Supplemental Information

**AAV vector production**

The packaging cell line, HEK293, was maintained in Dulbecco’s modified Eagles medium (DMEM), supplemented with 5% fetal bovine serum (FBS), 100 units/ml penicillin, 100 µg/ml streptomycin in a 37°C incubator with 5% CO₂. The cells were plated at 30-40% confluence in CellSTACS (Corning Incorporated, Corning, NY) 24 h before transfection (70-80% confluence when transfected). 730 µg of pAAV 2/9, 1180 µg pHelper, and 590 µg rAAV transfer plasmid containing the gene of interest were co-transfected into HEK293 cells using the calcium phosphate precipitation. The cells were incubated at 37°C for 3 days before harvesting. The cells were lysed by three freeze/thaw cycles. The cell lysate was treated with 25U/ml of Benzonase at 37°C for 30 min. After centrifugation at 10,000 g for 20 min, the supernatant was collected and precipitated in PEG (final concentration of PEG: 8%) overnight. After centrifugation at 2,600 g for 30 min, the supernatant was discarded and the pellet was re-suspended with lysis buffer (150 mM NaCl, 50 mM Tris-HCl, pH 8.5). In a 38.5 ml polyallomer tube, 5 ml of CsCl (1.5 g/ml) was added and 12 ml of CsCl (1.37 g/ml) was overlaid along the side of the tube. The sample was ultracentrifuged at 24,000 rpm (182,000 g), 20°C for 24 h. A 21-gauge needle was inserted through the bottom side of the centrifuge tube. A 1-ml fraction was collected. Vector-containing fractions were pooled and diluted with 1.37 g/ml CsCl. The sample is loaded to a 13.5 ml Quick-seal tube and centrifuged with an ultracentrifuge at 67,000 rpm (384,000g), 20°C for 16-20 h. 0.5-ml fractions were collected. Vector-containing fractions were pooled and then concentrated with Vivaspin 20 100K concentrator (Sartorius, Göttingen, Germany). The vector titer was determined by Dot blot assay. All of the procedures above were performed by Hope Center Viral Vectors Core at Washington University in St. Louis.
Supplemental Figure

Figure S1

Figure S1. Manf expression level is not significantly changed by Wfs1 deficiency in INS-1 832/13 cells.

qPCR analysis of Wfs1 and Manf in Wfs1 wild type (WT) and knockout (KO) INS-1 832/13 cells. Total RNA was extracted from INS-1 832/13 cells as described in the Method section of the main text. Manf expression level was not significantly elevated in Wfs1 KO INS-1 832/13 cells. Also, Manf expression was not changed even in Wfs1 knockdown INS-1 832/13 cells (data not shown). (n=3, **** P<0.0001)
Figure S2. Viability of Wfs1 knockout INS-1 832/13 cells was increased by MANF overexpression. GFP or human MANF were overexpressed in Wfs1 wild type (WT) and knockout (KO) INS-1 832/13 cells by lentivirus transduction at multiplicities of infection (MOI) 5. Twenty four hours after the virus transduction, the medium was changed to fresh medium not containing lentivirus. After another 24 h, total protein was collected for western blot (left panel). Cell viability assay (right panel) was performed as described in the Method section of the main text. MANF overexpression increased the cell viability of Wfs1 knockout INS-1 832/13 cells. (n=6, * P<0.05, ** P<0.001)
Figure S3. The proliferative effect of MANF for exocrine pancreatic cells

Quantification of Ki67 positive exocrine pancreatic cells in AAV9-control or AAV9-MANF injected βWfs1−/−mice (n=6 in each group, not significant).

Supplemental Table

| Gender | Age | BMI | HbA1C (%) | History                                                        | Beta cell proliferation by MANF peptide |
|--------|-----|-----|-----------|----------------------------------------------------------------|---------------------------------------|
| Female | 51  | 22.6| 5.6       | Ruptured cerebral artery aneurism leading to brain death       | Yes                                   |
| Male   | 31  | 24  | 5.3       | Military person died of self-inflicted gun shot wound to head  | Yes                                   |
| Male   | 42  | 32.8| 5.6       | Brain dead from stroke with intracranial hemorrhage           | No                                    |
| Male   | 68  | 35.6| 6.5       | Type-2 diabetes, brain dead from stroke                       | No                                    |
| Female | 23  | 24.5| 4.9       | Brain dead following blunt trauma from motor vehicle accident | No                                    |
| Male   | 23  | 21.4| 5.5       | Died from motor vehicle accident with head trauma             | No                                    |