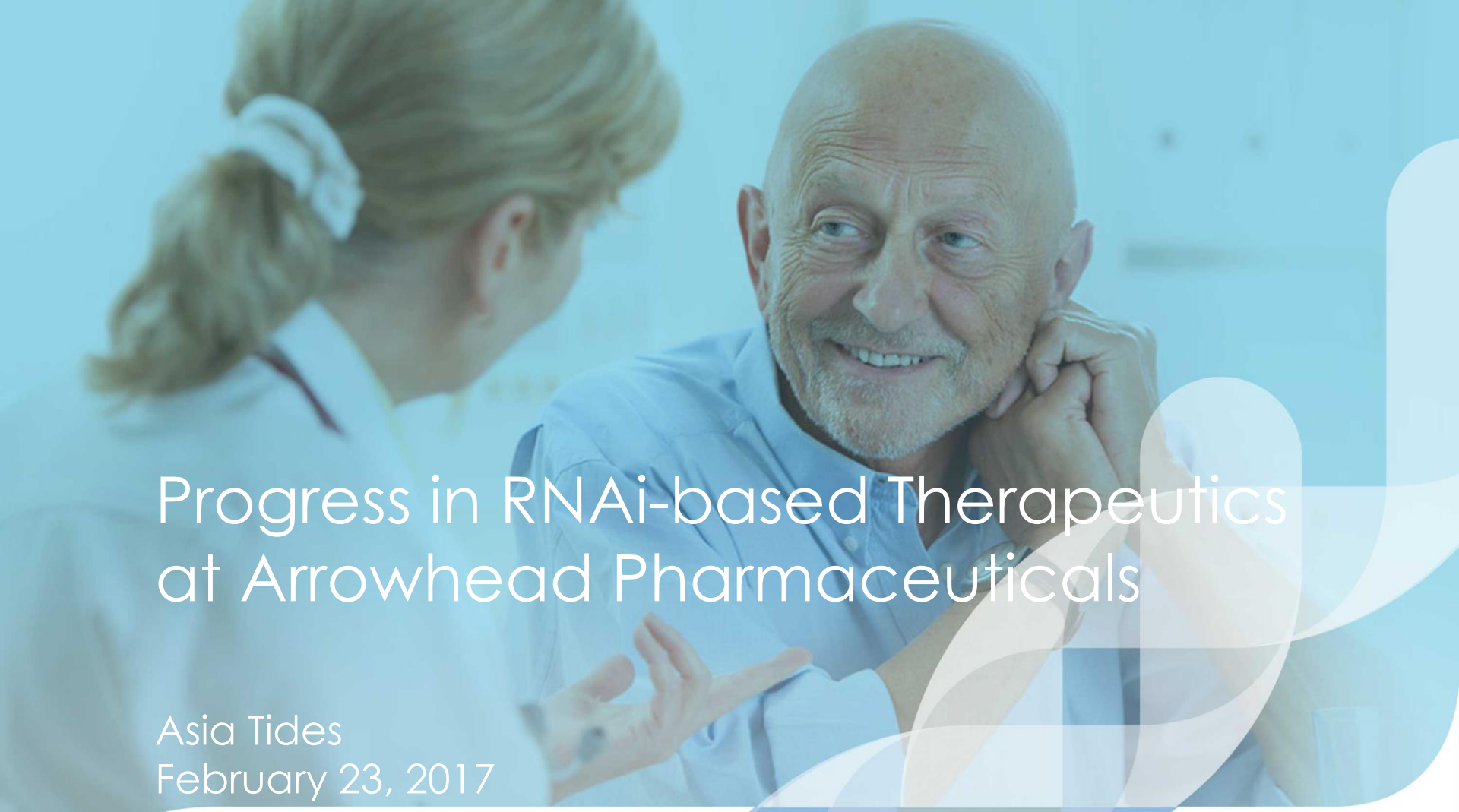


Progress in RNAi-based Therapeutics at Arrowhead Pharmaceuticals

Asia Tides
February 23, 2017

arrowhead
pharmaceuticals

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.

Comprehensive Platforms Yield Optimal RNAi Medicines

RNAi Chemistry
Broad FTO for Canonical siRNA
Broad FTO for Dicer siRNA
Broad FTO for Meroduplex siRNA
Broad FTO for UNAs
Novel proprietary RNAi triggers
Intracellular targeting ligands ➢ **Activity booster**
ALNY IP license for 30 targets

Proprietary technologies and acquired/licensed fundamental IP from:
Roche, Novartis, Alnylam, Mirus Bio, City of Hope Cancer Center, Marina

Clinical PoC with HBV and AAT Programs

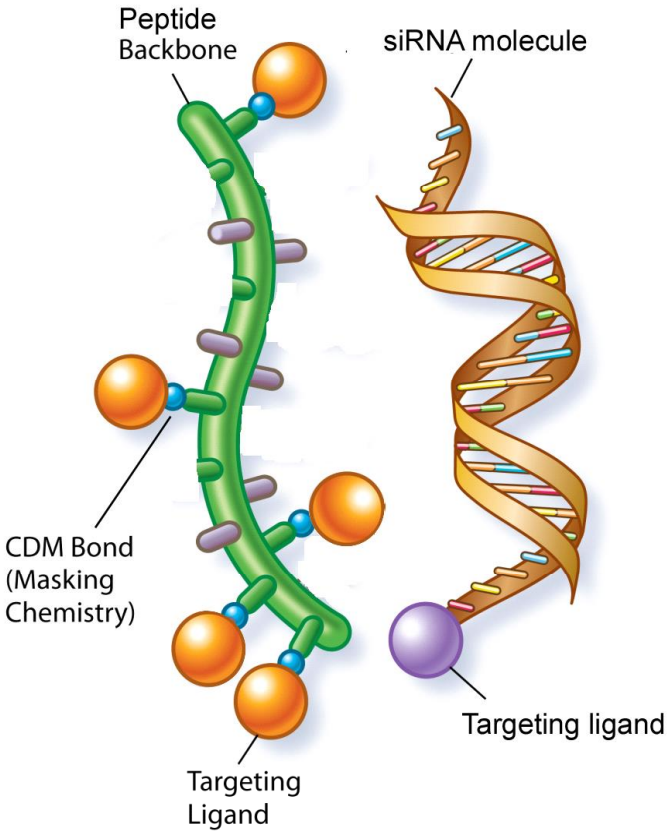
The field has moved a long way in 5 years

- When Arrowhead bought Roche's RNA assets in late 2011
  - No large pharma had made it to the clinic with RNAi
    - And Roche, Novartis and Merck never did!
  - RNA stabilization was still immature
    - GalNac conjugates had poor potency and duration
  - Liposomal delivery was getting better but…..
    - Even today, requires high dose steroid pre-treatment
    - Inherently toxic approach
    - Not easily disposed to targeting
- Roche had obtained rights to DPC (Dynamic Polyconjugates) with the acquisition of Mirus Bio but had not progressed to the clinic
  - Arrowhead felt that DPCs were ready to move to the clinic and held potential advantages over liposomes with respect to toxicity and targetability

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



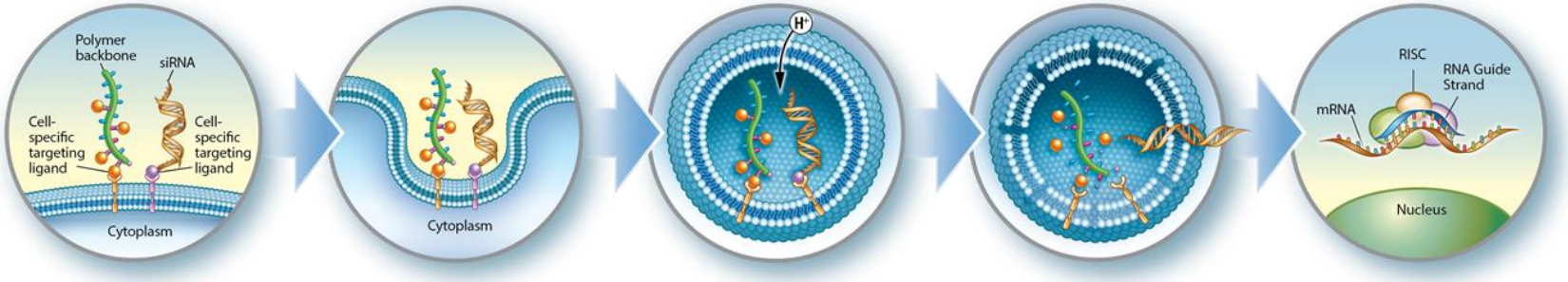
RNAi Trigger

- Canonical siRNA or other format with minimal modifications
- Liver-tropic targeting ligand (eg. cholesterol)

DPC and RNAi trigger do *NOT* form a complex, they are separately targeted to the liver

arrowhead pharmaceuticals

Mechanism of DPC-mediated siRNA delivery to cells



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

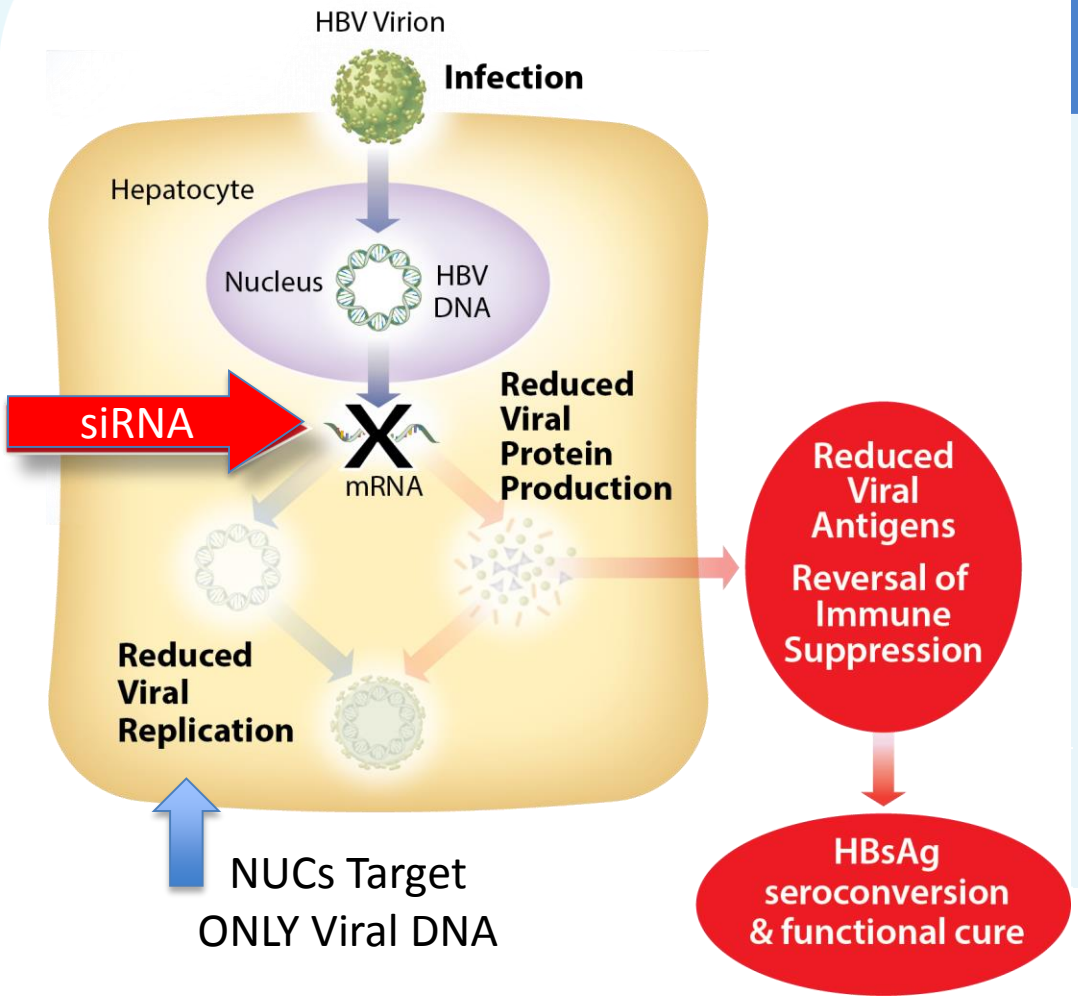
DPC™ peptide and RNAi trigger are internalized

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

Simplified Theory of an HBV RNAi Therapeutic



Silence Entire HBV Genome

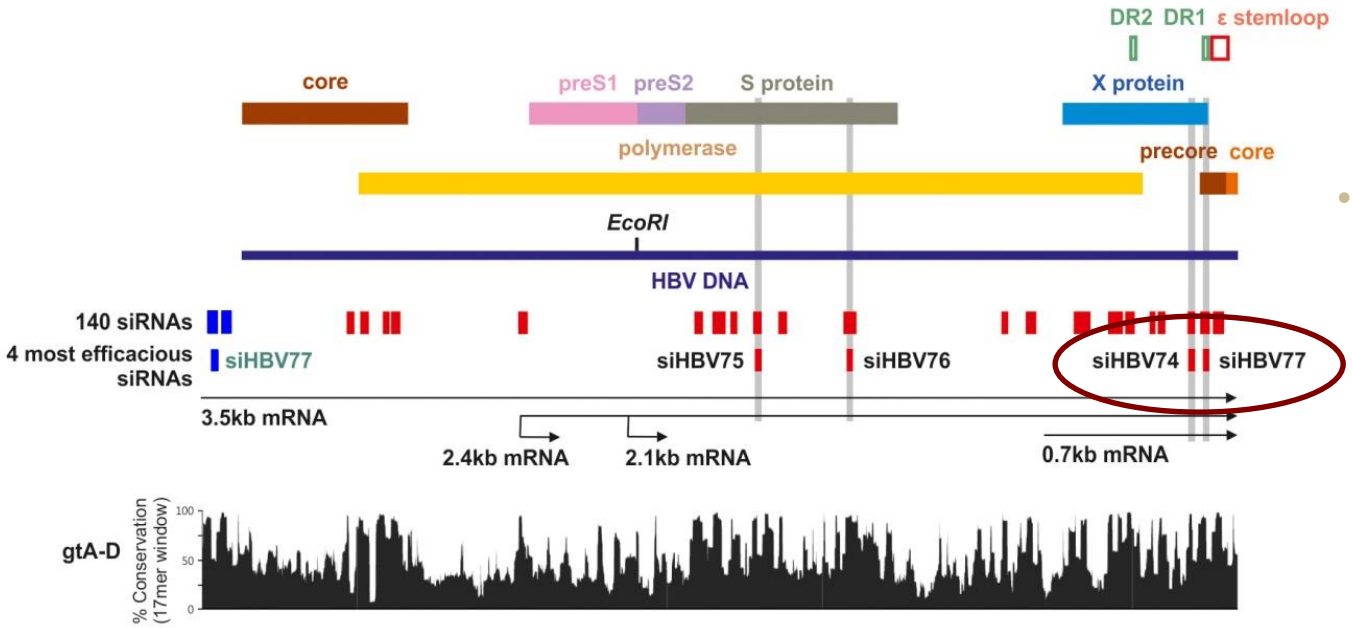
1. "HBsAg Theory"
   - Reducing HBsAg enables host immune system de-repression and long term control of virus
2. Destabilizing Viral Function
   - Silencing all antigens could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus

ENABLE A FUNCTIONAL CURE

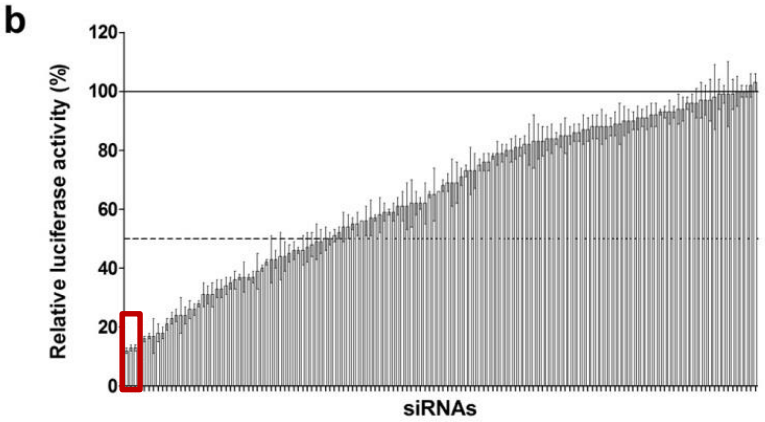
arrowhead pharmaceuticals

RNAi for treatment of chronic Hepatitis B

siRNA design and in vitro screening



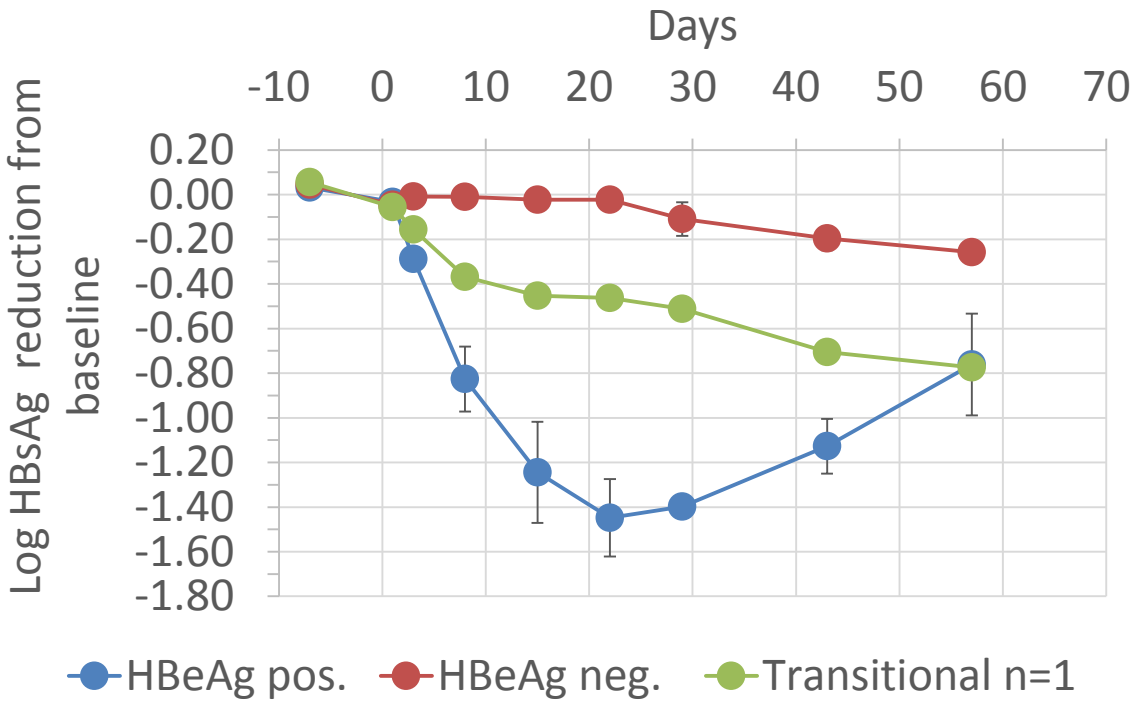
- Designed 140 siRNAs targeting conserved regions in GenBank HBV sequences (2,754)



- Screened candidate siRNAs in a cell culture system
- 4 highly potent siRNAs chosen for further testing in animal models
- siHBV-74 and siHBV-77 chosen as leads

Roche-Kulmbach (Axolabs GmbH)

ARC-520 in treatment naïve chronic HBV patients:



- High level knockdown of HBsAg in HBeAg positive patients
- HBeAg negative patients respond less well
- HBeAg transitional patient is intermediate

HBeAg positive patients likely produce significant amounts of HBsAg from integrated DNA not targeted by ARC-520

arrowhead pharmaceuticals

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 enzyme replacement therapy

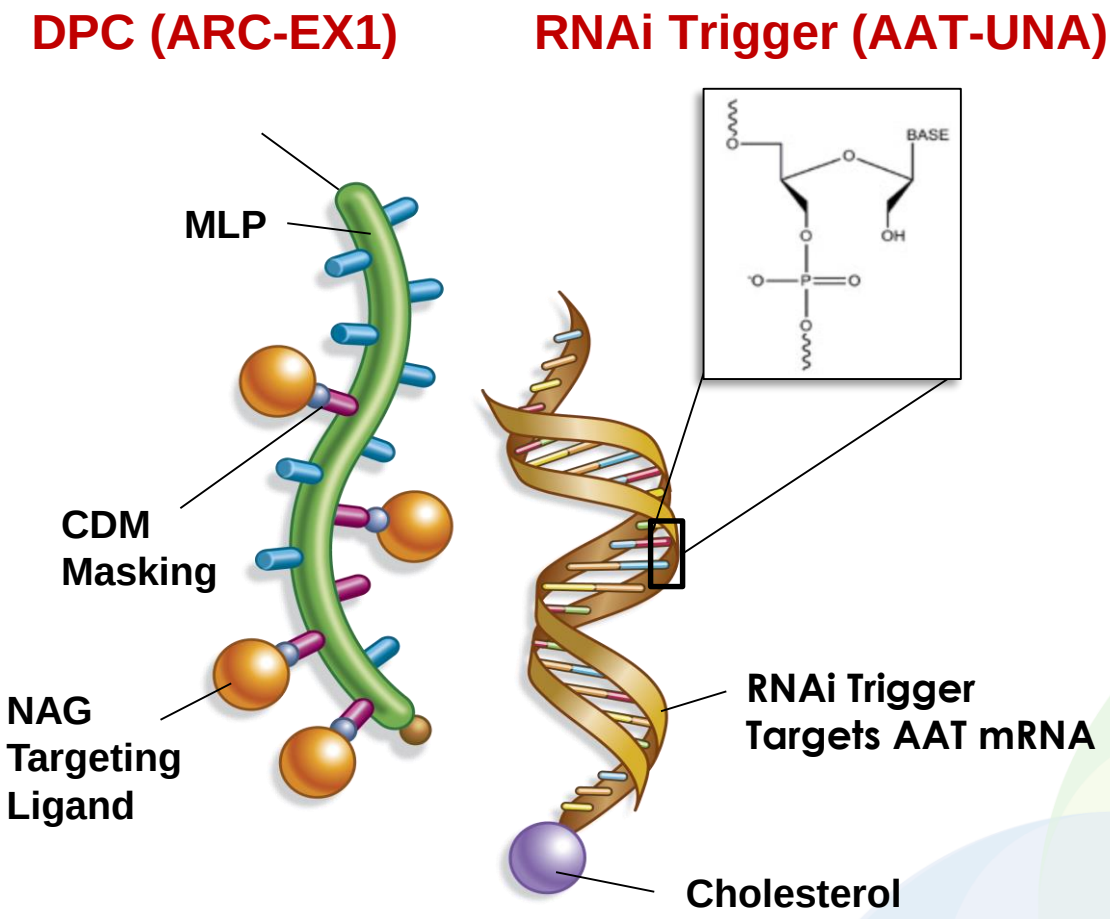
Liver

Accumulation of mutant Z-AAT protein can cause cirrhosis and HCC

↓

Currently no treatment

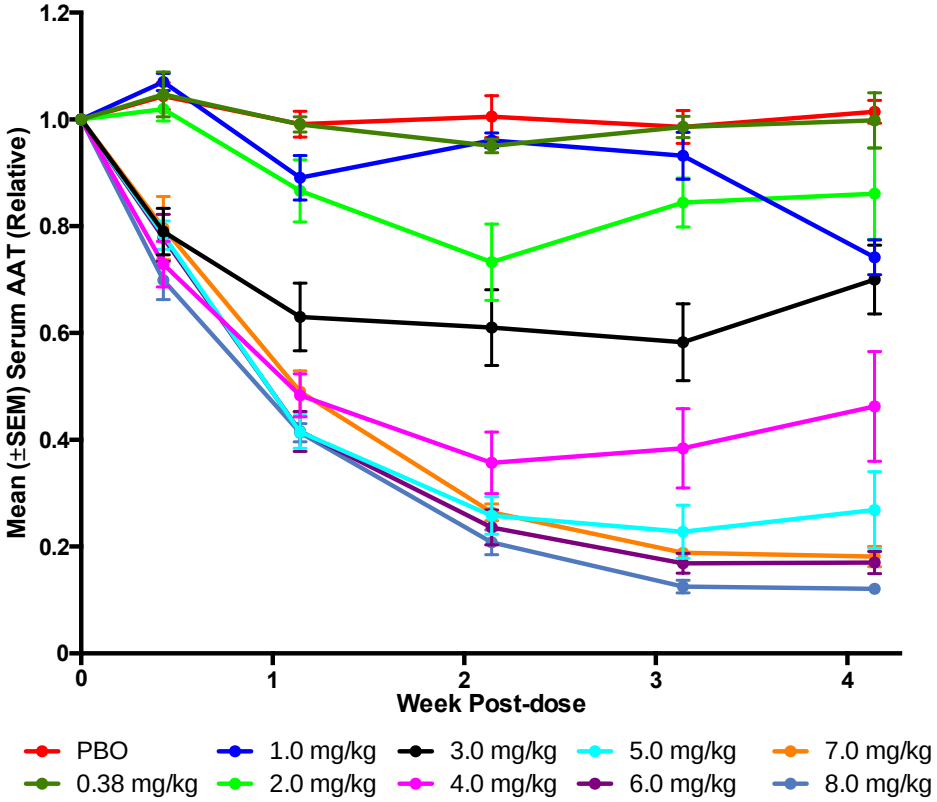
ARC-AAT: An RNAi therapeutic for AATD-associated liver disease using Dynamic PolyConjugate (DPC™) technology



MLP: melittin-like peptide
CDM: carboxy-dimethylmaleamide
NAG: N-acetyl-galactosamine

arrowhead pharmaceuticals

ARC-AAT Dose-response Serum AAT Reductions in normal volunteers



Dose Level (mg/kg)	3	4	5	6	7	8
Max KD	61.0%	76.1%	86.7%	87.1%	85.1%	89.8%
Mean Max KD ± SEM	45.3% ±6.8%	64.8% ±6.1%	78.1% ±4.4%	83.3% ±1.9%	82.6% ±1.3%	88.3% ±0.8%

arrowhead pharmaceuticals

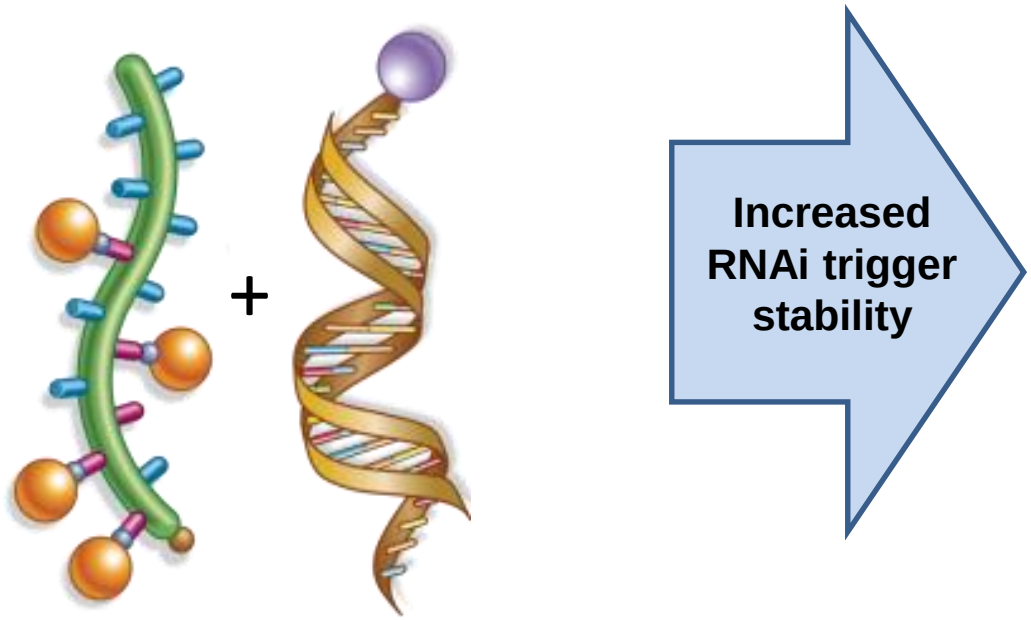
Just when things are going great……

- Toxicology testing with ARC-520 and ARC-AAT had shown that cholesterol RNA conjugates were benign. High doses of Nag-MLP, however, could produce toxicity.
- At the doses used in the clinic, our DPC™ programs were proving to have good safety and tolerability
- In our third DPC program – ARC-521 – the highest dose tested was increased and resulted in NHP deaths leading to a regulatory hold. *Ultimately, all 3 programs were discontinued.*
- In the last 5 years, RNA chemistry has advanced to the point that with targeted delivery, knockdown approaching that seen with endosomal escape has emerged.
- **Arrowhead had already made the transition internally**

Evolution of RNAi candidates at Arrowhead

Intravenous administration, "active" endosomal release

Subcutaneous administration, stabilized trigger

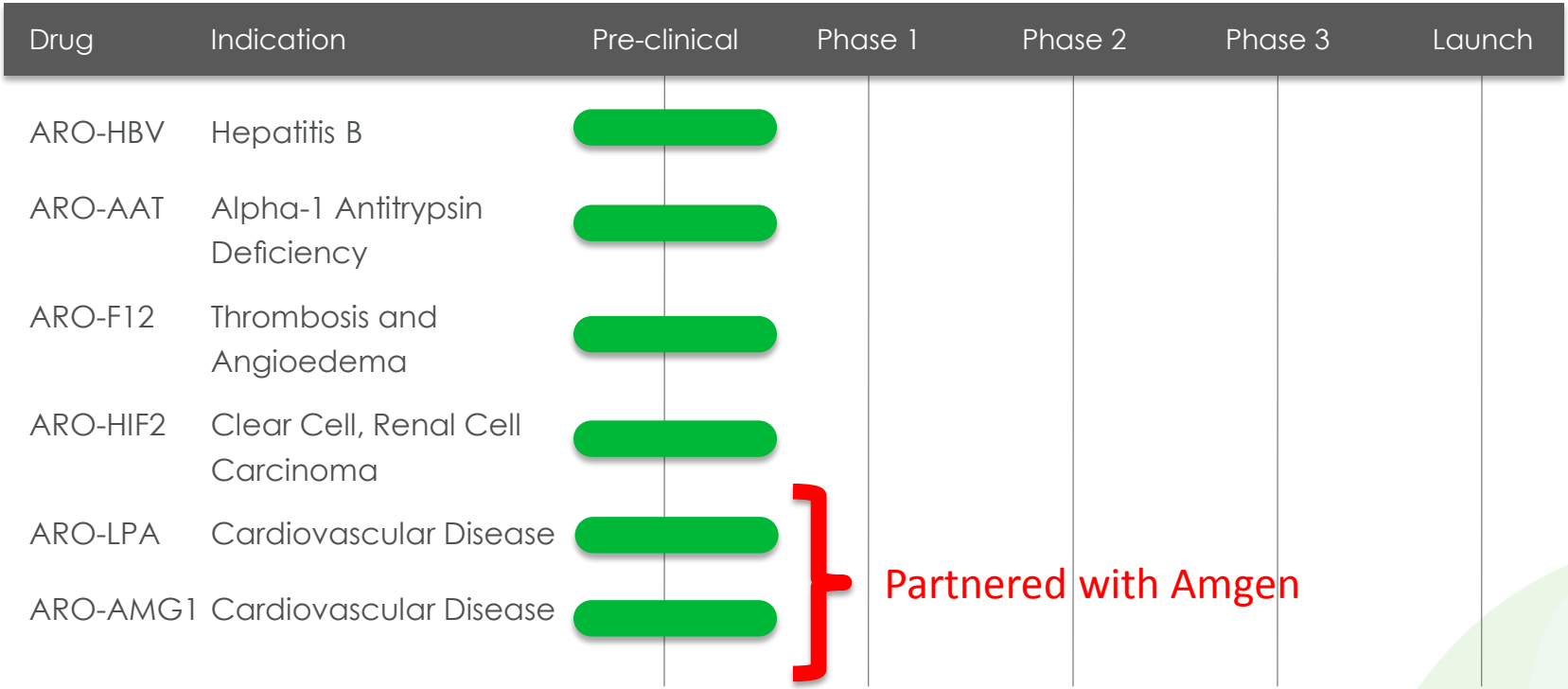


ARC-EX1 + cholesterol-linked RNAi triggers

Increased RNAi trigger stability

Ligand trigger conjugates

Novel Drugs that Treat Intractable Diseases



Diverse pipeline targeting high value, underserved indications

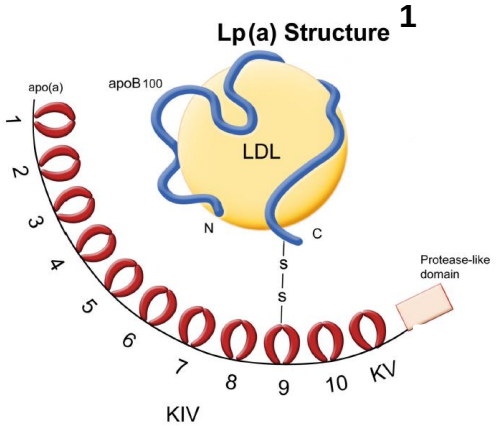
Discovery/development stage partnerships extract maximum value from platform

Clinical experience with HBV and AATD

arrowhead pharmaceuticals

Lp(a) background

- **Lp(a) is a heterogeneous lipoprotein particle expressed predominantly in liver**
  - Lipid rich particle composed of apolipoprotein(a) linked to LDL via a disulfide bond to apoB-100
  - Restricted to humans and non-human primates
- **Lp(a) levels in humans are genetically defined**
  - Levels not changed significantly with diet, exercise, etc.
  - ~25% of US population has >30 mg/dL (normal levels: 0.1 – 25 mg/dL)
- **Lp(a) is an independent risk factor for cardiovascular disease (CVD) through its atherogenic potential**
  - Higher levels of Lp(a) correlate with increased risk of CVD[2-4]
  - Indications include myocardial infarction, stroke, calcific aortic valve stenosis

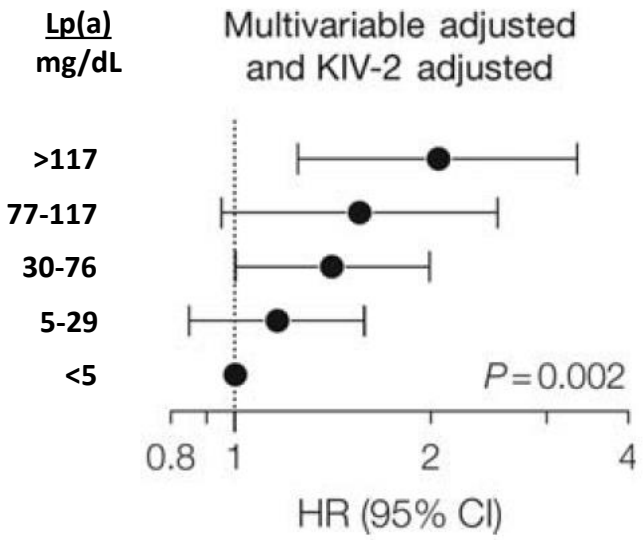


[1]Hoover-Plow J and Huang M (2013) Metabolism 62:479-491
[2]Nordestgaard BG *et al.* (2010) Eur. Heart J. 31:2844-2853
[3]Clarke R *et al.* (2009) N. Engl. J. Med. 361:2518-2528
[4]Kampstrup PR *et al.* (2009) JAMA 310:2331-2339

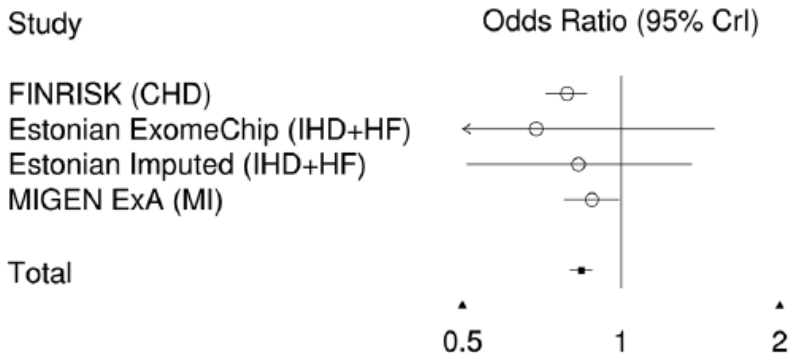
arrowhead pharmaceuticals

Lp(a) levels correlate with CV disease risk

Elevated Lp(a) – increased risk



LoF variants exhibit reduced risk

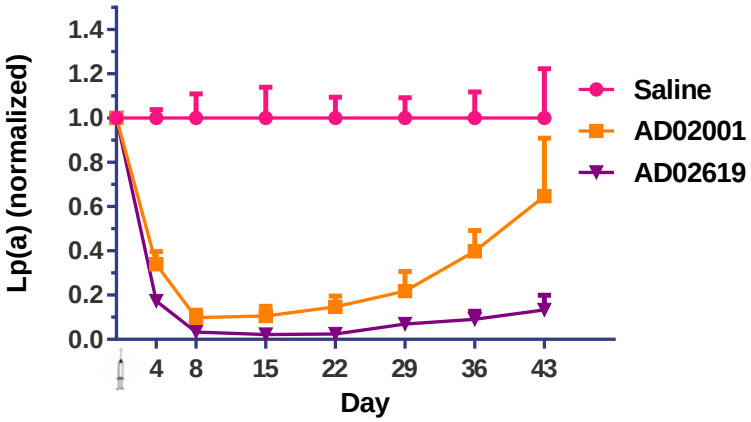


1. Nordestgaard *et al.* (2010) *Eur. Heart J.* 31:2844
2. Clarke *et al.* (2009) *NEJM 361*:2518
3. Kampstrup *et al.* (2009) *JAMA 310*:2331
4. Lim, E.T. et al. (2014) *PLoS Genet* 10:e1004494

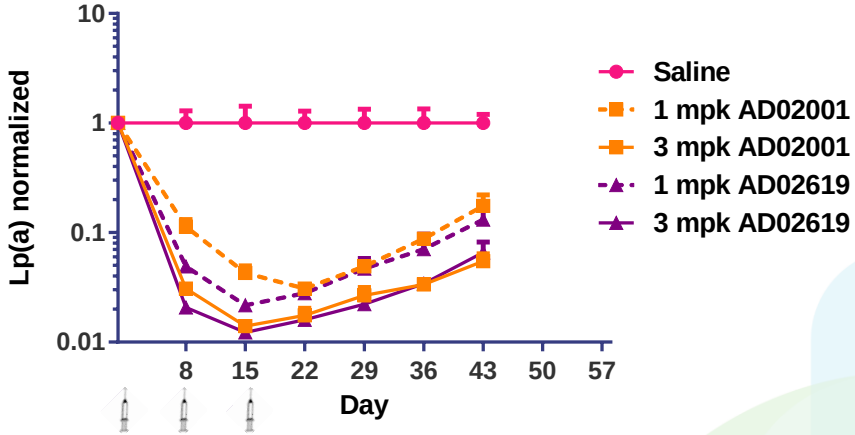
arrowhead pharmaceuticals

SQ RNAi trigger development – dose regimens

***Single** 3 mpk SQ RNAi trigger dose in Lp(a) Tg Mice, n=3 per group*

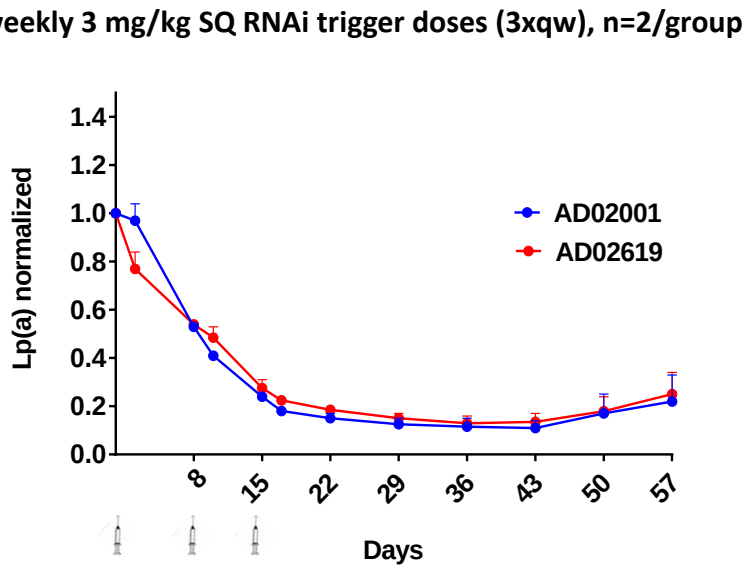


***Three weekly** 3 mpk SQ RNAi trigger doses (3xqw) in Lp(a) Tg mice, n=4 per group*



- Dose response observed for both AD02001 and AD02619
- In multiple-dose studies, both AD02001 and AD02619 exhibit greater depth and duration of knockdown compared to a single dose

Trigger Evaluation in NHPs



- RNAi triggers AD02001 and AD02619 exhibit similar depth and duration of Lp(a) reduction in NHP
- Lp(a) reduction of 85-90% observed between days 29 and 43, with >75% knockdown at 6 weeks after the final dose

Third and fourth generation triggers show continued potency gains[1]

[1]Data unpublished

Why are we developing Factor 12 ?

- The long sought alternatives to Coumadin - after a slow start - are now major drugs.
  - They are decidedly easier to use
  - They produce better outcomes
  - Reversibility agents should be available soon
- However, the risk of bleeding remains significant and, as seen by the constant tort lawyer ads, leaves a major unmet need still unsatisfied
- Also, adherence remains a bane and undoubtedly effects real world outcomes in the post-elective surgery setting
  - A 2-3 times delivered subQ administered in office/hospital would eliminate this concern
- Arrowhead's Factor 12 RNAi program is designed to address both issues

F12 is an attractive target for RNAi therapeutics

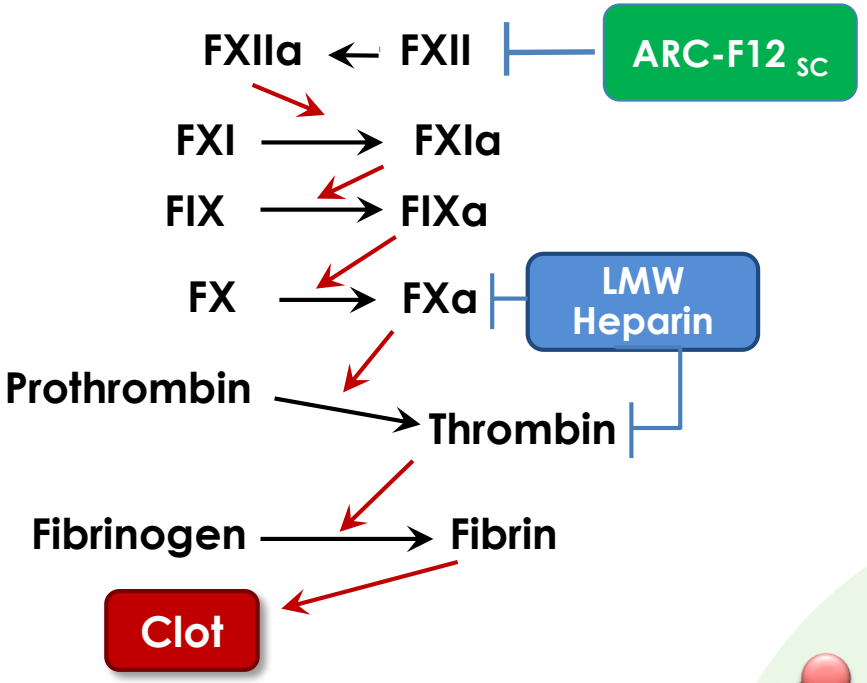
Factor XII (F12)

- Key component of contact activation pathway
- Predominantly expressed in the liver; circulates in plasma

F12 inhibition is genetically validated

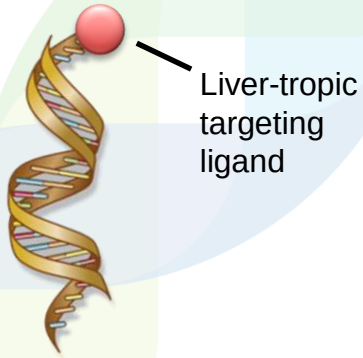
- F12-deficient mice:
  - viable and fertile[4]
  - do not show bleeding defects[4,5]
  - protected from thromboembolic disease[5]
- F12 deficiency in humans is *not* associated with either bleeding or thrombotic disorders[1,2,3]

Contact (intrinsic) coagulation cascade



ARO-F12 RNAi trigger

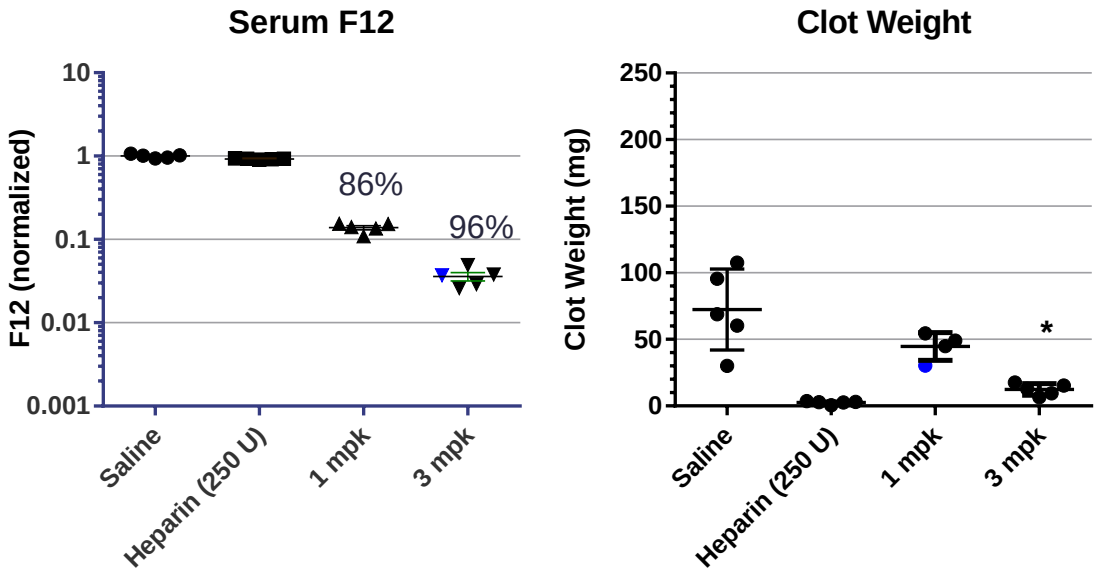
- Liver-tropic targeting ligand
- Injected subQ



[1] Girolami A. *et al.* (2004) J. Thromb. Thrombolysis 17:139–143
[2] Koster A. *et al.* (1994) Br. J. Haematol. 87:422–424
[3] Zeerleder S. *et al.* (1999) Thromb. Haemost. 82:1240–1246
[4] Pauer, H. U., *et al.* (2004) *Thromb. Haemost.* 92:503
[5] Renne, T. *et al.* (2005) *J. Exp. Med.* 202:271
* Figure modified from Albert-Weissenberger, C., *et al.* (2014) *Front. Cell Neurosci.* 8:345

Rat arterio-venous shunt model – dose responsive

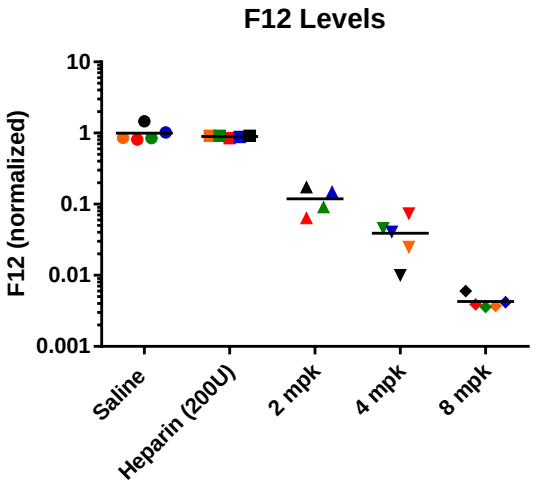
- ***Measure thrombus weight by collection from Tygon tubing shunt***
- ***Single dose ARO-F12, 14 days prior to assessment, n=5/group***

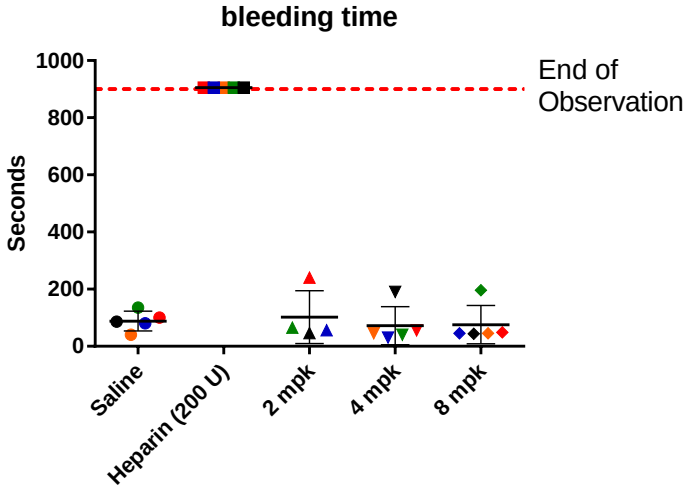


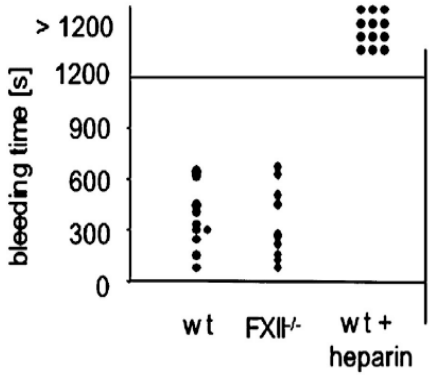
- **Dose response observed for serum F12 levels and thrombus weight**
- **Statistically significant reduction in thrombus weight at >95% F12 knockdown (p=0.002)**

No increase in bleeding risk in mouse model

- ***Transverse cut of tail vein, monitor time to clotting***
- ***Single dose, 7 days prior to assessment, n=5/group***







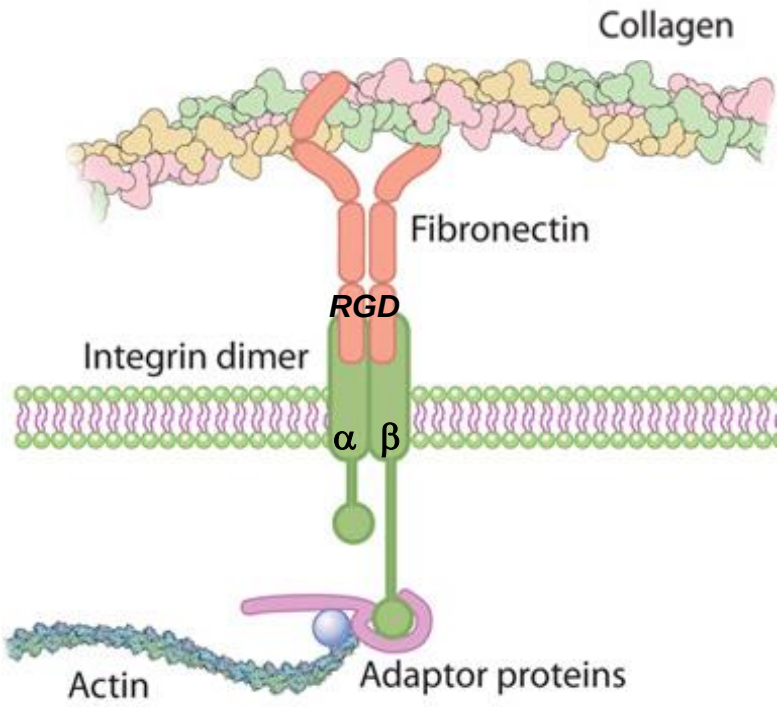
- **No increased bleeding observed, even with >99% knockdown of F12 levels**
- **Consistent with F12 $^{(-/-)}$ mice showing no increase in bleeding over wild type controls**

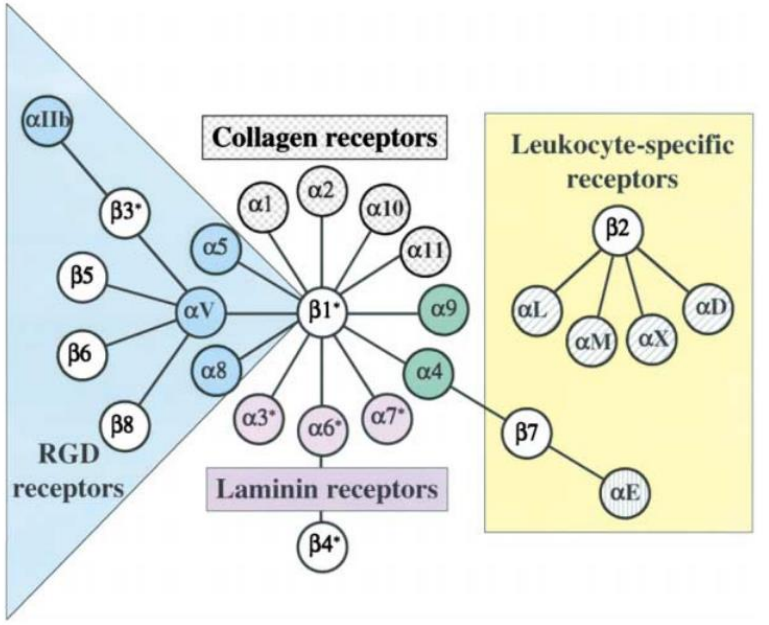
arrowhead pharmaceuticals

Right panel from: Renné T, et al. (2005) J. Exp. Med. 202:271-281

Proprietary Tumor Targeting

- Targeting integrin receptors with proprietary RGD mimetic ligands
- Cell adhesion and signaling
- Heterodimers: 18 a and 8 b subunits
- Diverse natural ligands: ECM, growth factors, etc.
- RGD mimetic: high-affinity, selective aV integrin ligand

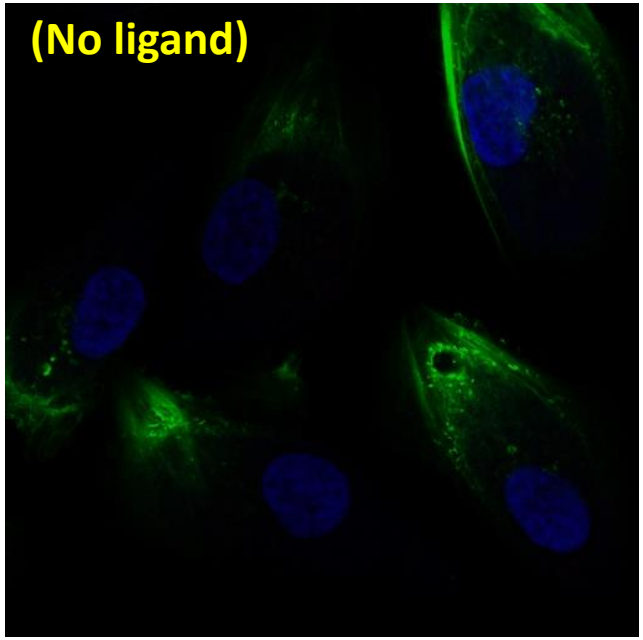


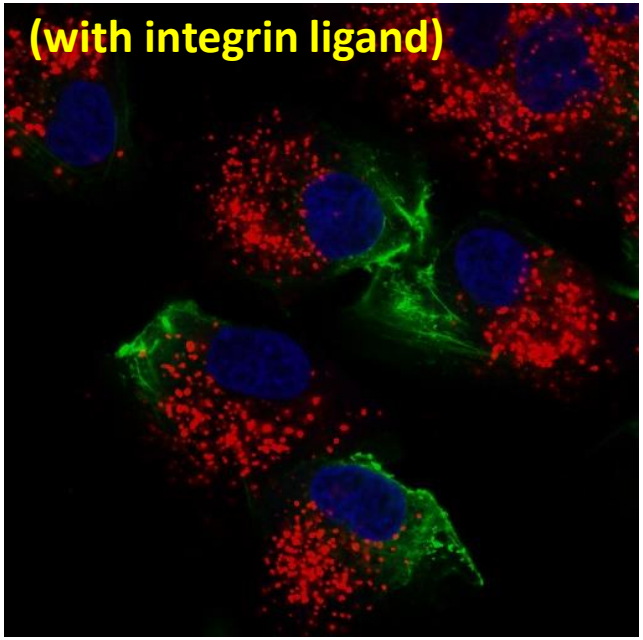


- aV integrins overexpressed in many tumors
- Promote angiogenesis and invasiveness
- aV integrin ligands: tumor delivery & imaging

arrowhead pharmaceuticals

Ligand-dependent uptake in ccRCC tumor cell line





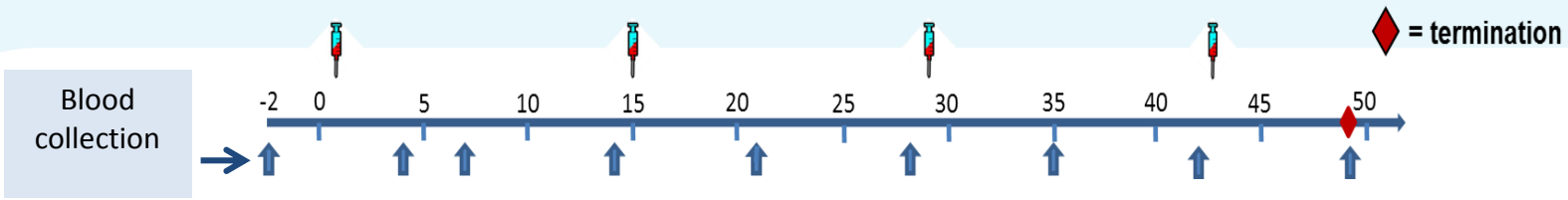
Green: Actin
Blue: Nuclei
Red: RGD-DPC

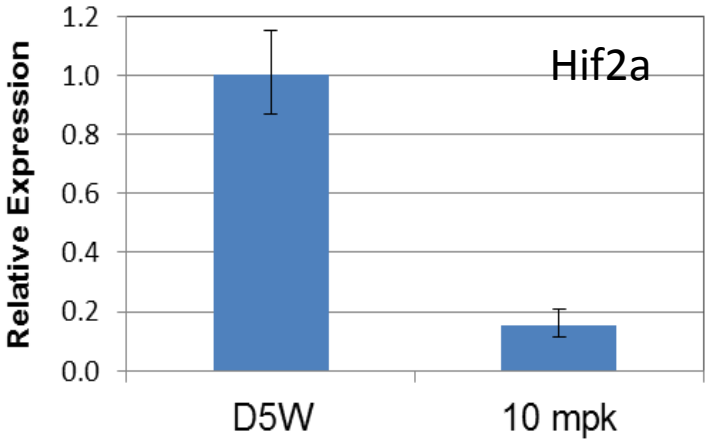
B Given, OTS, 2015

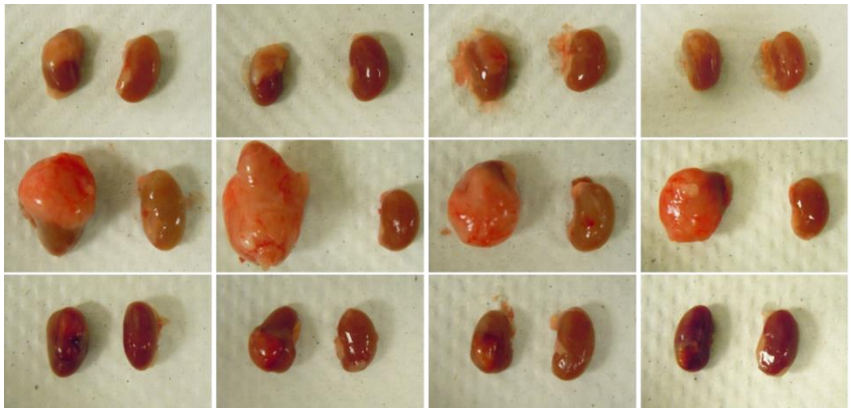
HIF2α is an important driver in ccRCC

- HIF2a as gene target for clear cell renal cell carcinoma (ccRCC)
  - Normally expressed in response to low oxygen conditions
  - Overexpression of HiF2a in tumors drives tumor growth and metastasis
  - Overexpression of HIF2a is due to mutations in Von Hippel-Lindau protein which normally promotes degradation of HIF2a
  - 90% of ccRCC have Von Hippel-Lindau mutations

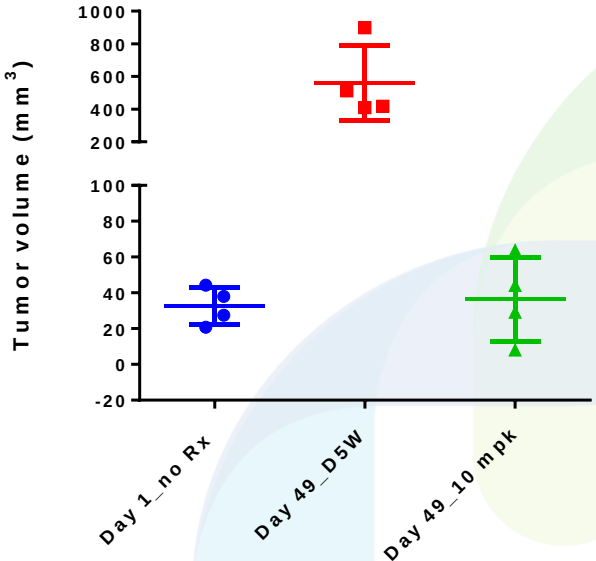
Tumor growth inhibited after 4 bi-weekly doses in orthotopic ccRCC mice







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



arrowhead pharmaceuticals

B Given, OTS, 2015

What we've learned over the past 5 years

- Endosomal escape can be a powerful tool to achieve rapid release of intact RNAi triggers into the cytoplasm
  - We have demonstrated single dose knockdown nearing 2 logs, >3 logs with multiple dosing in humans
  - Tolerability in humans was good at therapeutically maximal doses
  - Toxic doses in NHPs could be fatal
  - Nag-MLP required IV delivery, which was not advantageous for marketing
- Using DPC™s, we were able to achieve solid proof of concept in HBV and AAT, demonstrating the power of RNAi
- We are far advanced with ligand targeted conjugates for hepatic subcutaneous delivery in HBV, AAT, Lp(a), Factor 12 and other unannounced targets.
- We have also demonstrated successful extra-hepatic delivery in renal cell carcinoma
- Expect to see us back in clinical studies next year

Arrowhead Madison