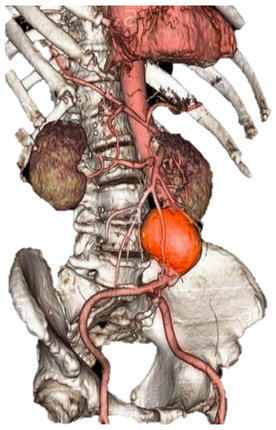
Nitric Oxide (NO) Donor Drug Delivering Nano Platforms for Elastic Matrix Repair and Regeneration in Abdominal Aortic Aneurysms

Suraj Bastola, BE* and Anand Ramamurthi, PhD, FAHA

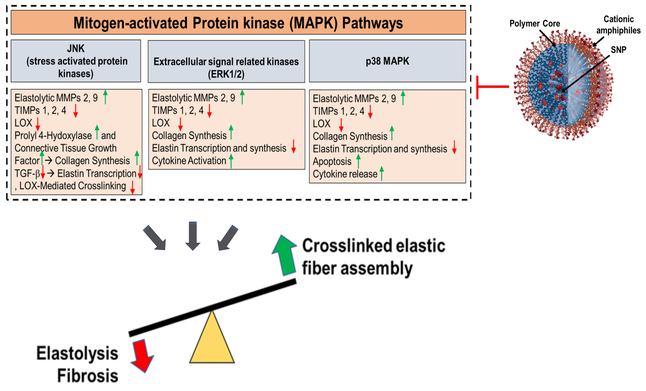
Department of Bioengineering, Lehigh University, Bethlehem, PA



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
- Grows slowly > 5 years
- Culminates in potentially fatal rupture

Hypothesized Mechanism for Treatment



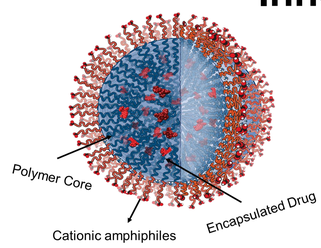
- C-Jun N terminal kinase (JNK) is overexpressed in the AAA wall and triggers downstream increases in matrix degradative enzymes (MMPs) and decreases in elastin synthesis and fiber assembly
- Prior work indicates Nitric Oxide (NO) inhibits MMP2.
- We hypothesize that local delivery of NO in aneurysmal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

Risk Factors and Clinical Significance

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

- Rupture AAA has > 90% mortality rates3, emphasizing need for early treatment
- Public health cost burden: $10 billion in 20114
- Early surgical repair provide no benefit, there are no non-surgical treatment available

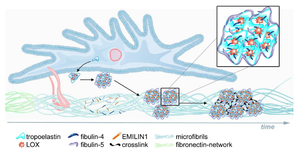
Innovation: Matrix Regenerative Nanotherapeutics



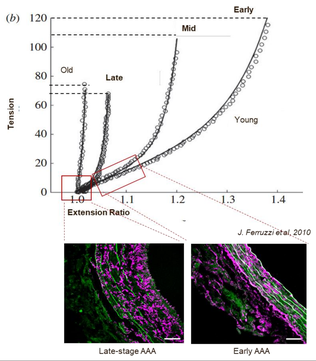
Component	Role
Cationic Amphiphiles (amine)	-Repeals elastases -Inactivates MMPs -Attracts negatively charged LOX to increase crosslinking
Hydrocarbons	-Hydrophobically associates with elastin -Engages active sites of MMPs to inactivate
Polymer core	Core of the PLGA polymer for drug encapsulation
Encapsulated drug	Drug provides anti-MMP and pro-elastogenic stimuli

- Biodegradable polymer (PLGA) nanoparticles (NPs) enable localized and sustained release of encapsulated NO donor drug, SNP, in the AAA wall
  - NO donor accelerates matrix synthesis and attenuates proteolysis of elastic matrix via TGF-β dependent and/or independent pathway
- 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

Elastic Matrix: The 'missing link' in AAA Repair

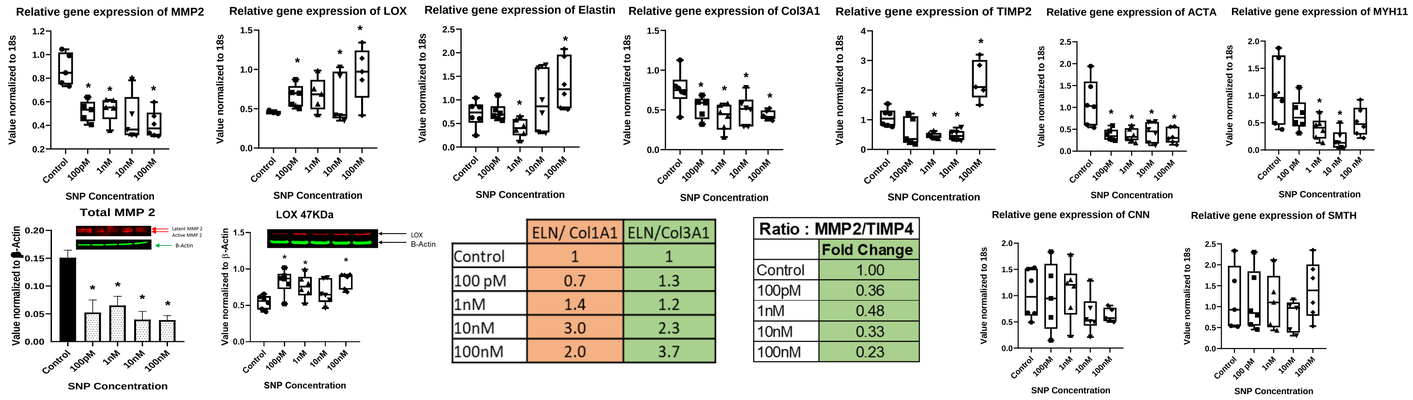


- Adult and diseased SMCs have poor capacity for elastin synthesis and are aberrant in elastic fiber assembly (schematic of elastic matrix formation at left).



- Disrupted elastic fibers (green) in AAAs, results in loss of vessel elasticity (loss of toe-region of Stress-Strain curve at left) and slow expansion to a rupture stage.
- Need to provide a sustained & localized stimulus to new elastic fiber assembly & deterrent to enzymatic matrix breakdown in the AAA wall

Key Outcomes

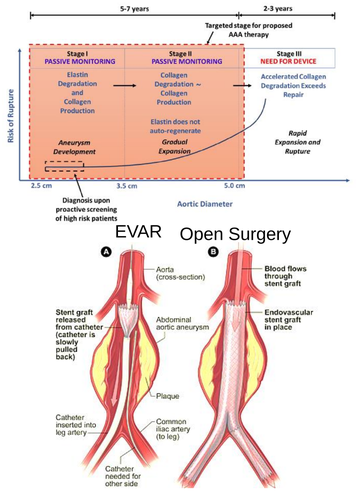


	ELN/ Col1A1	ELN/Col3A1
Control	1	1
100 pM	0.7	1.3
1nM	1.4	1.2
10nM	3.0	2.3
100nM	2.0	3.7

Ratio : MMP2/TIMP4	Fold Change
Control	1.00
100pM	0.36
1nM	0.48
10nM	0.33
100nM	0.23

- Efficacious dose appears to be 100 nM and higher. Dose escalation studies required
- Data suggests enhanced elastic fiber assembly, crosslinking, and decreased elastolytic activity
- Results promising towards future development of actively targeted polymer-based nanotherapeutics for onsite regenerative repair of AAA wall.

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

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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