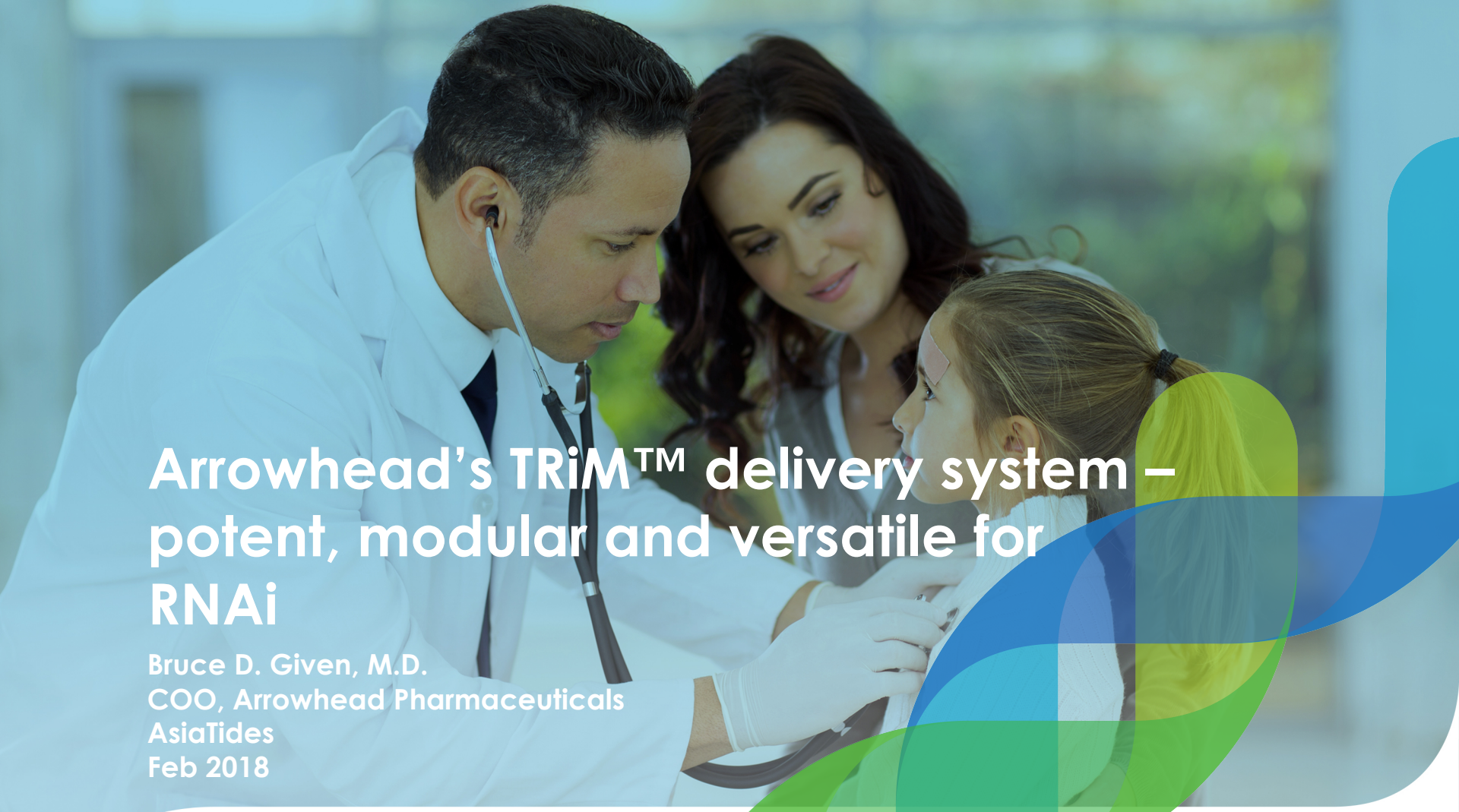

Arrowhead's TRiM™ delivery system – potent, modular and versatile for RNAi

Bruce D. Given, M.D.
COO, Arrowhead Pharmaceuticals
AsiaTides
Feb 2018

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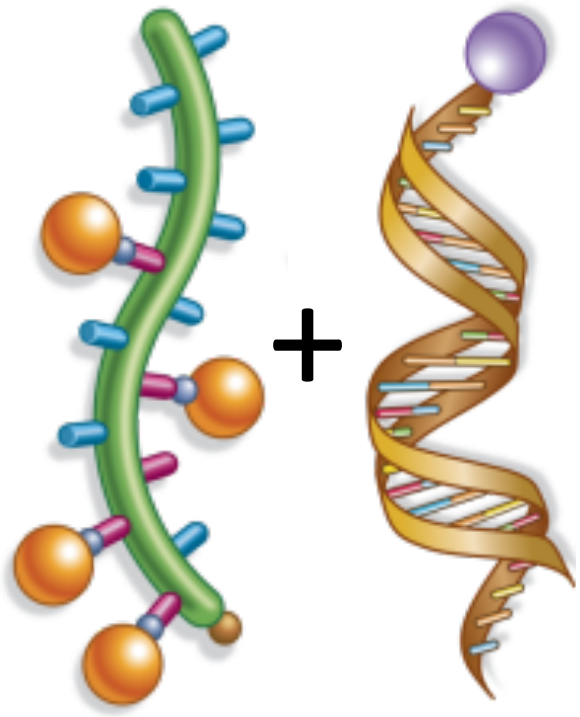
pharmaceuticals

Arrowhead Pharmaceuticals

- Company focused on developing siRNA therapeutics
- Working in RNAi for over 15 years
- Exclusively focused in RNAi since 2011
- Worked with multiple delivery systems
  - Polymer nanoparticles
  - Liposomes
  - Dynamic Polyconjugates (DPCs)™
  - NAG targeted conjugates
  - Conjugates targeting extra-hepatic tissues

Dynamic Polyconjugates

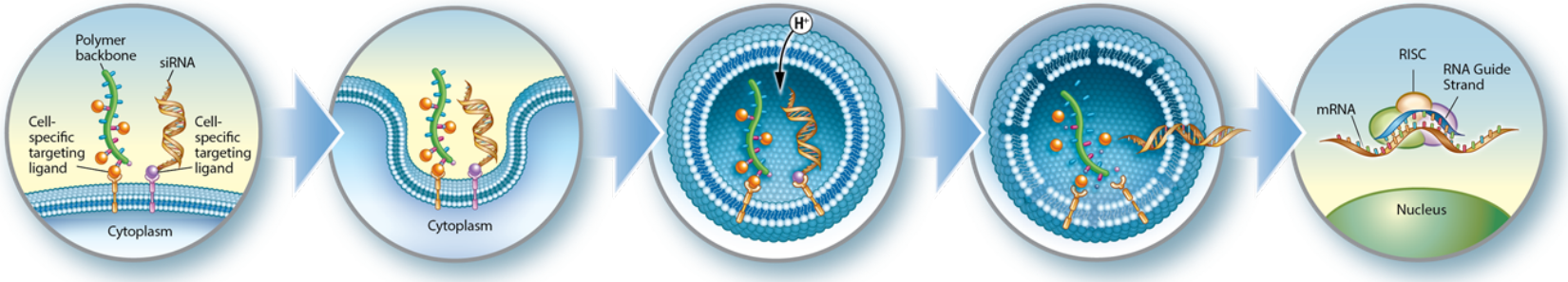


DPC (EX-1) and
cholesterol-linked RNAi trigger

DPC™ system consists of:

- Vial 1: DPC Polymer
- Vial 2: liver targeted siRNA
- Mixed in pharmacy and co-administered via IV infusion

Mechanism of DPC™-mediated siRNA delivery to cells



DPC™ peptide and RNAi trigger attach to their respective cell surface targets

DPC™ peptide and RNAi trigger are internalized

DPC™ peptide and RNAi trigger are enclosed in endosomes. Low pH results in peptide unmasking

DPC™ peptide promotes endosomal escape of RNAi trigger into cell cytoplasm

RNAi trigger engages the cell's interference machinery, resulting in knockdown of target gene expression

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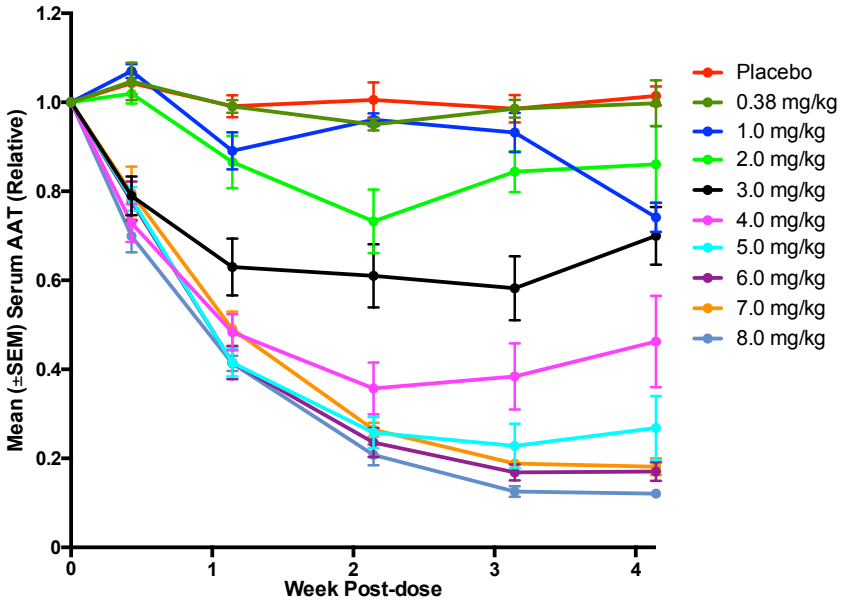
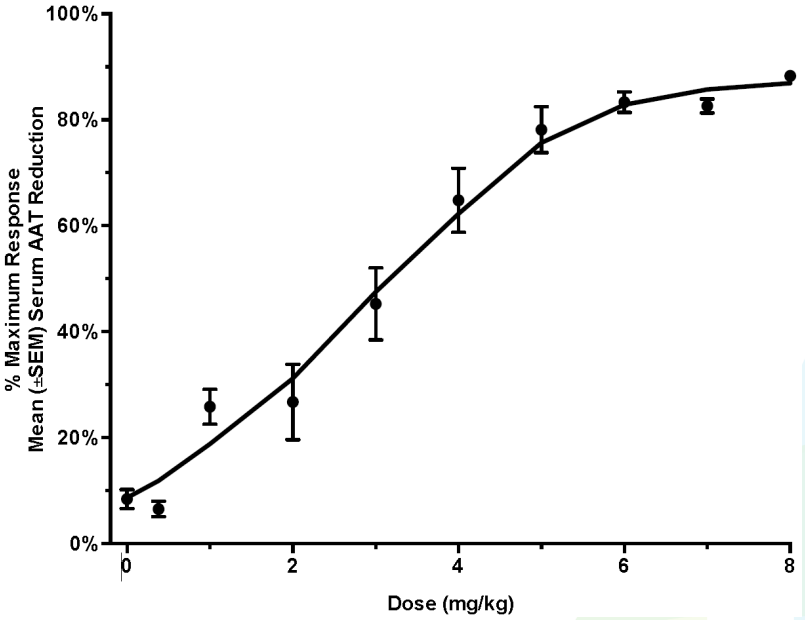
ARC-AAT: Phase 1 Healthy Volunteer AAT Levels





Dose Level (mg/kg)	PBO (n=18)	0.38 (n=4)	1 (n=4)	2 (n=4)	3 (n=4)	4 (n=4)	5 (n=4)	6 (n=4)	7 (n=3)	8 (n=3)
Max KD	24.8%	9.3%	31.9%	36.3%	61.0%	76.1%	86.7%	87.1%	85.1%	89.8%
Mean Max	8.4%	6.6%	25.9%	26.7%	45.3%	64.8%	78.1%	83.3%	82.6%	88.3%
P value	N/A	0.6363	0.0004	0.0014	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

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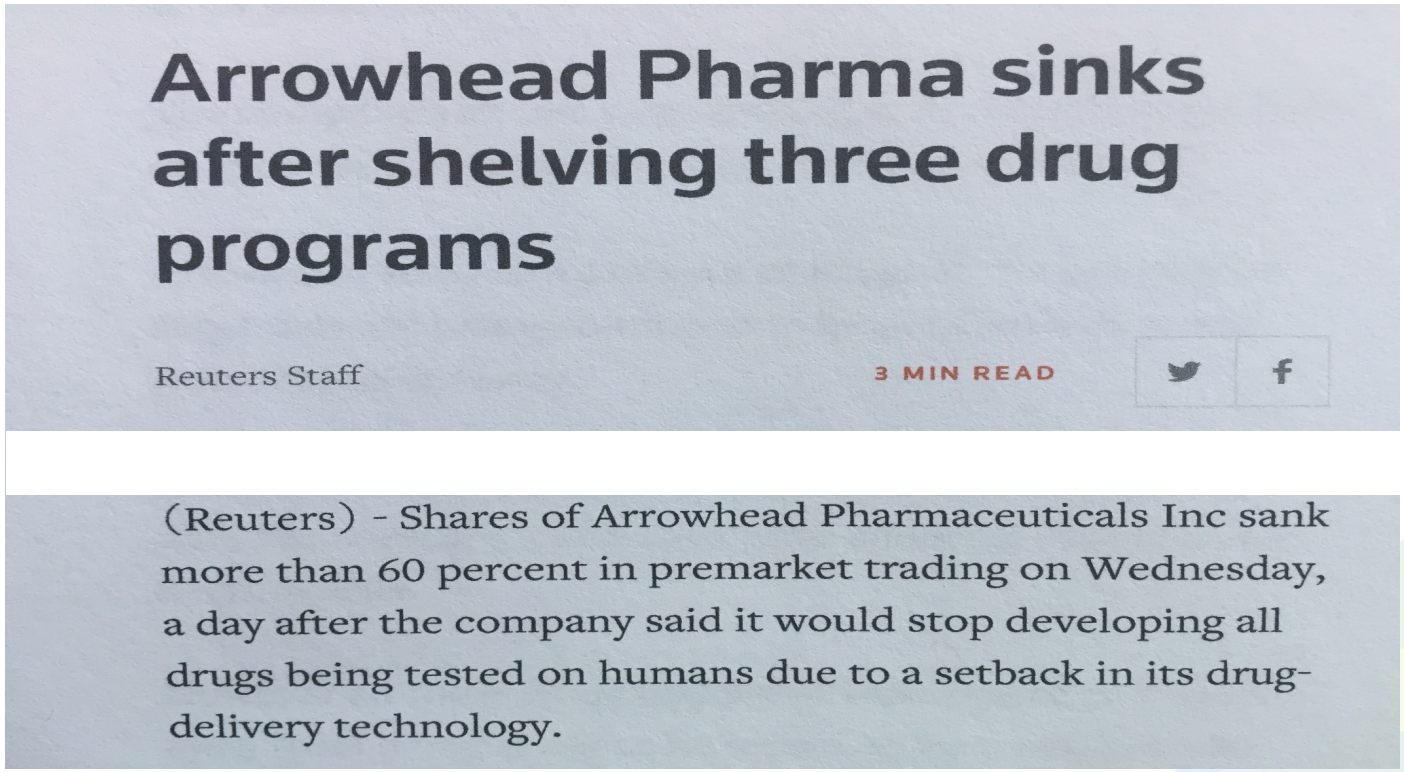
DPCs Found to Produce Toxicity in NHPs



Arrowhead Pharma sinks after shelving three drug programs

Reuters Staff

3 MIN READ

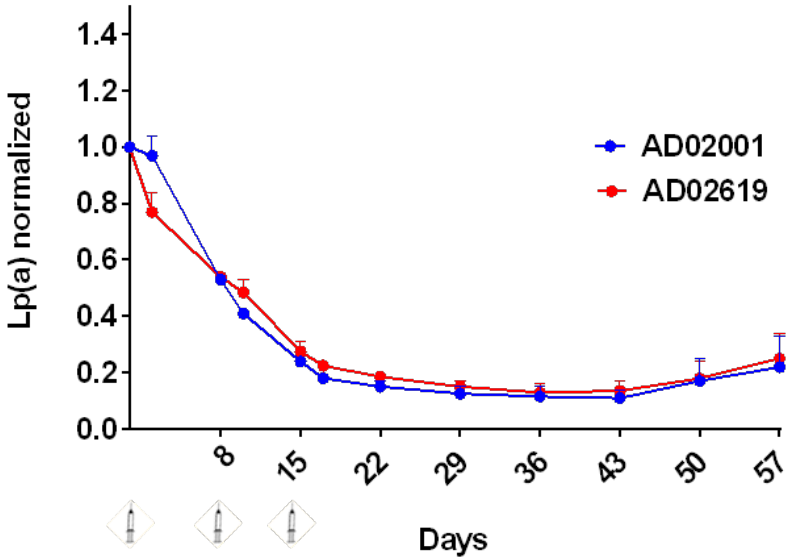
(Reuters) - Shares of Arrowhead Pharmaceuticals Inc sank more than 60 percent in premarket trading on Wednesday, a day after the company said it would stop developing all drugs being tested on humans due to a setback in its drug-delivery technology.

The Painful Learnings

- RNAi happens in the cytoplasm and triggers require extensive modification to get there unaided
  - Early emphasis on delivery platforms
  - Several promising programs lost to delivery-related toxicities
  - Polymer, nanoparticle, LNP etc. . . delivery systems all have toxicity issues
- Delivery vehicle toxicity eliminated with conjugates
  - Assumes chemistries around ligands, linkers and RNA stabilization don't create new issues
- Does not eliminate typical small molecule drug concerns
  - Off-target toxicity, target/biology risk, idiosyncratic reactions (e.g. DILI), etc.
  - Specific tissue targeting may reduce risk

TRiM™ Platform Enables Amgen Partnership

Three weekly 3 mg/kg SQ RNAi trigger doses (3xqw), n=2/group

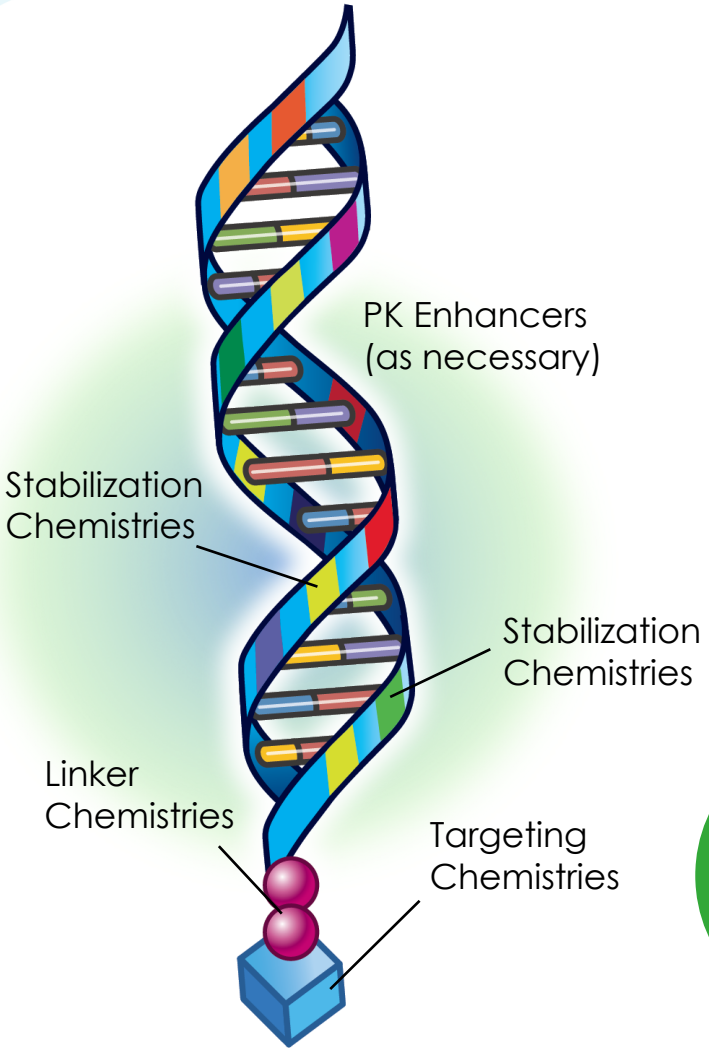


American Heart Association. life is why™ | SCIENTIFIC SESSIONS

Targeting apolipoprotein(a) with a novel RNAi delivery platform as a prophylactic treatment to reduce risk of cardiovascular events in individuals with elevated lipoprotein(a)

Amgen strikes $674M cardiovascular RNAi pact with Arrowhead

TRiM™: Simplicity, Specificity, and Activity



Components:

- Stabilization chemistries
- pk enhancers as necessary
- Linker chemistries
- Targeting ligands

Now capable of achieving deep KD in diverse tissues using subQ, iv, and inhaled administration routes
Without active endosomal escape

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ARO-AAT/ARO-HBV: Key Design Elements Expected for the Next Generation

Check List:

Subcutaneous dosing, monthly or less frequent

No need for endosomal escape agent

Full suppression of liver AAT production (ARO-AAT)

Coverage of full HBV transcriptome (ARO-HBV)

Expectation of wide therapeutic index

ARO-AAT/ARO-HBV: Key Design Elements Expected for the Next Generation

Check List:

- ✓ Subcutaneous dosing, monthly or less frequent
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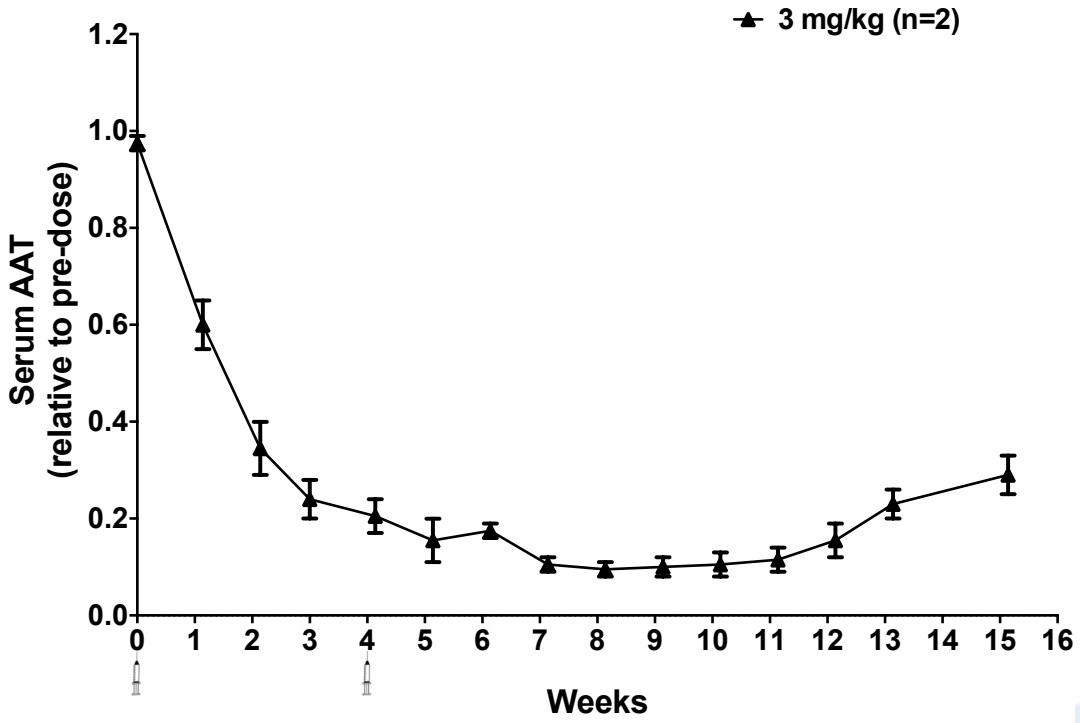
- ✓ Full suppression of liver AAT production (ARO-AAT)
- ✓ Coverage of full HBV transcriptome (ARO-HBV)
- ✓ Expectation of wide therapeutic index

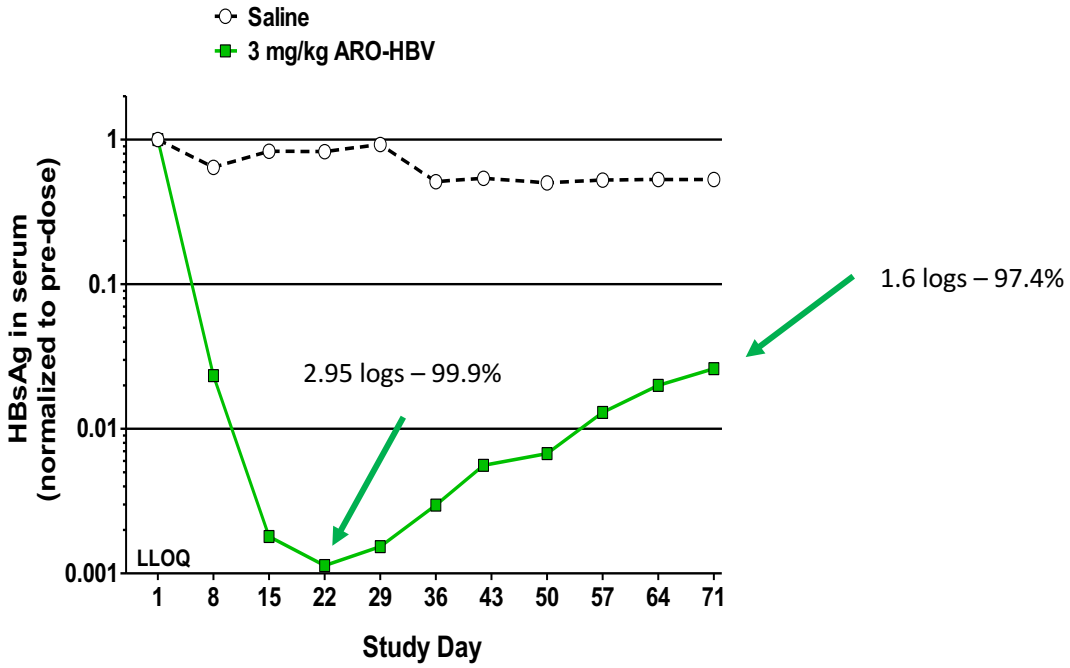
ARO-AAT Provides Durable AAT knockdown: Multi-dose in NHP, dosed subcutaneously

- 92% maximum serum AAT knockdown achieved
- Knockdown sustained for 7+ weeks following second dose



Durable knockdown supports once monthly or less frequent dosing

Integration Modeled in a New, Mutated pHBV Transfected Mouse



HBsAg knockdown is deep and prolonged despite loss of HBx-trigger site

Preliminary Safety Evaluation (non-GLP)

Based on clinical observations, clinical pathology and histopathology evaluations, ARO-HBV and ARO-AAT were well tolerated in repeated dose studies in rats and monkeys administered 3 weekly subcutaneous doses at dose levels of 30, 60, 120, and 300 mg/kg.

Expect wide safety margin

ARO-HBV and ARO-AAT poised to enter the clinic

Dec 22, 2017

Arrowhead Pharmaceuticals Files for Regulatory Clearance to Begin Phase 1/2 Study of ARO-HBV

Dec 20, 2017

Arrowhead Pharmaceuticals Files for Regulatory Clearance to Begin Phase 1 Study of ARO-AAT

Building Out CV Portfolio Using TRiM™ platform

Already building candidates for Lp(a) and Gene X with Amgen,
Now adding as wholly-owned assets:

ARO-APOC3

- For treatment of hypertriglyceridemia
- Up to 90% KD in TG rodent models (intestines also a source of production)
- SubQ administration
- NHP work and non-GLP tox studies to follow

CTA planned in Q4 2018

ARO-ANG3 (against ANGPTL3)

- For treatment of hypertriglyceridemia/dyslipidemia
- >90% KD in rodent models with several good triggers
- SubQ administration
- Still optimizing chemistries
- NHP work and non-GLP tox studies to follow

CTA planned in Q4 2018

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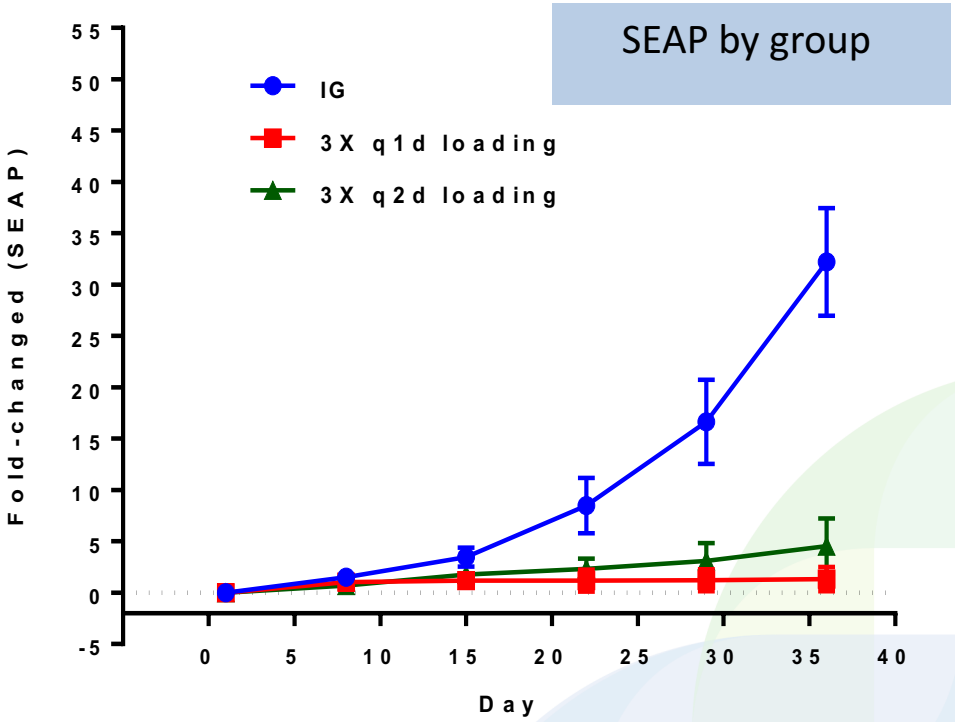
The Next Frontier - Extra-hepatic Delivery

- Why the hepatocyte space is crowded
  - ASGPR receptor is very high density
  - It is a clearance receptor with low stringency and rapid cycling
  - In a organ designed for high clearance
- Reciprocal challenges outside of the liver
  - Receptor density generally lower
  - Receptor stringency often higher
  - Internalization and recycling times differ
  - Cell availability to circulating molecules often less
- Implications - Every aspect has to be optimized
  - Need internalizing receptors of sufficient density
  - Highly optimized targeting ligands
  - Highly optimized RNAi triggers

Delivery and Efficacy in Renal Cell Carcinoma Mouse Model using TRiM™

ARO-Hif2

- Up to 85% KD
- iv or sq administration
- Tumor targeting



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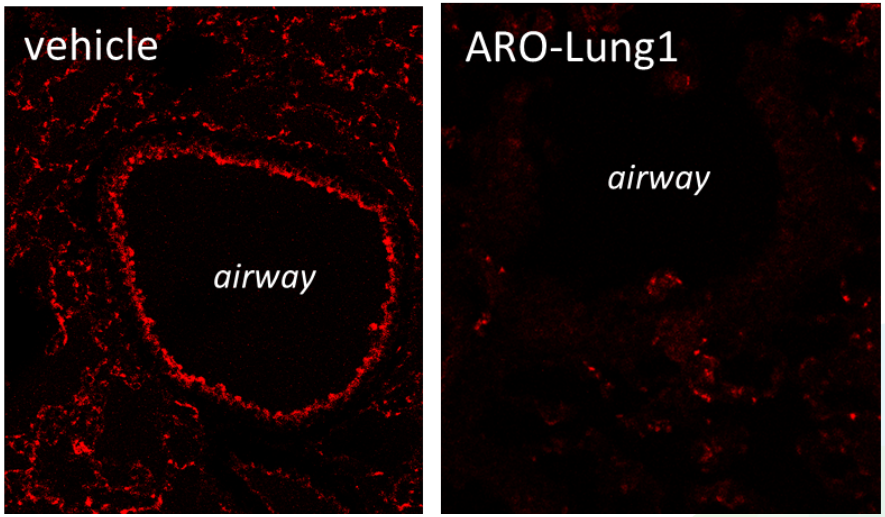
Targeting Lung Using TRiM™ Platform

ARO-Lung1

- Almost 90% KD in rodent models
- 30 day duration after single dose
- Inhaled administration
- Large animal studies and disease models underway
- Non-GLP tox studies underway

CTA planned in Q4 2018

Red: lung target protein expression by IHC



Arrowhead Pipeline

Drug	Indication	Pre-clinical	Pre-IND	Phase 1	Phase 2	Phase 3
ARO-AAT	Alpha-1 Antitrypsin Deficiency				FIH planned Q1 2018	
ARO-HBV	Hepatitis B				FIH planned Q1 2018	
ARO-APOC3	Hypertriglyceridemia			CTA planned Q4 2018		
ARO-ANG3	Hypertriglyceridemia			CTA planned Q4 2018		
ARO-Lung1	Undisclosed			CTA planned Q4 2018		
ARO-HIF2	Renal Cell Carcinoma			CTA planned 2019		
ARO-F12	Thrombosis/Hereditary Angioedema			Available for partnering		
ARO-LPA	Cardiovascular Disease				Partnered with Amgen	
ARO-AMG1	Cardiovascular Disease			Partnered with Amgen		

Conclusions

- Complex delivery systems often bring difficult safety issues in clinical use
- Direct conjugation has shown good performance for achieving RNAi activity in hepatocytes and can be expected to offer safety/tolerability
- With thoughtful target selection and appropriate SAR chemistry work, it is now feasible to move out of the liver and still achieve strong RNAi activity

Thank you !

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