What took RNAi so long – the delivery saga

Bruce D. Given, MD

COO, Arrowhead Pharmaceuticals

Nov 2017

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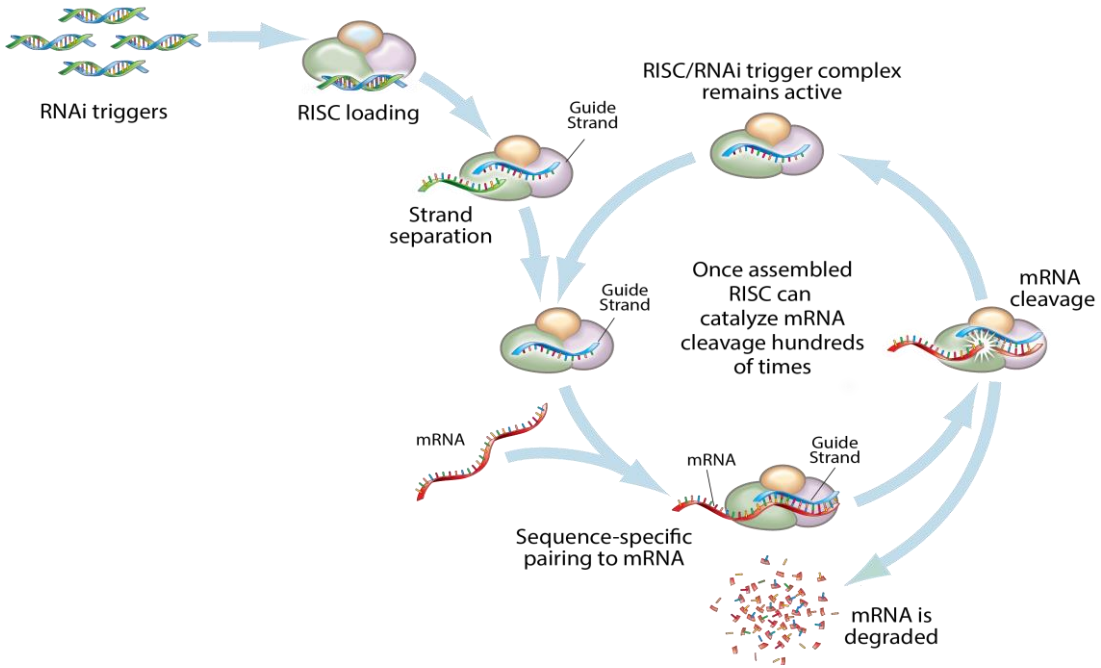
Safe Harbor Statement

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.

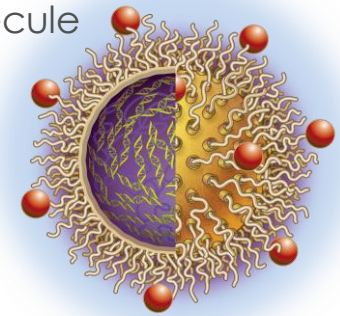
Target the Gene, Silence the Disease



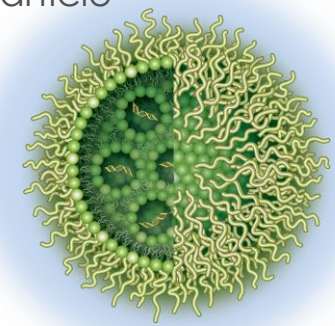
Therapeutic gene silencing with **RNA interference** is highly precise and efficient

Evolution in RNAi: Drive toward Max Activity

Rondel Molecule



Lipid Nanoparticle



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

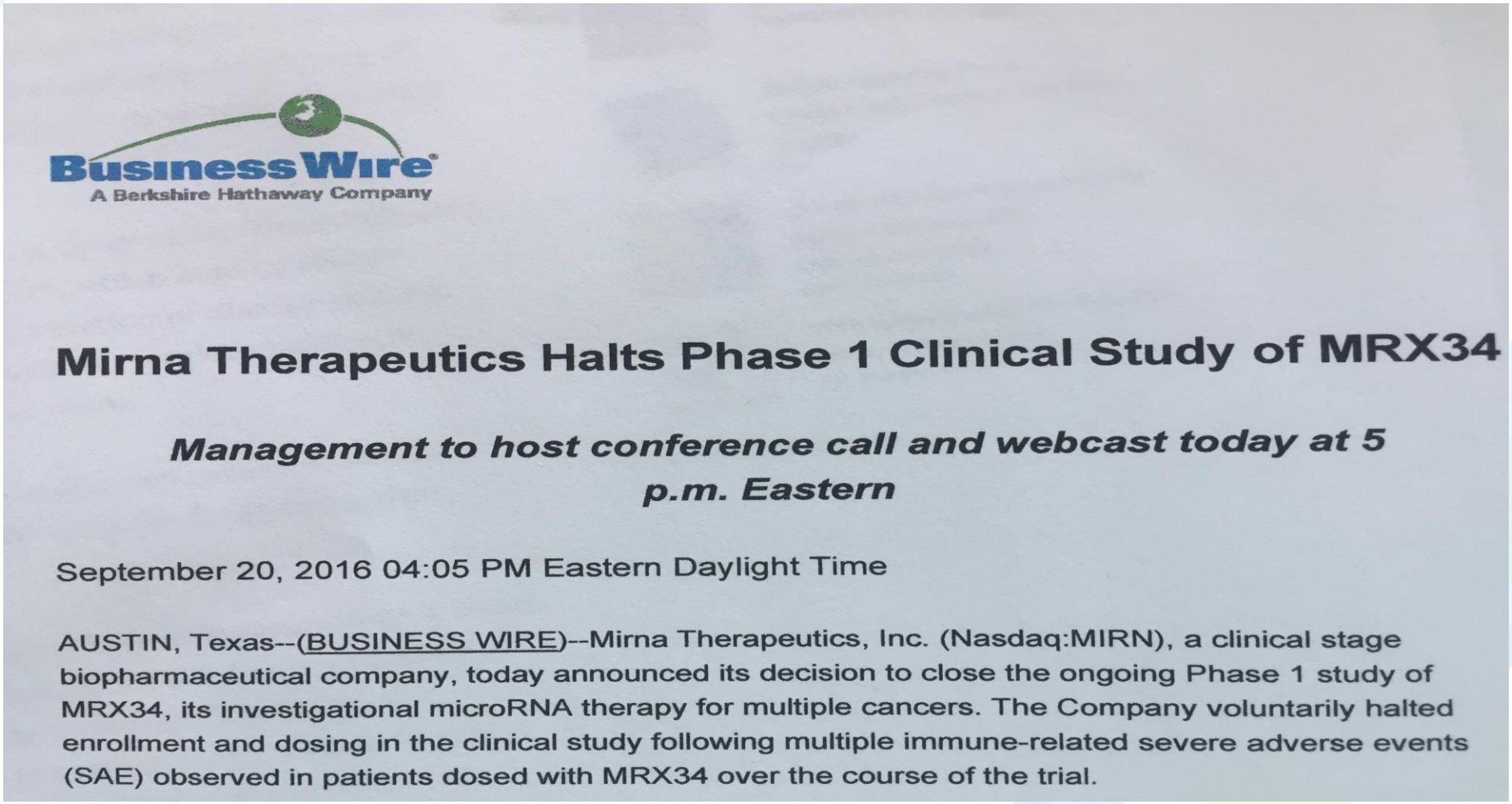
Vol 464|15 April 2010|doi:10.1038/nature08956 nature

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]

Mirna Cancels Clinical Programs due to Cytokine Syndrome



BusinessWire
A Berkshire Hathaway Company

Mirna Therapeutics Halts Phase 1 Clinical Study of MRX34

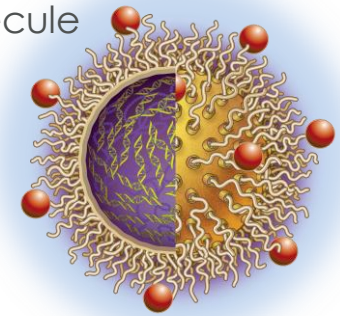
Management to host conference call and webcast today at 5 p.m. Eastern

September 20, 2016 04:05 PM Eastern Daylight Time

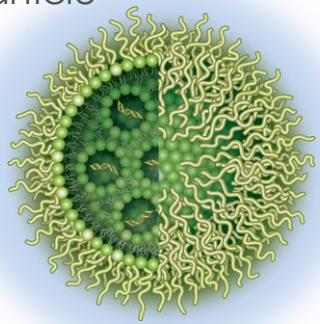
AUSTIN, Texas--(BUSINESS WIRE)--Mirna Therapeutics, Inc. (Nasdaq:MIRN), a clinical stage biopharmaceutical company, today announced its decision to close the ongoing Phase 1 study of MRX34, its investigational microRNA therapy for multiple cancers. The Company voluntarily halted enrollment and dosing in the clinical study following multiple immune-related severe adverse events (SAE) observed in patients dosed with MRX34 over the course of the trial.

Evolution in RNAi: Drive toward Max Activity

Rondel Molecule

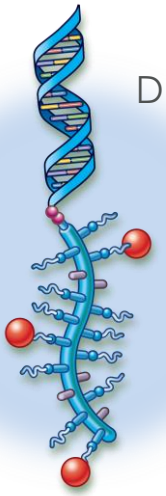


Lipid Nanoparticle

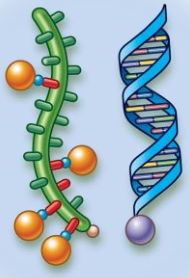


DPCs provided deepest KD; Required active endosomal escape

DPC-1



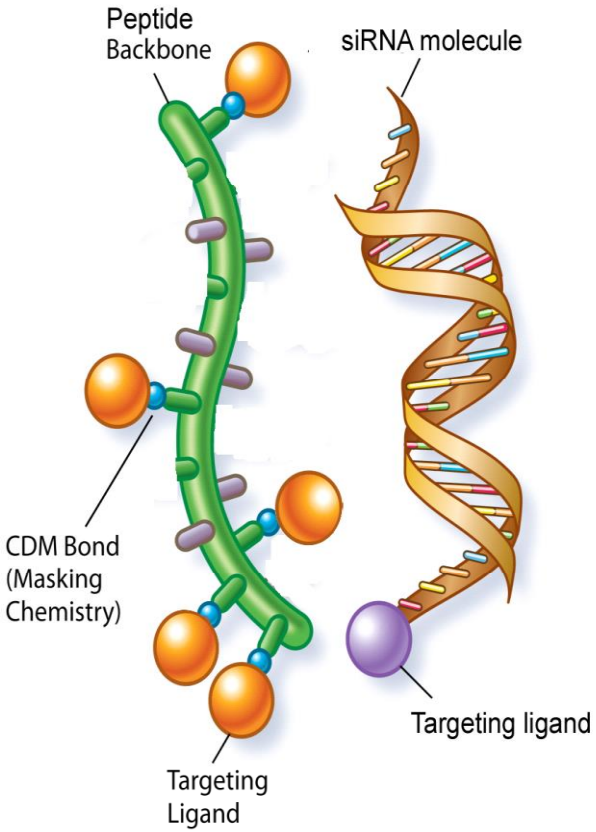
DPC-2



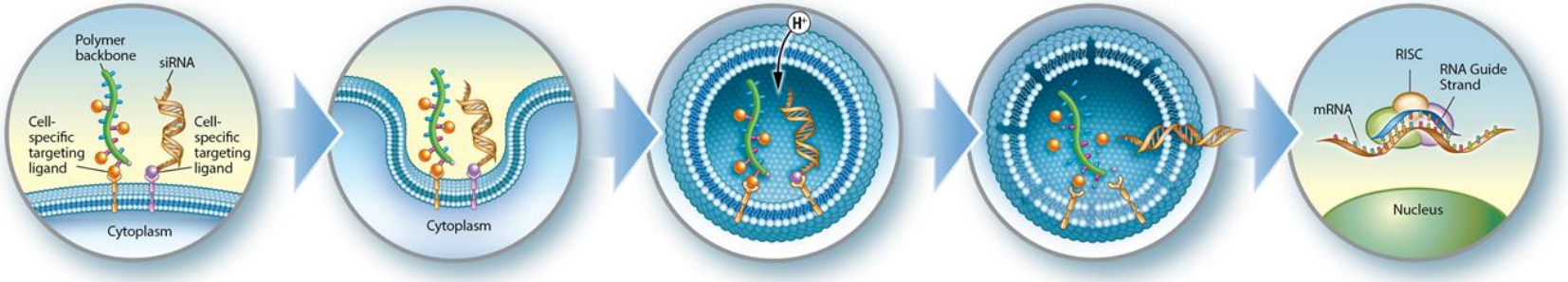
DPC™ for liver delivery of RNAi triggers

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



Mechanism of DPC™-mediated siRNA delivery to cells



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

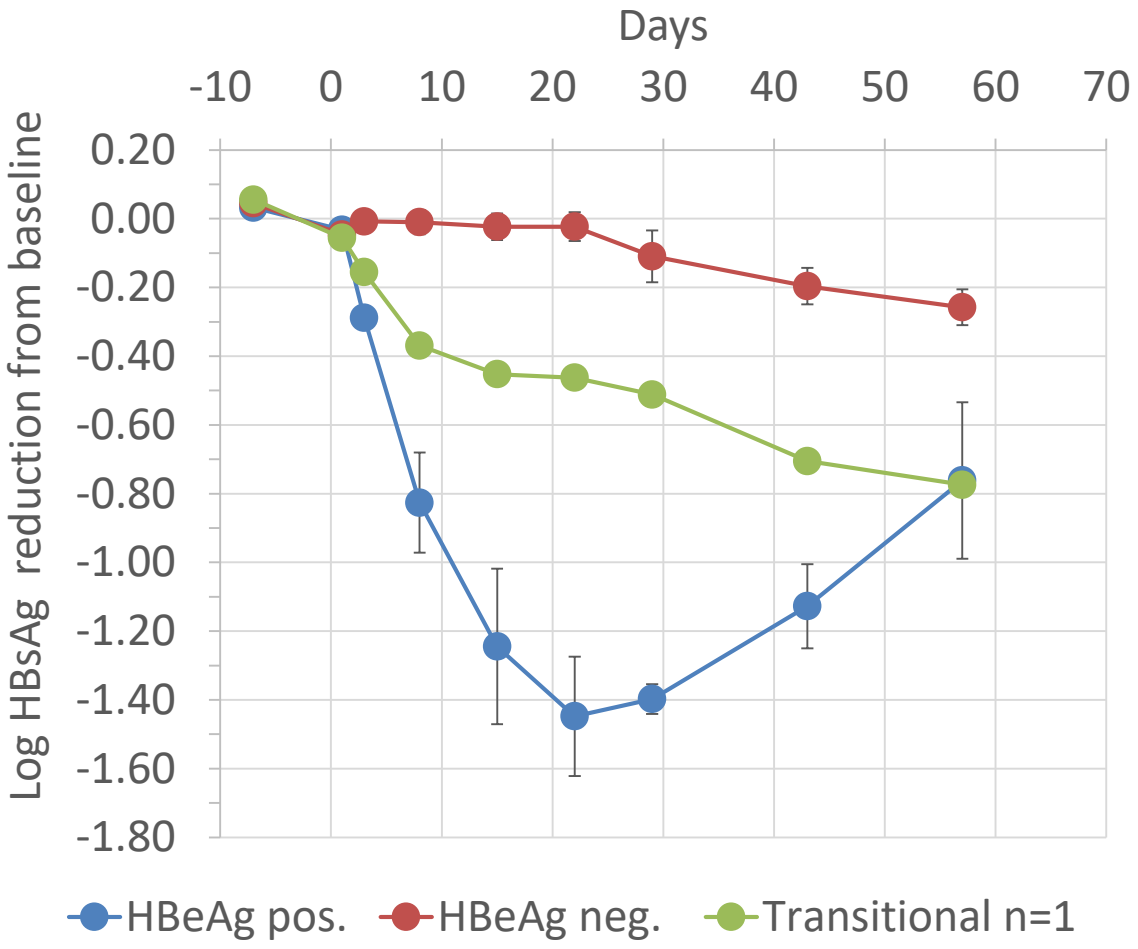
DPC™ peptide and RNAi trigger are internalized

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

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



- High level knockdown of HBsAg in HBeAg positive patients

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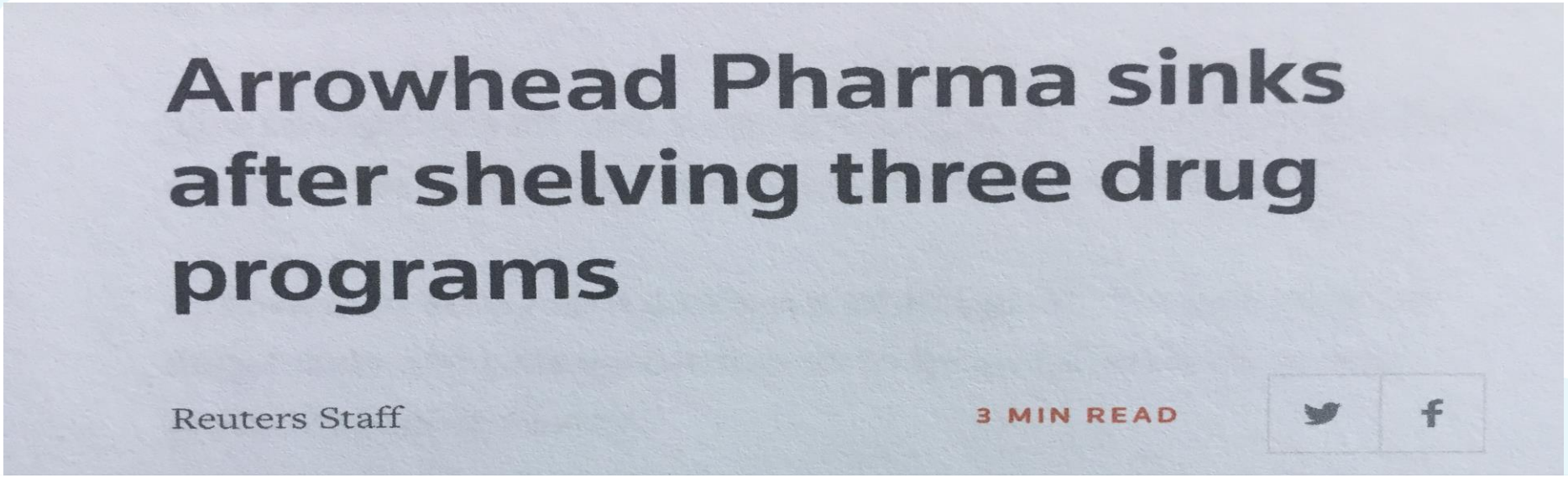
DPCs Found to Produce Toxicity in NHPs

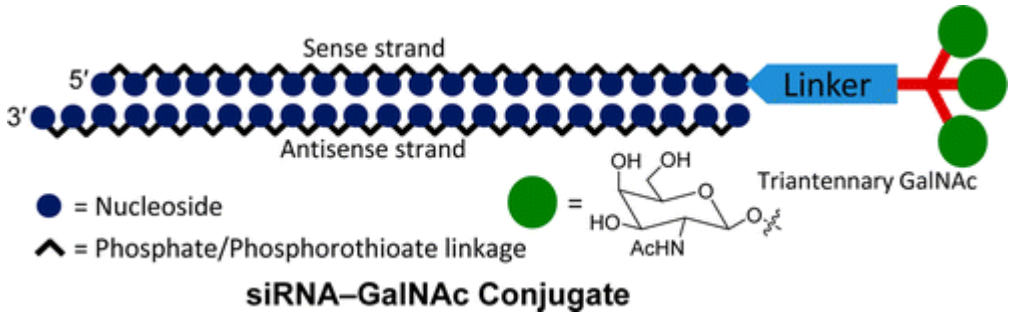


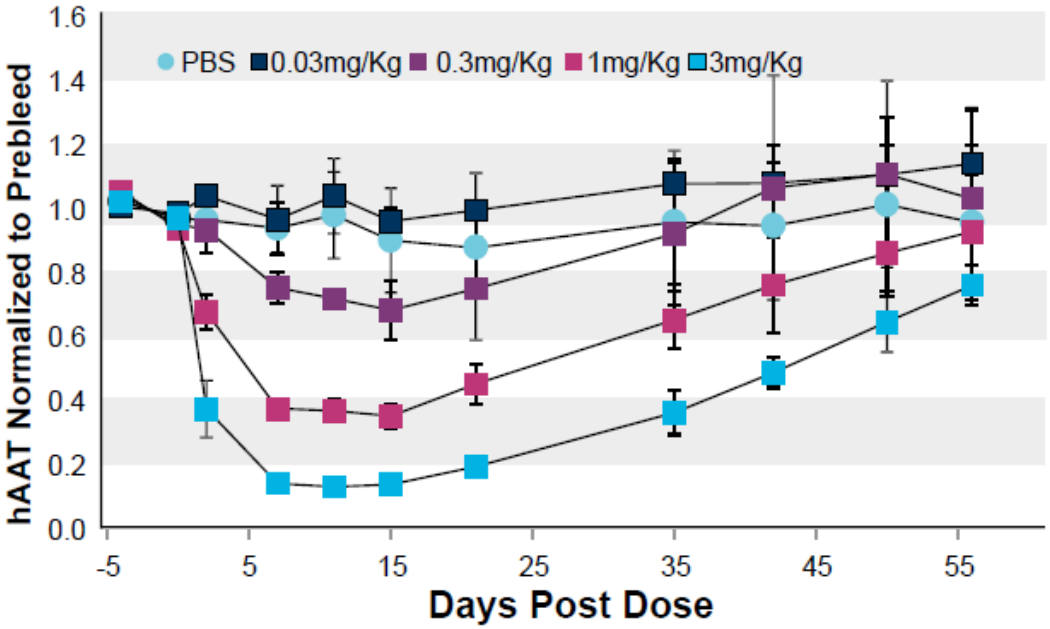
Arrowhead Pharma sinks after shelving three drug programs

Reuters Staff

3 MIN READ

Alnylam Breaks Through with Direct Conjugation





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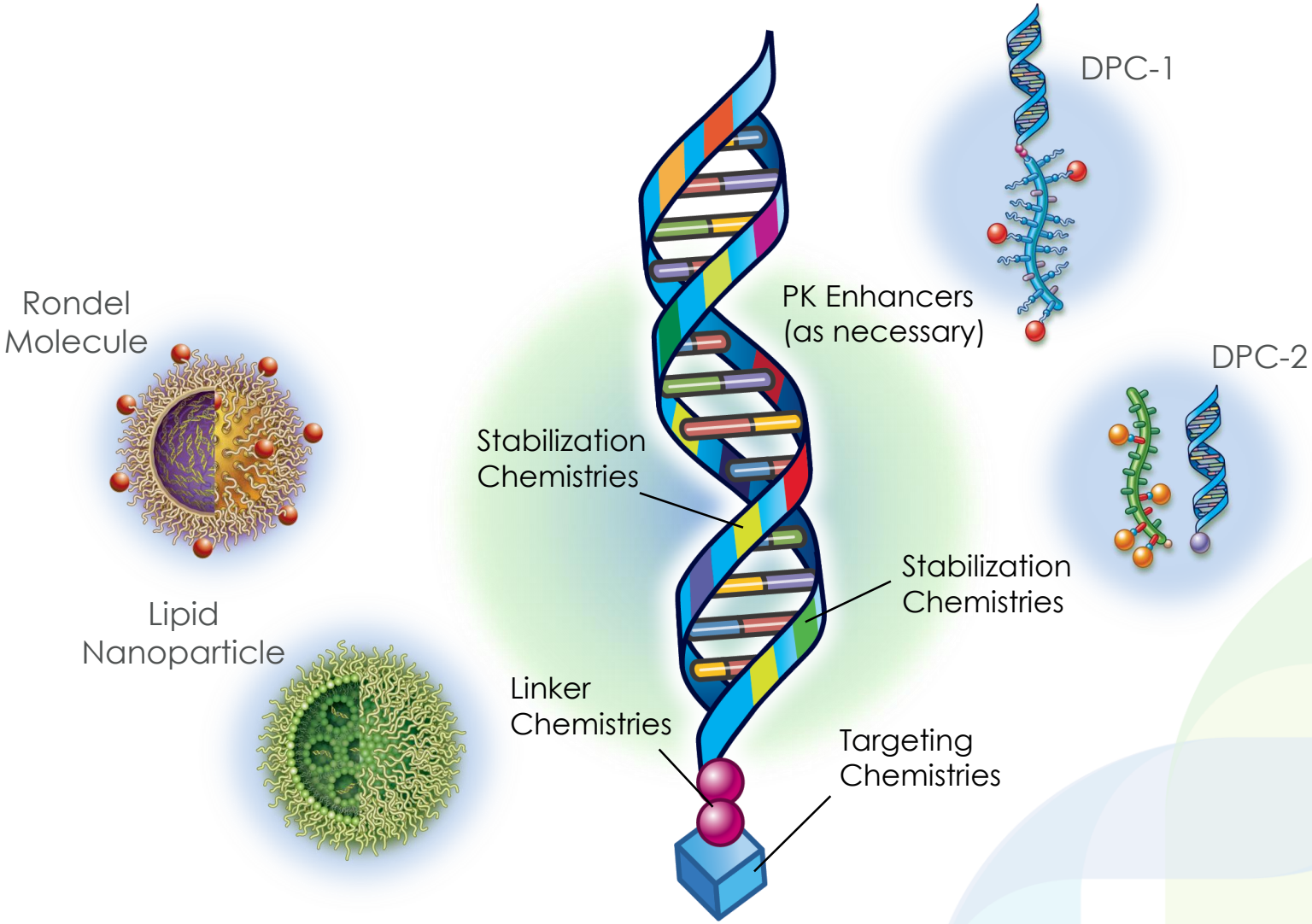
The Field is Moving on to Direct Conjugation

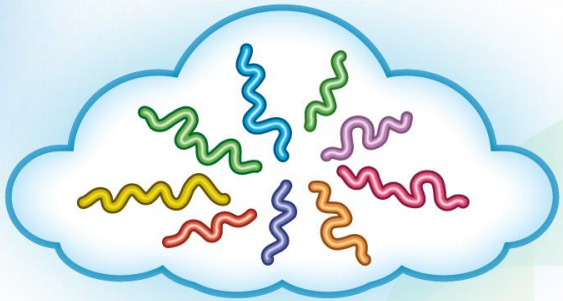


TRiM™ chemical modifications

Linker/Branch Point Chemistries

Targeting Ligands

Stabilization Chemistries



Structures to Enhance Pharmacokinetics

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TRiM™ chemical modifications

Linker/Branch Point Chemistries

Targeting Ligands

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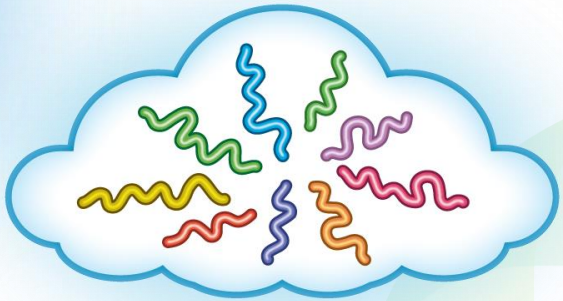

Structures to Enhance Pharmacokinetics

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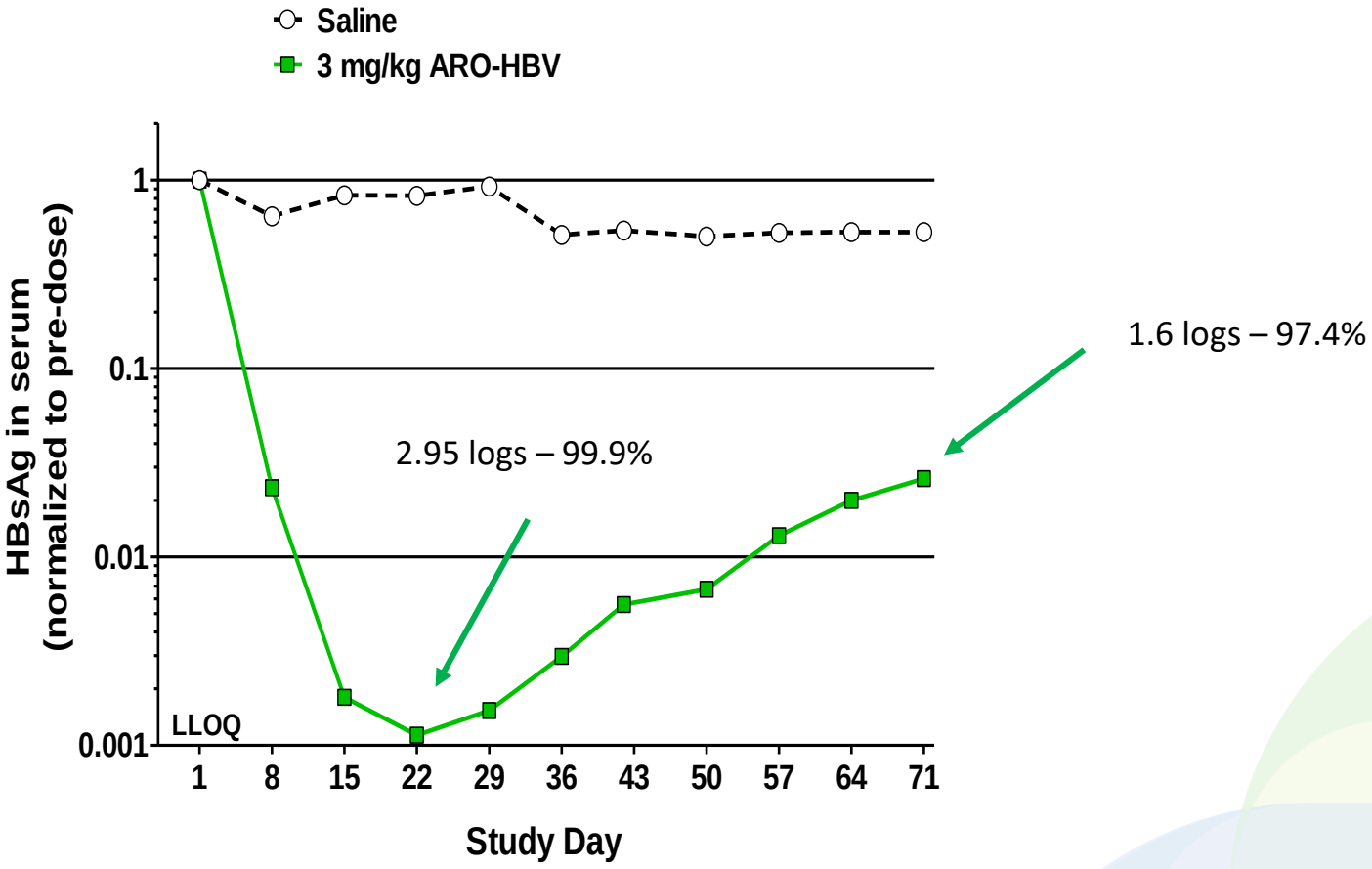
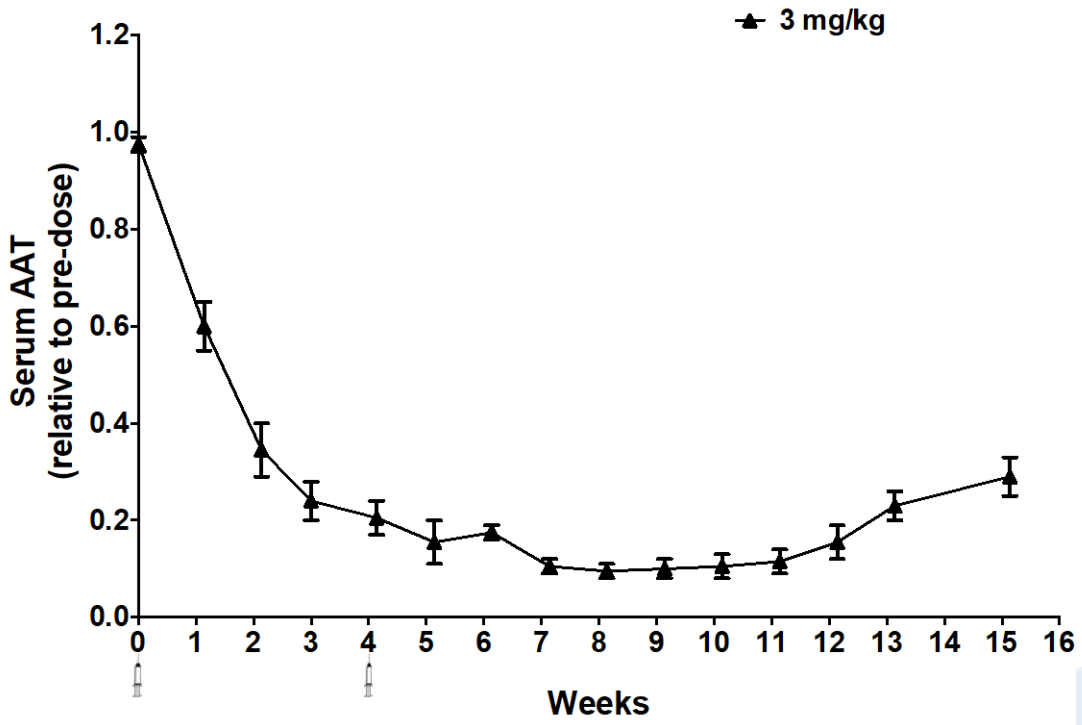
What's Possible Today?

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



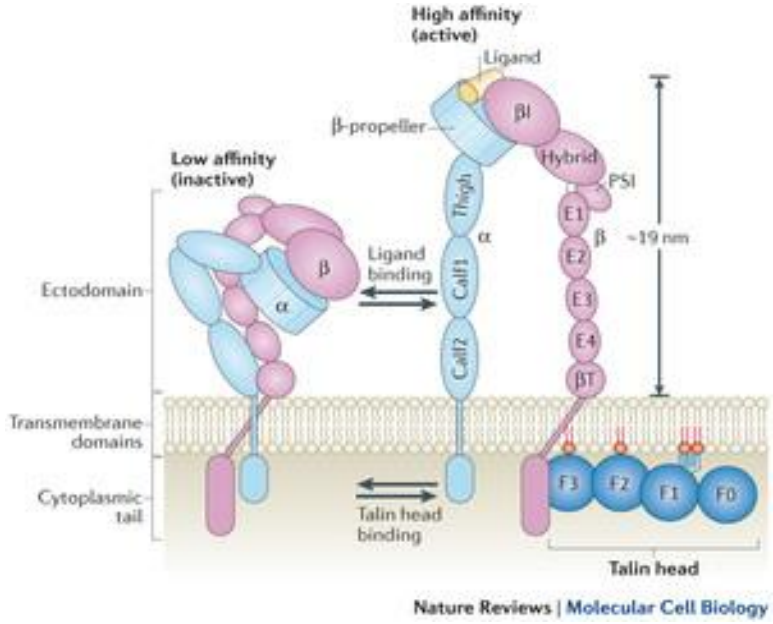
Durable knockdown supports once monthly or less frequent dosing

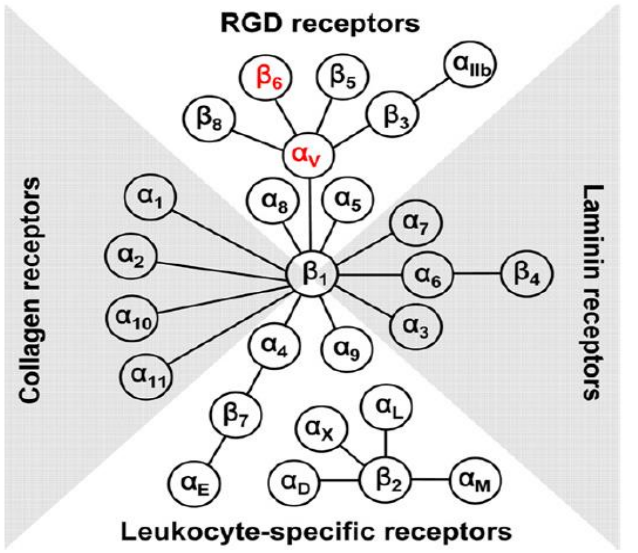
The Field Continues to Push Ahead

- We can deeply knockdown most, if not all, hepatocyte genes
  - ….and probably eliminate off target risks too with careful bioinformatics
- Where sufficient potency can be gained, SQ dosing will be the norm beyond the liver
  - 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

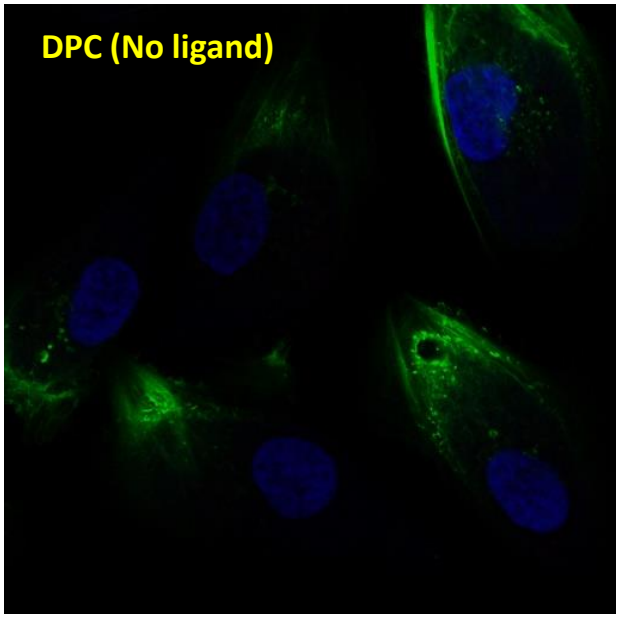
Extra-hepatic Targeting with integrin ligand

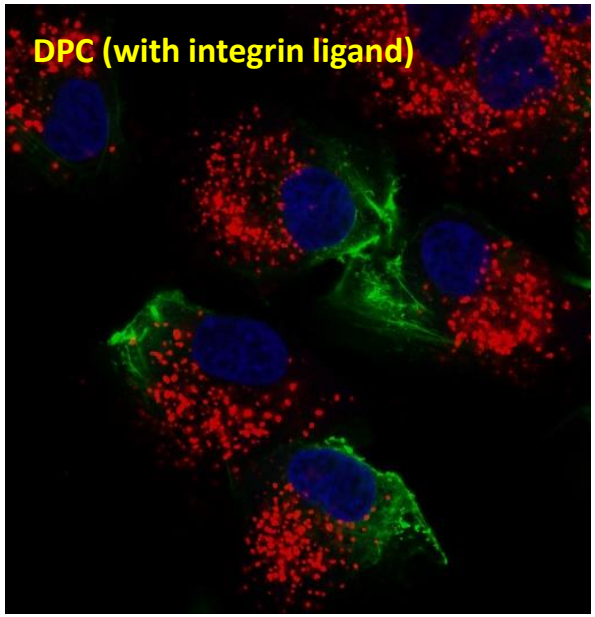
- Integrins involved in cell adhesion and signaling
  - Heterodimers: 18 α and 8 β subunits
  - Diverse ligands: ECM, growth factors, etc.
  - Exploited by tumor cells
  - Proprietary ligand binds αVβ3 in ccRCC





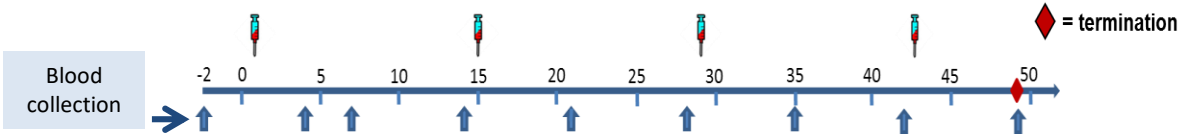
Ligand-dependent DPC™ uptake in ccRCC tumor cell line

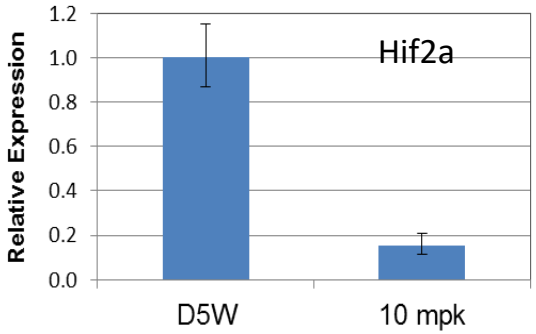


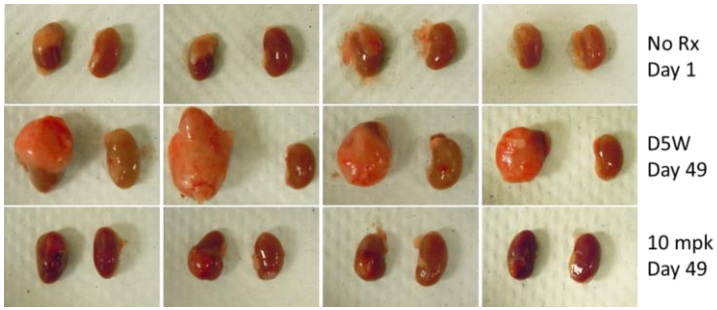


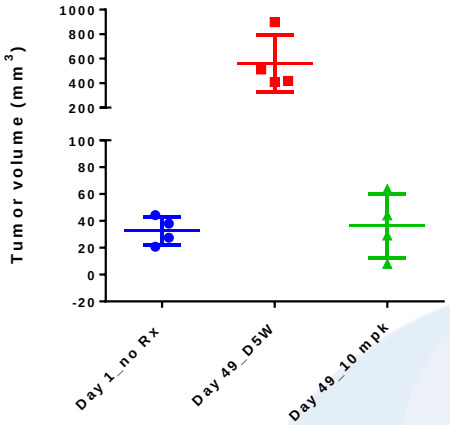
Green: Actin
Blue: Nuclei
Red: RGD-DPC

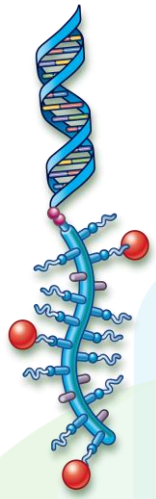
Tumor growth inhibited after 4 bi-weekly doses in orthotopic ccRCC mice











- Tumor volumes unchanged in the treatment group, suggesting tumor stasis
- Histological examination revealed extensive tumor destruction
- Treatment was well tolerated

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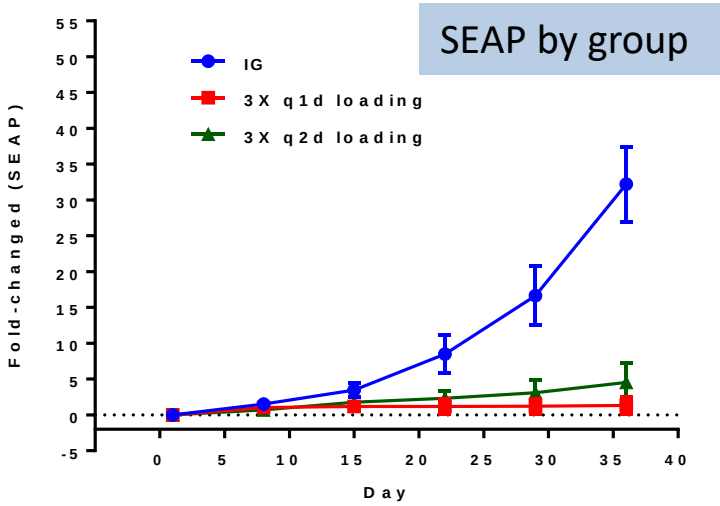
Targeting New Tissues Using TRiM™ Platform

ARO-Hif2

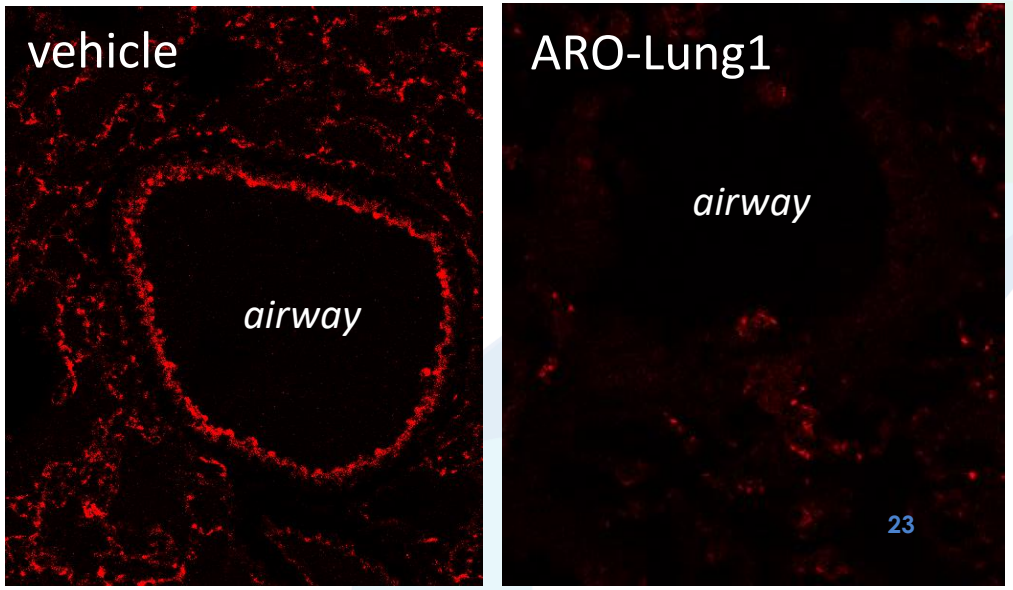
- Up to 85% KD in rodent tumor model
- iv administration
- Solid tumor targeting



ARO-Lung1

- Almost 90% KD in rodent models
- Inhaled administration

Red: lung target protein expression by IHC



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The Future is Bright!

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  - 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
- RNAi will achieve its full potential when it can reach a broad range of tissues

Arrowhead Team