Combination Approaches Towards a Functional Cure for Chronic Hepatitis B

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HEP DART 2019

December 10th

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Disclosures

- Lawrence M. Blatt is an employee and stockholder of Aligos Therapeutics, Inc.

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Aligos' Chronic Hepatitis B Clinical Development Strategy

- Target multiple important processes in the viral life cycle using combinations of Aligos novel therapeutics with the goal of achieving
  - Complete shutdown of viral replication allowing turnover of infected hepatocytes and prevention of infection of new hepatocytes
  - Suppression of HBsAg production resulting in removal of immunosuppressive effect of HBsAg allowing the reactivation of the exhausted immune system
- Treatment success is currently defined as the achievement of functional cure*
  - Sustained, undetectable HBsAg and HBV DNA in serum with or without seroconversion to hepatitis B surface antibody (anti-HBs) after completion of a finite course of treatment, resolution of residual liver injury, and a decrease in risk of hepatocellular carcinoma (HCC) over time

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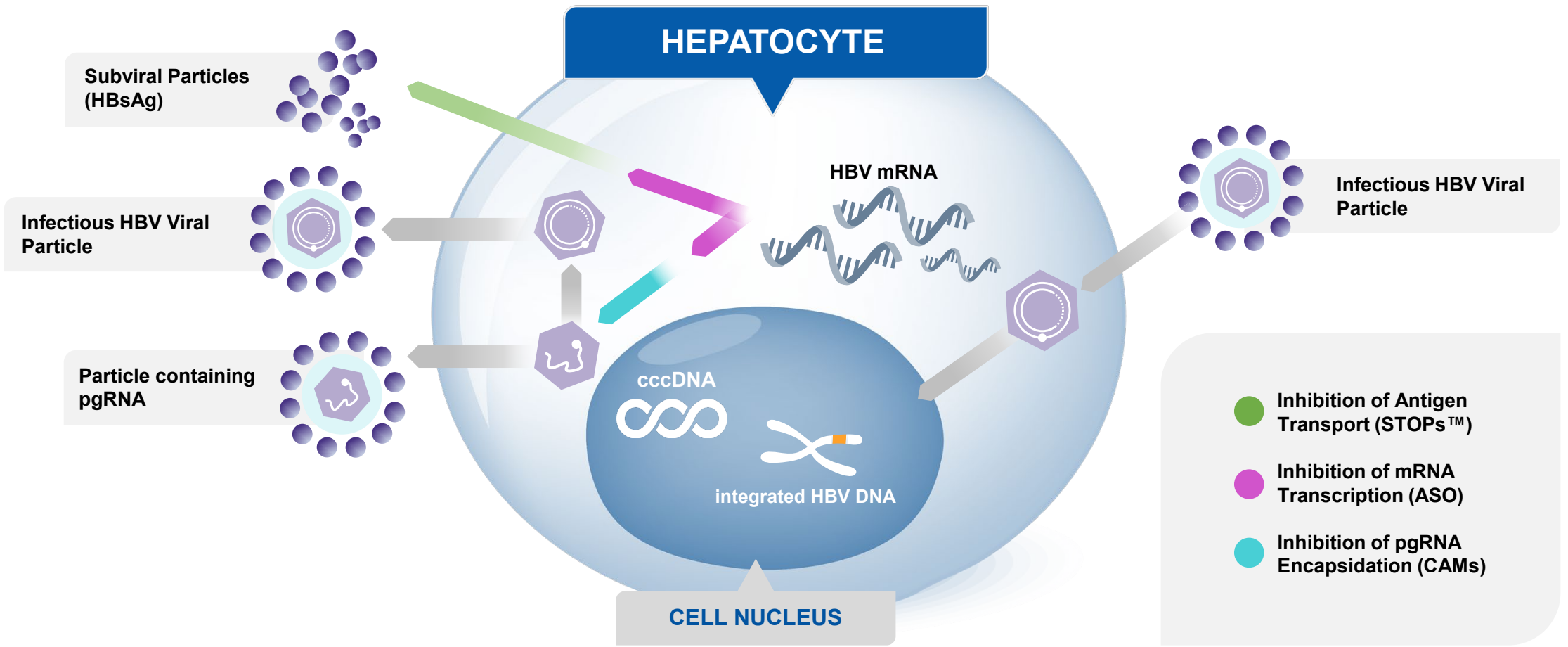
*A. Lok, F. Zoulim, G. Dusheiko, M.G. Ghany, Journal of Hepatology 2017 vol. 67, 847-861

Targeting Clinically Validated Mechanisms for Treating CHB



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Capsid Assembly Modulators (CAMs)

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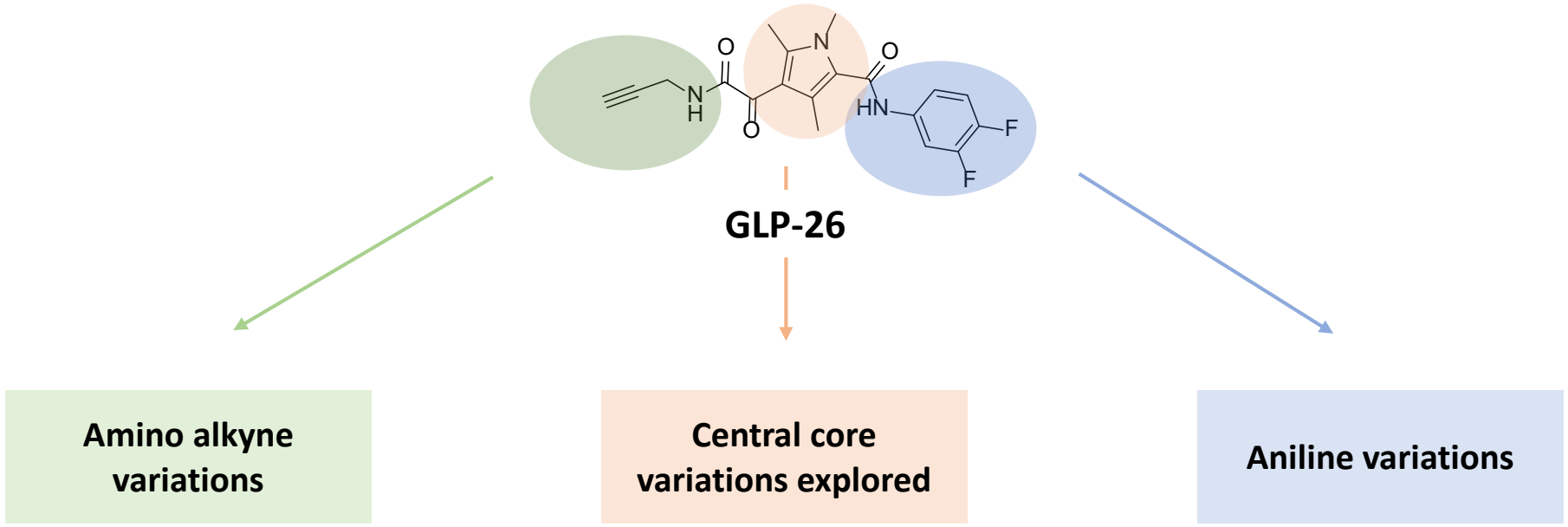
Novel Class-II Capsid Assembly Modulator Estate Advanced in Collaboration with Professor Raymond Schinazi (Emory U)



- **>250 new analogs have been exemplified**
- **Multiple compounds prepared have improved properties relative to GLP-26**
- **ALG-001075 discovered and successfully advanced through dose range finding studies**
- **ALG-000184, a prodrug of ALG-001075, identified with improved DMPK properties**
- **Currently advancing ALG-000184 into GLP toxicology studies to enable 2020 clinical entry**

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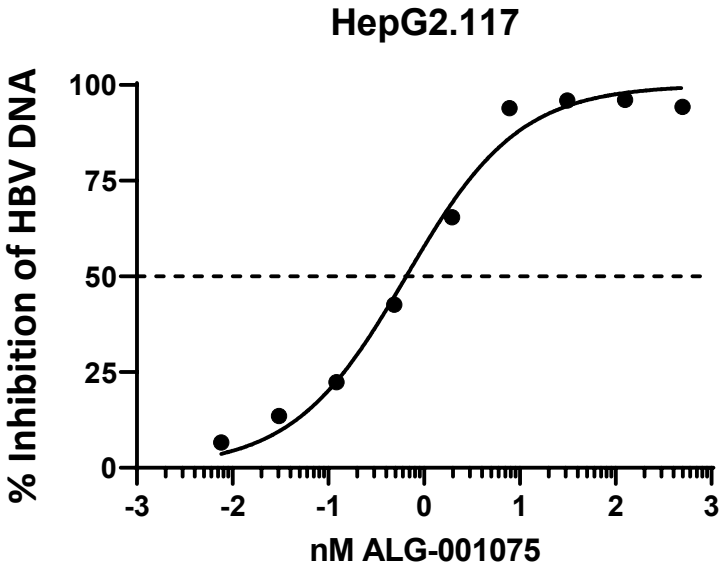
ALG-001075 Demonstrates *Best-in-Class In Vitro* Properties

	ALG-001075
EC_{50} / EC_{90} (nM) HepG2.117	0.63 / 3.17 (n = 12)
GSH adduct (HLM)	Not observed
M/R/D/H LM $t_{1/2}$ (min)	> 60 all
M/R/D/C/H Hep $t_{1/2}$ (min)	Stable
M/R/D/C/H % protein binding	74-88%
Papp $_{A->B}$ (10^{-6} cm/s) [A-B, B-A/A-B]	1.8, 7.8
CYP inhibition IC_{50} 1A2/2B6/2C8/2C9/2C19/2D6/3A4	> 10 µM all
Time Dependent Inhibition	Low Potential
hERG Testing, 0.3 –> 10 µM	IC_{50} > 10 µM
CEREP Screening at 10 µM	No hits
Ames / MNT	Negative / Negative
Proteasome Screening	No hits
Aqueous Solubility	Low

Inhibition of HBV DNA in HepG2.117 Cells



Concentration of ALG-001075 (nM)

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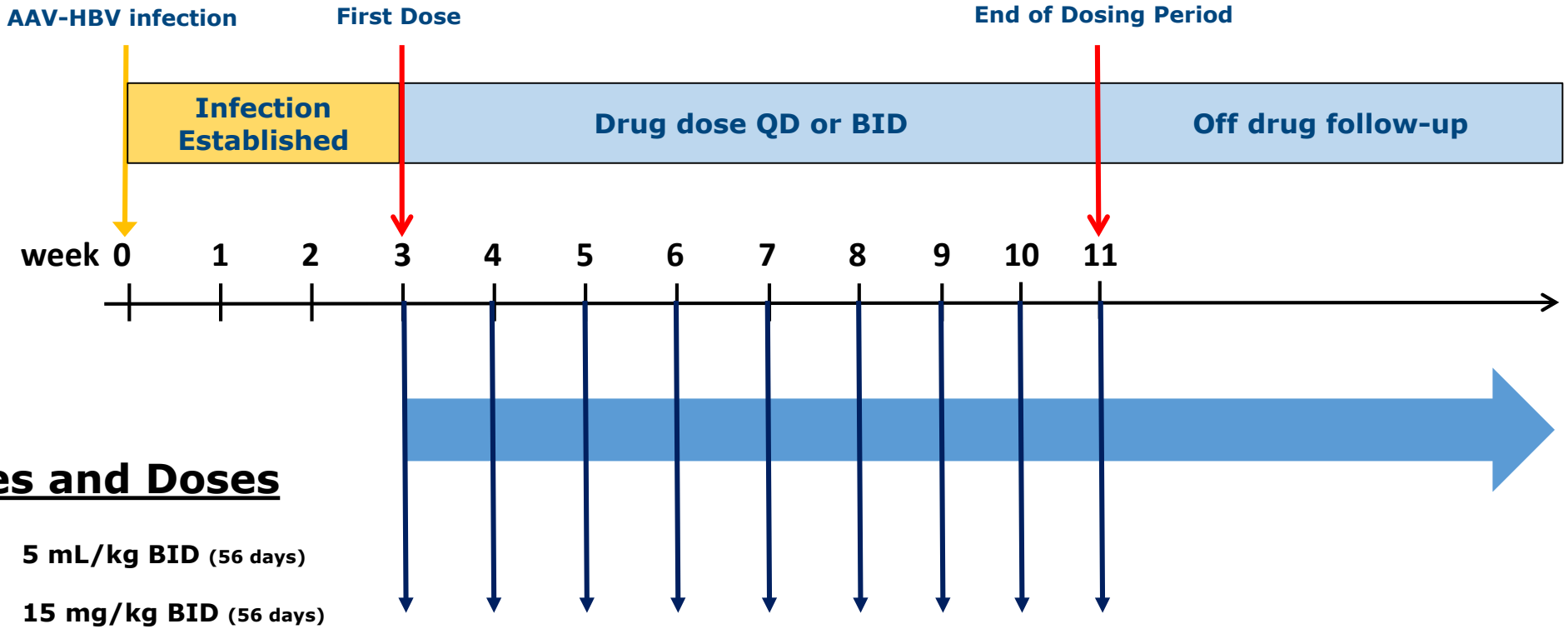
ALG-001075 AAV-HBV *In Vivo* Mouse Efficacy Model

Serum collected weekly for HBV monitoring and measurement of other parameters



Test Articles and Doses

Vehicle	**5 mL/kg BID (56 days)**
ALG-001075	**15 mg/kg BID (56 days)**
ALG-001075	**15 mg/kg QD (56 days)**
ALG-001075	**50 mg/kg QD (56 days)**

Evaluated HBV DNA weekly

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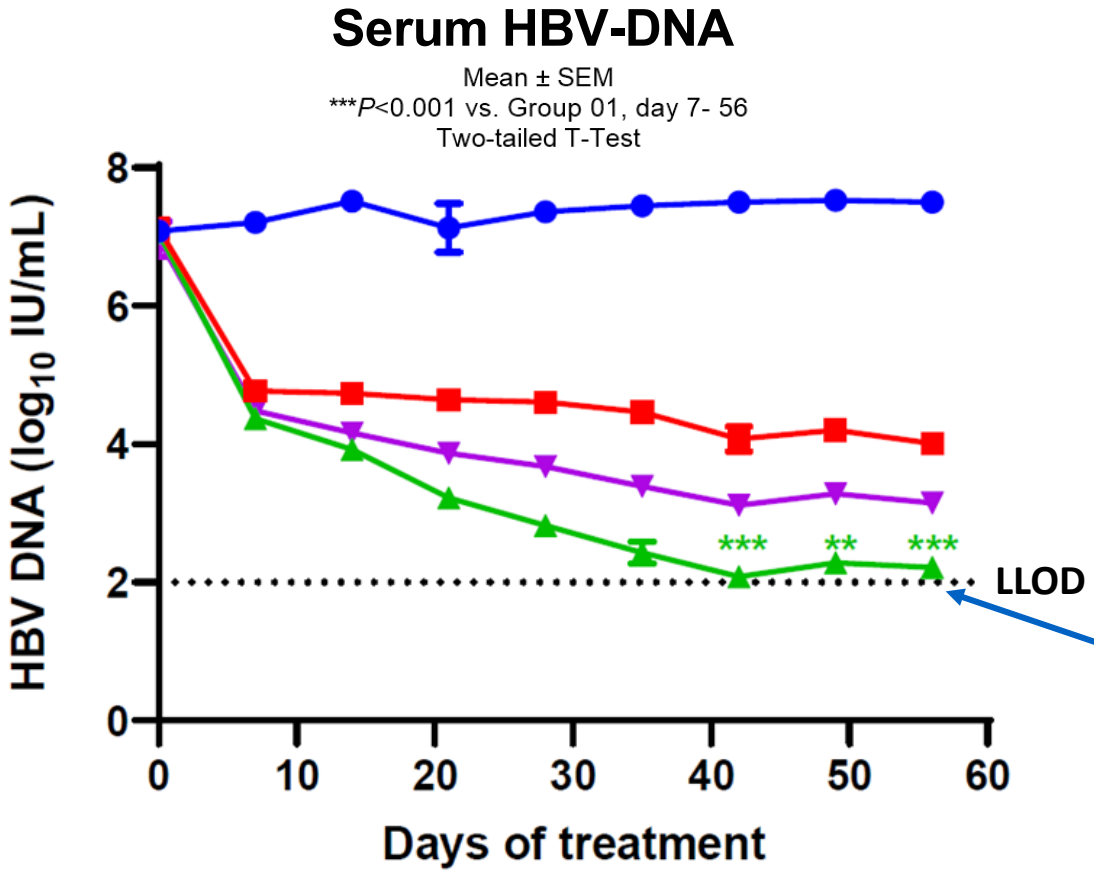
ALG-001075
5-Log$_{10}$ IU/mL Drop in HBV DNA in the AAV-HBV Mouse Model



56-day Study, all compounds dosed PO

- **Vehicle**
- **ALG-001075 15 mg/kg QD**
- **ALG-001075 15 mg/kg BID**
- **ALG-001075 50 mg/kg QD**

50% (3/6) of animals below lower limit of detection (LLOD; 2 log$_{10}$ IU/mL HBV DNA)

- **Dose dependent reduction in HBV DNA observed in all treatment groups**
- **No changes in HBsAg levels noted**
- **No significant changes in body weight**

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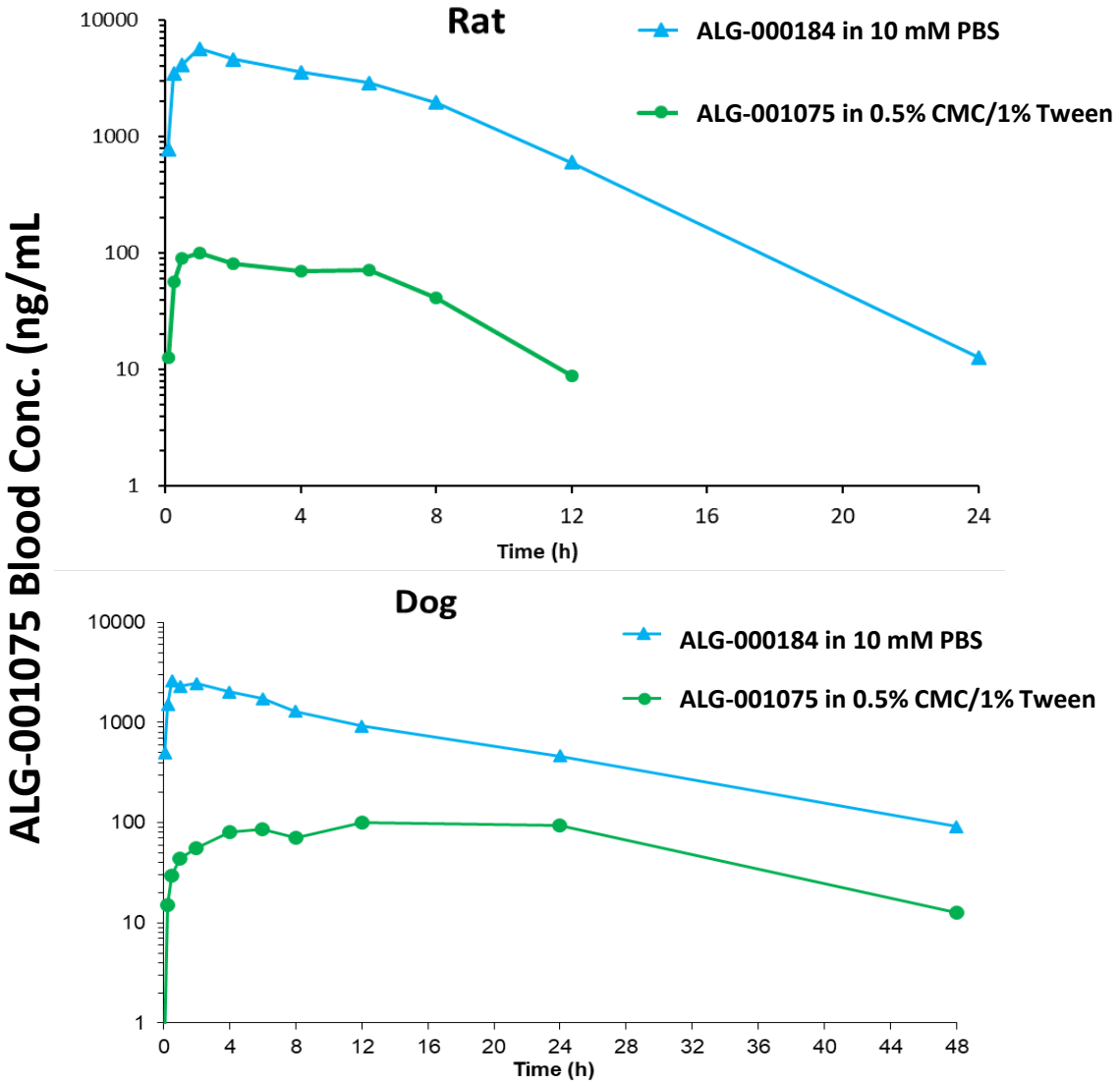
ALG-000184, A Prodrug of ALG-001075

- Designed to markedly improve solubility
  - ALG-000184 solubility: >120 mg/mL in PBS
- Stable in SGF/SIF with no degradation observed following >14-days in PBS solution
- ALG-000184 efficiently delivers ALG-001075 following oral dosing in aqueous solution
  - Rat: 30 mg/kg, Dog: 5 mg/kg
- Projected efficacious dose in humans
  - 100-250 mg QD



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S-Antigen Transport-inhibiting Oligonucleotide Polymers (STOPs™)

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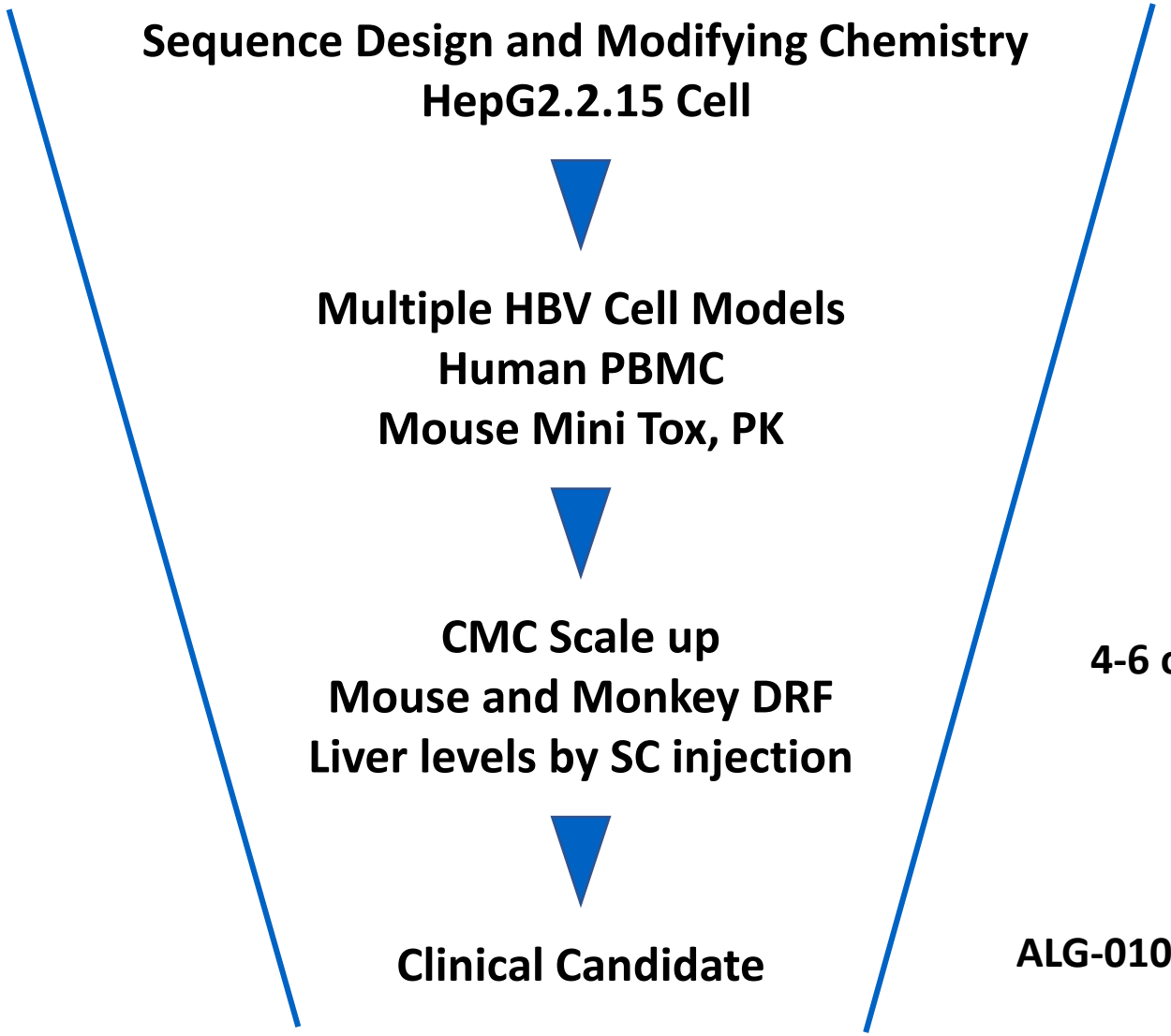
Poly AC Oligonucleotides Targeting HBsAg Reduction

Comprehensive Structure Activity Relationship Established

Sugar, base, sequence, length, linker and backbone modifications

Exploration of MOA



>400 oligonucleotides exemplified

18-24 oligonucleotides

4-6 oligonucleotides

ALG-010133

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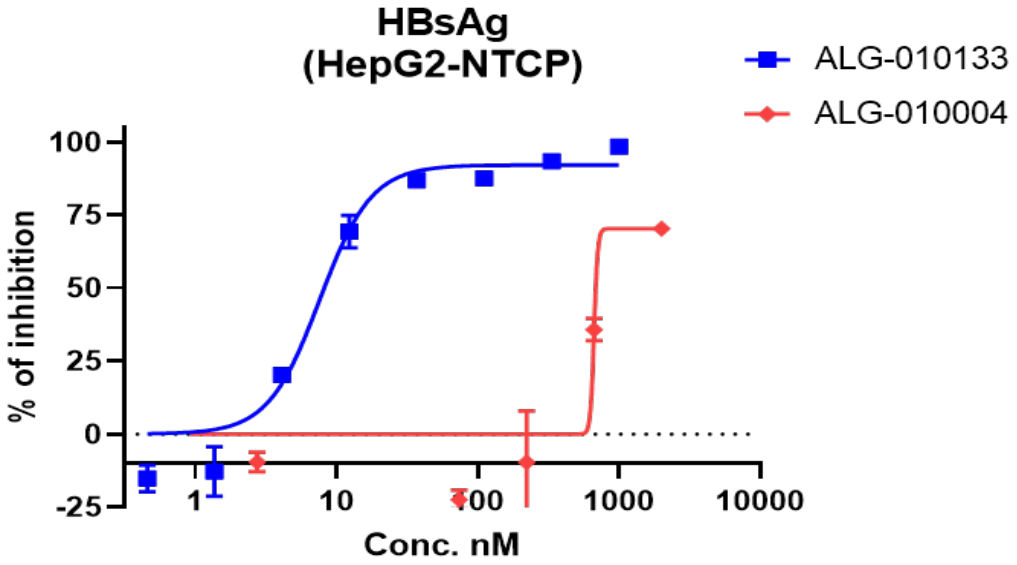
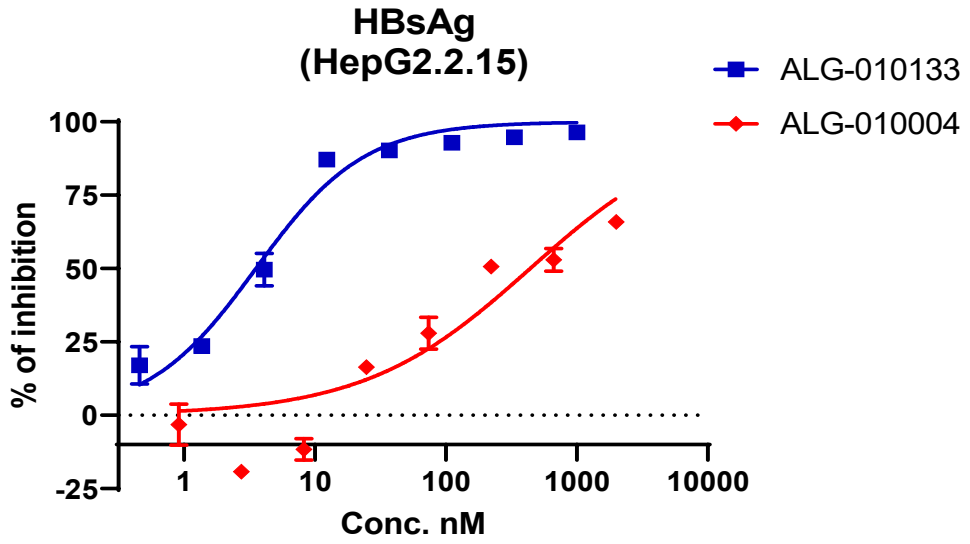
ALG-010133 Demonstrates >100-fold Potency vs. Reference





	Structure	PBMC Activation	Live HBV / HepG2-NTCP		HepG2.2.15	
			EC_{50} nM	CC_{50} nM	EC_{50} nM	CC_{50} nM
ALG-010004 (Reference)*	$(AC)_{20}$ [2'-OMe-A, 2'-OMe-5-MeC, all PS]	+	665	>2000	442	>2000
ALG-010133	Aligos STOP™	-	4.9	>2000	3.5	>2000

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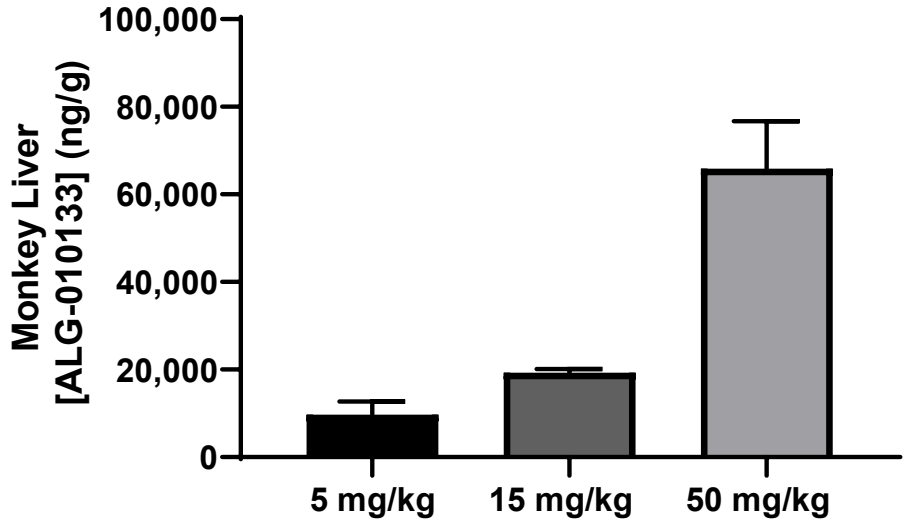
*A. Vaillant, Antiviral Research 133 (2016) 32

ALG-010133
Non-Human Primate Multiple Dose Exposure in Liver

- Much higher liver exposure observed for SC compared to IV dosing
- High and dose proportional exposure in liver following three weekly SC doses



Data collected 48-hours after the third dose

ALG-010133 Liver Concentrations Following 3 SC weekly doses			
Dose	5 mg/kg	15 mg/kg	50 mg/kg
Liver (µg/g)	9.7	19.3	65.9

Projected human efficacious dose: 6-10 mg delivered weekly, SC

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Antisense Oligonucleotides (ASO)

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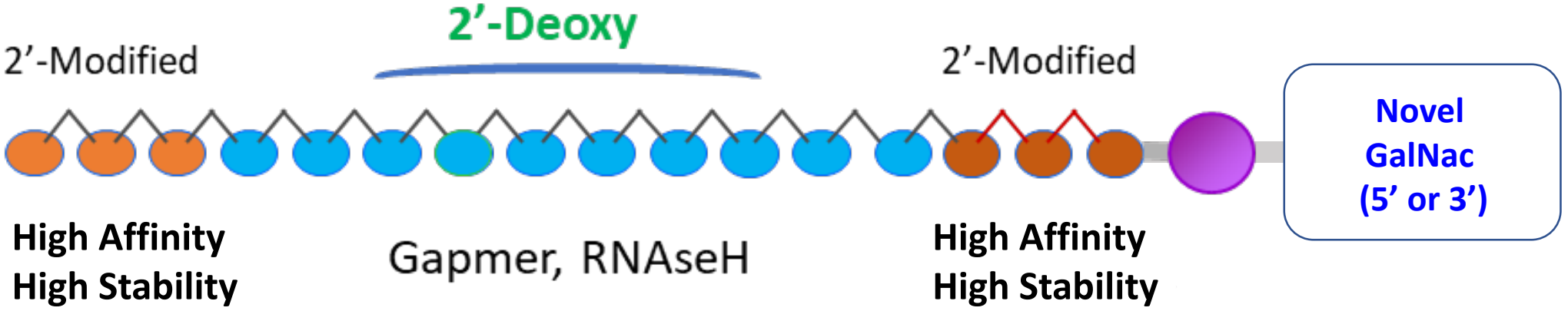
Aligos' Two Trigger Strategy for Antisense Oligos



- Aligos' two trigger strategy
  - Bioinformatics conducted using latest available data (>8000 sequences)
  - Benefits of the two-trigger strategy
    - Increased resistance barrier, better coverage of genotypes & integrated genomes
      - X trigger: High homology, more potent, close to high integration region
      - S trigger: Good sites for targeting integrated HBV

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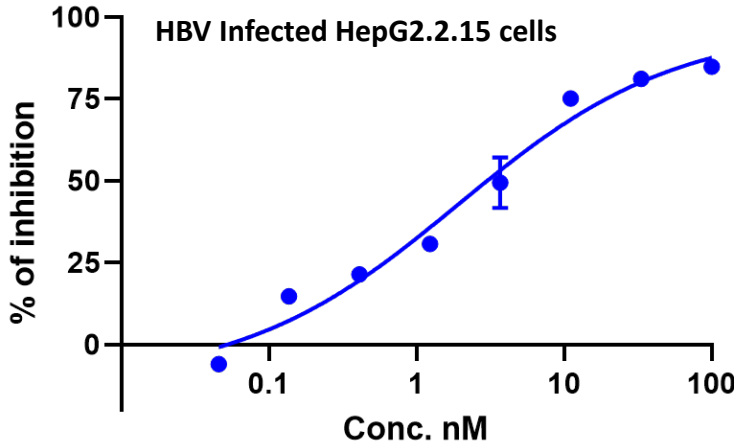
Selected Triggers are Potent *In Vitro*

- ALG-020093 (S-trigger)
  - Potent *in vitro*
  - Excellent genotypic coverage

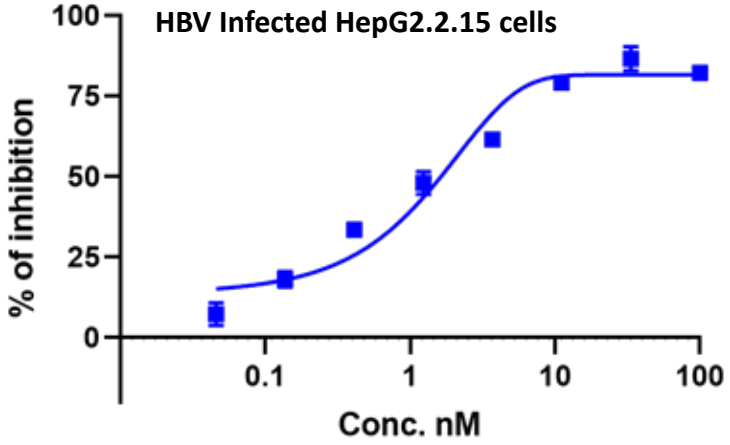
HBsAg Release Assay
EC_{50} = 1.9 nM



Genotype	A	B	C	D	E	F	G	H	I	J
% Homology	98%	100%	99%	100%	100%	100%	100%	100%	100%	100%

- ALG-020090 (X-trigger)
  - Potent *in vitro*
  - Excellent genotypic coverage

HBsAg Release Assay
EC_{50} = 0.88 nM



Genotype	A	B	C	D	E	F	G	H	I	J
% Homology	100%	100%	99%	100%	96%	100%	99%	100%	100%	97%

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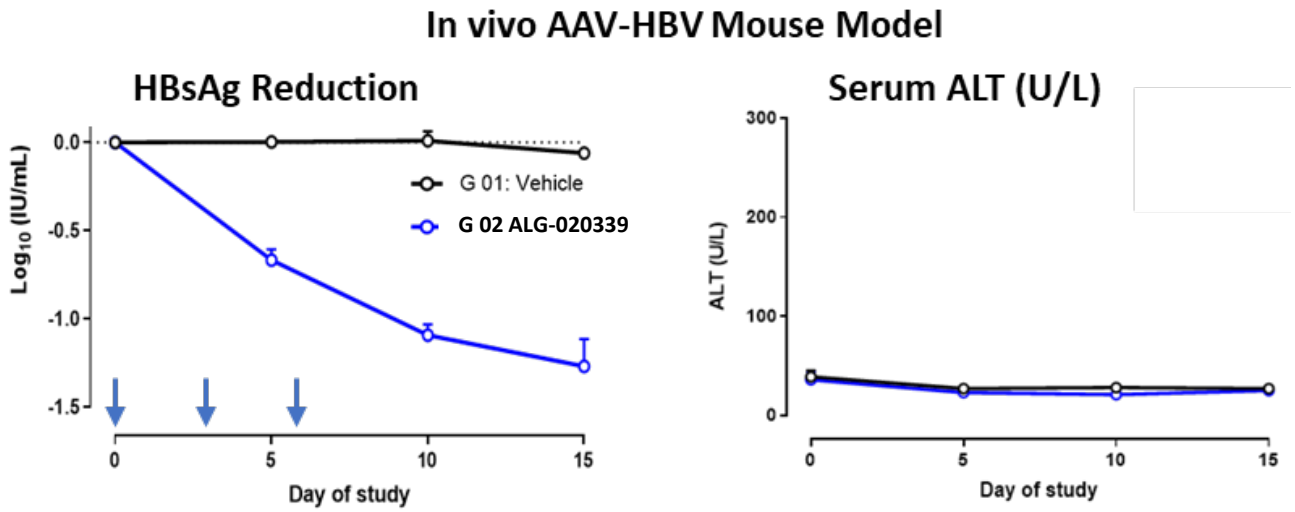
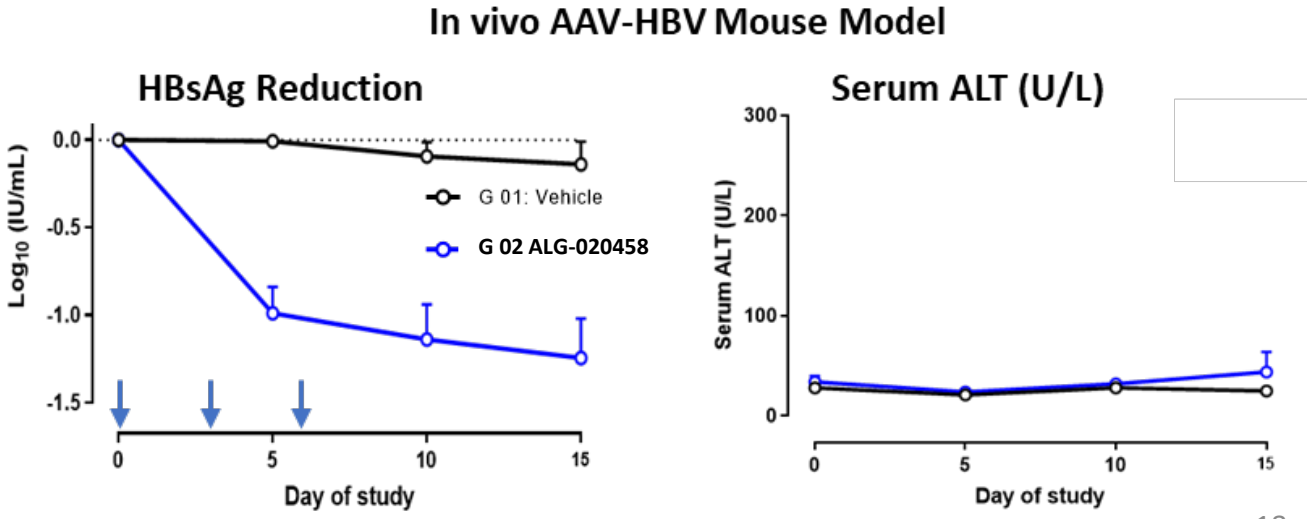
Selected Triggers are Potent *In Vivo*

- ALG-020339 (S-trigger)
  - ALG-020093 derived GalNAc modified construct
  - Potent *in vivo*
    - 3 X 10 mg/kg
    - Dosing days 0, 3, 6
    - No increase in ALT



- ALG-020458 (X-trigger)
  - ALG-020090 derived GalNAc modified construct
  - Potent *in vivo*
    - 3 X 10 mg/kg
    - Dosing days 0, 3, 6
    - No increase in ALT



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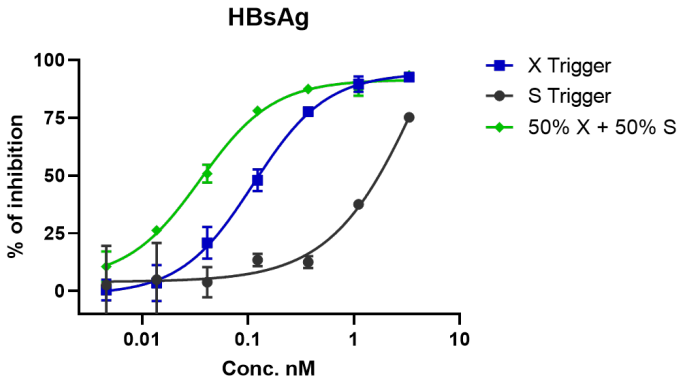
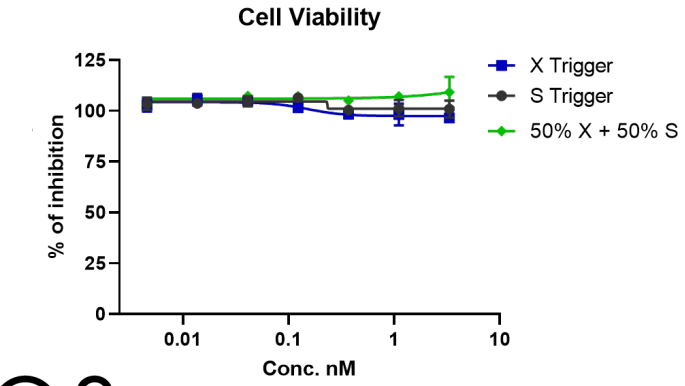
Targeted Mechanisms of Action are Synergistic *In Vitro*

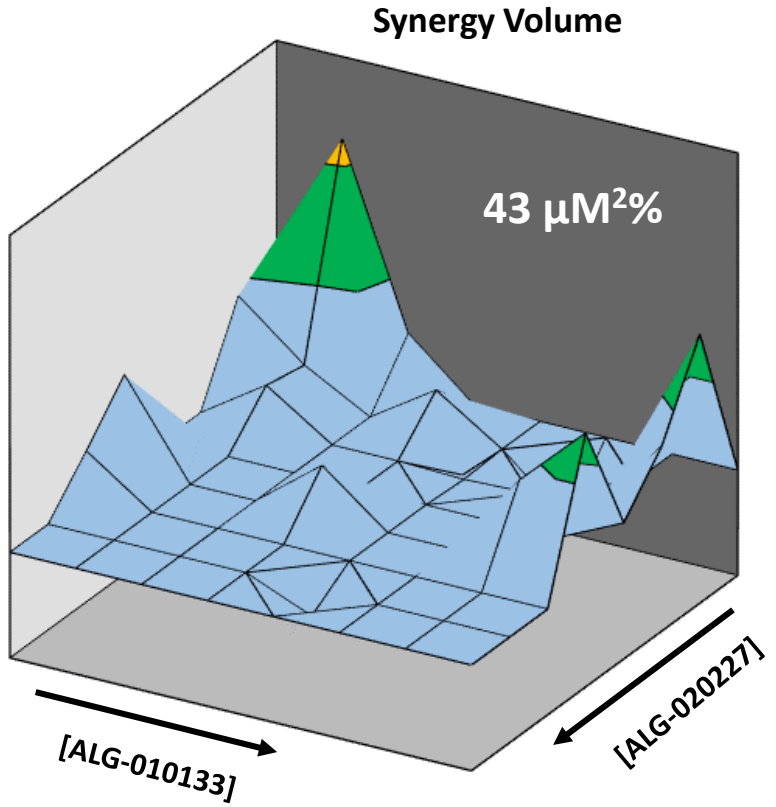
- Representative S + X ASO triggers in 1:1 combination in HepG2.2.15
  - Synergy with no observed cytotoxicity





In vitro HepG2.2.15 cells

- STOP + ASO in combination
  - HBsAg reduction in HepG2.2.15 cells
  - Synergy for ALG-010133 + ASO X trigger



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Towards Development of a Functional Cure for CHB

- Aligos is pursuing a strategy to discover and develop multiple agents acting against distinct, clinically validated targets
  - Capsid assembly modulators (CAM)
    - Sub-nanomolar compounds discovered in collaboration with Emory University
    - ALG-000184, a prodrug of ALG-001075, advancing in GLP toxicology studies
  - S-antigen transport inhibiting oligonucleotide polymers (STOPs™)
    - SAR thoroughly explored with analogs >100-fold more potent than existing clinical agents
    - ALG-010133 advancing in GLP toxicology studies with SC dosing enabled
  - Antisense oligonucleotides (ASO)
    - Lead sequences identified using latest bioinformatics, advancing in DRF toxicology studies
    - Novel two-trigger (X + S) strategy to maximize genome coverage and minimize resistance

- Clinical entries anticipated in 2020 to enable exploration of multiple combination regimens towards achievement of a functional cure

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Acknowledgements

Thanks to the entire Aligos and Emory team!

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