ALN-HBV

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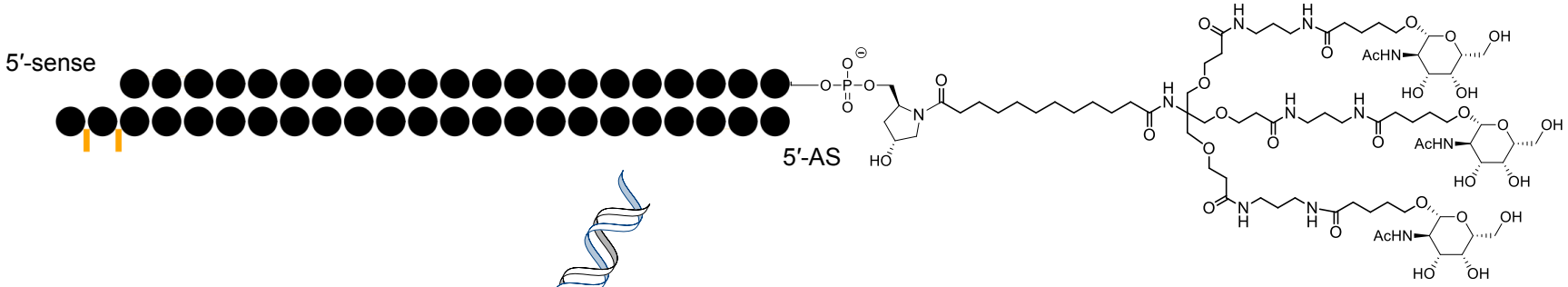
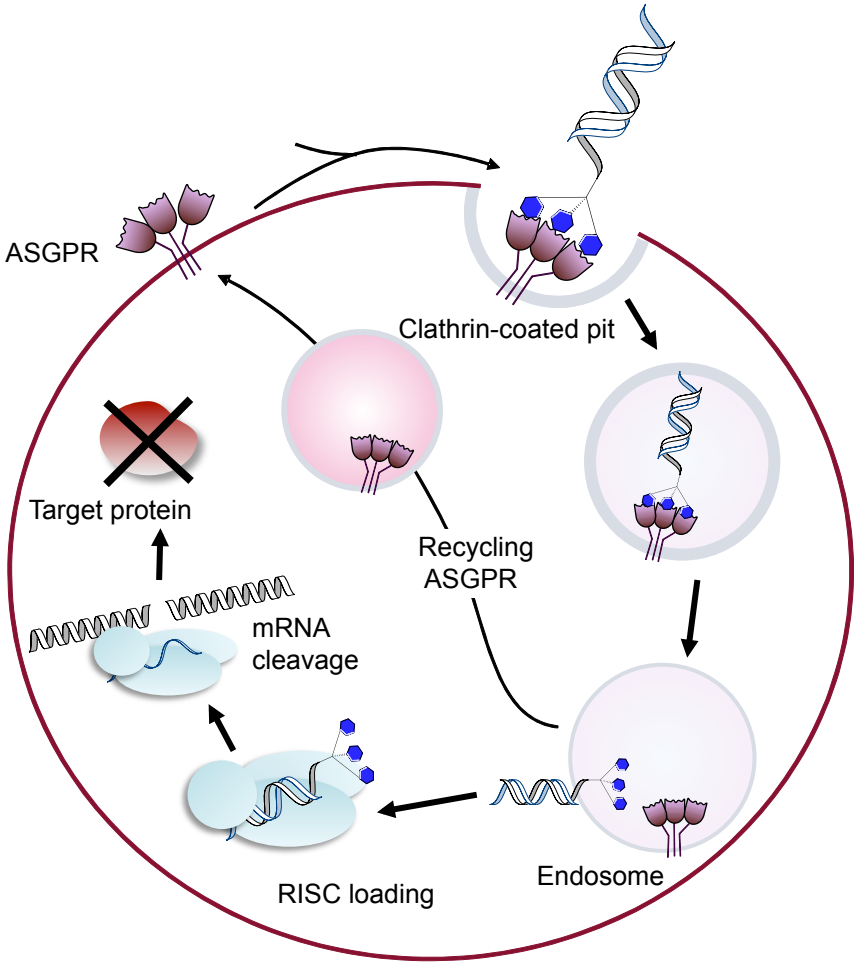
N-Acetyl Galactosamine (GalNAc) siRNA Conjugates

Subcutaneous Investigational RNAi Therapeutics





siRNA

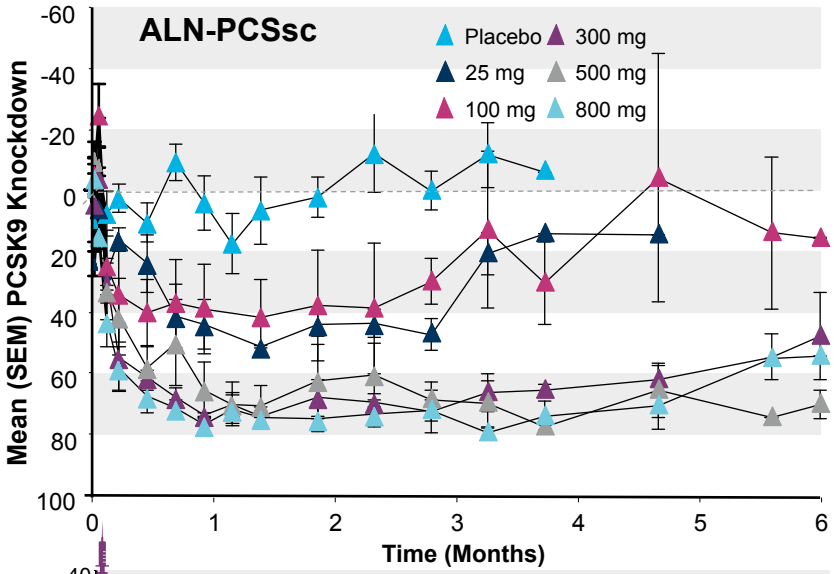
- Chemically-modified siRNA
- Potent and durable activity
- Metabolically stable
- No innate immune activation

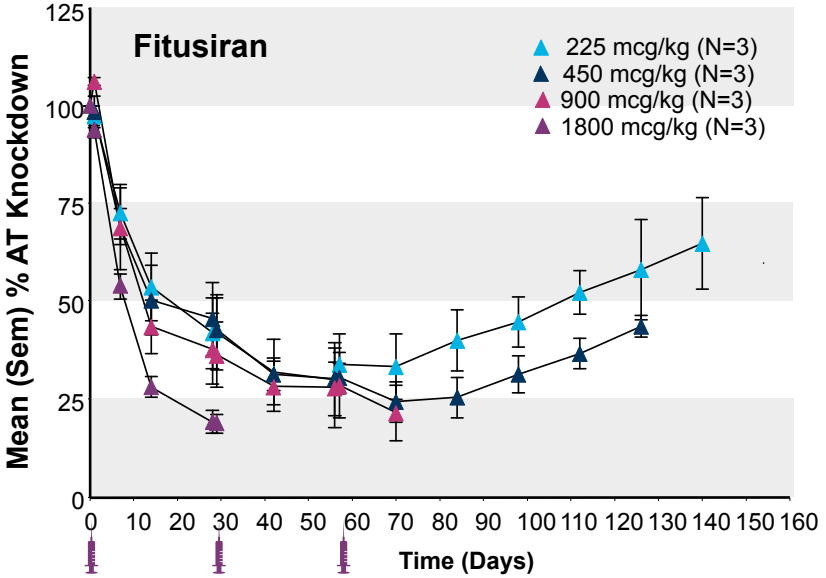
Asialoglycoprotein Receptor (ASGPR)

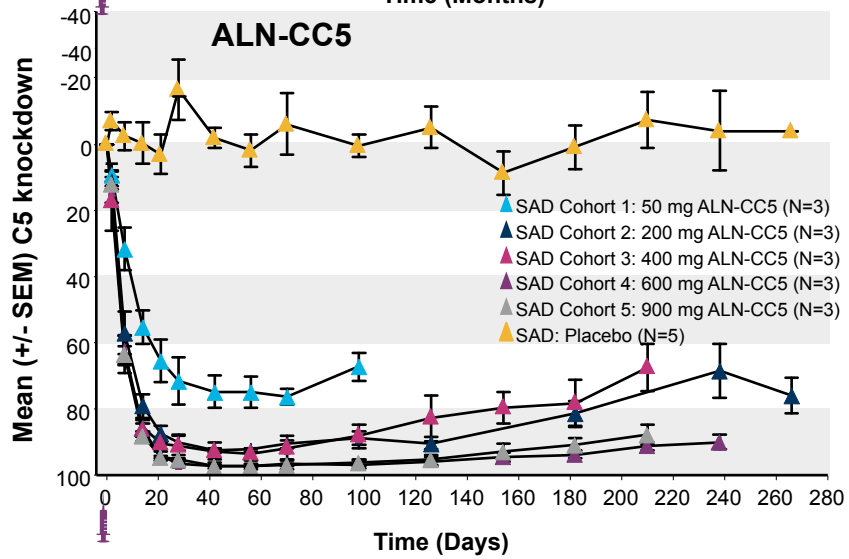
- Highly expressed in hepatocytes
- High rate of uptake
- Recycling time ~15 minutes
- Conserved across species

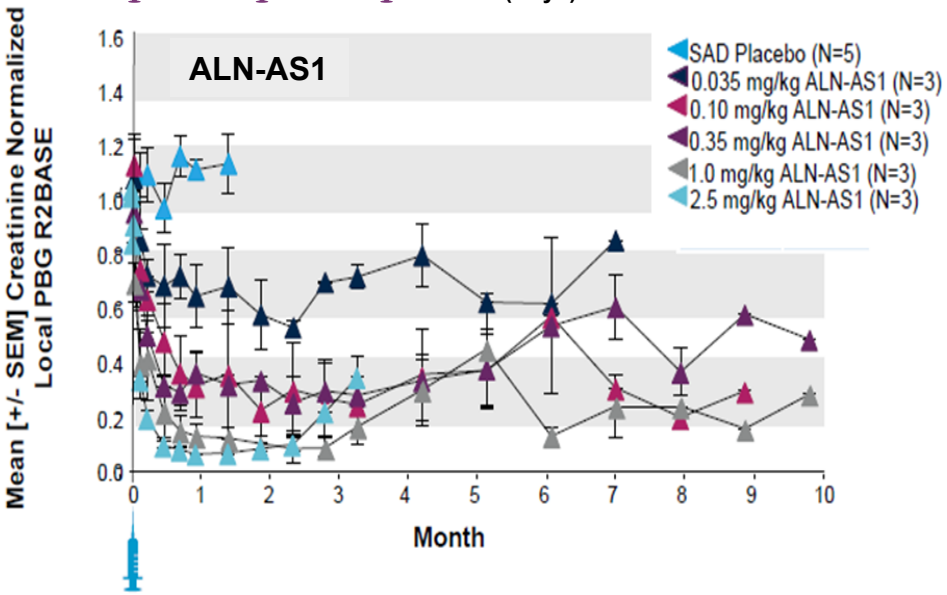
Adapted from *Essentials of Glycobiology* (2009)

Potent and Durable Target Silencing in Humans by ESC-GalNAc-siRNA Drug Candidates

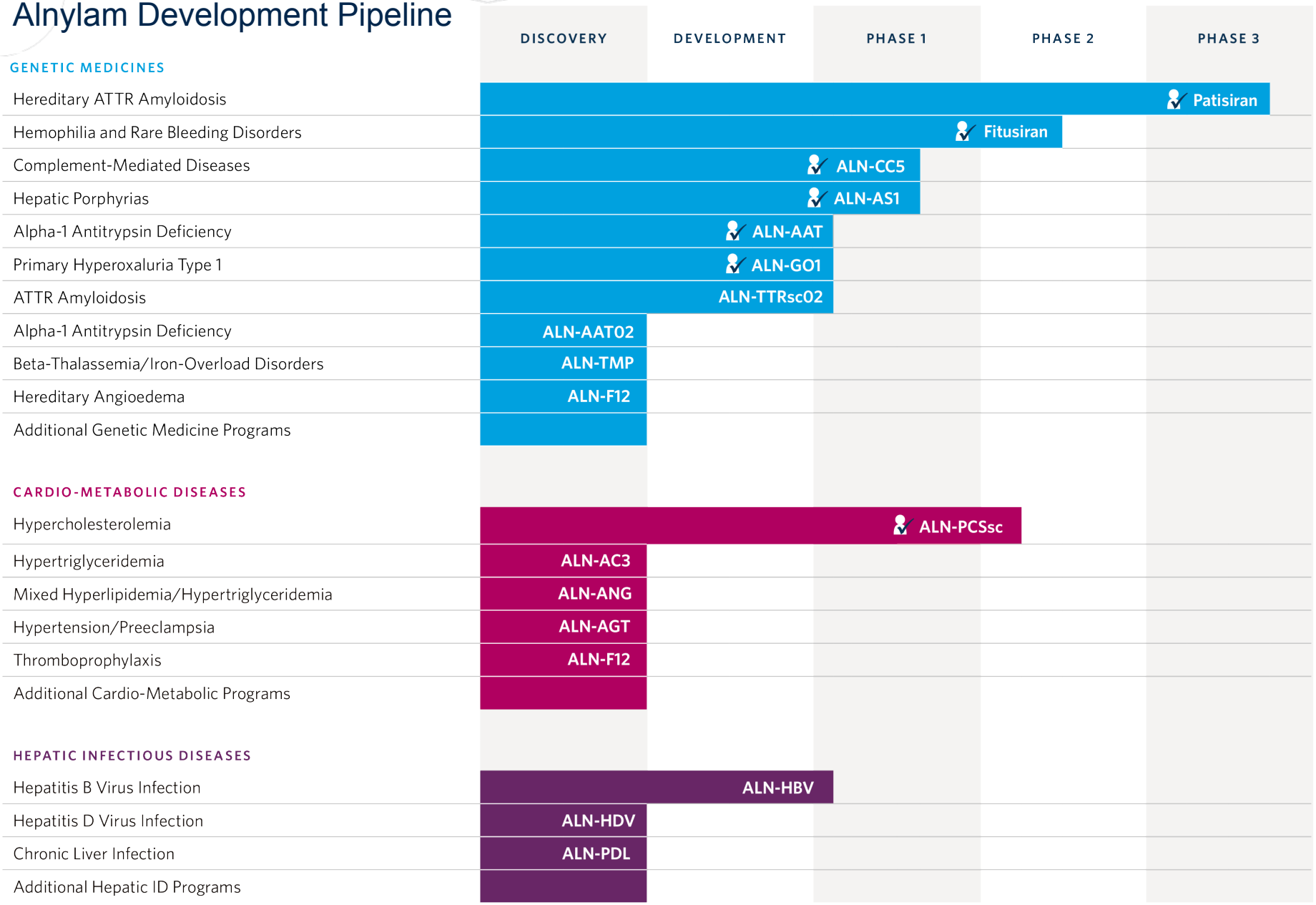








Alnylam Development Pipeline

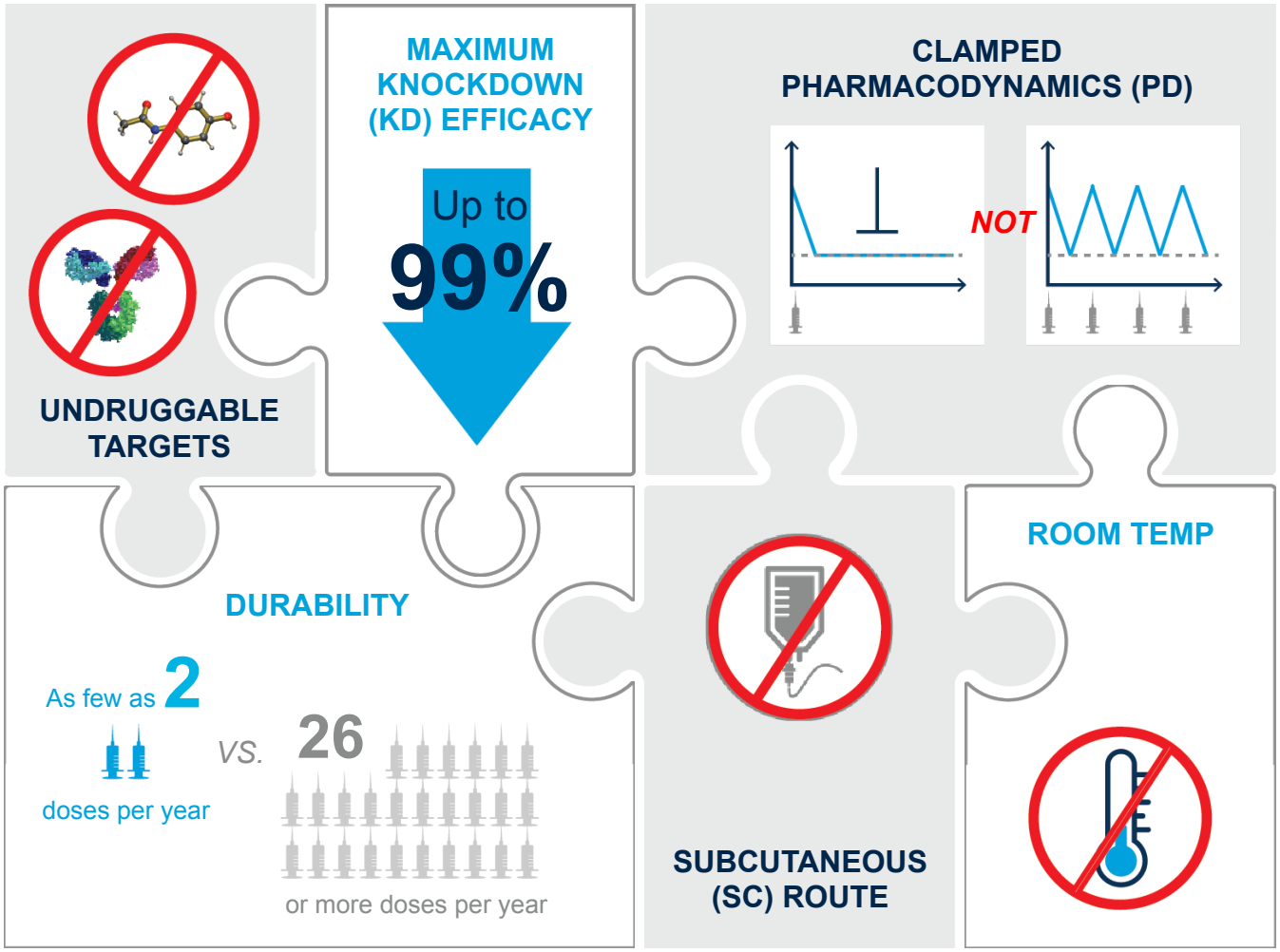


Updated October 4, 2016

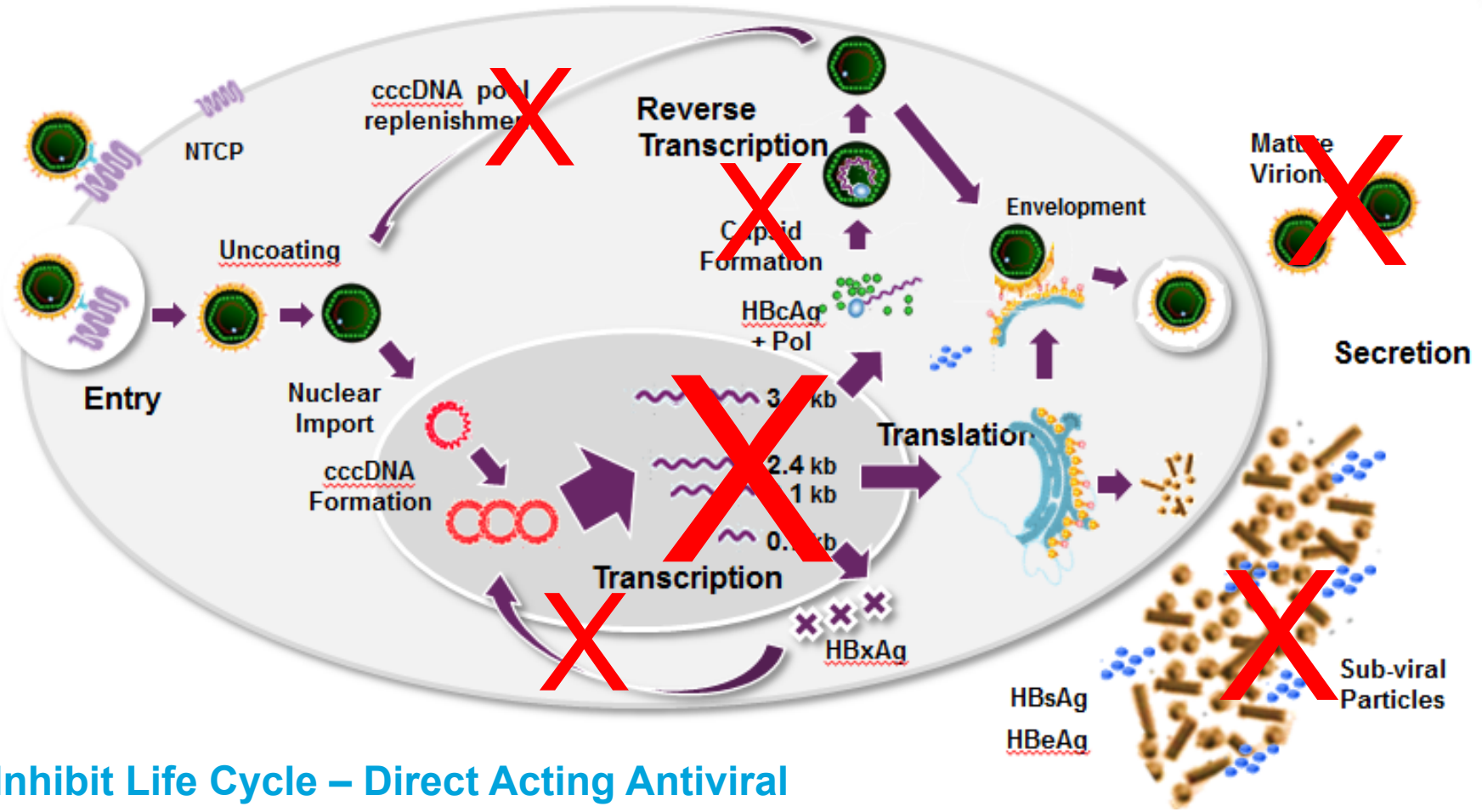
Human Proof of Concept Achieved

Key Features of Alnylam Investigational RNAi Therapeutics

Potential Attributes for Differentiation and Value



ALN-HBV Mechanism of Action



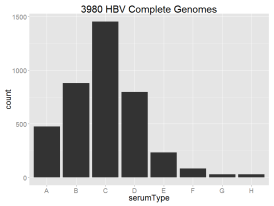
Inhibit Life Cycle – Direct Acting Antiviral

- KD replication template, core, polymerase, surface, X-protein

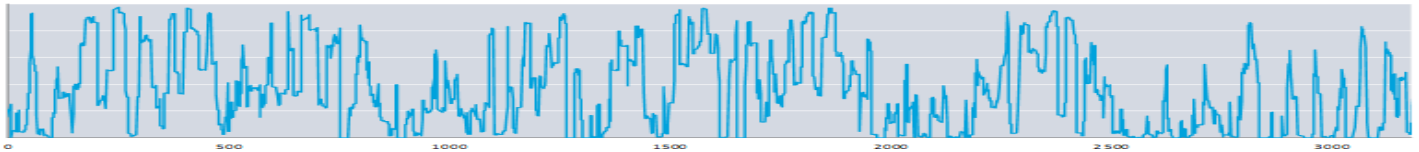
Break Immune Tolerance – Enhance Host Immunity

- Reducing expression of tolerogenic antigens (HBsAg, HBeAg, core)

ALN-HBV Targets a Highly Conserved Sequence in HBV X Orf

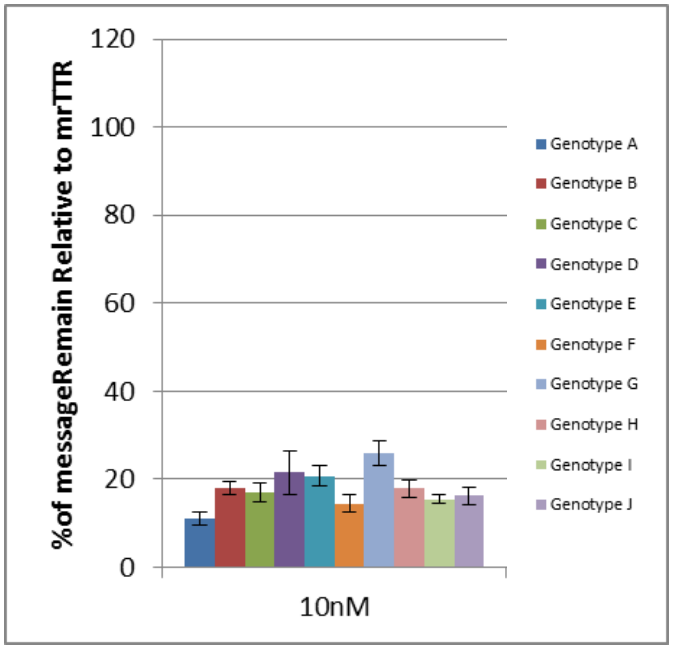


3980 HBV complete genomes, A-H



pg RNA 3.5 kb
PreS1 2.4 kb
PreS2 2.1 kb
X 0.7 kb

ALN-HBV



- Target site is conserved across genotypes A-J
  - Perfect homology (2-18): 97.2%
  - Allow 1 mismatch: 99.7%
- Site is upstream from integration hotspot

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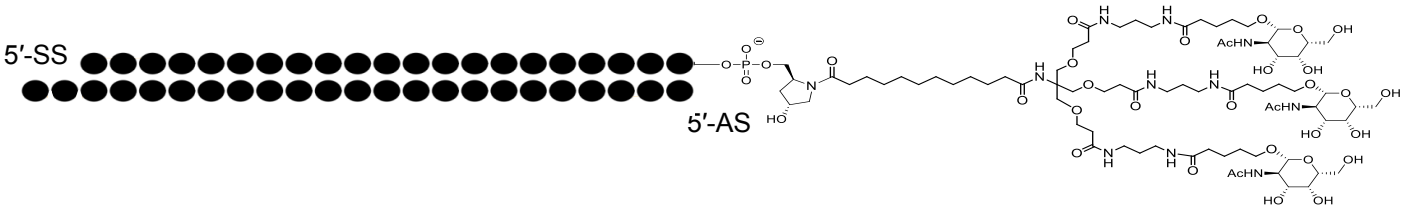
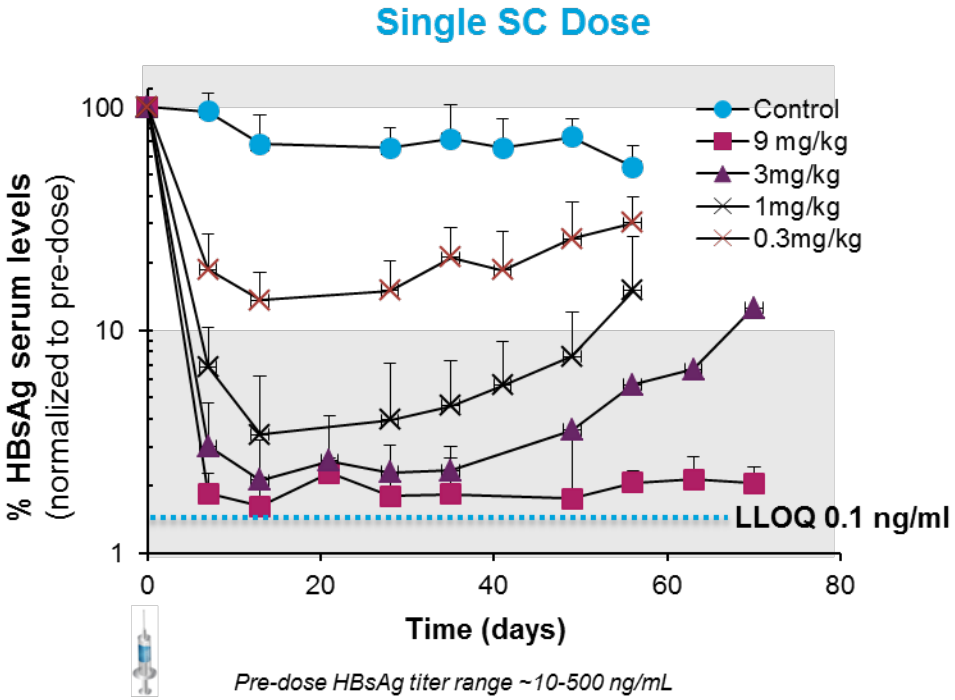
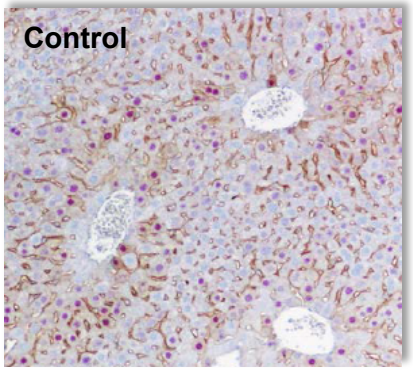
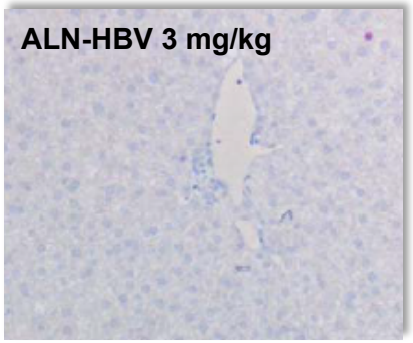
ALN-HBV Mediates Potent and Highly Durable HBsAg Knockdown in AAV-HBV Murine Model









HBsAg IHC

- Up to 3.6 $\log_{10}$ HBsAg reduction
- Single SC dose achieves >2 $\log_{10}$ HBsAg reduction lasting >30 days

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ALN-HBV001 Phase 1/2 Study

A Study of ALN-HBV in Healthy Adult Volunteers and Non-cirrhotic Patients With Chronic Hepatitis B Virus (HBV) Infection

Primary objectives

Safety and tolerability

Secondary objectives

PK & antiviral activity (sAg, eAg, HBV DNA)

Part A: Single-Ascending Doses in HV (SAD) | Randomized 3:1, 4-6 cohorts, n=16-24

0.1 mg/kg as starting dose

Part B: Single-Ascending Doses in Pts on NUC tx for >12 months (SAD) | Randomized 3:1, 4-7 cohorts, n=16-28

0.1 mg/kg as starting dose

Part C: Multiple-Ascending Dose (MAD) in Pts on NUC tx for >12 months | Randomized 6:2, 3-6 cohorts, n=24-48

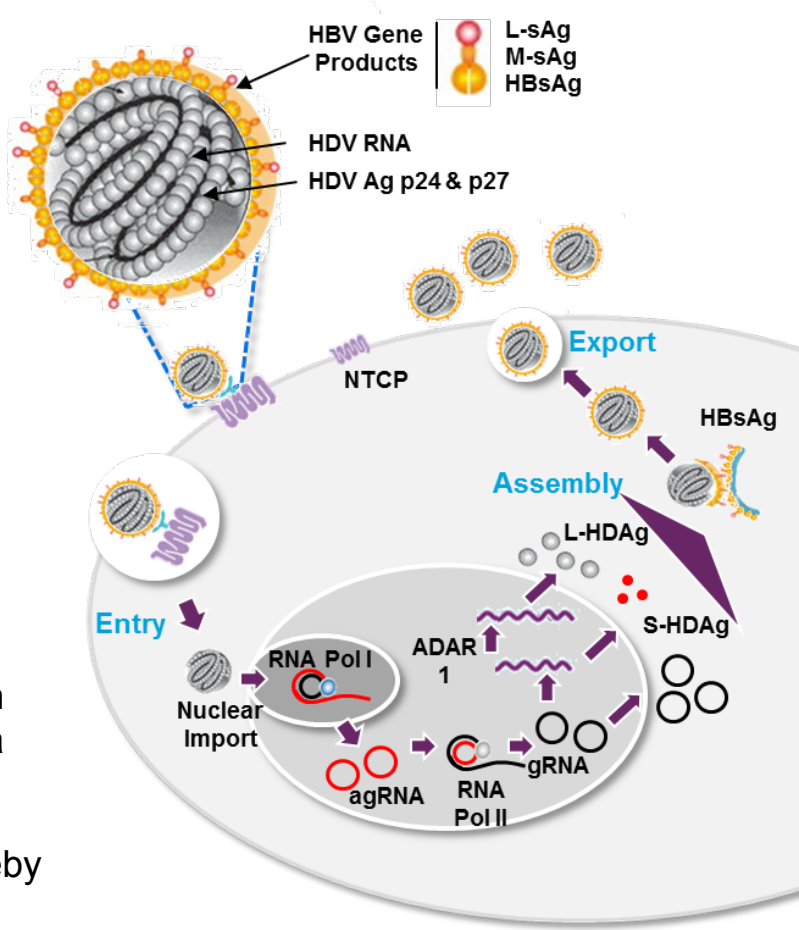
Dose TBD, QW*13 doses to Q4W*4 doses

clinicaltrials.gov_NCT02826018

Chronic Hepatitis D Virus (CHD) Infection

Chronic HBV/HDV infection is more aggressive than CHB
No therapies available

- HDV is RNA sub-virus, which can only propagate in presence of HBV
- 15-20M patients infected WW, 80K in US
- Acquired at same time or subsequent to HBV infection
- No curative therapies available



Target Product Profile for ALN-HBV in HDV

- **HDV Suppression**
  - Chronic, on-going therapy to inhibit HBsAg production thereby suppressing HDV replication and HDV viremia
- **HDV Cure**
  - Finite treatment resulting in functional CHB cure thereby resulting in CHD cure

Gish et al. 2013; Farci & Niro, 2012; Ciancio & Rizzetto 2014; http://hepatitis-delta.org/

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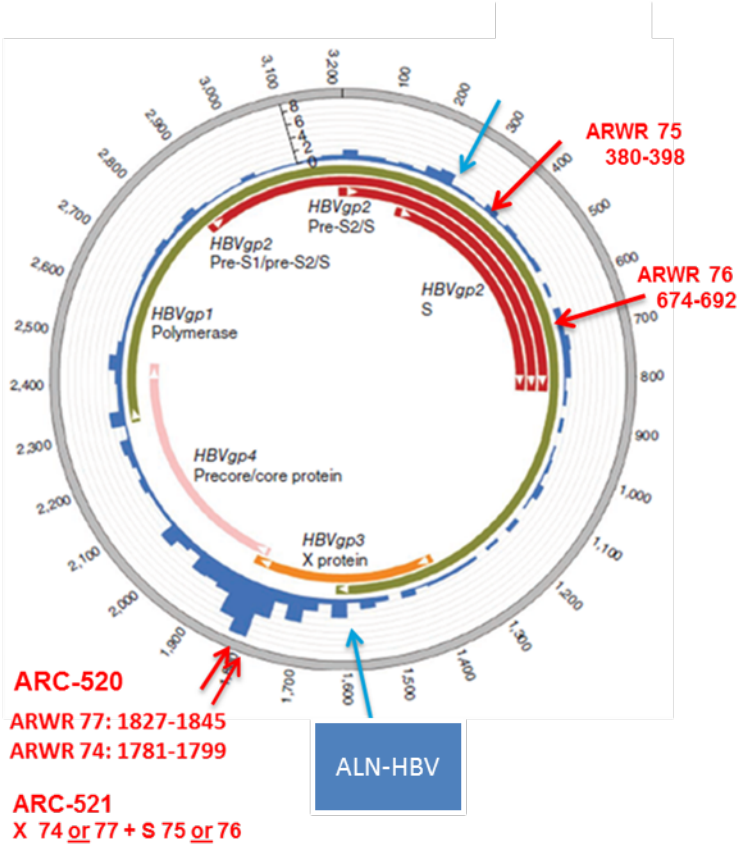
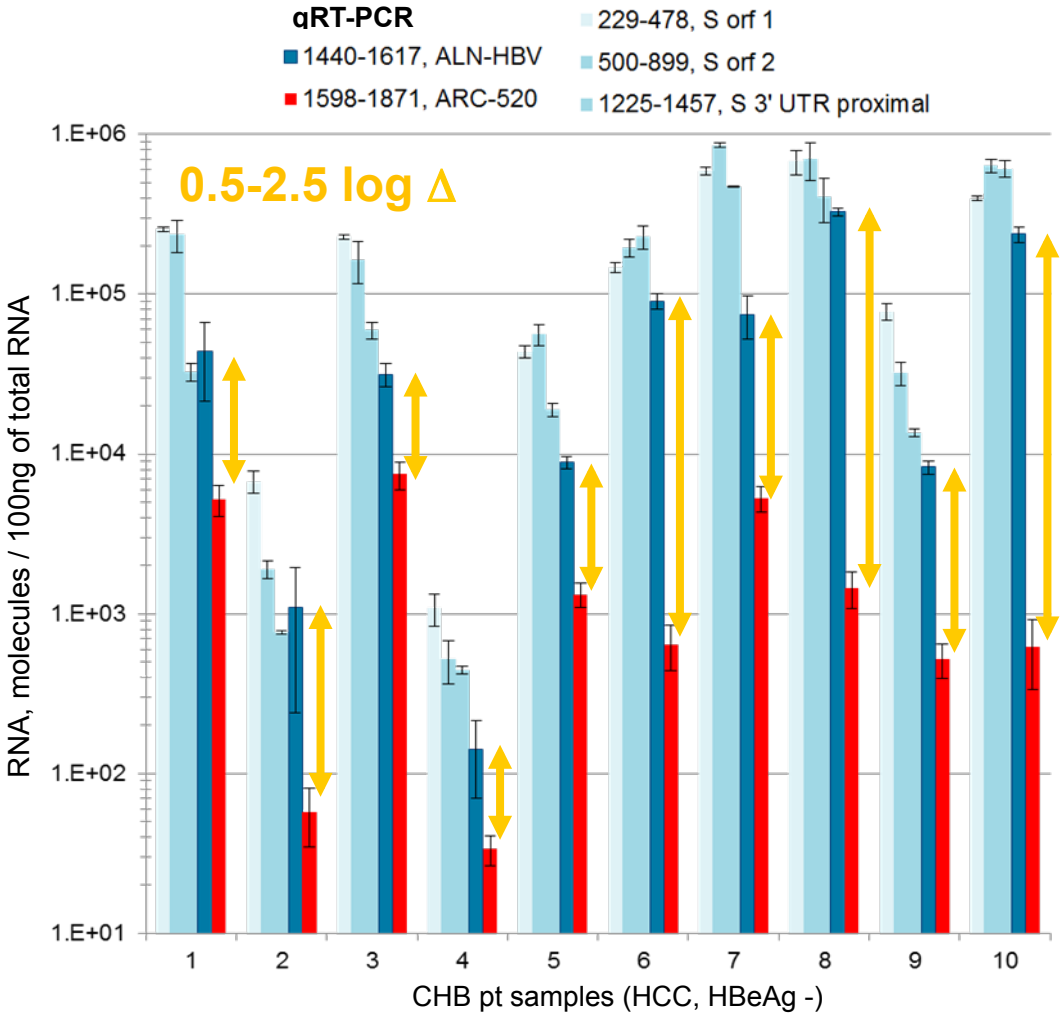
ALN-HBV Product Opportunity

Significant potential for CHB functional cures & CHD chronic therapy

- Potent and durable silencing of all HBV gene products, pan-genotypic
  - Elicit multiple synergistic antiviral mechanisms in CHB and CHD
  - Endpoint: sustained virological response off all therapies after finite therapy
    - Combination with standard of care Polymerase inhibitors (NUCs) and novel agents
- Improved compliance: infrequent subcutaneous dosing and tolerability
- Expected efficacy across CHB patient segments, including young immune tolerant and patients outside treatment guidelines
- Room temperature stability simplifies global distribution

ALN-HBV's Target Site is Upstream from Integration Hotspot, and Expressed at Higher Levels in CHB vs Competitor's





Sung et al., Nature Genetics 44:765 (2012)