**sFigure 1. Hyperglycemia and growth retardation in STZ-treated B6 mice.** Eight-week-old mice were intraperitoneally injected with 50mg STZ/kg daily for 5 days with age-matched control mice injected with citrate buffer only. **(A)** Blood sugar levels and **(B)** body weight were measured at indicated times, starting at day 3 of the initial 5-day-treatment. N=20 \*p < 0.05, \*\*P < 0.01. **(C)** The levels of glycosylated HbA1c were measured at the end of 8 weeks after the initial initial 5-day treatment using 500ul whole blood drawn from the facial vein and an automatic glycosylated hemoglobin analyzer. The results were presented as “% (mmol/mol). N=10, \*\*\*p < 0.001.

**sFigure 2. VIP is expressed healing human NL corneas and in infiltrated mouse neutrophils and other immune cells.** (**A**) Human normal and diabetic corneas with or without epithelium wounding (5 mm debridement wound) were cultured in 5 and 30 mM glucose, respectively. The wounded corneas were allowed to heal for 48 h. Both unwounded and wounded corneas were embedded in OCT and subjected to Cryostat sectioning. The sections were stained for VIP. E, epithelia; L, leading edge. Note: healing epithelia of NL corneas were stained more intensively than that of DM corneas. (**B**) B6 mouse healing corneas were sanctioned and co-stained with LY6G for neutrophils and VIP. E, epithelia; L, leading edge. Arrows, cells both LY6G and VIP; Arrowheads: VIP positive and LY6G negative cells. Note: In addition to healing epithelia, VIP positive cells were also detected in the stroma, some, but not all infiltrated cells were LY6G positive, suggesting neutrophils are one cell type that express VIP in wounded corneas. The strong epithelium staining of VIP for both NL and DM corneas may be due to overexposure for detecting immune VIP positive cells.

**sFigure 3. VIP promotes diabetic cornea epithelial wound closure is concentration dependent.** Diabetic corneas were pretreated with 250, 125, 50 (not shown) ng per cornea and then wounded. The wounds were allowed at heal to 22 h and then staining for the remaining wounds. Note: 250 ng per cornea is more effective than 125 ng/cornea in promoting epithelial wound healing in DM corneas.

**sFigure 4. ERK activation and Shh expression increases in NL healing corneas, a time course study.** At 0 h, the corneas were wounded by epithelium-debridement (2 mm diameter) and allowed to heal for indicated time. **(A)** Corneal epithelial cells (CECs) collected during wounding (0h) and isolated from the original wound beds at indicated times were subjected to Western blot analysis for Shh and phospho(P)-ERK. For each condition, two samples were used with 20 µg protein of CEC extracts loaded. (**B**) The band intensity was analyzed with Image J with the number of pixels as readout. The results were presented as fold change (mean ± SD) over the non-wounded control corneas set as a value of 1 (B, n=2). NS: Non-significantly difference. \*p< 0.05 (One-way ANOVA).

**sFigure 5. VIP upregulates ERK activation and Shh expression in cultured mouse corneal epithelial cells, a dose-dependent study.** Confluent TKE2 cells were treated with 10, 50, 250, 500 and 1000 ng/ml VIP. After 3h, mouse CECs were collected and subjected to Western-blot analysis for phospho-ERK **(A)** and SHH expression **(B)**. Two samples for each condition were used and 30 µg total protein from collected mouse CECs was analyzed for each sample (A and B). The pixels of bands were analyzed with ImageJ, and the results were presented as fold change (mean ± SD, C and D) over the control cells set as a value of 1 (CT). \*p< 0.05, \*\*p< 0.01 (One-way ANOVA).

**sFigure 6. VIP affects SHH expression and ERK phosphorylation in unwounded corneas.** NL and DM corneas were subconjunctivally injected with 250 ng VIP. The corneas were harvested at 6 h post VIP treatment and then subjected to Western assessing SHH and phosphor-RRK expression. Note, VIP enhances both SHH expression and ERK activation in NL and to a less extent, DM corneas.

**sFigure 7. Exogenous VIP accelerates wound healing and nerve regeneration in healing corneas of NL mice.** NL corneas pretreated with BSA as the control or VIP (50ng/ul, 5ul per eye) 4h prior to epithelium debridement. At 0h, the corneas were wounded by epithelium-debridement (2 mm diameter) and allowed to heal for 22h or 3 days. **(A)** At 22 hpw, the remaining wounds were stained with fluorescein and photographed. Each presented images are representative of 3 corneas. **(B)** The wound healing rates were calculated using Image J and presented as percent of original wound size (mean ± SD, n = 6). \*\*p< 0.01 (Student’s t-test). **(C)** At 1dpw, an additional subconjunctival injection of BSA or VIP was performed. At 3 dpw, corneas were excised and processed for WMCM with beta-tubulin III antibody. The image for each condition is a representative of three corneas and were shown as whole cornea (top panels) and central area (bottom panels). Nerve densities at the central areas (bottom panels) were calculated from the areas covered with beta-tubulin III staining with Image J and presented as % areas (mean ± SD, n = 3) (D). \*p< 0.05 (Student’s t-test). Two independent experiments were performed.

**sFigure 8. Exogenous SHH accelerates corneal epithelial wound healing in high glucose cultured porcine corneas.** At 0h, porcine corneas were wounded by epithelium-debridement (6 mm diameter) and cultured in either 25 mM mannitol with or without Sant-1 (250nM) or 25 mM glucose in MEM with or without rmShh (50ng/ml) for 42h. At 42 hpw, the cultured porcine corneas were stained with Richardson's staining solution to mark the remaining wound area and photographed (A). The remaining wound sizes were calculated using Image J and presented as pixels of the defect area (mean ± SD, n = 5) (B). \*p< 0.05, \*\*\*p < 0.001 (Student’s t-test).