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Poster presentation



# Thrombospondin-1 is a universal inhibitor of soluble guanylate cyclase activation

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## Background

Soluble guanylate cyclase (sGC) is the signal transduction enzyme most responsible for mediating the effects of nitric oxide by producing cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). NO-cGMP signaling is vital to proper cardiovascular function. Deficiencies in the production of either NO or cGMP contribute to cardiovascular disorders. Therapies designed to increase in vivo NO levels (such as organic nitrates) have well documented clinical limitations due to drug tolerance. Recently, a variety of NO-independent small molecule activators of sGC have been reported that activate nearly or as well as NO and have promising clinical activities. Previous results from our lab have shown that the secreted matrix protein thrombospondin-1 (TSP-1) binds to CD47 and potently inhibits NO stimulation of sGC.

## Results

Here we show that TSP-1 signaling via CD47 also inhibits sGC stimulation by NO-independent sGC stimulating small molecules. Pretreatment of both porcine vascular smooth muscle cells (VSMCs) and washed human platelets with TSP-1 (1 μg/ml) significantly inhibited the ability of the heme dependent stimulators YC-1 (100 μM), BAY 41-2272 (10 μM), and heme-independent activator meso-porphyrin IX (10 μM) to elevate cGMP levels. TSP-1 pretreatment also completely inhibited the ability of these agents to delay thrombin induced aggregation of washed human platelets. sGC stimulating agents also failed to inhibit contraction of porcine VSMCs embedded in a collagen gel pretreated with TSP-1.

## Conclusion

This work demonstrates that sGC stimulation by NO independent sGC stimulators is greatly diminished in the presence of TSP-1/CD47 signaling. This data coupled with the reported increases in TSP-1 with age, diabetes, ischemia reperfusion, and atherosclerosis implies that the therapeutic potential of NO-independent sGC stimulating drugs could be compromised in disease states with elevated TSP-1/CD47 signaling.