Epoxide hydrolase inhibition and Thiazolidinediones: A therapy for cardiometabolic syndrome

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Scientists at the Medical College of Wisconsin and the University of California at Davis, led by Dr. John Imig and Dr. Bruce Hammock have determined the synergistic actions of inhibiting soluble epoxide hydrolase (sEH) with tAUCB (trans-4-(4-[3-adamantan-1-yl-ureid]-cyclohexyloxy)-benzoic acid) and activating peroxisome proliferator-activator receptorγ (PPARγ) with the thiazolidinedione rosiglitazone on the pathological progression of cardiometabolic syndrome. Cardiometabolic syndrome occurs with obesity and hypertension increasing the risks for cardiovascular disease and causing significant and rapidly progressive kidney disease.

The findings, which appear in the December 2012 issue of *Experimental Biology and Medicine*, demonstrate that sEH inhibition and PPARγ activation in combination had the greatest beneficial effects on the multi-disease features and progression of kidney disease associated with cardiometabolic syndrome.

"Inhibitors of sEH have recently reached a point where their ability to combat cardiovascular and kidney diseases can be determined in humans", states Dr. Imig. "In this study we show that when used in combination with a PPARγ agonist therapy for cardiometabolic syndrome that there is a synergistic effect to decrease cardiovascular risk factors and progressive kidney disease. Another potential positive aspect of this combination therapy is that sEH inhibition has beneficial actions

to counteract the edema and congestive heart failure that occurs in patients treated long-term with PPARγagonists."

Future studies would include combinational chemistry approaches to design and synthesize drugs with dual sEH inhibitory and PPARγ agonistic activities. Dr. Hammock states, "these approaches are currently being done by his laboratory and others". He also says "that combining sEH inhibition not just with PPARγ but also with other therapies for cardiovascular, inflammatory, and renal diseases are on the horizon and have therapeutic potential as both drug combinations and dual sEH inhibitors with PPARγ activity for treating cardiometabolic syndrome."

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said, " This study by John Imig and Bruce Hammack, performed on spontaneous hypertensive and spontaneous hypertensive obese rat models, suggests that a combined therapy with epoxide hydrolase inhibitors and thiazolidinediones may prove to be efficacious in treatment of the multi-disease characteristics of cardiometabolic syndrome. "

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