Discovery and Development of Arrowhead Clinical Candidates ARO-AAT and ARO-HBV

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arrowhead
pharmaceuticals

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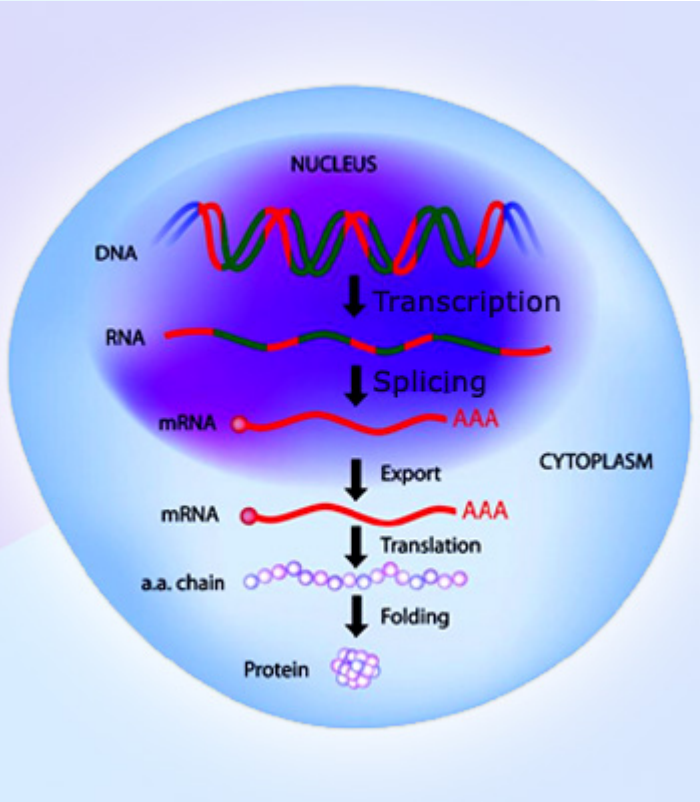
- I am an employee and shareholder of Arrowhead Pharmaceuticals, Inc.

Outline

- RNA Interference
- Arrowhead's Targeted RNAi Molecule (TRiM™) platform for targeting hepatocytes
- Discovery and development of Arrowhead clinical Candidates
  - ARO-AAT
  - ARO-HBV

RNAi Therapeutics – the Promise and Advantages

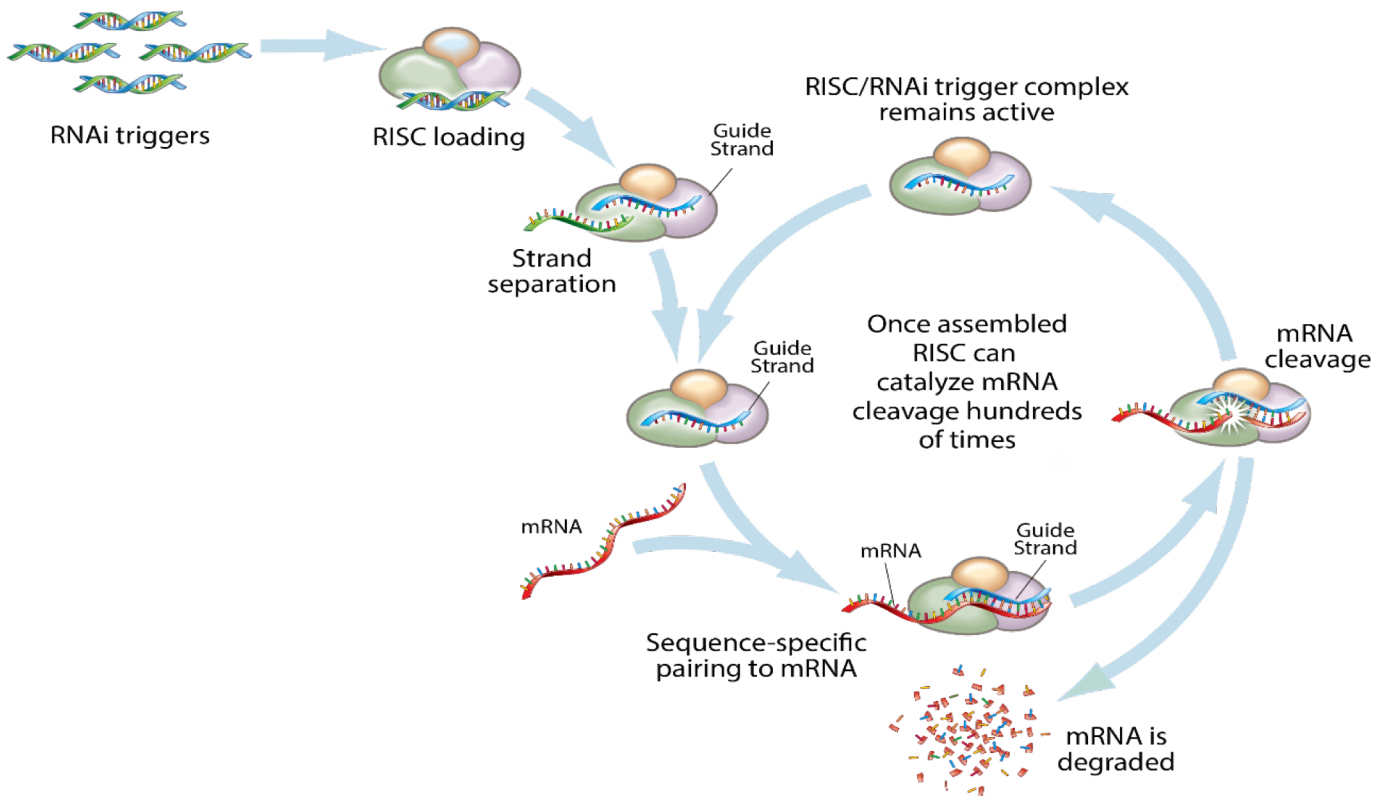
- Small molecule pharmaceuticals target proteins
  - Enzymes
  - Receptors
- RNAi
  - Cleave mRNA
    - Stop the translation process
    - Block the production of disease causing proteins
- The promise:
  - Treat and cure currently undruggable diseases
    - Genetic disorders, cancer, infectious diseases, cardiovascular diseases, pulmonary diseases
- The advantages over small molecule therapeutics
  - Platform technology
  - Target specific cell type
  - Target specific mRNA
  - Precision medicine
    - Only knockdown the target gene in the target cell type



DNA → mRNA → protein

RNAi

Target the Gene, Silence the Disease

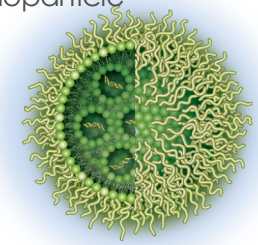


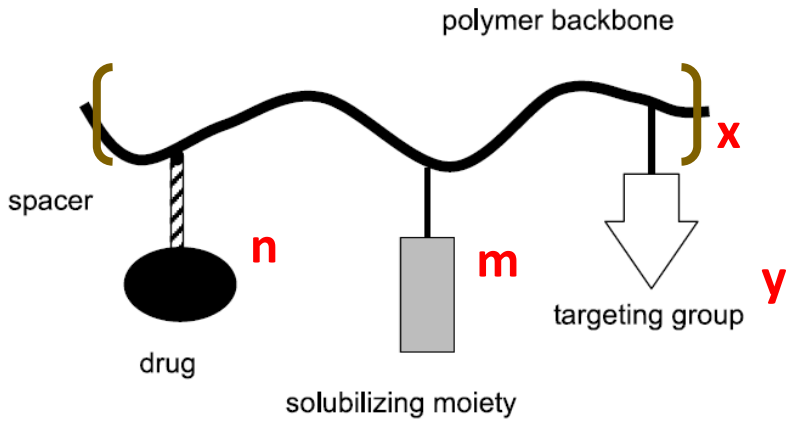
Therapeutic gene silencing with **RNA interference** is highly precise and efficient

A Long Journey for RNAi: Focused on the Vehicles Not Payloads

- Treated distinctly as two separate components: vehicles and payload
- The focus was on delivery vehicles for years in academia and industry
- The vehicles
  - Provided shielding for siRNA as in polymers and LNPs
  - Enabled rapid endosome escape as in polymers, LNP and DPC
- Lessons learned
  - Limited delivery
    - Mainly to the liver and some local deliveries
  - Observed toxicity from some delivery vehicles

Lipid Nanoparticle





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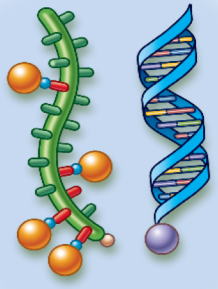
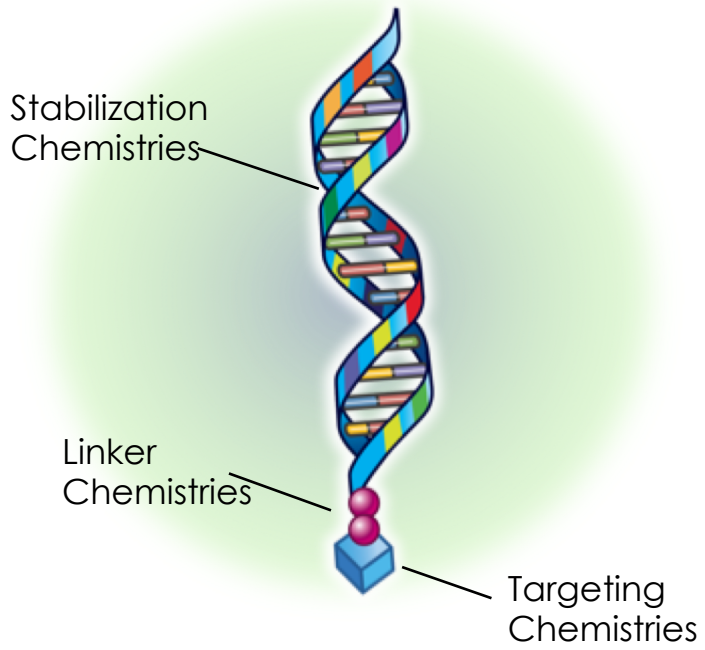


Arrowhead RNAi Platform: TRiM™

Simplicity, Specificity, and Activity



Targeted RNAi Molecule

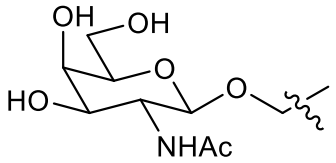
TRiM™ platform

TRiM™ has rules and algorithms to optimize trigger sequence

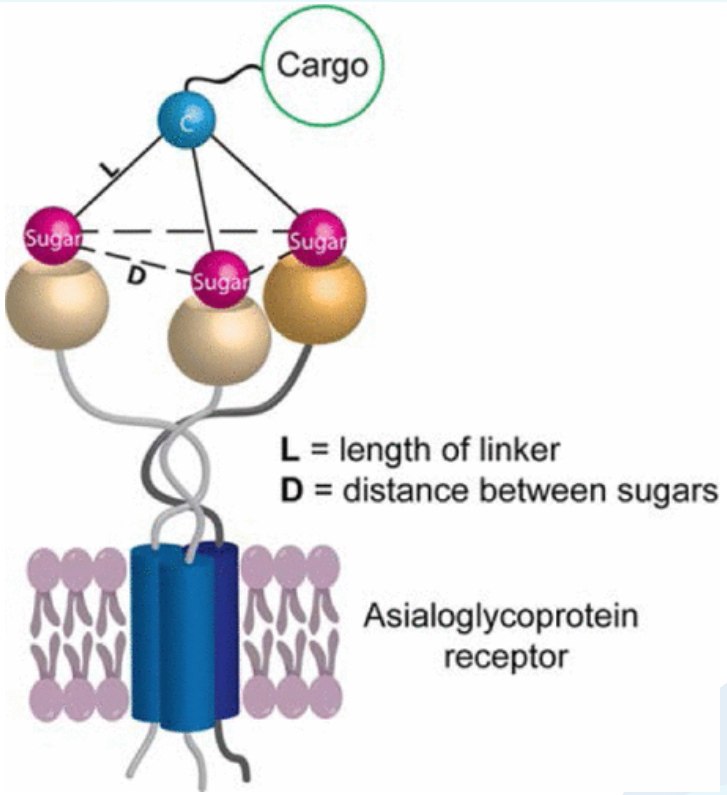
- Limit cross reactivity with off target genes
- Maximize activity
- Maximize innate stability
- Rational use and placement of modifying chemistries
- RNAi chemistry insights and expertise have allowed us to see what others have not

Direct Conjugation for Hepatocyte Delivery

- Asialoglycoprotein receptor (ASGP-R)
  - Tridentate receptor, overly expressed on the surface of hepatic cells, but minimally on extra-hepatic cells
  - Recycled every 15 mins
- Natural ligand to ASGP-R
  - N-Acetyl-Galactosamine (NAG)

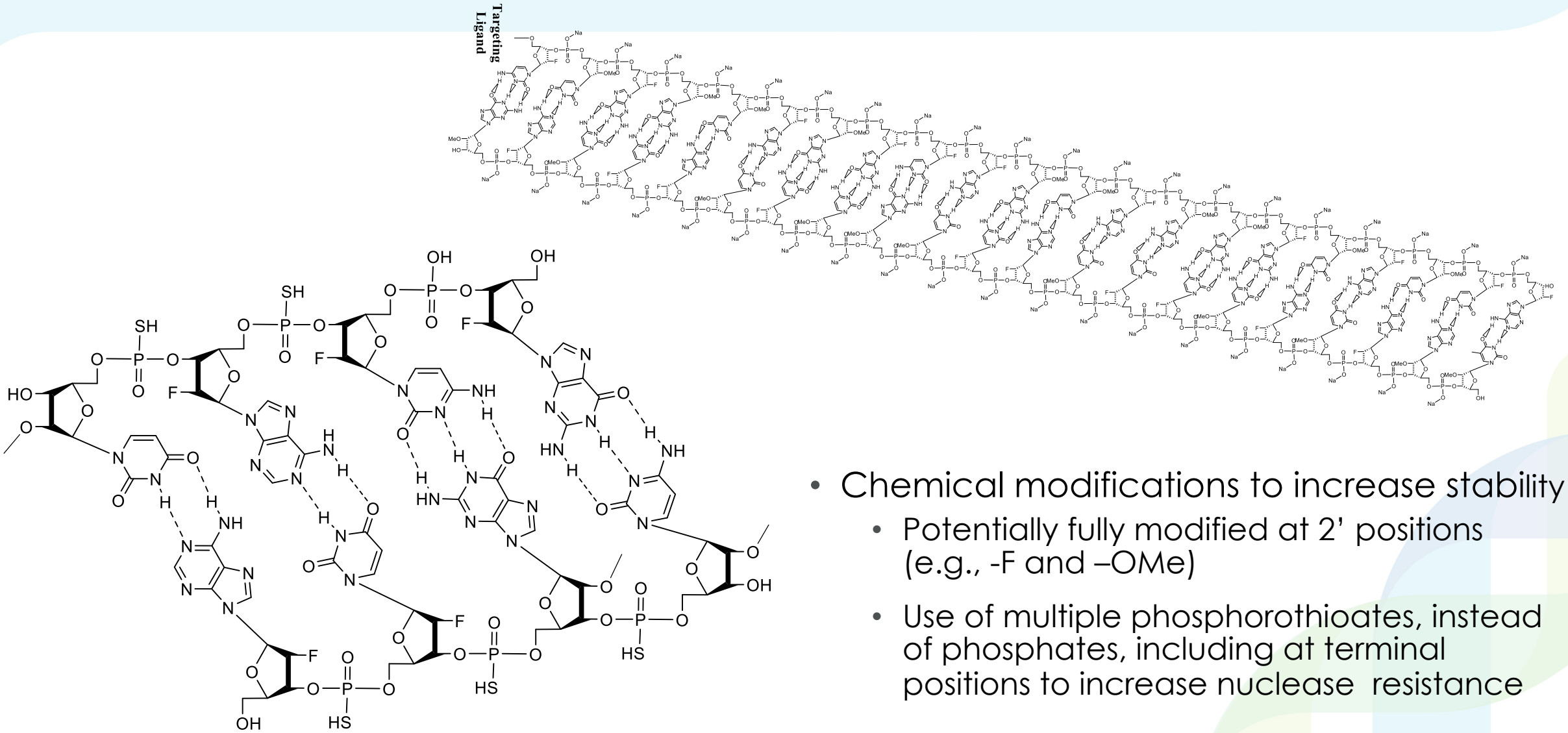


- Binding of NAG to ASGP-R initiates endocytosis



Huang etc. *Bioconjugation, 2016*

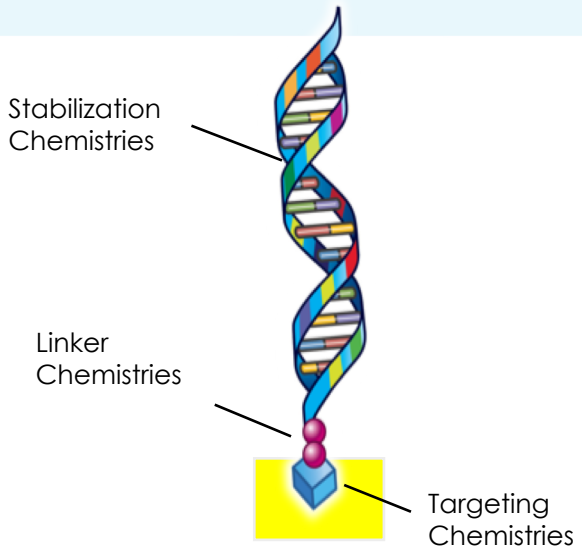
Chemical Modifications



- Chemical modifications to increase stability
  - Potentially fully modified at 2' positions (e.g., -F and –OMe)
  - Use of multiple phosphorothioates, instead of phosphates, including at terminal positions to increase nuclease resistance

Hepatic siRNA Discovery/Development

- **Key Design Elements in Hepatic Platform**
  - Subcutaneous dosing, monthly or less dosing frequency
  - Stable and potent sequences
    - No need for the use of endosome escape moieties
  - Expectation of wide therapeutic index



- Uncover new triggers
- Rational design of chemical modifications to improve
  - Stability in endosome and cytoplasm
  - Potency
- Targeting moiety investigation:
  - NAG cluster
  - Linker chemistry
  - Overall ligand design
  - Topology

Two challenges: RNAi CHEMISTRY and DELIVERY

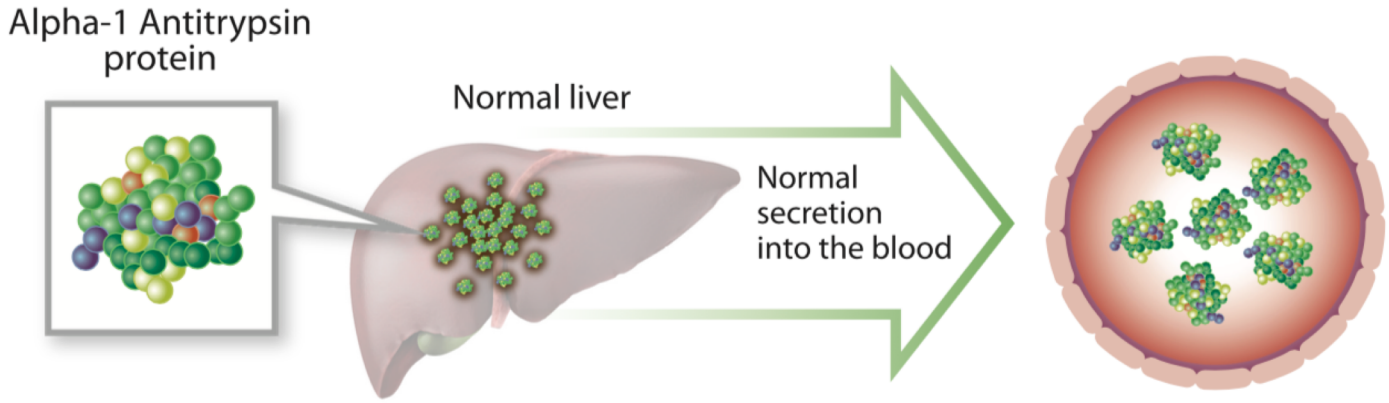
ARO-AAT

Alpha-1 Antitrypsin Deficiency (AATD)

- AAT is an abundant serum protein
  - Primarily synthesized in the liver, about 10% made extrahepatically
- Physiological function includes:
  - Inhibition of neutrophil proteases to protect host tissues during inflammation
  - Especially important in the lung
- 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

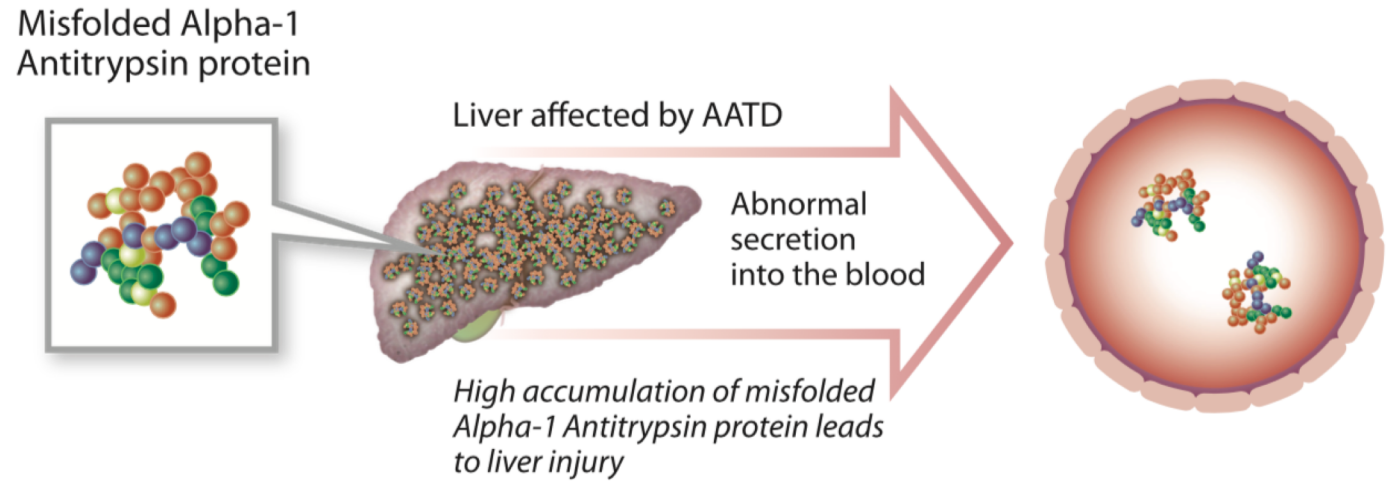
Alpha-1 Antitrypsin Deficiency

Normal AAT



Normal blood levels of normal protein protect lungs

Abnormal AAT (Z-AAT)



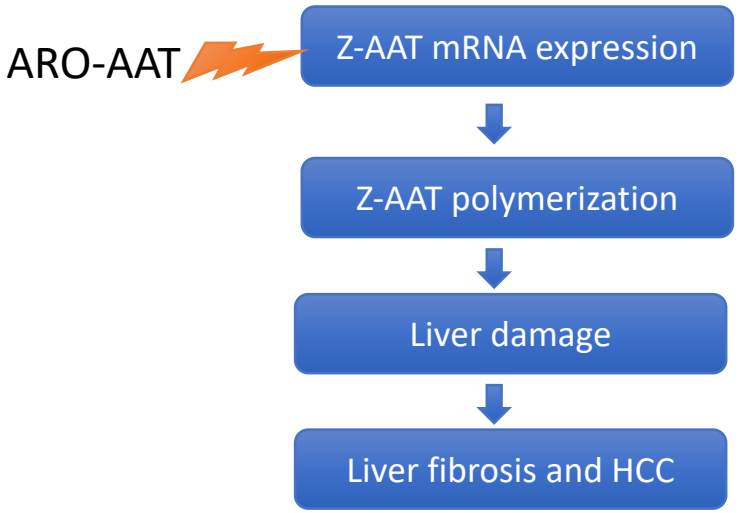
Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection

No current treatment

Treated with AAT protein replacement therapy today

ARO-AAT: Mechanism of Action

- ARO-AAT designed to stop Z-AAT production by silencing AAT gene via cleavage of mRNA to
  - Prevent production and accumulation of disease-causing protein in liver
  - Prevent repeated cycles of cellular damage
  - Allow clearance of accumulated protein
  - Reverse fibrosis associated with prior damage

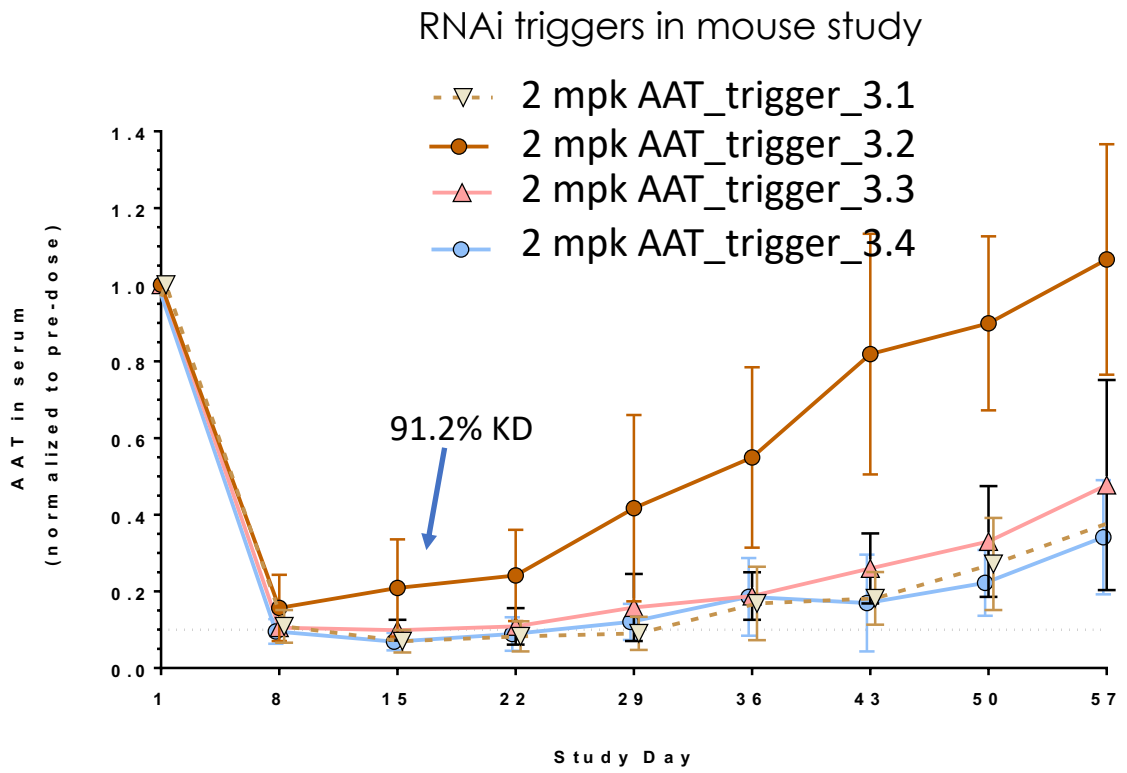


AATD is a large scale orphan disease

- Alpha-1 Foundation estimates 100,000+ in the US
- Approximately 100,000+ in Europe

Lead Optimization Leads to ARO-AAT

- 91% serum AAT knockdown achieved with one 2 mpk dose
- Knockdown sustained for 3 weeks with one 2 mpk dose

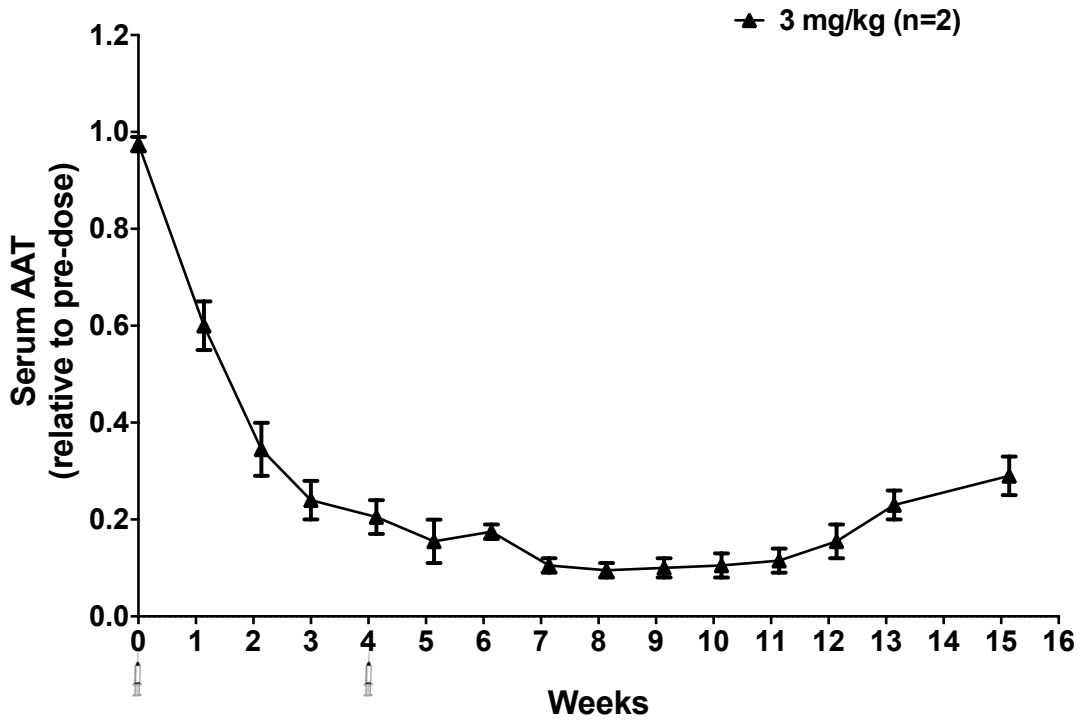


- **Chemical modifications led to deep reduction of AAT protein and long duration at dose of 2mg/kg**

ARO-AAT Provides Durable AAT knockdown in NHP

Multi-dose in NHP, dosed subcutaneously

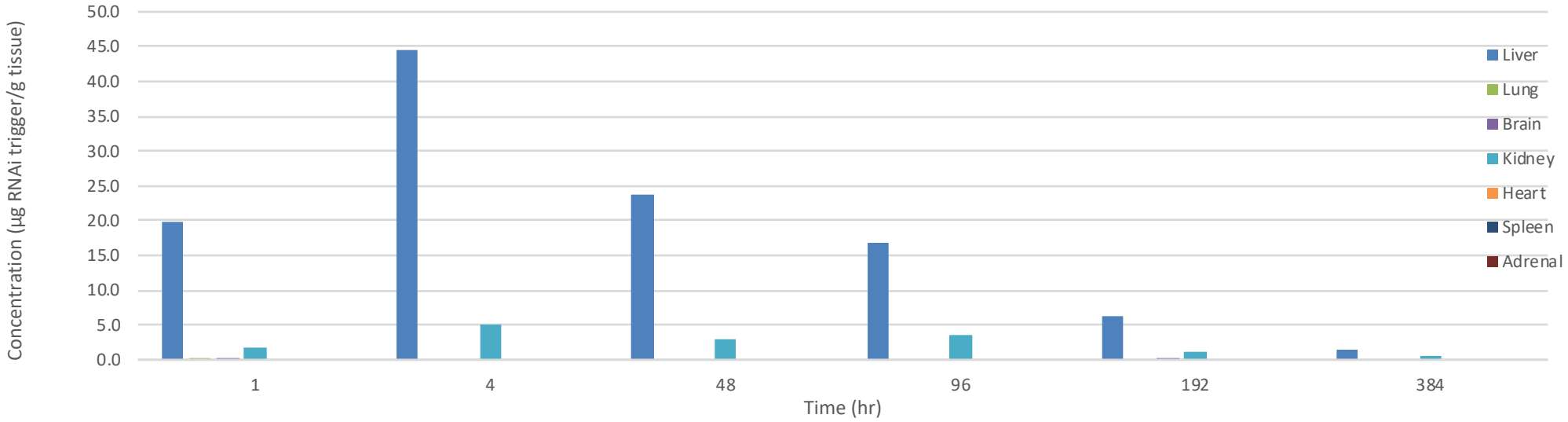
- 92% maximum serum AAT knockdown achieved in cynomolgus monkeys
- Knockdown sustained for 7+ weeks following second dose



- Completed GLP toxicology study
- No dose limiting toxicities were identified

Durable knockdown supports once monthly or less frequent dosing

ARO-AAT Biodistribution 3mpk SubQ Administration

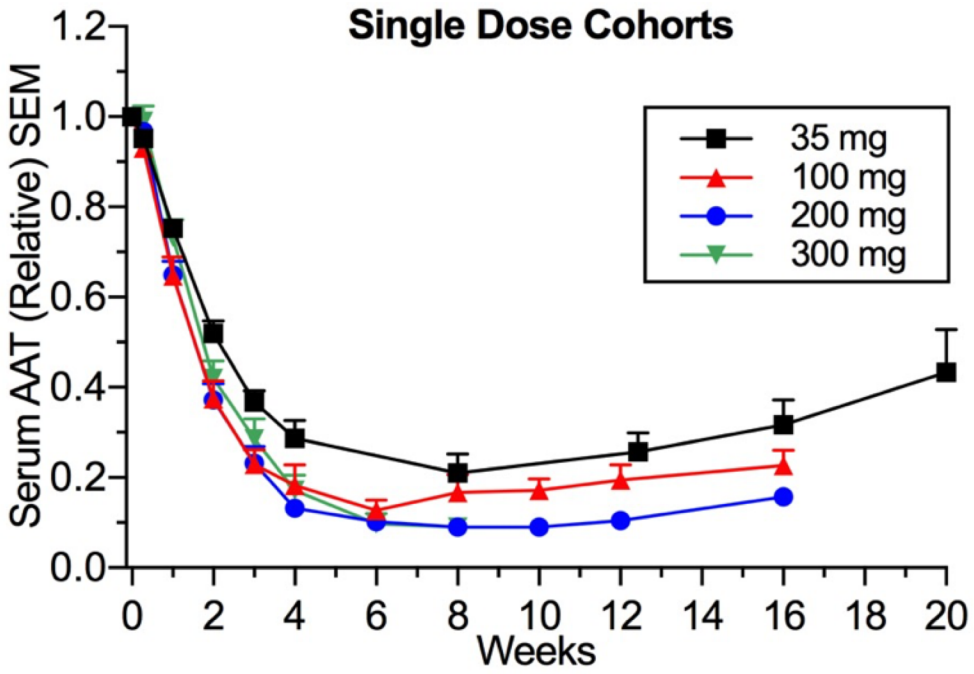


	Average Concentration of ARO-AAT (µg/g tissue)						
Time (h)	Liver	Kidney	Lung	Brain	Heart	Spleen	Adrenal
1	19.9	1.8	0.3	0.1*	BLQ	BLQ	BLQ
4	44.4	5.1	BLQ	BLQ	BLQ	BLQ	BLQ
48 (Day 2)	23.7	2.9	BLQ	BLQ	BLQ	BLQ	BLQ
96 (Day 4)	16.8	3.5	BLQ	BLQ	BLQ	BLQ	BLQ
192 (Day 8)	6.4	1.2	BLQ	BLQ	BLQ	BLQ	BLQ
384 (Day 16)	1.4	0.5	BLQ	BLQ	BLQ	BLQ	BLQ

*Only one rat showed quantifiable concentration other two were below limit of quantitation (BLQ).

ARO-AAT Clinical Data Shows Platform Profile

- Open Label AAT Plasma Data:
  Single Dose, Healthy Volunteers

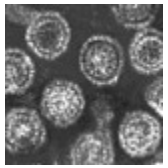


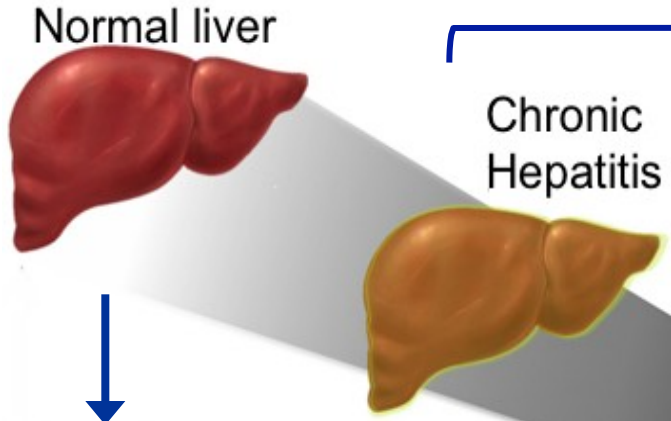
- **Potency, efficacy, durability**
  - 93%: Maximum Serum AAT reduction achieved 6-weeks following a single dose
  - 87%: Mean maximum serum AAT reduction achieved 6-weeks following a single dose
- **Safety**
  - No Severe AEs
  - Most AEs reported as mild (one moderate gastroenteritis)
  - Mild injection site AEs occasionally reported
  - No clinically meaningful adverse changes in BUN, creatinine, ALT, AST or total bilirubin or pattern of adverse laboratory changes seen

ARO-HBV

Chronic hepatitis B (CHB): Disease pathogenesis

2 billion infected with HBV → **250 million living with chronic HBV infection**





Therapeutic Virus suppression

1. Direct antiviral agents = Nucleos(t)ide Analogues (NA's: TDF, ETV, ADV, LAM)
2. 2. Immune modulators (Pegylated IFNa)

Primary prevention

1. Vaccination (EngerixB)

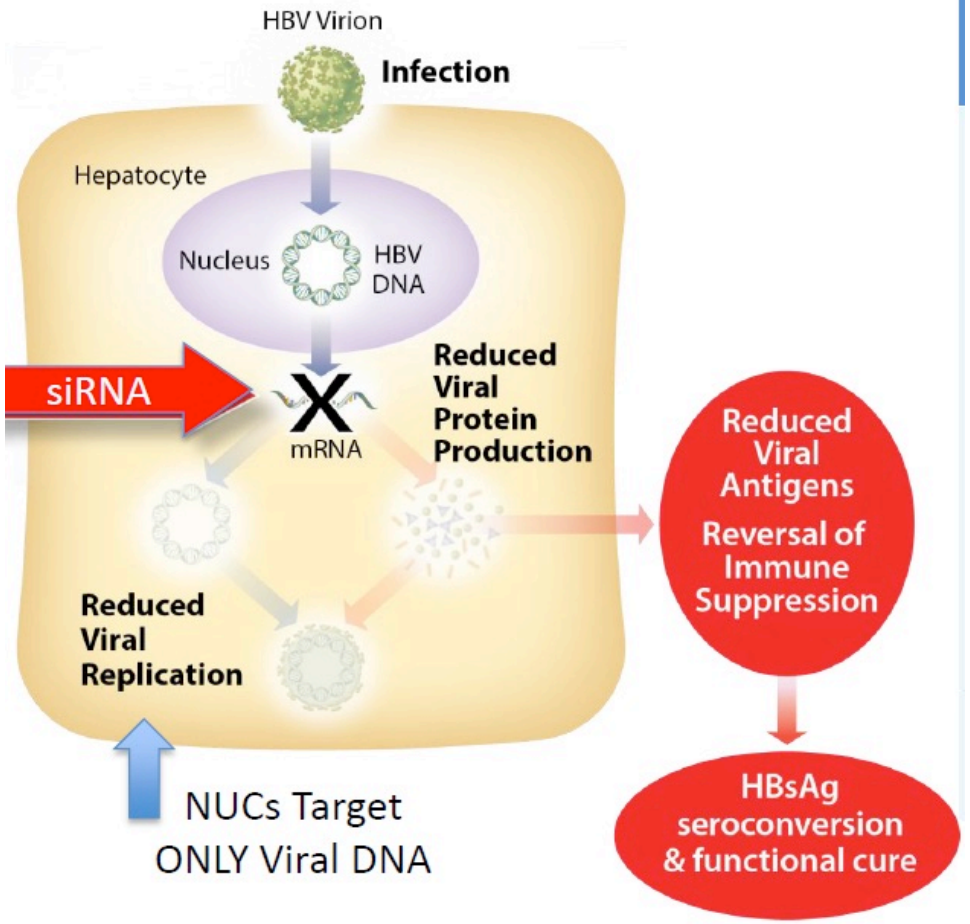
Develops in 15-25% CHB cases

30-50 years

Neither preventative vaccination nor viral suppression influence CHB cure

Liaw YF et al, N Engl J Med. 2004; Chang et al, Hepatology 2010; Marcellin et al, Lancet 2013; Hosaka et al, Hepatology 2013; Kim et al, Cancer 2015; Papatheodoridis et al, J Hepatol 2015; Seeger, Zoulim, Mason; Fields Virology; 2007-2013

Small Molecule Drugs vs RNAi Therapeutics



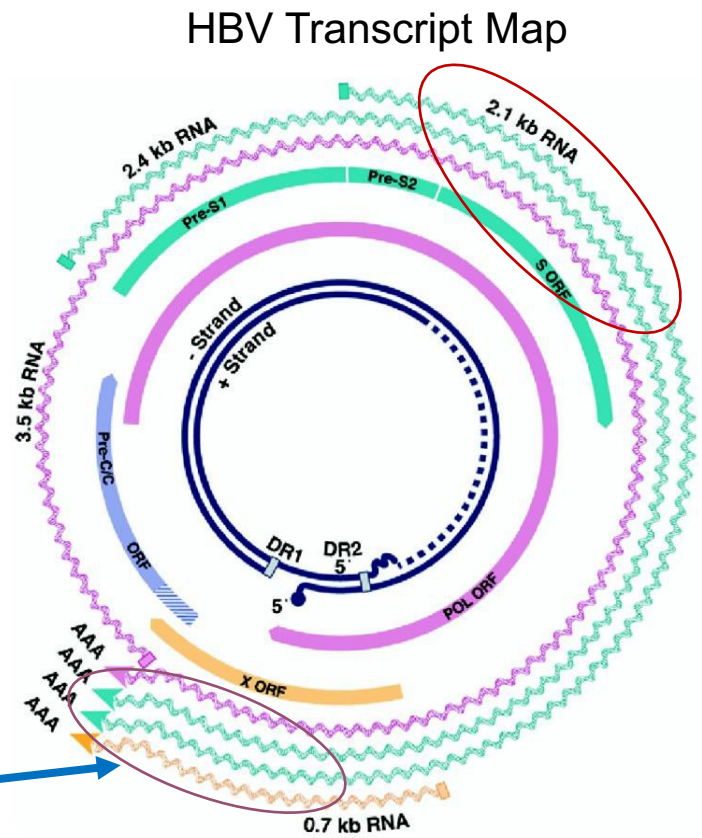
Silence Entire HBV Genome

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

POTENCIAL TO ENABLE A FUNCTIONAL CURE

Importance of Integrated DNA as mRNA Source has Changed RNAi Strategy

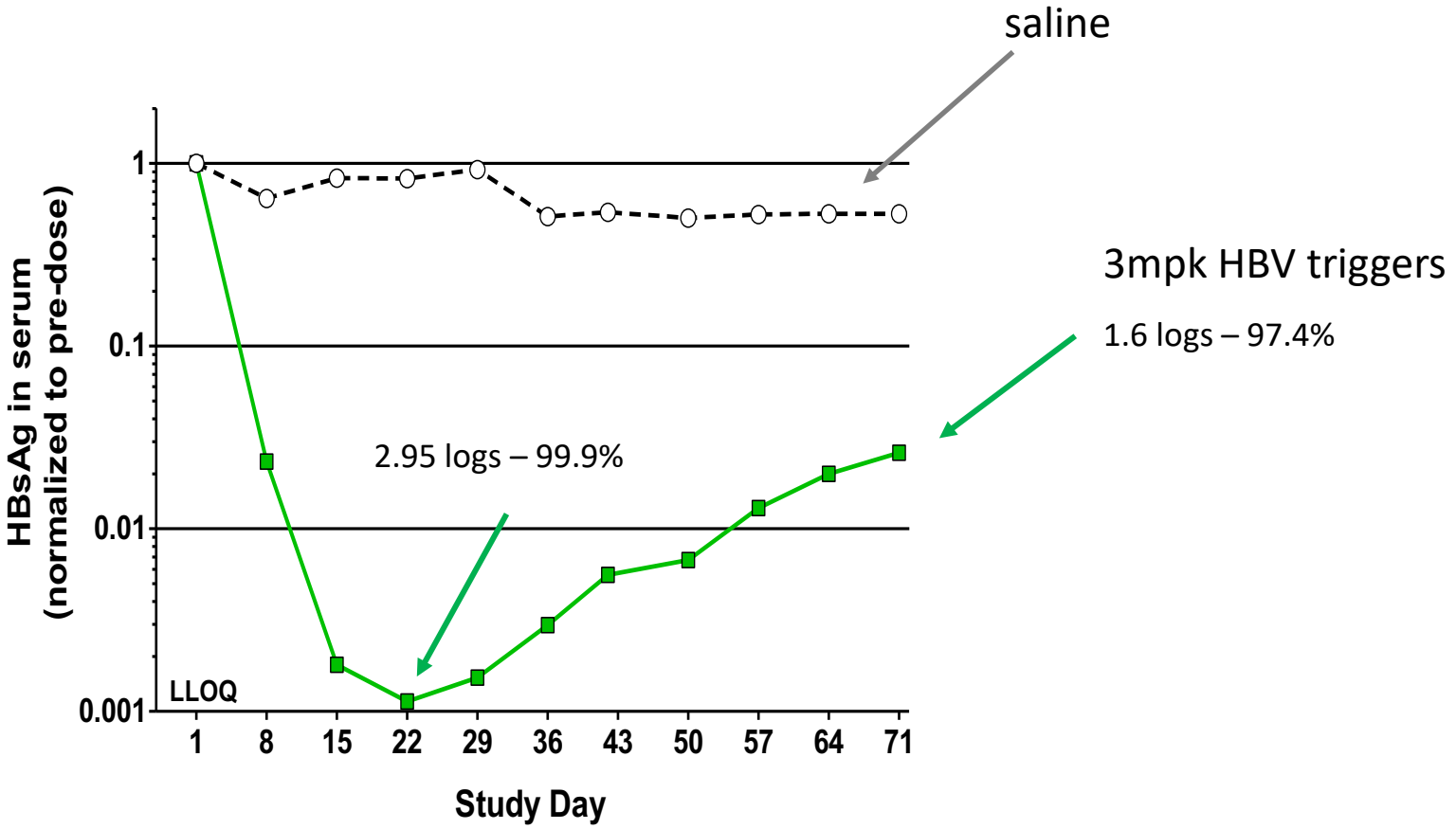
- All HBV transcripts, including pregenomic RNA, overlap and terminate with the same polyadenylation signal
- A single siRNA targeting this common region can reduce all HBV transcripts derived from cccDNA



Single siRNA can reduce all mRNA from cccDNA but can miss integrated-derived mRNA

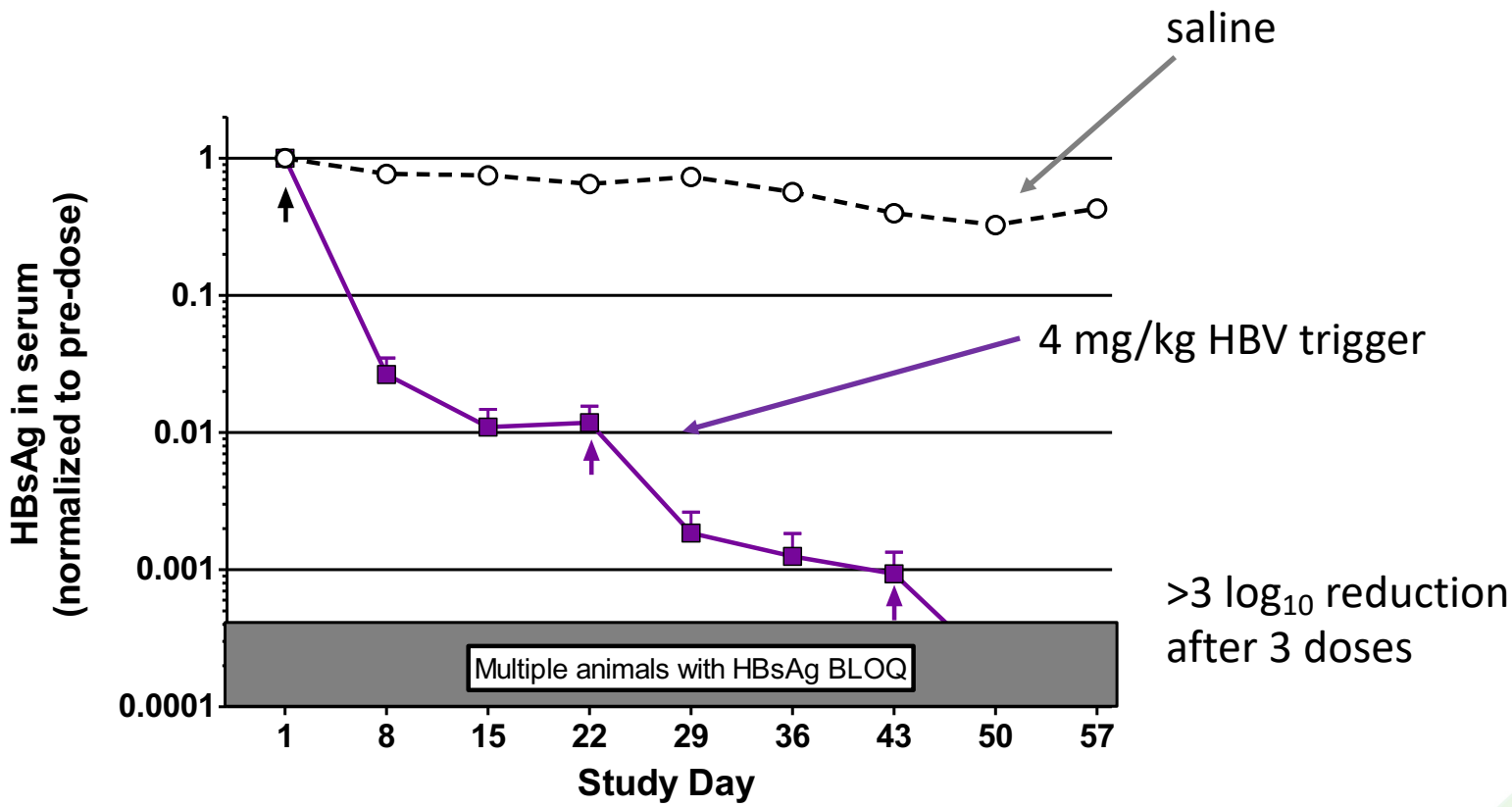
Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

We Modeled Integration in a New, Mutated pHBV Transfected Mouse

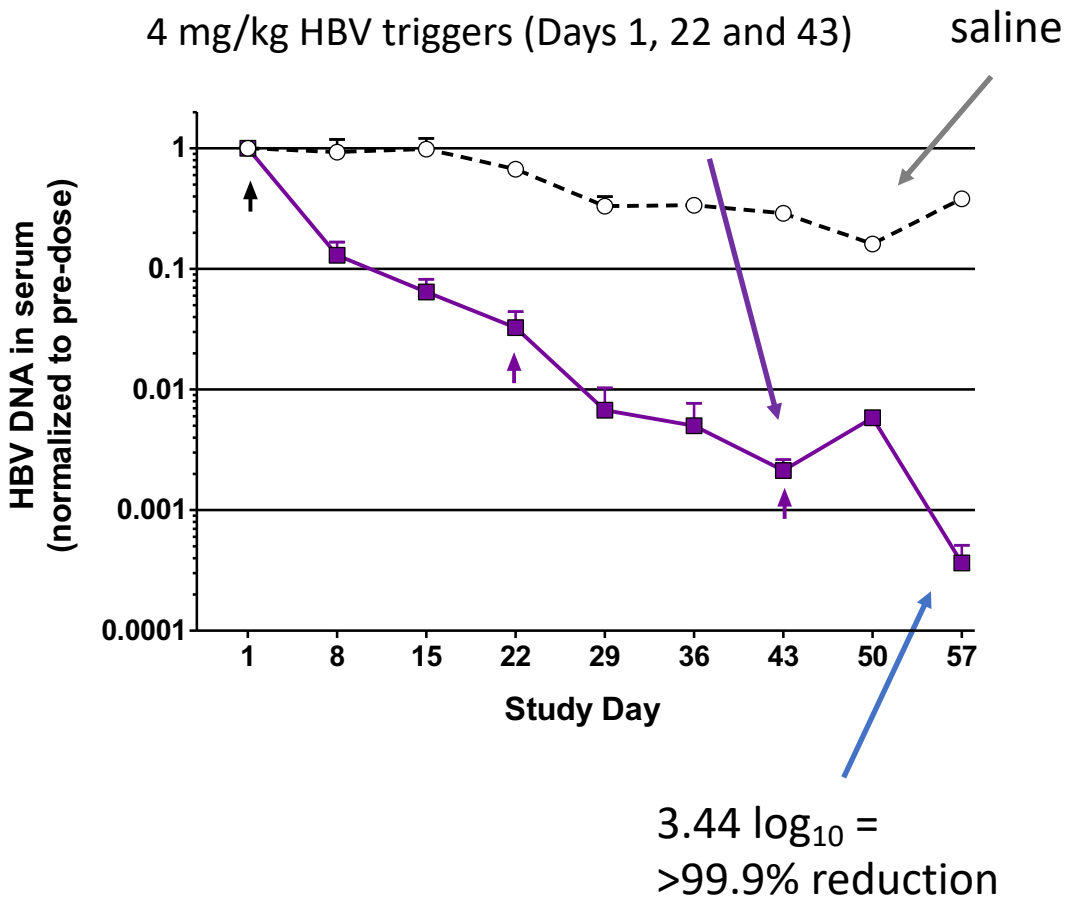


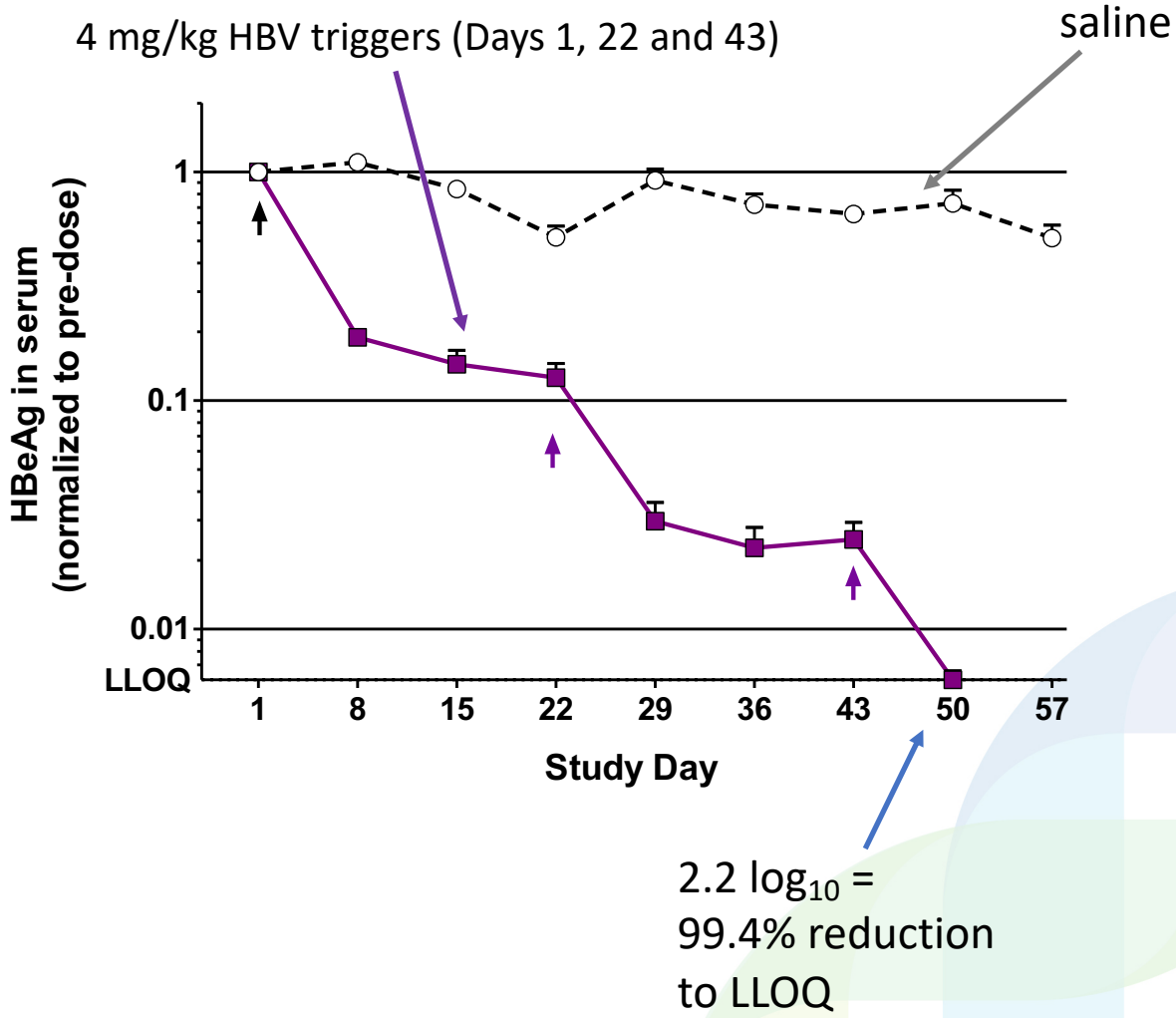
HBsAg knockdown is deep and prolonged despite loss of x trigger site

Multiple Dosing in Intact pHBV Mice Reduces HBsAg Below Level of Quantitation



With Deep Knockdown also Observed for HBeAg and HBV DNA





ARO-HBV Safety Evaluation

- GLP toxicology studies completed
  - ARO-HBV is well tolerated
- Significant therapeutic index achieved

Summary

- Arrowhead TRiM™ platform demonstrates consistent activity
- Subcutaneous dosing, monthly or less frequent
- No need for active endosomal escape agent
- Powerful HBsAg reduction for ARO-HBV
- Powerful AAT reduction for ARO-AAT
- Wide therapeutic index
- Good early signs of activity and safety in human subjects

Evolution from biologic complexity to small molecule precision and execution

Acknowledgement

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