History of RNAi Therapeutic Delivery at Arrowhead Pharmaceuticals

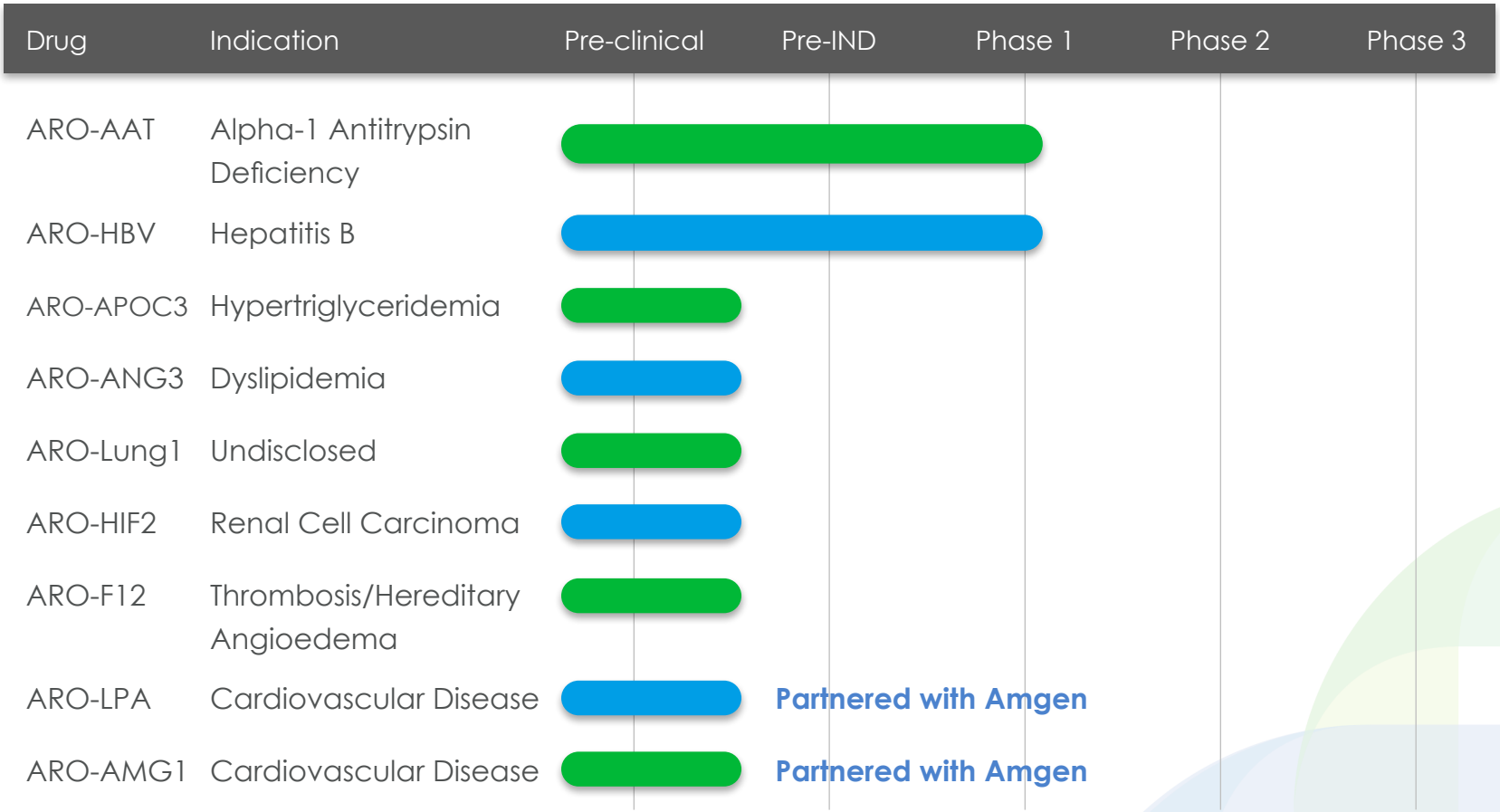
James C. Hamilton MD, MBA

2/22/2018

Arrowhead Pharmaceuticals

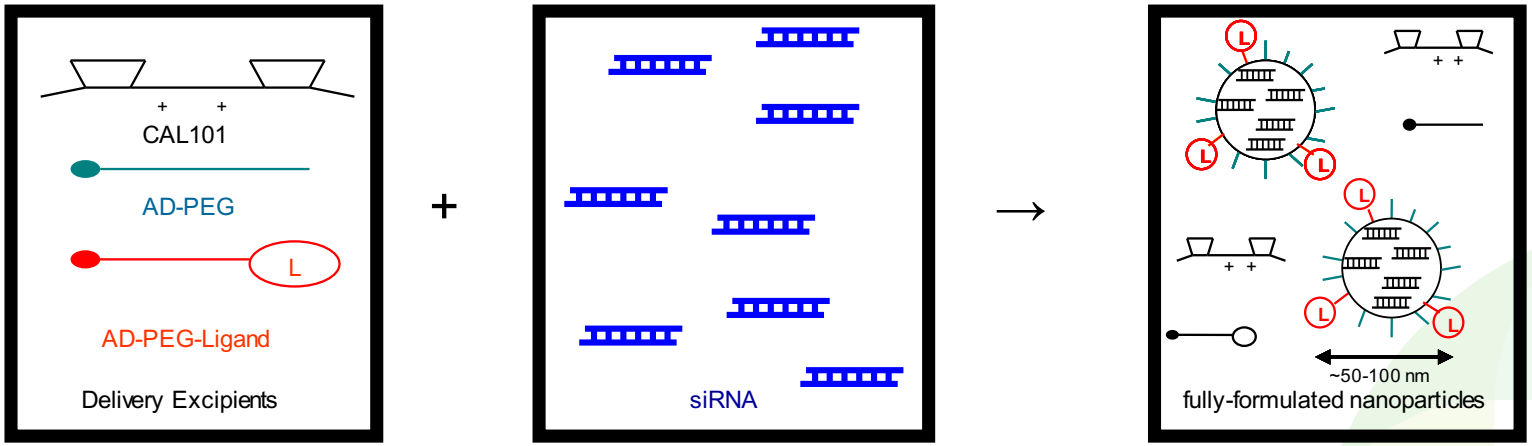
- Company focused on developing siRNA therapeutics
- Working in RNAi for over 15 years
- Exclusively focused in RNAi since 2011
- Worked with multiple delivery systems
  - Polymer nanoparticles
  - Liposomes
  - Dynamic Polyconjugates (DPCs)™
  - NAG targeted conjugates
  - Conjugates targeting extra-hepatic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

Pipeline: Using TRiM platform



Calando Pharmaceuticals: RONDEL

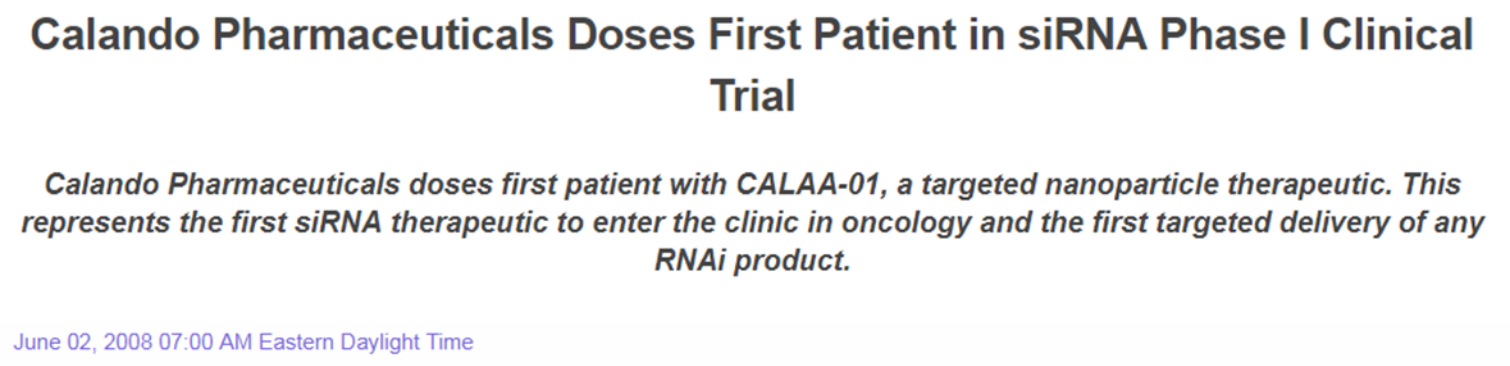
- Majority owned Arrowhead subsidiary
- Linear cyclodextrin polymers licensed from Caltech



Vial 1 **Vial 2** **Injectable Therapeutic**

Calando's "Two-Vial" System for RNAi Therapeutics

CALAA-01: an early siRNA clinical compound



Calando Pharmaceuticals Doses First Patient in siRNA Phase I Clinical Trial

Calando Pharmaceuticals doses first patient with CALAA-01, a targeted nanoparticle therapeutic. This represents the first siRNA therapeutic to enter the clinic in oncology and the first targeted delivery of any RNAi product.

June 02, 2008 07:00 AM Eastern Daylight Time

- Targeted M2 subunit of ribonucleotide reductase
- Completed Phase 1 MAD study in patients with solid tumors
- Several firsts for siRNA field:
  - First ligand targeted RNAi therapeutic
  - One of earliest siRNA drugs for use in oncology
  - One of first compounds to show RNAi effect in humans

CALAA-01 Phase 1 Clinical Trial

Vol 464|15 April 2010|doi:10.1038/nature08956 nature

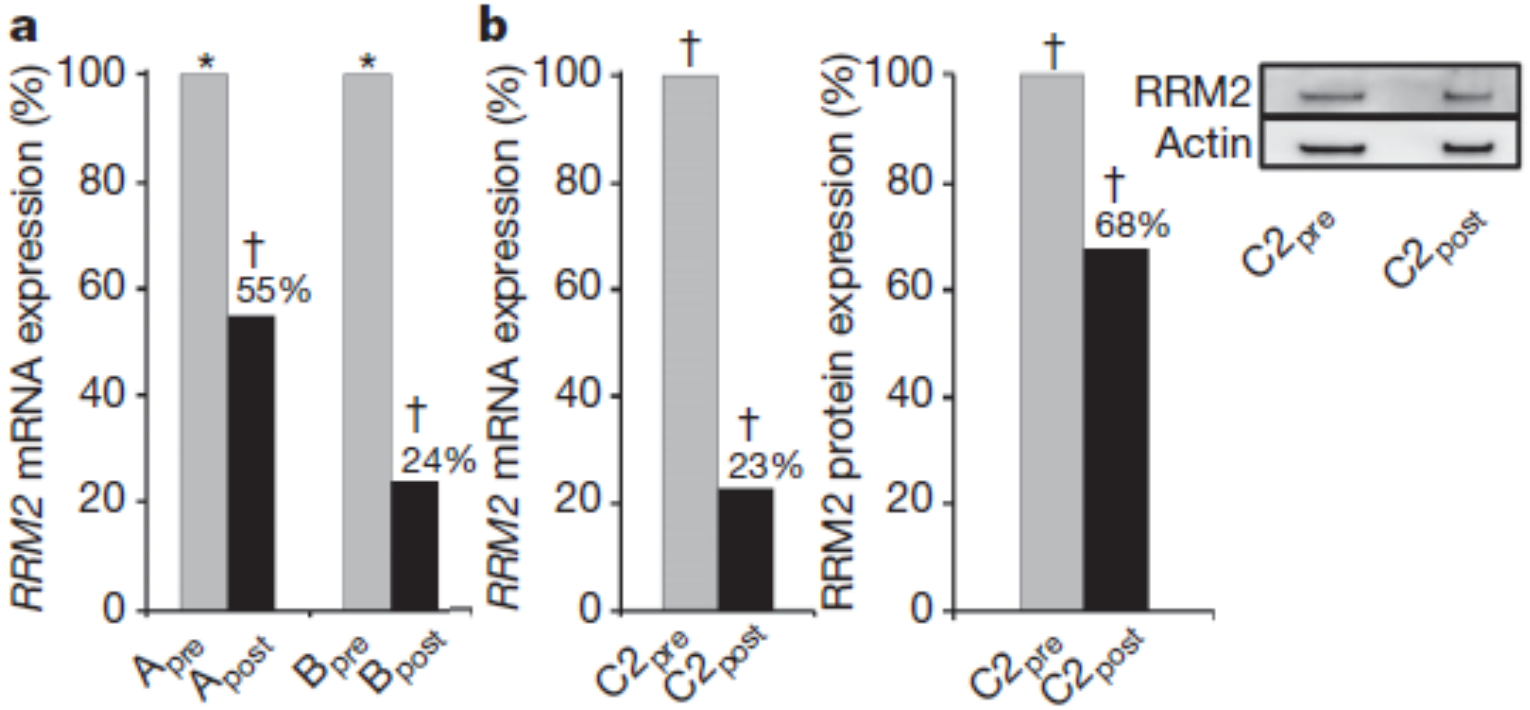
LETTERS

Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles

Mark E. Davis[1], Jonathan E. Zuckerman[1], Chung Hang J. Choi[1], David Seligson[2,3], Anthony Tolcher[5], Christopher A. Alabi[1]†, Yun Yen[6], Jeremy D. Heidel[7] & Antoni Ribas[2,4]

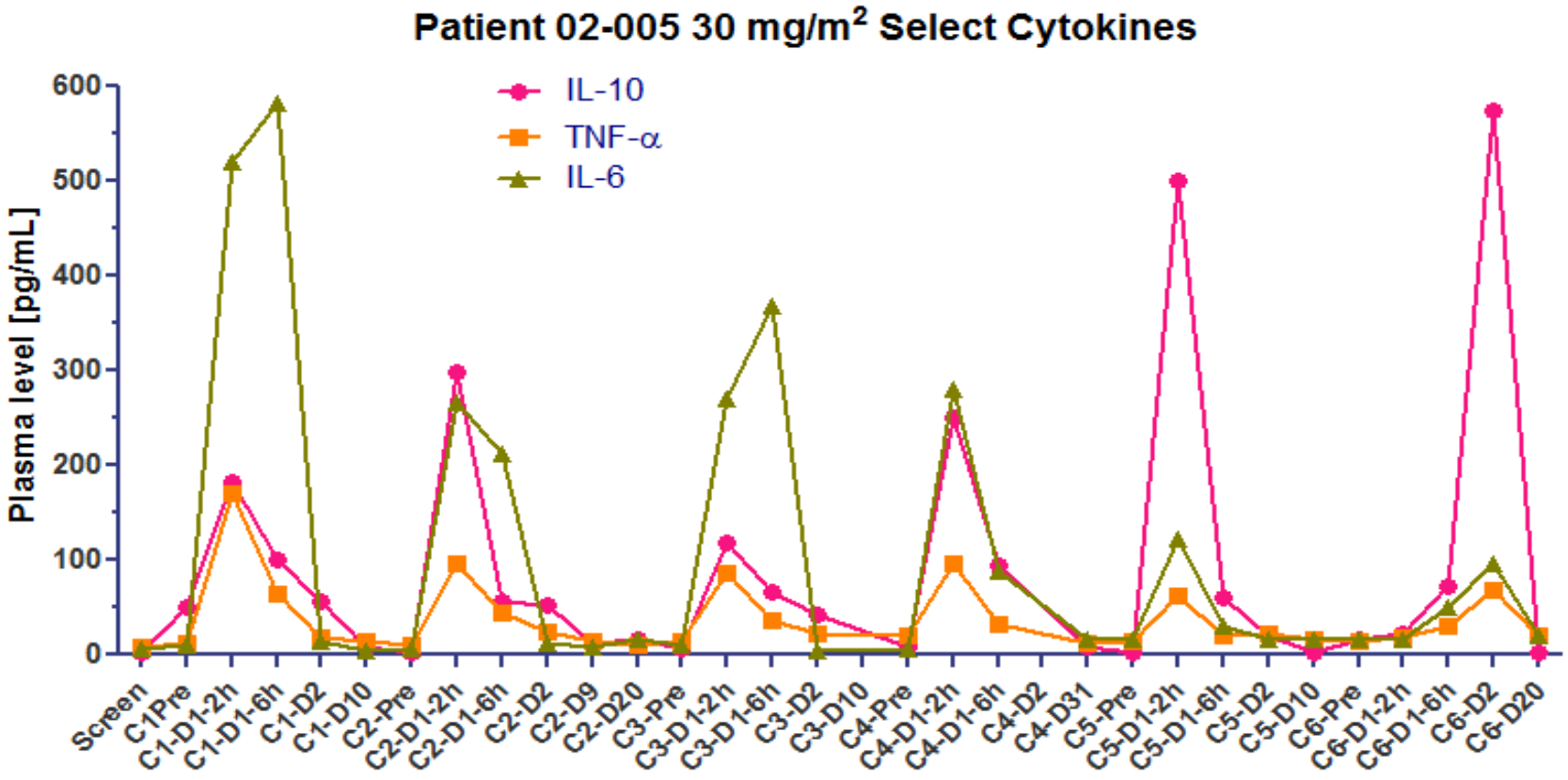
- 2010: Early evidence of RNAi in tumors in humans
- Tumor biopsies in melanoma patients performed pre-dose and post-treatment cycle showed:
  1. Dose dependent concentrations of nanoparticles
  2. Tumor RRM2 protein and mRNA reduction

CALAA-01 Phase 1 Clinical Trial



* Archived sample
† sample obtained during study

CALAA-01: Cytokine Release Ended the Program



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Transition to Dynamic Polyconjugates (DPCs)

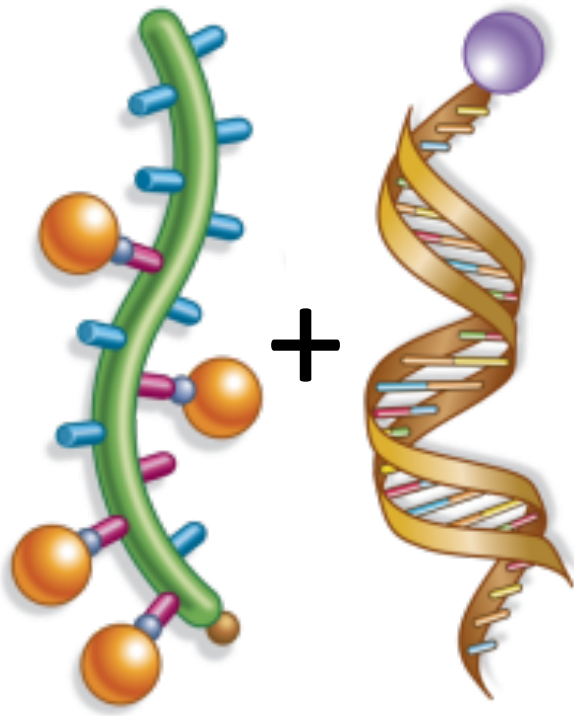
DPCs: Roche / Mirus Bio

Arrowhead Research Corporation Acquires Roche RNA Assets and Site

Three New Delivery Technologies, Broad RNAi IP, and Advanced Operations to Drive Clinical Development, Partnerships, and Revenue

Roche Takes Equity Stake in Arrowhead and Rights to Negotiate Future RNAi Candidates

Dynamic Polyconjugates

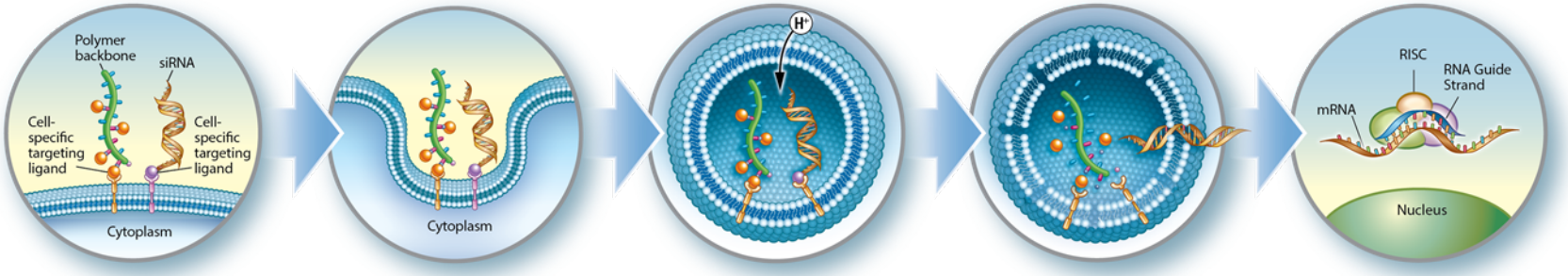


DPC (EX-1) and
cholesterol-linked RNAi trigger

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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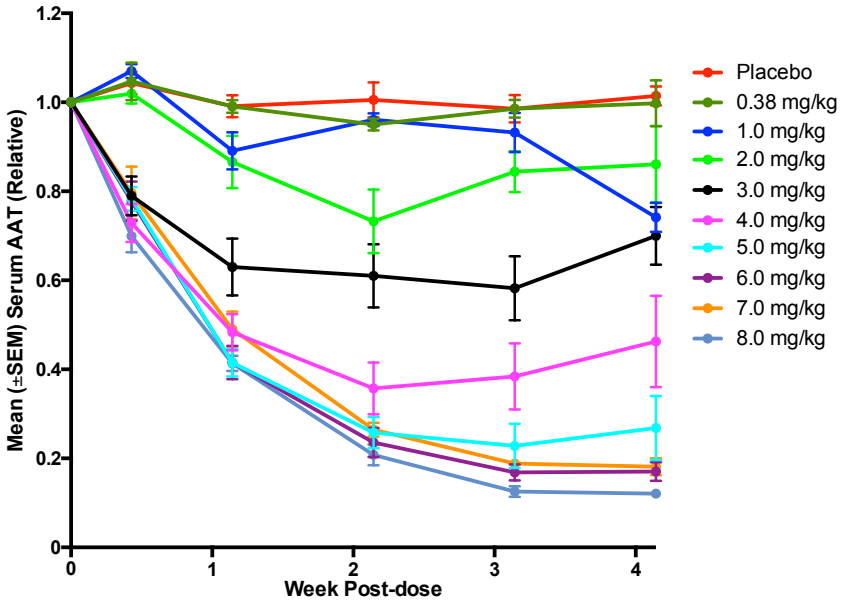
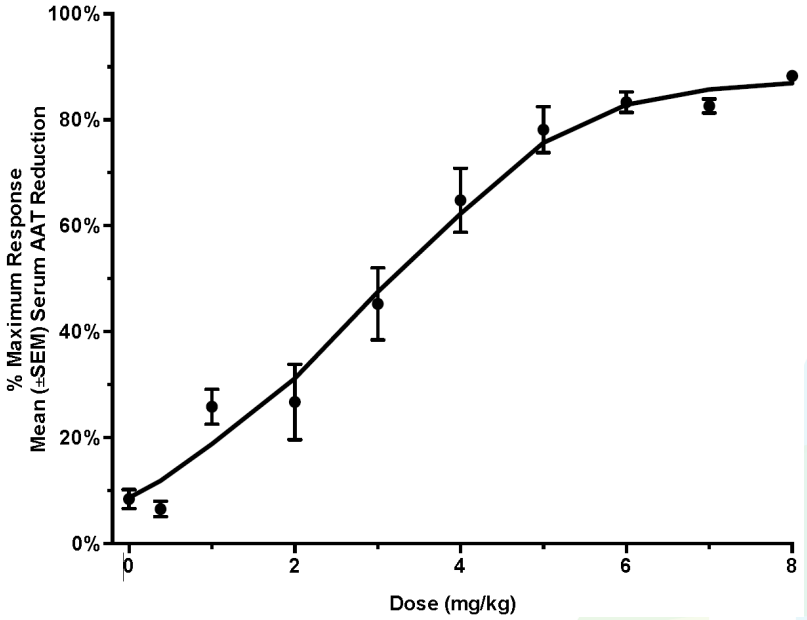
ARC-AAT: Phase 1 Healthy Volunteer AAT Levels





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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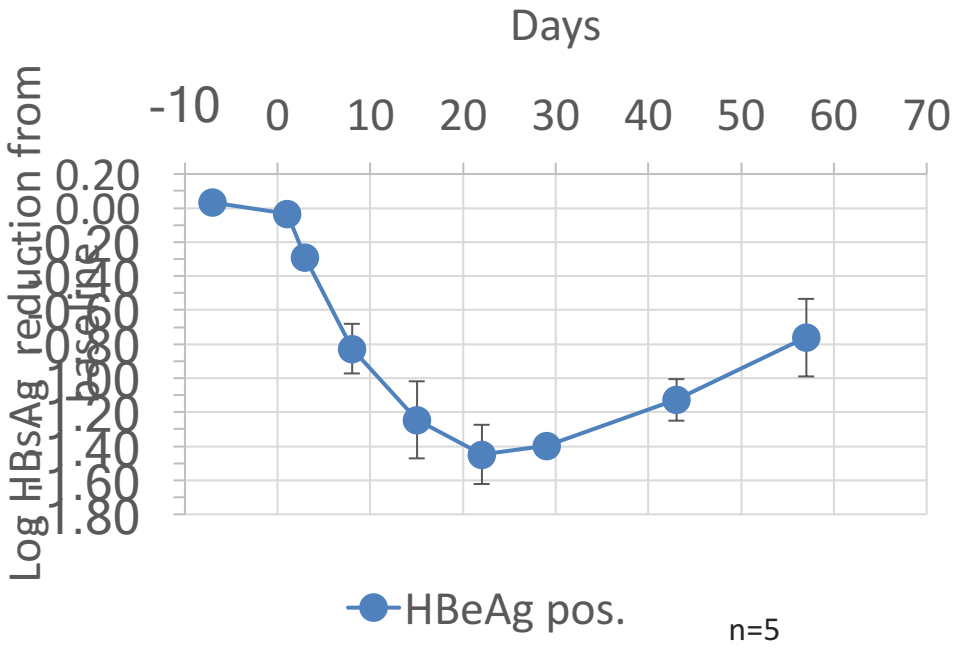
ARC-520 produces deep knockdown of Hepatitis B antigens



- Deep knockdown of HBsAg in HBeAg positive patients after a single dose

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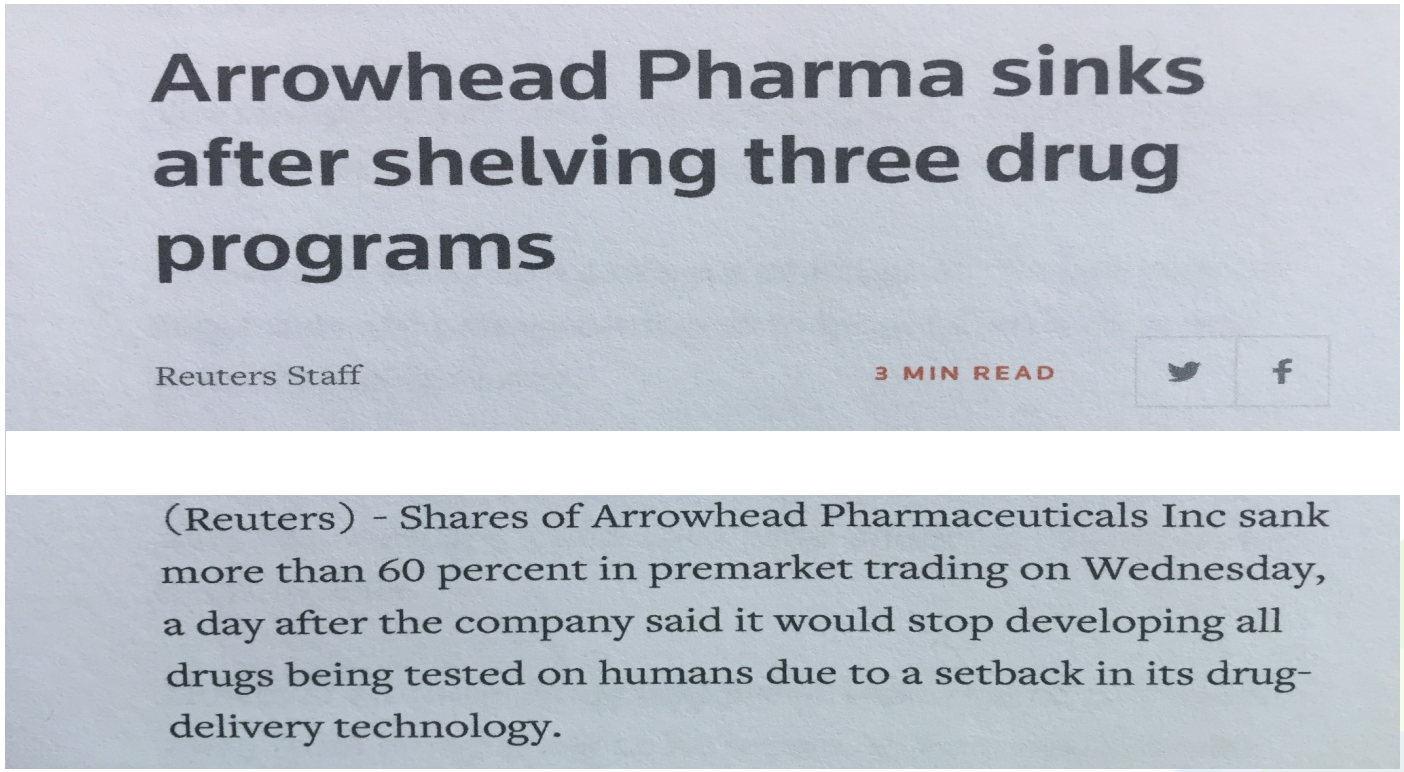
DPCs Found to Produce Toxicity in NHPs



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.

DPC toxicity in NHPs

- Monkey deaths seen at high doses in a chronic NHP toxicity study using ARC-521
  - Only in DPC arms, never with siRNA alone
- FDA informed, leading to U.S., and various ex-U.S. clinical holds
  - Hold was due to NHP toxicity, not due to safety findings in clinical trials
  - ARC-521/520/AAT all used DPCs, all programs impacted
- Given uncertainty around clinical hold and promise of TRiM platform, business decision made to focus limited resources on TRiM platform and discontinue DPCs.

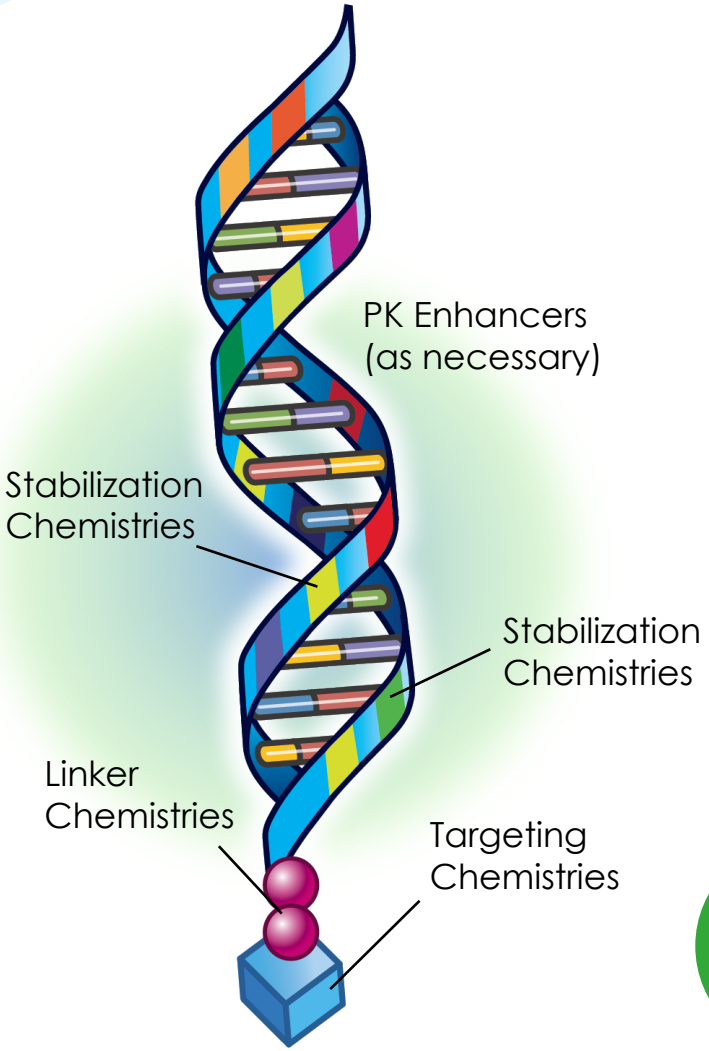
The Painful Learnings

- 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
  - Particulate, polymer, nanoparticle, LNP etc. . . delivery 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™: Simplicity, Specificity, and Activity



- Proprietary trigger selection technologies
  - Maximize activity and innate stability
- Stabilization chemistries
- 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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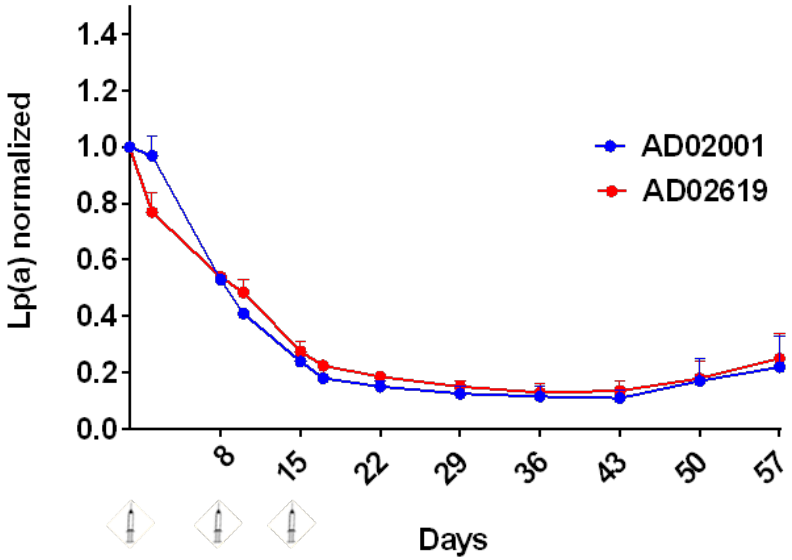
TRiM Platform Enables Amgen Partnership

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

ARO-HBV and ARO-AAT entering clinic Q1

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

ARO-AAT: Alpha-1 Antitrypsin Deficiency

- AATD is a large scale orphan disease
  - Alpha-1 foundation estimates ~100,000 in the US
  - Approximately 100,000+ in Europe
- Mutation in AAT gene (Z-AAT) leads to mis-folding of the protein and poor export from hepatocytes: low levels in circulation and accumulation in liver

Pathophysiology

Lung

Tissues susceptible to damage by neutrophil proteases: COPD

Treated with AAT protein replacement therapy today

Liver

Accumulation of mutant Z protein causes fibrosis/cirrhosis/HCC

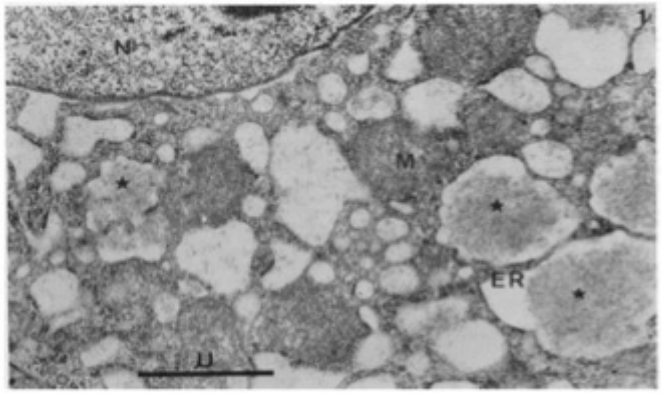
No current treatment

ARO-AAT Mechanism of Action

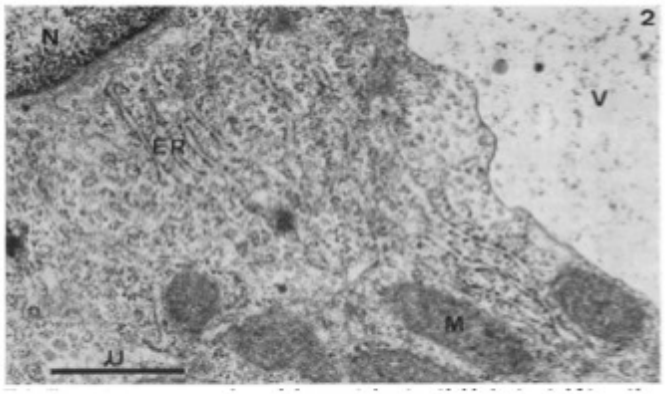
ARO-AAT designed to stop Z-AAT production by silencing AAT gene to:

- Prevent liver accumulation
- Allow clearance of accumulated protein
- Prevent cycles of cellular damage
- Prevent/Reverse progression of liver fibrosis

PiZZ phenotype (diseased)



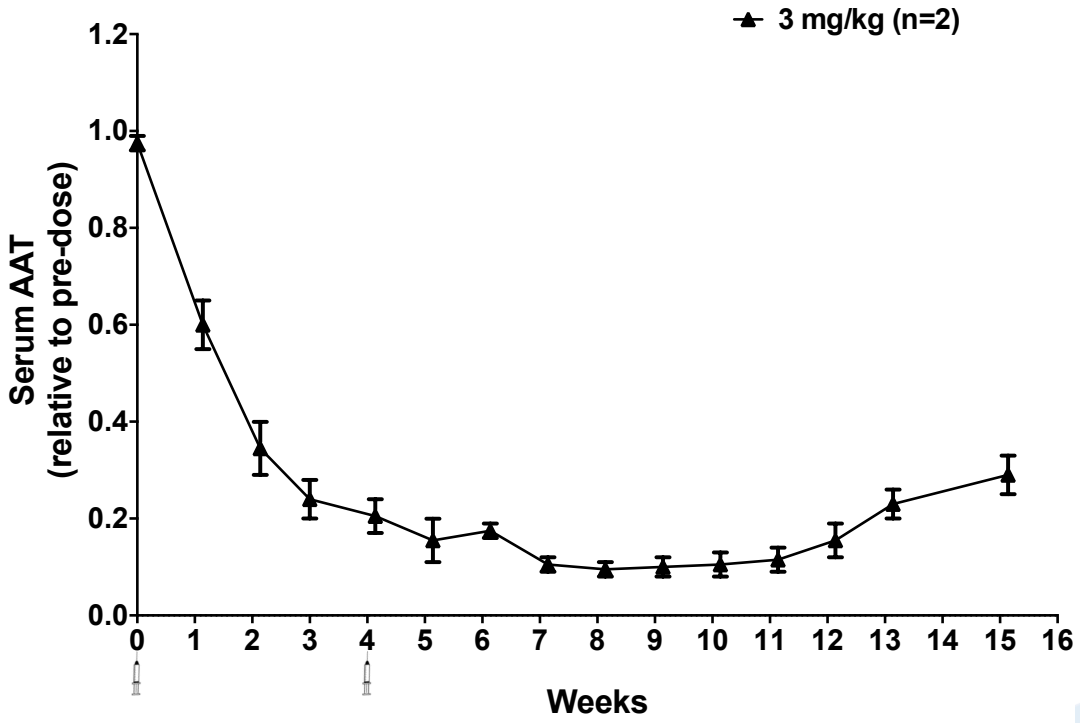
Pi null phenotype (normal liver)



Feldmann G et al., *Gut* 1975

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

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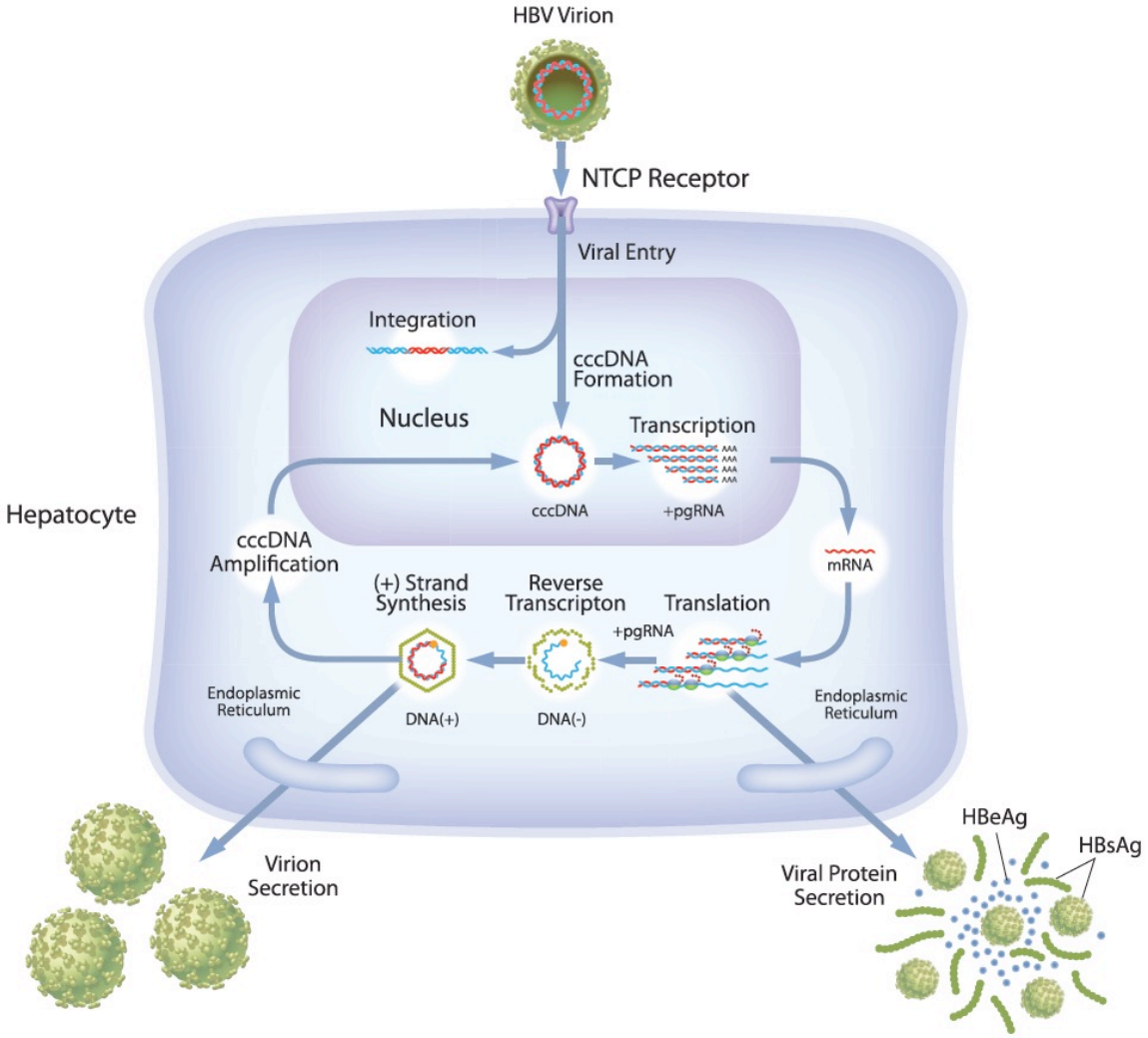
ARO-HBV: Hepatitis B Virus Life Cycle



- Immune suppression
- Liver cancer
- Cirrhosis
- Death

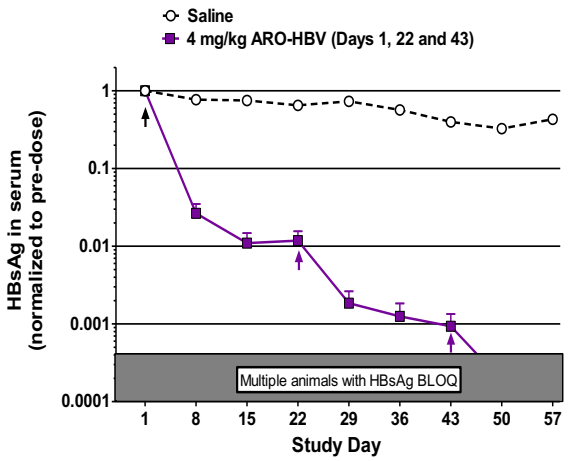
Why We see a Central Role for RNAi in HBV

- Attacks the entire transcriptome
  - Should synergize with **most/all** hepatocyte-active compounds (e.g. NUCs, capsid inhibitors, x protein drugs, RigI inhibitors, etc) by reducing their viral inputs
  - Can reduce HBsAg from integrated DNA, which other mechanisms likely can't
- Monthly (or less frequent) SQ dosing with unusually good tolerability should fit well with oral regimens
- ARC-520 data suggests that immune recovery and control is possible

Lessons from 9 clinical studies of ARC-520/521 inform development path of ARO-HBV

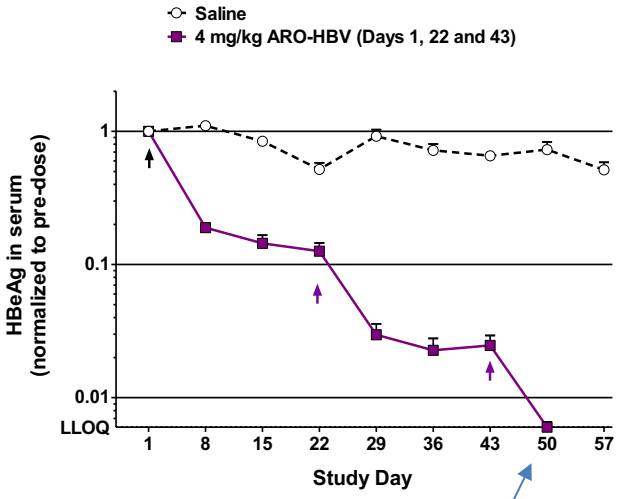
Multiple Dosing in WT pHBV Mice Reduces HBV DNA by 3.44 log10, HBsAg and HBeAg to LOQ

HBsAg



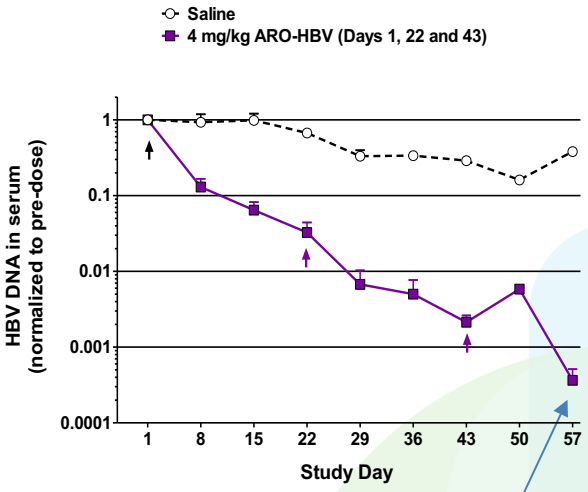
>3 log_{10} reduction after 3 doses

HBeAg



2.2 log10 = 99.4% reduction to LLOQ

HBV DNA



3.44 log10 = >99.9% reduction

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Preliminary Safety Evaluation

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

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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Thank you !

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