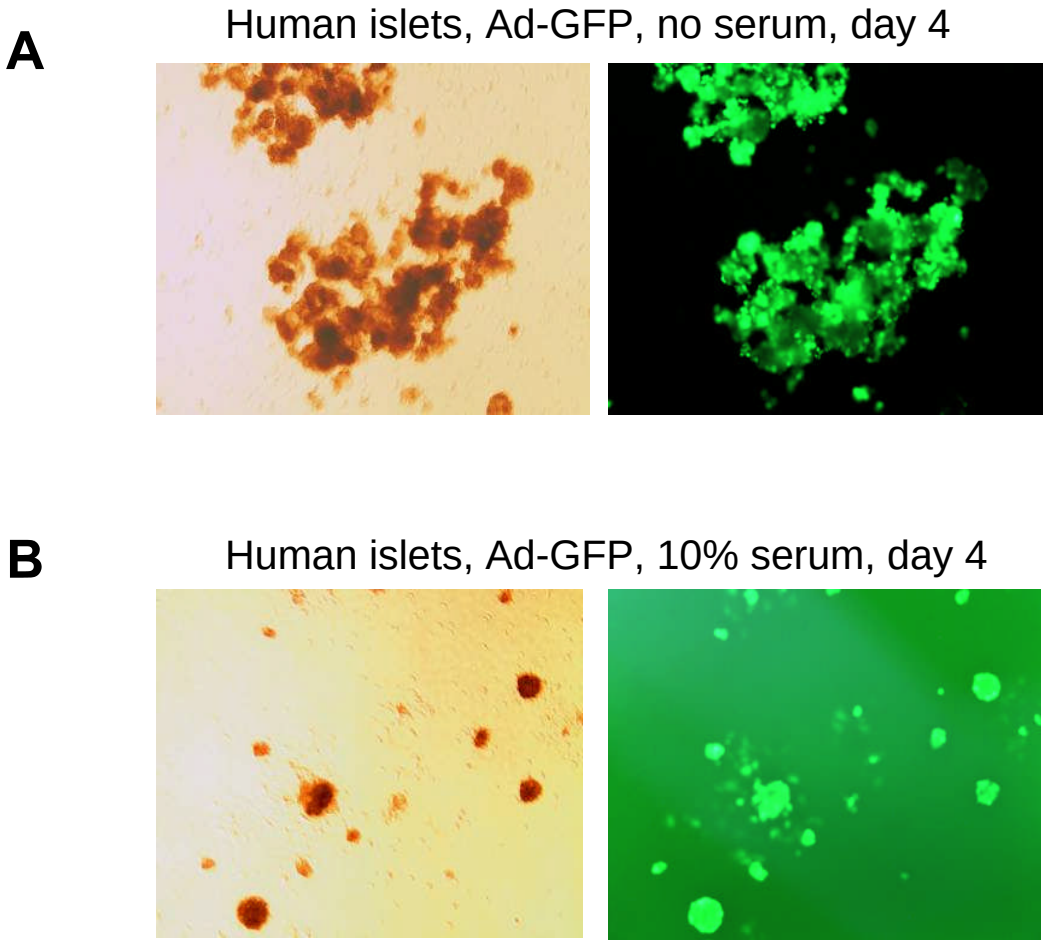
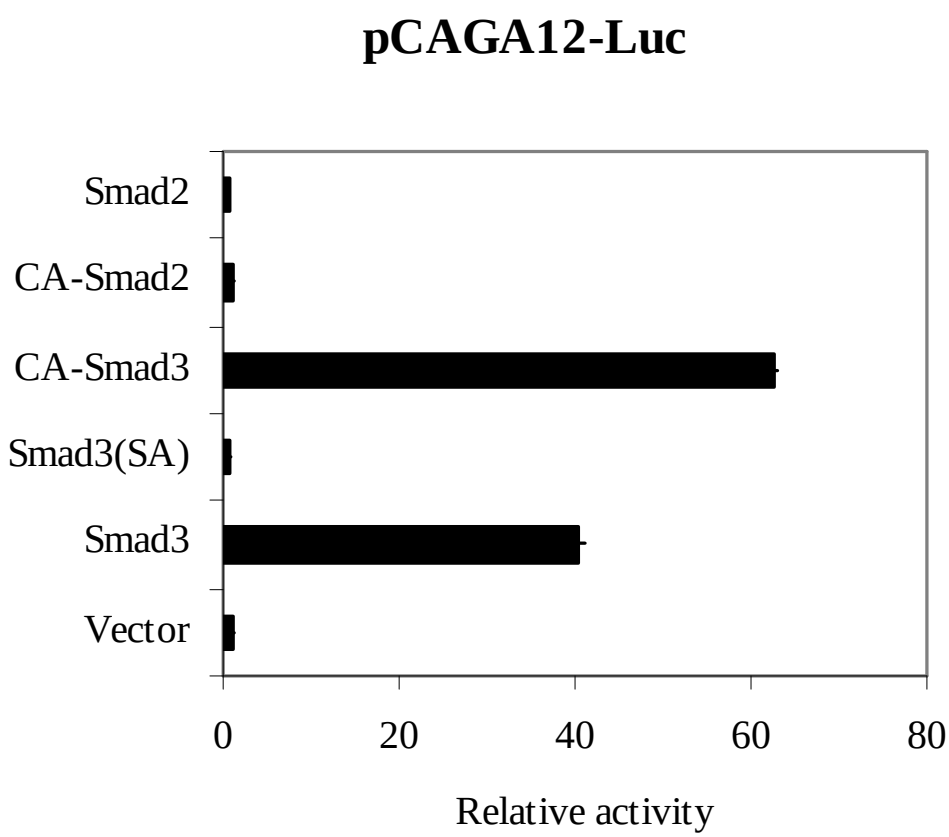
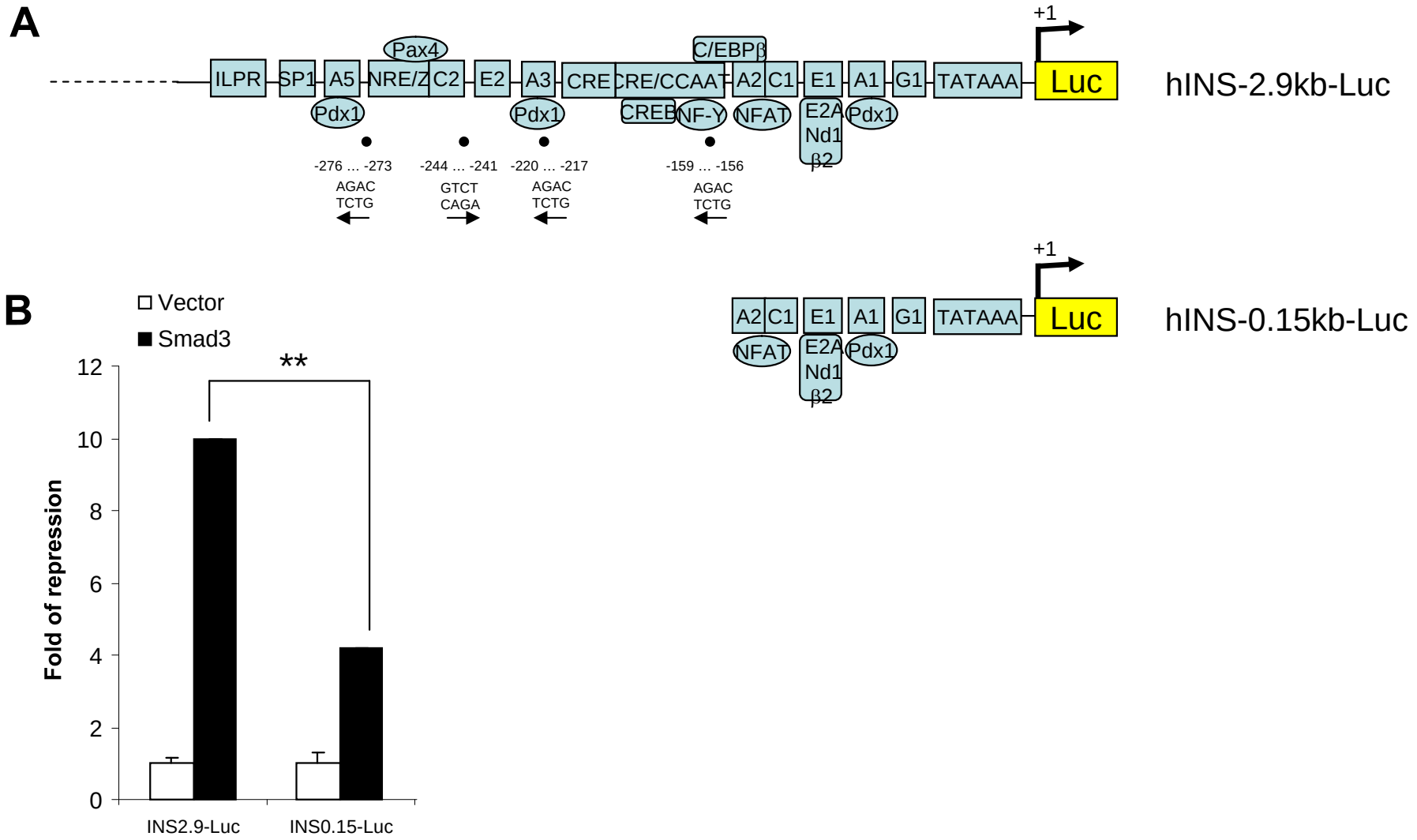


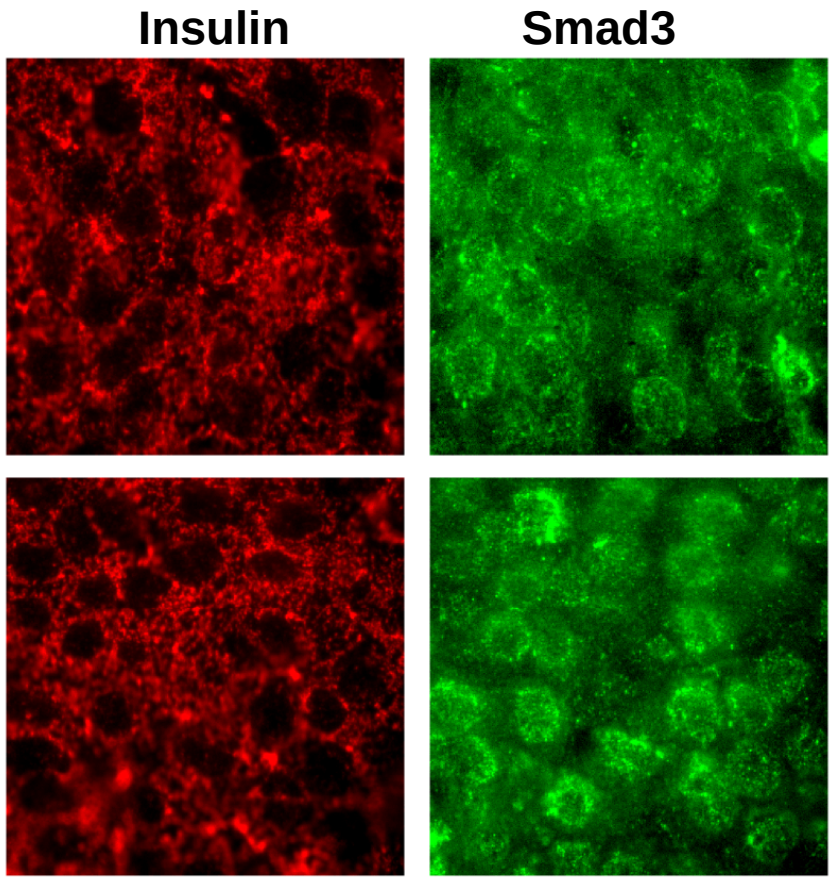
Supplementary Figure 1. Transduction of primary islets isolated from human cadaver donors with control adenoviruses Ad-GFP. GFP fluorescence was detected by microscopy at Day 4 after transduction of Ad-GFP in media (**A**) without serum or (**B**) containing 10% serum. Image in panel A was taken at high magnification compared to image shown in panel B. The panels on the left show phase contrast pictures while the panels on the right show GFP fluorescence.



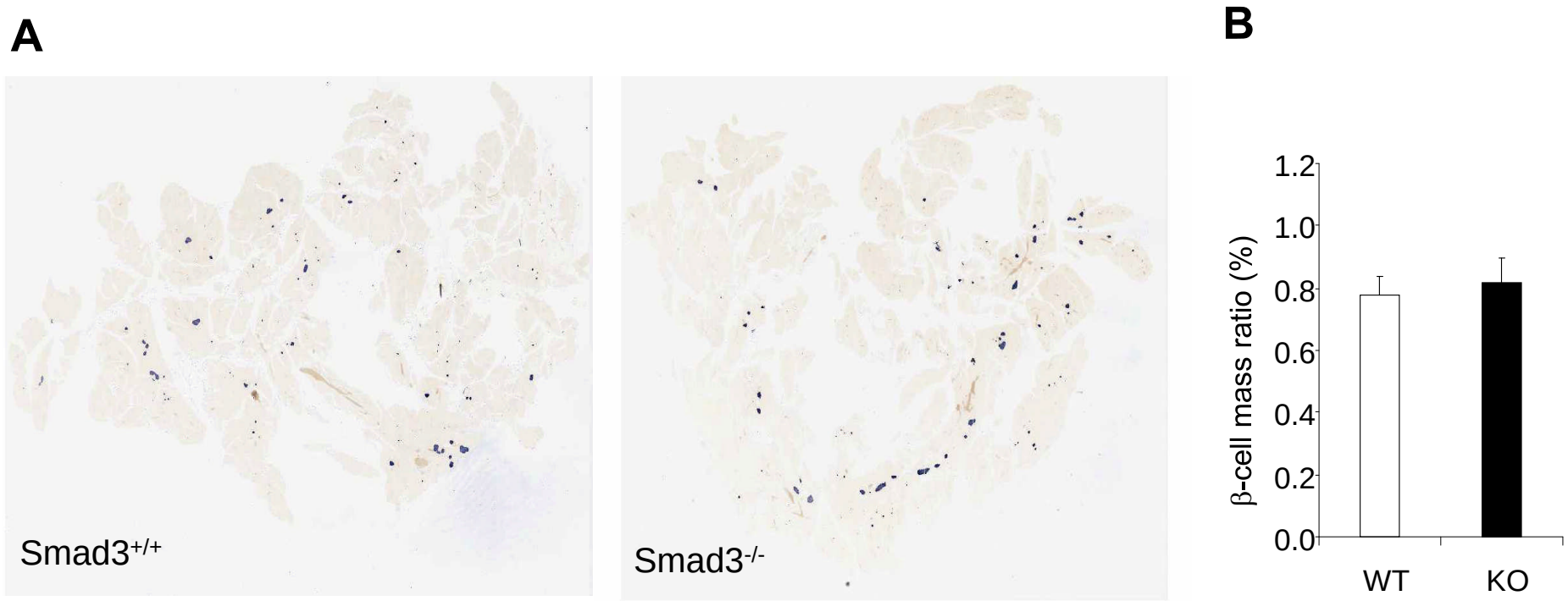
Supplementary Figure 2. Smad3, but not Smad2, dependent activation of CAGA12-luc reporter in INS-1E cells. Wild-type Smad3 and constitutively active Smad3 (CA-Smad3) can activate the CAGA12-luc reporter. In contrast, wild-type Smad2, CA-Smad2 or a phosphorylation-defective mutant of Smad3 (SA), cannot activate the CAGA12-luc reporter.



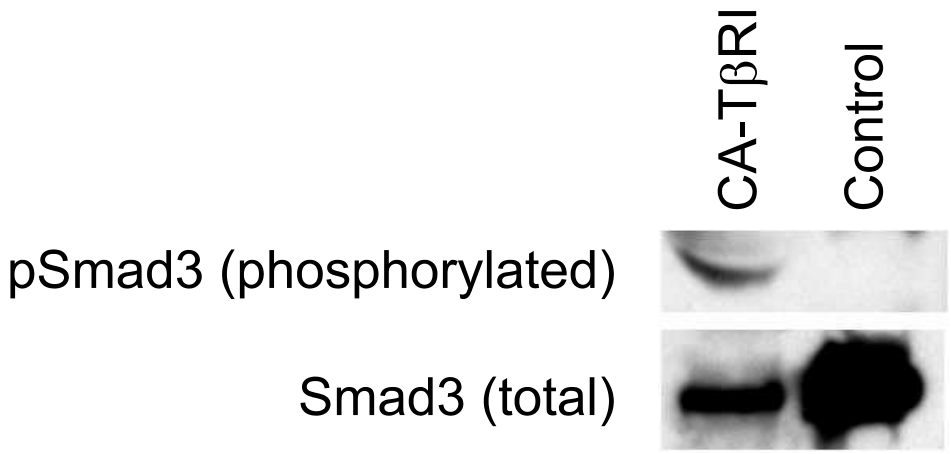
Supplementary Figure 3. (A) Cartoon depicting the human insulin promoter driven luciferase constructs. The hINS-2.9kb-Luc construct comprises the full length promoter. The elements representing binding sites for the key transcription factors are shown. Position and core sequences for the putative Smad3-binding sites within the first 300bp of the promoter relative to the transcription start site (+1) are identified (●). Arrows designate right or left orientation of the GTCT core elements within the putative Smad3-binding sites. The truncated hINS-0.15kb-Luc construct lacks all the putative Smad3-sites. **(B)** Relative fold repression of hINS-2.9kb-Luc and hINS-0.15kb-Luc by Smad3. INS-1E cells were transfected with luciferase constructs along with either control vector (open boxes) or Smad3 expression vectors (closed boxes) and activity of the promoter was determined. Smad3-mediated fold repression is significantly reduced in hINS-0.15kb-Luc (**, $p<0.01$).



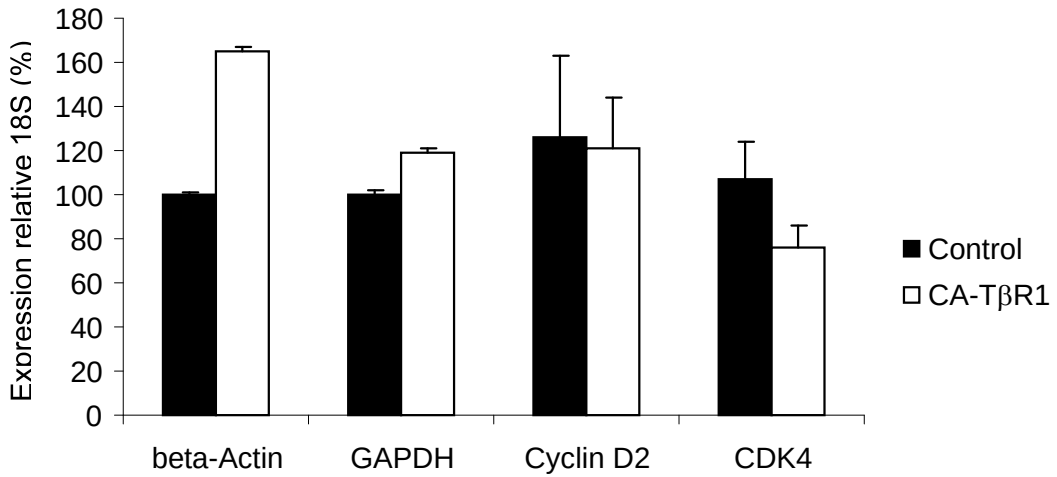
Supplementary Figure 4. Expression of Smad3 in islet β-cells. Insulin immunofluorescence was used to detect β-cells in pancreatic islets of *Smad3*$^{+/+}$ mice. Smad3 expression was detected using anti-Smad3 antibodies. Majority of insulin-expressing β-cells exhibit either perinuclear (top panels) or predominantly nuclear (bottom panels) Smad3.



Supplementary Figure 5. **(A)** Comparable pancreatic morphology as detected by insulin immunohistochemistry (purple) in two-month old *Smad3*$^{-/-}$ and *Smad3*$^{+/+}$ mice. A representative total pancreatic section is shown at a low magnification where the multilobular exocrine pancreas are light-colored and the endocrine pancreatic β-cells are purple-colored subsequent to insulin immmunohistochemistry. **(B)** β-cell mass ratio, as measured by insulin immunohistochemistry (see methods for details), is similar in two-month old male *Smad3*$^{-/-}$ (KO; n=7) and *Smad3*$^{+/+}$ (WT; n=9) mice.



Supplementary Figure 6. INS-1E cells were untreated (control) or infected with CA-TβRI retrovirus expressing the constitutively active (CA) form of TβRI. Cells were harvested and extracted protein was subjected to western blot analysis using total-Smad3 antibody and anti-phospho-Smad3 antibody to detect total and phosphorylated Smad3, respectively.



Supplementary Figure 7. Quantitative real-time RT-PCR expression analyses of the indicated genes was performed using cDNA prepared from INS-1E cells either uninfected (closed bars) or infected with CA-TβRI retrovirus (open bars). PCR was conducted on three independent samples and in triplicates.