Interleukin-6 Initiates Infrarenal Aortic Remodeling and Propagates Aneurysm Development

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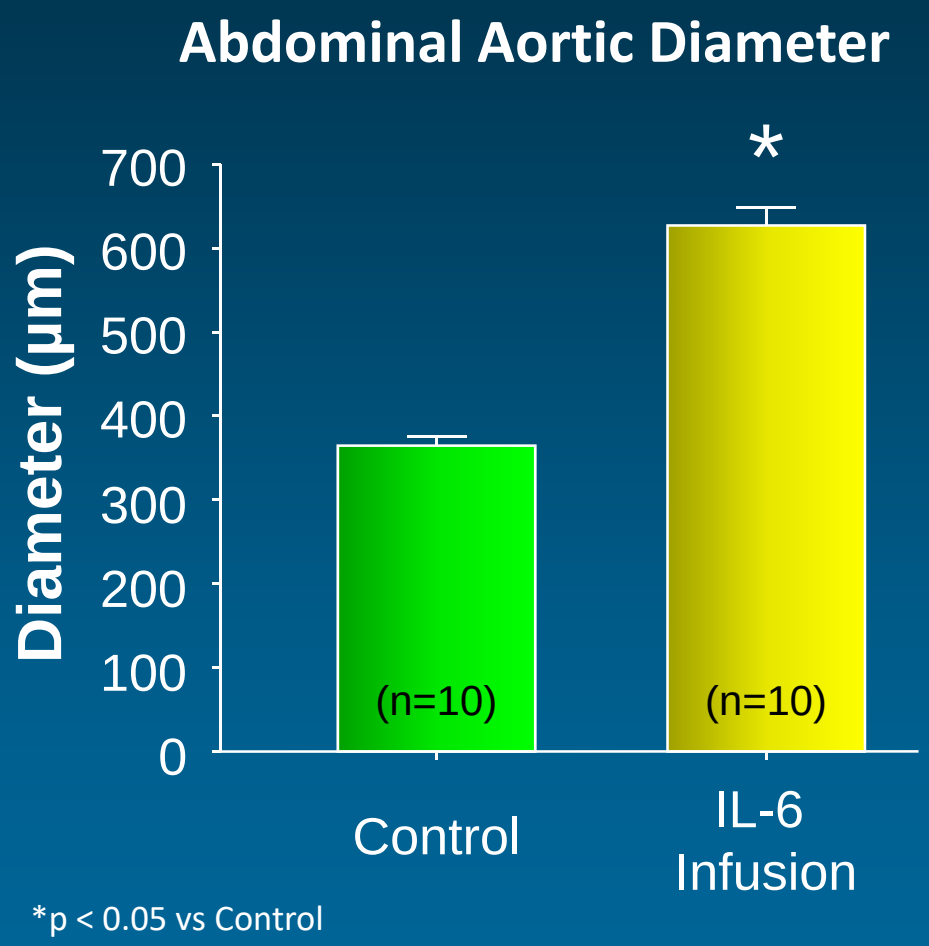
Background

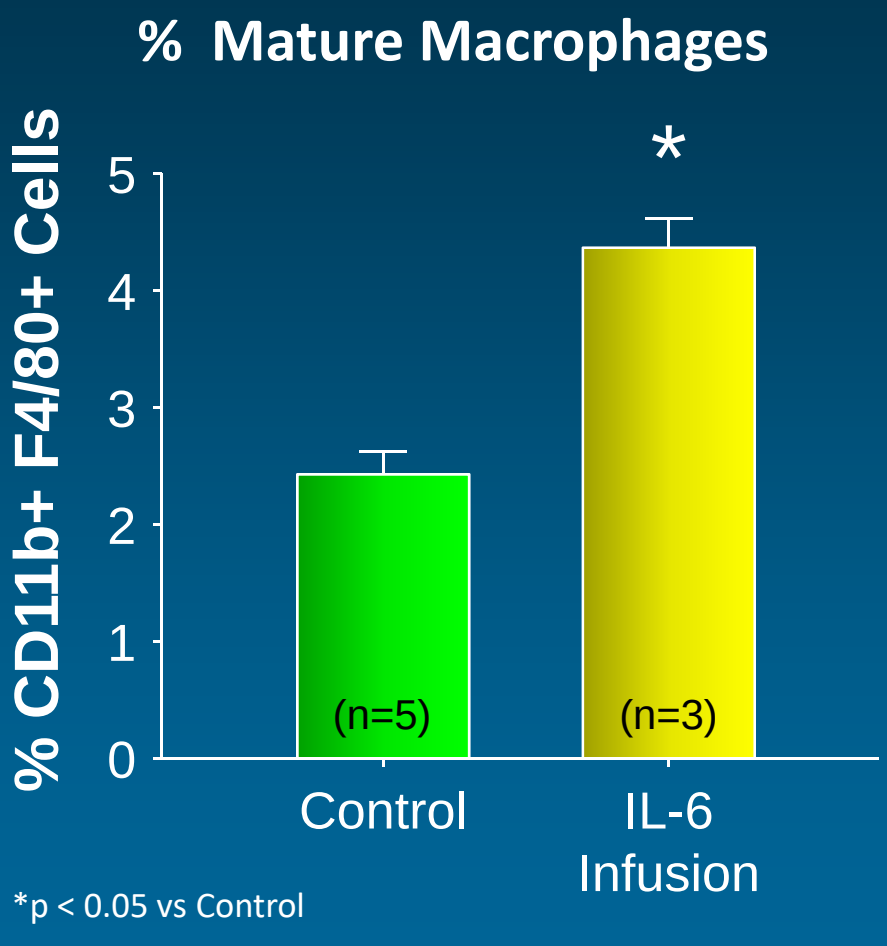
- Abdominal aortic aneurysms (AAA) initiation and progression
  - Complex interaction of genetic, cellular, and environmental risk factors

- Focusing on inflammatory pathophysiology of AAA
  - Interleukin-6 (IL-6) elevated in patients with AAA[1]
  - Abundance of macrophages to secrete proteases[2]

1. Juvonen J, et al. ATVB. 1997. 17(11):2843-2847.
2. Dale M, et al. ATVB. 2015. 35(8): 1746-1755.

Background





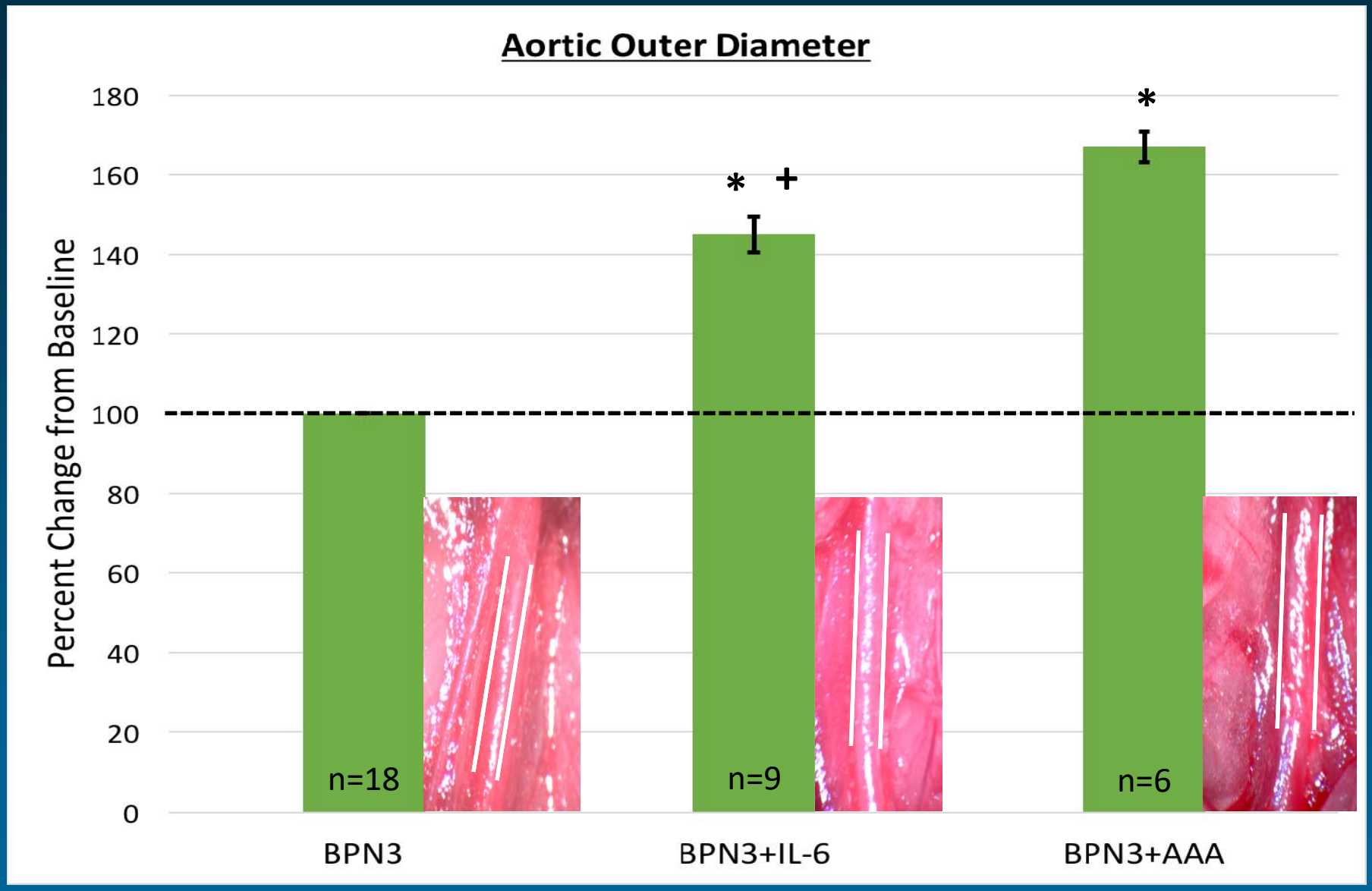
Akerman, AW, et al. Ann Vasc Surg. 2017. 46:193-204.

Hypothesis

IL-6 plays a central role in accumulating macrophages and initiating aortic remodeling

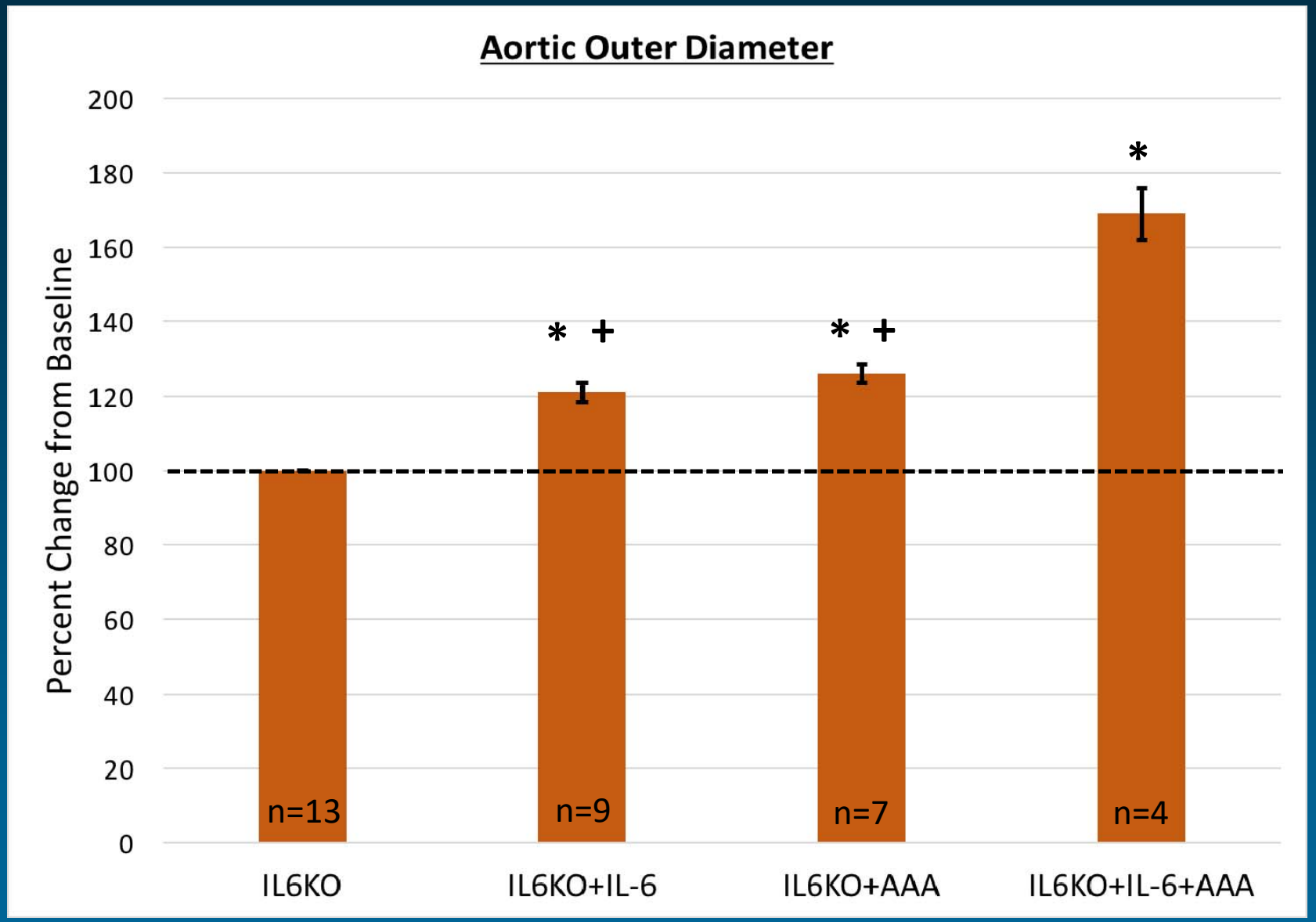
Mouse Models

- BPN3 normotensive mice
- IL6KO mice
  - IL-6 infusion (4.36µg/kg/day) x 21 days
  - Peri-adventitial $CaCl_2$ induction of AAA
- Flow Cytometry for Macrophages
  - Characterize phenotype
    - CCR2 – pro-inflammatory marker
    - CX3CR1 – anti-inflammatory marker



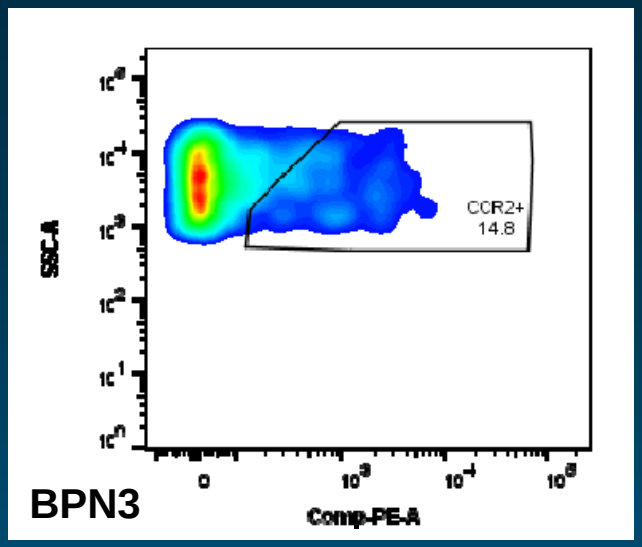
* p<0.05 vs BPN3

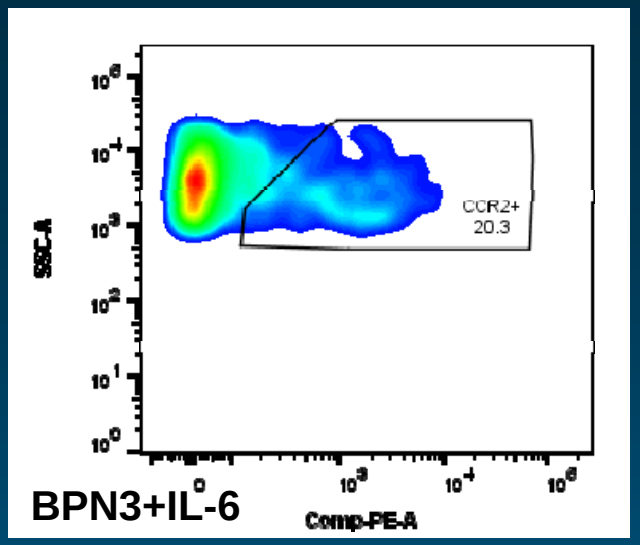
+ p<0.05 vs BPN3+AAA

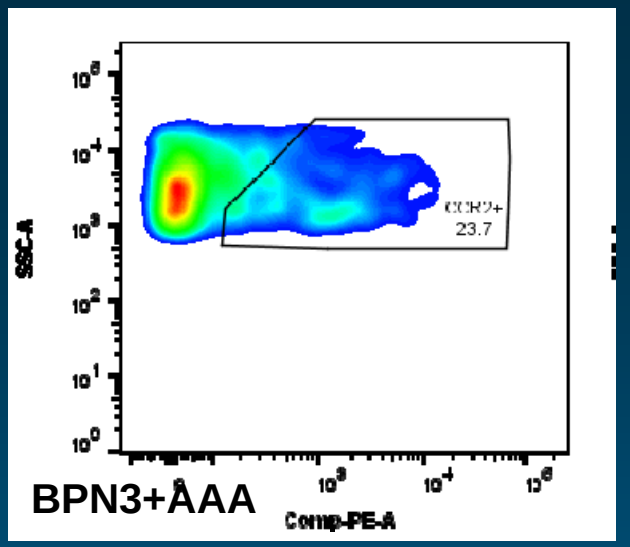


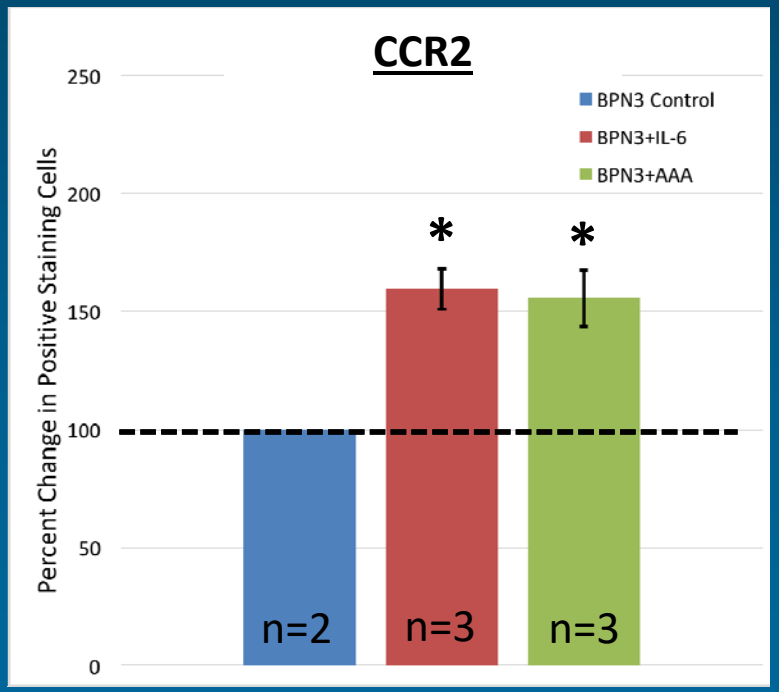
* p<0.05 vs IL6KO

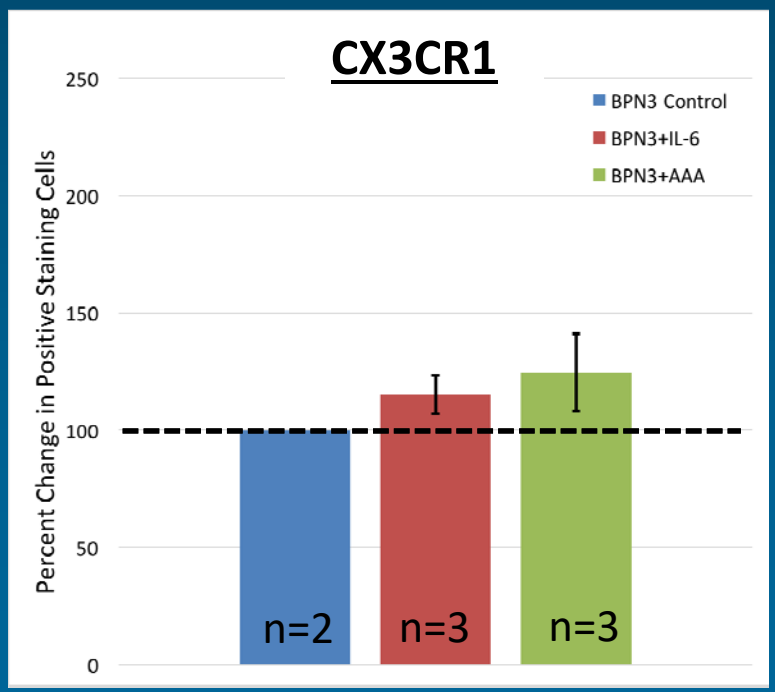
+ p<0.05 vs IL6KO+IL-6+AAA


SSC-A
CCR2+
14.8
Comp-PE-A
BPN3


SSC-A
CCR2+
20.3
Comp-PE-A
BPN3+IL-6


SSC-A
CCR2+
23.7
Comp-PE-A
BPN3+ÅAA


CCR2
Percent Change in Positive Staining Cells
250
200
150
100
50
0
BPN3 Control
BPN3+IL-6
BPN3+AAA
*
*
n=2
n=3
n=3


CX3CR1
Percent Change in Positive Staining Cells
250
200
150
100
50
0
BPN3 Control
BPN3+IL-6
BPN3+AAA
n=2
n=3
n=3

* p<0.05 vs BPN3

Summary

- IL-6 is necessary but not sufficient for degenerative aortic remodeling to progress to aneurysm
- Effected through the accumulation of pro-inflammatory macrophages in the abdominal aorta

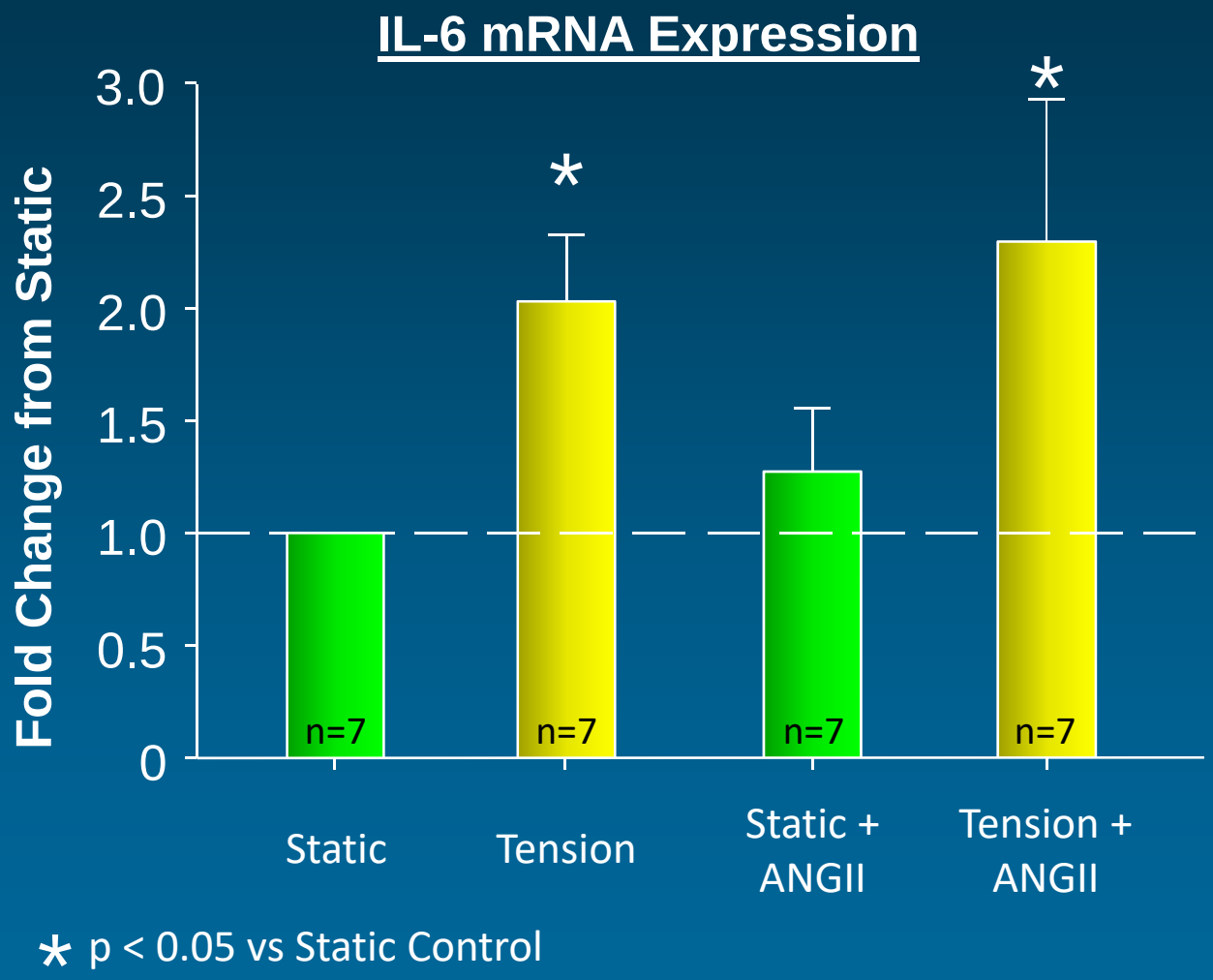
Clinical Correlation

- When considering the typical patient with AAA, what are their risk factors and how was this process initiated?
- IL-6 also associated with hypertension (HTN)[3]
- Can IL-6 expression represent the biomechanical link between HTN and AAA?

3. Chae C, et al. Hypertension. 2001;38:399-403.

Aortic VSMC Tension Model

- FlexCell
  - 12% Biaxial Cyclic Tension
- Treatments
  - 3 hour
  - AngiotensinII (AngII)



Akerman, AW, et al. Ann Vasc Surg. 2017. 46:193-204.

Preliminary Data

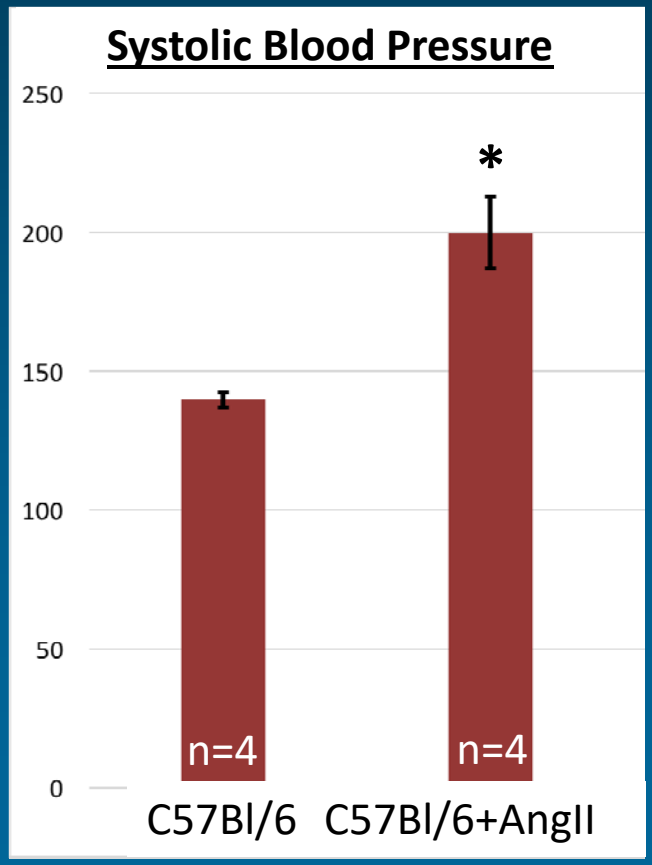
- What mechanosensitive kinase translates this physical force into cytokine expression in VSMCs?
- Serum glucocorticoid – inducible kinase 1 (SGK-1)
  - Tension-induced remodeling in vein graft intimal hyperplasia and pulmonary hypertension[4,5]
  - Linked to modulation of protease and IL-6 production[6]

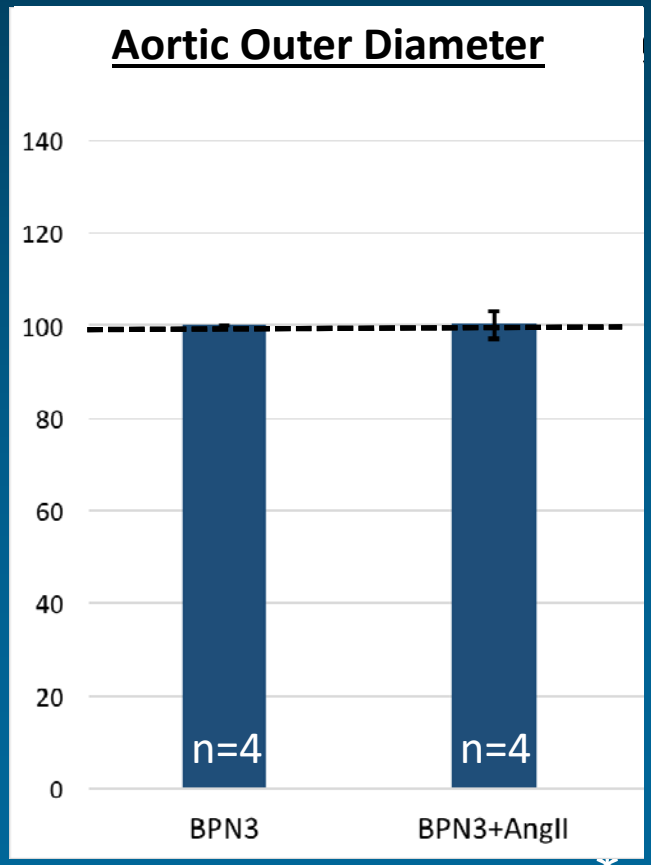
- Hypothesize that SGK-1 is activated by mechanical tension and augments IL-6 expression in VSMCs

4. Cheng J, et al. *Circ research.* 2010;107(10):1265-1274.
5. BelAiba RS, et al. *Circ research.* 2006;98(6):828-836.
6. Borst O, et al. *ATVB.* 2015;35(3):547-557.

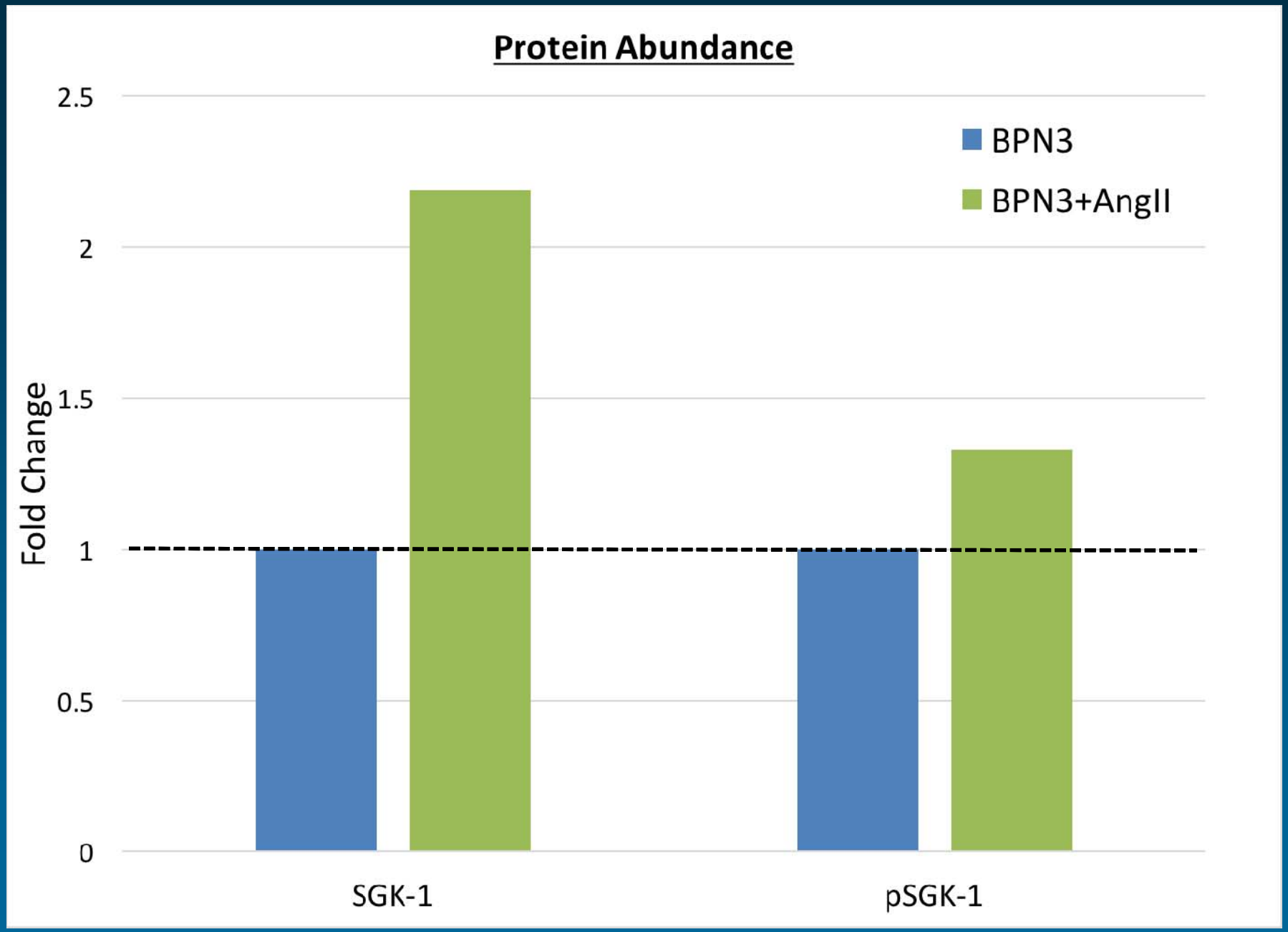
Mouse Model

- HTN induced by AngII infusion (1.46mg/kg/day) x 21 days

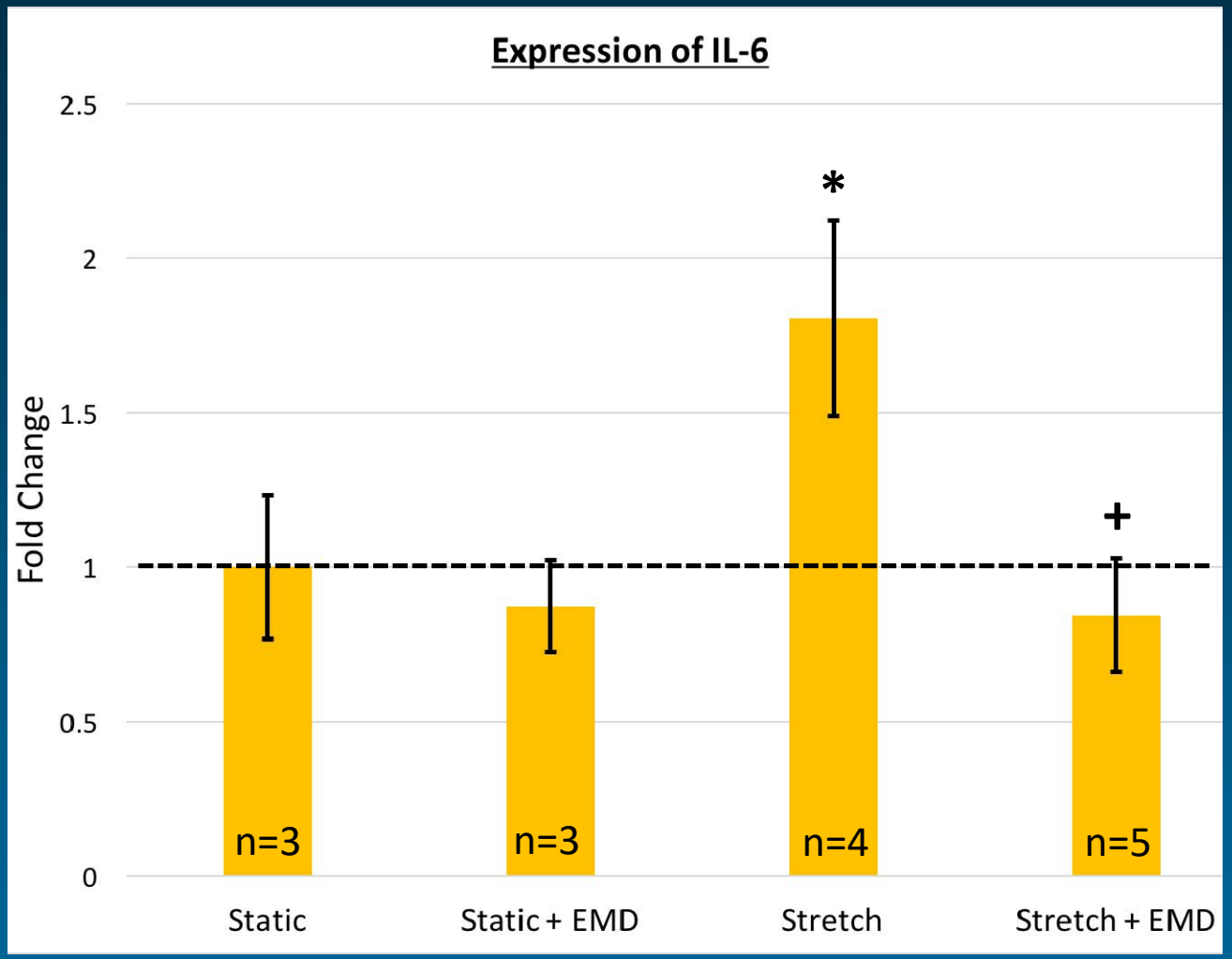




*p<0.05 vs BPN3

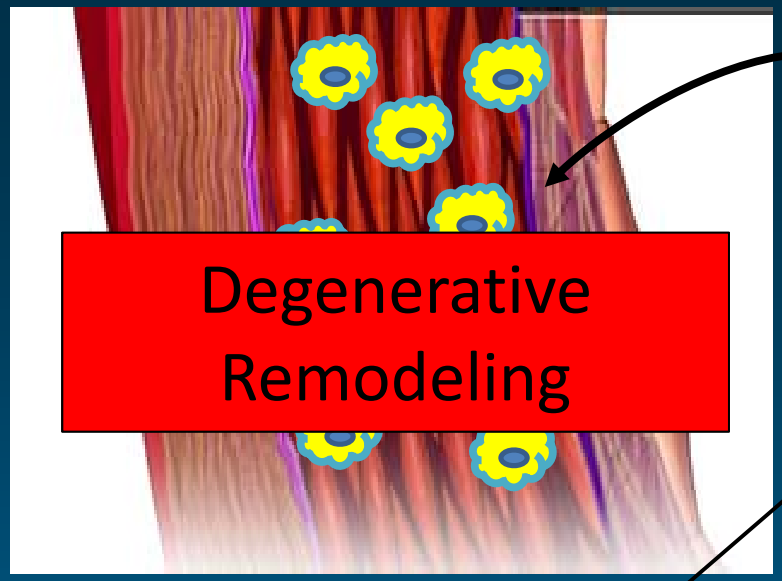

Protein Abundance
2.5
2
1.5
1
0.5
0
Fold Change
BPN3
BPN3+AngII
SGK-1
pSGK-1

- Aortic VSMC Tension Model
  - 12% stretch
  - EMD638683
    - SGK-1 inhibitor

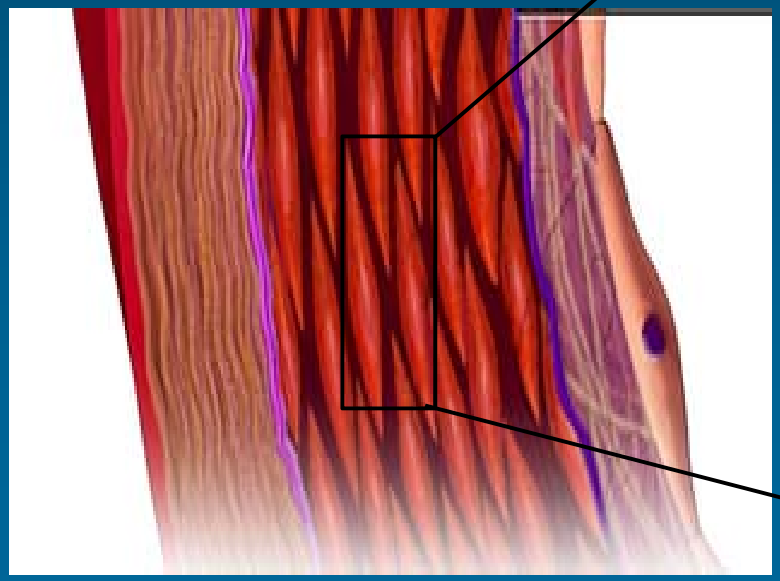


* p<0.05 vs Static

+ p<0.05 vs Stretch



Degenerative Remodeling



Pro-inflammatory Macrophage

SGK-1

P

SGK-1

IL-6

Acknowledgements

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