

**The Epigenetic Remodeling Protein Brg1 is implicated in Vascular Progenitor Cell Contribution to Pathological Vascular Remodeling and Fibrosis.** AJ Jolly, (MD/PhD, SOM), S Lu, AM Dubner, MF Mutryn, N Navarro, MCM Weiser-Evans. Department of Medicine, University of Colorado Anschutz Medical Campus.

Vascular fibrosis describes irreversible stiffening of the blood vessels that develops in response to many forms of cardiovascular disease including hypertension and atherosclerosis. We identified a unique population of multipotent smooth muscle-derived progenitor cells that reside in the adventitial layer of mouse arteries and express the stem marker Sca1 (**AdvSca1-SM cells**). After acute vascular injury, AdvSca1-SM cells expand in the adventitia, differentiate into myofibroblasts, and greatly contribute to vascular fibrosis. The chromatin remodeling protein Brahma-related gene 1 (Brg1) is upregulated in AdvSca1-SM cells in response to vascular injury, but how Brg1 influences AdvSca1-SM differentiation remains unknown. Using *in vitro* systems and animal models, we aim to define the role of Brg1 in AdvSca1-SM cells. We hypothesize that Brg1 modulates chromatin to preferentially drive AdvSca1-SM cell differentiation towards pathologic myofibroblasts and inhibition of Brg1 will disrupt AdvSca1-SM – myofibroblast differentiation and reduce vascular fibrosis.

Results: Mice subjected to carotid ligation and treated with the Brg1 inhibitor PFI-3 exhibit decreased vascular fibrosis, smaller neointima, and decreased expansion of AdvSca1-SM cells as compared to control mice. *In vitro*, AdvSca1-SM cells stimulated with TGF- $\beta$  express myofibroblast genes such as  $\alpha$ SMA and periostin, and co-treatment with PFI-3 blocks TGF- $\beta$  induced myofibroblast gene expression at the mRNA and protein level. Ultimately, these results support the conclusion that Brg1 is a major regulator of AdvSca1-SM myofibroblast differentiation and may be a targetable protein to treat vascular fibrosis.

