Matrix Regenerative Nanotherapeutics for Aortic Aneurysm Repair

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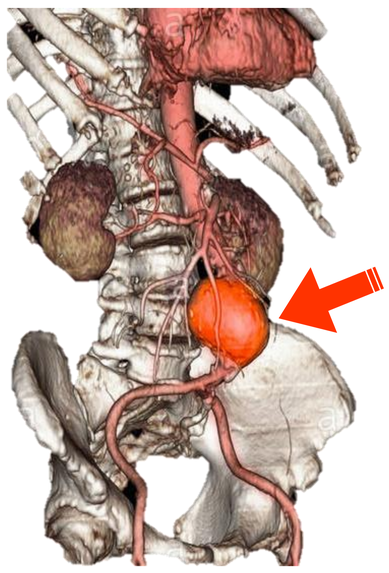
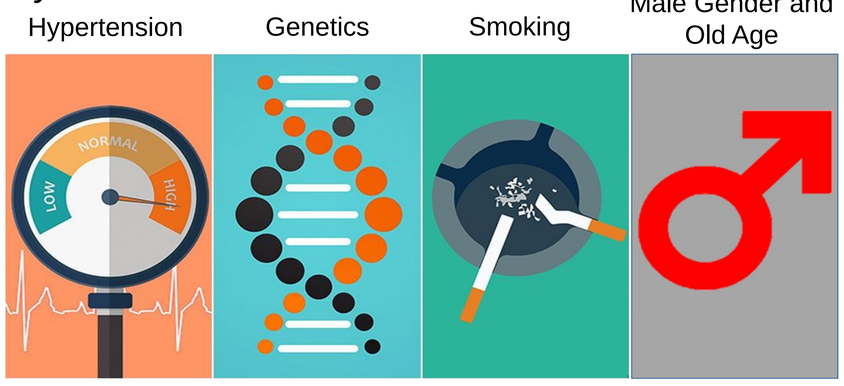
What are AAAs?



- Disorder characterized by chronic enzymatic breakdown of the structural framework (matrix) of the aorta wall
- Gradual thinning and weakening of aortic wall and loss of wall stretch and recoil properties
- Aorta grows in size over > 5 years
- Culminates in potentially fatal rupture

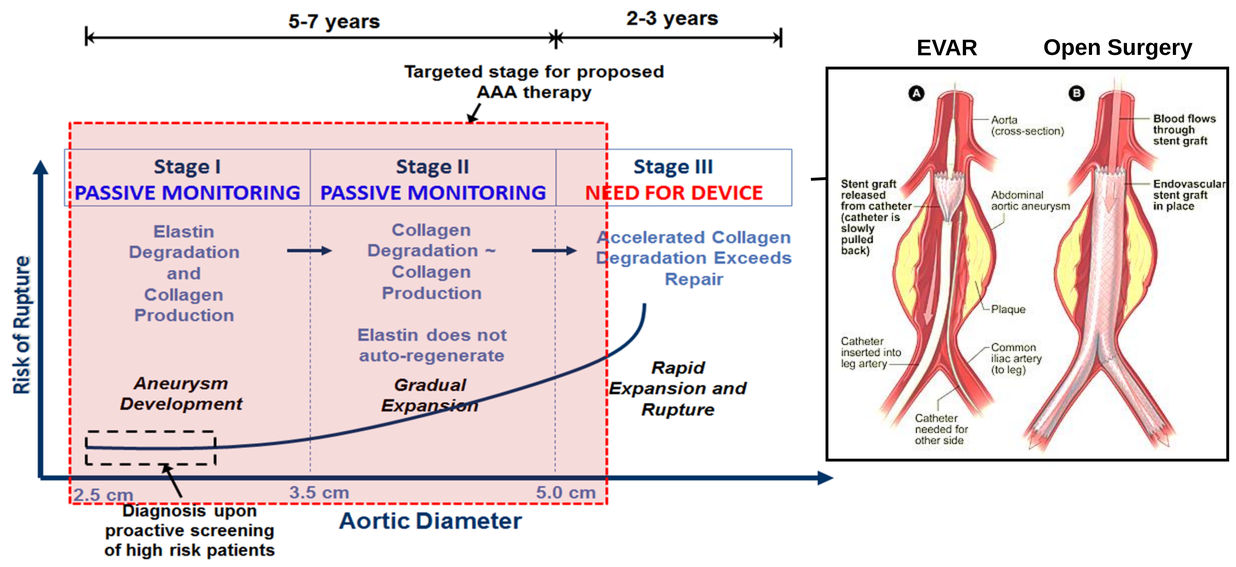
Who are at Risk?

- Afflict 9% of men & 3% of women in 50-84 age group[1,2]
- Primary risk factors



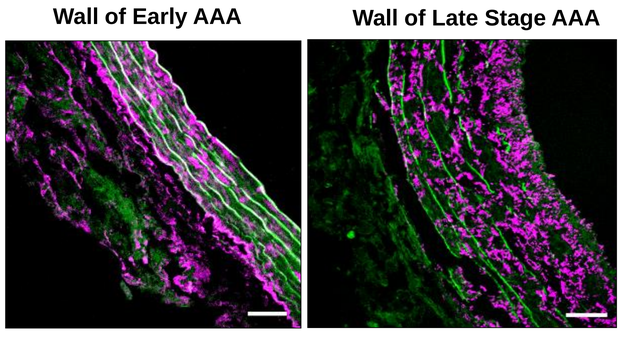
- Patients with AAAs larger than 5.5 cm in diameter have high risk of aortal rupture. Rupture has > 90% mortality rates[3], emphasizing need for early treatment
- Public health cost burden: $10 billion in 2011[4]

Why are new treatments needed?



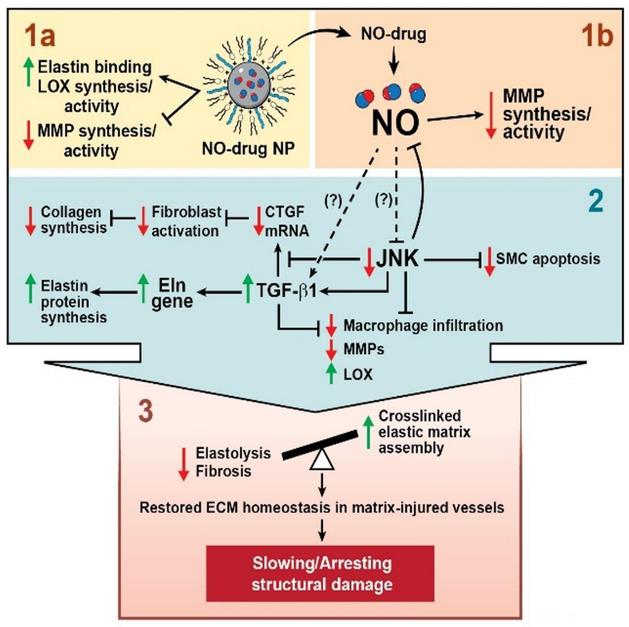
- Endovascular aneurysm repair (EVAR) and open surgery have high risk & complications and so are performed only on pre-rupture AAAs
- No established drug treatments to slow, arrest, or reverse growth of **small AAAs** (<5.5 cm maximal diameter) and restore healthy vessel structure during the 5-7 years leading to rupture

Elastic Matrix: The 'missing link' in AAA Repair



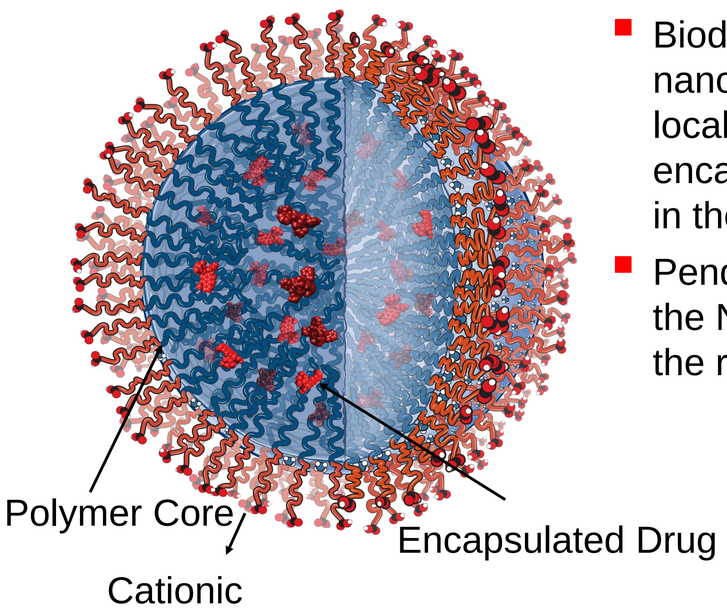
- Elastic fibers in the aorta wall (green) are disrupted in AAAs, resulting in loss of vessel elasticity. Since elastic fibers do not regenerate or repair naturally in adults, restoring healthy vessel state is difficult
- Need to provide a sustained & localized stimulus to new elastic fiber assembly & deterrent to enzymatic matrix breakdown in the AAA wall

Hypothesized Mechanism for Treatment



- C-Jun N terminal kinase (JNK) is overexpressed in the AAA wall & triggers increases in matrix degradative enzymes (MMPs) & attenuates elastin synthesis and fiber assembly.
- Prior work indicates Nitric Oxide (NO) inhibits MMP2.
- We hypothesize that local delivery of NO in aneurysmal smooth muscle cells (SMCs) can inhibit elastic fiber breakdown by MMPs and stimulate new elastic matrix assembly to arrest AAA growth

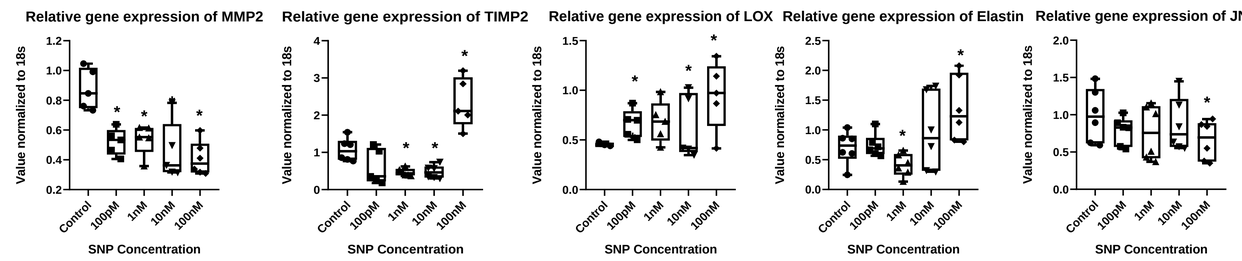
Matrix Regenerative Nanotherapeutics



- Biodegradable polymer (PLGA) nanoparticles (NPs) enable localized and sustained release of encapsulated NO donor drug, SNP, in the AAA wall
- Pendant cationic amphiphiles on the NP surface provide synergy to the regenerative effects of drug by
  - Inhibiting MMPs, elastases
  - Stimulating activity of LOX, elastin cross-linker enzyme
  - Facilitating NP binding to disrupted elastic fibers

Key Outcomes

A

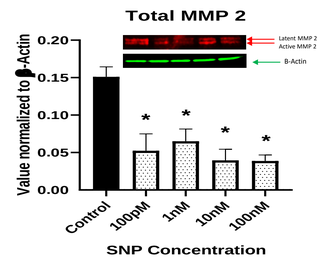


B

	ELN/ Col1A1	ELN/Col3A1
Control	1	1
100 pM	0.7	1.3
1nM	1.4	1.2
10nM	3.0	2.3
100nM	2.0	3.7

	TIMP2/MMP2	Fold increase
Control	1.1	1.0
100 pM	1.4	1.3
1 nM	0.9	0.9
10 nM	1.0	0.9
100 nM	5.2	4.9

C



- **A:** SNP treatment to AAA SMCs attenuates expression of JNK and MMP-2 (elastin degrading enzyme) and increases expression of LOX, elastin, TIMP2. These outcomes were found to SNP dose dependent
- **B:** The elastin to collagen and TIMP2 to MMP2 gene expression ratios was upregulated by 3.7 and 4.9 fold respectively at 100nM SNP
- **C:** MMP2 protein expression was significantly decreased at all SNP doses (100 pM – 100 nM).

Prospective Benefits

Our treatment, intended as a simple IV injection-based administration of matrix regenerative NPs with NO donor drug can potentially transform the current standard of care for small AAAs. Availability of a minimally-invasive outpatient treatment to slow or arrest growth of small AAAs can potentially reduce/eliminate the need for future surgery on larger, more rupture-prone AAAs in the mostly elderly patients who are at high risk.

References

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Funding (Ramamurthi)

National Heart Lung and Blood Institute
NIBIB
American Heart Association Learn and Live
NIH NICHD
NSF