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Curing Chronic Hepatitis B

Durable inhibition of hepatitis B virus replication and antigenemia using subcutaneously administered siRNA agent AB-729 in preclinical models

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EASL International Liver Congress

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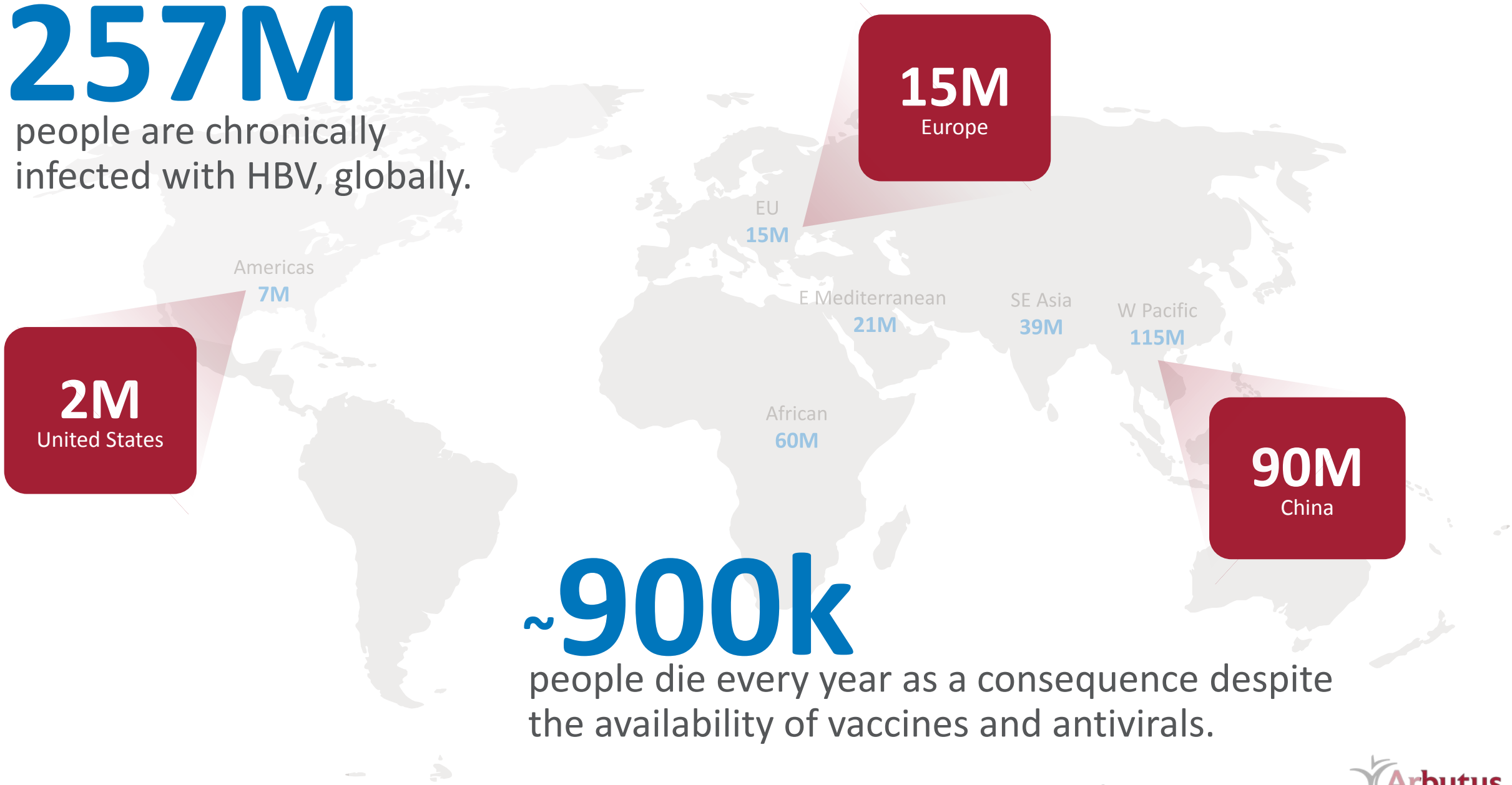
257M

people are chronically infected with HBV, globally.



~900k

people die every year as a consequence despite the availability of vaccines and antivirals.

Source: Hepatitis B. WHO (2017) http://www.who.int/mediacentre/factsheets/fs204/en/

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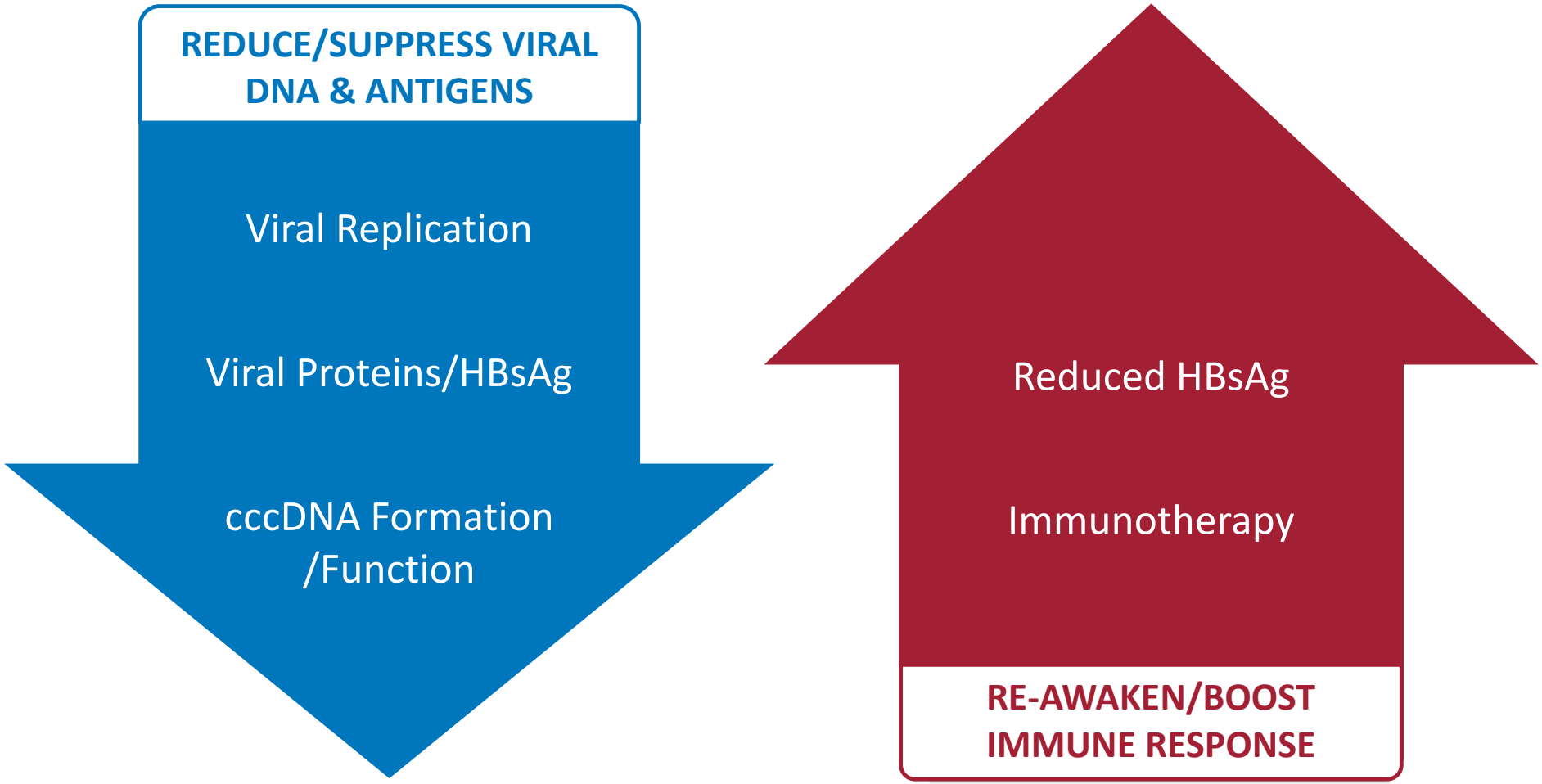
Key to Therapeutic Success in HBV



A combination approach to these key factors will drive cures

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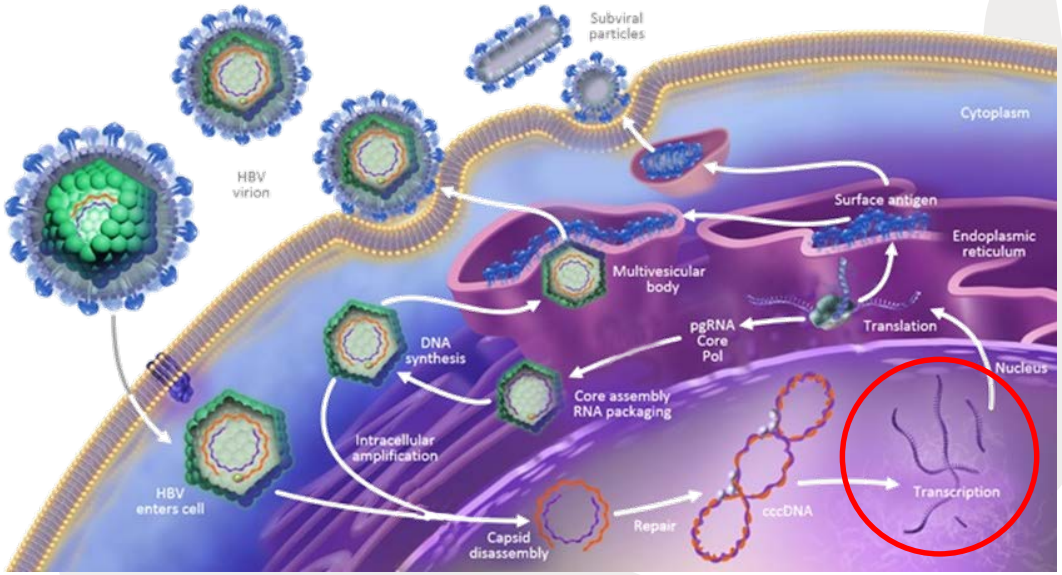
AB-729

- Novel RNA interference agent
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
- Proprietary liver targeting technology
- Durable activity following a single subcutaneous dose



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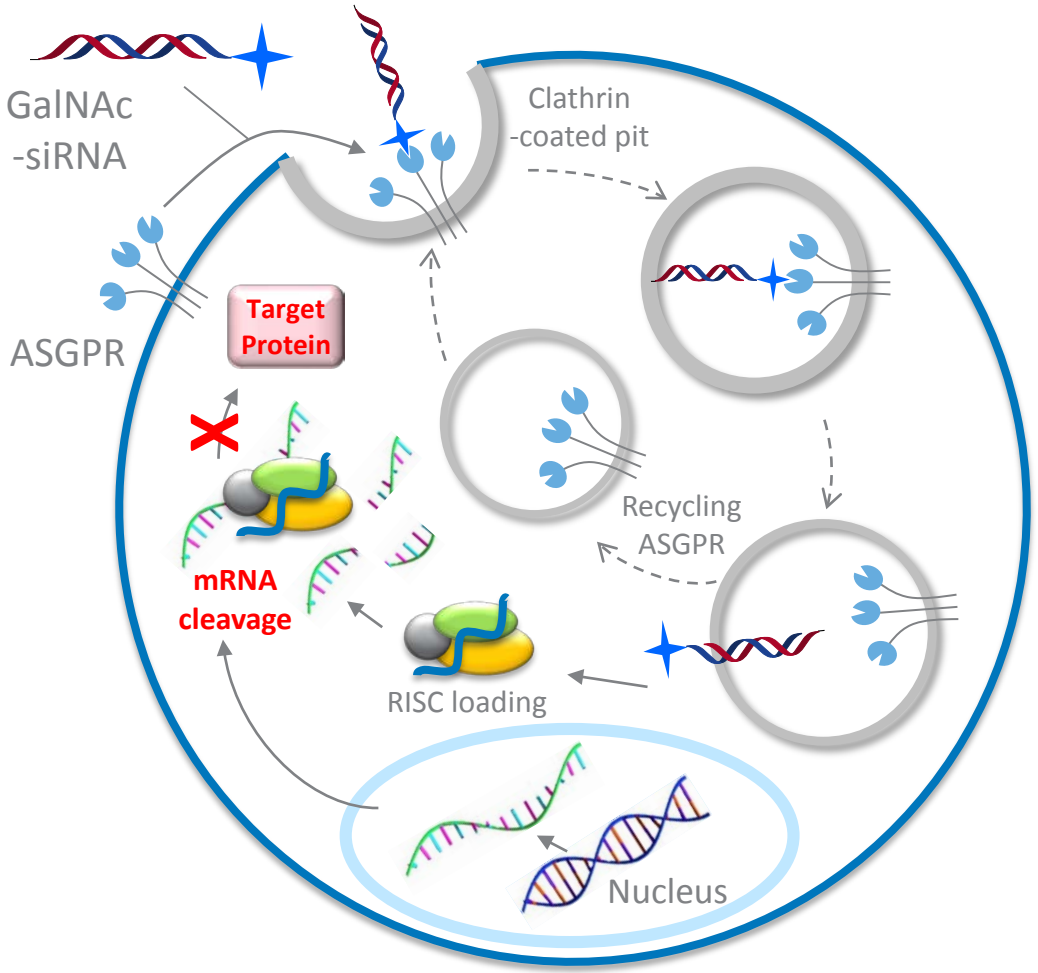
AB-729 Mechanism of Action



siRNA delivery is mediated by a conjugated targeting ligand; GalNAc

- **Cell uptake via GalNAc interaction with ASGPR**
- Asialoglycoprotein Receptor
  - Helps clear desialylated proteins from serum
- High capacity uptake system
  - 0.5-1 million copies/cell
  - Rapid 15 min recycling time
- **Advantageous tissue specificity**
  - Highly expressed in hepatocytes
  - Conserved across species

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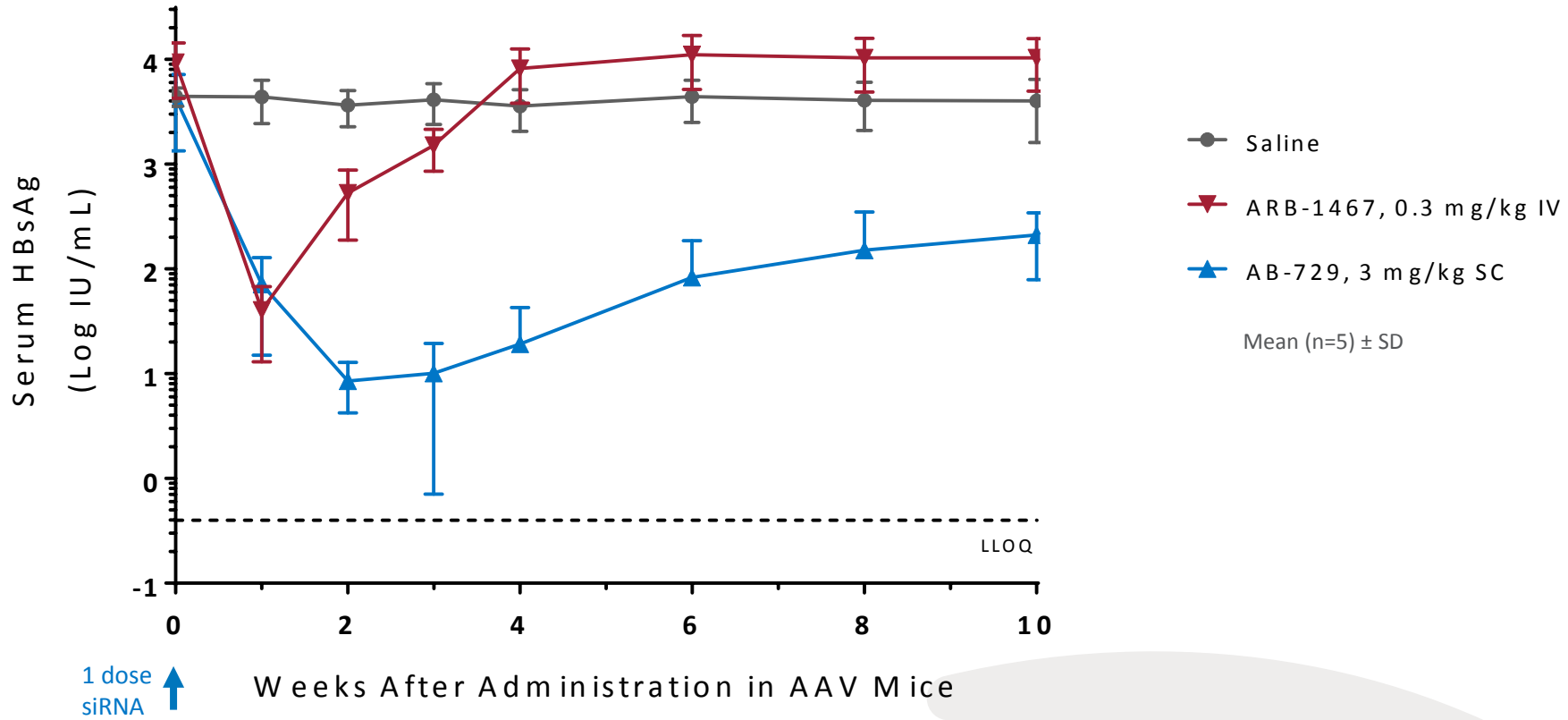
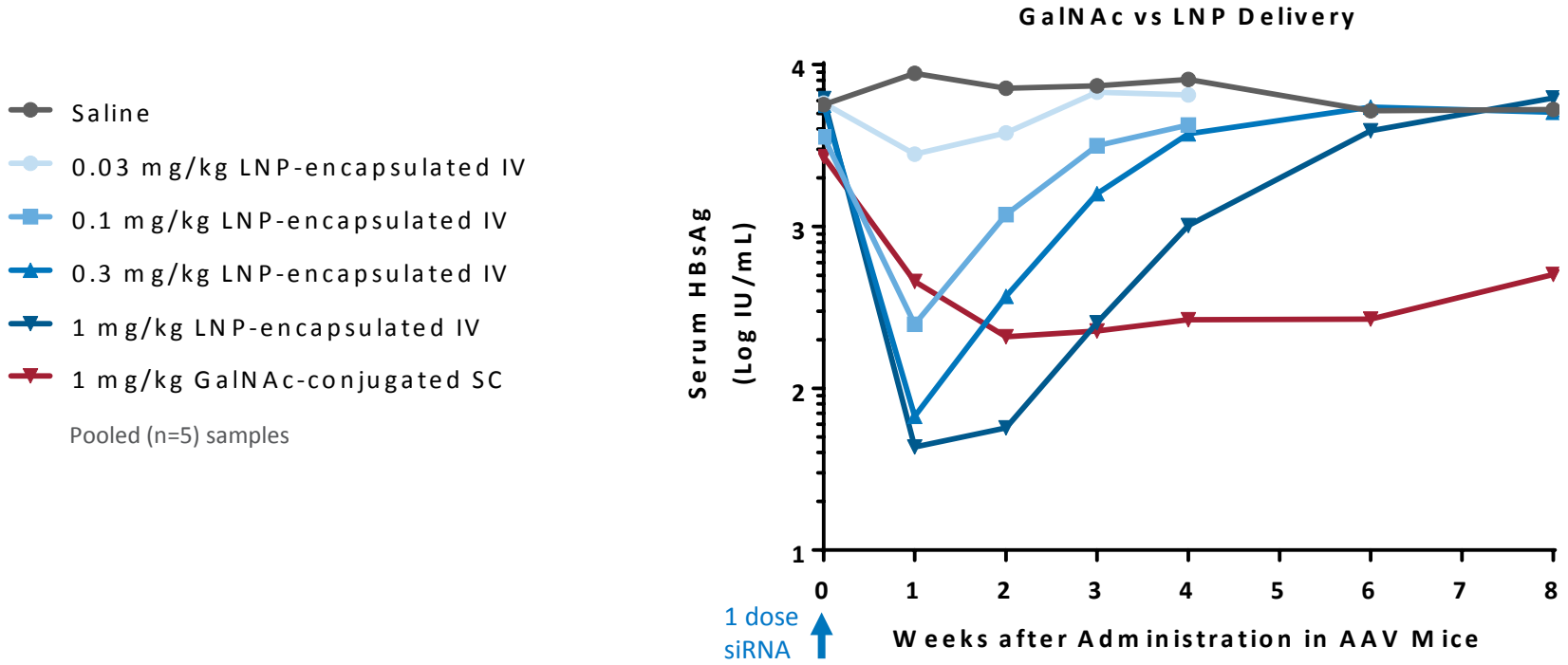
Adding New Value to Arbutus HBV Portfolio

AB-729 has longer duration of activity than ARB-1467, a Ph2 LNP siRNA agent



GalNAc-Conjugates Have More Durable siRNA Activity

- This study utilized an early discovery-stage siRNA



- GalNAc delivery provides more durable siRNA activity than LNP
  - All LNP dose groups had resolved activity before end of study, whereas GalNAc activity persisted

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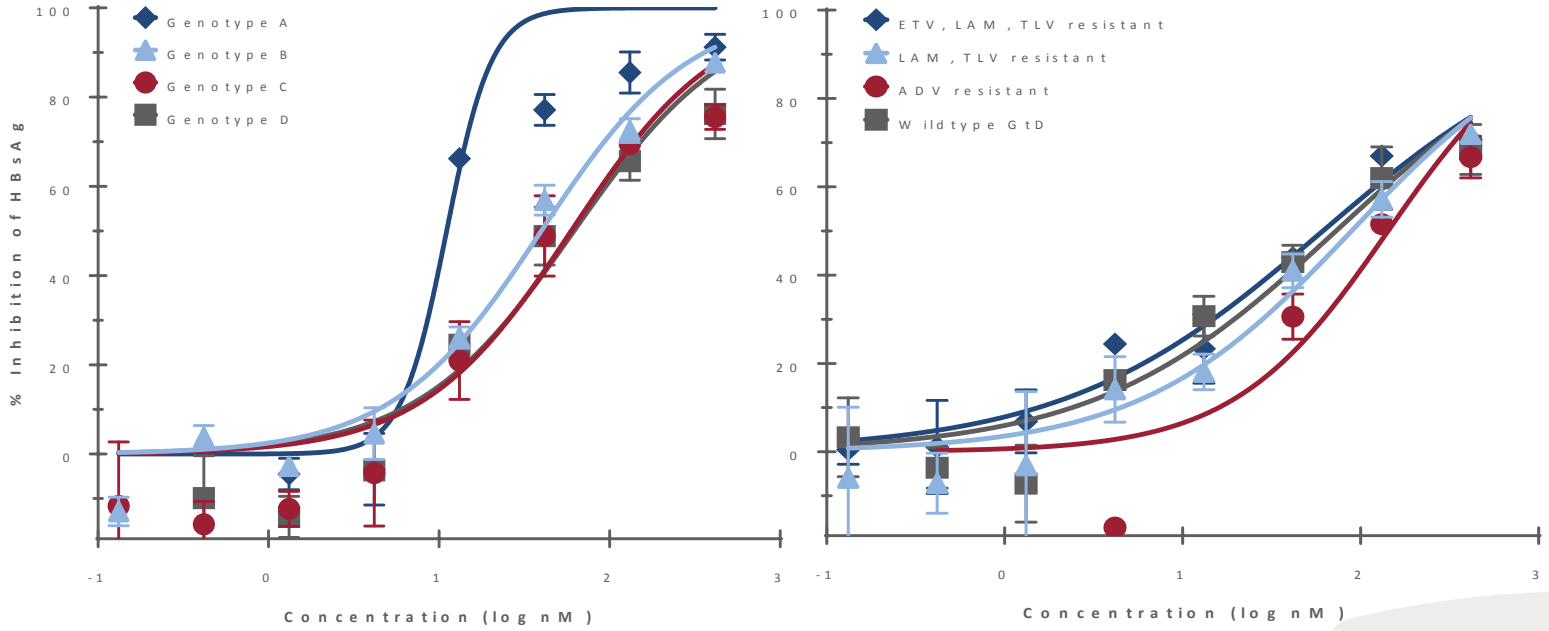
AB-729 has Pan-Genotypic Activity

The siRNA functions well against all tested genotype & Nuc-resistant variants

- Targeted HBV genome site is highly conserved across gt A-H



HBV Variant		HBsAg EC_{50} (nM)
	Genotype A	11
	Genotype B	40
	Genotype C	59
	Genotype D	62
ETVr	L528M/M552V /T532G/S550I	61
TLVr	M552V+L528M	89
ADVr	A529V	143
	Wildtype	73

Mean (n=2) ± SD

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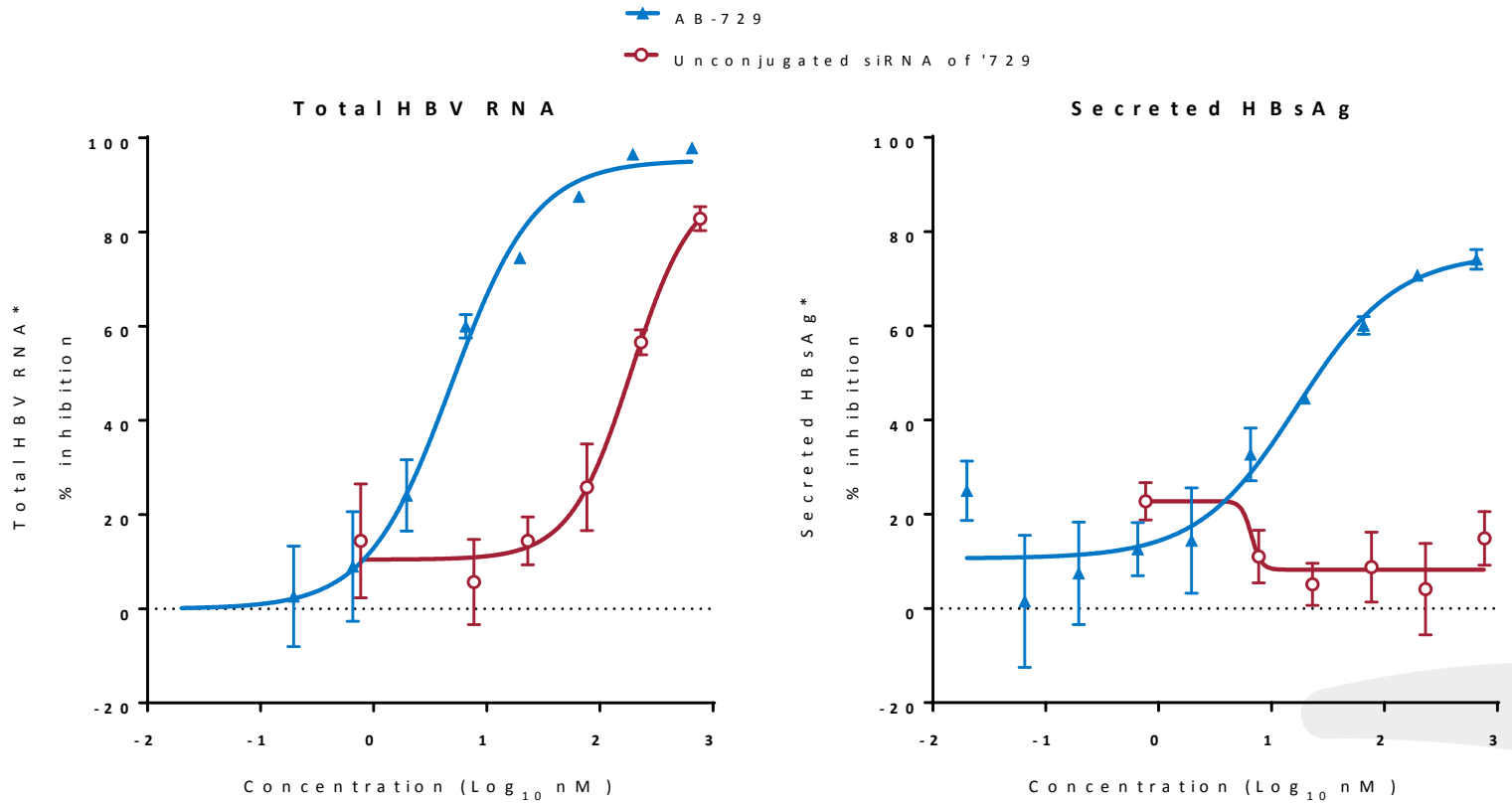
AB-729 *In Vitro* Potency

Pleiotropic Effects on HBV Demonstrated in AAV-HBV Mouse Primary Hepatocytes

- Effect of ligand-mediated delivery shown with ~2 log right shift versus unconjugated control
- No cytotoxicity detected up to highest AB-729 dose tested



	AB-729 EC_{50} (nM)
HBsAg (secreted)	16.9
HBeAg (secreted)	10.1
3.5 kb HBV RNA	3.2
Total HBV RNA	4.9
Cytotoxicity	> 19,591
CC_{50}/EC_{50} for sAg	> 1,158

Mean (n=3) ± SD
* Normalized to GAPDH mRNA

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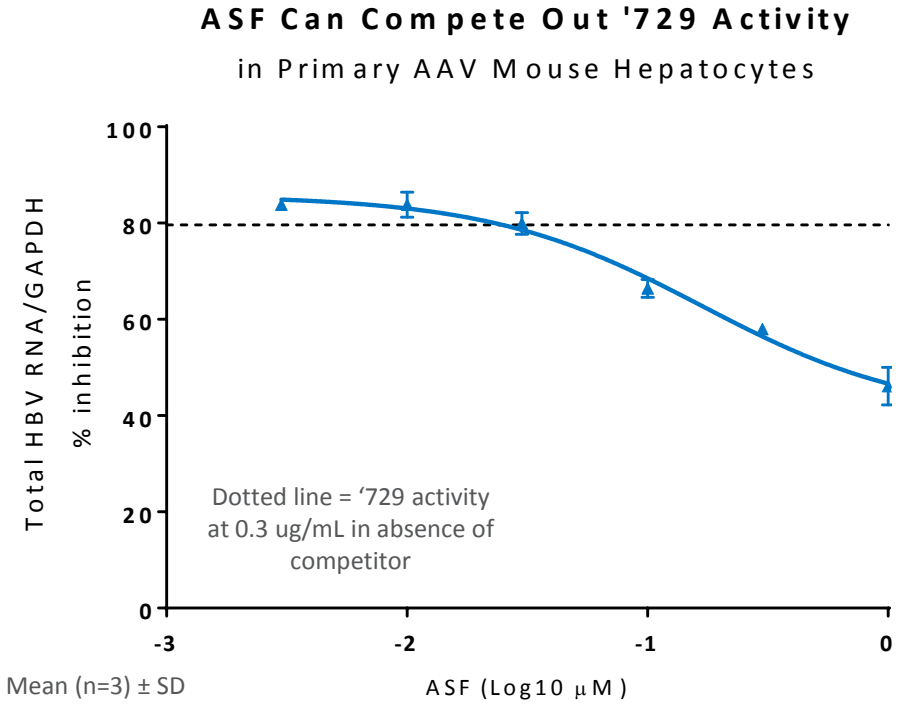
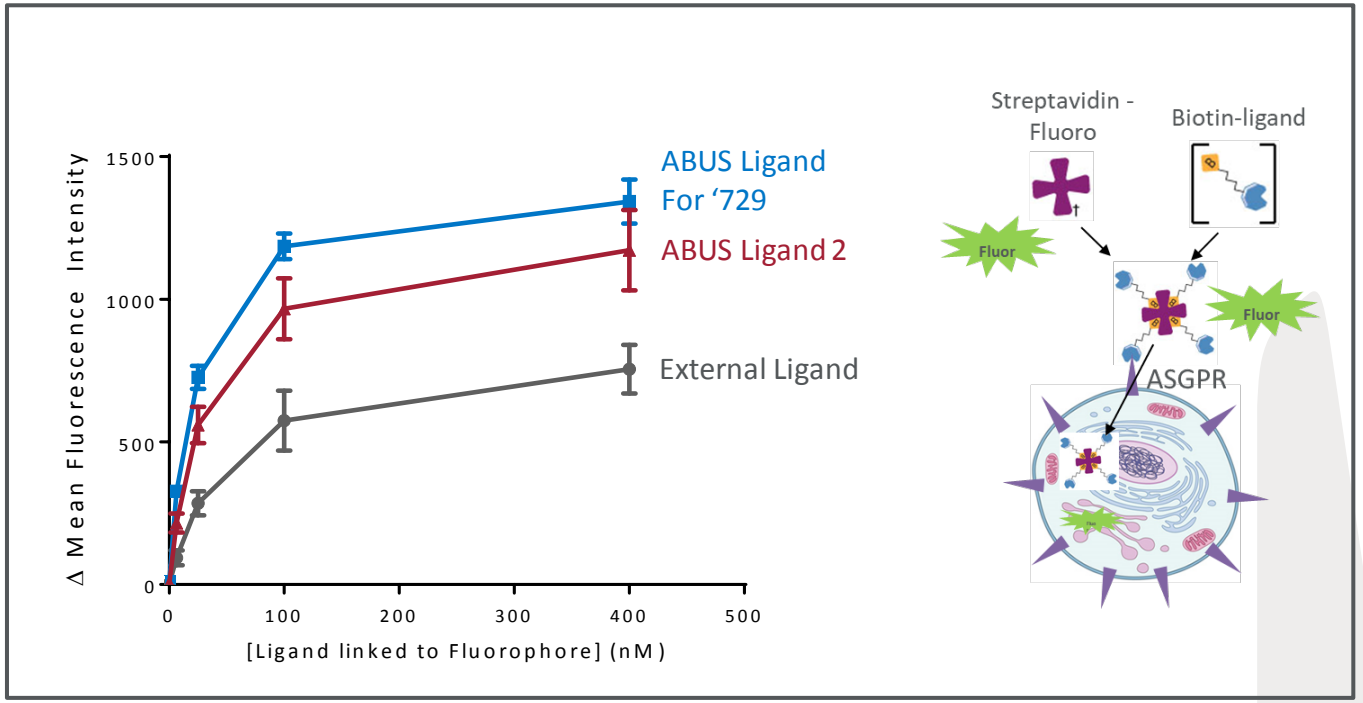
Confirmation of Mechanism of Action

Asialoglycoprotein Receptor Interaction Demonstrated *In Vitro*





- Concentration dependent asialofetuin (ASF) suppression of GalNAc-siRNA effect on multiple HBV markers* verifies drug activity is occurring through ASGPR interaction
- Novel GalNAc ligand conjugates provide excellent avidity for receptor binding

* sAg, eAg data similar; not shown

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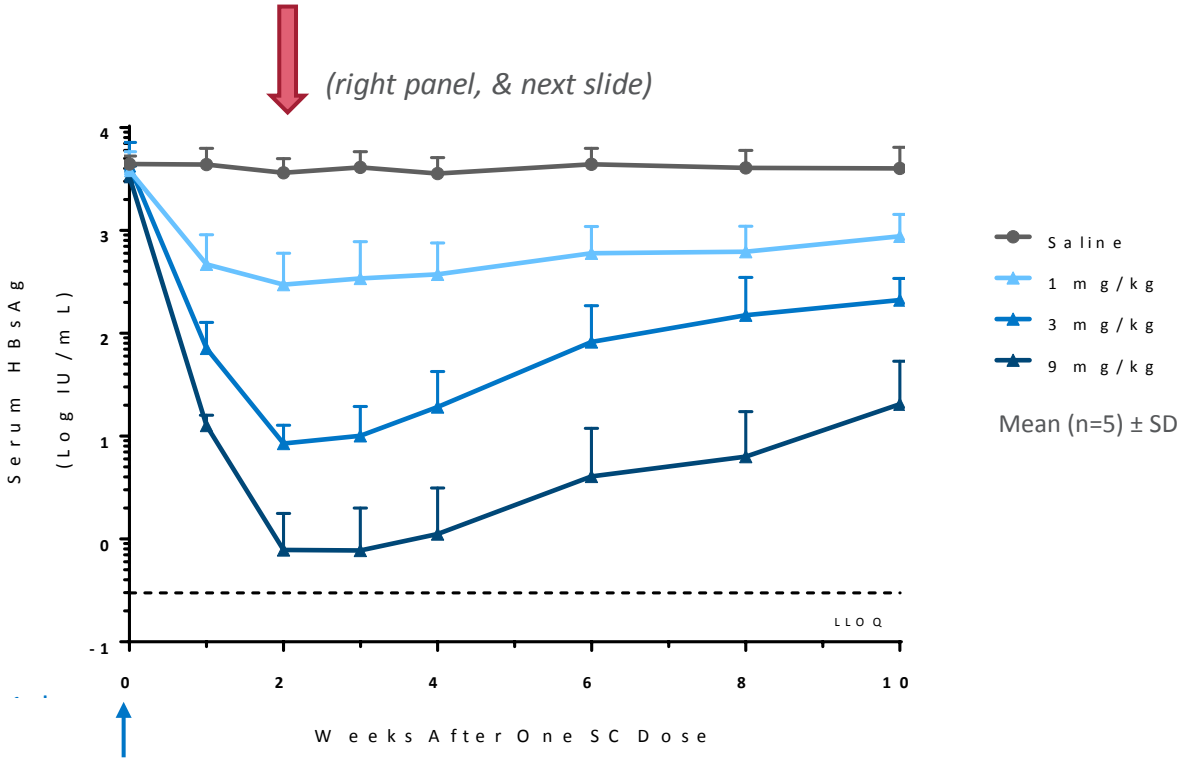
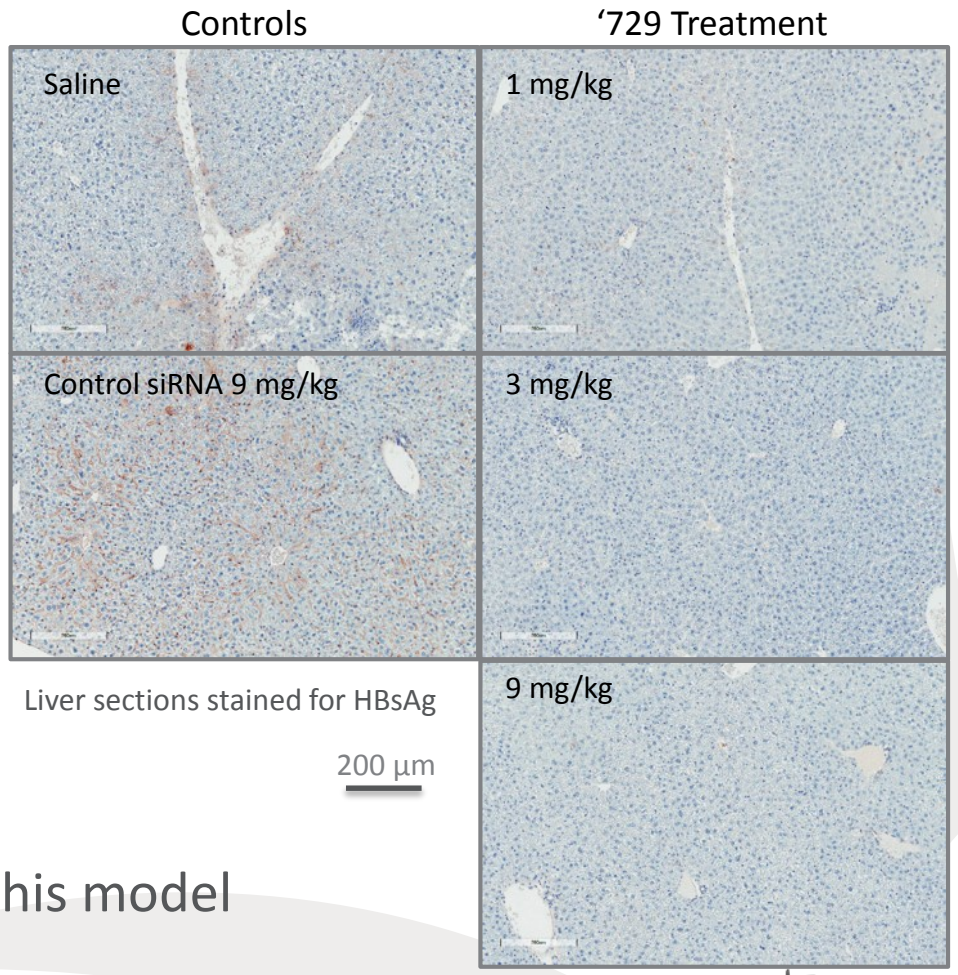
AB-729 *In Vivo* Single Dose Response & Duration

In AAV Mouse





- Clear dose response, achieved max effect detectable in this model
- Supports clinical dosing frequency of 1 month (or more)

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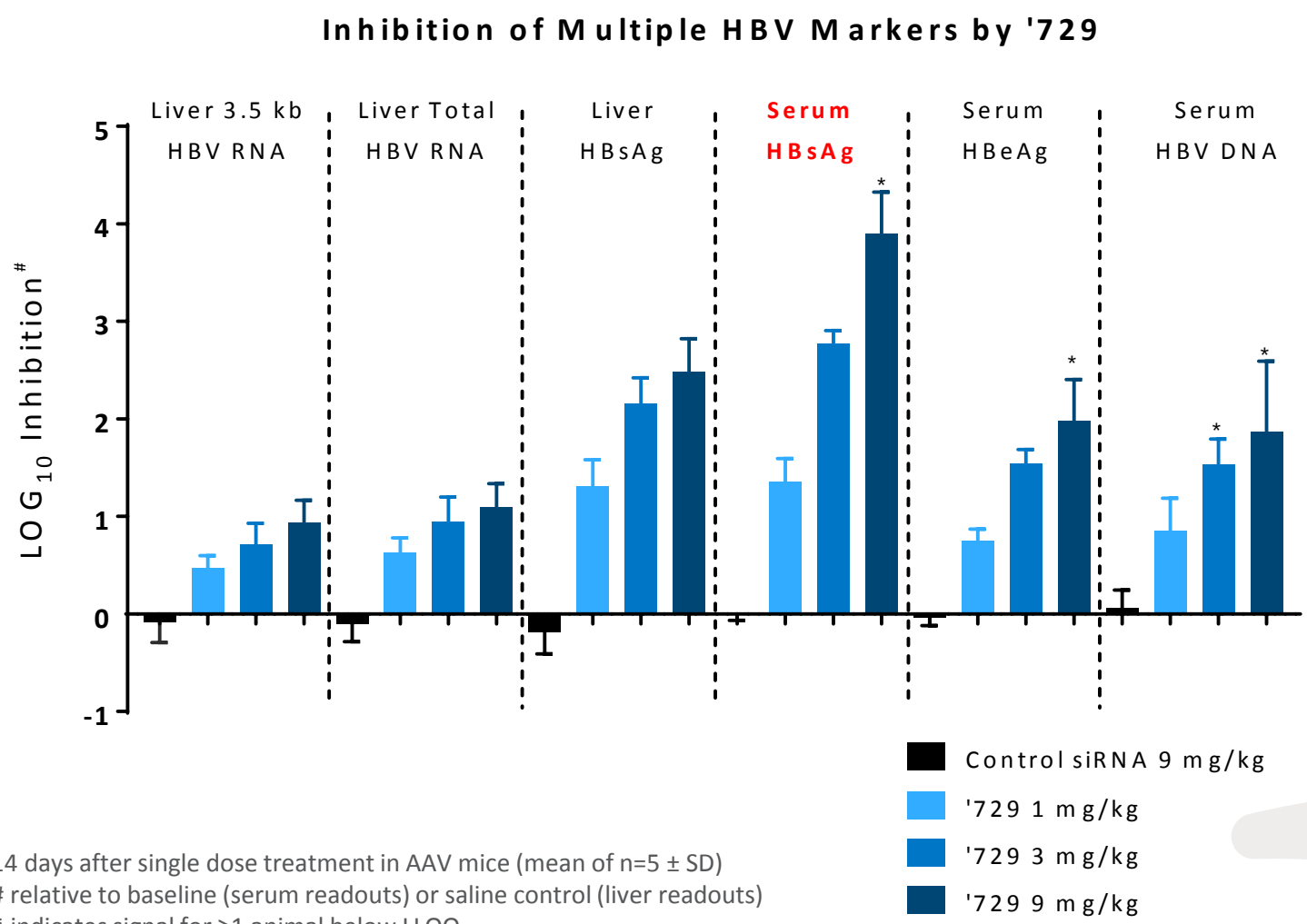
Pleiotropic Effects of AB-729 on HBV *In Vivo*



14 days after single dose treatment in AAV mice (mean of n=5 ± SD)
relative to baseline (serum readouts) or saline control (liver readouts)
* indicates signal for ≥1 animal below LLOQ

Effects are consistent with RNAi mechanism of action

- Dose responsive effects on all measured HBV markers
- cccDNA not significantly present in this model; not expected to be directly impacted by RNAi

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AB-729

- Novel RNA interference agent
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
- Proprietary GalNAc-conjugate liver targeting technology
- Pan-genotypic activity
- Multi-month duration of surface antigen inhibition after a single SC dose
  - Significantly improved over ARB-1467, a Phase 2 IV LNP siRNA agent

- **Next:** Initiate GLP safety studies

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