RBT-1: Therapeutic Renal Preconditioning for AKI Prevention

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BACKGROUND

Preconditioning consists of short-term exposure to stressors that render the organ resistant to subsequent injury. However, there are currently no effective ways of inducing the preconditioning state in humans.

RBT-1 is a novel therapeutic designed to induce renal preconditioning by inducing mild, transient (4 hr) renal oxidant stress. RBT-1 is a combination product, containing a *novel iron sucrose preparation* (FeS) and *tin protoporphyrin* (SnPP). It is hypothesized that RBT-1's two components will synergistically upregulate redox-sensitive cytoprotective proteins in the kidney (eg, heme oxygenase-1, ferritin, hemopexin, haptoglobin, p21) and, by so doing, confer protection against diverse types of ischemic and toxic AKI.

This study was designed to assess the efficacy of RBT-1 in various animal models of AKI and to better define RBT-1's mechanism of action.

OBJECTIVES

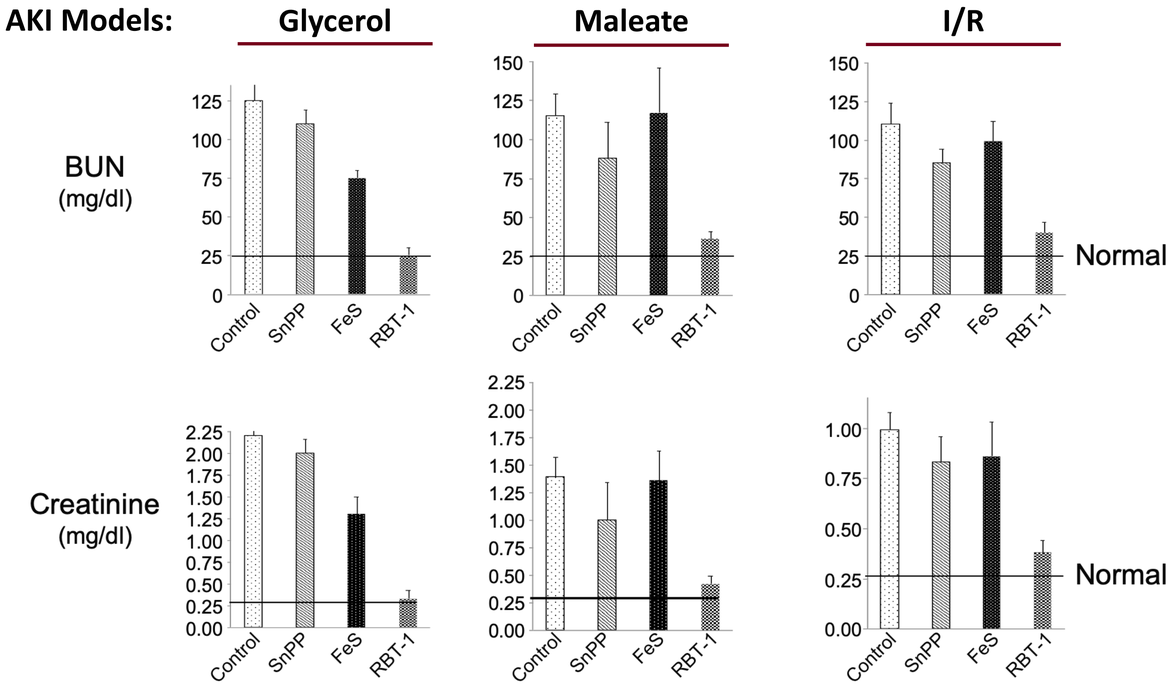
- Evaluate the efficacy RBT-1 in various animal models of AKI: glycerol-induced (rhabdomyolysis), maleate (ATP depletion), ischemia/reperfusion (I/R), and post-AKI progression to CKD (long-term progression)
- Identify the mechanism of action of RBT-1

METHODS

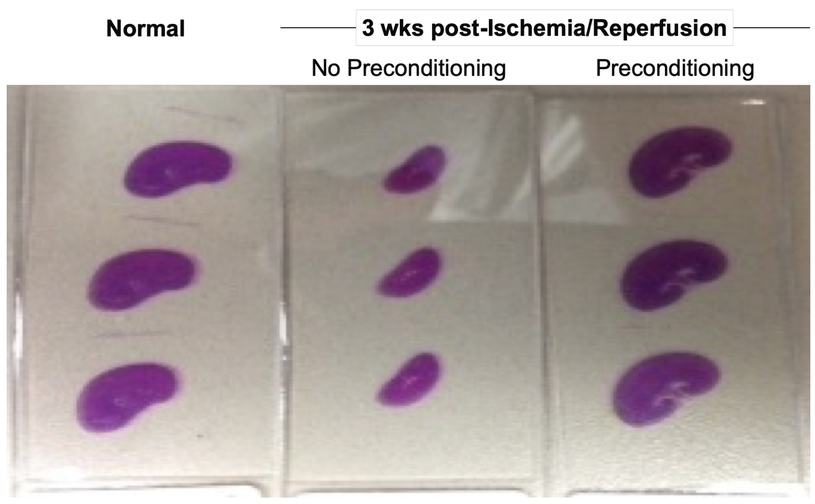
Male CD-1 mice were pretreated with RBT-1 18 hours before induction of one of the following AKI models: maleate, glycerol, or bilateral kidney I/R injury. Vehicle injected mice served as controls. Mice were sacrificed 18 hours later, and the severity of AKI was determined by blood urea nitrogen (BUN), plasma creatinine, and renal histology. Additive or synergistic protective effects of FeS and SNPP were sought. Post-AKI progression to CKD was also assessed in another cohort of mice 3 weeks post-unilateral I/R injury.

Mediators of RBT-1-induced cytoprotection were sought by RNA sequencing of RBT-1-treated and control kidney cortex. Upregulated genes that encode for cytoprotective proteins were identified, and then, these proteins were measured in renal cortex by ELISA or Western blotting. Plasma troponin I was measured as a marker of AKI-induced myocardial injury in the maleate and I/R models. Finally, the ability of RBT-1 to mitigate ischemic AKI in Nrf2-/- mice was assessed.

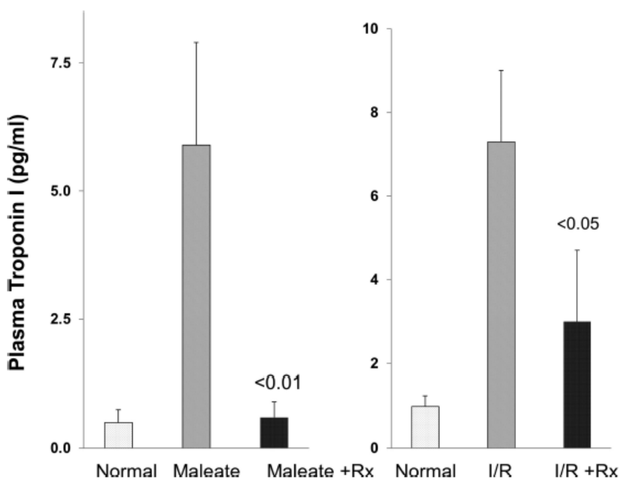
RESULTS



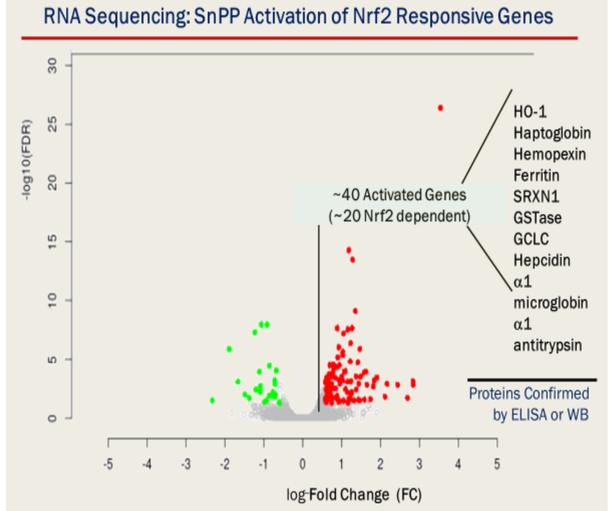
Post-AKI Progression to CKD



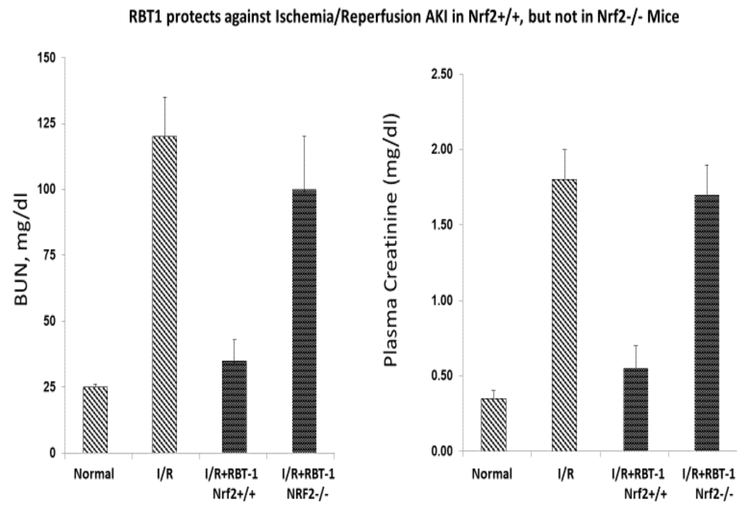
Myocardial Injury Biomarker Troponin I



RNA Sequence: Mediators of Cytoprotection



Ischemic AKI in Nrf2-/- Mice Treated with RBT-1



CONCLUSIONS

RBT-1 is a novel therapeutic that provides broad-based protection against diverse forms of AKI and some of its adverse extrarenal consequences (eg, myocardial injury). It can also prevent AKI progression to CKD. Nrf2 activation is a key mediator of the RBT-1-induced preconditioning state. A Phase 1b study has demonstrated excellent drug tolerance. Unique plasma and urinary biomarkers of RBT-1-induced preconditioning have been identified. A Phase 2 AKI prevention trial is planned for this year.