Novel Biomarker Platform for Aortic Aneurysm Disease

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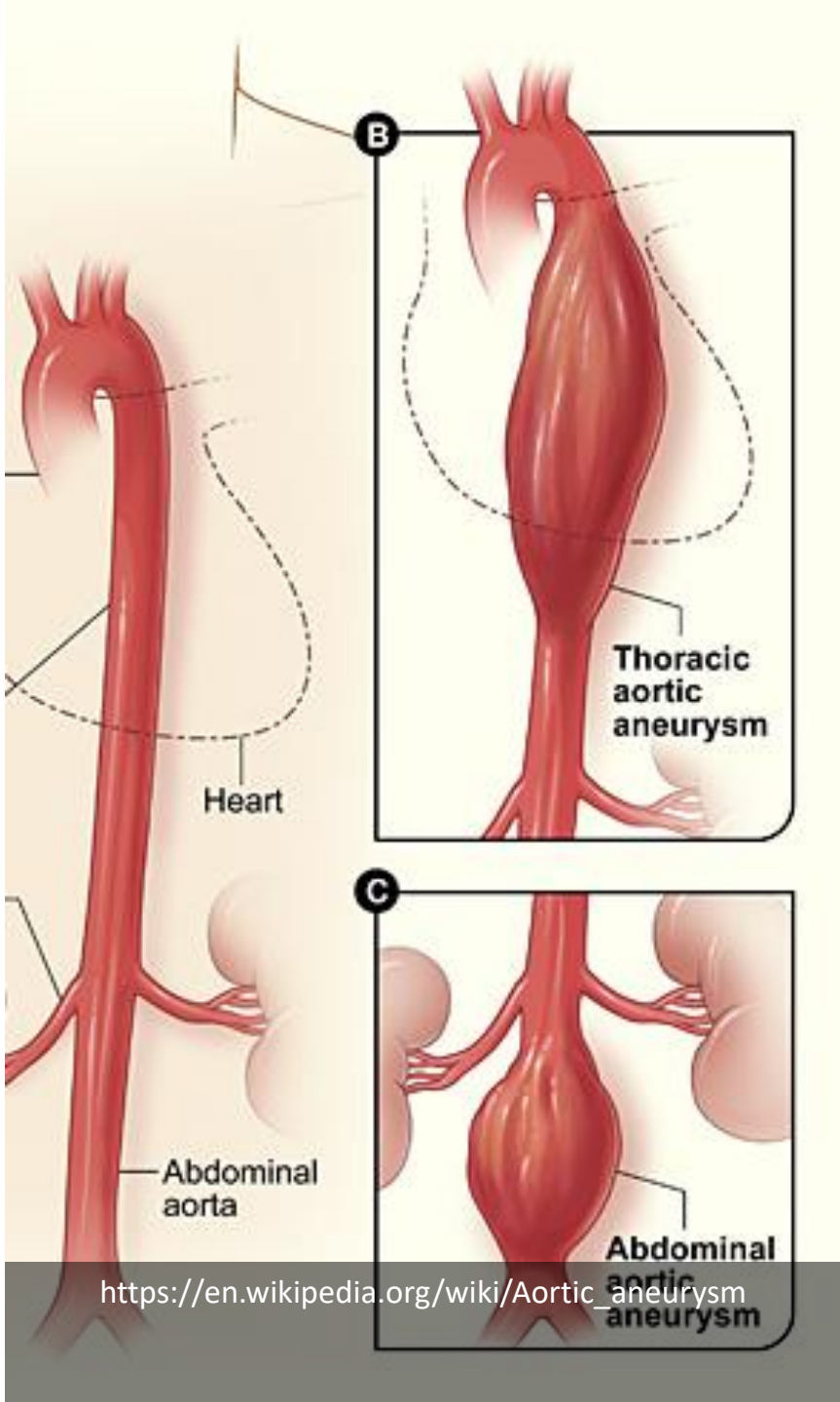
Aortic Aneurysm Disease

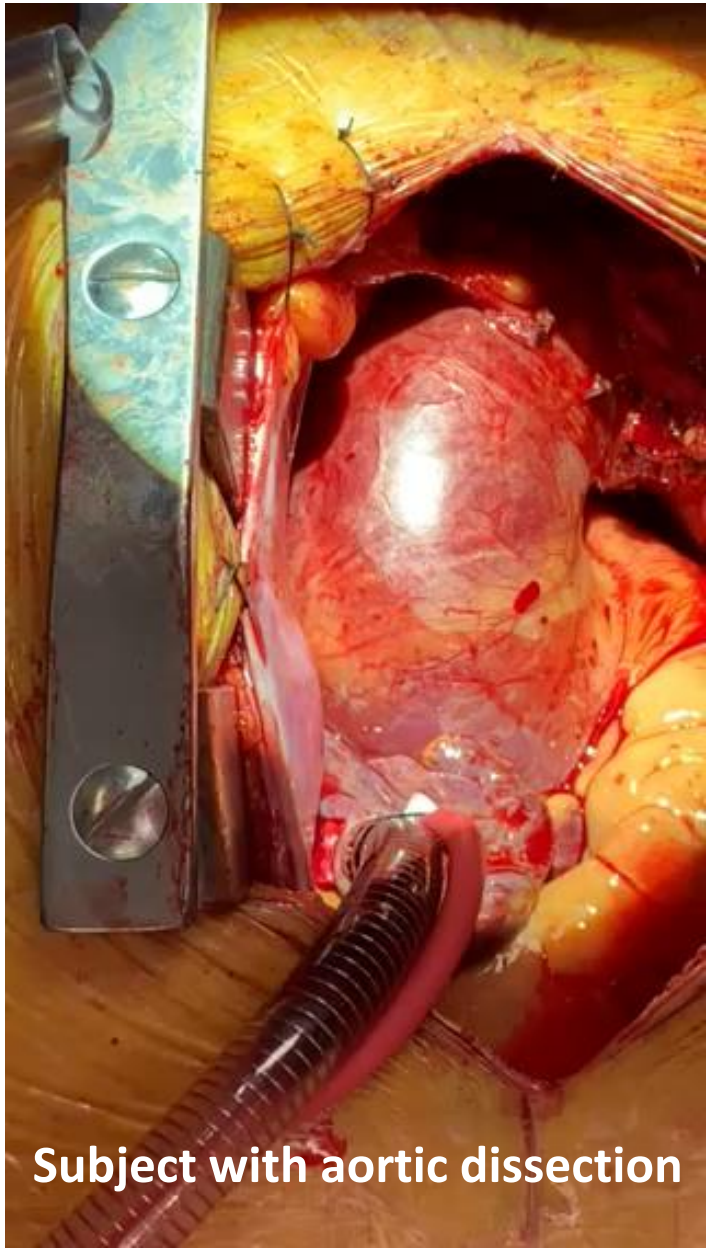
- Up to 5 million Americans have asymptomatic aortic aneurysm disease making its diagnosis and management extremely difficult
- Aneurysm complications present without warnings, such as acute aortic rupture or dissection, resulting in sudden death in 80% of the cases - THE SILENT KILLER
- Once detected, lifelong surveillance is recommended, with surgical intervention as the only therapeutic option
- Current guidelines for ongoing surveillance versus surgical intervention are primarily based on imaging modalities, which only provide macroscopic information, with NO available biomarker/ blood test in conjunction to help guide treatment



https://en.wikipedia.org/wiki/Aortic_aneurysm

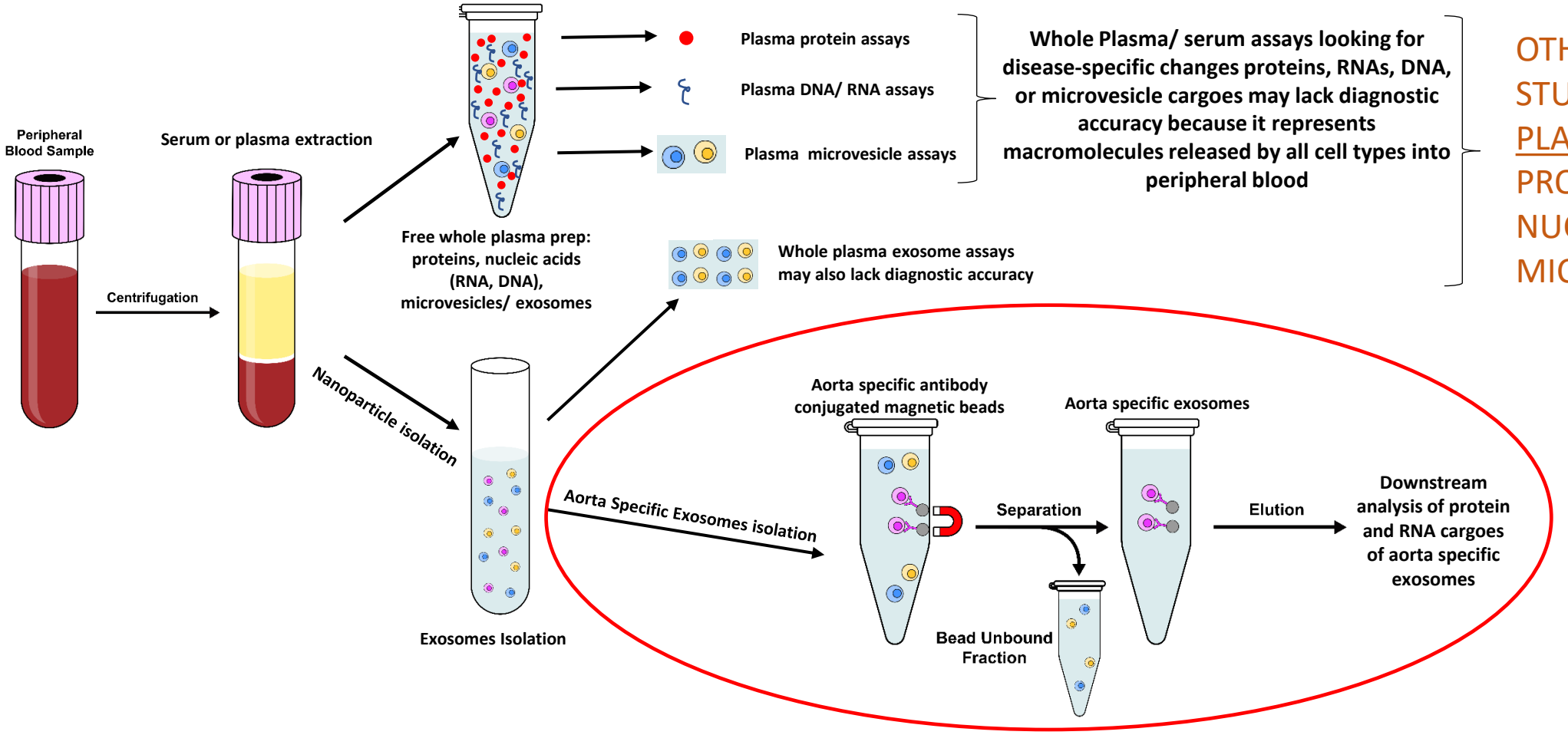
Major Clinical Gaps with Aortic Aneurysm Management Guidelines

- Huge mismatch between guideline recommendations for surgical intervention versus clinical outcomes
  - Majority of patients die from aneurysm complications at size below recommended surgical trigger
- No distinction for location of aortic aneurysm or pathophysiology leading to aneurysm development
- No molecular window into aneurysm progression or stability
- Poor clinical penetrance of imaging modalities in surveillance
- Imaging modalities are expensive, impractical for repeated testing



Subject with aortic dissection

Biomarker Development Unique to our Lab

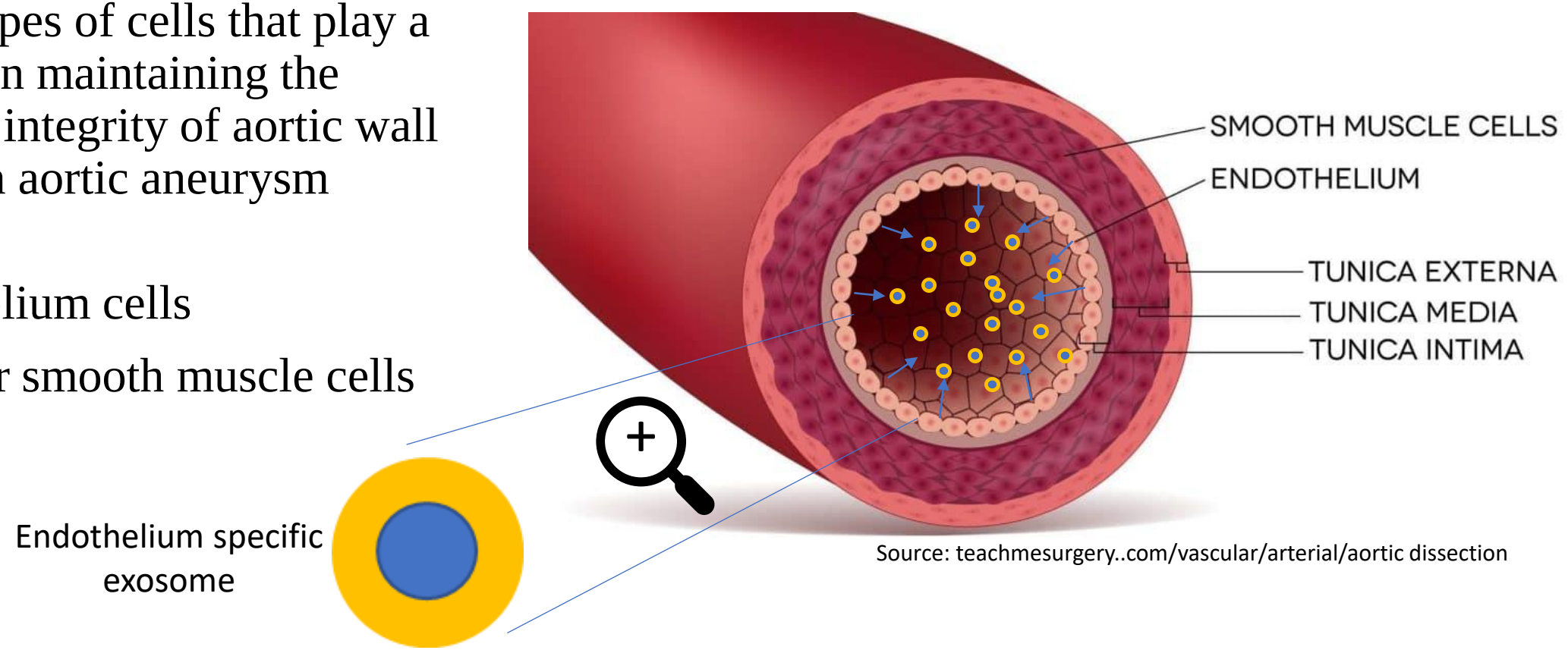


OTHER LABS STUDY WHOLE PLASMA PROTEINS, NUCLEIC ACIDS, MICROVESICLES

WE ARE THE ONLY LABORATORY ENRICHING AORTIC ENDOTHELIAL EXOSOMES

Aortic Aneurysm Disease

- Two main types of cells that play a critical role in maintaining the strength and integrity of aortic wall are altered in aortic aneurysm disease:
  1) endothelium cells
  2) vascular smooth muscle cells



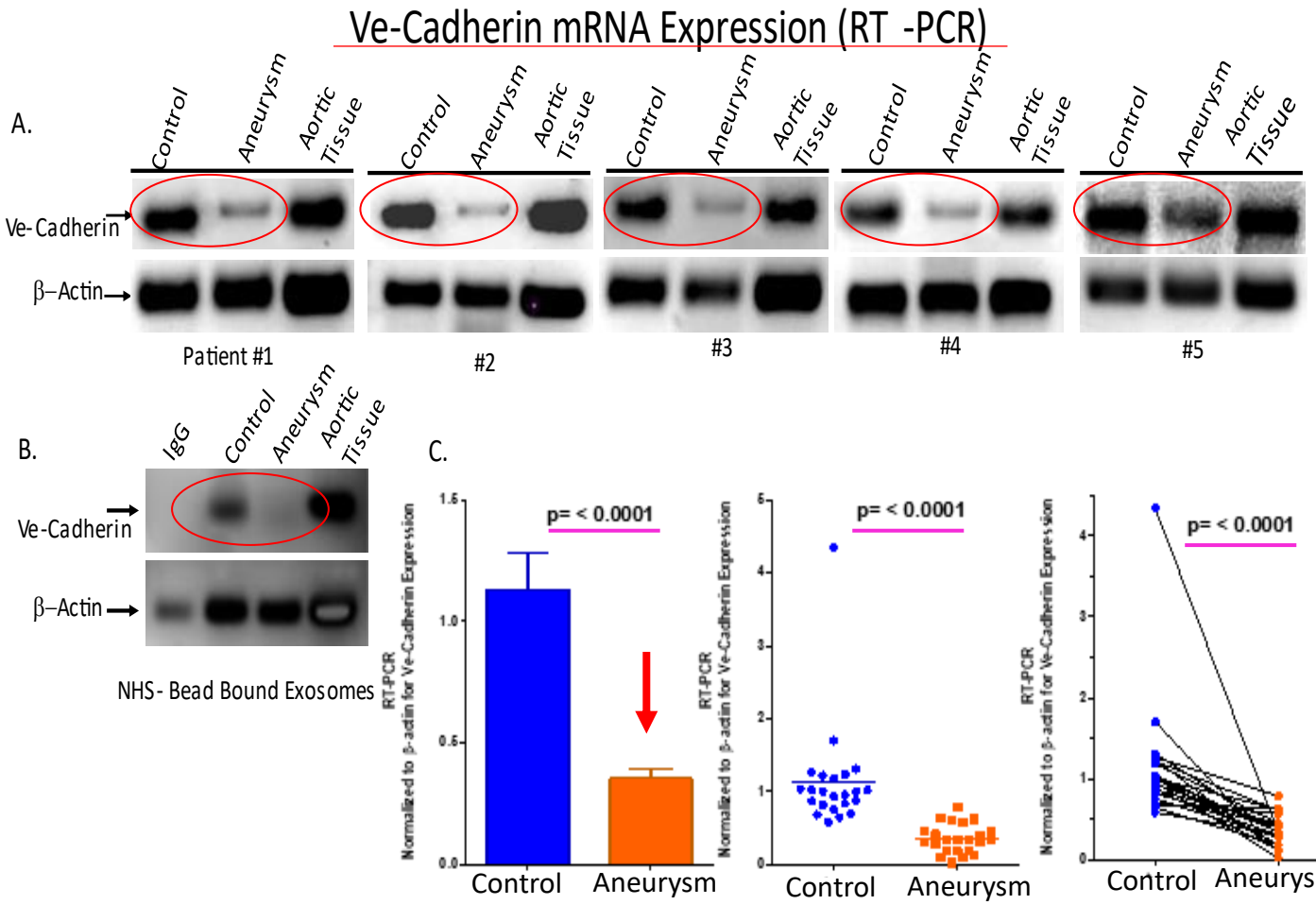
Source: teachmesurgery..com/vascular/arterial/aortic dissection

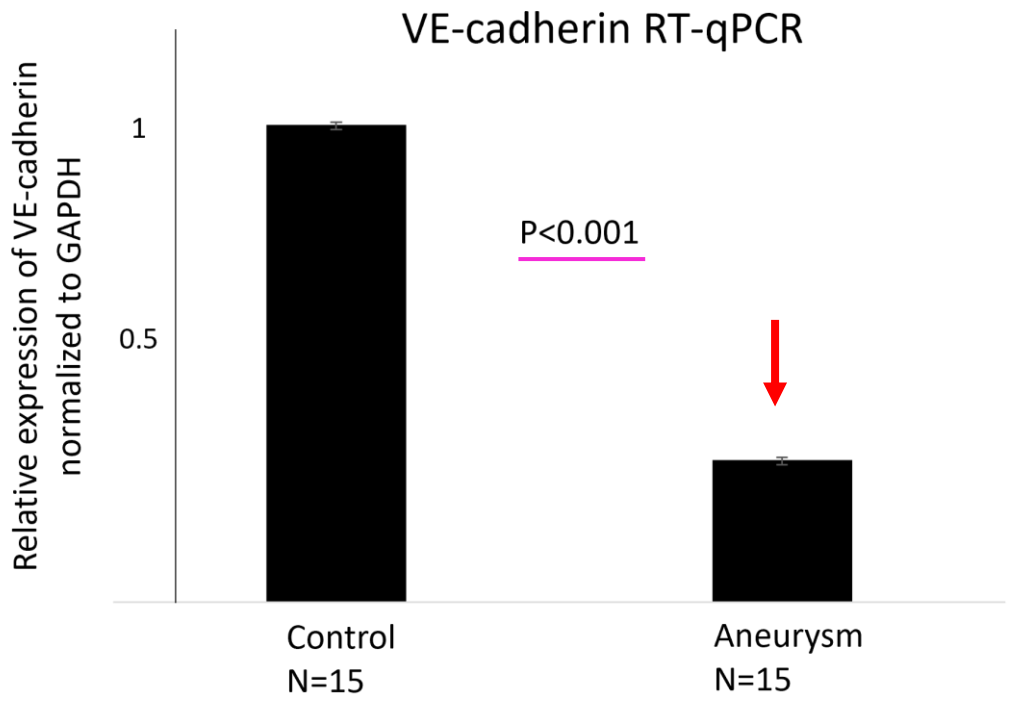
A NOVEL BIOMARKER PLATFORM BASED ON PROFILING THE PROTEIN AND RNA CARGOES OF EXOSOMES RELEASED BY AORTIC ENDOTHELIUM INTO PERIPHERAL BLOOD

Results

Cross sectional study comparing 40 patients with aortic aneurysm disease to 40 age-matched patients without aortic aneurysm disease

VE-cadherin expression

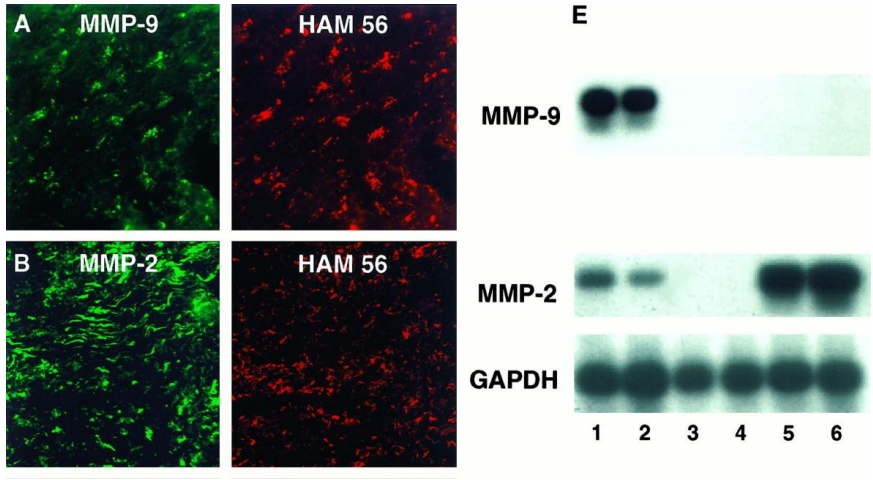




Aneurysm tissue and aortic dissection tissue show increased expression of matrix metalloproteinases

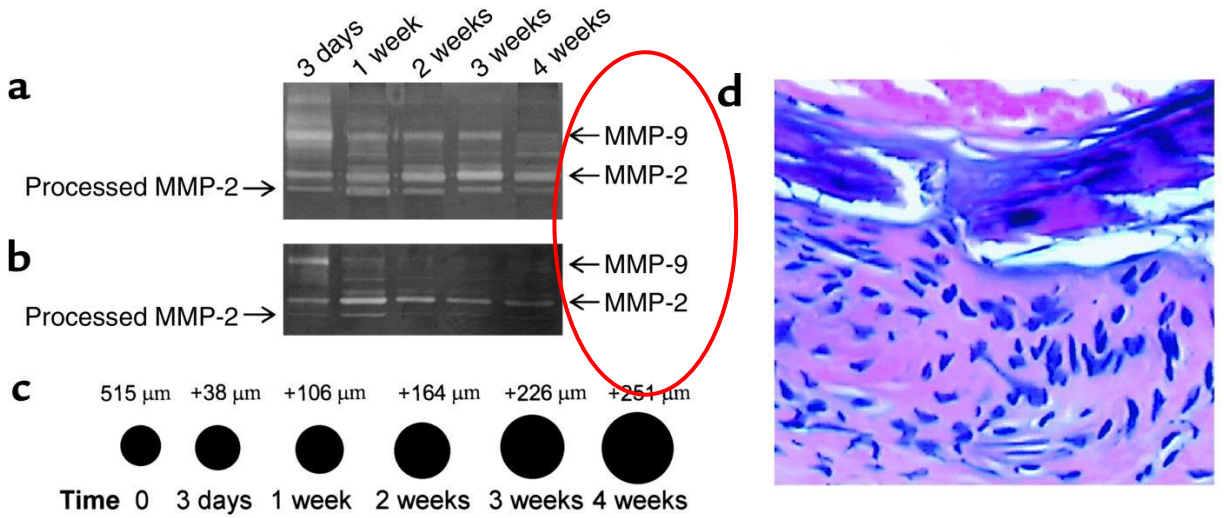
- Matrix metalloproteinases (MMPs) are class of proteins that breakdown the aortic wall architecture, and several studies have shown increased expression of these proteins in aortic aneurysm tissue and aortic dissection tissue

Davis et al. MMP upregulation in abdominal aortic aneurysms. Arteriosclerosis, Thrombosis, and Vascular Biology. 1998. 18(10):1625-1633



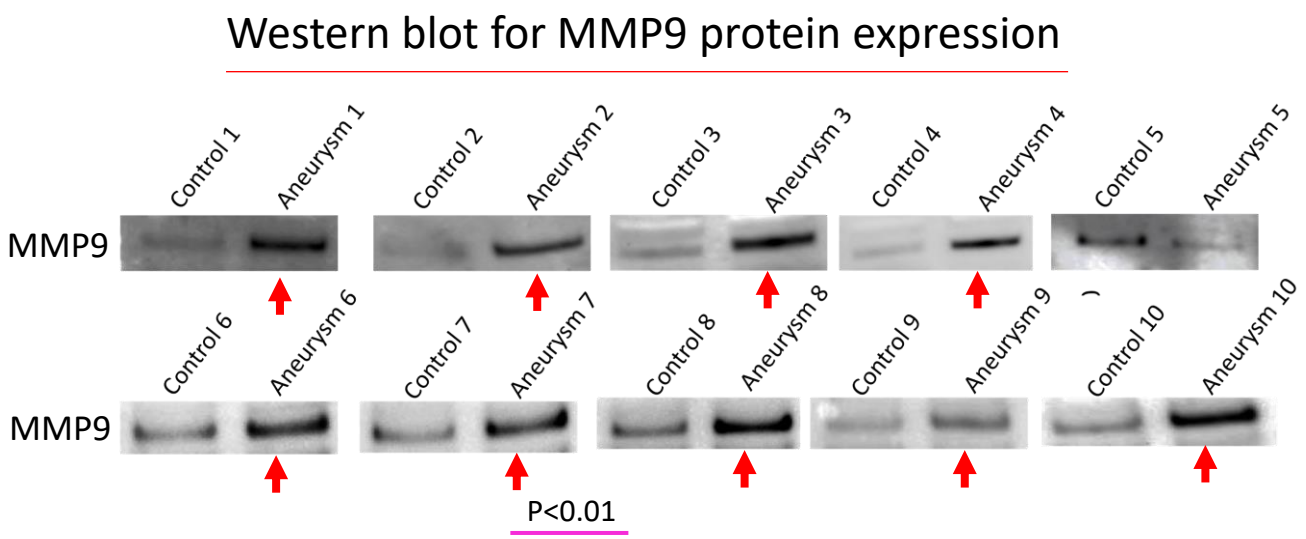
MMP-9 and MMP-2 upregulated in aortic aneurysm tissue

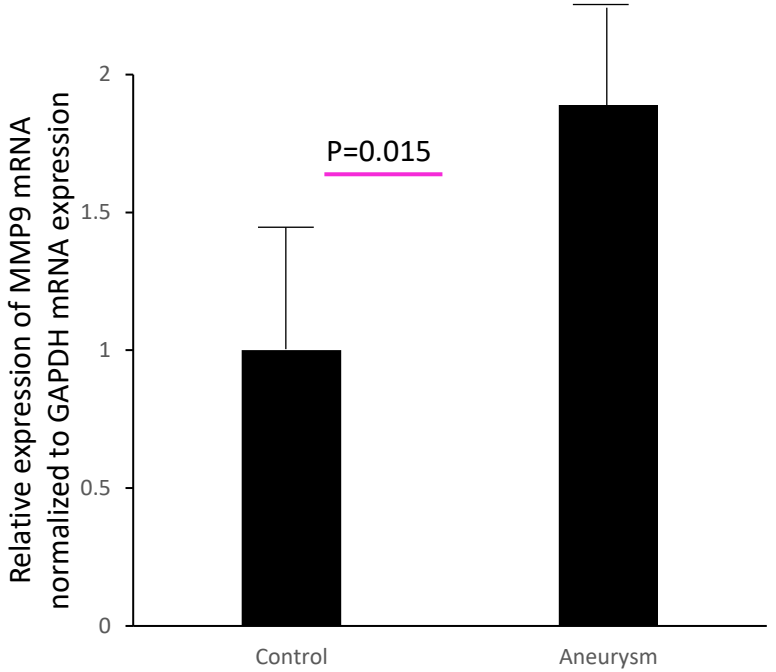
Longo et al. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. Journal of Clinical Investigation. 2002. 110(5): 625-632

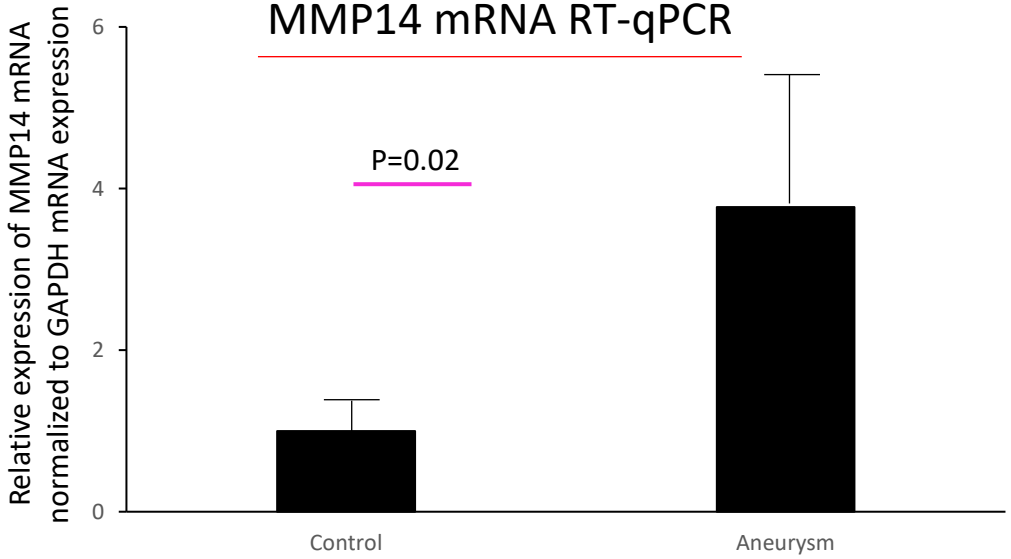


MMP-9 and MMP-2 upregulated in aortic aneurysm tissue

Aortic endothelial exosomes also upregulate MMPs







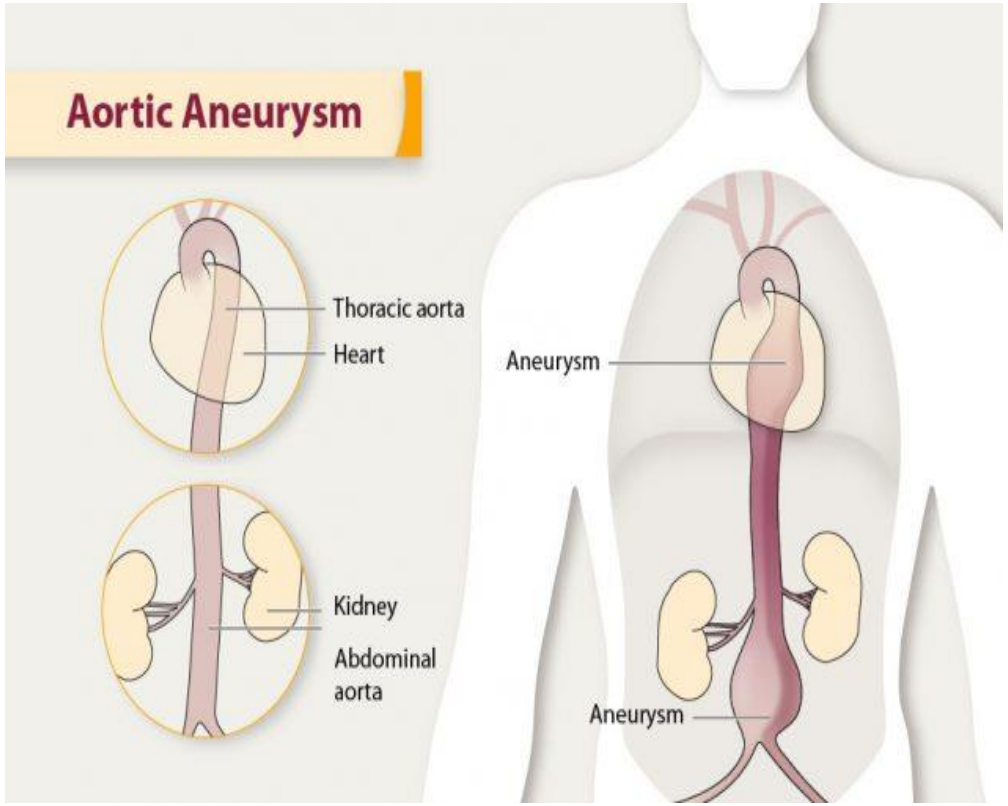
Two tested MMPs, MMP-9 and MMP-14 mRNA expression is significantly upregulated in aortic endothelial exosomes from aneurysm patients

Blavatnik Accelerator Award Goals

1) COMPLETE ANALYSIS OF CROSS-SECTIONAL STUDY TO VALIDATE THE BIOMARKER POTENTIAL OF AORTIC ENDOTHELIAL EXOSOME PLATFORM FOR MARKERS ALREADY IDENTIFIED
   - VE-cadherin, MMP-7, MMP-9, MMP-14 protein and mRNA expression profiles in 120 subjects with aortic aneurysm disease and 120 age-matched control subjects

2) INVESTIGATE NOVEL MICRO RNA BIOMARKERS IDENTIFIED BY NEXT GENERATION SEQUENCING ANALYSIS OF AORTIC ENDOTHELIAL EXOSOMES

3) INVESTIGATE BIOMARKER POTENTIAL OF AORTIC ENDOTHELIAL EXOSOME PLATFORM IN PATIENTS PRESENTING WITH ACUTE AORTIC SYNDROMES – AORTIC DISSECTION, AORTIC RUPTURE
   - ~60 patients present to the Yale-New Haven Health system each year with acute aortic syndrome



Source: www.cdc.gov/heartdisease/aortic_aneurysm.htm