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Title: Therapeutic Effects of BB3, a Small Molecule Hepatocyte Growth Factor Mimetic, in Kidney Reperfusion Injury. Prakash Narayan\textsuperscript{1*}, Bin Duan\textsuperscript{1}, Xingxi Peng\textsuperscript{1}, Kai Jiang\textsuperscript{1}, Latha Paka\textsuperscript{1}, Michael A Yamin\textsuperscript{1} and Itzhak D Goldberg\textsuperscript{1}. \textsuperscript{1}Angion Biomedica Corp.

Background: Activation of the hepatocyte growth factor (HGF)/cMet pathway is therapeutic in ischemia-reperfusion (IR)-related acute kidney injury (AKI). However poor half-life makes clinical use of recombinant protein therapy in settings such as AKI or kidney transplantation (Tx) challenging. We investigated the effects of a unique and novel small molecule with HGF-like activities, BB3, in models of AKI and Tx. BB3 selectively phosphorylates cMet and triggers the HGF/cMet pathway in multiple in vitro assays.

Methods: IR: Adult male rats had 45 min normothermic renal artery occlusion. At reperfusion, the contralateral kidney was excised. BB3 (2 mg/kg) was administered QD starting at 24 hour into reperfusion. Tx: Kidneys from adult male Lewis rats were cold-preserved (\textasciitilde 4\textdegree C) for 4 hr and transplanted into syngeneic recipients whose native kidneys were excised. BB3 (2.0 mg/kg, QD) was administered until sacrifice on Day 14.

Results: IR: Treatment with BB3, starting 24 hr after reperfusion, increased tubular cMet phosphorylation \textit{in vivo} 3.5-fold (\textit{p}<0.01). BB3 decreased tubular expression of kidney injury marker-1 (KIM-1), decreased tubular apoptosis, enhanced preservation of tubular integrity, improved urine output and reduced serum creatinine (figure1) Tx: BB3 improved recipient survival (60\% vs 30\% for control) and mitigated renal dysfunction (e.g., Day 7 SCr: 0.84 mg/dL vs 2.72 mg/dL for control; \textit{p}<0.05).

Conclusions: Starting as late at 24 hour after AKI, activation of the HGF/cMet pathway with BB3 mitigates renal injury and improves renal function. These data together with the expanded window for therapeutic intervention support the use of BB3 in Angion’s Phase 2 GUARD study in AKI patients and Phase 3 GIFT study in kidney Tx recipients presenting with delayed graft function. Funded by DK-062592.