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Abstract to be presented at the American Society of Nephrology 2015 Annual Meeting
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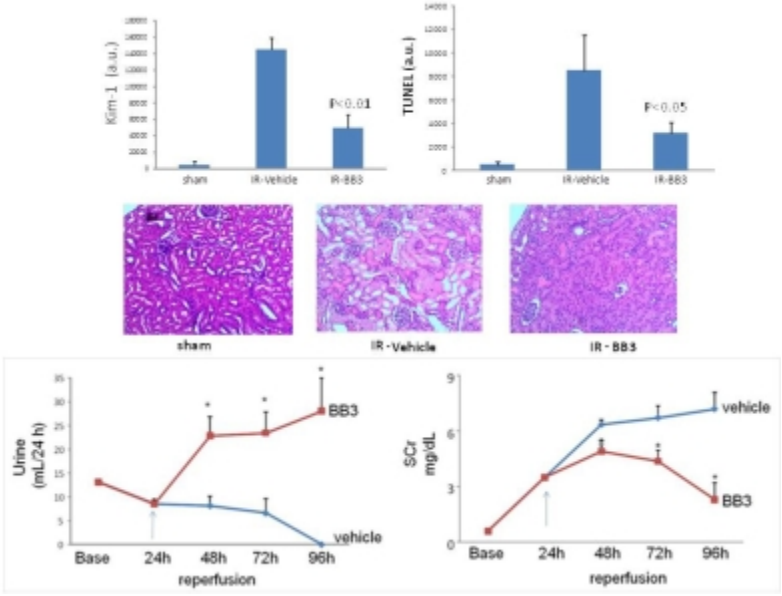
Title: Therapeutic Effects of BB3, a Small Molecule Hepatocyte Growth Factor Mimetic, in Kidney Reperfusion Injury. Prakash Narayan[1]*, Bin Duan[1], Xingxi Peng[1], Kai Jiang[1], Latha Paka[1], Michael A Yamin[1] and Itzhak D Goldberg[1]. [1]Angion Biomedica Corp.

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 (~4^{o}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 *in vivo* 3.5-fold ($p<0.01$). 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; $p<0.05$).



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.