Discussant: RNAi therapeutics for lipid disorders

American Heart Association Scientific Sessions
Late Breaking Science VI:
New Frontiers in Lipid Therapy
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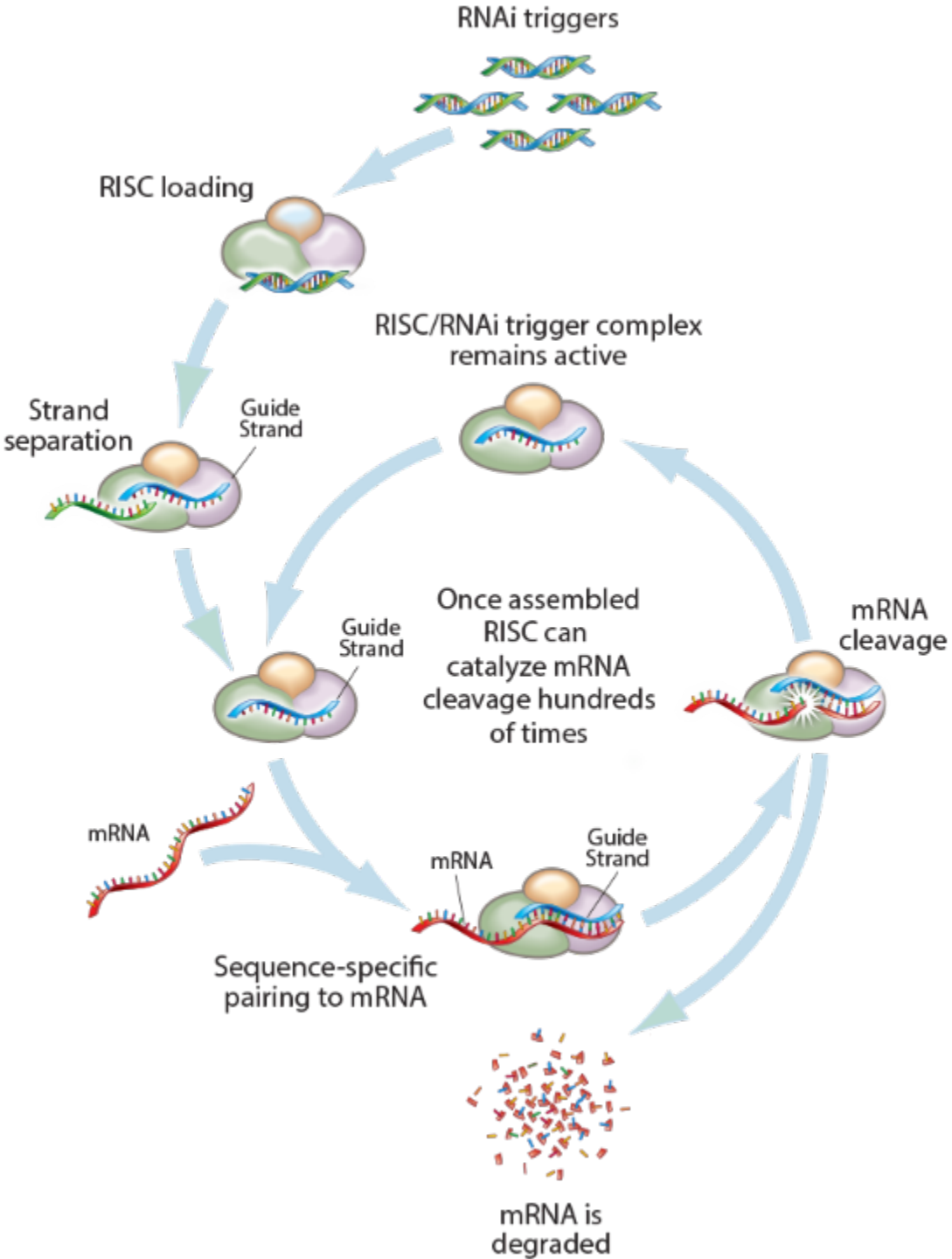
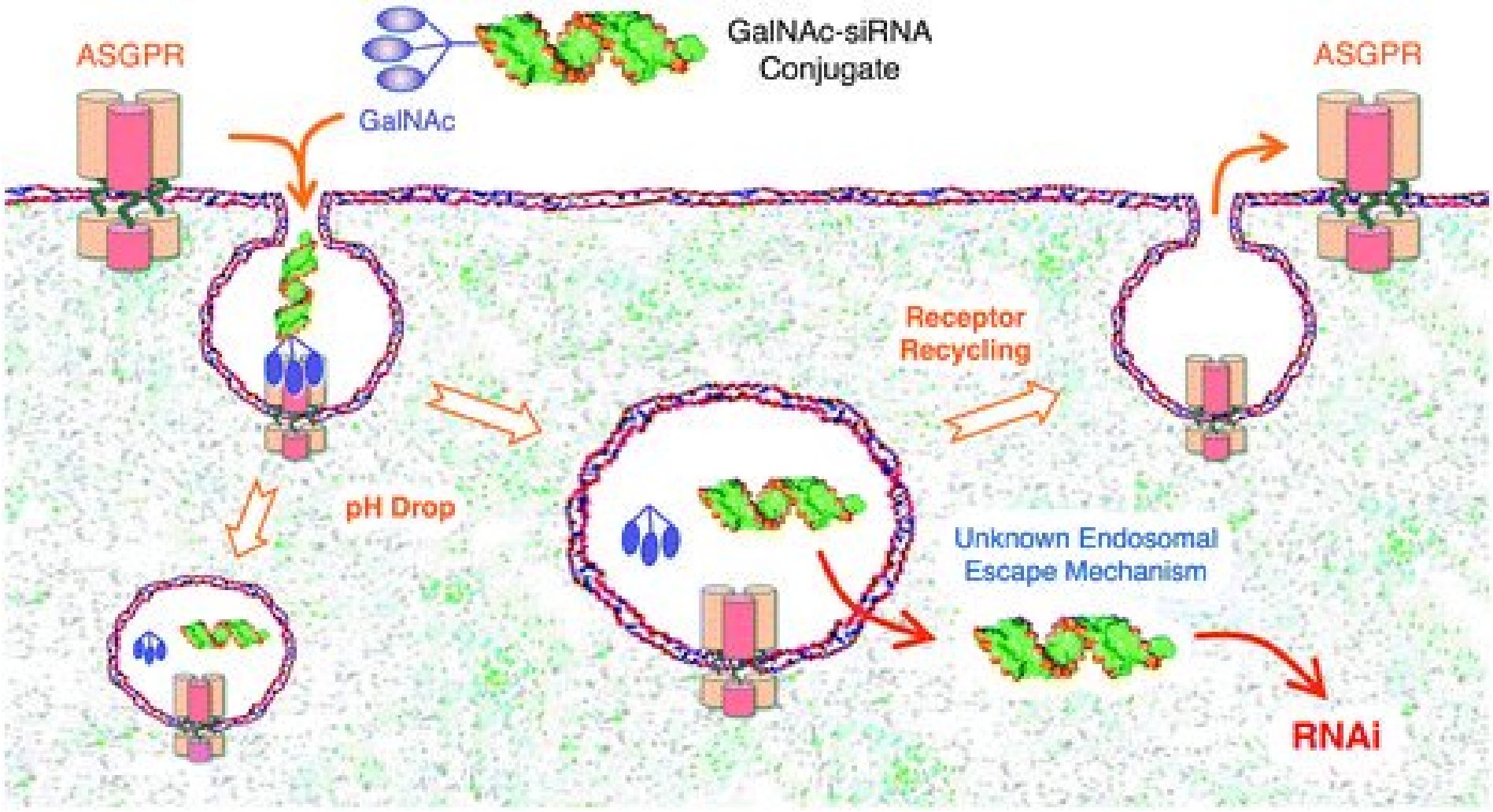
Disclosures

Consultant: Akcea, Alnylam, Novartis, Pfizer, Verve

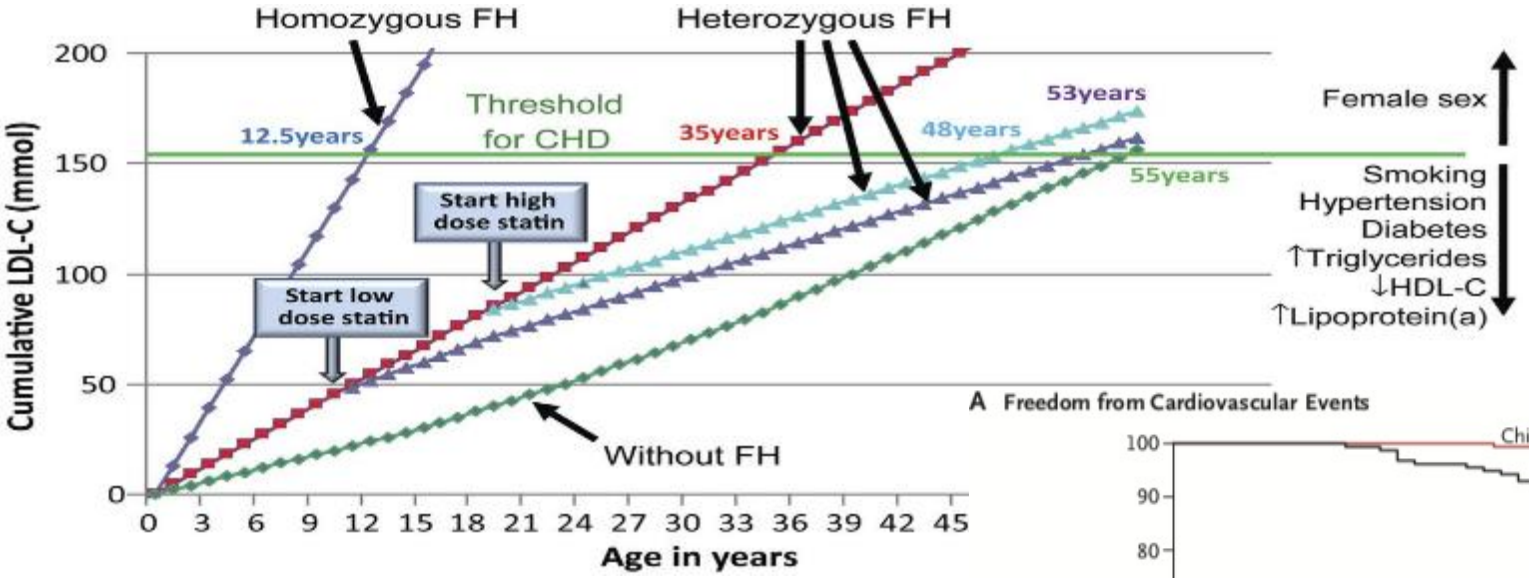
Co-Founder: Staten Biotech, VascularStrategies


RNAi triggers
RISC loading
RISC/RNAi trigger complex
remains active
Strand
separation
Guide
Strand
Guide
Strand
Once assembled
RISC can
catalyze mRNA
cleavage hundreds
of times
mRNA
cleavage
mRNA
mRNA
Guide
Strand
Sequence-specific
pairing to mRNA
mRNA is
degraded

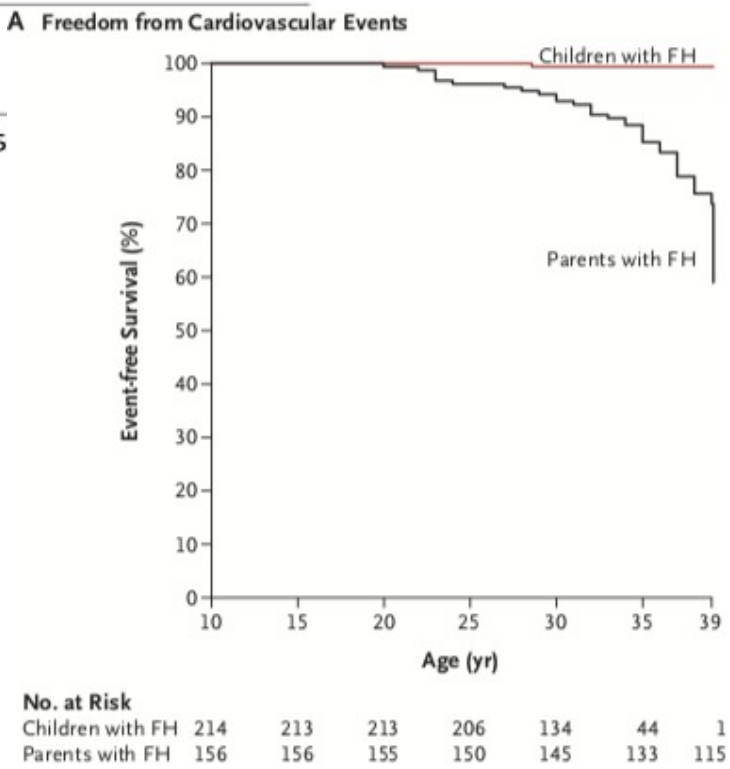
RNAi molecules conjugated to GalNAc specifically target the liver via the ASGPR



Familial hypercholesterolemia: lifelong exposure to high LDL causes early onset coronary disease and early treatment markedly reduces risk



Nordestgaard, et al. Eur Heart J 2013



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D., D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D., Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.

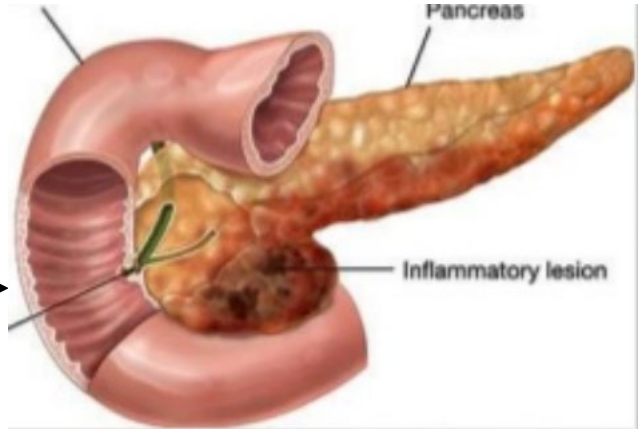
ORION 9: Inclisiran in heFH

- Effective (50% LDL-C reduction) in heFH when added to statin +/- ezetimibe with q 6 month SQ injection
- 18 month safety profile appears good

Questions:

- Effects on Lp(a)?
- Efficacy in hoFH?
- Safe in children with FH?

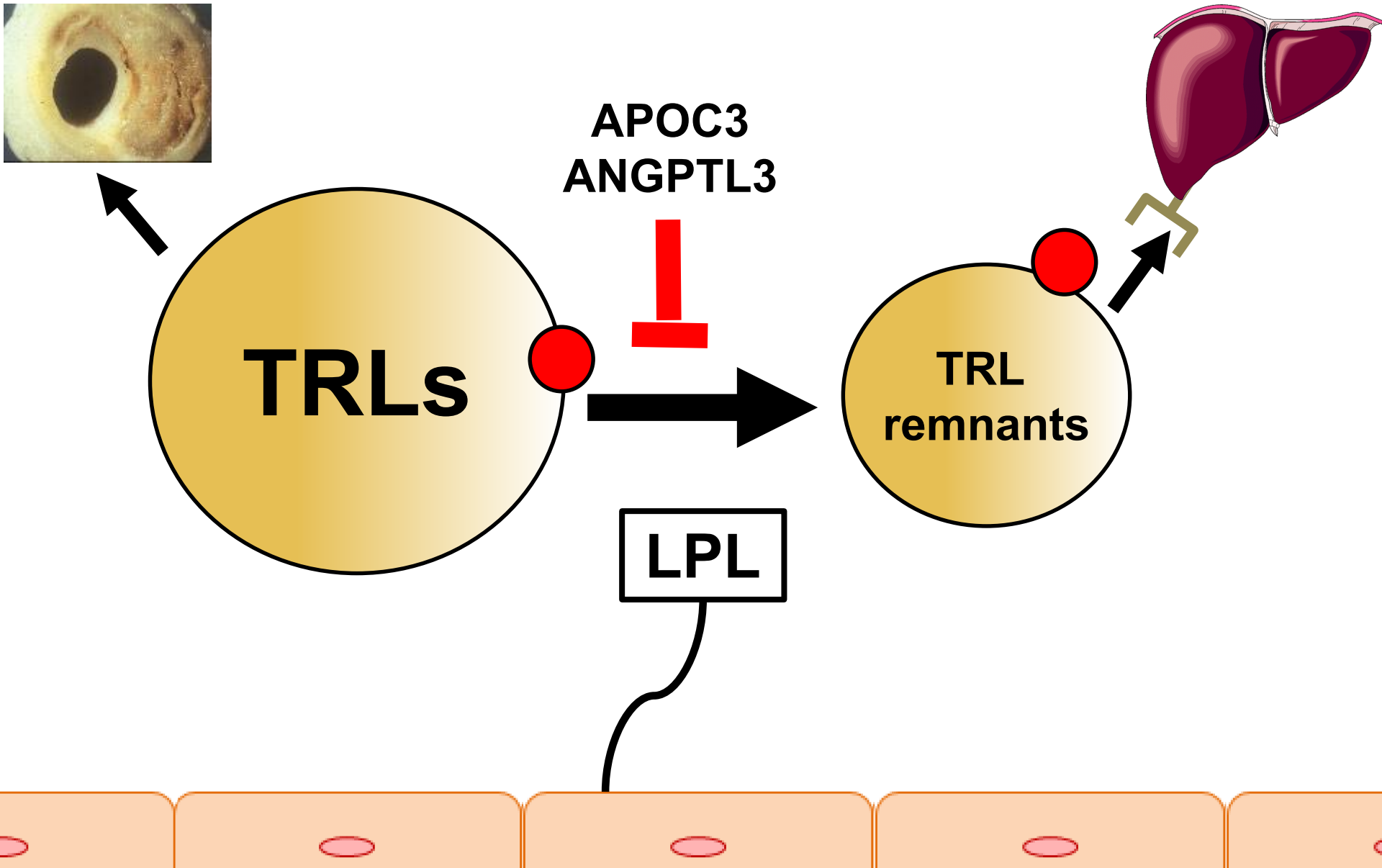
Consequences of hypertriglyceridemia and unmet medical need



B TG

TG-rich lipoproteins

APOC3 and ANGPTL3 are genetically validated targets for TG reduction and CAD risk reduction



Phase 1 single-dose studies of GalNAc-conjugated RNAi molecules targeted to APOC3 or ANGPTL3 in healthy volunteers

- Dose ranges 10-100 mg (APOC3) and 35-300 mg (ANGPTL3)
- Maximum target reduction 94% (APOC3) and 83% (ANGPTL3)
- Maximum TG reduction 64% (APOC3) and 66% (ANGPTL3)
- Stable reductions to 16 weeks after single dose
- More LDL-C reduction with ANGPTL3 than APOC3 silencing
- HDL-C increase with APOC3 and HDL-C decrease with ANGPTL3
- Safety profile appears to be acceptable after single dose

Questions:

- Which target is more likely to be efficacious in treating severe hypertriglyceridemia? In preventing major acute cardiovascular events?
- How frequently will these molecules need to be dosed?
- What is the role of intestinally-derived APOC3 that is not targeted?
- Is there a downside to the HDL-C reduction seen with ANGPTL3 silencing?
- How will RNAi approaches to these targets compare with antibody and ASO approaches?

Therapeutic targeting of dyslipidemia

Lipid-related targets

- PCSK9
- APOC3
- ANGPTL3
- ANGPTL4
- APOA

Targeting approaches

- Antibodies
- RNAi
- ASO
- Genome editing