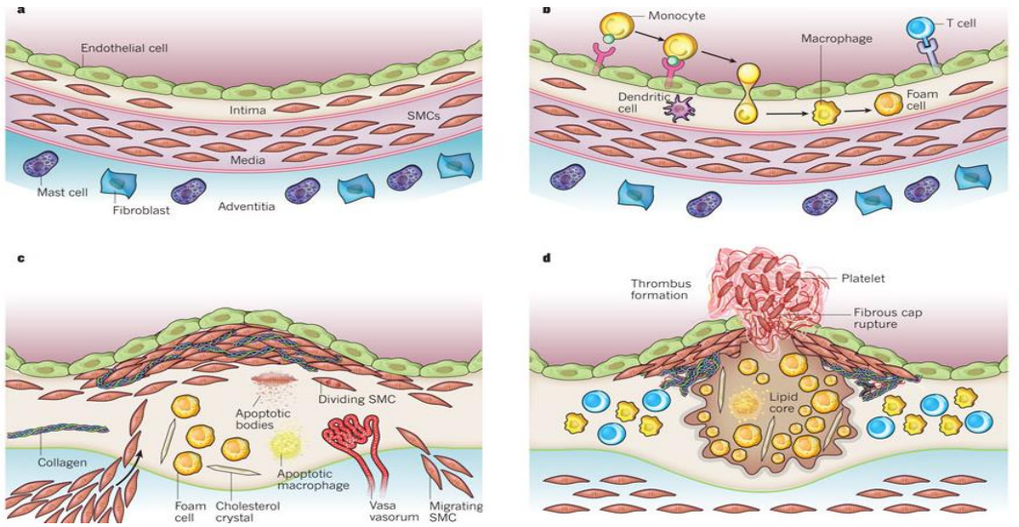
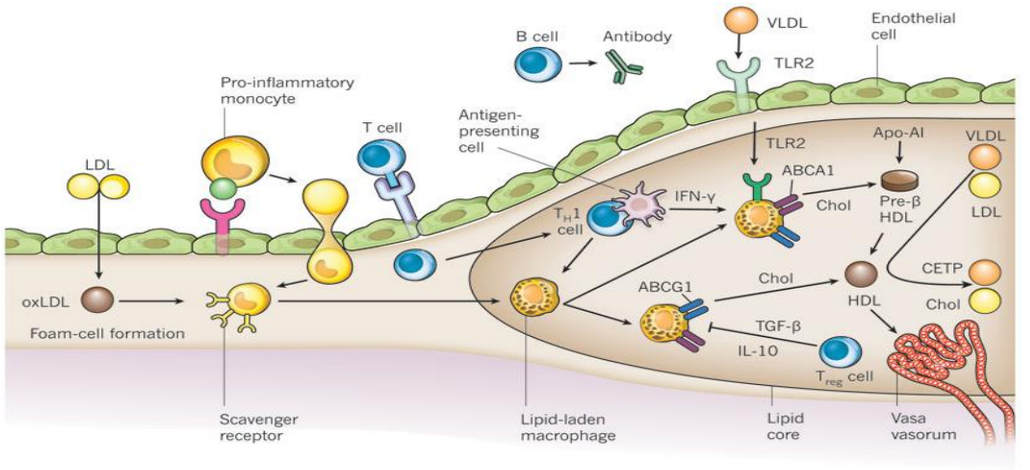
VasoRx: Atherosclerotic Plaque Regression

- A progressive disease characterized by plaque build-up in large arteries, leading to heart attacks, stroke, and peripheral vascular disease.
- Induced by a combination of high cholesterol and local mechanical factors.
- Leads to a chronic inflammation in the vascular wall.



Development of atherosclerosis



Vascular inflammation

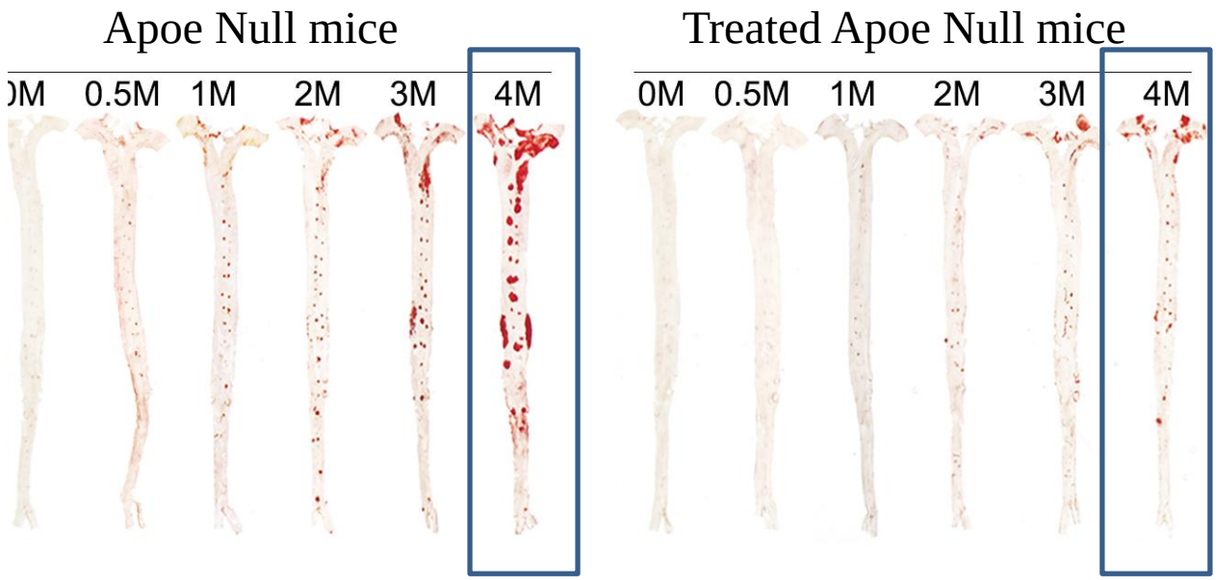
Key points: new biology, new targets, new technology

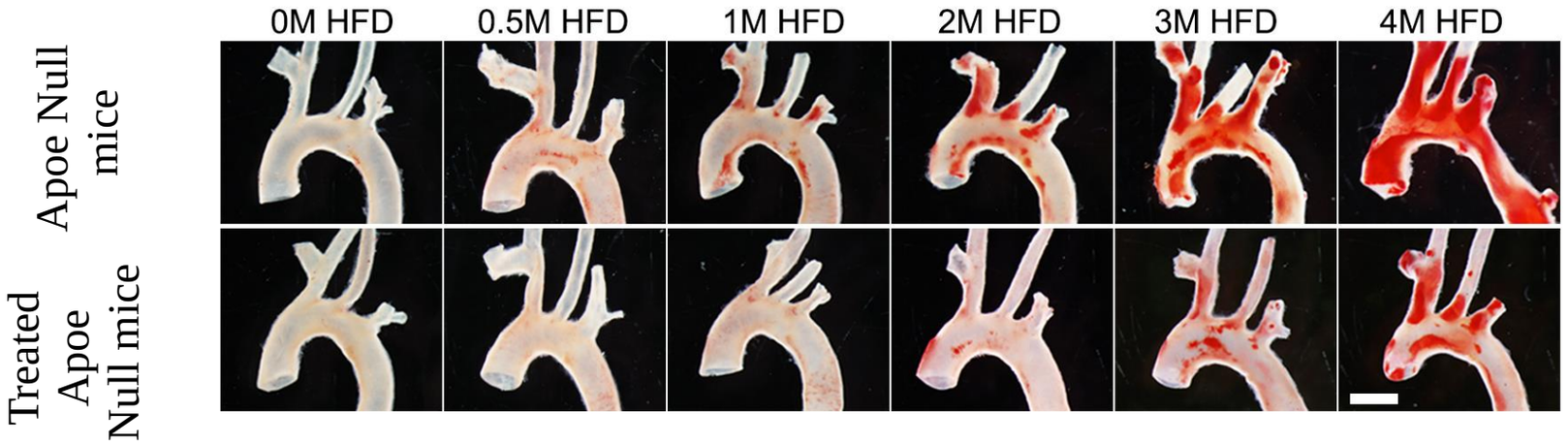
- Current treatment of atherosclerosis is limited to lipid-lowering therapies
  - Slows down disease progression
  - Does not reverse the disease or change its natural history
- We identified the primary driver of atherosclerosis initiation and progression
  - responsible for the feed-forward signaling loop that ensures disease progression even if underlying factors (e.g. hypercholesterolemia, hypertension, etc.) are corrected
  - In human coronary lesions the extent of pathway's activation strongly correlates ($r=0.83$, $p<0.001$) with the anatomic size of the plaque and the extent of coronary artery disease
- Inhibition of the signaling pathway:
  - **Slows down disease initiation**
  - **Stops progression**
  - **Induces plaque regression: *70% in 2 months; 92% with combined therapy***
- Endothelium-targeted therapy: systemic approach is not possible since suppression of the same signaling pathways in smooth muscle cells promotes atherosclerosis
- Endothelial targeting is achieved using specific nanoparticles
- Anti-atherosclerotic effect of endothelial-targeted therapy is potentiated by everolomus-like compounds on drug-coated stents (standard therapy)

Therapeutic platform

- miRNA/siRNAs designed to inhibit target gene signaling
- Endothelial-specific nanoparticles suitable for i.v. delivery
- Can be combined with everolomus-containing stents
- Complimentary to statin/pcsk9 therapy
- The same therapeutic strategy can be applied to diseases other than atherosclerosis including transplant arteriopathy, pulmonary hypertension, and cerebral cavernous malformations among others

Genetic demonstration of biological efficacy: atherosclerosis progression

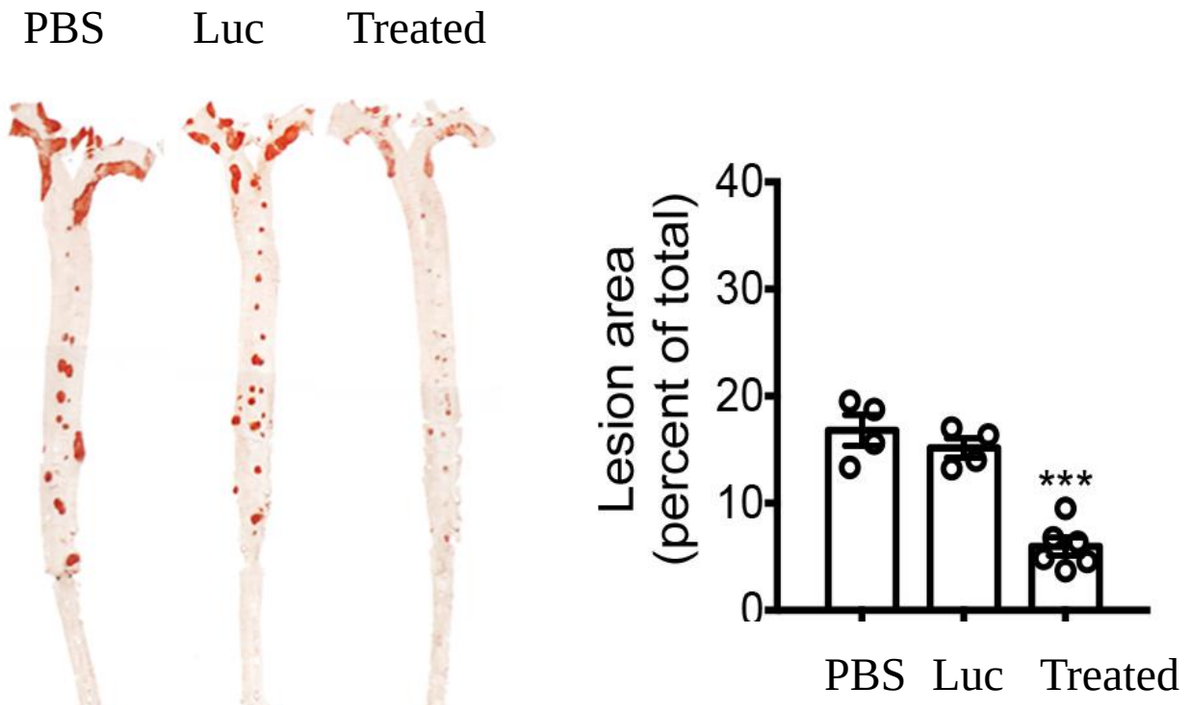




~60% reduction in plaque size

1 month HFD	62% plaque reduction
2 months HFD	72% plaque reduction
3 months HFD	52% plaque reduction
4 months HFD	60% plaque reduction

Therapeutic intervention:
Endothelium-specific delivery reduces **established** atherosclerosis



~60% reduction in total plaque burden in Apoe$^{-/-}$
~75% reduction in FRS2α/Apoe$^{-/-}$

Management Team

- Michael Simons, MD
  - RW Berliner Professor of Medicine and Cell Biology, Yale University
  - Holds ~12 patents and helped develop two companies

- Pei-Yu Chen, Ph.D.
  - Associate Research Scientist, Yale University

- Krisztina M. Zsebo, Ph.D.
  - Biotechnology executive with extensive operations and R&D experience in health care, with >$200M raised to support development operations and public and private company experience
  - CEO who took biotechnology company public in 2014
  - Prior experience as Venture Partner with leading life sciences venture firm
  - Extensive FDA biologics experience

- David Campbell, Ph.D., MBA
  - Biotechnology executive with extensive UK biotech experience
  - CEO, who took several companies public in the UK

- US statin market ~$11B
- Adults with known CAD 27.6 M
- Adults with high cholesterol 12% of >20 year olds

Potential target populations

- High risk CAD/PAD patients (recent MI, stroke, etc.)
- High risk CAD/PAD patients (unstable coronary syndromes, TIA, high risk PAD)
- Hypercholesterolemia in the presence of additional risk factors

Proof of principle clinical trial

- Non-invasive assessment of plaque regression (carotid duplex or MRA); ~200 patients

Milestones

• Validation of a novel endothelial-targeted nanoparticle:	6 months,	$600K
• Toxicity testing of a nanoparticle/let7 miR combination:	12 months,	$1M
• GMP preparation of nanoparticles/Let-7	12 months	$1M
• Efficacy/safety testing in a large animal model:	6 months,	$1M
• Salary/consulting funds for 2 years	24 months	$1.5M
• Phase I trial: safety 20-30 patients 3 months f/u	6 months	$2M
• Phase II trial: plaque size reduction/carotid duplex	12 months	$25M

200 patients with established CAD/stroke