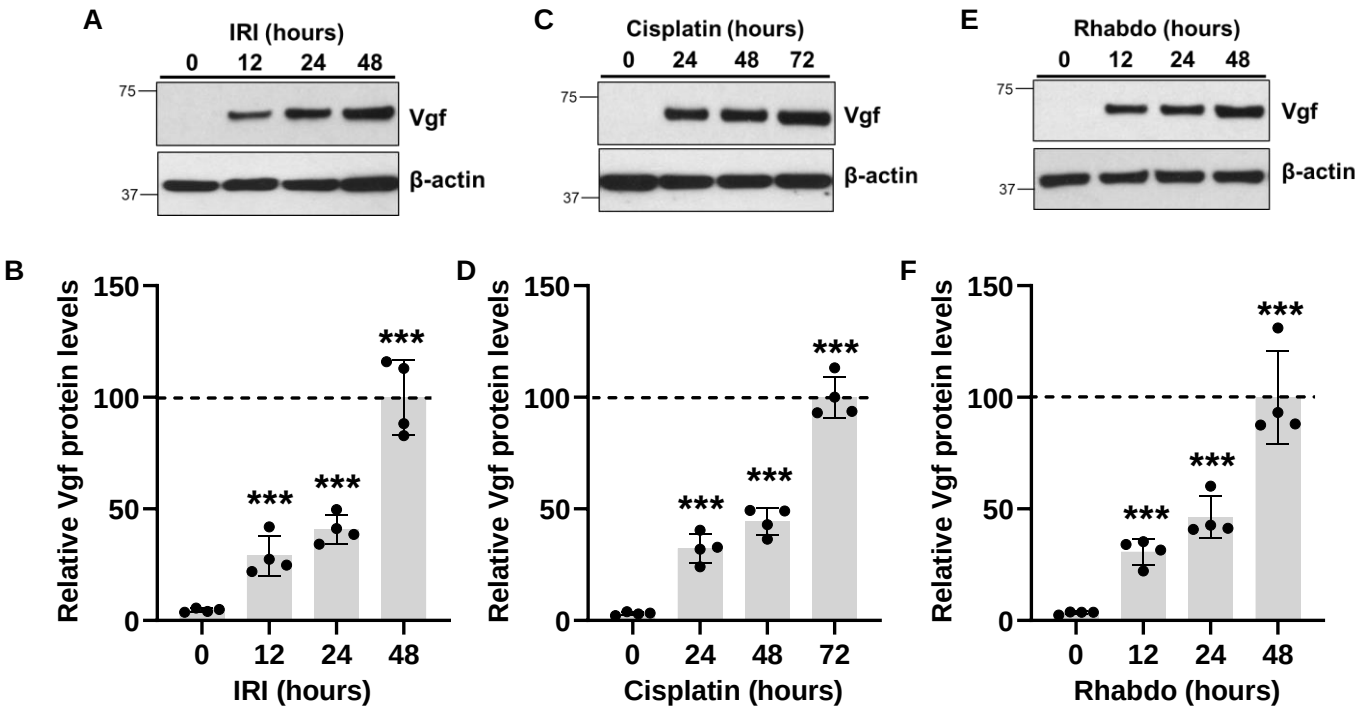
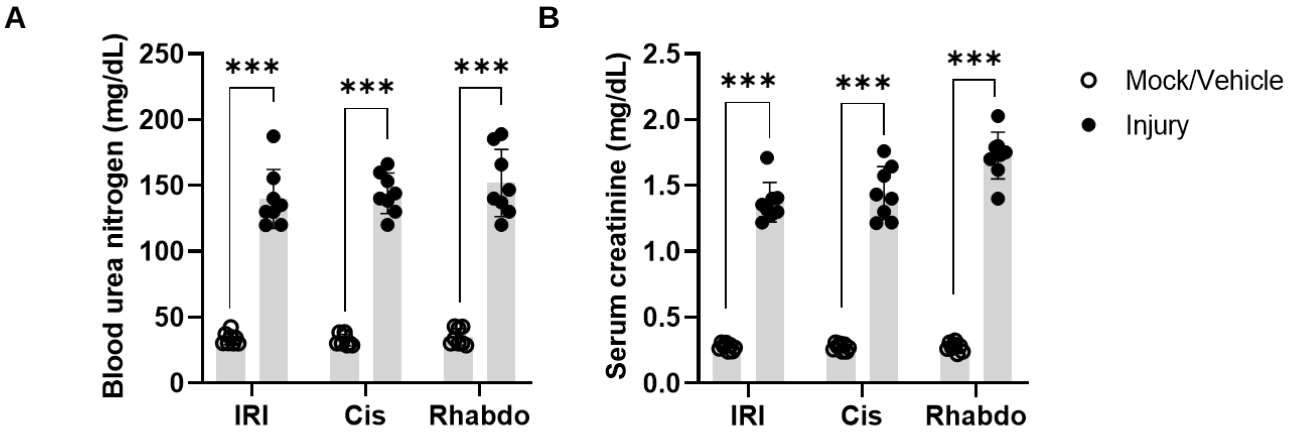
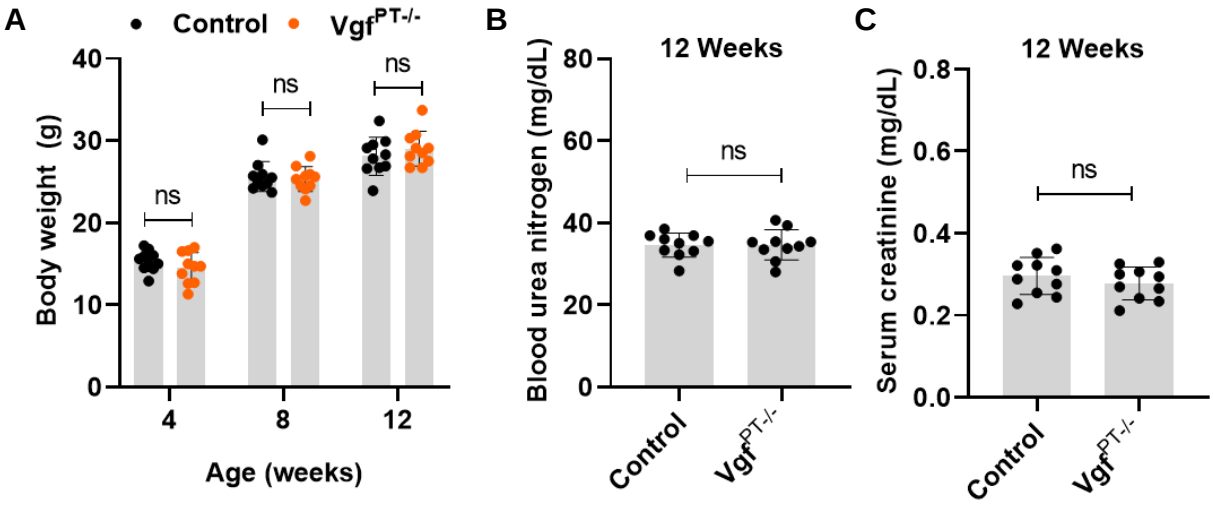


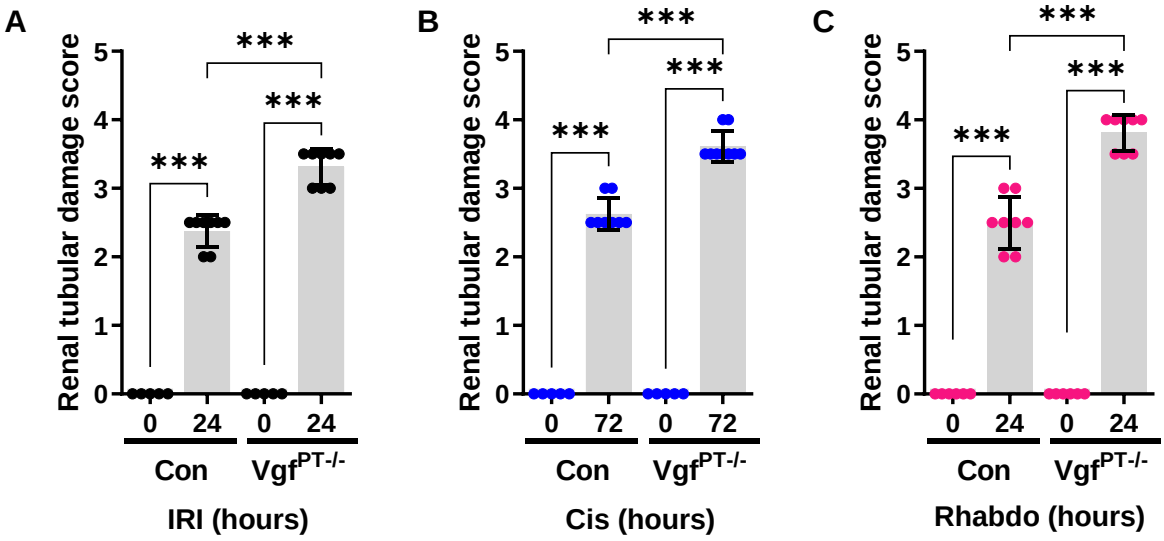
Supplementary Information Figure S1. ***Renal Vgf protein induction during AKI*.** 8-12 weeks C57BL/6J mice male were challenged with bilateral renal ischemia (30 minutes), cisplatin (30 mg/kg, single intraperitoneal injection) treatment, or glycerol-induced rhabdomyolysis (7.5 ml/kg 50% glycerol in the hind-leg muscles) followed by tissue collection at indicated time-points. Immunoblot analysis showed an early induction of Vgf protein during AKI. The blots (**A, C, and E**) are representative of three independent experiments. The graphs (**B, D, and F**) depict densitometric analysis of Vgf protein in renal tissues. In all the bar graphs (n=4 biologically independent samples), experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. 1-way ANOVA followed by Dunnett's multiple-comparisons test was carried out and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.



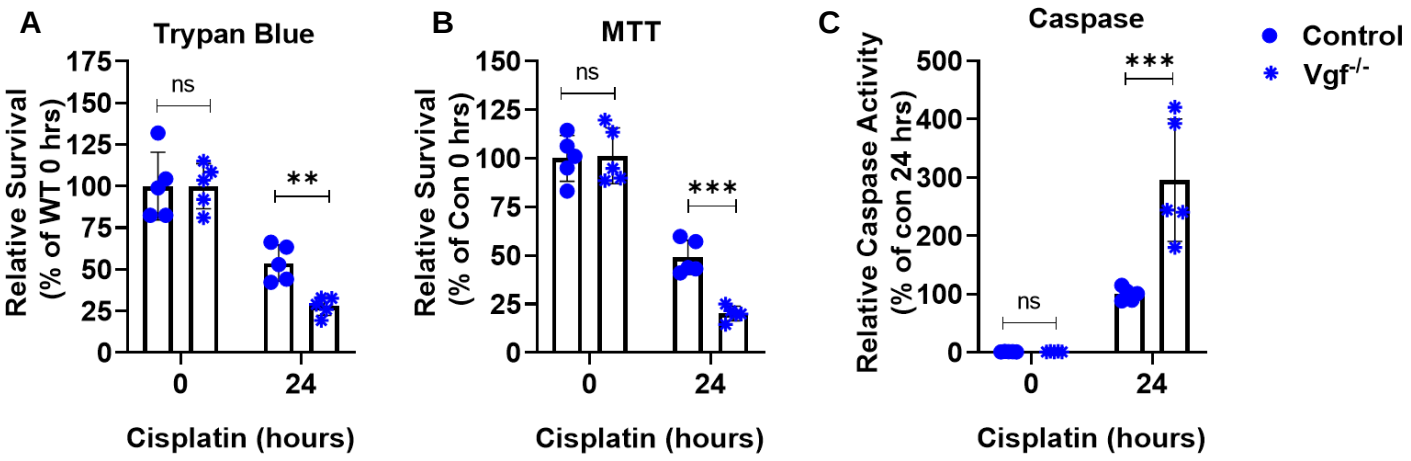
Supplementary Information Figure S2. ***Characterization of the RTEC-specific EGFP expressing reporter mice*.** Ggt1-Cre mice were crossed with ROSAmT/mG mice to generate transgenic mice that express membrane-localized EGFP in RTECs. 8-12 weeks male mice were then challenged with bilateral renal ischemia (30 minutes), cisplatin (30 mg/kg, single intraperitoneal injection) treatment, or glycerol-induced rhabdomyolysis (7.5 ml/kg 50% glycerol in the hind-leg muscles) followed by examination of renal structure and function. The mock/vehicle groups represent respective control groups (with no injury). (**A**-**B**) Representative graphs depicting injury-induced increase in blood urea nitrogen and serum creatinine levels (IRI and Rhabdo at 24 hours and Cisplatin at 72 hours). The graphs ($n = 8$) are representative of three independent experiments. In all the bar graphs, experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. Student's t test was carried out, and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.



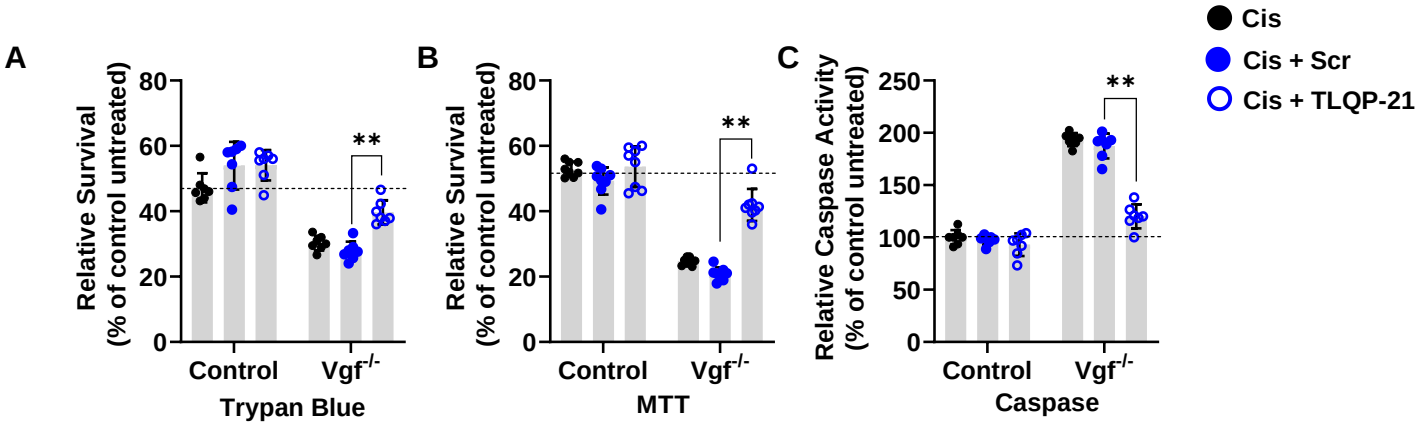
Supplementary Information Figure S3. ***Characterization of the RTEC-specific Vgf deficient mice.*** Ggt1-Cre mice were crossed with Vgf-floxed mice to generate RTEC-specific Vgf deficient mice. (**A**) Body weight measurements showed no differences between the control and Vgf deficient mice up to 12 weeks of age. (**B-C**) Renal function (BUN and Creatinine) was examined in littermates with indicated genotypes at 12 weeks of age under baseline conditions. These results show that RTEC-specific Vgf knockout does not affect kidney function under normal conditions. Data are presented as individual data points (n = 10), from a single long-term experiment. In all the bar graphs, experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. Student's t test was carried out, and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ns= not significant.



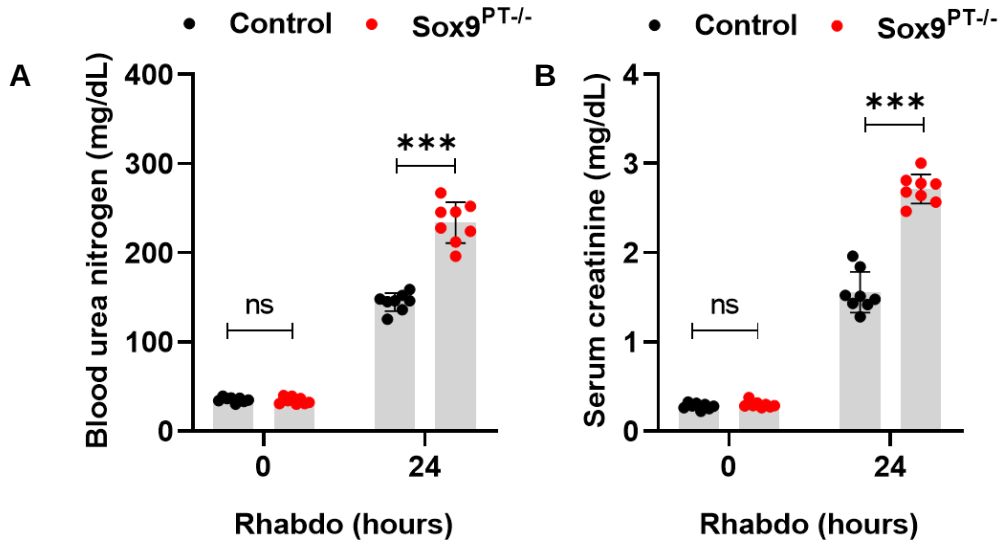
Supplementary Information Figure S4. ***Histological analysis shows higher renal damage in Vgf-deficient mice*.** 8-12 weeks old littermate control and Vgf conditional knockout male mice (indicated by $Vgf^{PT-/-}$) were challenged with bilateral renal ischemia (30 minutes), cisplatin (30 mg/kg, single intraperitoneal injection) treatment, or glycerol-induced rhabdomyolysis (7.5 ml/kg 50% glycerol in the hind-leg muscles) followed by examination of renal histology by H&E staining. (A-C) Histological analysis showed that Vgf deificiency excerberates renal damage associated with ischemic, nephrotoxic, and rhabdomyolysis-associated injury. In all the bar graphs (n=8 biologically independent samples), experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. One-way ANOVA followed by Tukey's multiple-comparison test was carried carried out, and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.



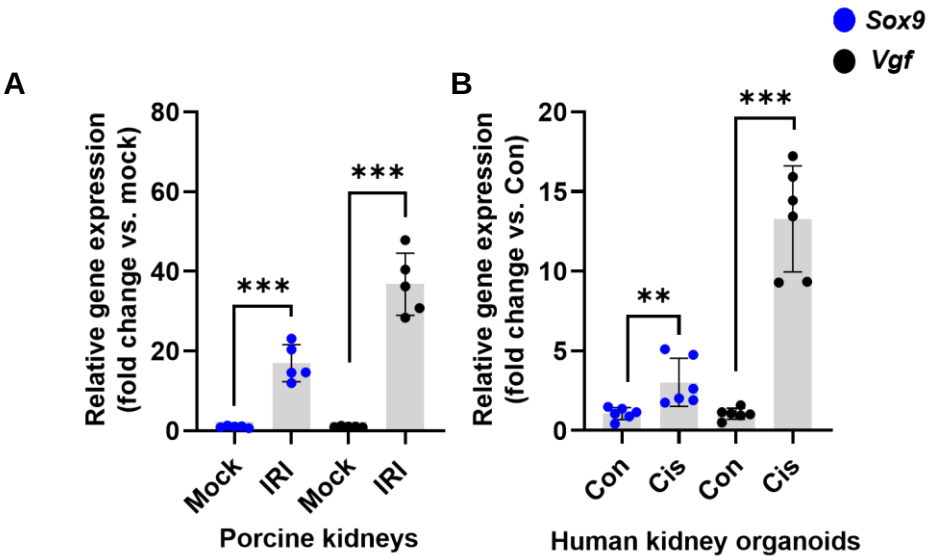
Supplementary Information Figure S5. ***Vgf deficiency sensitizes RTECs to cisplatin-induced cell death.*** Primary RTECs from mice with indicated genotypes were treated with 50 μM cisplatin, followed by cell viability assessment using trypan blue staining (**A**), MTT assay (**B**), and measurement of caspase activity (**C**) in cellular lysates. In all the bar graphs (n=8 biologically independent samples), experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. One-way ANOVA followed by Dunnett's was carried out, and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$



Supplementary Information Figure S6. TLQP-21 protects Vgf deficient RTECs from cisplatin-induced cell death. Primary murine renal tubular cells of indicated genotypes were treated with 50 μM cisplatin followed by treatment with 25 nM scrambled peptide or TLQP-21 four hours later. At 24 hours examination of cell viability by trypan blue staining (**A**), MTT assay (**B**) and caspase assays (**C**) showed that TLQP-21 can reverse the hyper-sensitive response of Vgf deficient cells to cisplatin treatment. In all the bar graphs (n=8 biologically independent samples), experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. One-way ANOVA followed by Dunnett's was carried out, and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$



Supplementary Information Figure S7. ***Sox9 plays a protective role during Rhabdomyolysis-associated AKI.*** To generate mice with renal tubule-specific Sox9 knockout, Ggt1-Cre mice were crossed with Sox9-floxed mice. Control and $Sox9^{PT-/-}$ male littermates (8-12 weeks age) were challenged with glycerol-induced rhabdomyolysis (7.5 ml/kg 50% glycerol in the hind-leg muscles) followed by examination of renal impairment. (**A-B**) Blood urea nitrogen and serum creatinine measurements showed that RTEC-specific Sox9 deficiency exacerbates rhabdomyolysis-associated AKI. In all the bar graphs (n=9 biologically independent samples), experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. One-way ANOVA followed by Tukey's multiple-comparison test was carried out, and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.



Supplementary Information Figure S8. ***Sox9-Vgf axis in porcine and human organoid models of kidney injury*****. (A)** Female pigs (55-65kg) were anaesthetised for general surgery and bilateral renal artery cross-clamping (40min) with 48h post-surgical recovery (IRI). Sham-controls had an equivalent surgical experience but the renal arteries remained patent ('Mock') as described previously (Ref. 42). qPCR based-analysis of renal cortical tissues showed that ischemic injury results in Sox9 and Vgf mRNA upregulation. (**B**) Pluripotent stem cell-derived human kidney organoids were treated with vehicle (Con) or Cisplatin as described recently (Ref. 43). qPCR examination of renal epithelial cells isolated from human organoids showed that Sox9 and Vgf mRNA is upregulated by cisplatin treatment. In all the bar graphs experimental values are presented as mean ± s.d. The height of error bar = 1 s.d. and $p < 0.05$ was indicated as statistically significant. Student's t-test was carried out, and statistical significance is indicated by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.