

Role of smooth muscle-derived vascular progenitor cells in atherosclerosis

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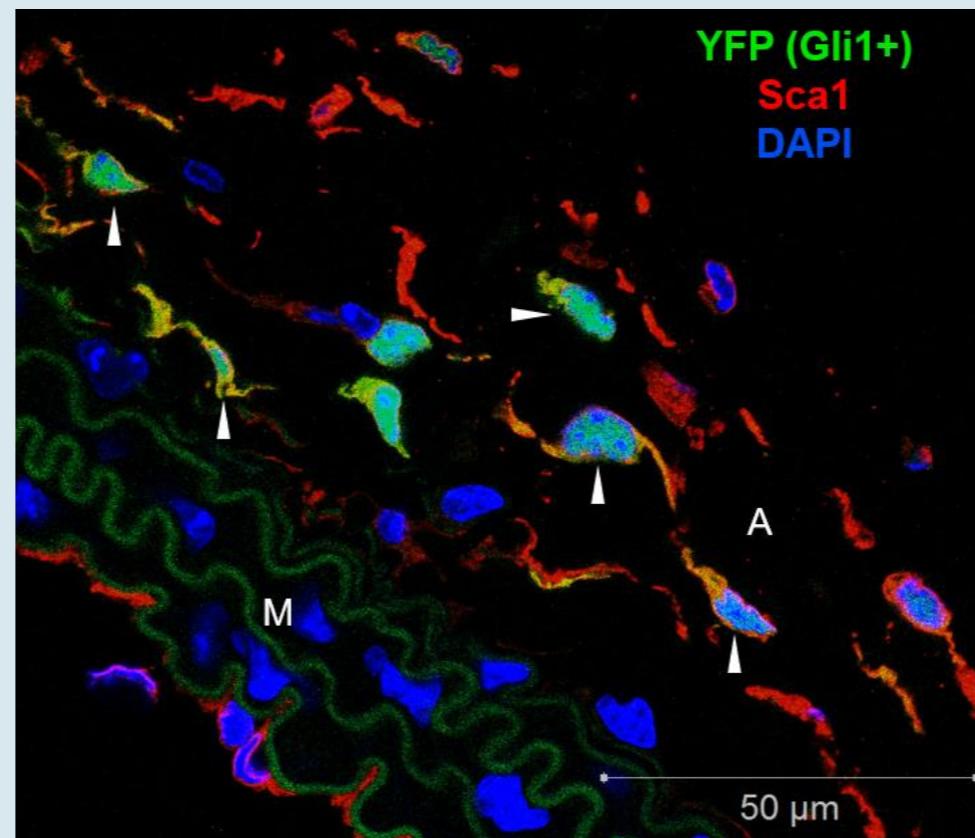
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Background

- Atherosclerosis is a major cause of morbidity and mortality worldwide, but current therapies fail to meet clinical needs.
- Expansion of adventitial microvessels, the vasa vasorum (VV), is believed to drive atherosclerosis progression by facilitating inflammatory cell infiltration.

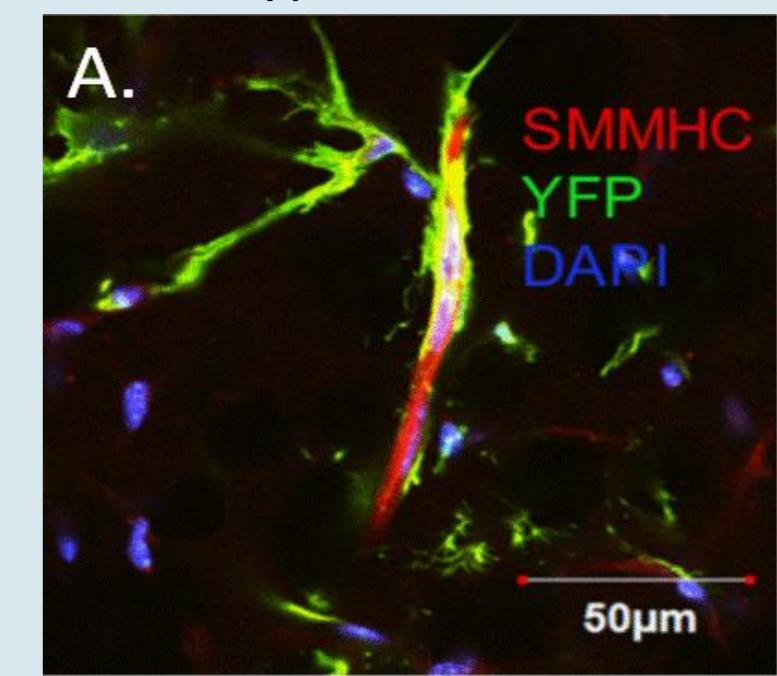


Image adapted from <https://www.earthslab.com/physiology/vasa-vasorum/>



Lu, Sizhao, et al. "Smooth muscle-derived progenitor cell myofibroblast differentiation through Klf4 downregulation promotes arterial remodeling and fibrosis." *JCI insight* 5.23 (2020).

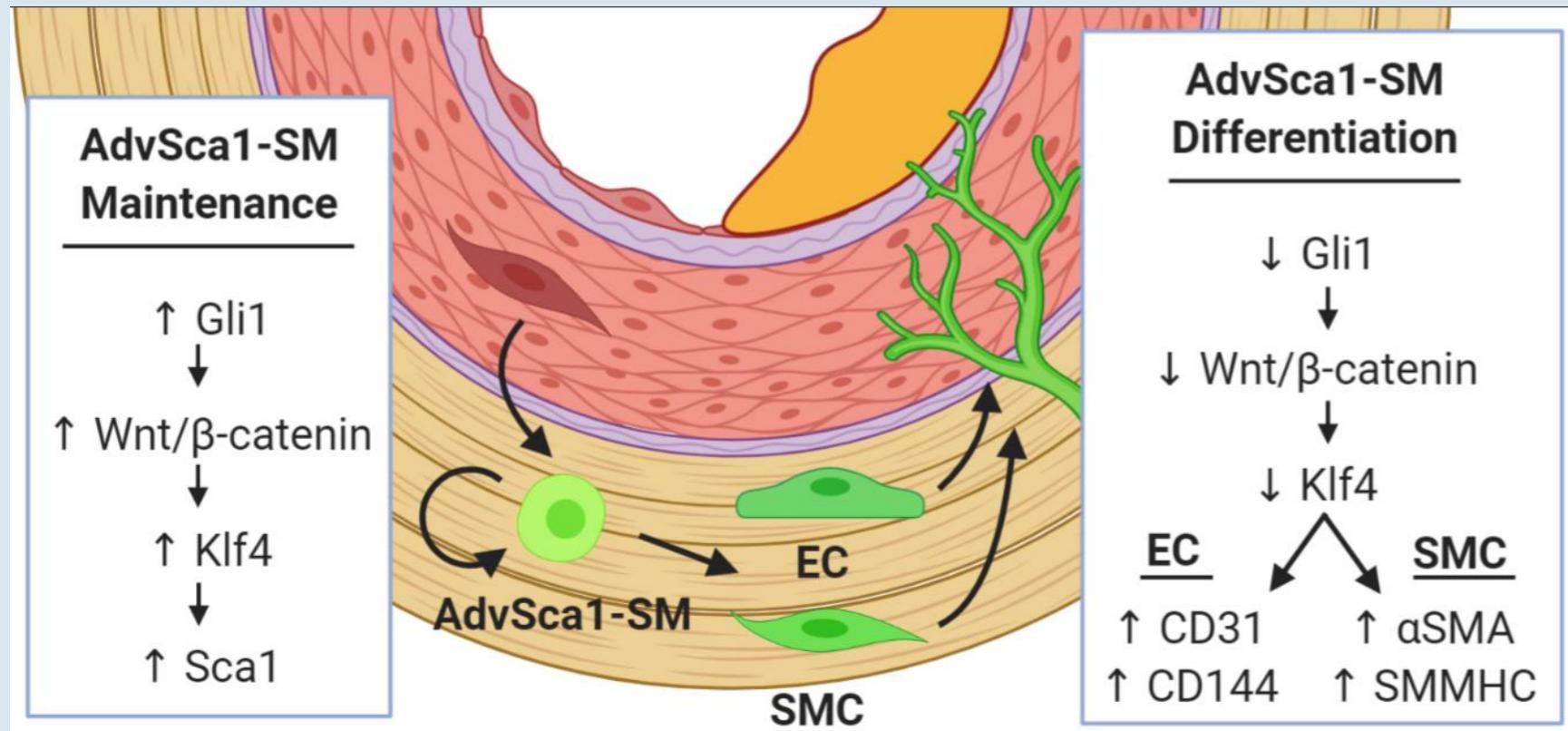
- Our group previously identified a unique population of resident stem cells (**AdvSca1-SM cells**) that derive from mature vascular smooth muscle cells (SMCs) and reside in the vessel adventitia.
- AdvSca1-SM cells are selectively enriched for Gli1 compared to other vascular cells.
- This allowed us to develop the Gli1-Cre/Rosa-YFP mouse model, which selectively and permanently labels AdvSca1-SM cells with YFP, even if they differentiate into other cell types.



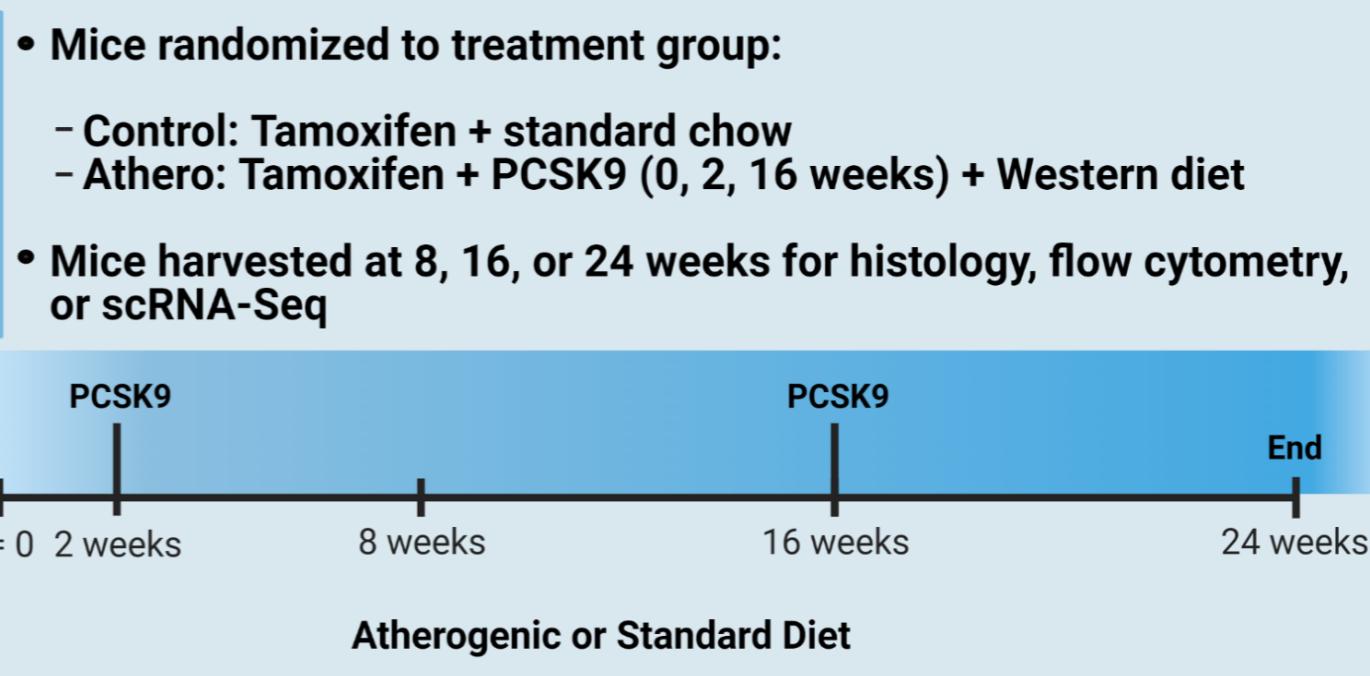
Majesky, Mark W., et al. "Differentiated smooth muscle cells generate a subpopulation of resident vascular progenitor cells in the adventitia regulated by Klf4." *Circulation research* 120.2 (2017): 296-311.

Hypothesis

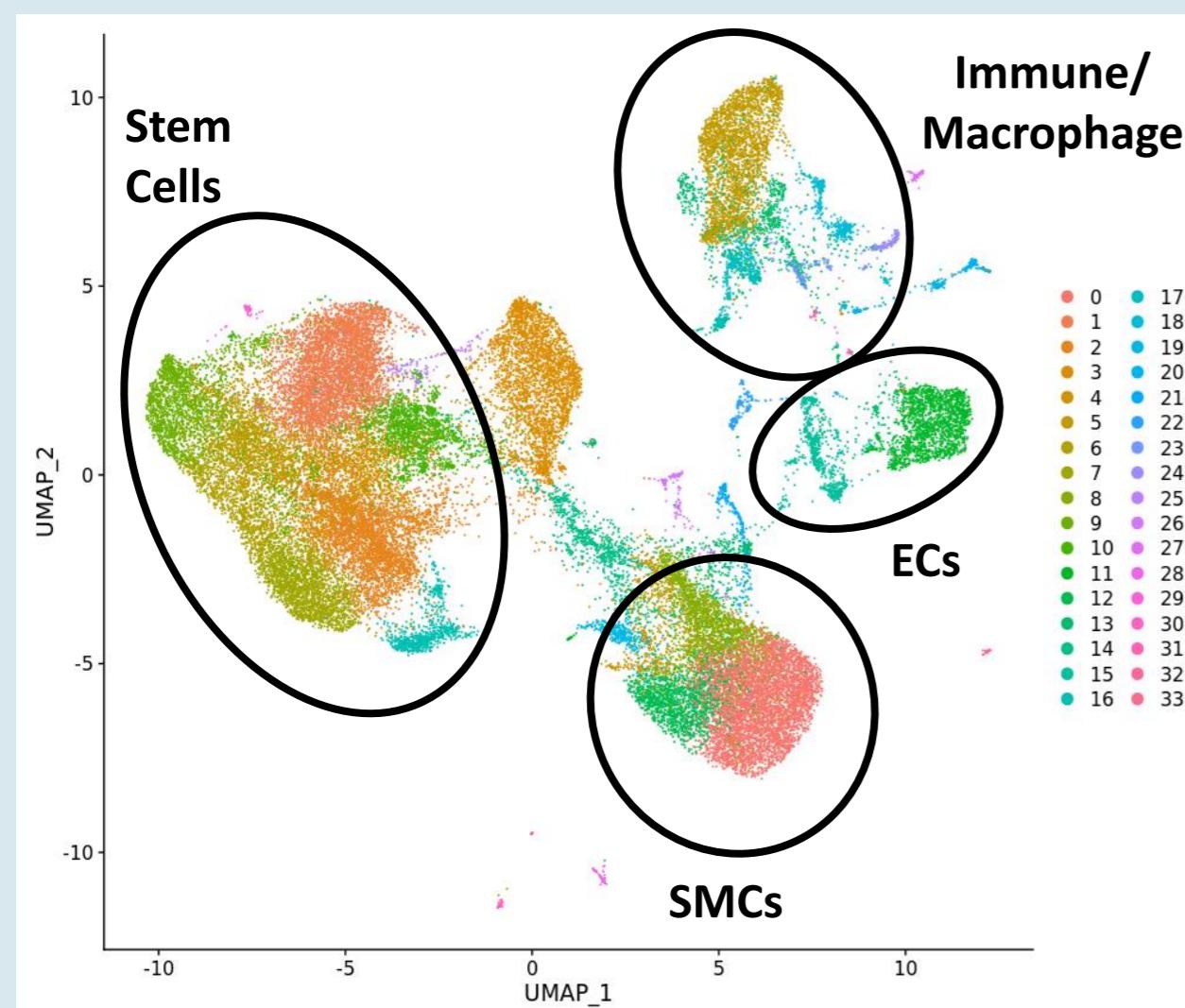
In atherosclerosis, AdvSca1-SM cells will reprogram into smooth muscle or endothelial cells to contribute to vasa vasorum expansion and plaque progression.



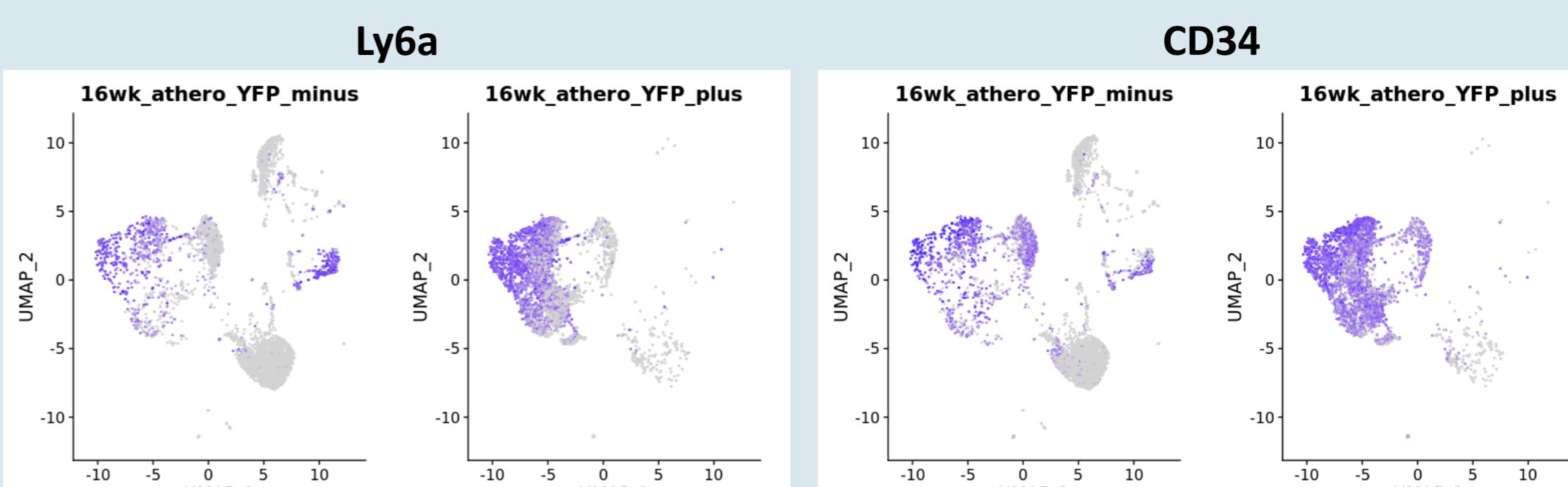
Methods



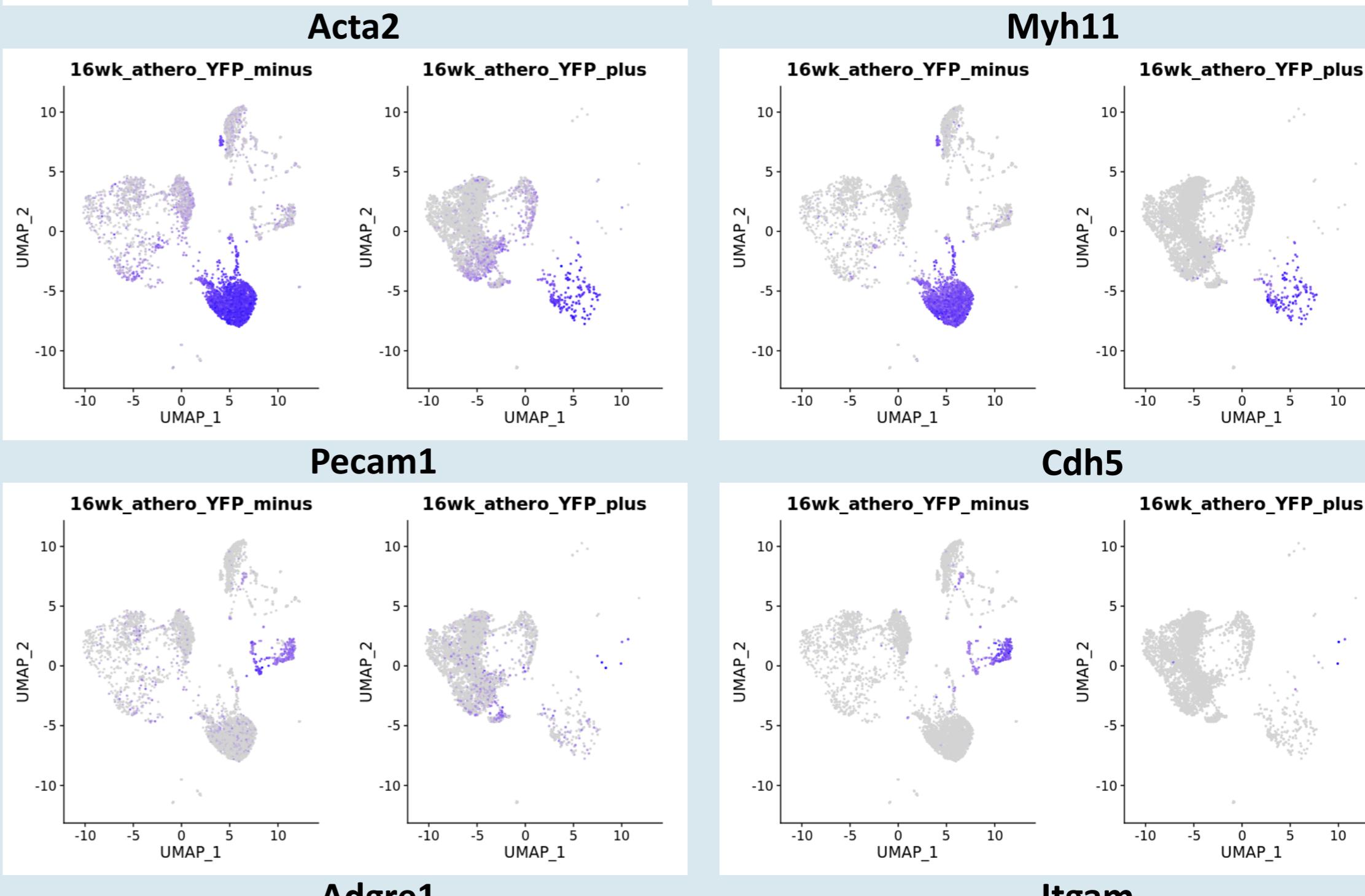
Results



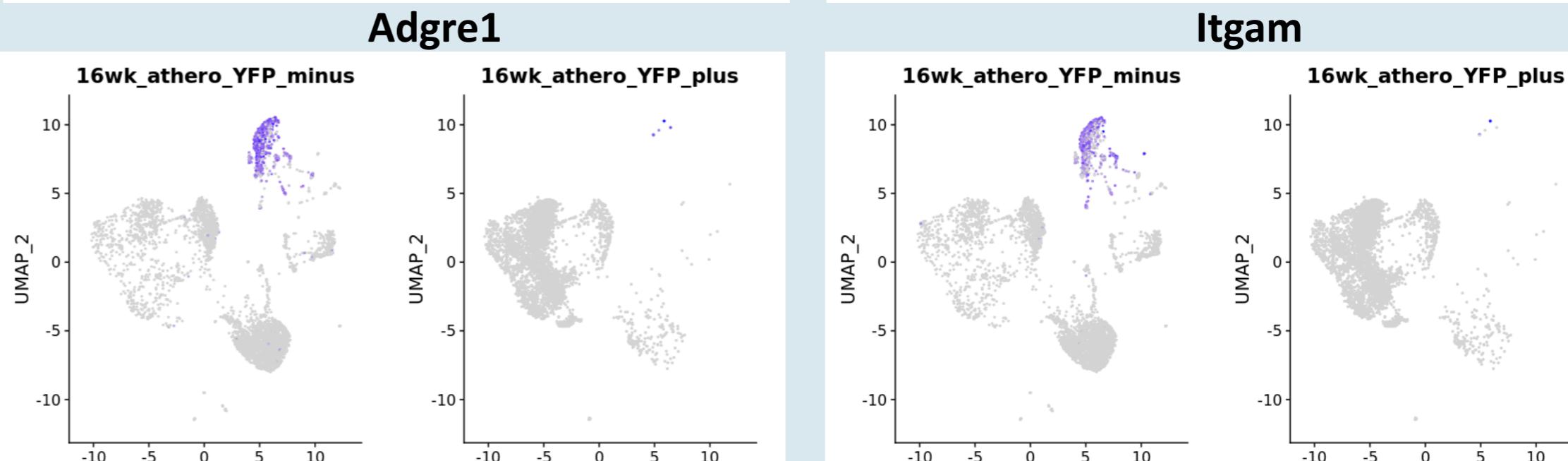
Stem Cells



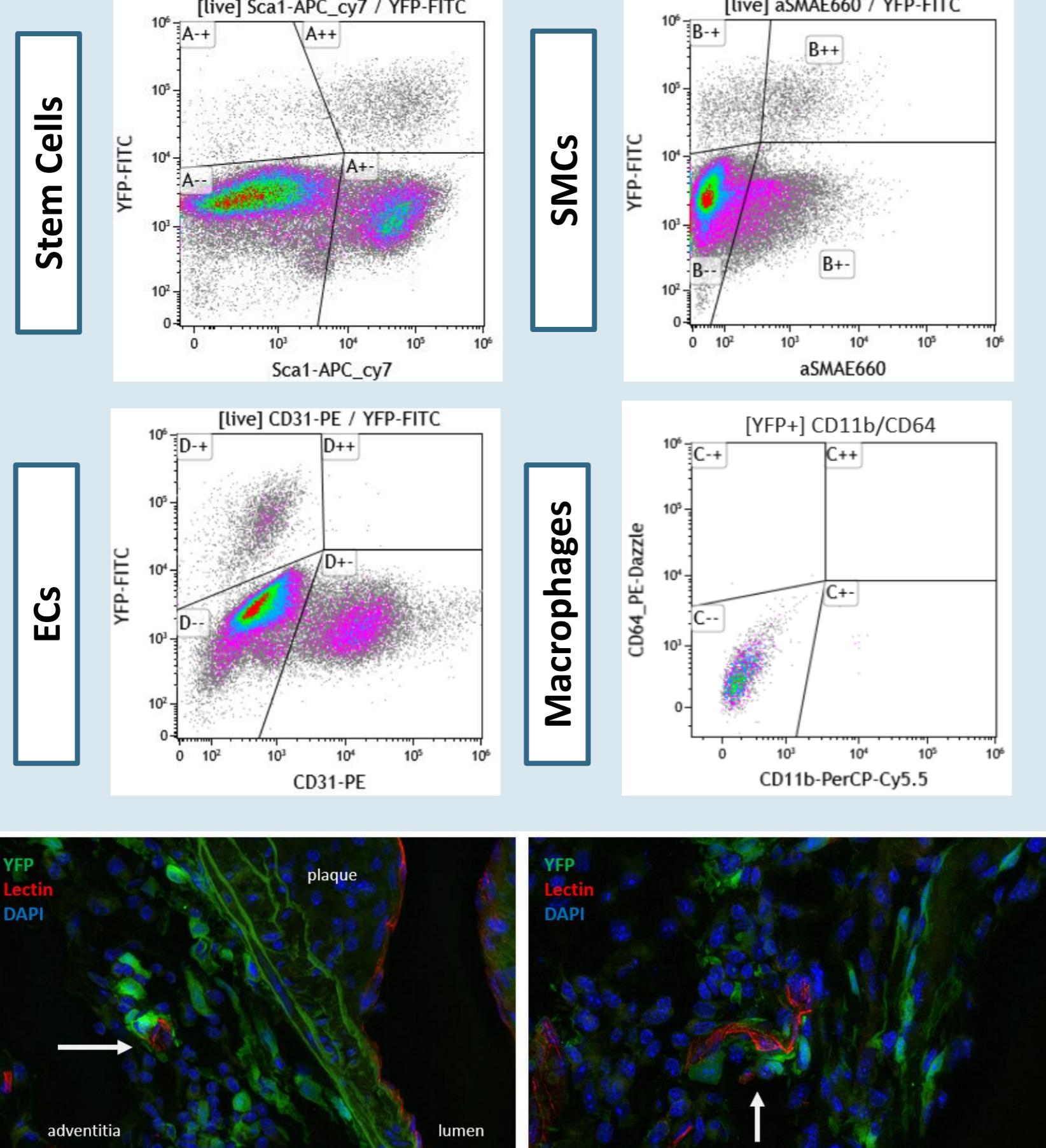
SMCs



ECs



Macrophages



Conclusions & Future Directions

- AdvSca1-SM cells in atherosclerosis primarily differentiate into mature SMCs, modulated SMCs, and myofibroblasts. In addition, there remains a large reservoir of AdvSca1-SM cells in a stem-like state.
- AdvSca1-SM cells very rarely differentiate into endothelial cells.
- Despite previous evidence of SMCs gaining a macrophage-like phenotype in atherosclerosis, we identified only rare instances of AdvSca1-SM cells contributing to macrophage populations.
- Ongoing work with advanced lesions (24-30 weeks of treatment) will more fully define the functional role of AdvSca1-SM cells in atherosclerotic plaque progression.

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