PPARδ modulator MTB-2 enhances FAO in vitro and attenuates IR-induced gene expression changes in vivo, 48 hours and 14 days post AKI

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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.

Methods and Analysis
In vitro assays: Human hTERT RPTECs were treated with 500nM MTB-2 for 24 hours and analyzed for gene expression by qPCR and their ability to utilize palmitate to drive mitochondrial oxygen consumption by Seahorse.

Animal model: Sprague-Dawley (SD) rats underwent 45 minutes of bilateral renal pedicle ischemia followed by reperfusion. Post-reperfusion, MTB-2 or vehicle was dosed IV QD for 2 days; termination was at either 48 hours or 14 days. Renal function was measured by plasma creatinine and GFR estimated by creatinine clearance. Kidney cortex gene expression was analyzed by either qPCR or nanostring.

MTB-2 enhances fatty acid oxidation

MTB-2 rescues loss of proximal tubule genes, reduces kidney injury genes

MTB-2 effectively attenuates AKI

MTB-2 PK/PD Relationship

Drug concentration and target engagement were measured in normal rats administered a single IV dose of MTB-2. Exposure of MTB-2 in plasma is above Human EC50 at all doses tested for up to 8 hours. Kidney exposure is equivalent to plasma (not shown). This translates to target engagement for up to 12 hours post dose.

Conclusions and future directions
Selective PPARδ modulation by MTB-2after AKI in rats recovered renal function through preservation of proximal tubular and mitochondrial gene expression and reduction of kidney injury and profibrotic genes. 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