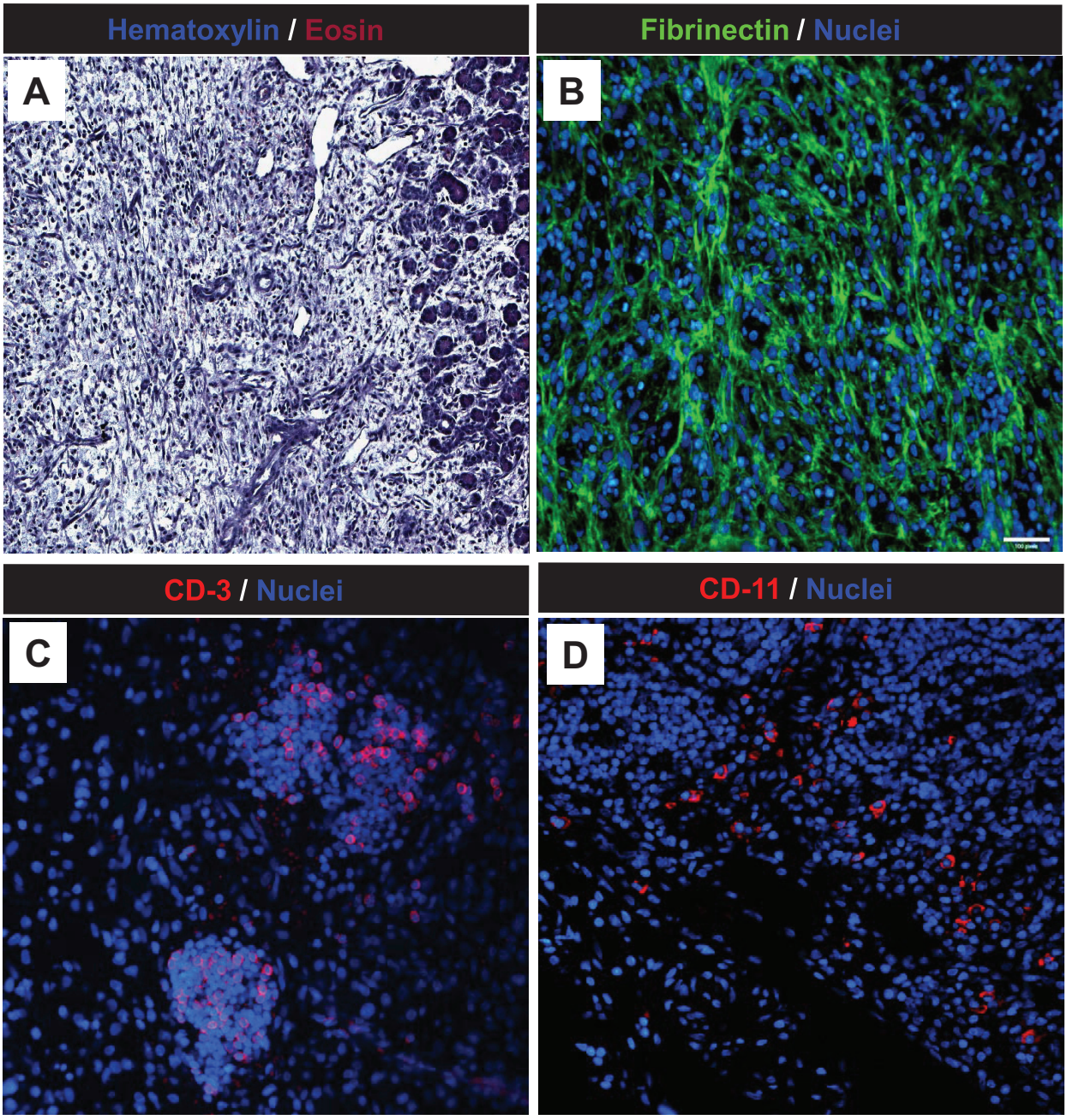
Supplemental Table 1

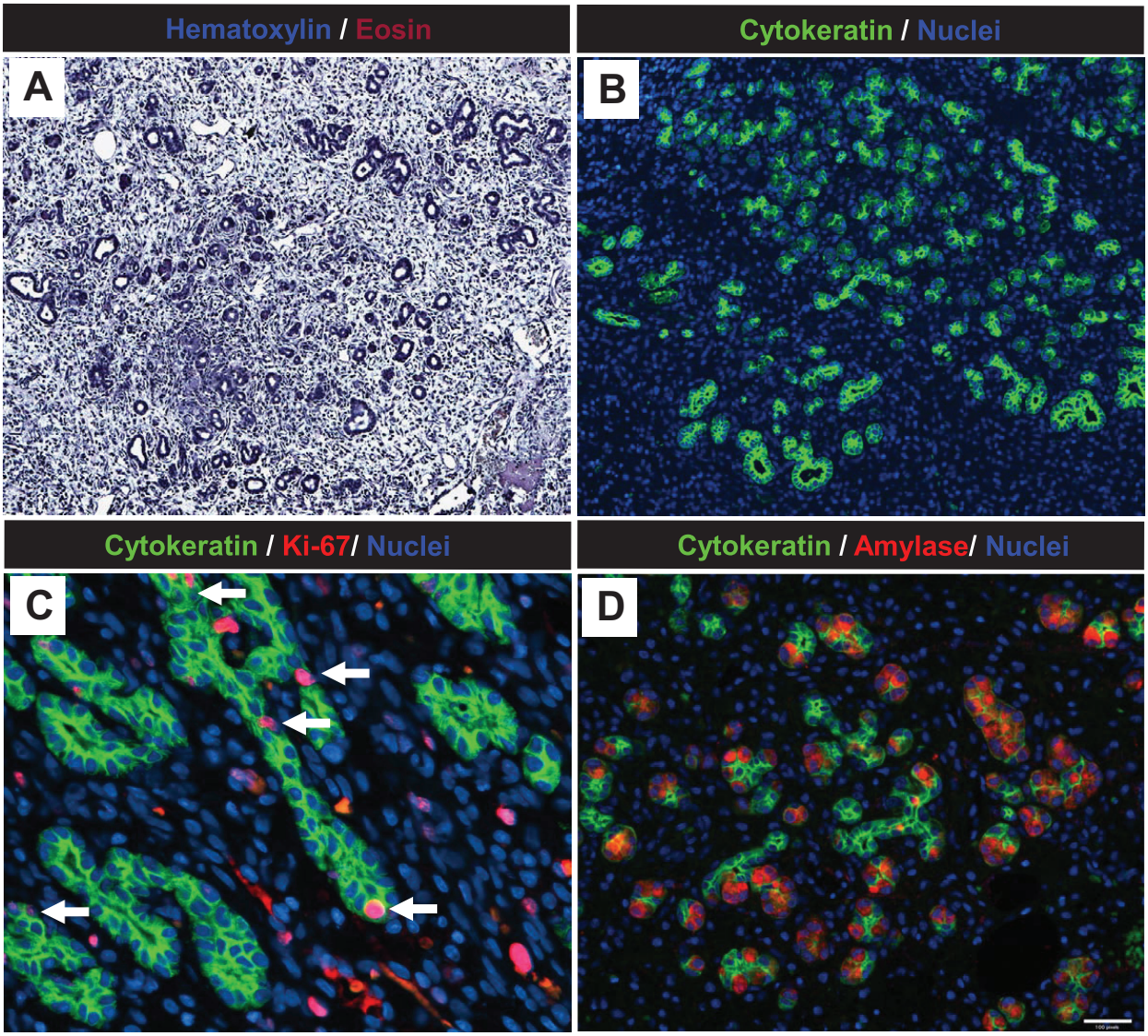
Insulin sensitivity and glucose turnover.

	WT	HIP	HIP+SIT	HIP+MET	HIP+SIT+MET
Clamp Glucose (mg/dl)					
Fast	102±3	178±35	145±13	134±8	125±8
Clamp	96±4	98±4	97±6	100±1	99±4
Glucose Infusion rate ($mg \cdot kg^{-1} \cdot min^{-1}$)					
Clamp	9±2*	5.3±1.5	11.4±1.7*	14.2±1.4*	15.6±1.1*
Hepatic glucose release ($mg \cdot kg^{-1} \cdot min^{-1}$)					
Fast	5.1±1.3*	9.7±1.4	8.3±0.4	6.4±0.3*	6.9±0.4*
Clamp	-0±0.4*‡	9±1	7.6±0.6*	2.5±0.4*†	3.2±0.8*†
Glucose Disposal ($mg \cdot kg^{-1} \cdot min^{-1}$)					
Fast	5.1±1.3*	9.7±1.4	8.3±0.4	6.4±0.3*	6.9±0.4*
Clamp	10±1.5	15.6±1.7	19.7±2.6	19.2±2.5	20±1.1

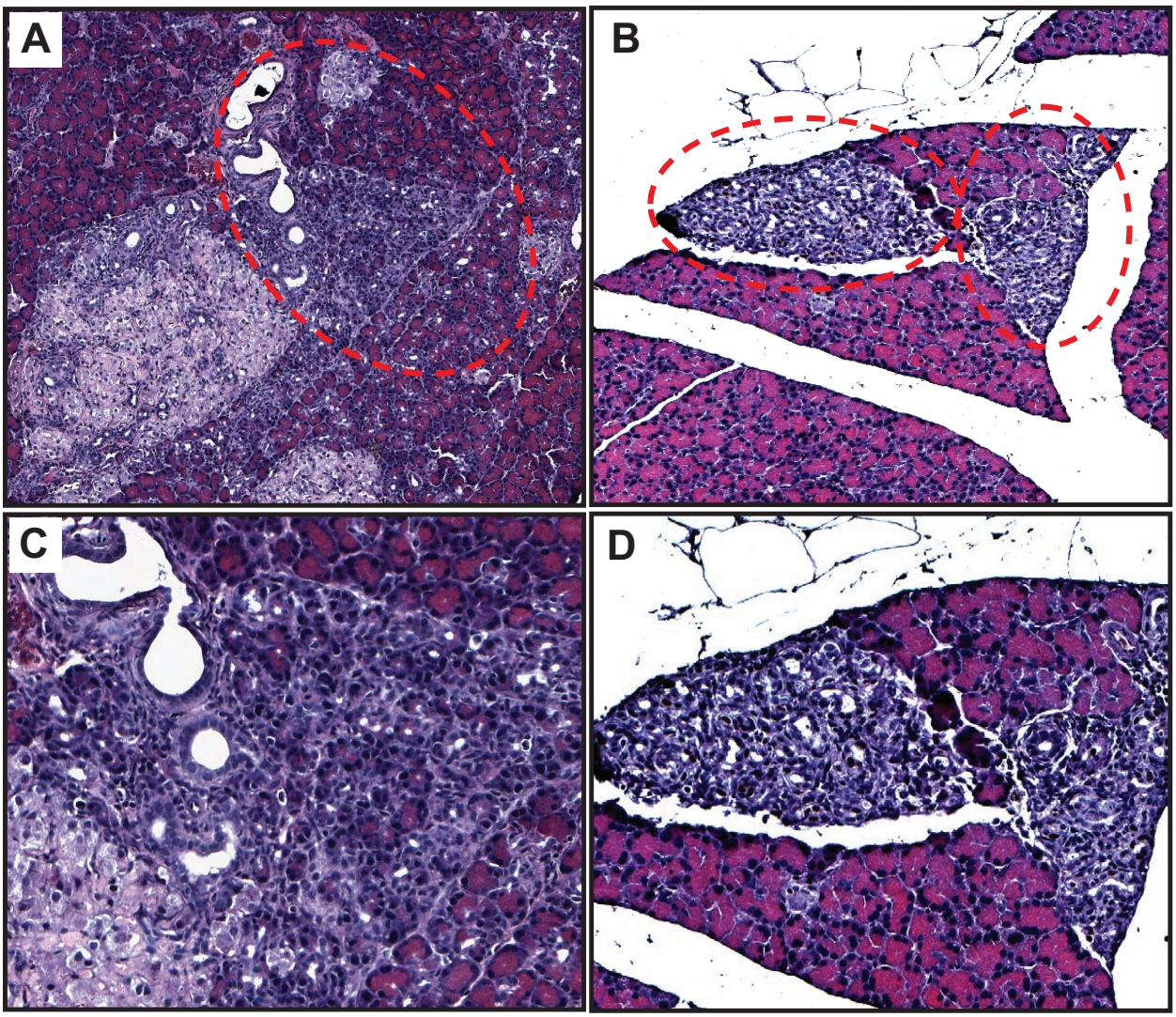
Data are expressed as mean ± SE. *P<0.05 vs. HIP. †P<0.05 for HIP+MET and HIP+SIT+MET vs. HIP+SIT.
‡ P<0.05 for WT vs. all HIP groups.



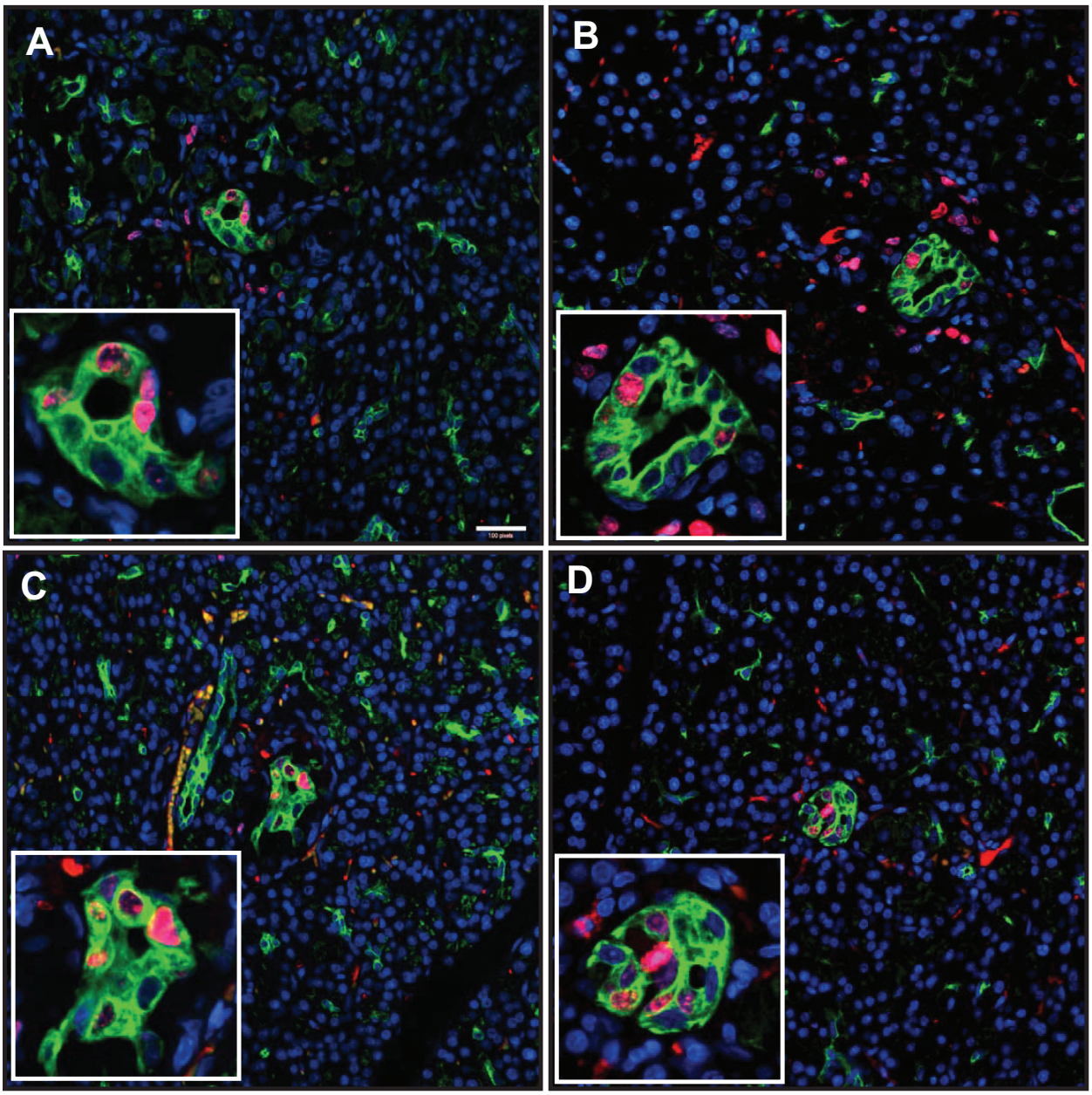
<u>Supplemental Figure 1.</u> Pancreatitis in a HIP rat treated with sitagliptin is characterized by tissue fibrosis and immune cell infiltration. (A) 5X: representative image of the exocrine pancreas stained for Hematoxylin and Eosin from a rat treated with sitagliptin for 12 weeks with necrotizing pancreatitis. Note almost complete loss of acinar cells and evidence of acinar cell fibrosis and necrosis. **(B)** 20X: the same area of pancreatitis is now stained for a marker of fibroblasts (Fibrinectin-green) and nuclear stain (DAPI-blue). **(C)** 20X: the area of pancreatitis stained for a marker of T-cell infiltrate (CD-3-red) and nuclear stain (DAPI-blue). **(D)** 20X: the area of pancreatitis stained for a marker of macrophage infiltrate (CD-11C-red) and nuclear stain (DAPI-blue).



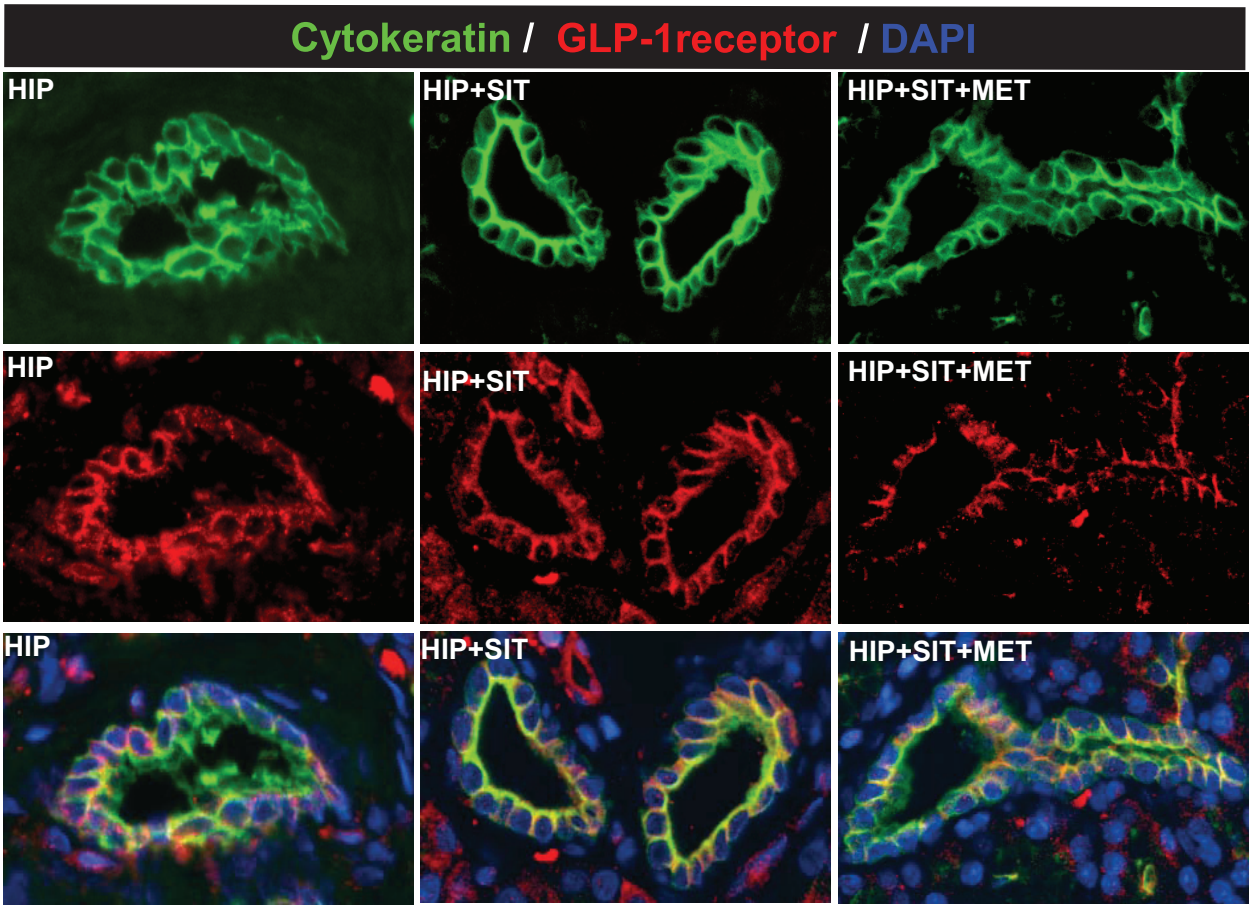
<u>Supplemental Figure 2.</u> Pancreatitis in a sitagliptin treated rat is characterized by extensive ductal metaplasia with ducts showing strong immunoreactivity for cytokeratin, cell replication marker (Ki-67) and acinar cell marker (amylase) (A) 10X: representative (Hematoxylin and Eosin) image of extensive ductal cell metaplasia in a HIP rat that also exhibited necrotizing pancreatitis treated with sitagliptin for 12 weeks. **(B)** The same area of ductal metaplasia was stained for ductal cell marker (Cytokeratin-green), and nuclear stain (DAPI-blue). **(C)** 20X: The same area of ductal cell metaplasia stained for ductal marker (Cytokeratin-green), cell replication marker (Ki-67-red) and nuclear stain (Dapi-blue). White arrows illustrate proliferating ductal cells. **(D)** 20X: The same area of ductal cell metaplasia stained for ductal marker (Cytokeratin-green), acinar cell marker (amylase) and nuclear stain (Dapi-blue).



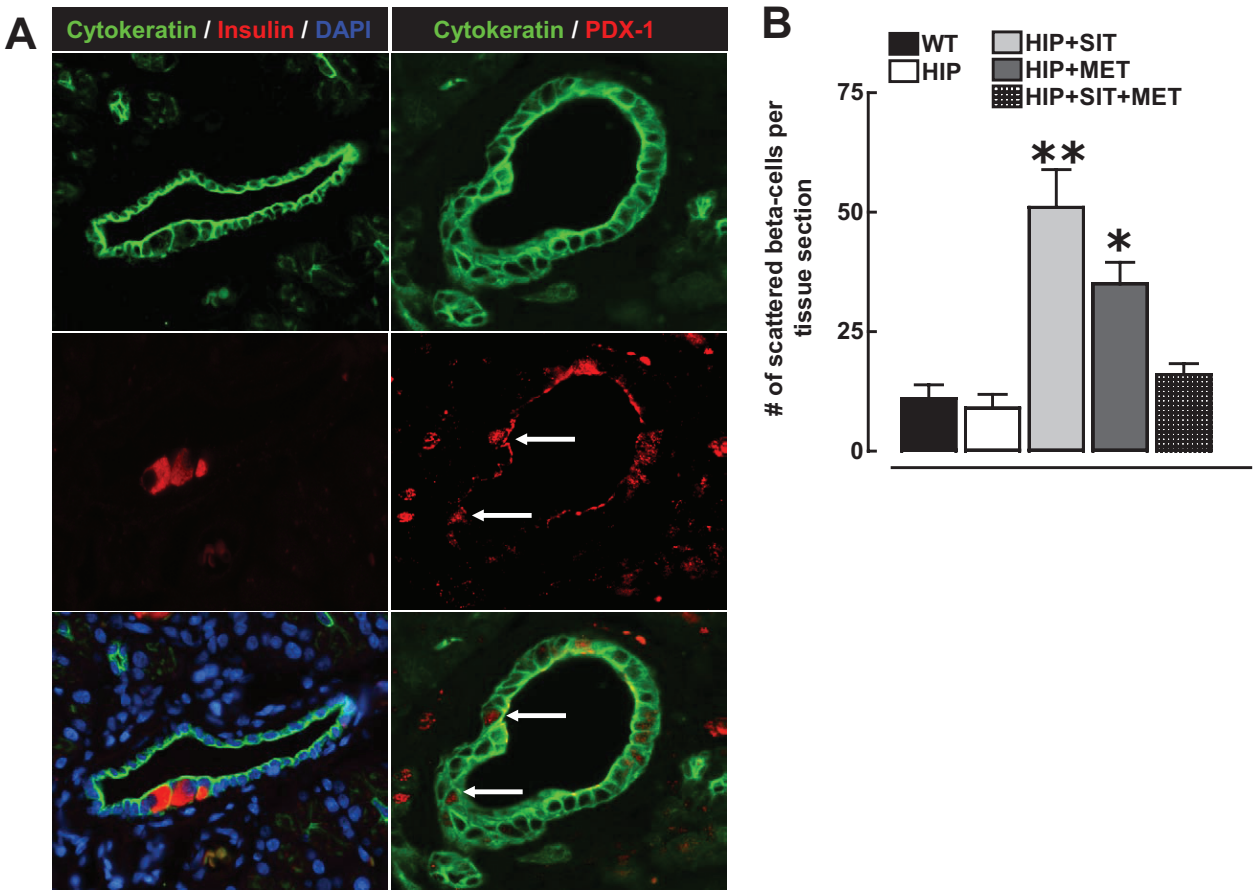
<u>Supplemental Figure 3</u>. Additional examples of ductal metaplasia in HIP rats treated with sitagliptin for 12 weeks. (A and B) 10X: representative images of ductal cell metaplasia observed in rats treated with sitagliptin for 12 weeks. Metaplastic regions consisted of angulated tubular structures, interspersed fibrosis and inflammatory cells and were located both adjacent to islets of Langerhans (A: circle) as well as separated from islets (B; circle). **(C and D)**: at this magnification presence of extensive angulated tubular ductal structures and surrounding tissue fibrosis within the metaplastic region is better appreciated.



<u>Supplemental Figure 4.</u> Additional examples of increased ductal cell replication in HIP rats treated with sitagliptin for 12 weeks. (A-D) 20X: representative images of exocrine ducts stained for Cytokeratin (green), replication marker Ki-67 (red) and nuclear stain Dapi (blue) in HIP rats treated with Sitagliptin *Note that examples represent metaplasia and pancreatitis free areas of the exocrine pancreas.



Supplemental Figure 5. GLP-1 receptor immunoreactive was not affected by sitagliptin or sitagliptin+metformin treatment in HIP rats. 20X: representative images of exocrine ducts stained for Cytokeratin (green), GLP-1 receptor (red) and nuclear stain Dapi (blue) in diabetic HIP rats, HIP rats treated with Sitagliptin or with combination therapy of Sitagliptin+Metformin.



<u>Supplemental Figure 6</u>. PDX-1 and insulin expression in exocrine ducts of sitagliptin treated HIP rats. (A) Staining for Cytokeratin (green) and Insulin or PDX-1 (red) in HIP rats treated with sitagliptin for 12 weeks. Arrows mark expression of Cytokeratin positive/PDX-1 positive cells. **(B)** Quantification of the frequency of scattered beta-cells within the exocrine pancreas in Wild type (n=7), HIP rats (n=8), HIP rats treated with sitagliptin (HIP+SIT, n=8), metformin (HIP+MET, n=9) and combination therapy (HIP+SIT+MET, n=8). Data are expressed as mean ± SE. **P<0.05 vs. all groups and * P<0.05 vs. WT, HIP and HIP+SIT+MET