RNAi Comes of Age – Where it has been, Where it is, Where it is Going

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Arrowhead Pharmaceuticals
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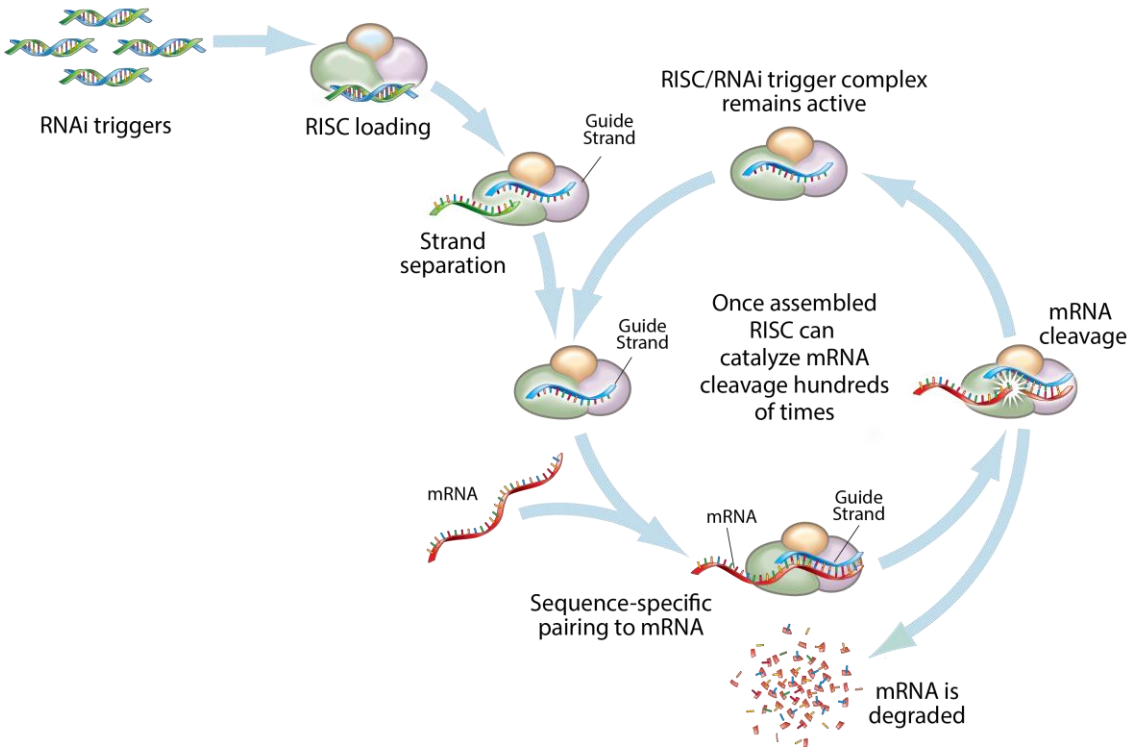
Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Target the Gene, Silence the Disease



Therapeutic gene silencing with **RNA interference** is highly precise and efficient

RNAi – A History of Highs and Lows (and highs again???)

- 1992 - SiRNA founded
- 1998 – Fire and Mello publish RNAi in nematodes
- 2002 – Alnylam founded
- 2005 – Alnylam Novartis alliance announced
- 2006 – Merck buys SiRNA for $1.1 Billion
- 2007 – Alnylam Roche alliance announced
- 2008 – Alnylam Takeda alliance announced
- 2010 – First systemic demonstration of RNAi in humans (by Arrowhead)
- 2011 – Roche sells RNAi assets to Arrowhead
- 2014 – Merck sells RNAi assets to Alnylam
- 2015 – Novartis sells RNAi assets to Arrowhead

- September, 2017 – Alnylam announces positive results in Phase 3 for patrisiran in hereditary amyloidosis with polyneuropathy
  - Seems likely to be the first approved siRNA

What led to the long delay getting to the market and the mass exodus by big pharma?

Delivery

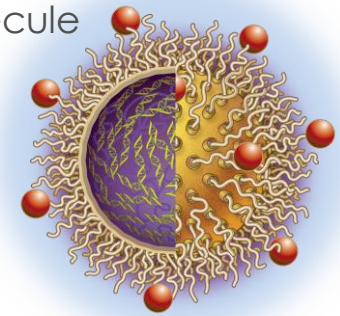
Delivery

Delivery*

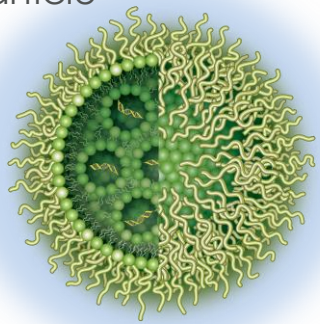
* And toll receptor activation

Evolution in RNAi: Drive toward Max Activity

Rondel Molecule



Lipid Nanoparticle



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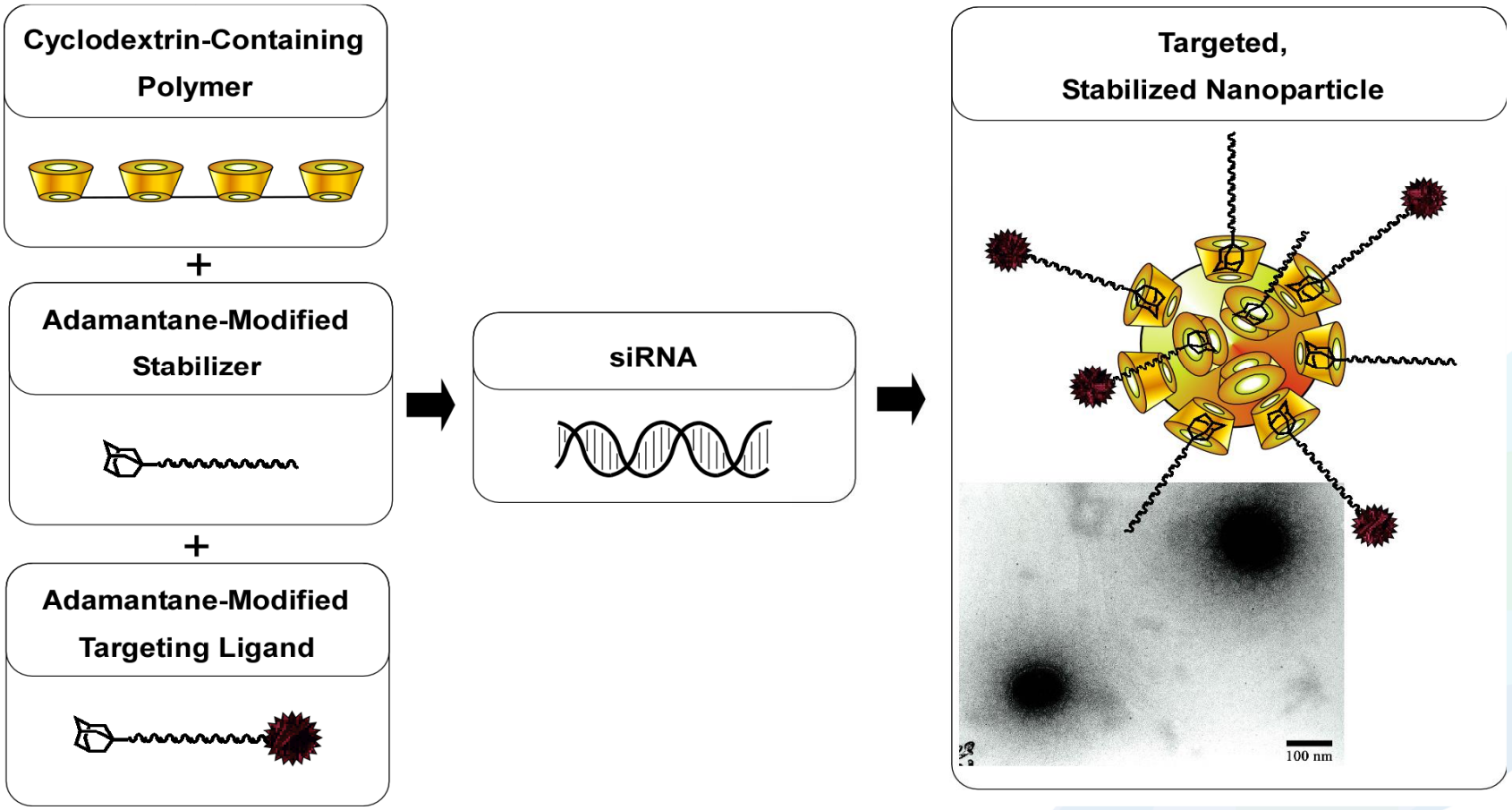
Composition of RONDEL™



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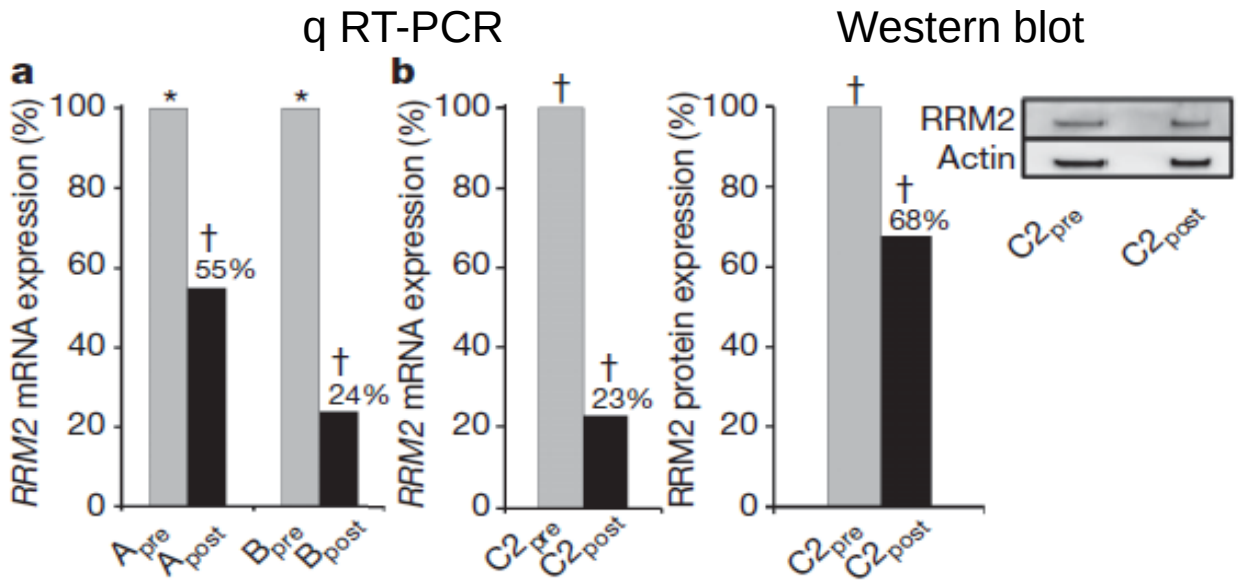
CALAA-01 Results in Target Knock Down in Patient Biopsies by RNAi mechanism



- Histology shows dose dependent accumulation of nanoparticles
- Histology confirms reduced RRM2 protein expression
- RNAi mechanism confirmed by 5'-RACE in dose dependent manner

Nature (2010) 464:1067-70

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RONDEL Delivery System: First Evidence of RNAi in Humans

- CALAA-01: The first systemically administered siRNA targeting human tumors
  - Demonstrated mRNA and protein knockdown in tumor biopsy samples taken from melanoma patients

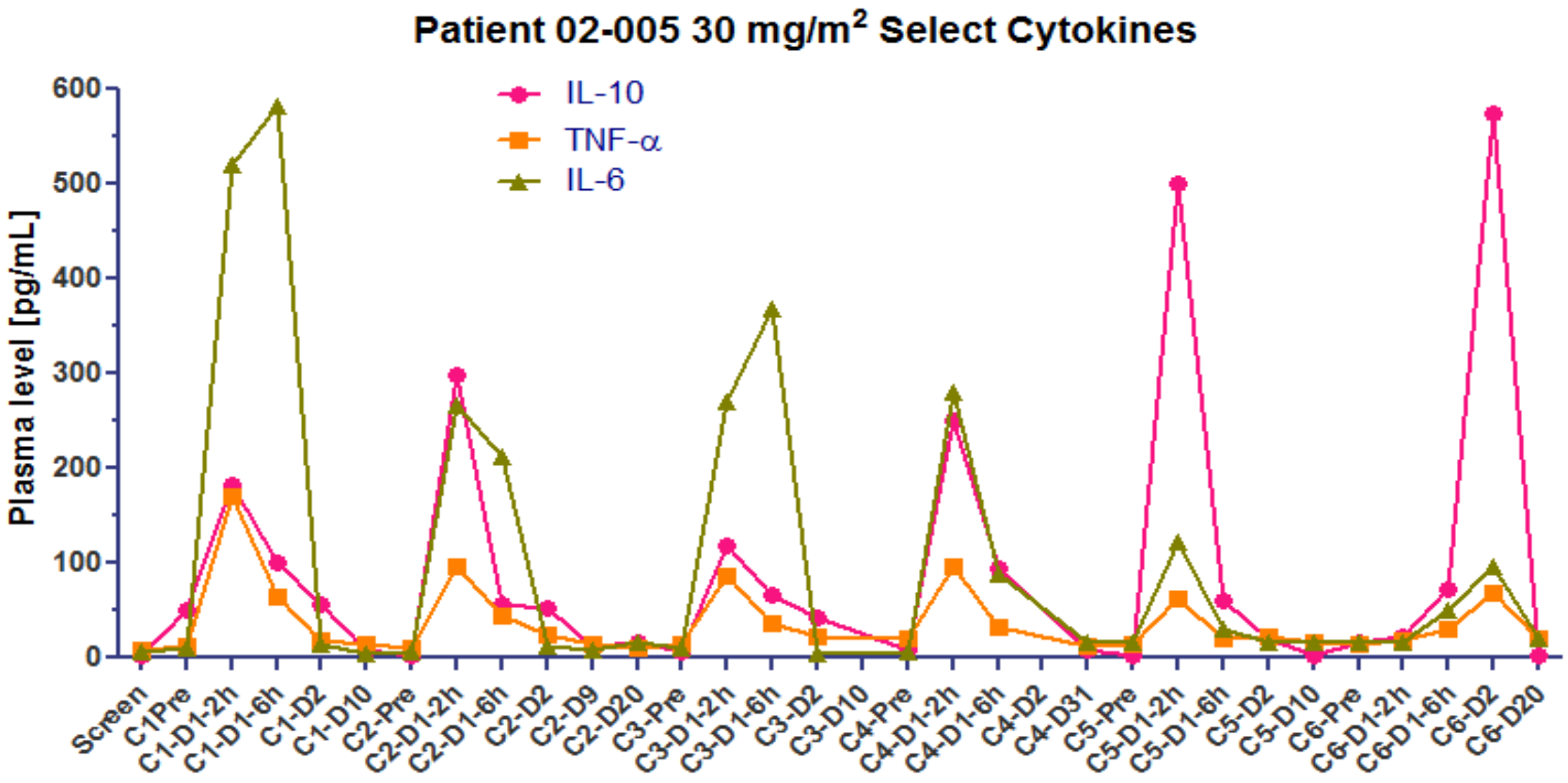
Vol 464|15 April 2010|doi:10.1038/nature08956 nature

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]

Cytokine Responses Ended the Program



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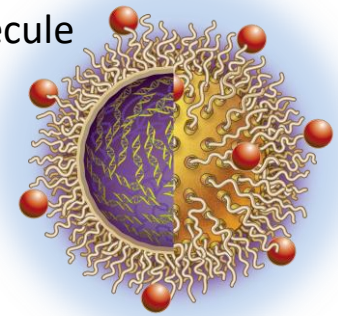
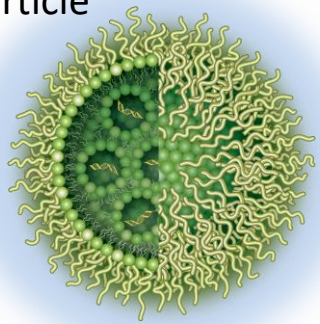
Evolution in RNAi: drive toward max activity

Rondel Molecule

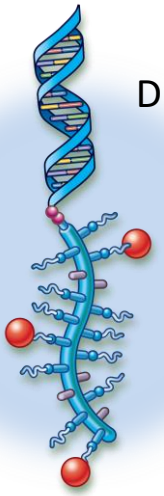


Lipid Nanoparticle

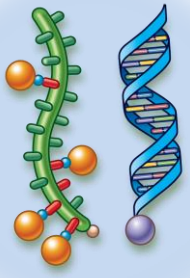


DPCs provided deepest KD Required active endosomal escape

DPC-1



DPC-2



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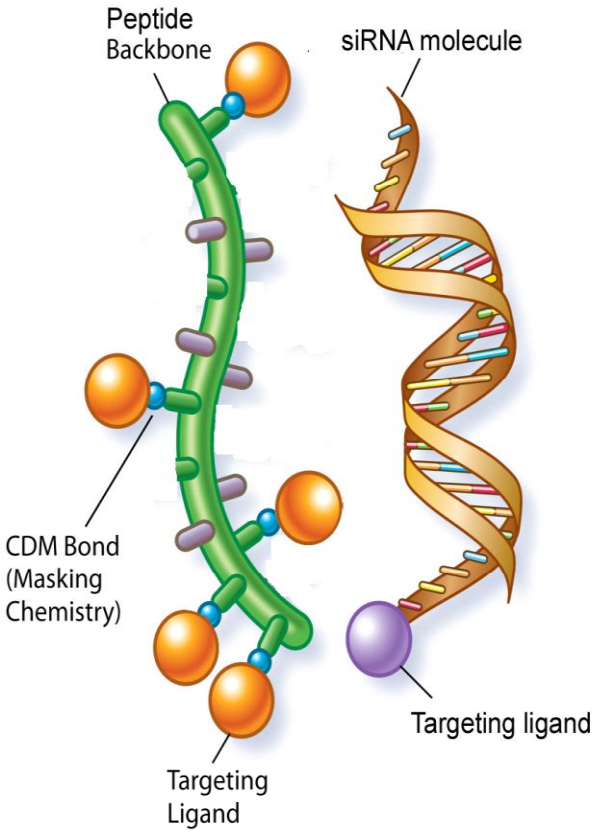
DPC™ for liver delivery of RNAi triggers

DPC™

- Amphipathic polymer/peptide for endosomal escape
- Polymer/peptide amines "masked" with pH-labile moiety, unmasked in endosome
- Targeted to liver with NAG (ASGPr receptor on hepatocytes)
- Co-injected with RNAi trigger



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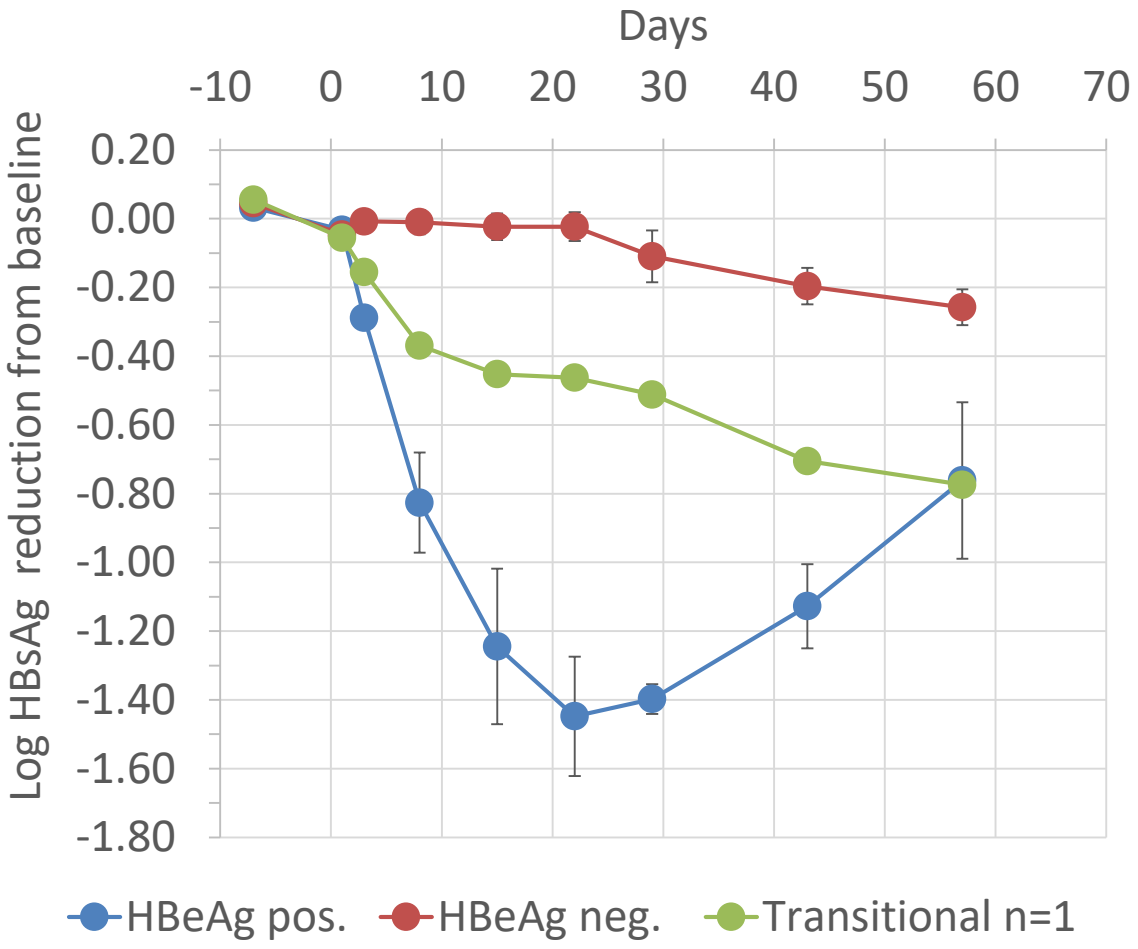
RNAi with ARC-520 produces deep knockdown of Hepatitis B antigens



- High level knockdown of HBsAg in HBeAg positive patients

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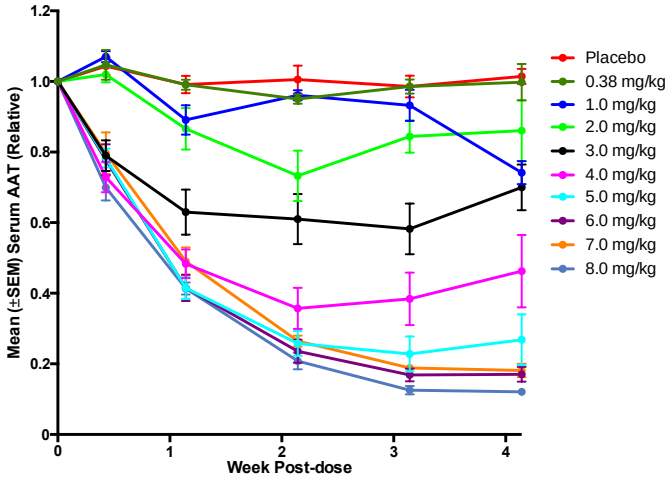
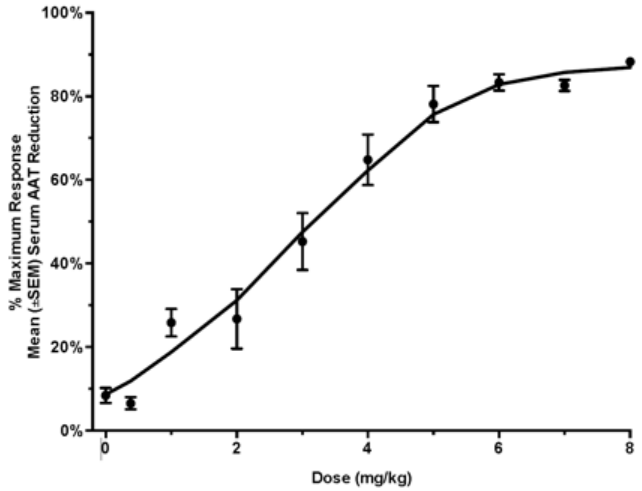
Dose Response in Healthy Volunteers with Single-dose ARC-AAT

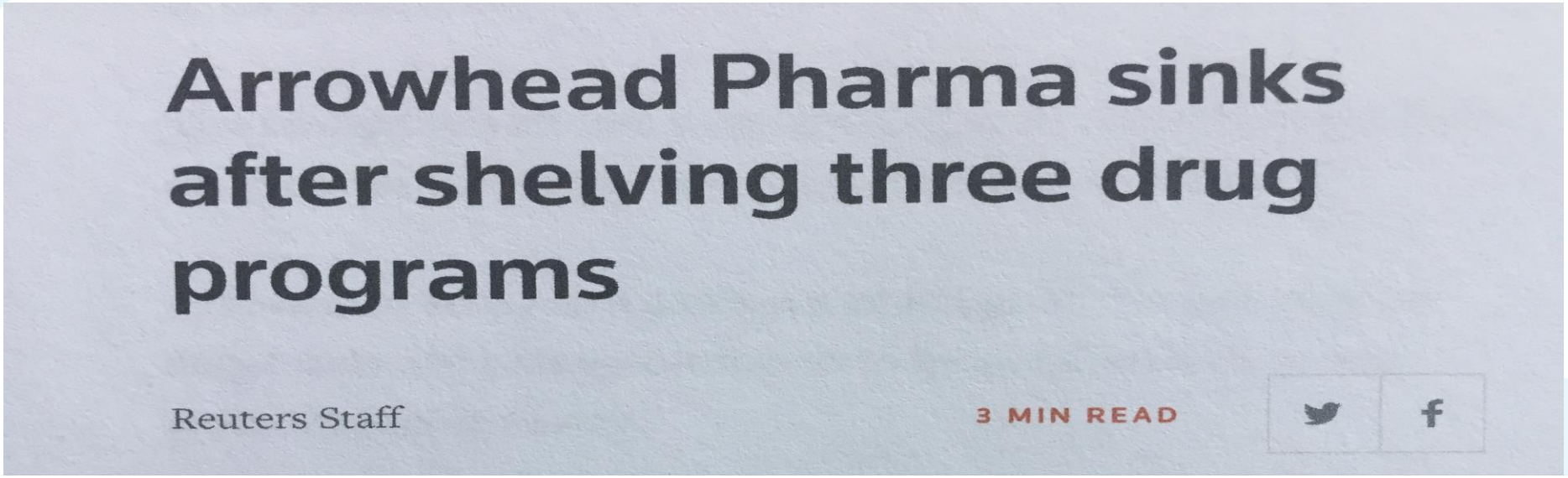




Dose Level (mg/kg)	PBO (n=18)	0.38 (n=4)	1 (n=4)	2 (n=4)	3 (n=4)	4 (n=4)	5 (n=4)	6 (n=4)	7 (n=3)	8 (n=3)
Max KD	24.8%	9.3%	31.9%	36.3%	61.0%	76.1%	86.7%	87.1%	85.1%	89.8%
Mean Max	8.4%	6.6%	25.9%	26.7%	45.3%	64.8%	78.1%	83.3%	82.6%	88.3%
P value	N/A	0.6363	0.0004	0.0014	< 0.0001	< 0.0001	< 0.0001	< 0.0001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

89.9 % maximum serum AAT knockdown achieved in healthy volunteers

DPCs Found to Produce Toxicity in NHPs

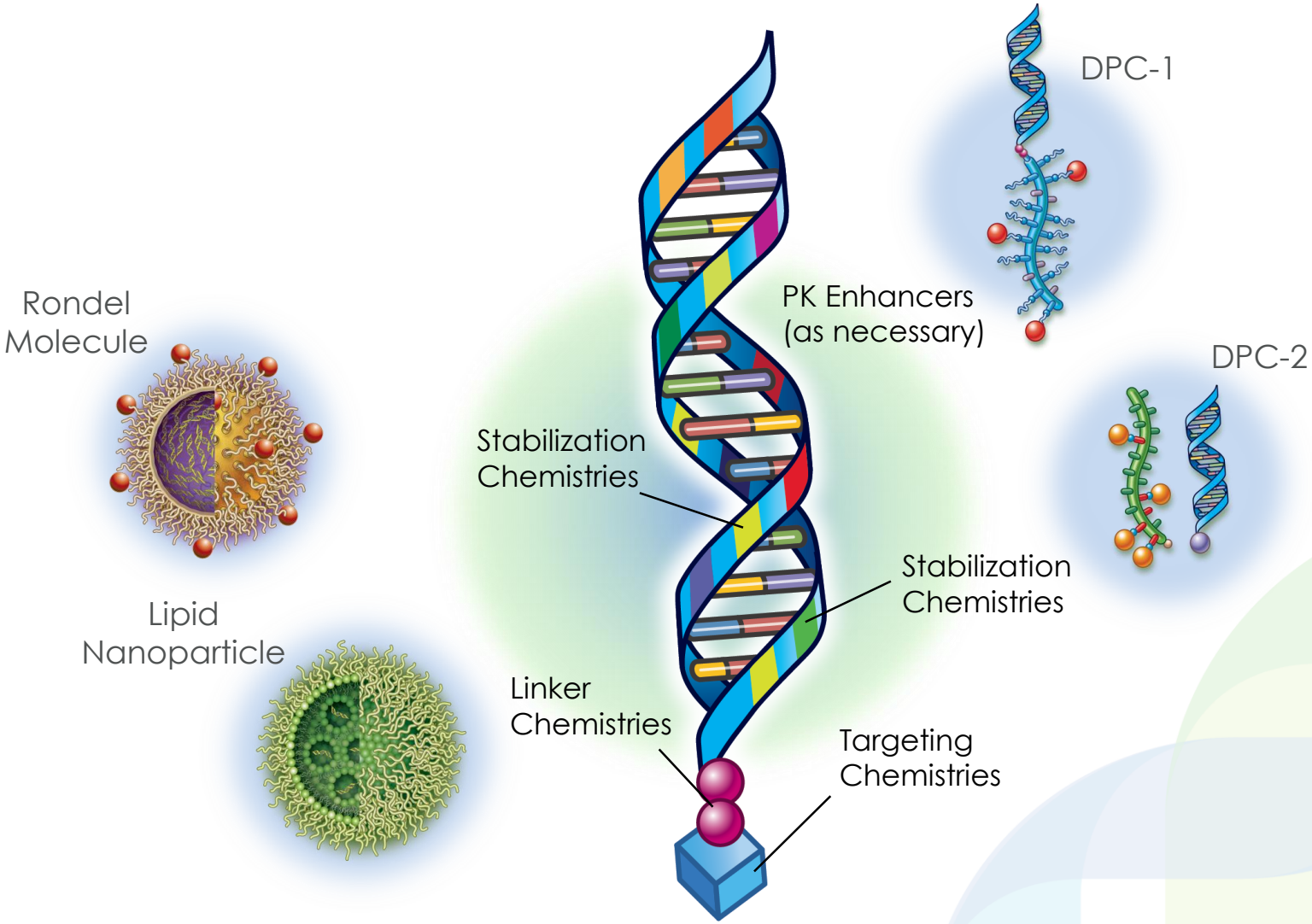


Arrowhead Pharma sinks after shelving three drug programs

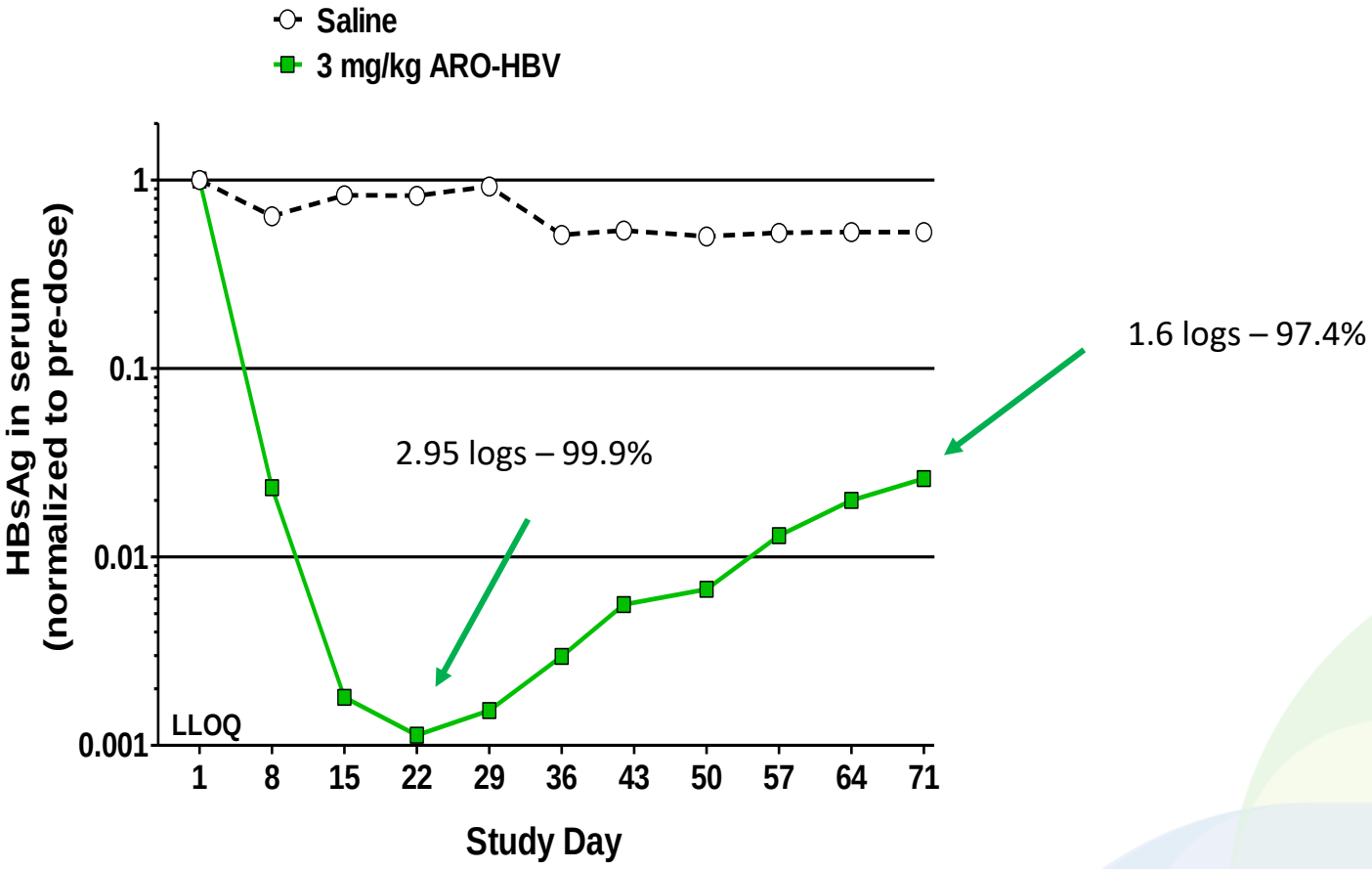
Reuters Staff

3 MIN READ

The Field is Moving on to Direct Conjugation

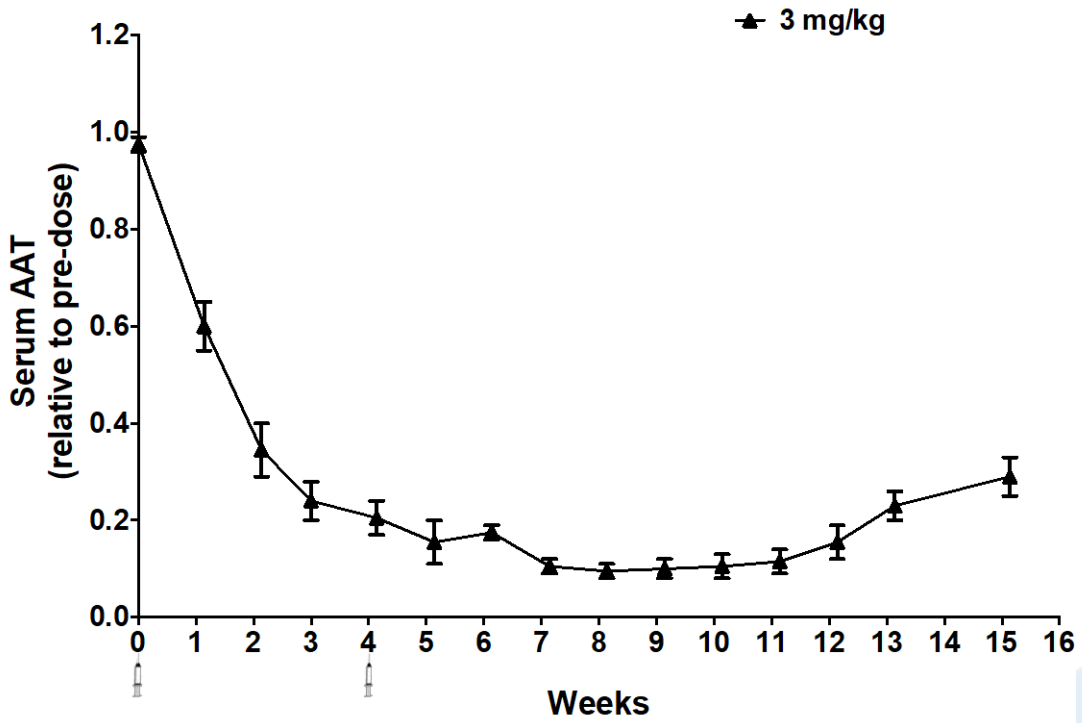


Example knockdown in a transgenic mouse model of Hepatitis B



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

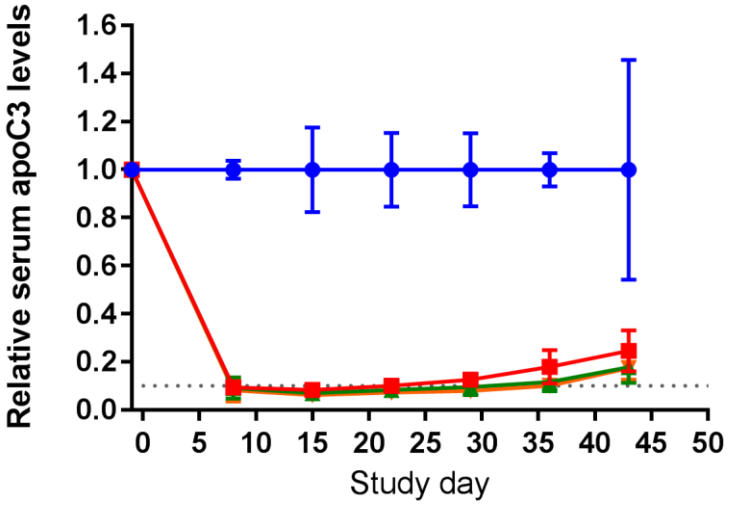


Durable knockdown supports once monthly or less frequent dosing

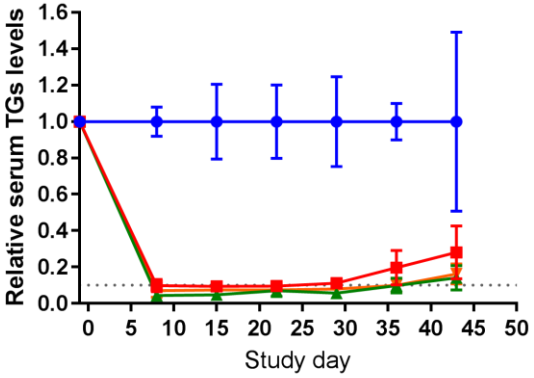
Single dose study in ApoC3 transgenic mice

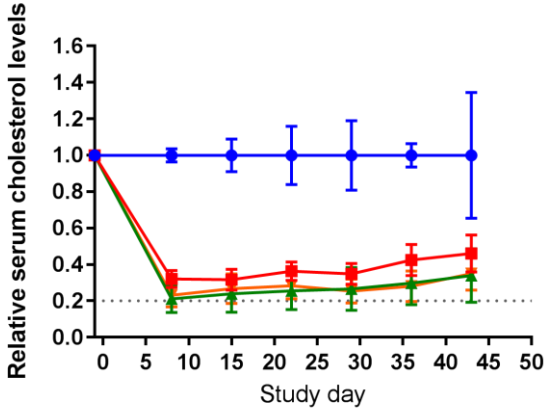
All dosed on study day 1 at 2 mpk

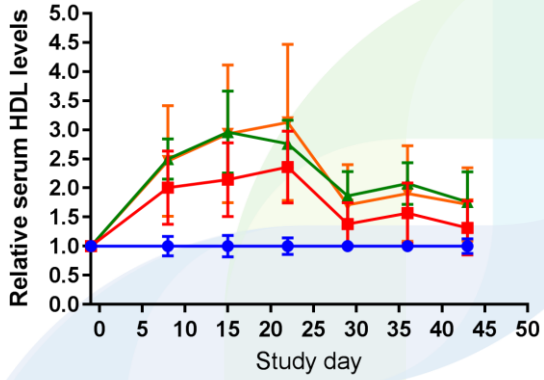
Data normalized to pre-dose and D5W control



- Deep KD after a single dose
- Max KD sustained for 3 weeks
- Expected effects on lipid profile



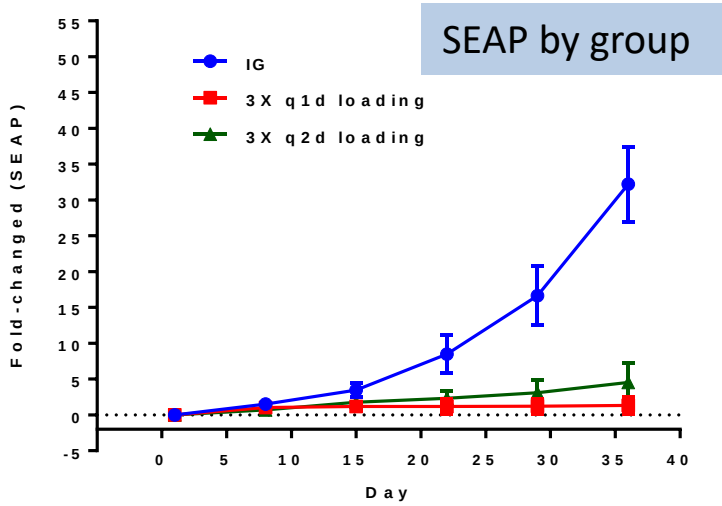




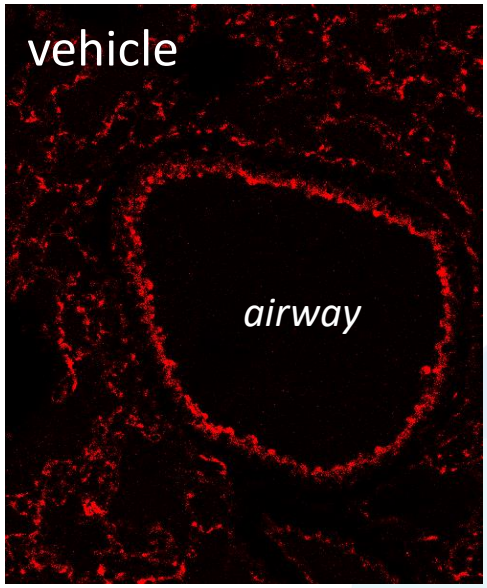
And Direct Conjugates are now Escaping the Liver

ARO-Hif2

- Up to 85% KD in rodent tumor model
- iv administration
- Tumor targeting



Red: lung target protein expression by IHC



ARO-lung-1

- Almost 90% KD in rodent models
- Inhaled administration

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The Painful Learnings

- RNAi happens in the cytoplasm and triggers require extensive modification to survive to get there unaided
  - Early emphasis on delivery platforms
  - Several promising programs lost to delivery-related toxicities
- Probably eliminated with direct 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.

The Future is Bright!

- As a field, we can deeply knockdown most, if not all, hepatocyte genes
- Where sufficient potency can be gained, SQ dosing with direct conjugates will be the norm
  - Much better market acceptability, especially given infrequent dosing
- Arrowhead is now achieving deep knockdown outside of the liver with direct conjugates
  - Others will surely follow
- Careful bioinformatics should prevent most of the recent clinical missteps

Arrowhead Team