Prevention-of-Fibrosis-and-Organ-Protection

Novel therapeutic approaches and agents for the prevention, treatment and/or delaying progression of chronic injury, progressive loss of functional parenchymal cells, or fibrosis of an organ. The technology is based on a novel signaling axis.

Challenge

Injury in an organ triggers a complex signaling cascade that involves various cellular and molecular responses, ultimately culminating in tissue fibrosis, loss of functional parenchyma and organ failure. Progressive fibrosis and impaired regenerative capacity is still an unmet biomedical challenge, because once chronic lesions have manifested, no effective therapies are available as of yet for clinical use. (i.e. progression of chronic kidney disease (CKD) towards end-stage renal disease (ESRD)). It has been known that parenchymal organs including the kidney can be preconditioned to resist later acute ensuring tissue injuries, preventing both progressive loss of functional epithelium and kidney fibrosis.

Our Solution

Novel therapeutic approaches and agents for the prevention, treatment and/or delaying progression of chronic injury, progressive loss of functional parenchymal cells, or fibrosis of an organ. The technology is based on a novel signaling axis. An increase of the ALK3-K-level in cells, activates BMP signaling responses, which ultimately result in an anti-fibrotic and pro-regenerative response. These effects protect an organ against chronic injury, progressive loss of functional parenchymal cells or fibrosis.

The novel agents may be:

1. an inhibitor of protein phasphatase 2A (PP2A), i.e. LB-100 or vivo morpholinos
2. an inhibitor of the transcriptional repressor complex FKBP12/YY1, i.e. GPI-1046 or vivo morpholinos
3. an expression construct, which is capable of rising the expressing of ARNT in said organ

EXPERIMENTAL RESULTS

Several in vivo experimental results have been achieved:

- In vivo low-dose tacrolimus (FK506) protects kidney from chronic kidney injury in UUO mice.
- GPI-1046 protects from chronic renal failure in UUO mice.
- Modulation of ARNT with in vivo morpholinos (VMO) achieved in UUO mice.
- Selective PP2A inhibition with LB-100 reduced tubulointerstitial fibrosis and attenuated chronic kidney failure in UUO mice.
- Kidney protection in diabetic model of chronic kidney injury with low-dose tacrolimus or GPI-1046.

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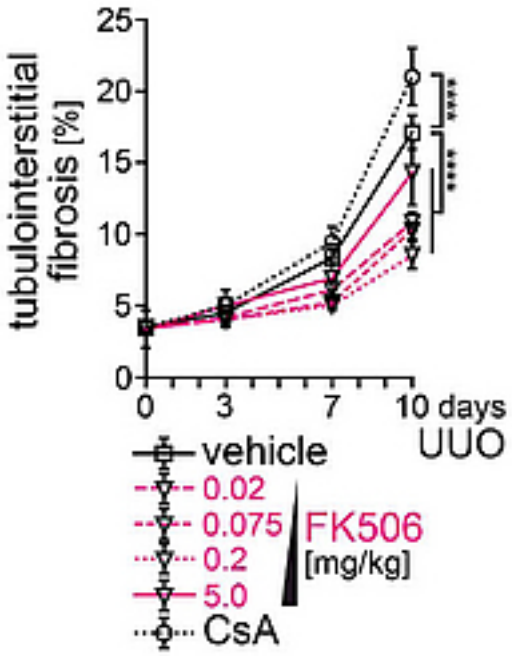
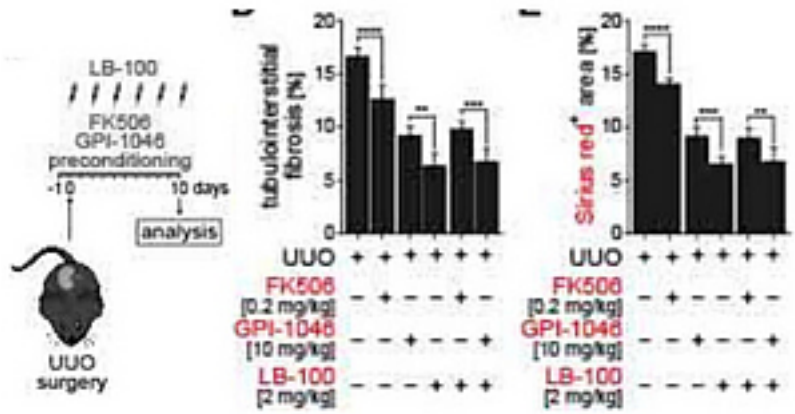


Example 1: The use of low-dose FK506/tacrolimus protects the kidney from chronic kidney injury by decreasing the ARNT suppressor complex FKBP12/YY1

Results: Histopathological analysis demonstrated that sub-immunosuppresive low-dose FK506 reduced both, chronic tubular injury and interstitial fibrosis with an optimum dose of 0.075 and 0.2 mg/kg FK506 per day. Administration of cyclic peptide immunosuppresant Cyclosporine A (CsA) failed to attenuate tubular injury or interstitial fibrosis, suggesting an alternate mechanism for low-dose FK506.

Experimental: UUO mice model: challenged C57BL/6 mice with the non-immunological, mechanical model of unilateral ureter obstruction (UUO), resulted in injury of the tubular epithelium and severe interstitial fibrosis within 10 days after ureteral obstruction. Low-dose FK506 (0.02, 0.075 and 0.2 mg/kg orally per day) were administered to mice starting one day prior to challenge with UUO. As control standard-immunosuppresive dose FK506 (5.0 mg/kg orally per day) and Cyclosporine A (CsA, 10 mg/kg orally per day) were used.



Example 2: Inhibition of PP2A with LB-100 protects against chronic kidney injury

Results: Selective PP2A inhibition increases endogeneous ARNT-levles (by protection from degradation) associated with enhanced ARNT homodimer formation.

Experimental: LB-100 (small molecule) has been developed for in vivo usage to overcome toxicity of PP2A inhibitors. The efficacy of previous established preconditioning regimes with either low-dose FK506 (0,2 mg/kg s.c.) or GPI-1046 (10 mg/kg s.c.) in combination with LB-100 (2 mg/kg) was tested. No injury was observed in parenchymal organs incl. kidney, heart, liver, pancreas.

Advantages

- Modulation of the new ARNT signaling pathway is possible with multiple drugs
- Effective attenuation of fibrosis in multiple organs
- In vivo proof of concept achieved.
- Prevention and delay of organ injury.

Applications

Organ protection against chronic injury through (1.) preventive preconditioning (administered before organ injury), or (2.) interventional treatment (initiated when injury had already been established).

Protective effect targets parenchymal organs like kidney, heart and liver.

Development Status

In vivo proof of concept successfully achieved. Some tested drugs are already in clinics.

Patent Status

We filed PCT international IP rights in the name of the Georg-August-Universität Göttingen, University Medical Center, and are looking for a licensing partner, who develops and markets a product.

References

J Clin Invest. 2018. doi.org/10.1172/JCI89632., Tampe et al.

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