**Supplemental Figure 1:** Metabolic characterization of the DNTβRII mice. (A-B) Comparison of baseline body weights (A) and fasting blood glucose (B) of the DNTβRII mice (grey line) and FVB control mice (black line) receiving standard drinking water. (C-D) Insulin tolerance testing (C) and glucose tolerance testing (D) of FVB control mice (black line) and DNTβRII transgenic mice (grey line) at 8 weeks of age. (E-H) Fasting blood glucose (E), insulin tolerance tests (F), glucose tolerance tests (G), and weight (H) of the DNTβRII mice (grey line) receiving zinc water compared to the FVB control mice (black line) at 8 weeks of age. (I-J) Insulin tolerance (I) and glucose tolerance tests (J) for FVB mice before (black line) and four weeks after PPx (grey line). (K-L) Serum insulin level before and after PPx for FVB control mice (black line) and DNTβRII mice receiving zinc water (grey line, K) or standard water (L). ITT – Insulin Tolerance Test, GTT – Glucose Tolerance Test, * p <0.05

**Supplemental Figure 2:** Ontogeny of intra-islet ducts in young mice. (A-C) Representative immunohistochemistry showing intra-islet pancreatic ducts (arrows) in islets of young wild-type FVB mice at 4, 6, and 7 weeks of age. (D) is a whole-mount immunostained image from the same pancreas as (B), with the inset in (D) showing a confocal 3-D reconstruction, confirming the pancreatic duct penetrating deeply into the middle of the islet (arrow), and arising from the pre-existing ductal tree. (E) Quantification of the percentage of islets that contained intra-islet ducts at increasing ages. Scale bar 20 μm.

**Supplemental Figure 3:** Ontogeny of intra-islet ducts in young humans. (A,B) Representative histological section from a 2 month old human pancreas displaying intra-islet ducts (arrows). PanCK – pan-cytokeratin stain for human ducts. (C) Whole-mount image of a 3-year old human pancreas demonstrating intra-islet ducts (arrow). (D) A 3-D reconstruction confirms that the ducts (arrow) seen in (C) are within the islet. Scale bar 20μm.

**Supplemental Figure 4:** BrdU pulse-chase experiment. (A) Schematic for the BrdU pulse-chase experiment with BrdU given once a day intraperitoneally for only the first 7 days after PPx. (B) Proliferation analysis in wild type and DNTβRII mice (n=3 for all groups) immediately after 7 days of
daily intraperitoneal BrdU injections after PPx, and in sham-operated control pancreas. * indicates 
p<0.05. † indicates a trend towards statistical significance, p=0.07.

**Supplemental Figure 5:** Characterization of intra-islet ducts. Intra-islet ducts 4 weeks post-PPx in the 
*DNTβRII* mice are positive for the ductal marker HNF1β (A, arrows) and Sox9 (B, arrows). (C,D) 
Representative whole-mount confocal image of an islet harvested from a pancreas of a *DNTβRII* mouse 4 
weeks post-PPx co-stained with the β-cell marker Pdx1. The cells in the duct arising from the pre-existing 
ductal tree are positive for Pdx1 (arrow in D). (E,F) Representative FACS plot from an isolated islet 
fraction from *DNTβRII* sham treated and post-PPx mice. In the sham condition, 0.03% of islet cells are 
DBA+ duct cells, while in the post-PPx condition 7% of islet cells are DBA+. Scale bar 20μm.

**Supplemental Figure 6:** Analysis of lineage labeling in *Sox9CreERTM* mice. *Sox9CreERTM* mice crossed with 
*R26R<sup>Tm-RED</sup>* mice, one week after tamoxifen injection, results in a high labeling efficiency in nearly all of 
the intestinal crypts (A) and pancreatic ducts (B). (B) One week after tamoxifen injection, nearly all ducts 
contain DBA+ cells that also express tomato red, although some acinar cells are labeled as well (arrow). 
(C,D) The no-tamoxifen (No Tmx) controls reveal some pre-labeling of acinar cells (C, arrow) and 
pancreatic ducts (D, arrows) on whole-mount imaging, but no islet cells were labeled, either before or 
within 3-5 days after tamoxifen. (E) Shows tamoxifen-treated, sham-operated *Sox9CreERTM*, *DNTβRII*; 
*R26R<sup>Tm-RED</sup>* pancreas with no islet cell lineage-tagging. (F) When *Sox9CreERTM*, *DNTβRII*; *R26R<sup>Tm-RED</sup>* triple 
transgenic mice underwent PPx and were harvested 4 weeks later, some insulin-positive cells co-localized 
tomato red by confocal imaging. (G) Further, no islet cells were labeled with tomato red in *Sox9CreERTM*, 
*R26R<sup>Tm-RED</sup>* mice (no *DNTβRII*) that underwent PPx and were harvested 4 weeks later. Scale bar C: 
100μm, A-B, D-G: 20 μm.

**Supplemental Figure 7:** Viral-induced cell labeling in young mice. (A, B) Representative confocal 
imaging of whole-mount stained 5-week old *R26R<sup>Tm-RED</sup>* mouse pancreas 3 days after an AA6-Sox9-cre 
viral duct infusion shows baseline duct-specific lineage-tagging. (C) 2 weeks after viral infusion in a 5-
week old *R26R<sup>Tm-RED</sup>* mouse, a lineage-tagged islet (arrow) is seen with yellow cells indicating duct-
derived insulin-positive cells, with higher magnification of that islet in (D). Some islets are not labeled with tomato red 2 weeks after Sox9-cre viral infusion (arrowhead in C). Scale bar 20 μm.
Figure S1
Figure S4
Figure S5
Figure S6