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

- Apoe null mice
  - 0M HFD
  - 0.5M HFD
  - 1M HFD
  - 2M HFD
  - 3M HFD
  - 4M HFD
- Treated Apoe null mice
  - 0M HFD
  - 0.5M HFD
  - 1M HFD
  - 2M HFD
  - 3M HFD
  - 4M HFD

~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 FRS2\(\alpha\)/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
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