Development of a Dual Functional RNAi Therapeutic, ARO-DIMER-PA, for Mixed Hyperlipidemia

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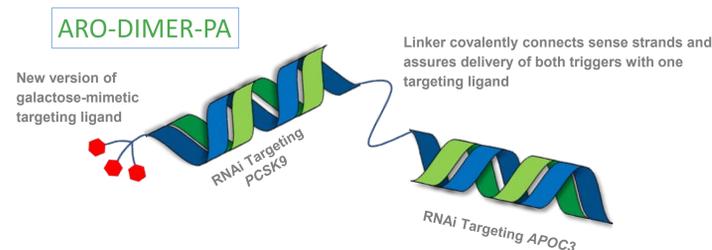
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BACKGROUND

- Mixed hyperlipidemia, characterized by hypercholesterolemia, hypertriglyceridemia, hyperlipoproteinemia B, and high rate of coronary artery disease, is the most common hereditary lipid disorder with a prevalence of about 1-2% in general population.
- RNAi therapeutics targeting *APOC3* and *PCSK9* have demonstrated their efficacy for hypertriglyceridemia and hypercholesterolemia separately in patients.
- A single RNAi molecule silencing both *PCSK9* and *APOC3* mRNA in liver could represent a desirable mono-therapeutic for mixed hyperlipidemia.

PURPOSE

- To evaluate the biodistribution, pharmacodynamics and pharmacological effects of the dual functional RNAi drug, ARO-DIMER-PA.

METHODS

ARO-DIMER-PA

New version of galactose-mimetic targeting ligand

Linker covalently connects sense strands and assures delivery of both triggers with one targeting ligand

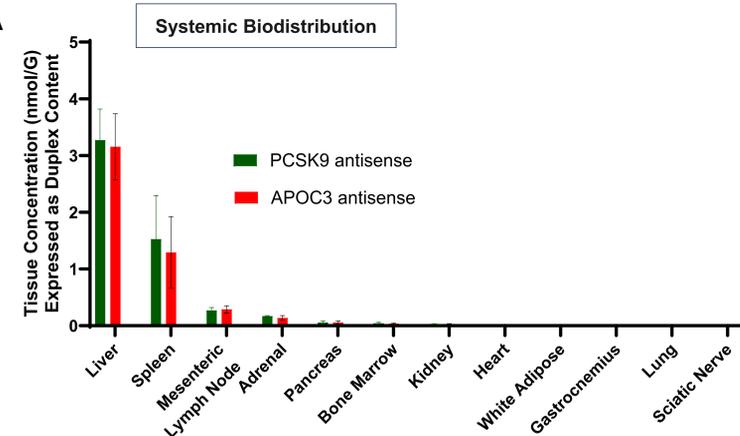RNAi Targeting PCSK9

RNAi Targeting APOC3

- ARO-DIMER-PA is a single RNAi molecule designed to silence both *PCSK9* and *APOC3* expression in hepatocytes.
- Biodistribution, pharmacodynamics and pharmacological effects of ARO-DIMER-PA were evaluated in spontaneously dyslipidemic cynomolgus monkeys.
- Tissue concentration of ARO-DIMER-PA was analyzed by LC-MS spectrometry.
- Circulating APOC3 and PCSK9 (ELISA), triglycerides, LDL-C, and total cholesterol were analyzed using respective available detection assays (Roche cobas).
- *In situ* liver RNAi content was detected by microRNAscope (miRNAscope)

RESULTS

Figure 1: Biodistribution of ARO-DIMER-PA in cynomolgus monkeys

**A. Systemic distribution**
- ARO-DIMER-PA was administered via subcutaneous injection at 6 mg/kg
- Tissues/organs were collected on Day 29
- Tissue concentrations of ARO-DIMER-PA *PCSK9*- and *APOC3*-targeting antisense were measured using mass spectrometry
- After 29 days, ARO-DIMER-PA was primarily detected in liver (~30% of initial dose--<2% detected in all other tissues)
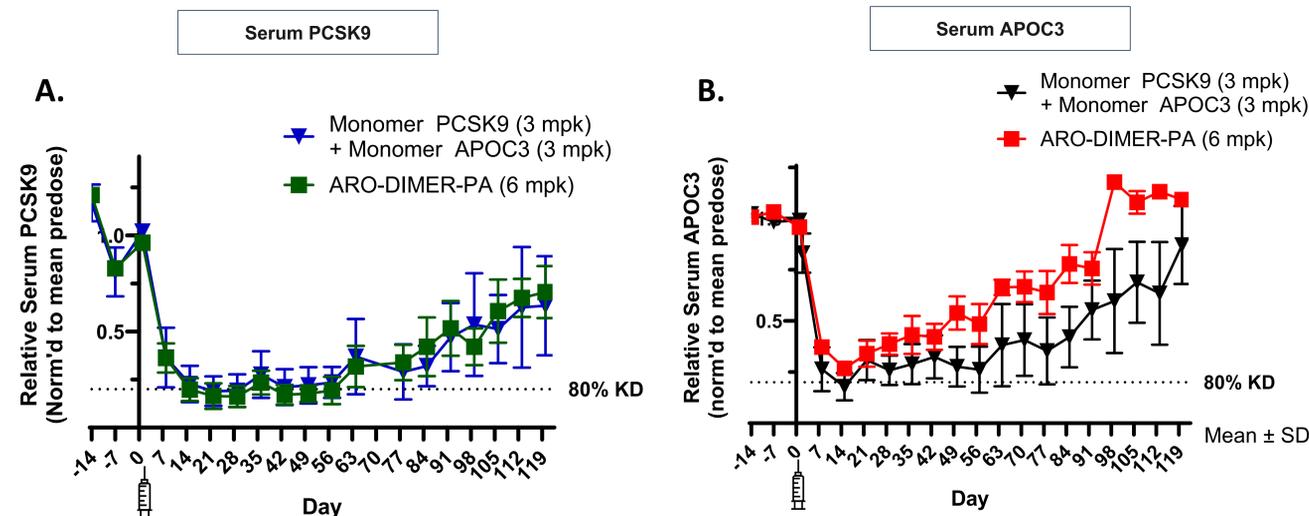

Systemic Biodistribution

B. Cellular distribution in liver
- Hepatic ARO-DIMER-PA was detected by miRNAscope
- Similar to monomer RNAi targeting *PCSK9*, ARO-DIMER-PA was primarily detected in hepatocytes.

Cellular Biodistribution in Liver

PCSK9 Monomer   ARO-DIMER-PA
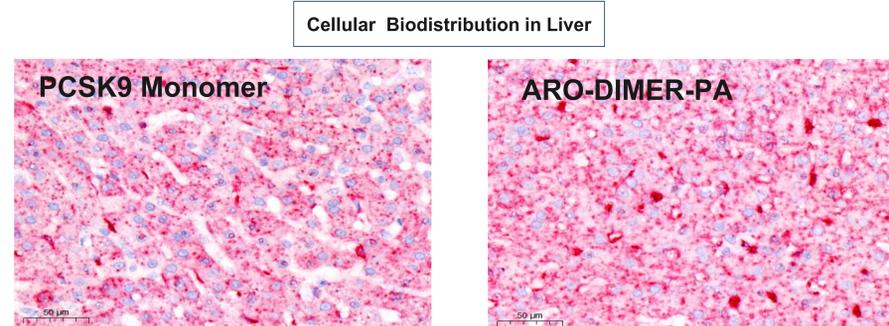
Figure 2: Potency similarity between ARO-DIMER-PA and equivalent monomeric RNAi therapeutics

- Cynomolgus monkeys were administered ARO-DIMER-PA via subcutaneous injection on D1 at 6 mg/kg
- ARO-DIMER-PA exhibited similar potency in lowering serum PCSK9 (**A**) and APOC3 levels (**B**), respectively, when compared to equivalent monomeric therapeutics (targeting only *PSCK9* or *APOC3)*.

Serum PCSK9

Serum APOC3

A.
Monomer PCSK9 (3 mpk) + Monomer APOC3 (3 mpk)
ARO-DIMER-PA (6 mpk)

B.
Monomer PCSK9 (3 mpk) + Monomer APOC3 (3 mpk)
ARO-DIMER-PA (6 mpk)

Figure 3: Pharmacologic effects of ARO-DIMER-PA lowering lipids in dyslipidemic Cynomolgus Monkeys

A. Non-HDL Cholesterol — Mean ± SEM

B. LDL Cholesterol
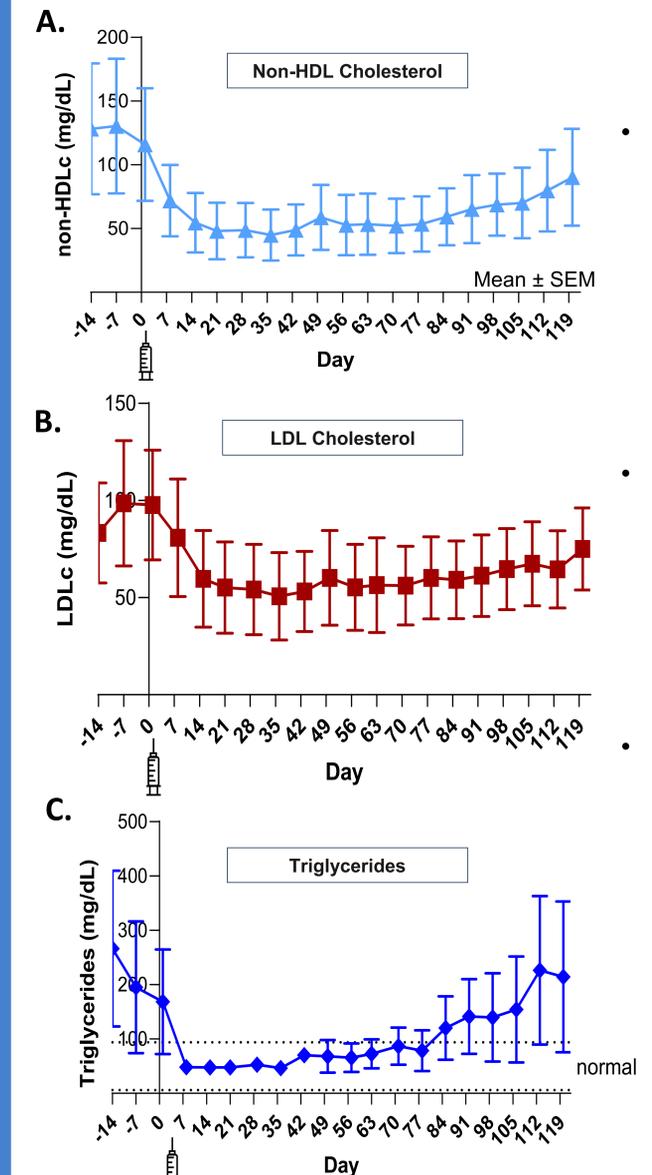
C. Triglycerides

- Spontaneously dyslipidemic monkeys were identified and administered a single 6 mg/kg subcutaneous dose of ARO-DIMER-PA on D1
- A single dose of ARO-DIMER_PA was sufficient to reduce non-HDL cholesterol (**A**), LDL cholesterol (**B**) and triglyceride levels by ~ 50% (**C**).
- Duration of PCSK9 and APOC3 decreases (Figure 2) are consistent with that of lipid lowering

CONCLUSION

- ARO-DIMER-PA, a single RNAi molecule designed to silence both *PCSK9* and *APOC3* in liver, potently lowers serum *PCSK9* and *APOC3,* and ameliorates high levels of non-HDLc, LDLc, and triglycerides in dyslipidemic nonhuman primates
- ARO-DIMER-PA holds great potential to be an effective therapeutic for mixed hyperlipidemia.