



RNAi Subcutaneous Delivery Platform Development and ARO-F12

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Presentation Outline

- Arrowhead Pharmaceuticals
- RNAi Subcutaneous (subQ) platform development for hepatic delivery
 - Targeting ligand at 5' end of sense strand
 - Proprietary linker development
 - Novel phosphate mimic
- ARO-F12
 - Early generation
 - Later generation

Company Overview

- Arrowhead (NASDAQ: ARWR) - currently ~90 employees
- Corporate HQ in Pasadena, CA. R&D facilities located in Madison, WI
- Active in RNAi since 2001, capabilities to *rapidly* develop RNAi-based drug candidates
 - Acquired Roche (2011) and Novartis (2015) RNAi businesses
- Active pipeline programs
 - Hepatic targets: HBV, AATD, F12, LPA & others
 - Extrahepatic targets: oncology
- Recent >\$670M collaboration announced with Amgen in cardiovascular disease – September 2016

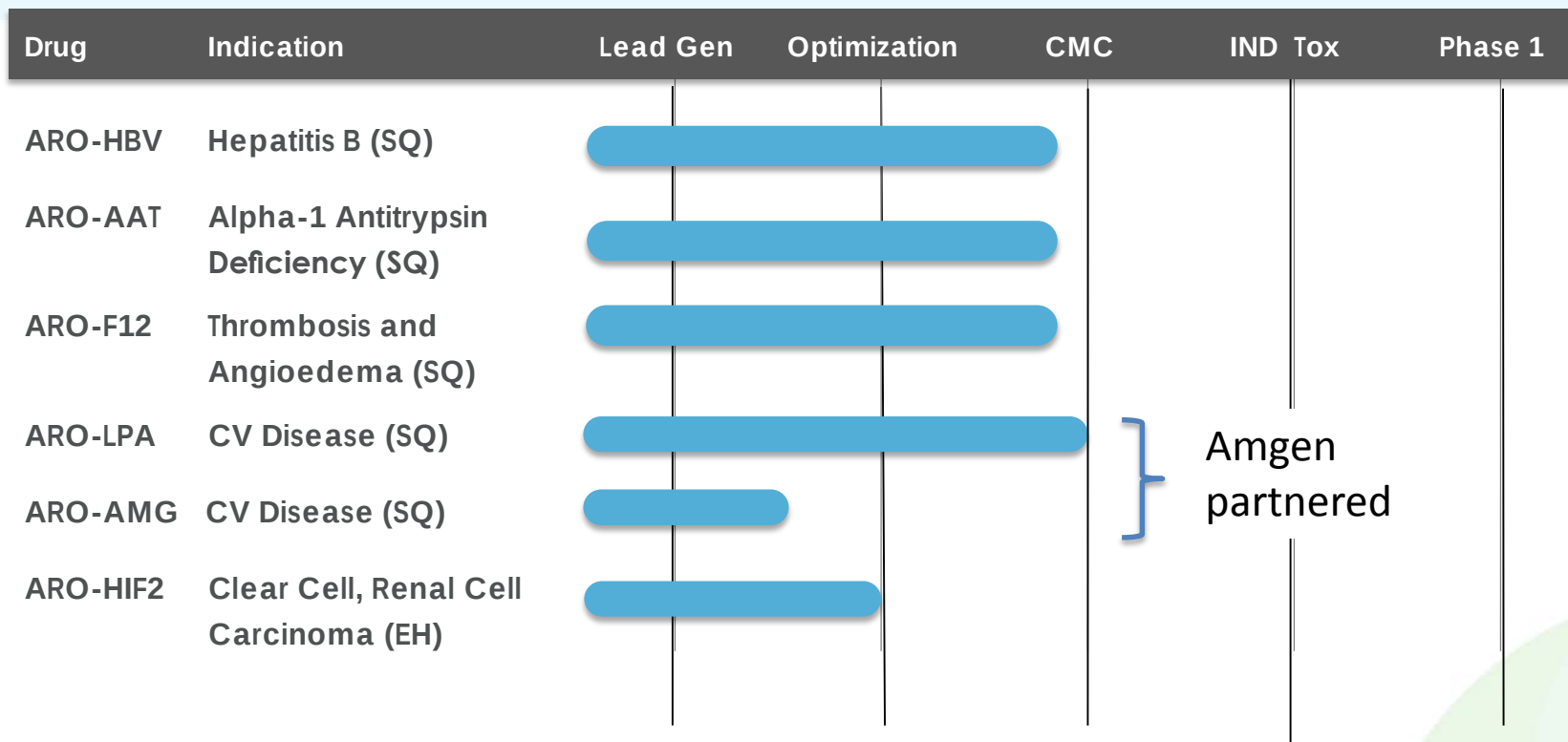
Arrowhead R&D Facility in Madison, Wisconsin

Newly renovated (2016)
laboratories, >40,000 total sq. ft.
space



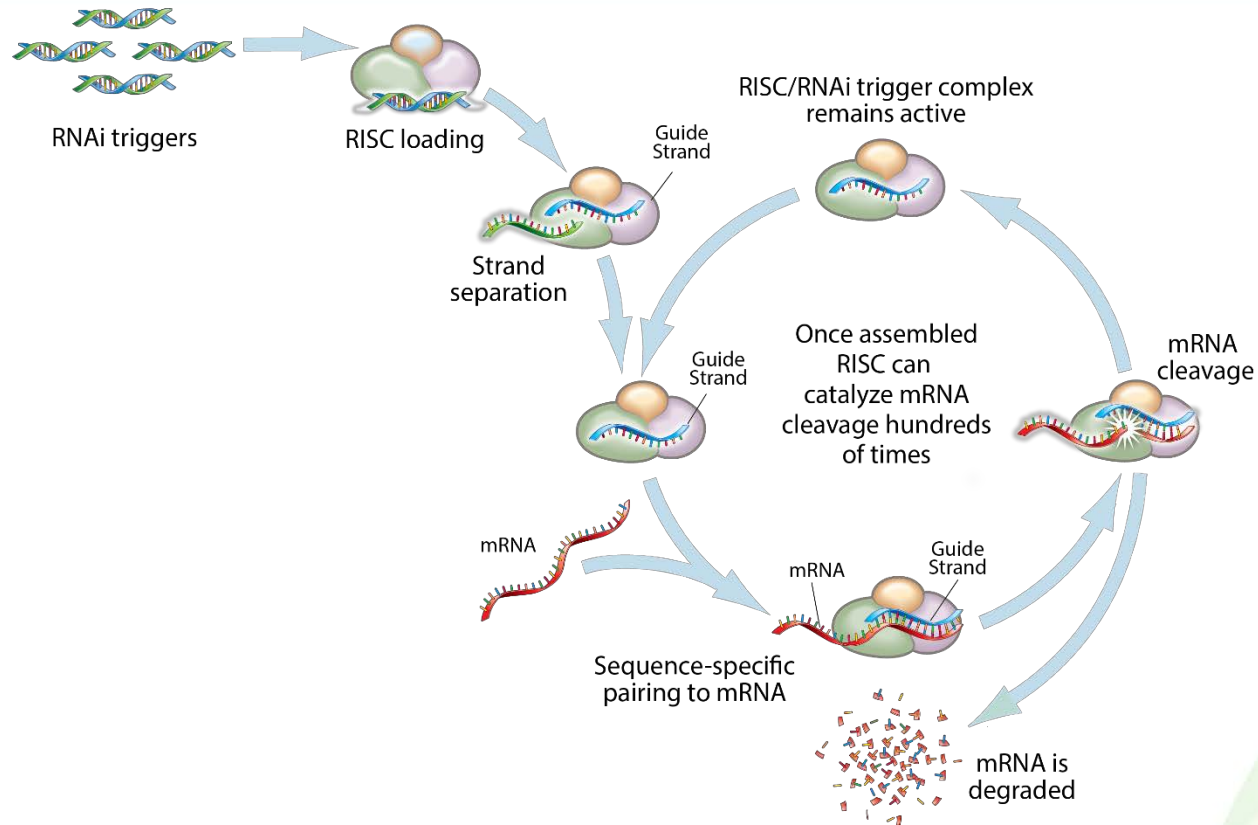
- In-house capabilities:
 - Discovery chemistry – RNAi trigger design and modification
 - Oligo, peptide, polymer, small molecule synthesis and analytics
 - Oligonucleotide biodistribution, DMPK/ADME
 - Cell culture, confocal microscopy, flow cytometry, molecular biology
 - Small animal facility (plus primate colony at University of Wisconsin)
 - Animals models for CV/metabolic, viral and oncology
 - Safety assessment capabilities including clin chem and histopath
 - Process development and analytical chemistry

Pipeline Breadth At Discovery Stage



SQ = subcutaneous, EH = extrahepatic,
EH incorporates IV and SQ routes of administration

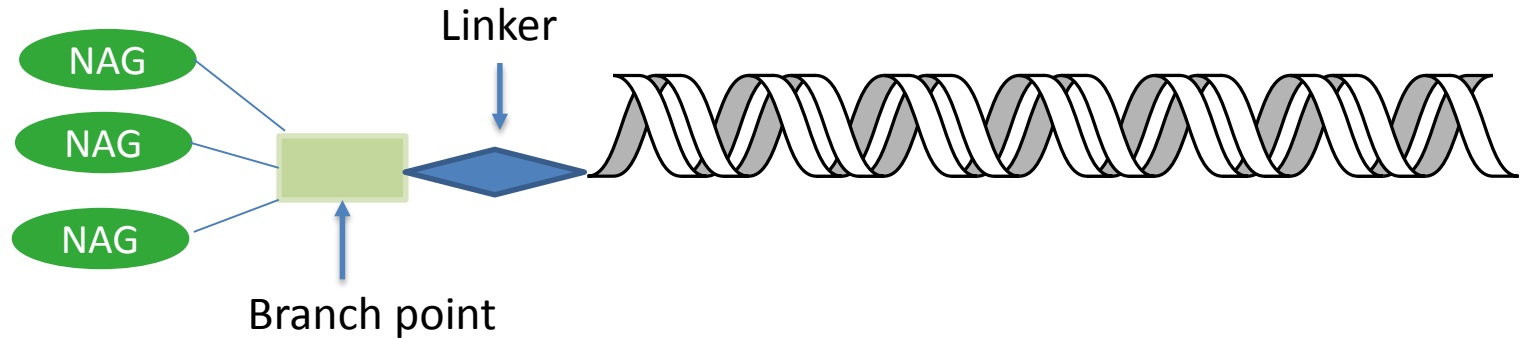
Target the Gene, Silence the Disease



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

Subcutaneous (SubQ) Platform Development for Hepatic Delivery

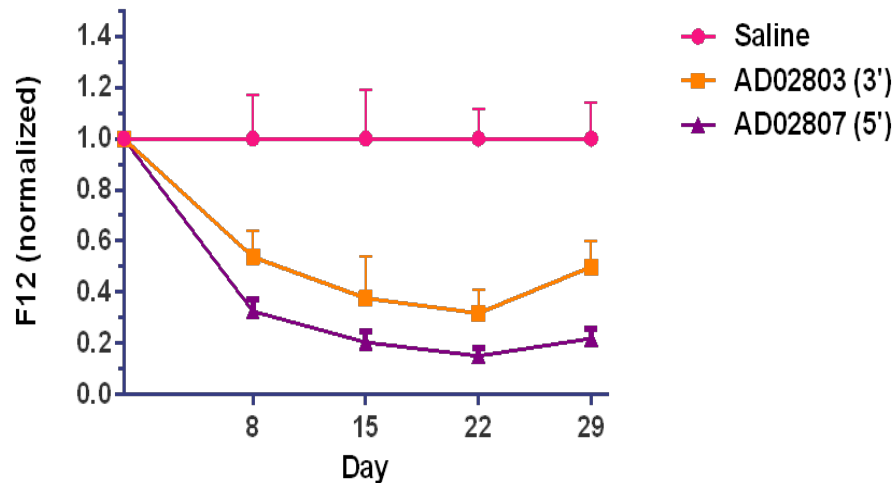
N-Acetyl-Galactosamine (NAG) Linker Investigation



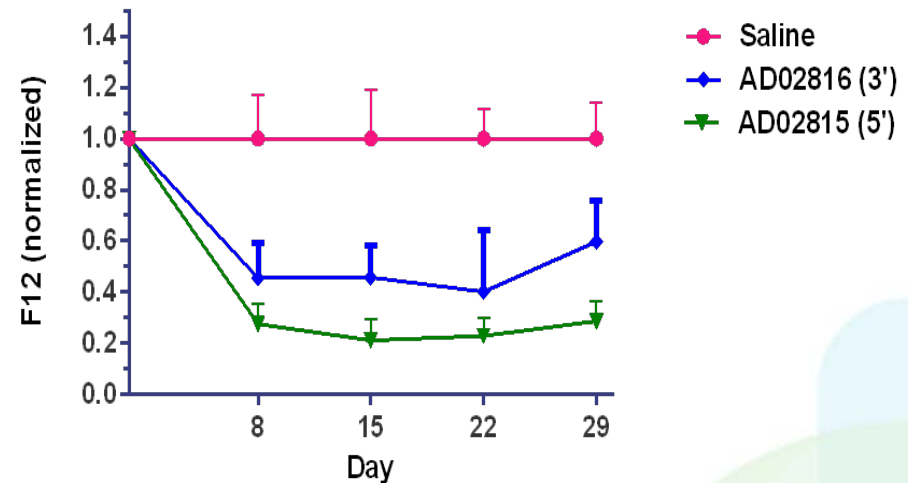
- **NAG cluster attachment point: 3' end or 5'end?**
 - Impact on potency
 - COG consideration
- **Linker study**

NAG Cluster at 5' End of Sense Strand Superior to 3'End

3 mpk RNAi trigger, Single SQ dose, n=3/group



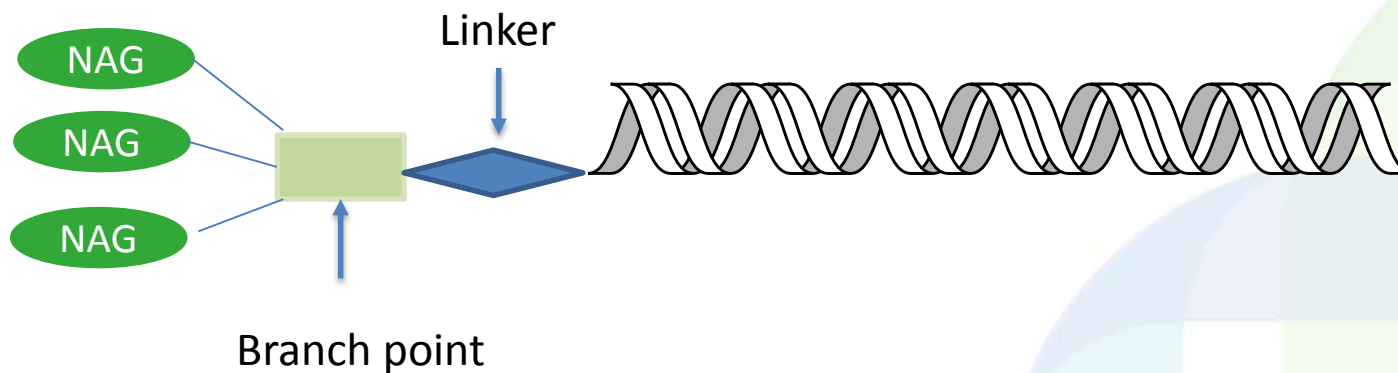
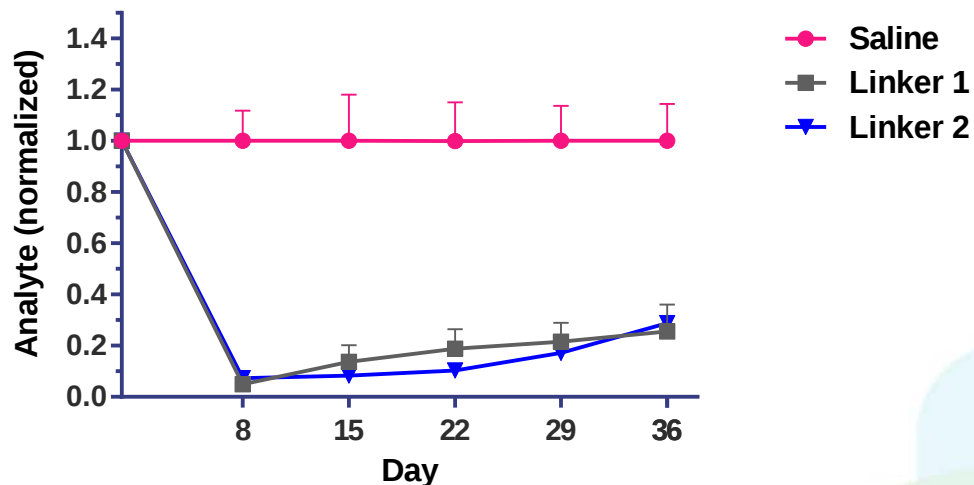
3 mpk RNAi trigger, Single SQ dose, n=3/group



- 5'end NAG cluster compared with 3'end NAG cluster
 - More potent conjugate compared with 3'end NAG cluster
 - COG effective
 - Most expensive moiety installed last

NAG Cluster Linker Study

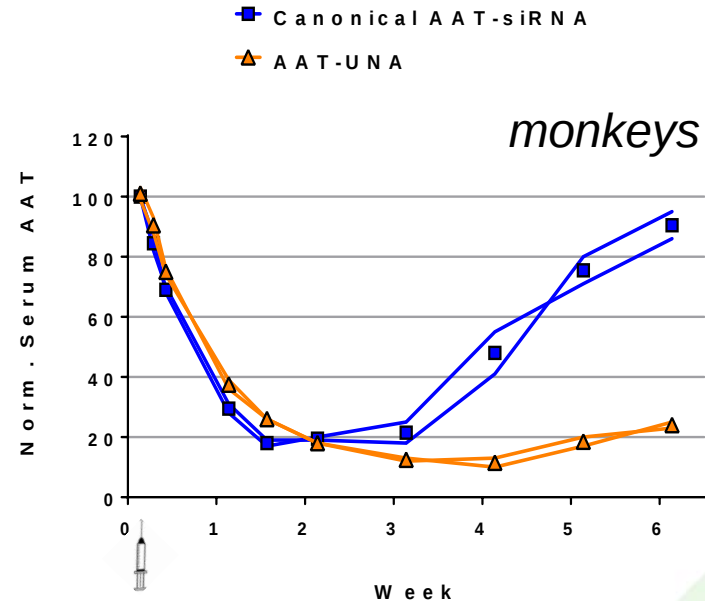
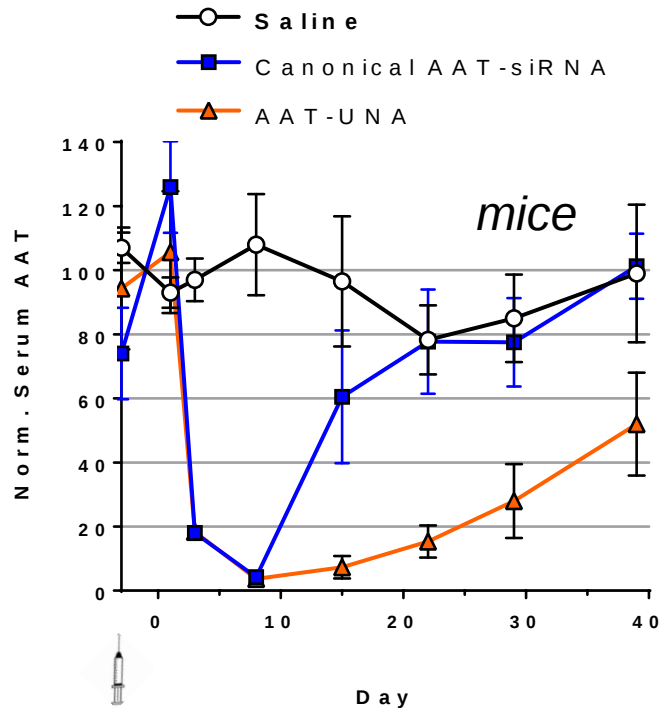
- Carried out linker SAR studies
- Discovered and developed Arrowhead proprietary linkers
 - Equal or greater KD in *in vivo* studies in multiple programs
 - Manufacturability



Modification of RNAi Sequences

- Chemical modifications
 - Use of UNA
 - PAZ ligand
- Novel phosphate mimic development
 - Metabolic stability improvement

UNA Improves Target Knockdown in ARC-AAT Program



Knockdown at nadir:

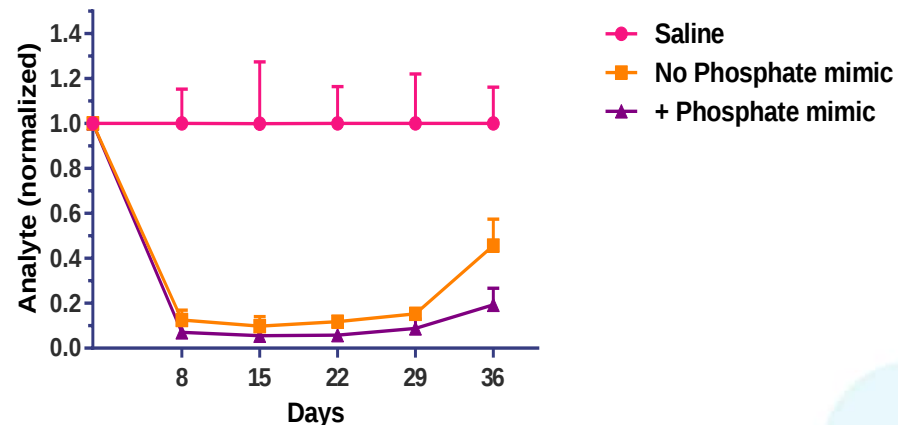
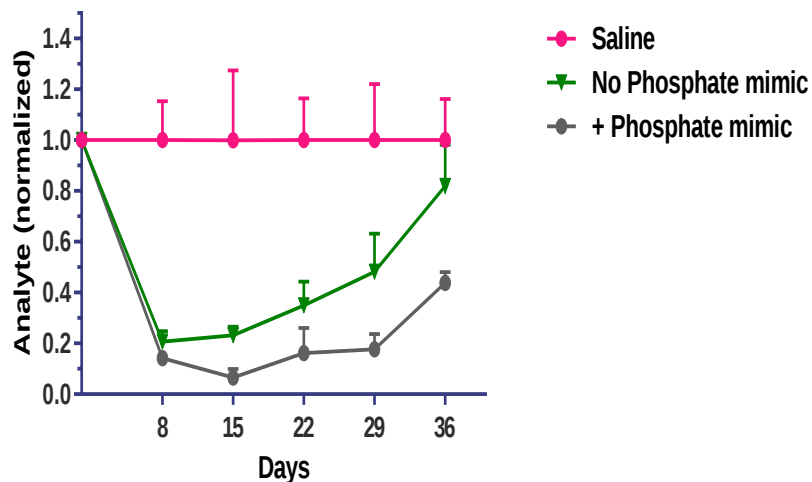
UNA $\approx$ canonical siRNA

Duration of effect:

UNA > canonical siRNA

- Used with DPC, IV delivery

Proprietary Phosphate Mimic Increases Pharmacological Activities



Arrowhead proprietary phosphate mimic increases depth of KD and duration in *in vivo* studies in multiple programs

ARO-F12 Program

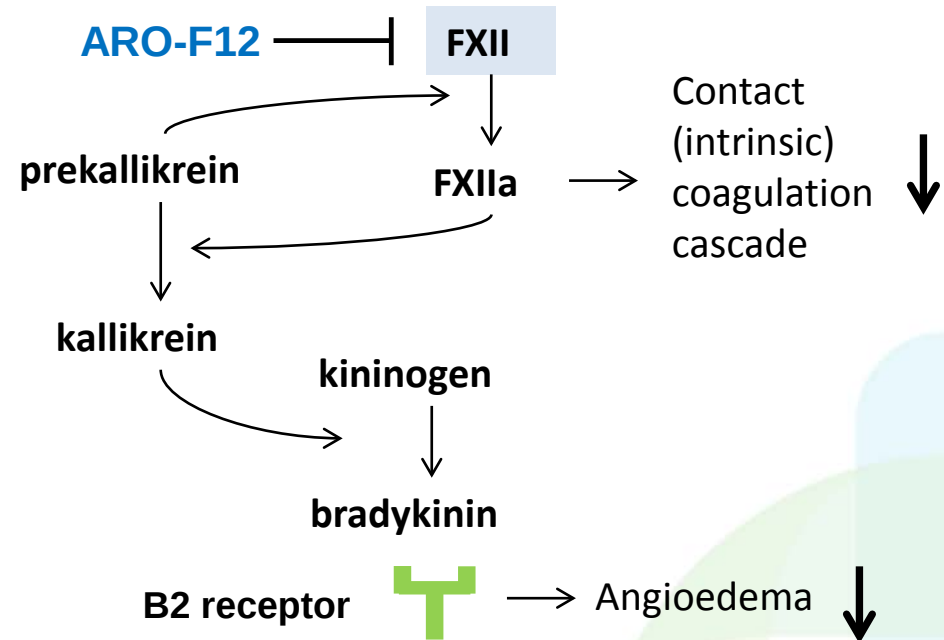
F12 is an Attractive Target For RNAi Therapeutics

Factor XII (F12)

- Key component of contact activation pathway (thrombosis) and kinin-kallikrein system (angioedema)
 - Cleavage of FXII by prekallikrein generates FXIIa: FXIIa generates FXIa (coagulation) and kallikrein (angioedema)
 - Predominantly expressed in the liver; circulates in plasma

F12 inhibition is genetically validated

- F12-deficient mice:
 - viable and fertile⁴
 - do not show bleeding defects^{4,5}
 - protected from thromboembolic disease (stroke, pulmonary embolism)⁵
- F12 deficiency in humans is not associated with either bleeding or thrombotic disorders^{1,2,3}



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

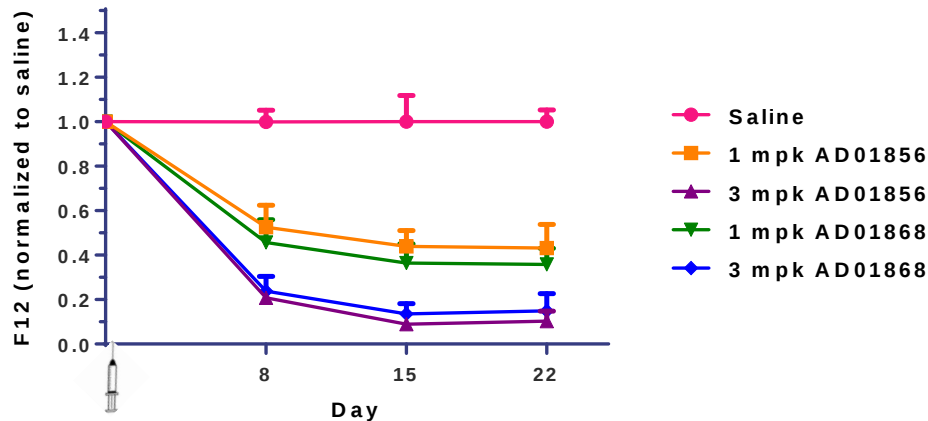
⁴ Pauer, H. U., *et al.* (2004) *Thromb. Haemost.* 92:503

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

Early Generation RNAi Triggers – Mouse *in vivo* Study

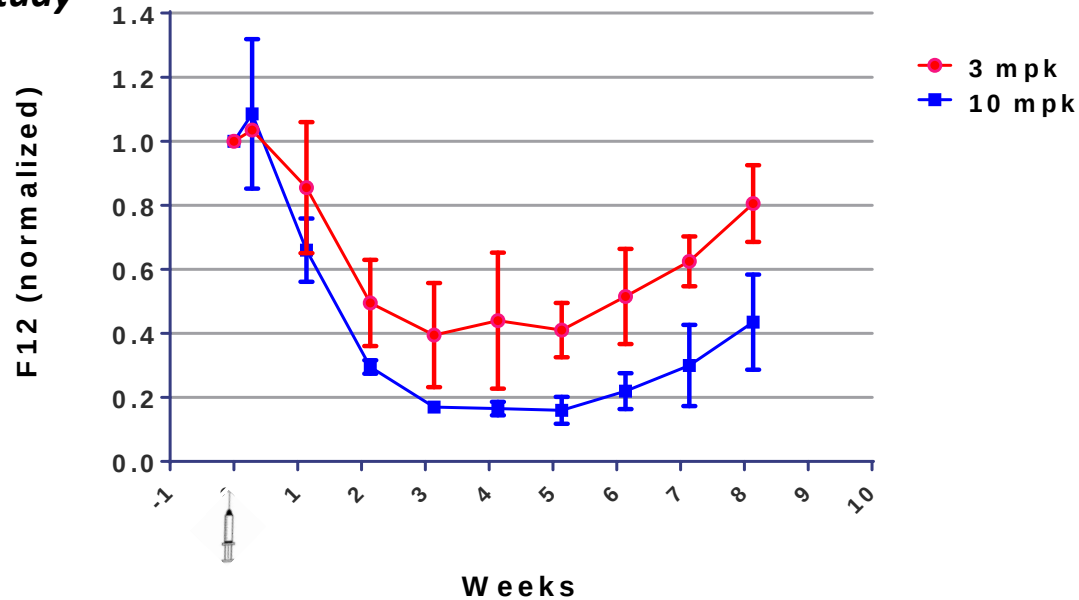
Single SQ dose, WT mice



- Dose response observed with both AD01856 and AD01868
- >85% knockdown at day 15 for both triggers at 3 mg/kg dose
- ~60% knockdown at day 15 at 1 mg/kg dose

Early Generation RNAi Triggers: Evaluation in NHP

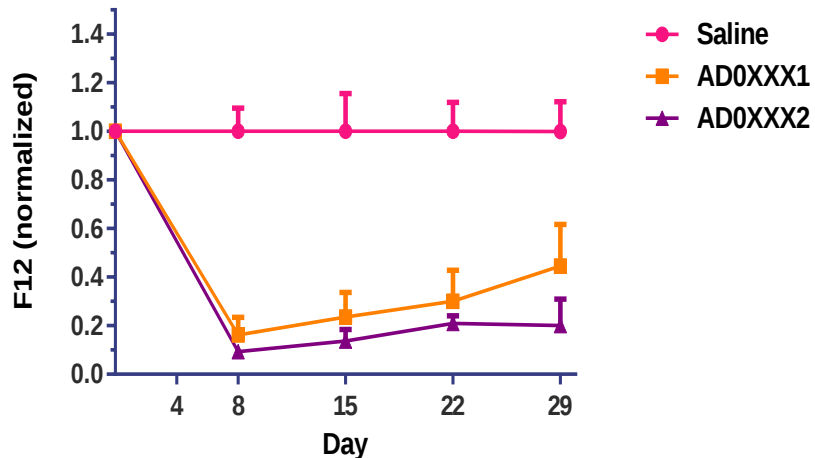
Single SubQ dose study



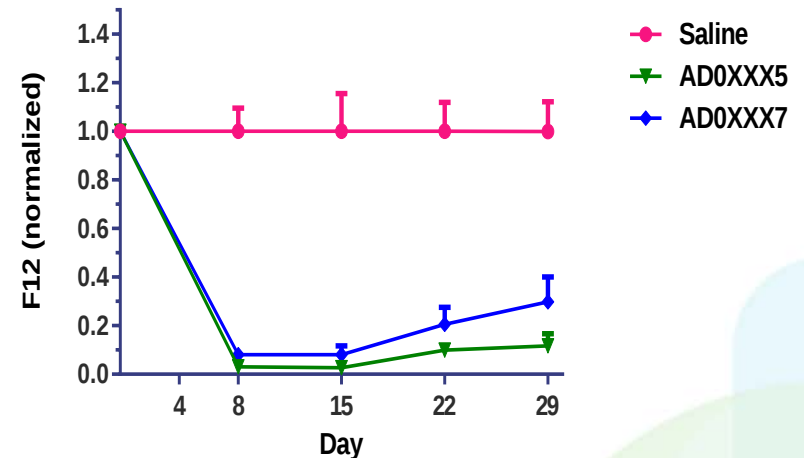
- ~85% knockdown of F12 observed at 3-5 weeks post 10 mg/kg injection
- Dose response observed

Later Generation RNAi Conjugates – Increased Potency and Duration

*1mpk RNA conjugate
Single SubQ dose
Mouse study*



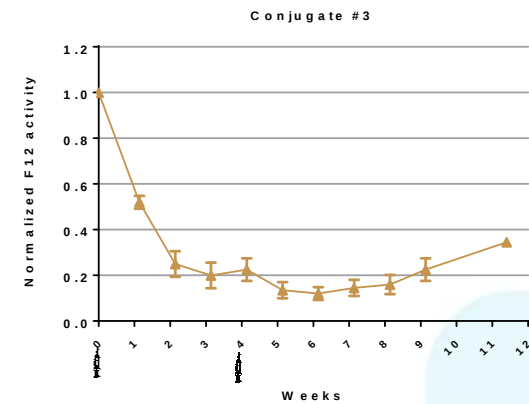
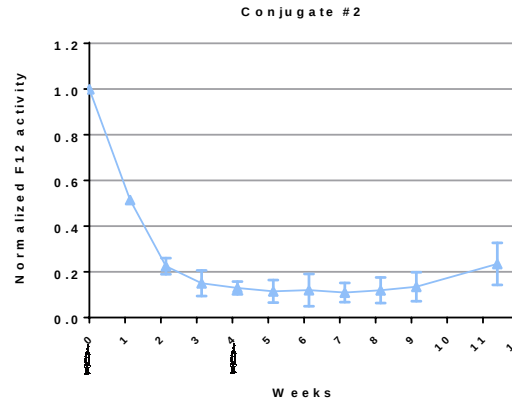
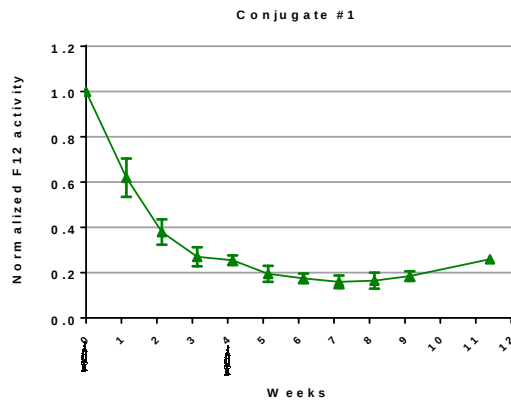
*1mpk RNAi conjugate
Single SubQ dose,
Mouse study*



- **Chemistry modifications improved both level of knockdown and duration**
 - **97% knockdown and duration of effect (~90% knockdown at 1 month) at 1 mg/kg dose**

Later Generation RNAi Conjugates in NHP Studies

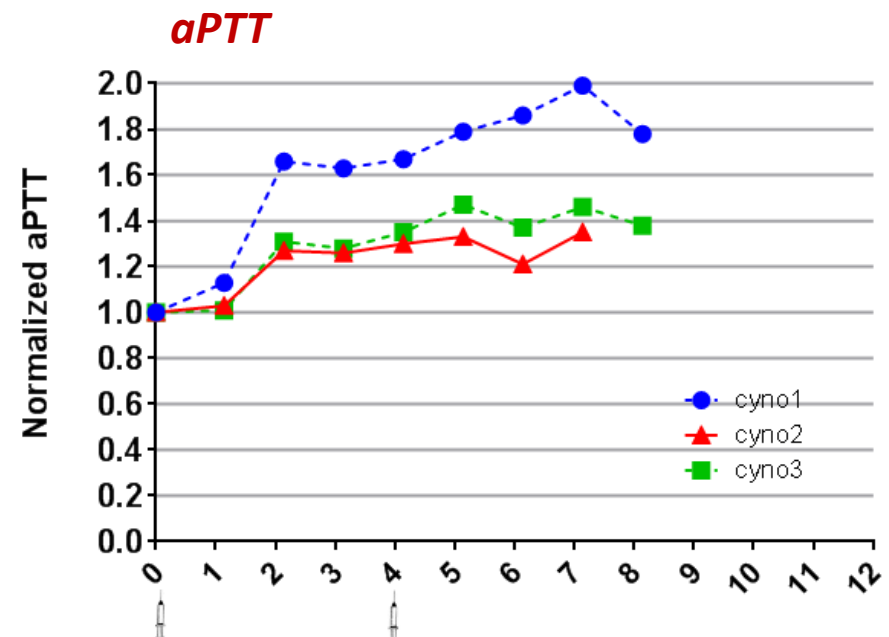
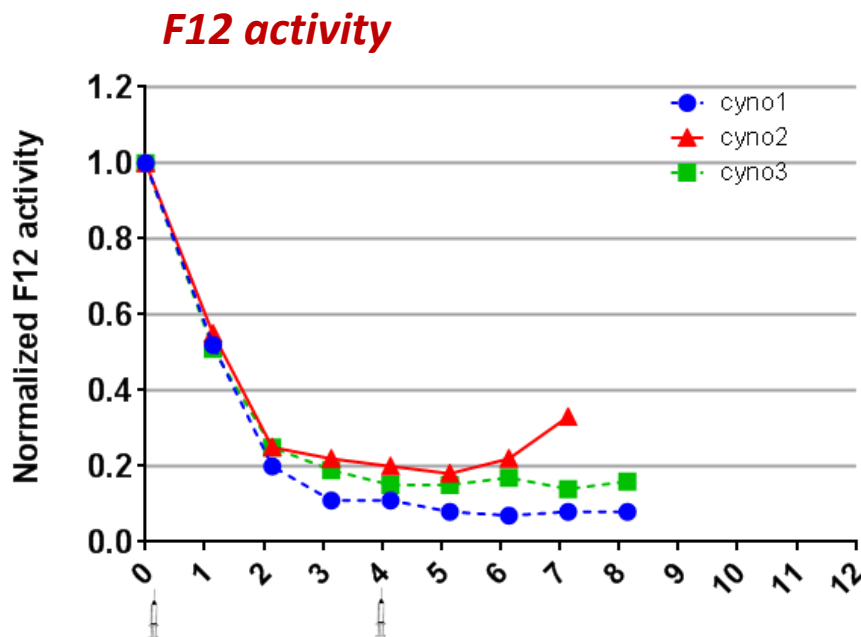
SQ delivery on Day 1 (3 mpk) and Day 29 (1.5 mpk)



- Achieved >90% knockdown of F12 in NHP after the 2nd dose at 1.5 mg/kg with up to 5 weeks duration

Knockdown of F12 in NHPs Correlates with Increase in aPTT

- Initial subcutaneous dose of 3 mg/kg, followed by 1.5 mg/kg at week 4
- One NHP did not receive second dose (solid line)



>1 log₁₀ knockdown of F12 activity correlates with substantial increase in aPTT (Activated Partial Thromboplastin Time)

Summary

- **NAG-RNAi Trigger Conjugate: Arrowhead's Novel Subcutaneous Liver Delivery Platform**
 - 5' end NAG cluster
 - Novel linker to NAG cluster
 - Proprietary phosphate mimetics
- Enhance potency
- Reduce COG
- Arrowhead Pharmaceutical has demonstrated high knockdown levels (>95%) in mice and with > 1 month duration of effect at 90% KD at dose of 1 mg/kg in F12 program
- >90% reduction in serum F12 in NHPs, with long duration of effect at 1.5 mg/kg maintaining dose after 3mg/kg loading dose



**NAG-RNAi trigger
conjugate**

Acknowledgement

Arrowhead Pharmaceutical

Chemistry Department

Biology Department