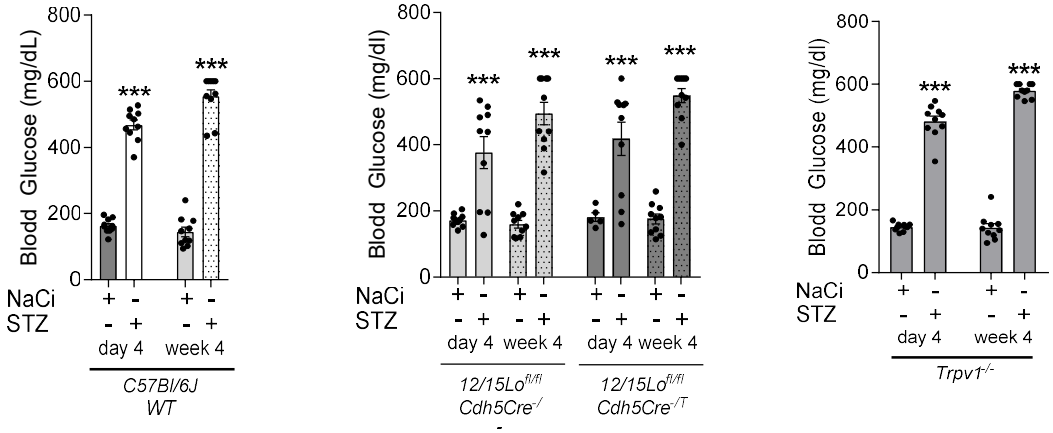
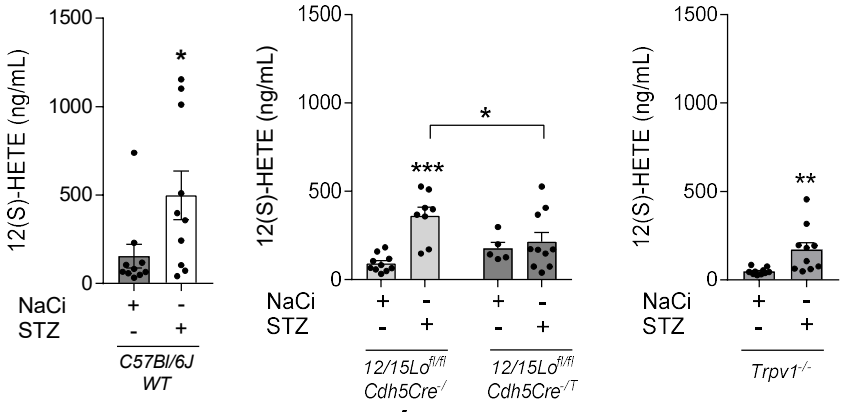
Supplemental Figure 1.



Supplemental Figure 1. Mouse blood glucose levels.

Blood glucose levels in mice on day 4 and 4 weeks after type I diabetes mellitus induction by a single injection of streptozotocin. One-way ANOVA/Bonferroni, n=10 mice/group. All data is presented as mean±SEM.

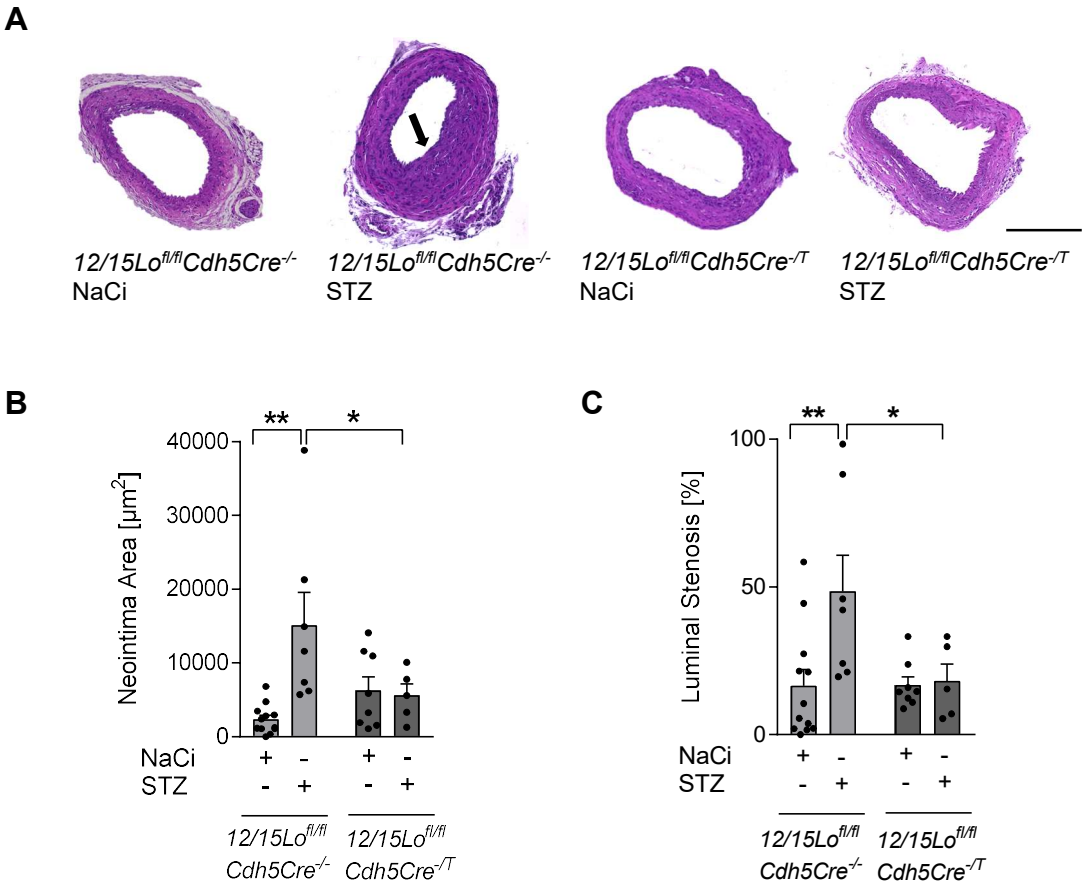
Supplemental Figure 2.



Supplemental Figure 2. Mouse 12(S)-HETE plasma concentrations.

12(S)-HETE plasma concentrations in mice four weeks after diabetes induction. One-way ANOVA/Bonferroni, n=10 mice/group. All data is presented as mean±SEM.

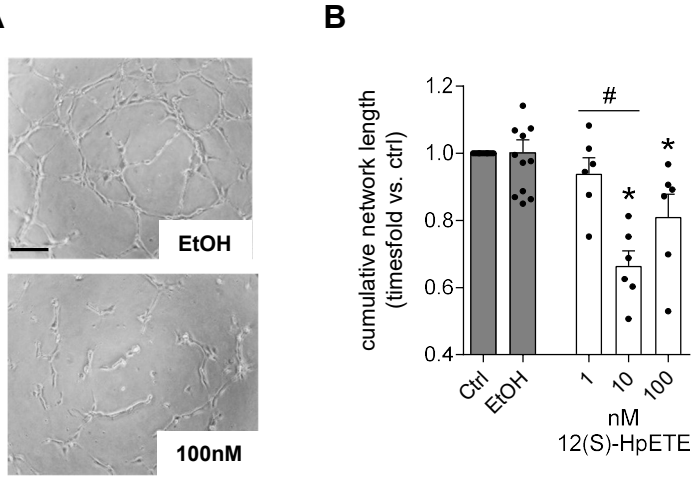
Supplemental Figure 3.



Supplemental Figure 3. Endothelial specific *12/15Lo* knock out protects against diabetes induced impaired vascular regeneration.

A Representative histomorphologies of carotid arteries 3 weeks after ferric chloride-induced carotid artery injury. The arrow indicates neointima formation in diabetic control animals. NaCi sodium citrate used as vehicle control for streptozotocin (STZ). **B** Quantitative summary of neointima area and **C** luminal stenosis. One-way ANOVA/Bonferroni, *P<0.05 and **P<0.01 vs. as indicated, n=7 mice/group. All data is presented as mean±SEM, the bar indicates 200µm.

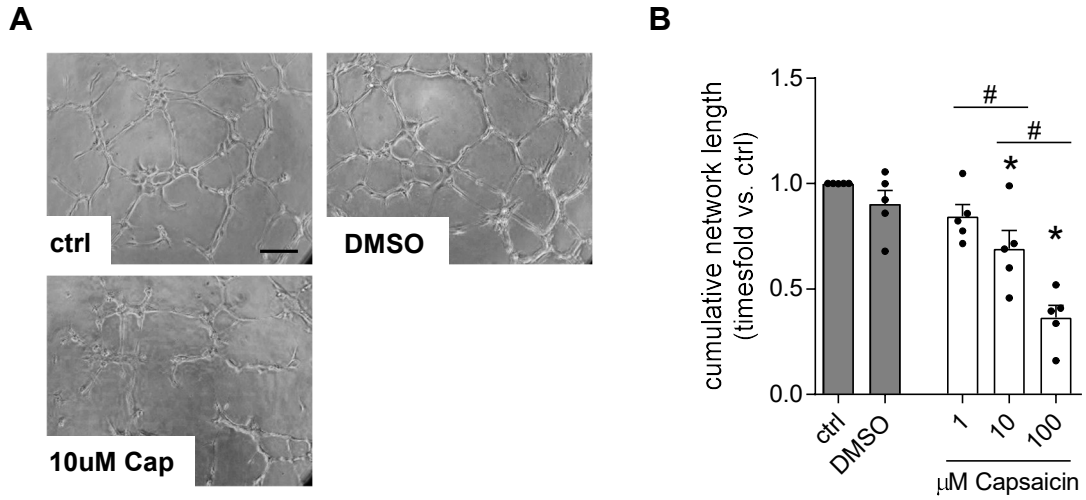
Supplemental Figure 4.



Supplemental Figure 4. 12(S)-HpETE induces dysfunction in human endothelial cells.

A, B Capillary networks formed by human umbilical vein endothelial cells on extracellular matrix in response to treatment with 12(S)-HpETE. *P<0.05 vs. EtOH, #P<0.05 as indicated. One-way ANOVA/Bonferroni, n=6/group. Bar represents 100µm. Graphs show mean±SEM.

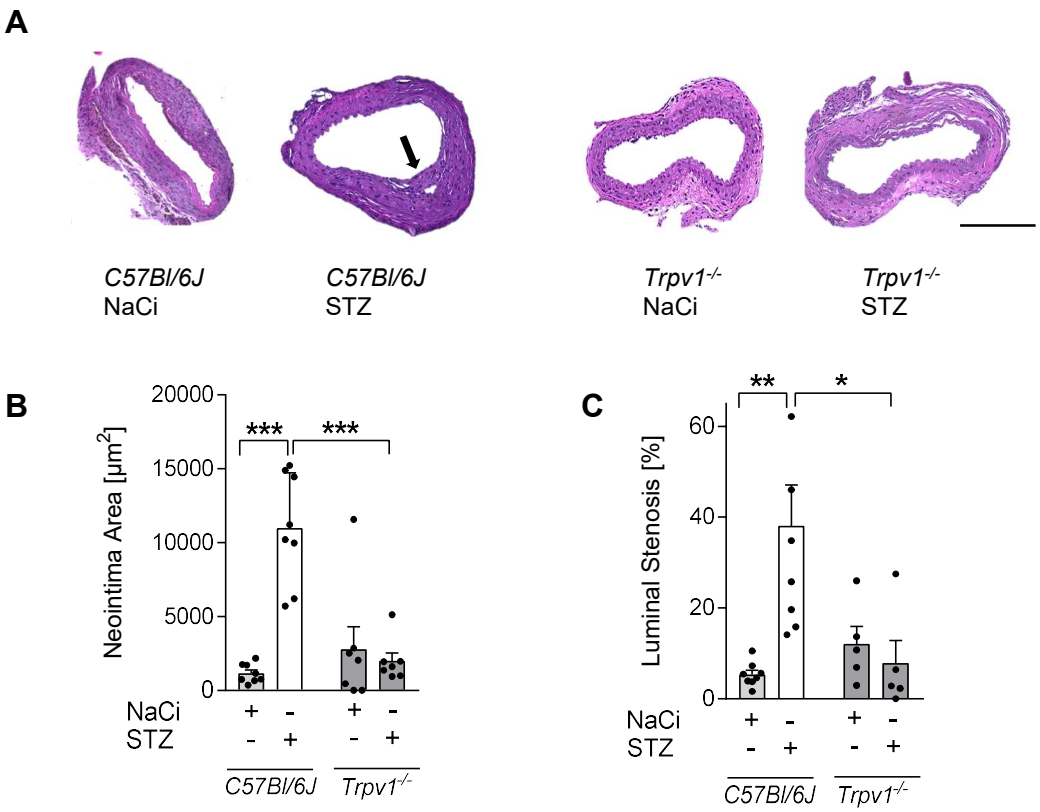
Supplemental Figure 5.



Supplemental Figure 5. Capsaicin induces dysfunction in human endothelial cells.

A, B Effects of capsaicin on endothelial capillary formation on extracellular matrix. *P<0.05 vs. DMSO, #P<0.05 vs. as indicated. One-way ANOVA/Bonferroni, n=5 independent experiments. Bar respresents 100µm. Graphs show mean±SEM.

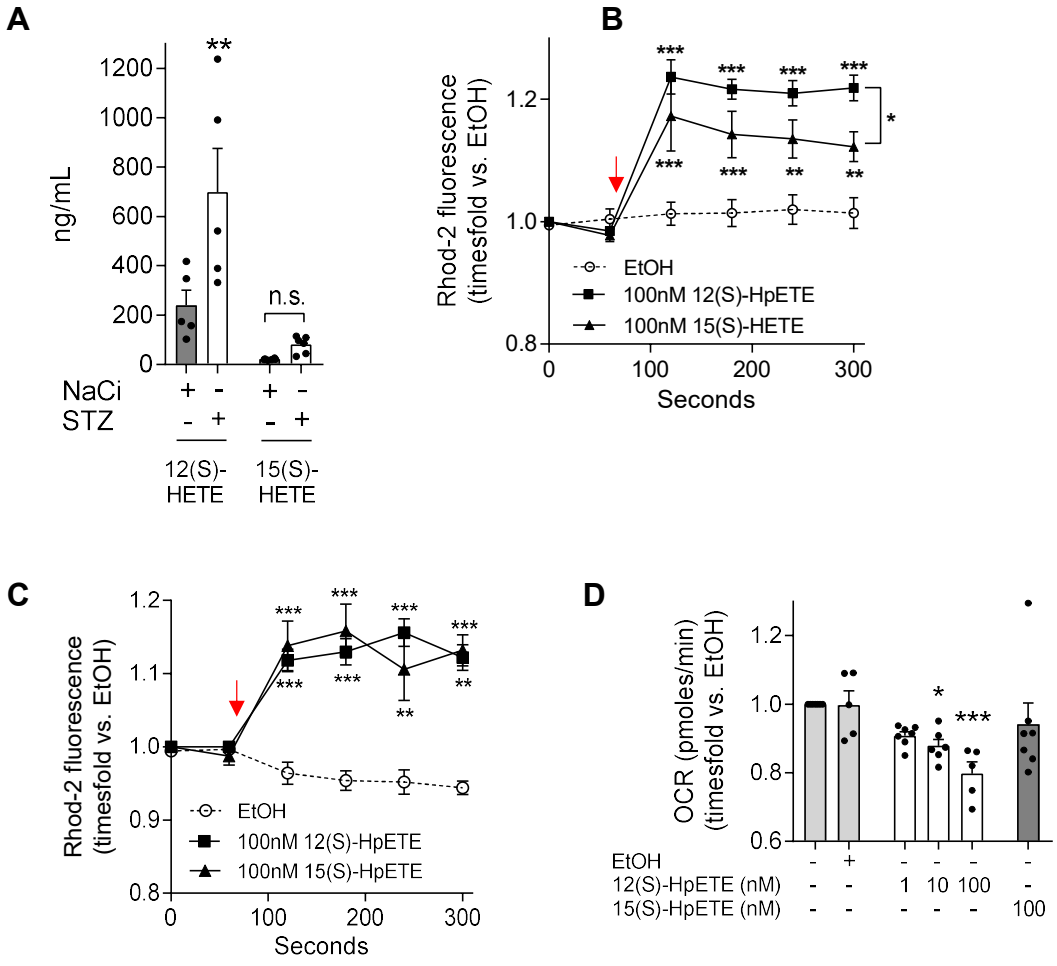
Supplemental Figure 6.



Supplemental Figure 6. TRPV1 knock out mice are protected against diabetes induced impaired vascular regeneration.

A Representative histomorphologies of carotid arteries 3 weeks after ferric chloride-induced carotid artery injury. The red arrow indicates neointima formation in diabetic control animals. NaCi sodium citrate used as vehicle control for streptozotocin (STZ). **B** Quantitative summary of neointima area and **C** luminal stenosis. One-way ANOVA/Bonferroni, *P<0.05, **P<0.01 and ***P<0.001 vs. as indicated, n=5-8 mice/group. All data is presented as mean±SEM, scale bar indicates 200µm.

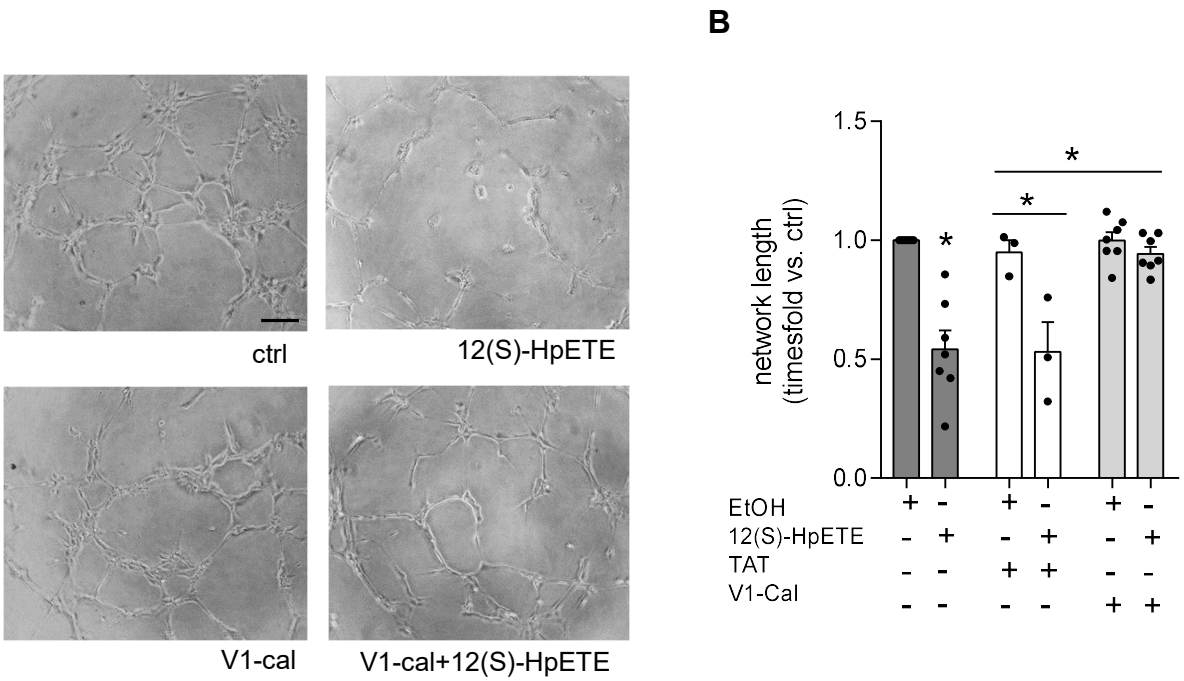
Supplemental Fig. 7



Supplemental Figure 7. Murine 15(S)-HETE and 12(S)-HETE plasma concentrations and 15(S)-HpETE effects on mitochondrial calcium and function in endothelial cells.

A 15(S)-HETE and 12(S)-HETE plasma levels in mice four weeks after type I diabetes induction. One-way ANOVA/Bonferroni, n=5 mice/group. All data is presented as mean±SEM. **B, C** Induction of mitochondrial calcium influx detected as fluorescence intensity changes by flow cytometry in rhodamine (rhod-2)-loaded human (**B**) and murine endothelial cells (**C**) by 100nM 12(S)- vs. 15(S)-HpETE. Time of addition is indicated by red arrows. EtOH Ethanol served as vehicle control. Two-way ANOVA/Bonferroni, *P<0.05, **P<0.01 and ***P<0.001 vs. EtOH or as indicated, n=5 independent experiments. **D** Effects on mitochondrial oxygen consumption rate (OCR) in human endothelial cells induced by 12(S)-HpETE and 15(S)-HpETE. One-way ANOVA/Bonferroni, ***P<0.001, *P<0.05 vs. EtOH, n=5-8 independent experiments. All graphs show mean±SEM.

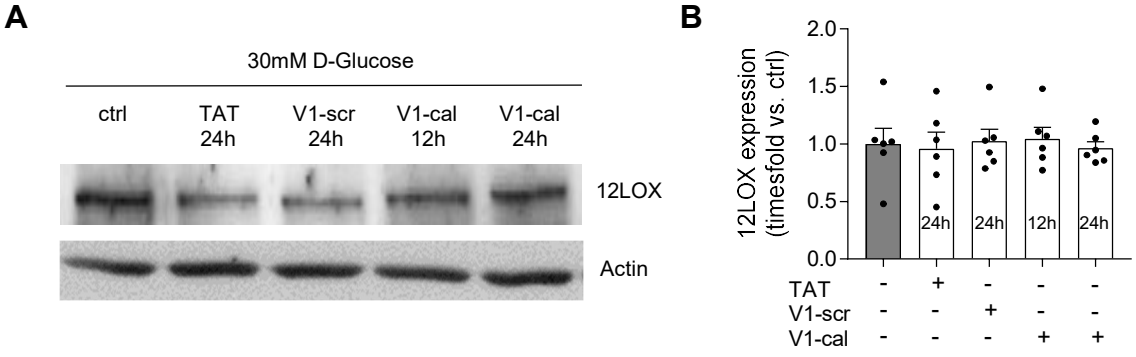
Supplemental Figure 8.



Supplemental Figure 8. 12(S)-HpETE induced effects on endothelial capillary formation are absent after preincubation of endothelial cells with the V1-cal peptide.

A, B 1µM V1-cal vs. 1µM TAT-linker effects on 100nM 12(S)-HpETE-induced reduction on endothelial capillary-like tube formation. One-way ANOVA/Bonferroni, n=3-7 independent experiments, *P<0.05 vs. as indicated. Bar indicates 100µm. All graphs show mean±SEM.

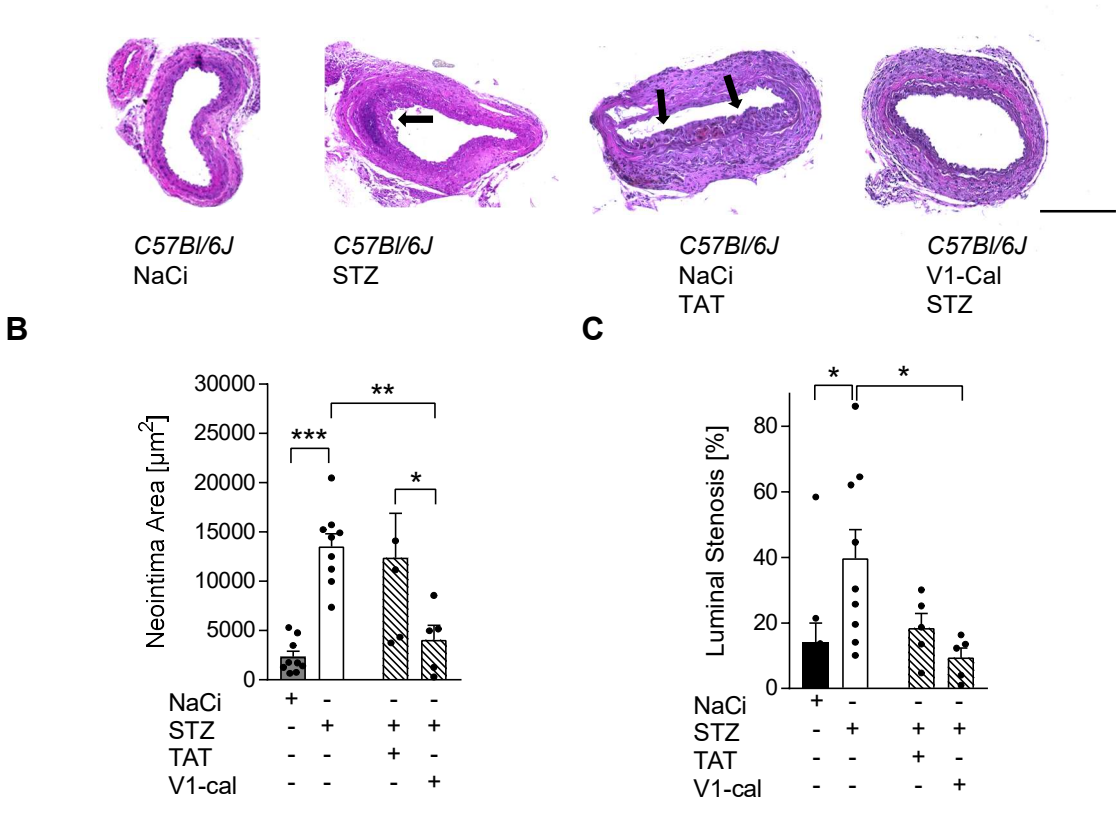
Supplemental Figure 9.



Supplemental Figure 9. V1-cal or control peptides do not alter 12LOX expression.

A Representative western blot showing that incubation of high glucose exposed human endothelial cells with 1µM TAT linker, V1-scr or V1-cal for 12h or 24h does not alter 12LOX expression. **B** Quantitative summary of n=6 independent experiments, graph shows mean±SEM.

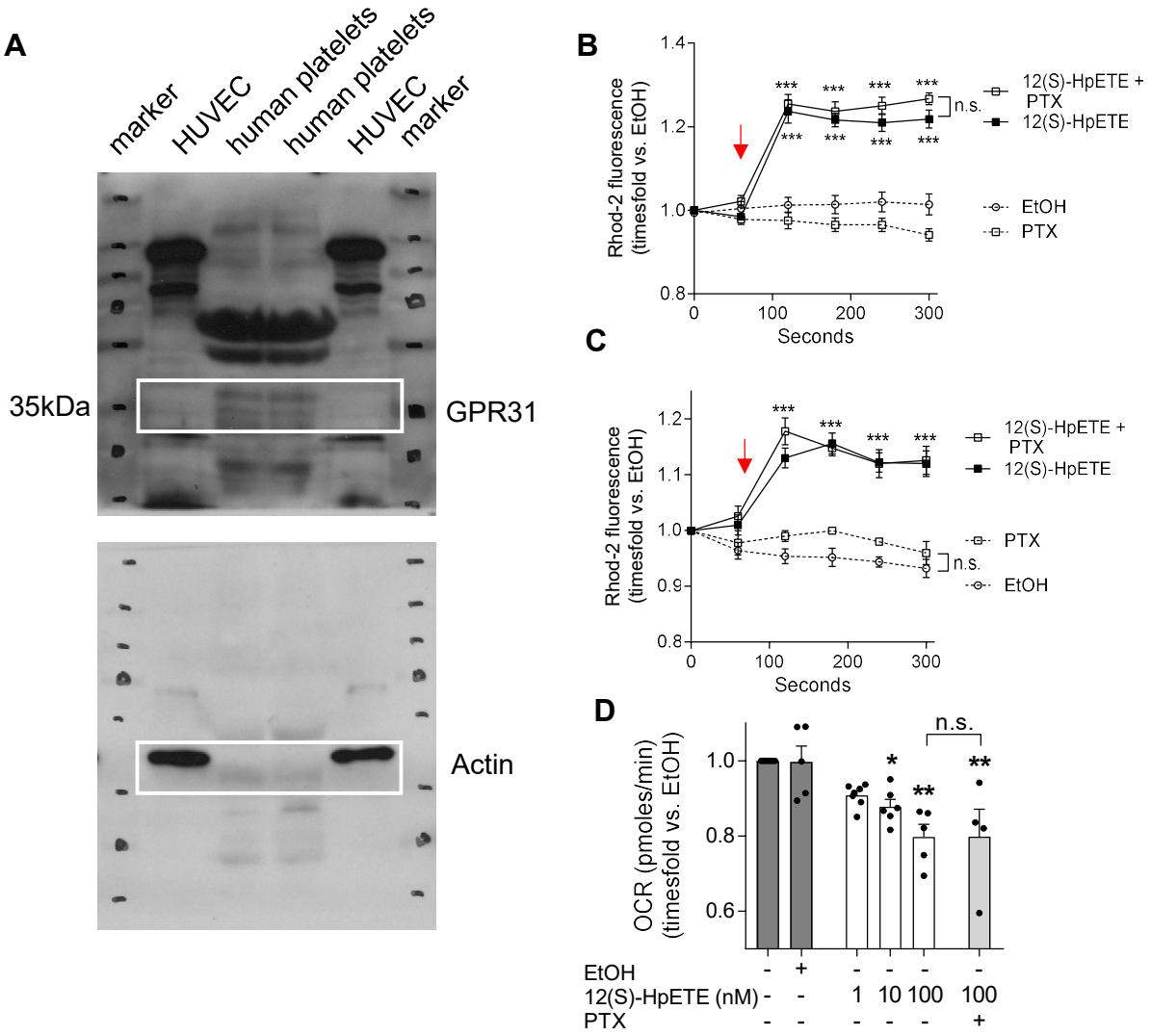
Supplemental Figure 10.



Supplemental Figure 10. Treatment of diabetic mice with V1-cal improves vascular regeneration.

A Representative histomorphologies of carotid arteries 3 weeks after ferric chloride-induced carotid artery injury. The arrows indicate neointima formation in diabetic control animals and diabetic animals treated with the TAT linker only continuously delivered by osmotic minipumps. NaCi sodium citrate was used as vehicle control for streptozotocin (STZ). **B** Quantitative summary of neointima area and **C** luminal stenosis. One-way ANOVA/Bonferroni, *P<0.05, **P<0.01 and ***P<0.001 vs. as indicated, n=4-9 mice/group. All data is presented as mean±SEM, bar indicates 200µm.

Supplemental Fig. 11



Supplemental Figure 11. 12(S)-HpETE effects are not mediated by G-protein coupled protein GPR31

A Western Blot analysis revealing that GPR31 is strongly expressed in human platelets serving as positive control but not in human umbilical vein endothelial cells (HUVEC). **B, C** 12(S)-HpETE-induced mitochondrial calcium influx detected by flow cytometry in Rhodamin-2 loaded human endothelial cells (**B**) or murine endothelial cells (**C**) is not altered by the inhibitor of G-protein coupled receptors pertussis toxin (PTX). Cells were stimulated with 100nM 12(S)-HpETE and 100ng/ml PTX. Time of addition is indicated by red arrows. Ethanol served as vehicle control. ***P<0.001 vs. EtOH, n.s. not significant, n=5 independent experiments. **D** Alterations on mitochondrial oxygen consumption rate (OCR) in human endothelial cells induced by 12(S)-HpETE and PTX. **P<0.01, *P<0.05 vs. EtOH, n.s. not significant as indicated, n=5-7 independent experiments. One-way ANOVA/Bonferroni, all graphs show mean±SEM.