Angion
Biomedica Corp.

51 Charles Lindbergh Boulevard
Uniondale, NY 11553
Phone: 516-326-1200
Fax: 516-307-1659
www.angion.com

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Identification of a new Aldosterone Synthase Inhibitor with Anti-Fibrotic activity in Animal Models

Bert Oehlen, Siobhan McCormack, Ping Zhou, Liming Zhang, Xingxi Peng, Jinsong Li, Xiaokang Zhu, Bijoy Panicker and Itzhak Goldberg

Angion Biomedica Corp., 51 Charles Lindbergh Blvd., Uniondale, NY 11553, U.S.A. Correspondence to: boehlen@angion.com

Background. The renin-angiotensin-aldosterone system (RAAS) plays a critical role in renal physiology. Inhibitors of ACE and ARBs are currently the mainstay in the clinical management of chronic kidney disease (CKD). Despite initial success in reducing aldosterone, concentrations return to pretreatment levels in 30-40% of patients. This “aldosterone escape” significantly limits the therapeutic effectiveness. Through mineralocorticoid receptor dependent and independent processes, aldosterone is thought to directly accelerate renal damage by sustaining inflammation and fibrosis. An attractive approach to deal with aldosterone escape is to inhibit aldosterone synthase (AS), the enzyme responsible for aldosterone production (encoded by the CYP11B2 gene).

Methods. We have identified a promising series of potent and selective small molecule inhibitors of AS. Lead compound ANG3586 has 7 nM potency against AS and excellent selectivity against other P450 enzymes. It is orally bioavailable in rodents and appears to be well tolerated. ANG3586 was tested in the rat remnant kidney model (25 mg/kg, po, bid) and the mouse unilateral ureteral obstruction (UUO) model (25 mg/kg, po, bid, ten days).

Results. In the rat remnant kidney model, animals with overt renal dysfunction were treated with vehicle or ANG3586. The elevated blood pressure in 5/6 nephrectomized animals was reduced to normal by compound treatment. ANG3586 also markedly reduced kidney collagen content and improved renal histology. Renal function, as determined by serum BUN and creatinine levels, urine albumin to creatinine ratio and urine NGAL, was found to be markedly improved. In the mouse UUO model, ANG3586 reduced the increase in kidney weight, kidney collagen and alpha-smooth muscle actin staining. Since UUO does not result in distinctly increased blood pressure, the anti-fibrotic activity appears independent of blood pressure lowering activity of ANG3586.

Conclusions. Taken together, ANG3586 shows promise as a potential novel anti-fibrotic agent.