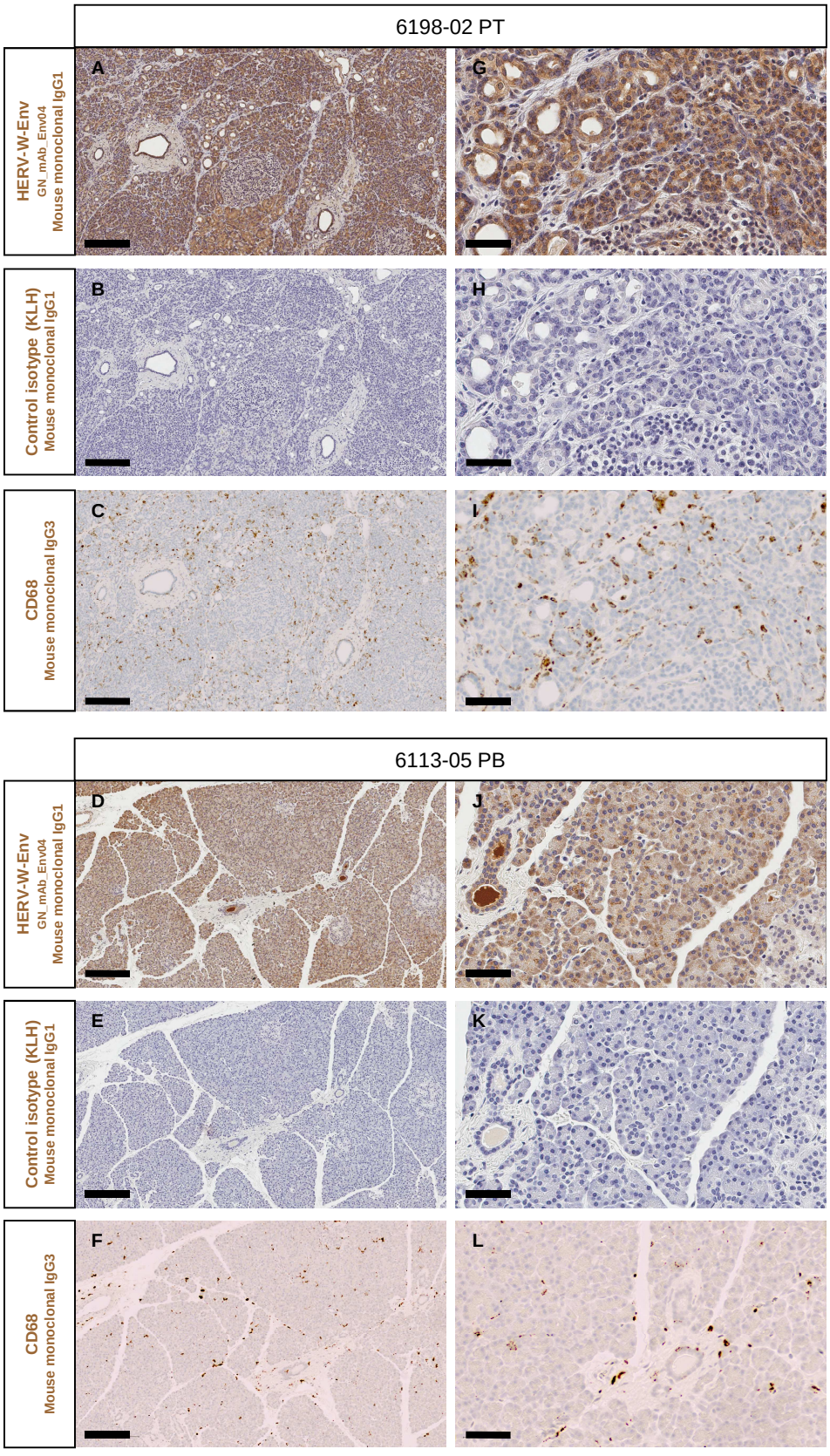
Supplemental figure 1: Performance of HERV-W-Env detection in human T1D patients and controls individuals.

Receiver Operating Characteristic (ROC) curves of HERV-W-Env detection by ELISA in serum (orange line), by RT-qPCR in PBMC (green line) and by IHC in pancreas (violet line). AUC of ROC curve for detection in the serum by ELISA is 0.8362 (CI95: 0.7464 to 0.926; $p < 0.0001$), AUC of ROC curve for detection in PBMC by RT-qPCR is 0.8462 (CI95: 0.7367 to 0.9556; $p < 0.0001$) and AUC of ROC curve for detection in the pancreas by IHC is 0.8461 (CI95: 0.7112 to 0.9809; $p = 0.0002$).



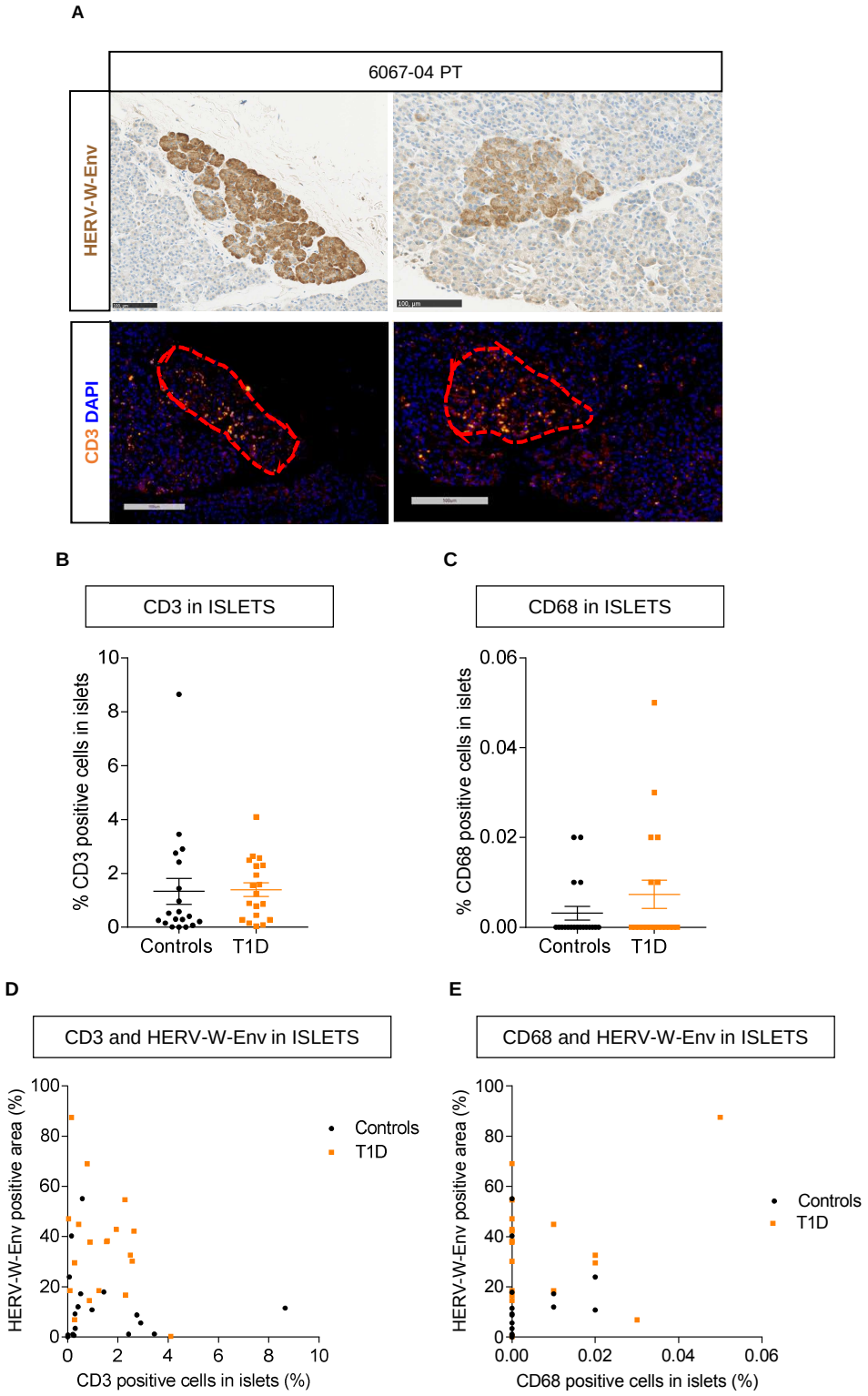
Supplemental Figure 2: Immunostaining of HERV-W-Env using GN_mAb_Env03 antibody and IgG2a control.

Two T1D nPOD cases stained with GN_mAb_Env03 are presented in **A** and **B** with their respective IgG2A controls in **C** and **D** on adjacent slides. nPOD case ID is indicated in the upper right corner, with block number and pancreas zone (PH: pancreas head). Scale bars: 100 µm.



Supplemental Figure 3: HERV-W-Env immunostaining using GN_mAb_Env04, control isotype IgG1 and CD68 immunostaining.

Two pancreas from T1D nPOD cases stained with GN_mAb_Env04 (Mouse monoclonal IgG1 antibody) are presented in **A**, **G**, **D** and **J**, with their respective IgG1 controls in **B, H, E** and **K** on adjacent slides (Control isotype (KLH) Mouse monoclonal IgG1 - ab 18448 Abcam). GN_mAb_Env04 does not recognize the same epitope that GN_mAb_Env03 used in the main IHC study. CD68 staining (mouse monoclonal IgG3 antibody - M087629-2 Dako) is also provided in **C**, **I**, **F** and **L** to show another specific staining with comparable macrophage infiltration than in the main study (Figure 3B). Same areas are presented for each staining; right panels correspond to magnifications of left panels. Right scale bars: 200µm; Left scale bars 50µm. PT: pancreas tail, PB: pancreas body.



Supplemental Figure 4: Pro-inflammatory features associated with HERV-W-Env expression within pancreatic islets

(**A**) Pancreas of nPOD case #6067, which presented several clusters of acinar cells over-expressing HERV-W-Env, was immunostained with GN_mAb_Env03 (upper panels) and anti-CD3 (lower panels) antibodies on adjacent slides. Upper and lower panels correspond to images of the same areas respectively. Clusters of acinar cells over-expressing HERV-W-Env are highlighted by red dot lines in lower panels. Scale bars: 100µm.

(**B**, **C**, **D**, **E**) Number of CD3 and CD68 positive cells in the endocrine part of the pancreas was assessed on pancreas slices from non-T1D controls (n=19) and T1D patients (n=20). Percentages of CD3+ cells (**B**) and CD68+ cells (**C**) in the endocrine pancreas are presented for controls and T1D patients and as a function of HERV-W-Env positively stained area (**D** and **E** respectively) (cf. figure 1 C). For **B** and **C**, results are presented as individual values, and as mean ±SEM.