Abstract Body: 

Objectives: Peripheral arterial disease represents a disabling and potentially fatal condition in the aging population. Intimal hyperplasia (IH) is the major pathologic event that leads to restenosis after balloon angioplasty. IH is a complex process which starts immediately after endothelial injury. Growth factors and extracellular matrix proteins are released by platelets and induce vascular smooth muscle cell (VSMC) migration and proliferation. Heat shock protein 90 (HSP90) is a chaperone that binds many proteins regulating their maturation. The HSP90 inhibitors 17-AAG and 17-DMAG are low toxicity geldanamycin derivatives. We hypothesized that HSP90 inhibition would reduce agonist-induced VSMC proliferation. In addition, localized HSP90 inhibition would inhibit post-angioplasty IH formation. 

Methods: To assess VSMC proliferation, quiescent VSMCs were treated with SFM, 17-DMAG or 17-AAG. The proliferative agents were SFM, PDGF (20 ng/ml) or fibronectin (20 µg/ml). After three days, proliferation was determined with an MTS dye assay. Drug toxicity was assessed by trypan exclusion. Balloon injury to the common carotid artery (CCA) was performed in Sprague-Dawley rats to induce IH. There were two groups, no treatment or 17-DMAG.
dissolved in 20% pluronic gel delivered to the adventitia of the CCA. After 14 days, animals were euthanized, CCAs perfusion fixed and sectioned. Sections were stained with hematoxylin and eosin for morphometric analysis. Data was analyzed by ANOVA or student’s t-test. p-values< 0.05 were considered significant.

**Results:** Local adventitial treatment with DMAG after balloon arterial injury reduced IH (46.5 % compared to injury alone). 17-AAG and 17-DMAG had no effect on cell viability (≥ 90%). PDGF and fibronectin increased VSMC proliferation. Both 17-AAG and 17-DMAG decreased proliferation to all agonists. There was no difference between 17-AAG and 17-DMAG in inhibiting VSMC proliferation.

**Conclusion:** HSP90 inhibitors suppressed chemoattractant induced VSMC proliferation without affecting cell viability. Local treatment with a HSP90 inhibitor (DMAG) decreased IH formation after arterial injury. Thus HSP90 may be a therapeutic target to prevent post-angioplasty restenosis. However, the mechanism by which HSP90 reduces IH and affects VSMC proliferation warrants further investigation.

**Author Disclosure Block:**