

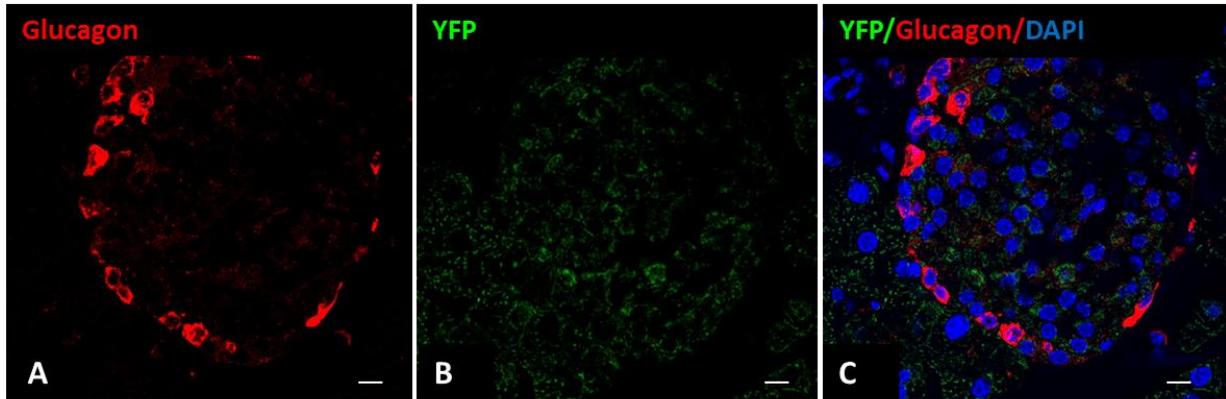
Supplementary Table 1. Primary and secondary antibodies used in this study.

Antibody	Source	Dilution	RRID
Chicken Anti-green fluorescent protein	Aves Laboratories, Tigard, OR; Cat# GFP-1020	1:5000	AB_10000240
Guinea pig Anti-insulin	Dako Cytomation, Carpinteria, CA ; Cat# A0564	1:300	AB_2617169
Rabbit Anti-glucagon	Millipore, Temecula, CA; Cat# AB932	1:300	AB_210732
Rabbit Anti-somatostatin	Immunostar, Hudson, WI; Cat# 20067	1:1000	AB_572264
Goat –Anti-pancreatic polypeptide	Abcam, Cambridge, MA; Cat# ab77192	1:150	AB_1524152
Biotin-SP-conjugated affini-pure-donkey anti-chicken	Jackson ImmunoResearch Laboratories Inc. West Grove, PA; Cat# 703-065-155	1:1000	AB_2313596
Goat-anti-guinea pig IgG Alexa fluor 594	Invitrogen, Life Technology Corporations, Eugene, OR; Cat# A11076	1:500	AB_141930
Donkey-anti-Rabbit IgG Alexa fluor 594	Invitrogen, Life Technology Corporations, Eugene, OR; Cat# A21207	1:500	AB_141637
Donkey-anti-Goat IgG Alexa fluor 594	Invitrogen, Life Technology Corporations, Eugene, OR; Cat# A11058	1:500	AB_2534105
Biotinylated Anti-streptavidin antibody	Vector Laboratories, Burlingame, CA Cat# BA-0500	1:1000	AB_2336221
Donkey-anti-Goat IgG Alexa fluor 647	Invitrogen, Life Technology Corporations, Eugene, OR; Cat# A-21447	1:200	AB_141844

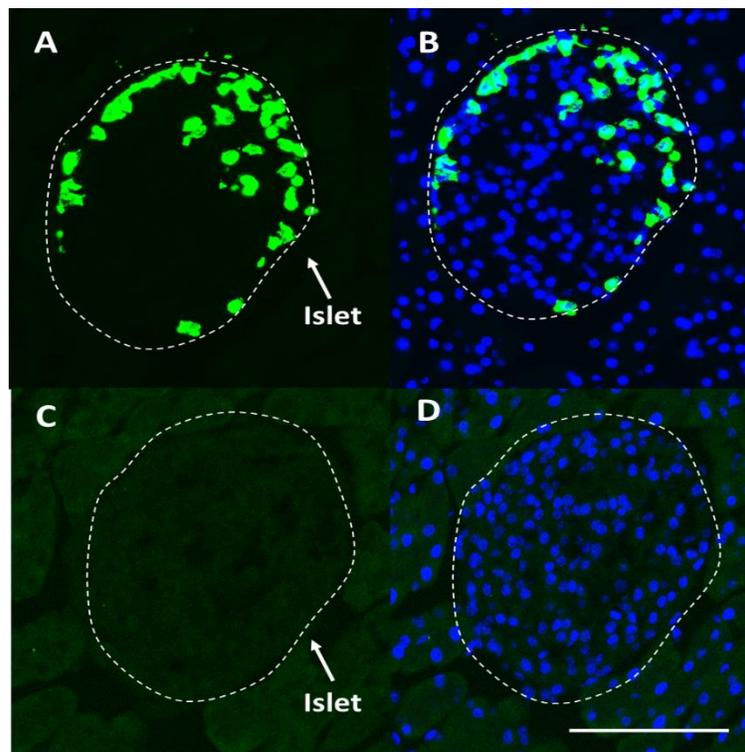
Supplementary Table 2. Effect of type 2 diabetes mellitus on gene expression of the four traditional islet hormones

Cell Cluster	<i>INS</i>				<i>GCG</i>				<i>PPY</i>				<i>SST</i>			
	Log ₂ FC	Average Expression	P value	FDR	Log ₂ FC	Average Expression	P value	FDR	Log ₂ FC	Average Expression	P value	FDR	Log ₂ FC	Average Expression	P value	FDR
Alpha1	-0.008	1.5903	9.323E-01	9.546E-01	0.203	6.1350	2.136E-02	4.676E-02	0.319	0.5482	1.137E-01	1.865E-01	0.358	1.6133	5.331E-02	1.012E-01
Alpha2	-1.711	1.7051	2.585E-07	3.639E-05	0.102	6.2060	6.286E-01	8.095E-01	-4.841	0.3713	5.710E-15	5.894E-12	2.052	1.2230	1.112E-06	1.012E-04
Beta1	-0.768	6.5372	2.236E-33	3.027E-31	-0.274	1.4247	7.128E-02	1.194E-01	-0.873	0.4705	1.172E-06	6.266E-06	1.601	2.0407	3.209E-21	1.470E-19
Beta2	-0.176	6.1570	7.201E-01	8.992E-01	1.358	1.5160	1.663E-01	4.395E-01	0.5235				4.203	2.2430	1.962E-05	1.773E-03
Delta	0.387	2.2880	1.557E-01	2.777E-01	-0.330	1.6925	3.616E-01	5.132E-01	-1.906	0.5593	2.027E-05	1.991E-04	0.187	6.8620	1.943E-01	3.262E-01
Gamma	-1.198	1.6140	2.459E-03	3.678E-02	1.071	1.6564	6.159E-03	6.585E-02	-0.786	6.4330	1.239E-07	2.547E-05	0.960	1.7824	2.533E-03	3.758E-02
Epsilon	1.374	2.2170	3.891E-01	9.609E-01	-2.743	1.5851	2.722E-01	8.881E-01	2.858	0.9273	4.983E-01	1.000E+00	-0.836	2.7421	8.212E-01	1.000E+00
Acinar	-0.148	1.2340	5.552E-01	6.731E-01	-1.183	1.0078	1.361E-04	6.837E-04	0.2828				2.726	1.1187	7.507E-18	5.364E-16
Ductal1	-1.367	1.3452	1.850E-07	3.623E-06	-1.998	1.4450	2.137E-09	7.335E-08	1.030	0.3207	2.094E-04	1.388E-03	-0.394	1.4520	2.164E-01	3.513E-01
Ductal2	-0.289	1.4838	6.482E-01	8.631E-01	-5.241	1.7490	4.786E-08	7.626E-05	-3.856	0.4068	3.346E-05	3.997E-03	0.984	1.6776	3.144E-01	6.301E-01
Endothelial	-1.963	2.5620	5.182E-02	3.102E-01	1.415	1.2750	2.445E-01	5.974E-01	0.3331				-0.599	2.1686	3.841E-01	7.163E-01
Macrophage	2.379	2.4020	3.910E-02	2.251E-01	-6.752	1.9720	4.197E-05	3.593E-03	6.465	0.6046	3.884E-08	5.154E-05	1.905	2.4280	7.112E-03	8.542E-02
Mast	-0.892	2.6490	5.184E-01	8.442E-01	-2.972	1.8840	3.481E-02	2.535E-01	-0.800	0.9149	7.329E-01	9.299E-01	9.280	2.9550	1.398E-04	1.610E-02
Stellate	-1.337	1.7116	6.925E-03	3.773E-02	-3.796	1.4830	1.489E-09	1.896E-07	3.389	0.3405	4.072E-11	7.521E-09	-0.704	1.7513	7.495E-02	2.083E-01

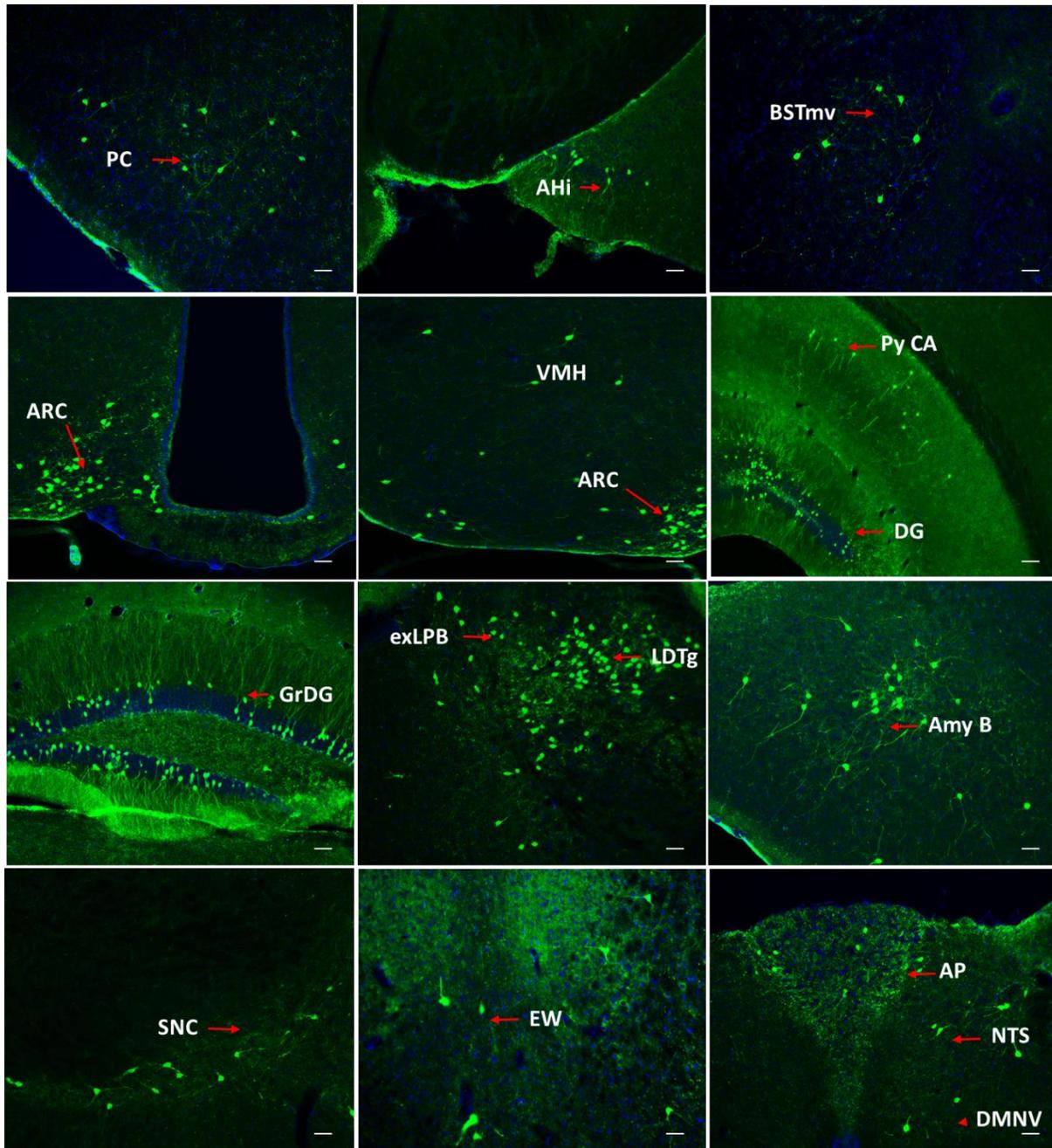
Log₂FC = log₂ fold-change. Average Expression = the mean log normalized expression level in all cells of that cluster regardless of diabetes status. FDR = false discovery rate. A positive Log₂FC value identifies a gene upregulated in T2DM, while a negative Log₂FC value identifies a gene downregulated in T2DM. A gene was considered to be differentially expressed if FDR < 0.1; those differentially expressed genes are highlighted using bolded font.



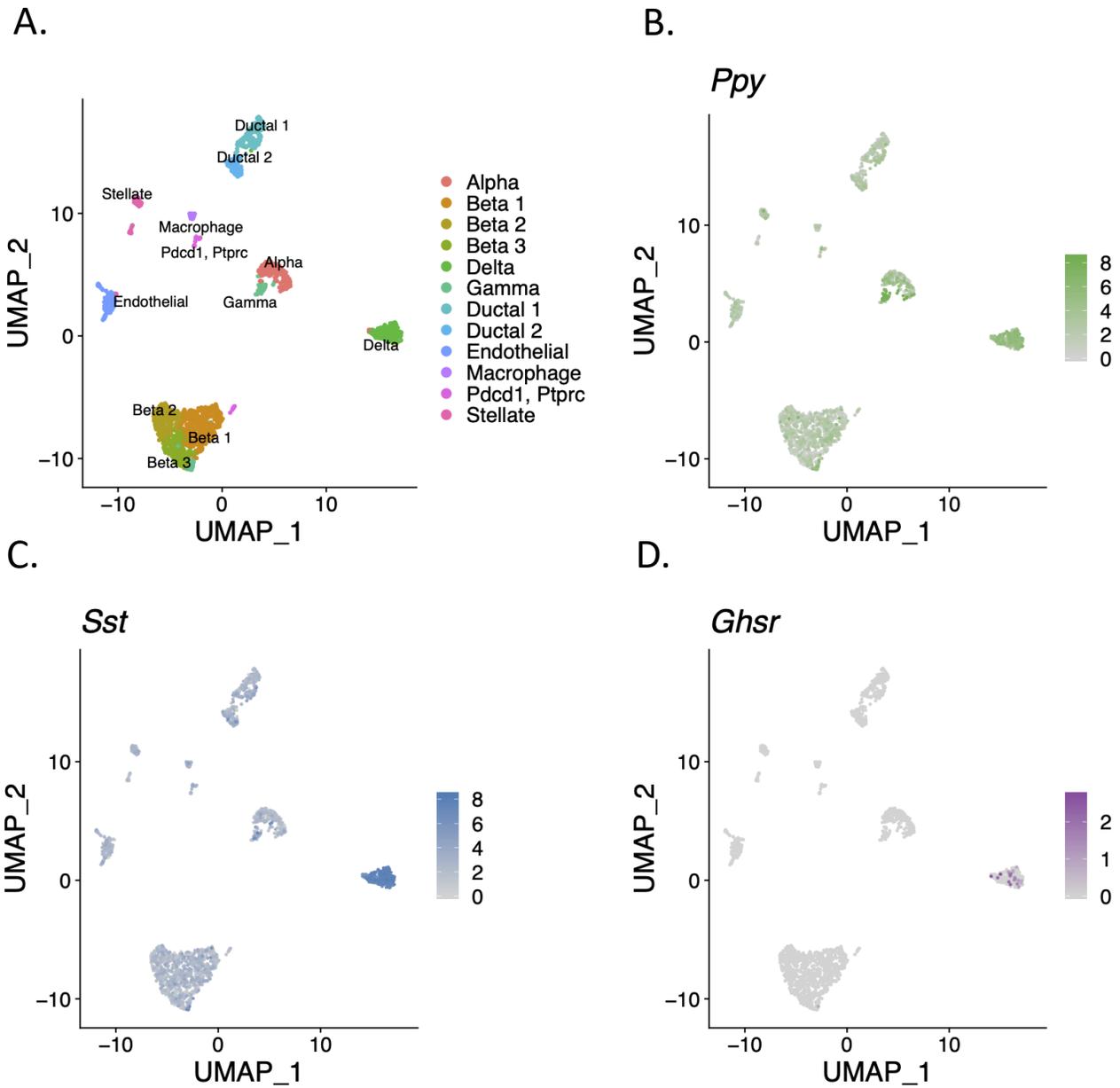
Supplementary Figure 1. YFP expression in a representative islet from a Cre-dependent ROSA26-YFP reporter mouse that lacks *Ghsr-IRES-Cre*. (A) glucagon-immunoreactivity (red), (B) YFP-immunoreactivity (green; none observed) and (C) merged glucagon-immunoreactivity (red) and YFP-immunoreactivity (green) with DAPI (blue, as a nuclear stain). Scale bars = 50 μ m.



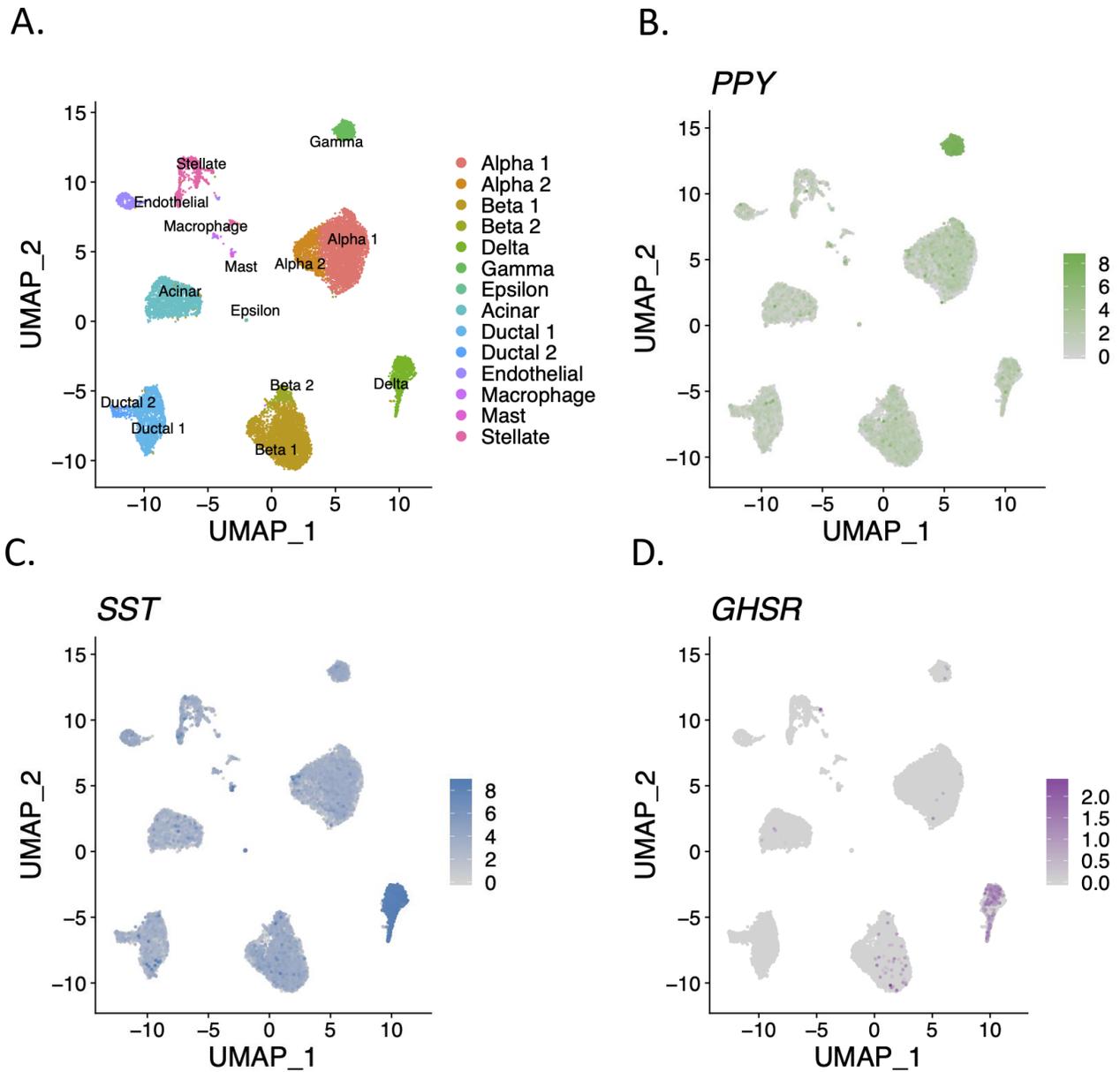
Supplementary Figure 2. Anti-PP antibody validation in mouse. (A) PP-immunoreactivity (green) within a representative islet from a Cre-dependent ROSA26-YFP reporter mouse carrying the *Ghsr-IRES-Cre* allele. (B) The same islet and staining as in (A), also showing DAPI (blue, as a nuclear stain). (C) Absence of PP-immunoreactivity within a representative islet from a Cre-dependent ROSA26-YFP reporter mouse carrying the *Ghsr-IRES-Cre* allele, using the same PP antibody which had been pre-absorbed with PP blocking peptide. (D) The same islet and staining as in (C), also showing DAPI (blue). Scale bars = 100 μ m, n = 3/group.



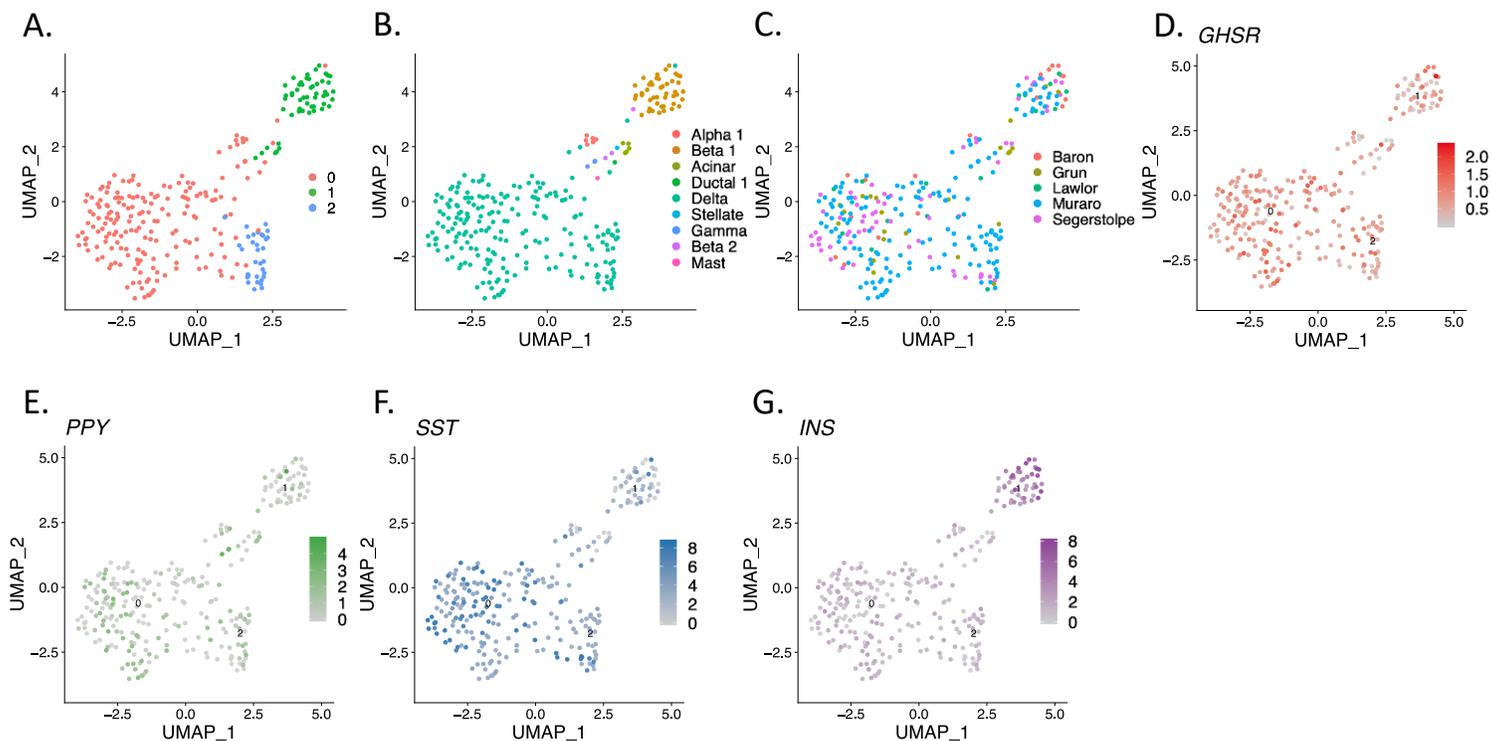
Supplementary Figure 3. YFP reporter expression (green) in coronal brain sections of one of the three *Ghsr-IRES-Cre* mice x *Cre*-dependent *ROSA26-YFP* reporter mice used to analyze islet GHSR expression. PC, Piriform cortex; AHi, Amygdaloid hippocampal area; BSTmv, medial division, ventral part of the Bed nucleus of the stria terminalis; ARC, Arcuate nucleus; VMH, Ventromedial hypothalamus; DG, Dentate gyrus; Py CA, Pyramidal Cornu Ammonis area; GrDG, Granular layer of dentate gyrus; exLPB, Lateral parabrachial nucleus, external; LDTg, Laterodorsal tegmental nucleus; Amy B, Basolateral amygdaloid nucleus; SNC, Substantia nigra, pars compacta; EW, Edinger Westphal nucleus; AP, Area postrema; NTS, Nucleus of the solitary tract; DMNV, Dorsal motor nucleus of the vagus. Scale bars = 50 μ m.



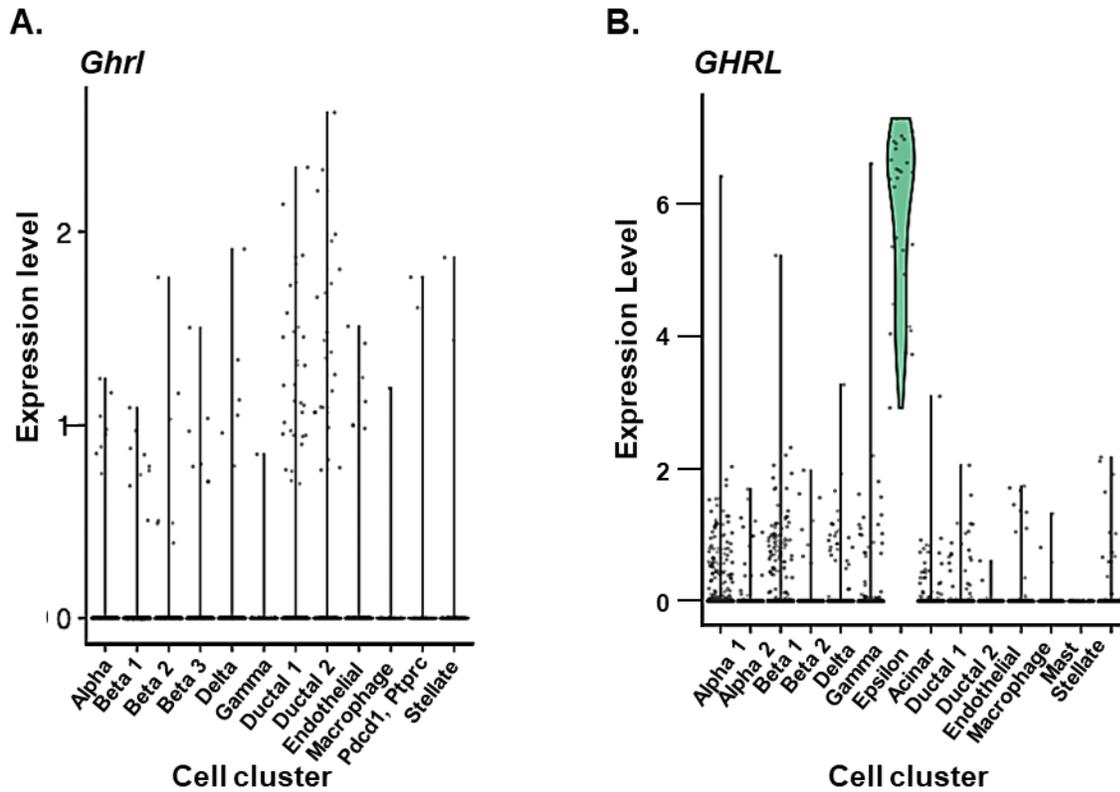
Supplementary Figure 4. UMAP (Uniform Manifold Approximation and Projection) plots of mouse pancreatic cells ($n = 1,886$) highlighting (A) the distribution of pancreatic cells into 12 cell clusters. Each dot represents a single cell. Different cell clusters are color-coded as per the legend. UMAP plots highlighting (B) *Ppy* expression, (C) *Sst* expression, and (D) *Ghsr* expression patterns within each cell cluster. Expression levels in (B-D) are color-coded according to the accompanying legends, with green, blue, or purple, respectively, indicating high expression.



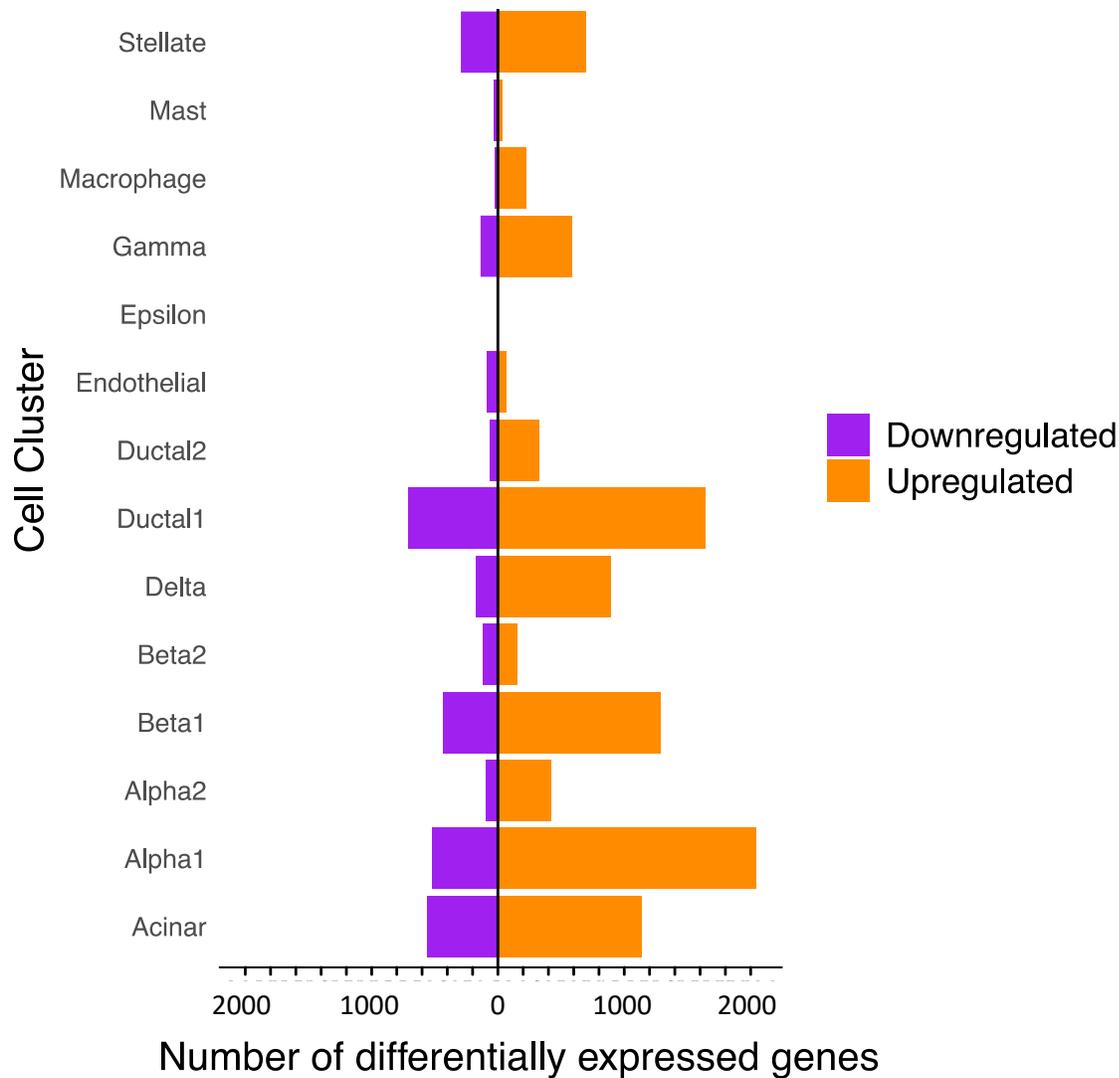
Supplementary Figure 5. UMAP (Uniform Manifold Approximation and Projection) plots of human pancreatic cells ($n = 14,011$) highlighting (A) the distribution of pancreatic cells into 14 cell clusters. Each dot represents a single cell. Different cell clusters are color-coded as per the legend. UMAP plots highlighting (B) *PPY* expression, (C) *SST* expression, and (D) *GHSR* expression patterns within each cell cluster. Expression levels in (B-D) are color-coded according to the accompanying legend, with green, blue, and purple, respectively, indicating high expression.



Supplementary Figure 6. UMAP (Uniform Manifold Approximation and Projection) plots of human pancreatic cells ($n = 276$) highlighting (A) the distribution (“re-clustering”) of *GHSR*-expressing cells (those cells expressing a minimum of one *GHSR* transcript) into 3 distinct clusters. (B-G) The 3 *GHSR*-expressing clusters color-coded according to each cell’s (B) original cell-cluster, (C) original study (Last name of the first author; see main text for full citations), (D) *GHSR* expression level, (E) *PPY* expression level, (F) *SST* expression level, and (G) *INS* expression level. Each dot represents a single cell. Expression levels in (D-G) are color-coded according to the accompanying legend, with red, green, blue, and purple, respectively, indicating high expression.



Supplementary Figure 7. Expression levels of mRNAs encoding ghrelin in (A) 12 different cell-clusters from mouse pancreas and (B) 14 different cell-clusters from human pancreas. Data are presented as violin plots whereby each black dot represents an instance of detectable expression of the transcript (*Ghrl* in mice; *GHRL* in humans) within a cell and the corresponding level of expression.



Supplementary Figure 8. Effect of type 2 diabetes on the expression of the genes expressed in the human pancreas. Differential gene expression analysis was performed to compare changes in gene expression between the cells within each cluster isolated from non-diabetic donors and donors with T2DM. $n = 8,167$ cells from 14 (10 male and 4 female) non-diabetic donors and 2,362 cells from 8 (3 male and 5 female) donors with T2DM. For each cluster, only genes that were expressed in a minimum of 25% of cells within that cluster were included in the analysis. A gene was considered to be differentially expressed if $FDR < 0.1$. The number of genes downregulated in T2DM are shown in purple, and the number of genes upregulated in T2DM are shown in orange.