**Modulation of PPARδ with MTB-2 post-reperfusion attenuates IR-induced AKI injury biomarkers and histopathology in rats**

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**Background**

Ischemic acute kidney injury (AKI) is characterized by persistent proximal tubule mitochondrial dysfunction. Due to their highly oxidative metabolism, proximal tubule cells utilize fatty acids to generate the energy required for their specialized function. We hypothesized that enhancing fatty acid oxidation with a potent and highly selective PPARδ modulator will restore mitochondrial function, offering a potential therapeutic treatment for AKI.

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**Methods and Analysis**

**Animal model:** Sprague-Dawley (SD) rats underwent 45 minutes of bilateral renal pedicle ischemia followed by reperfusion. Post-reperfusion, MTB-2 was dosed IV QD for 2 days; termination was at 48 hours. Two separate studies were performed to test doses from 0.3 to 10 mg/kg of MTB-2. IV. Plasma biomarkers and renal function: At indicated time points, urine volume was measured, creatinine and Na were analyzed in urine and plasma, BUN was analyzed in plasma using a colorimetric assay. GFR (creatinine clearance) and FENa were calculated according to standard calculations. Cystatin C was measured in plasma by ELISA at 24 and 48 hr post-reperfusion. Urinary biomarkers: Timp-2 and IGFBP-7 concentrations were determined by ELISA in urine collected from 4-10th post reperfusion; the resultant concentrations were multiplied and divided by 1000 to generate a rat Nephrocheck® equivalent value. Urinary FABP-1 and NGAL were analyzed by ELISA at 24 and 48 hr post-reperfusion, respectively. Data was normalized to the urine creatinine concentration of the same sample. Histology: Formalin-fixed, paraffin embedded kidney tissues were sectioned and stained with H&E, scoring was done by a Board Certified veterinary pathologist.

**MTB-2 reduces clinically relevant plasma biomarkers**

- **Plasma Creatinine**
- **Plasma BUN**
- **Plasma Cystatin C**

**MTB-2 reduces urinary biomarkers of AKI**

- **10 hr Urinary Rat NephroCheck® Equivalent**
- **24 hr Urinary FABP-1**
- **48 hr Urinary NGAL**

**MTB-2 restores renal and tubular function**

- **Creatinine Clearance**
- **Fractional Excretion of Sodium (FENa)**

**MTB-2 reduces tubular injury**

**Figure 5: Tubular injury is mitigated by PPARδ modulation post reperfusion.** At 48 hours post injury there is significant tubular injury. The score at left represents the sum of tubular necrosis, dilation, presence of tubular casts and loss of brush border. MTB-2 reduces the overall tubular injury score.

**Conclusions and future directions**

- Our data demonstrates that selective PPARδ modulation after an ischemic AKI event in rats is sufficient to recover renal and tubular function, reduce clinically relevant urinary and plasma injury biomarkers and improve kidney histopathology.
- In preclinical safety studies MTB-2 was shown to be safe and well tolerated. The next step will be to test this therapeutic in clinical trials. Developing clinical plan in partnership with Astellas Pharma.