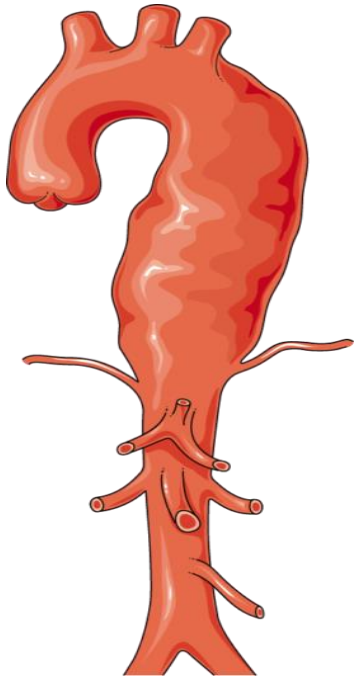

A humanized antibody to prevent thoracic and abdominal aortic aneurysm dissection and rupture

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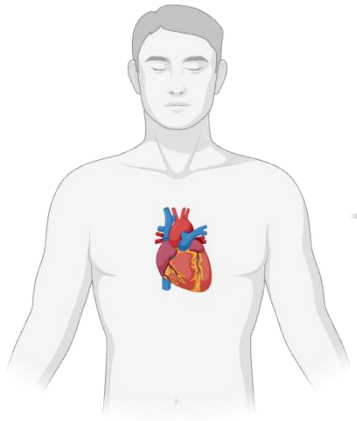
Executive Summary

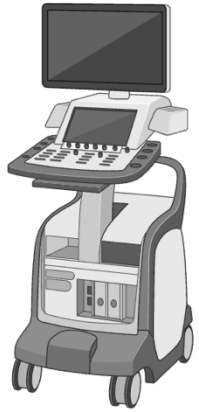
- **Novel target in cardiovascular disease:** The drug is a *monoclonal antibody* designed to neutralize a secreted protein upregulated in most if not all humans' thoracic and abdominal aortic aneurysms.
- **Key asset properties:** The antibody binds selectively to the elevated protein, preventing its detrimental effects on vascular integrity. The target of the antibody is **measurable** by ELISA, allowing for the titration of the antibody
- **Clinical validation**: A humanized antibody against this target has been tested in a cancer trial and found to be safe. The same antibody **fully rescued** aortic aneurysms in mice
- **Intellectual property**: The antibody is repurposed. We are generating novel analogs of this antibody. Future IP around antibodies will be generated as a result of Blavatnik funds.

New treatments are needed to prevent aortic aneurysms in high-risk patients

Aortic aneurysm: a common and preventable disease

- **Extremely common:** affecting **2–4 million** people in the US and **70–140 million** people globally.
- Patients with rapidly growing aortic diameter, those with certain inherited disorders like Marfan syndrome, and aortic diameter ≥4.5 cm, or a family history of aortic dissection or rupture and diameter ≥4 cm are at risk for dissection/rupture
- **Lethal:** Annual mortality rate of **10,000–15,000 in the U.S.**
- **90,000** undergo surgical repair/ 15000 reintervention in the US.





Diagnosed with echocardiogram (20% Americans)

High risk

Low risk

Aortic aneurysm

No treatment

Blood pressure medications *: preventive; ineffective*

Surgical intervention for aortic diameter ≥ 5 cm

We have used a novel antibody to **prevent aortic aneurysms and dissections/rupture in high-risk patients** – It can be used at any stage of the disease.

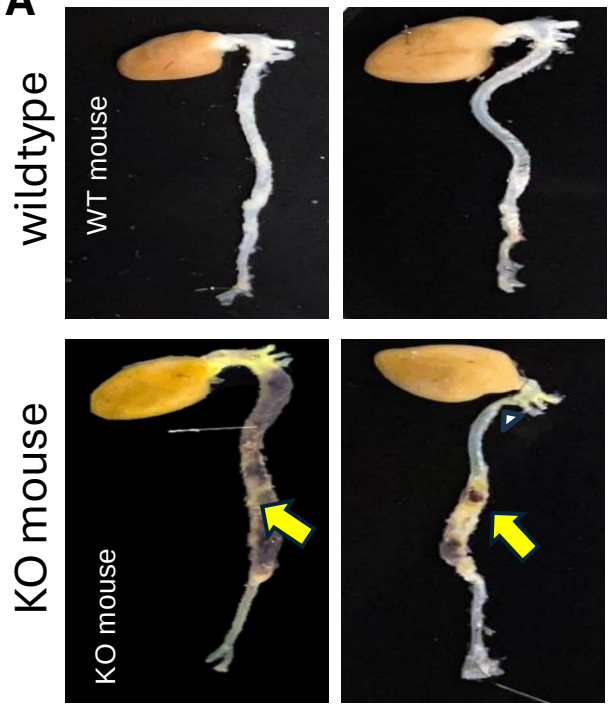
Treatment duration: 4 weeks, biweekly injections at any stage of the disease; Response evaluation: imaging assessments and plasma protein level measurements; therapy cycles can be repeated as needed.

Target validation: RNA-seq analysis identified target upregulation in mouse & human aortic aneurysms

Genetic validation

- We first screened genome-wide association studies for genes with strongest association with thoracic and abdominal aortic aneurysms.
- A gene with the strongest effect size was disrupted in mice, which developed thoracic and abdominal aneurysms and bleeding
- Analysis of the mouse aorta and plasma samples, along with all human aorta samples, revealed that a secreted protein—normally suppressed by the disease-associated gene—was significantly elevated at both the transcript and protein levels.
- An antibody against this protein was generated.

A



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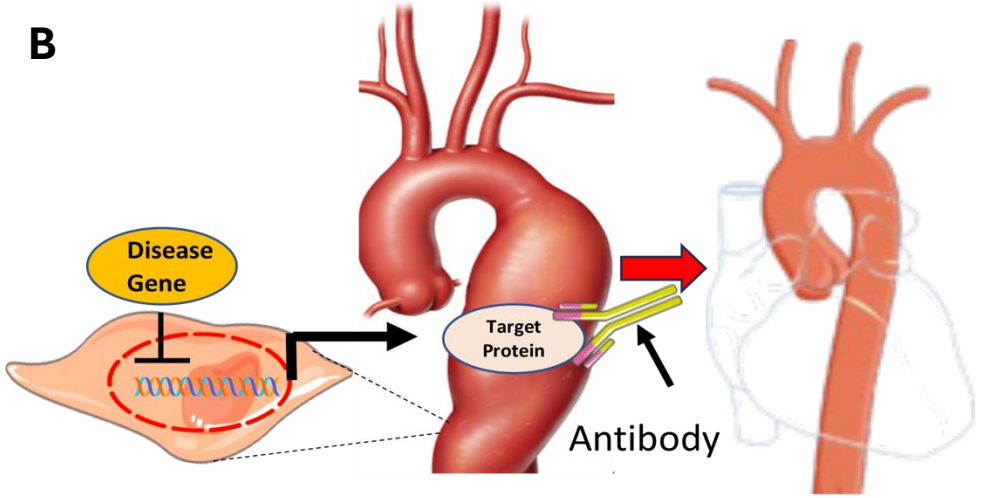

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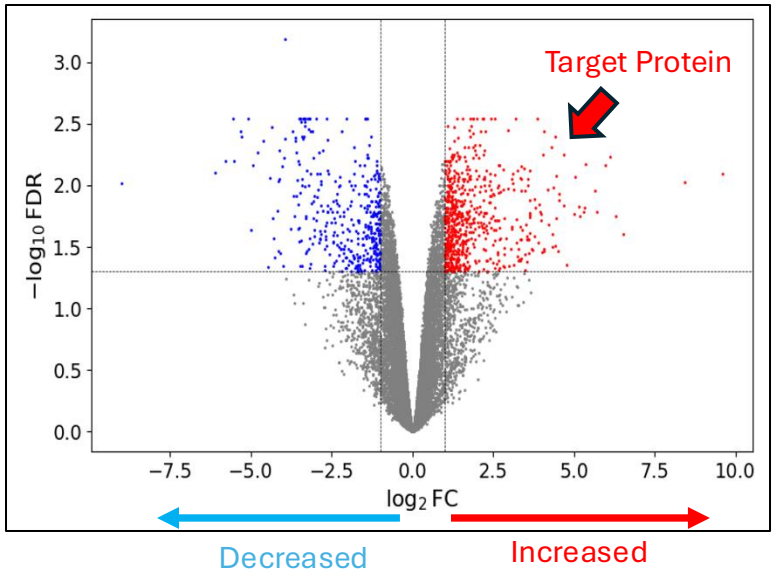
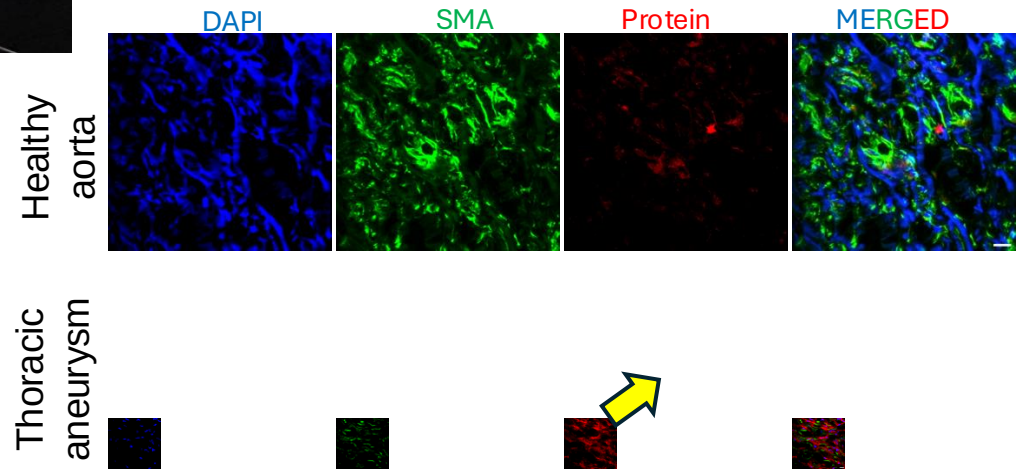


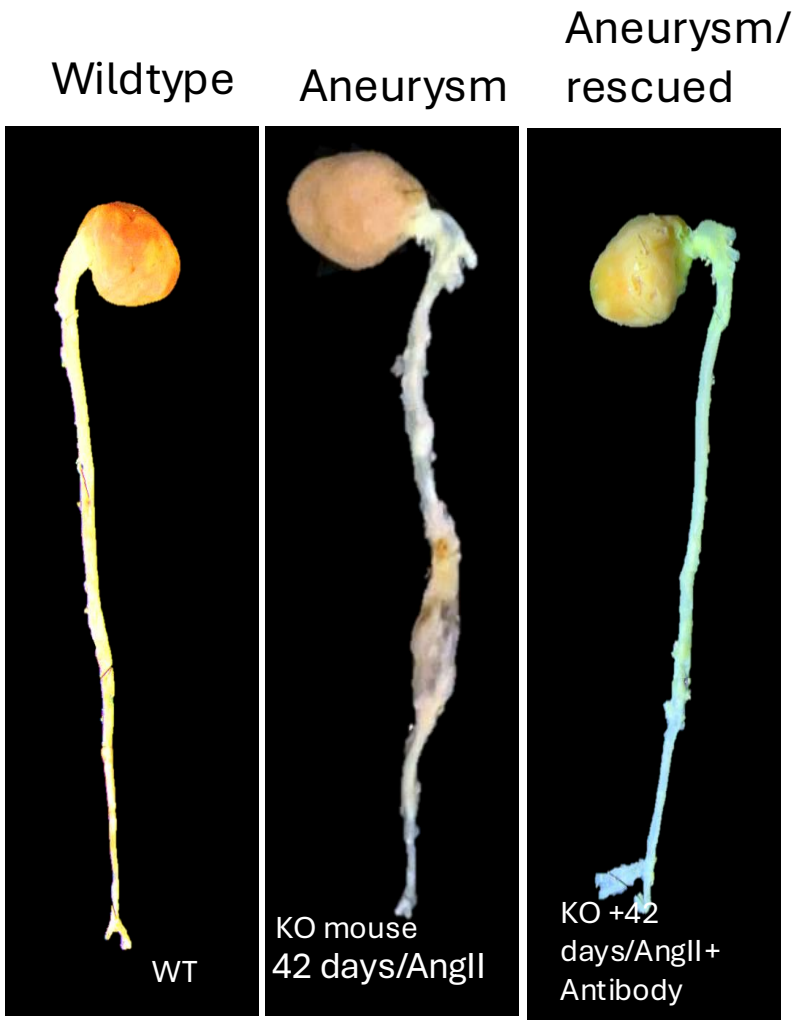
Human aortic Transcript

D

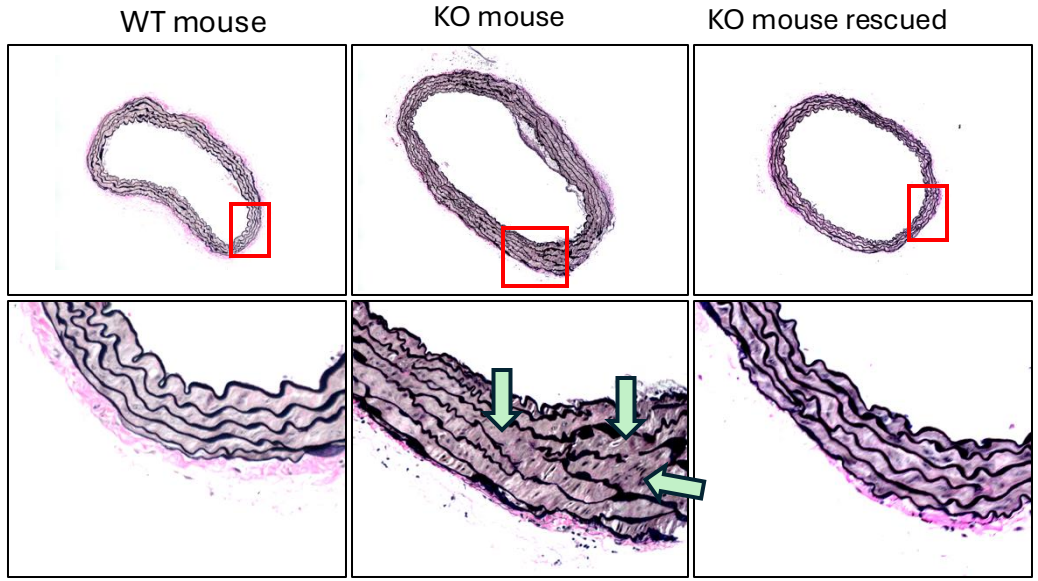


Target protein levels Human aortic aneurysms

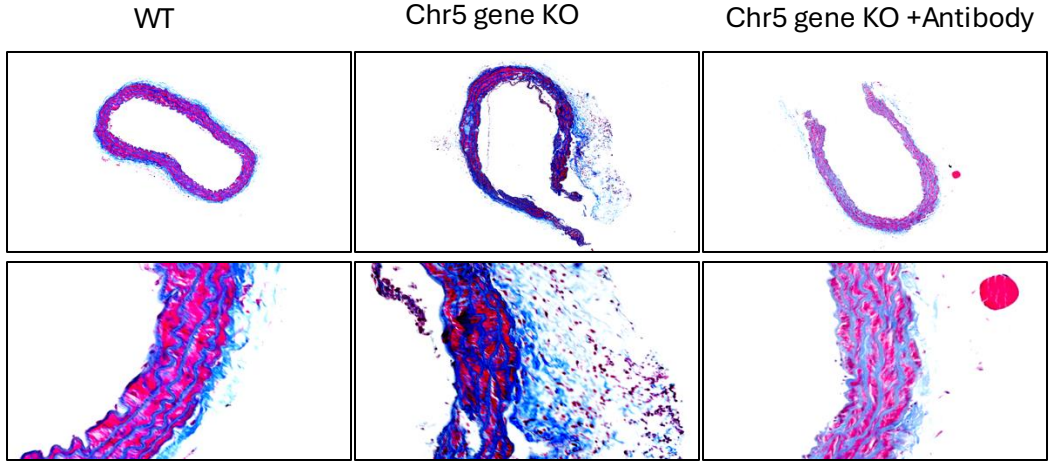
In vivo POC: The neutralizing antibody fully reversed both gross anatomical and microscopic signs of aortic aneurysm in mice, demonstrating its therapeutic potential.



Gross anatomy

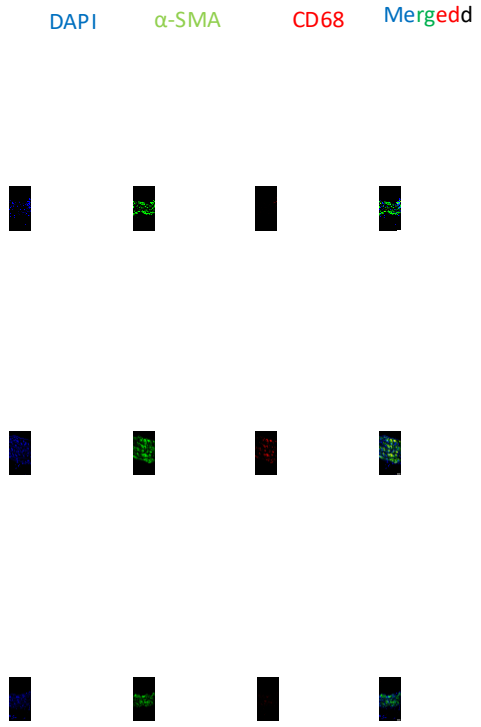


Elastic Fiber disruption EVG stain (Thoracic Aorta)



Collagen deposition -Trichrome stain (Thoracic Aorta)

Microscopic signs



Aortic Inflammation (CD68 macrophage marker)

Blavatnik Milestones: Advancing POC and generation of IP

New antibody generation & validation ($100K)

Funded through a generous donation to the medical school

The Blavatnik funding ($300K) will cover the following milestones:

- **Milestone 1 ($100K):** In vivo proof-of-concept (POC) compared to the standard of care and antibody optimization.
- **Milestone 2 ($200K):** small antibody scale-up for testing in a large animal model of aneurysms, and determining plasma levels of the target protein in the disease population versus the control population.

Thank you

from Mani team