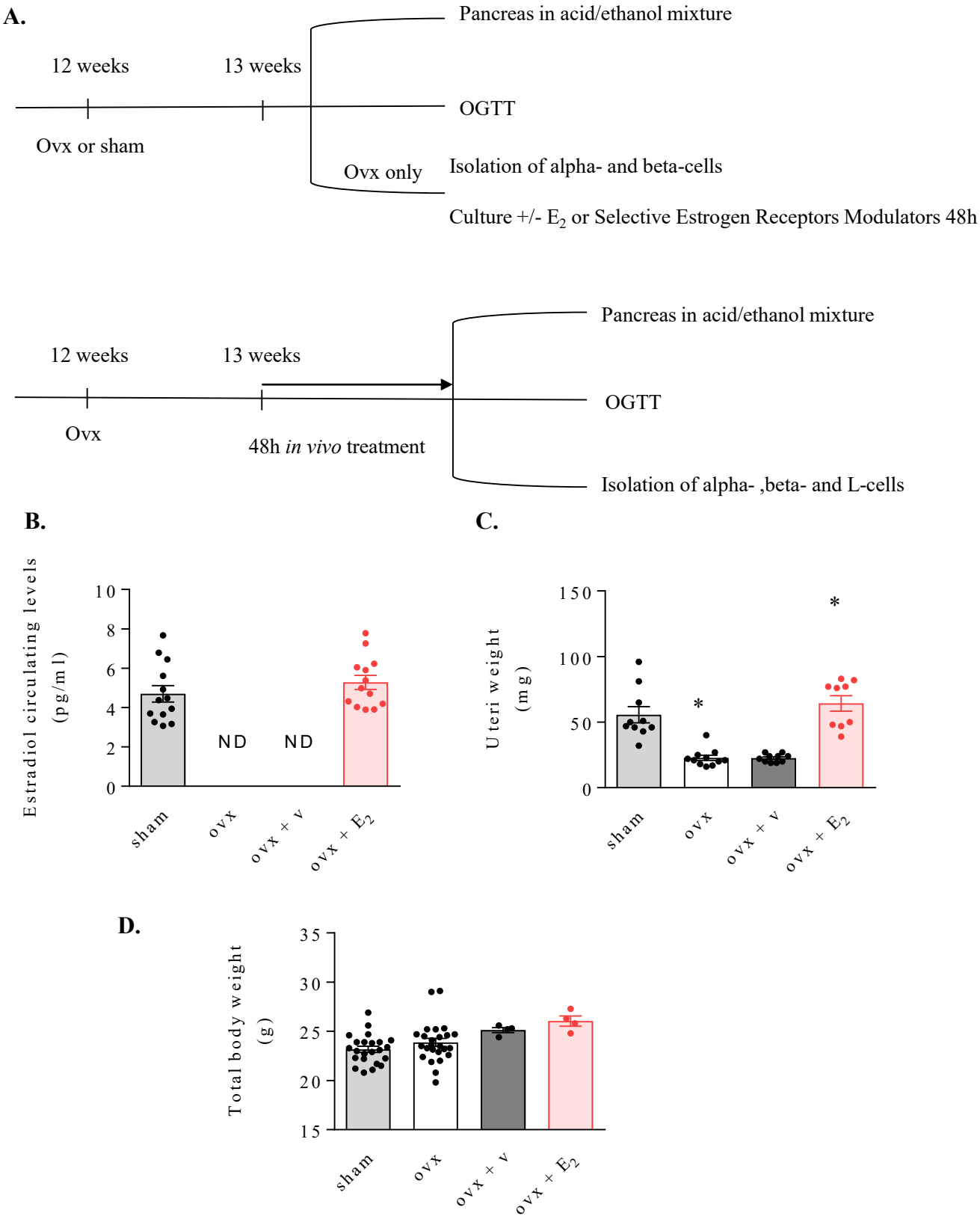
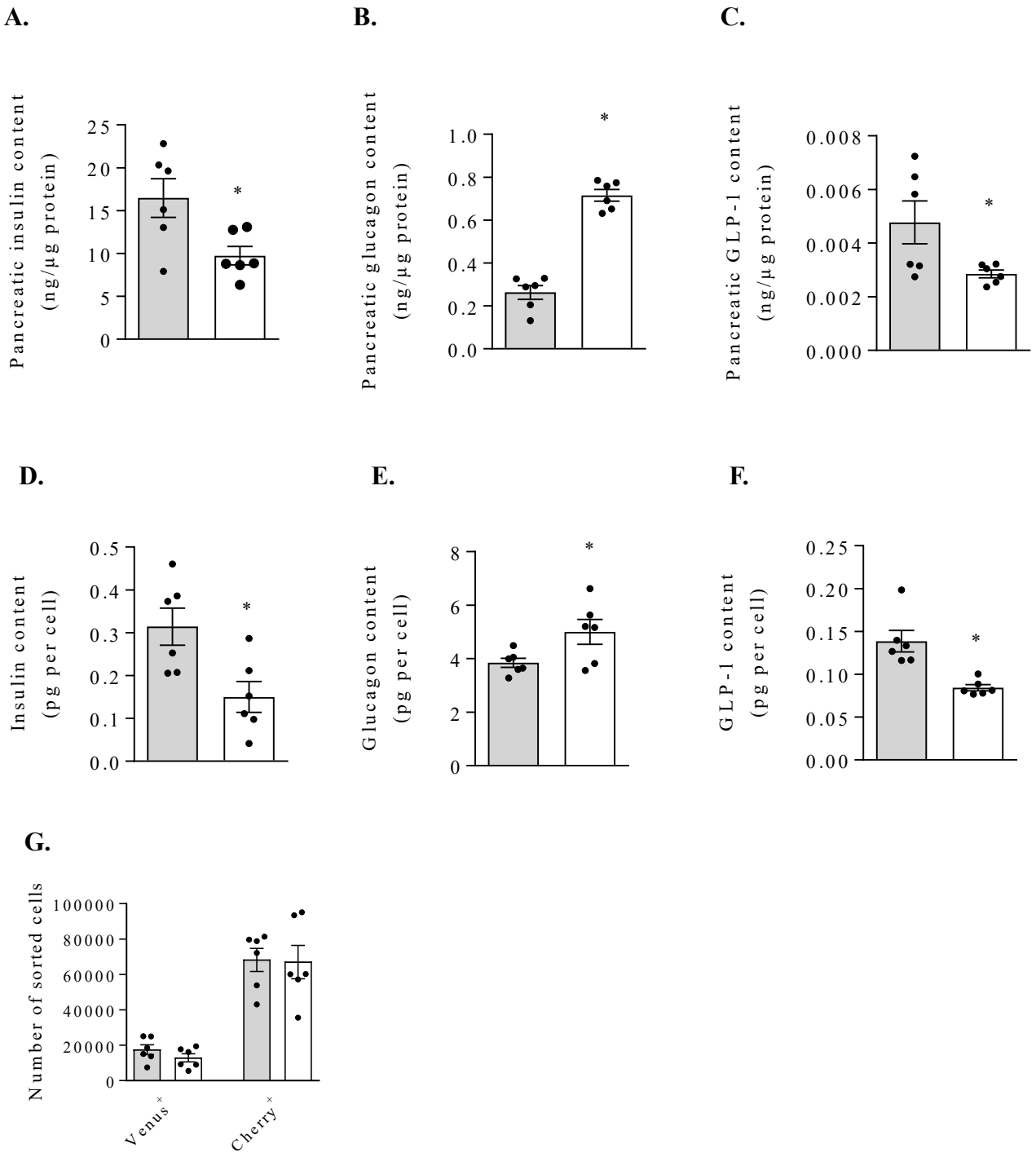
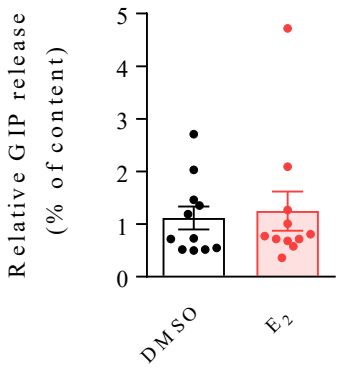


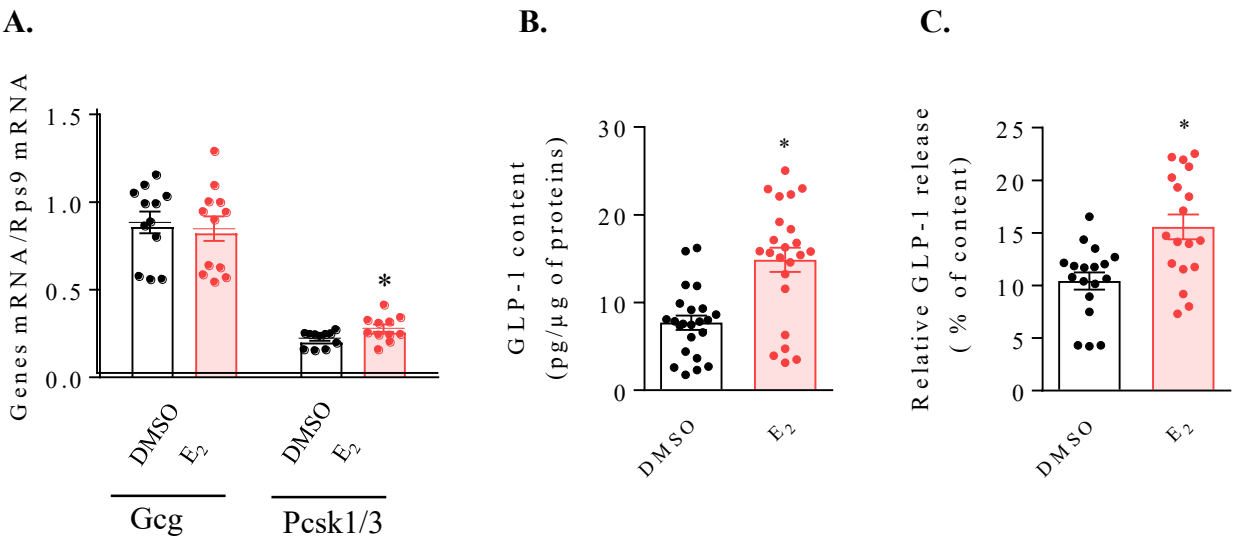
Supplementary Figure 1: Twelve week-old littermate female mice were either sham (sham) operated or ovariectomized (ovx). Ovariectomized littermate mice received either ERs agonists (ovx+E_2, ovx+WAY, ovx+PPT, ovx+G1) or placebo (ovx+v) by subcutaneous administration for two consecutives days, one week after surgery. Schematic representation of models (A). Plasma estradiol levels (B), uterus weight (C) and total body weight at 13 weeks (D) were evaluated. Student t-test statistical analyses: * $P \leq 0.05$ for sham *vs* ovx group and ovx+v *vs* ovx+E_2 mice (n=6 mice at least per group).



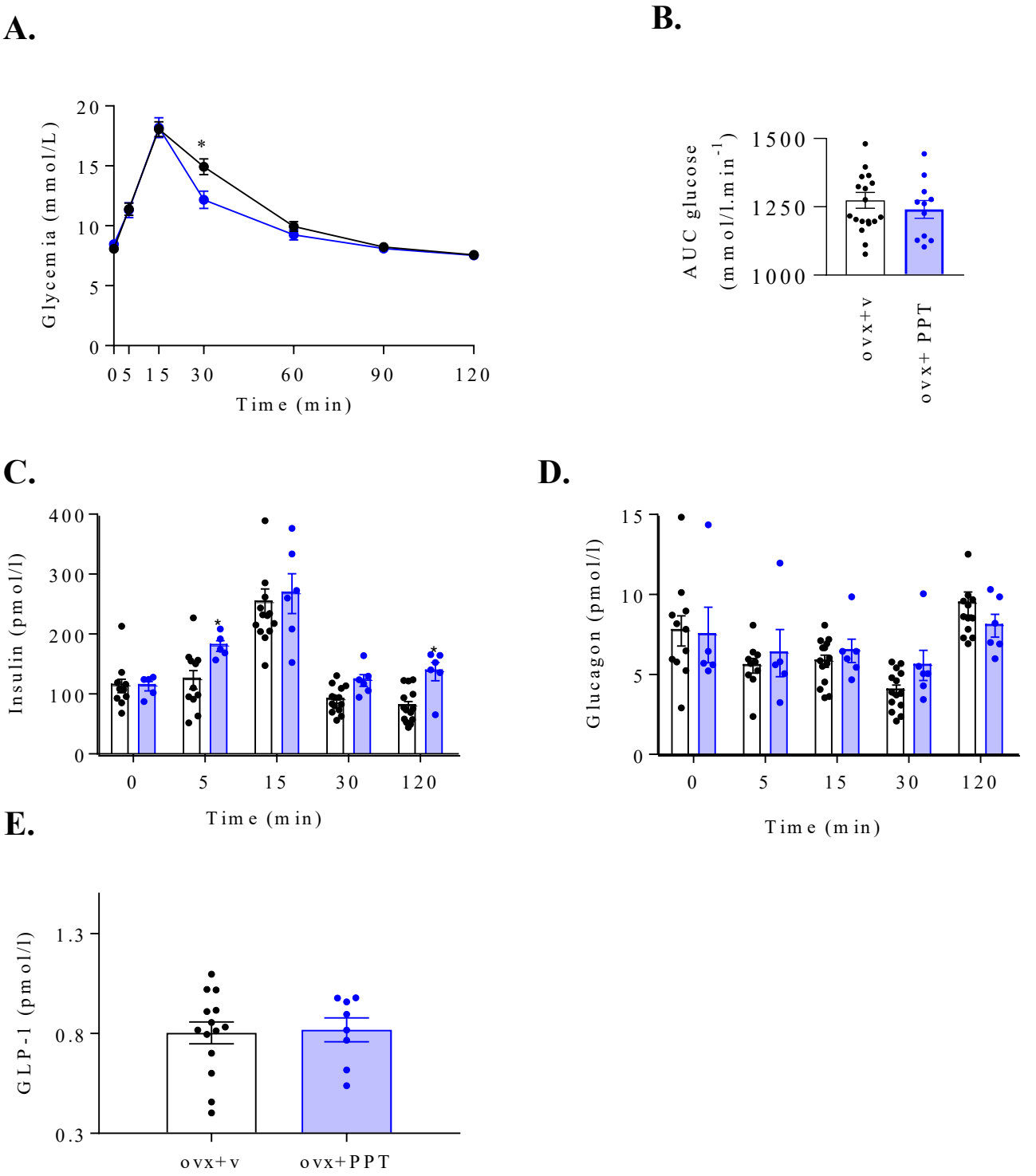
Supplementary Figure 2: Twelve week-old female mice were sham-operated or ovariectomized. Insulin (A), glucagon (B) and GLP-1 (C) contents were evaluated from pancreases of sham (grey bars, n=6) and ovx (white bars, n=6) mice. Pancreases were collected at the end of protocol and homogenized in acid-ethanol solution. Insulin, glucagon and GLP-1 contents were normalized to total protein amounts. Histograms represent the amount of insulin measured in FACS purified beta-cells (D) (n=6 mice per group), glucagon (E) and GLP-1 (F) measured in FACS purified alpha-cells (n=6 mice per group). Total number of sorted cells (n=6 mice per group) are represented in (G) . Student t-test statistical analyses: * $P \leq 0.05$ for sham *vs* ovx mice.



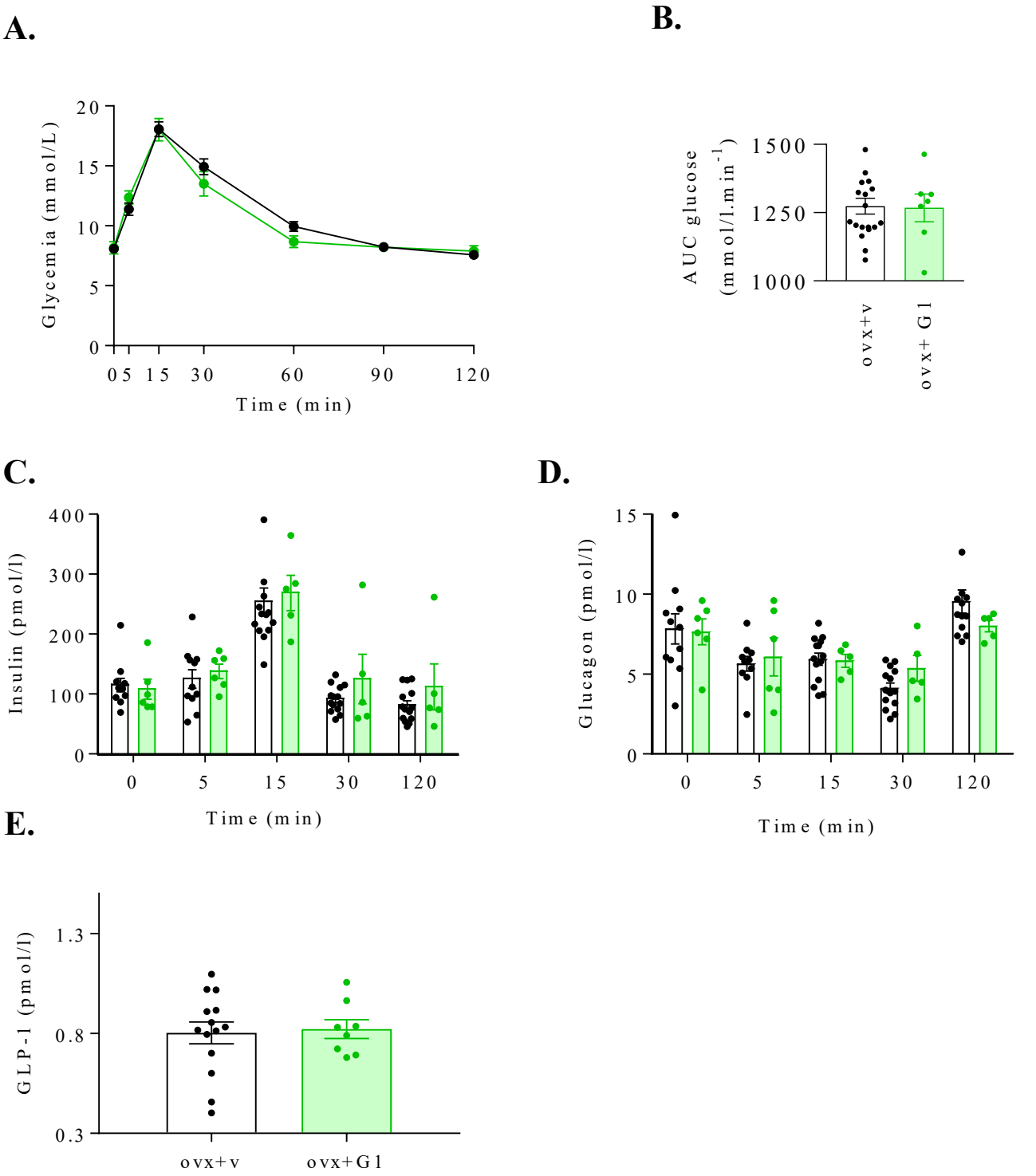
Supplementary Figure 3: Twelve week-old female mice were ovariectomized. One week after surgery we isolated explants from the distal part of the small intestine and treated cells with E_2(10^{-8}mol/l) (red bar, n=11) or DMSO (white bar, n=11) for 48 hours. GIP levels were measured in the supernatants and cell contents. GIP release was calculated from supernatant values relative to contents. Student t-test statistical analyses: * $P \leq 0.05$ for DMSO *vs* E_2 treated cells .



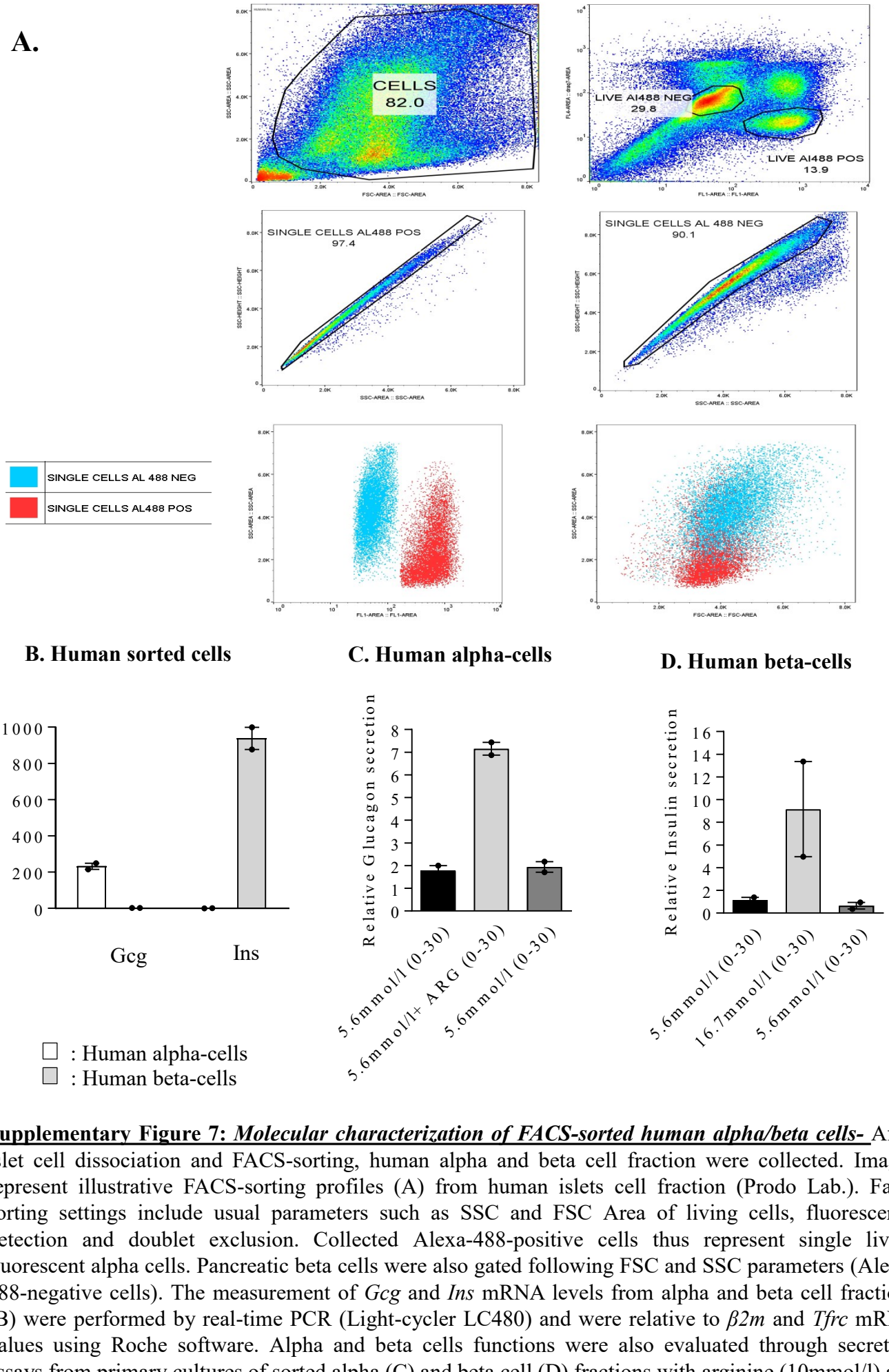
<u>Supplementary Figure 4:</u> Effects of E2 on GLUTag cells in response to estradiol treatment- GLUTag cells lines treated with E_2 (10^{-8}mol/l) for 48 hours, were studied for *Gcg* and *Pcsk1/3* mRNAs levels (A). GLP-1 content (B) and release (C) were evaluated in GLUTag cells. Student t-test statistical analyses: *P≤0.05 for vehicle *vs* E_2-treated cells (n=12 points per condition).



Supplementary Figure 5: Plasma glucose levels during OGTT (2g/kg) (A) and the related area under the curve (B) in ovx+vehicle (black circles, white bars, n= 20) and ovx+PPT (100mg/kg/48 hours; bleu circles, bleu bars, n=13) mice. Plasma insulin (ovx+v n=11; ovx+PPT n= 5) (C), glucagon (ovx +v n=11; ovx+PPT n= 5) (D) and GLP-1 levels at T5 min (ovx+v n=9; ovx+PPT n= 8) (E) during an OGTT. One-way repeated ANOVA with Bonferonni post hoc test analyses was performed for glycaemia (A), Student t-test statistical analyses were performed for the other figures: *P≤0.05 for ovx+v *vs* ovx+PPT mice.

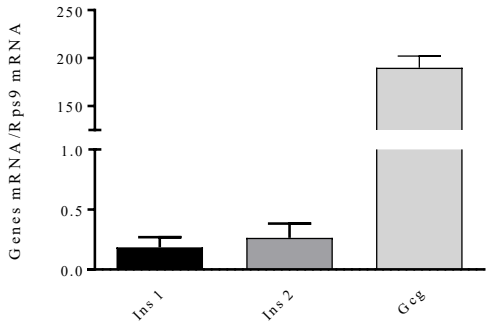


Supplementary Figure 6: Plasma glucose levels during OGTT (2g/kg) (A) and the related area under the curve (B) in ovx+vehicle (black circles, white bars, n= 20) and ovx+G1 (100mg/kg/48 hours; green circles, green bars, n=13) mice. Plasma insulin (ovx+v n=11; ovx+G1 n= 5) (C), glucagon (ovx+v n=11; ovx+G1 n= 5) (D) and GLP-1 levels at T5 min (ovx+v n=9; ovx+G1 n= 8) (E) during an OGTT. One-way repeated ANOVA with Bonferonni post hoc test analyses was performed for glycaemia (A), Student t-test statistical analyses were performed for the other figures: *P≤0.05 for ovx+v *vs* ovx+G1 mice.

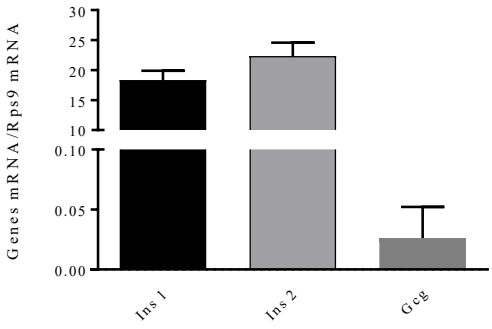


<u>Supplementary Figure 7:</u> ***<u>Molecular characterization of FACS-sorted human alpha/beta cells-</u>*** After islet cell dissociation and FACS-sorting, human alpha and beta cell fraction were collected. Images represent illustrative FACS-sorting profiles (A) from human islets cell fraction (Prodo Lab.). Facs-sorting settings include usual parameters such as SSC and FSC Area of living cells, fluorescence detection and doublet exclusion. Collected Alexa-488-positive cells thus represent single living fluorescent alpha cells. Pancreatic beta cells were also gated following FSC and SSC parameters (Alexa-488-negative cells). The measurement of *Gcg* and *Ins* mRNA levels from alpha and beta cell fractions (B) were performed by real-time PCR (Light-cycler LC480) and were relative to *β2m* and *Tfrc* mRNA values using Roche software. Alpha and beta cells functions were also evaluated through secretion assays from primary cultures of sorted alpha (C) and beta cell (D) fractions with arginine (10mmol/l) and glucose (16.7mmol/l) respectively.

A. Venus^{+} alpha-cells



B. Cherry^{+} beta-cells



<u>Supplementary method Figure 1:Purity of alpha- and beta- cell cultures</u>

Relative to Rps9 mRNA expression of Ins1, Ins2 and Gcg, mRNA levels in Venus^{+} (A) and Cherry^{+} (B) FACS-purified cells (n=6 points per group).