Combination treatment with AB-101, a small-molecule PD-L1 Inhibitor, and an HBV-targeting GalNAc-siRNA increases HBV-specific immune responses in a chronic Hepatitis B infection mouse model

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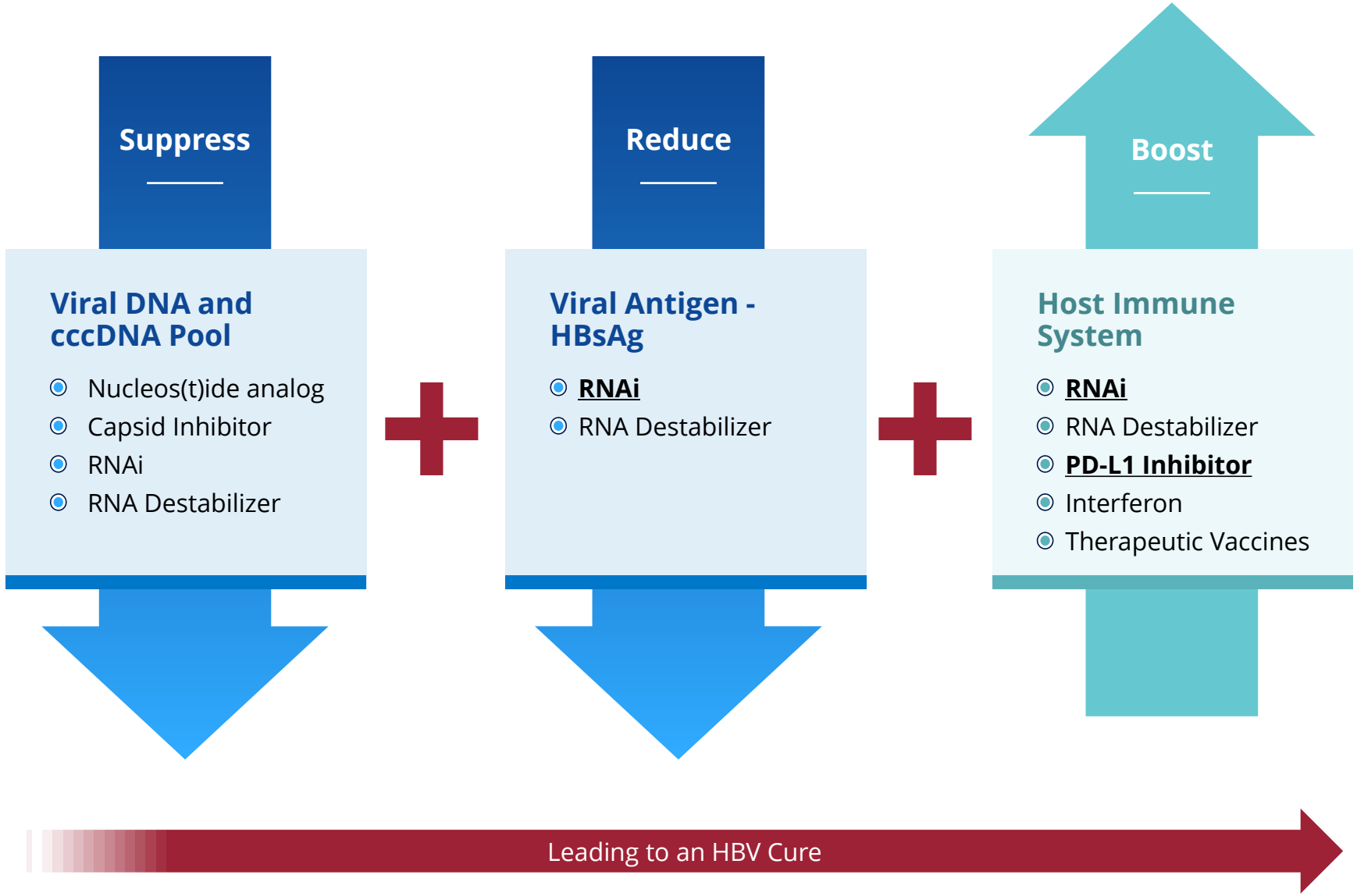
3-Pronged Approach to Therapeutic Success

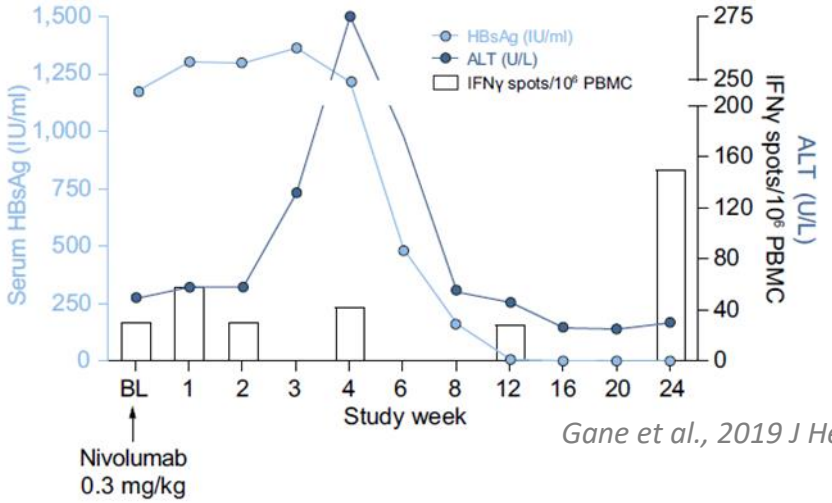
- **Suppress** HBV DNA
- **Reduce** viral antigens
- **Boost** host immune response

Therapeutic success will **require a combination of agents** with complementary MOAs.



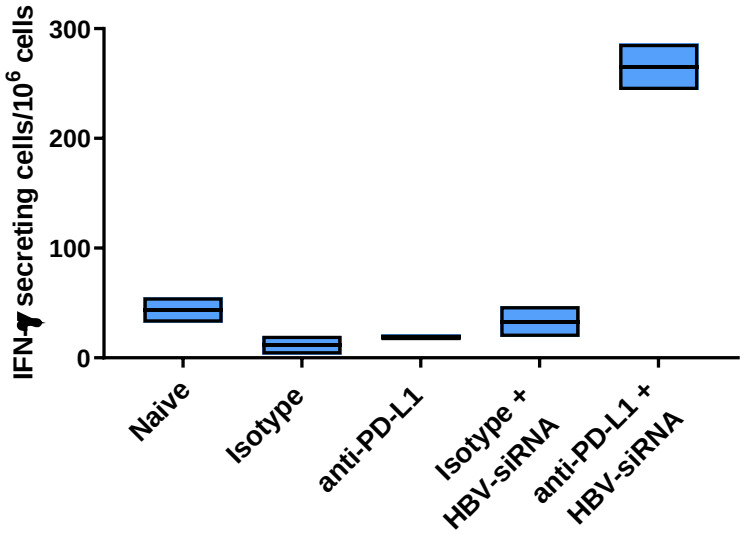
Checkpoint Blockade as a Target for HBV Immune Reawakening

- HBV immune tolerance is a critical driver of CHB infection
- PD-1:PD-L1 checkpoint axis plays a key role in immune tolerization
  - PD-L1 expression upregulated during HBV infection
  - PD-1 upregulated on HBV-specific T- and B-cells
  - Inhibition associated with HBsAg loss in some CHB patients



Gane et al., 2019 J Hep.

Preclinical combination of PD-L1 inhibitor with HBsAg reduction results in HBV immune response activation



PD-L1 mAb + siRNA

Liver HBV T Cell Response

AAV-HBV mouse
6 week tx: anti-PD-L1 mAb + LNP-siRNA

Fisicaro, et al., 2012 Gastroenterology
Fisicaro, et al., 2010 Gastroenterology
Wang, et al., 2021 AASLD
Thi, et al., 2017 AASLD

Why a Small Molecule Approach For Checkpoint Blockade For HBV

Antibodies

- IV dosing /infusion
- Long uncontrolled duration of effect
- Potential for serious AEs: colitis, pneumonitis, hypophysitis, hypothyroidism, hepatitis, myocarditis, inflammatory arthritis, rash

Small Molecule

- Oral dosing
- Tunable control of checkpoint inhibition
- Liver tropic: Minimizes systemic safety issues seen with antibodies
- Better tissue penetrance, potential for increased efficacy

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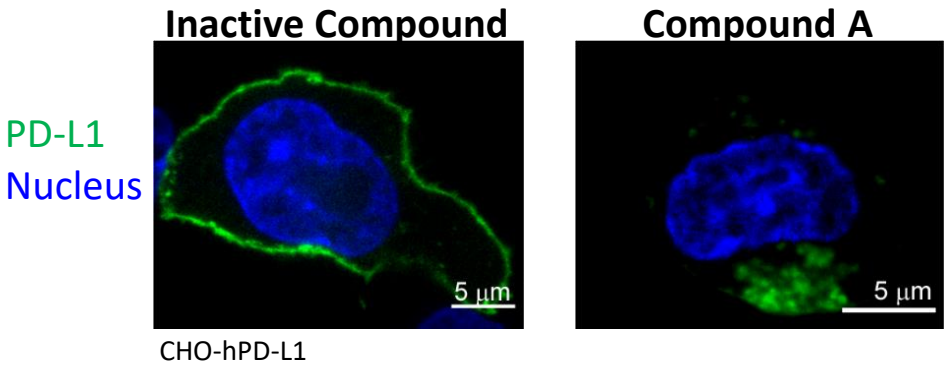
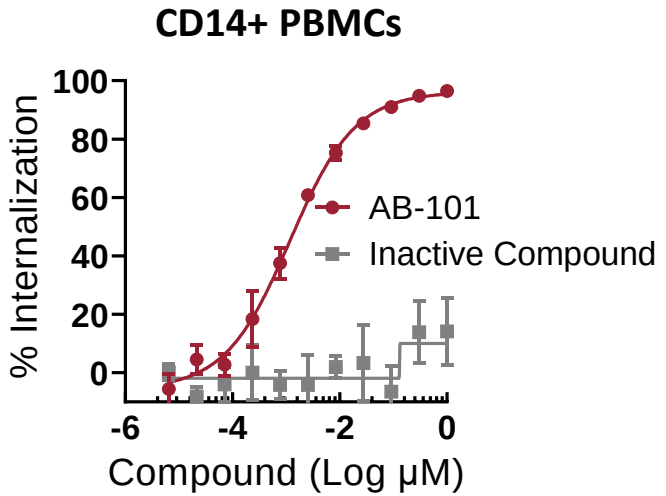
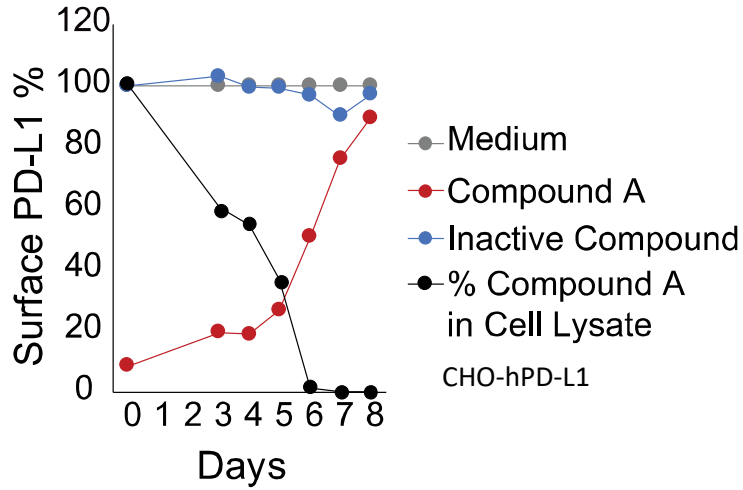
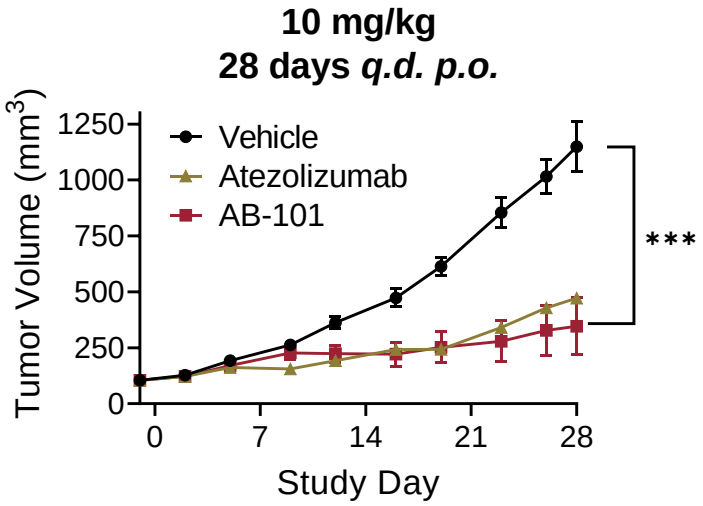
Small-Molecule PD-L1 Inhibitors Reduce PD-L1 Expression on Cell Surface Through a Novel Internalization Mechanism









MC38 hPD-L1 in hPD-L1/hPD-1 mouse

- Dimerization of PD-L1 protein results in internalization from cell membrane post-treatment with PD-L1 small-molecule inhibitor
- AB-101 is highly potent in inducing PD-L1 internalization in primary human myeloid cells (IC_{50} = 1.9 nM)
- Effect of small-molecule PD-L1 inhibitors is reversible, with rapid recovery of PD-L1 surface expression upon compound removal
- AB-101 treatment results in tumor growth inhibition comparable to anti-PD-L1 antibody

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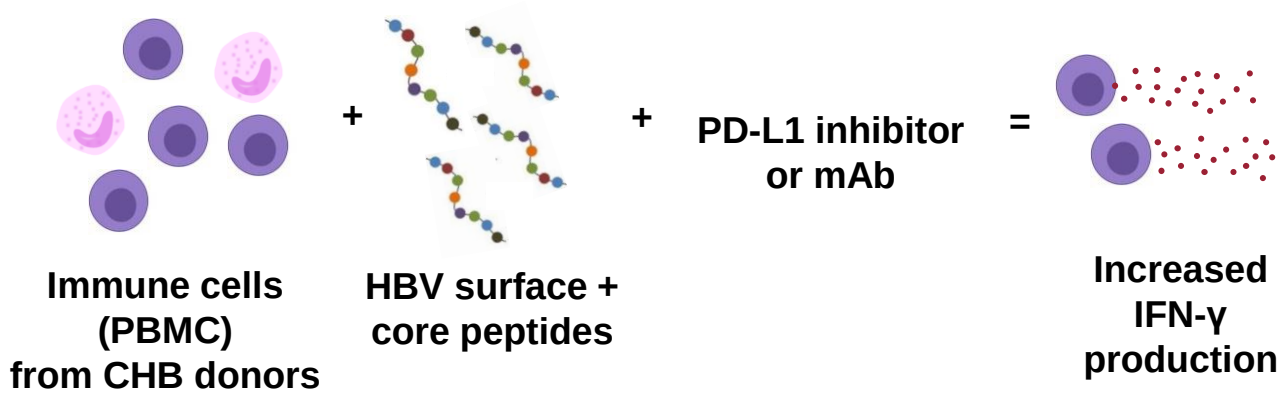
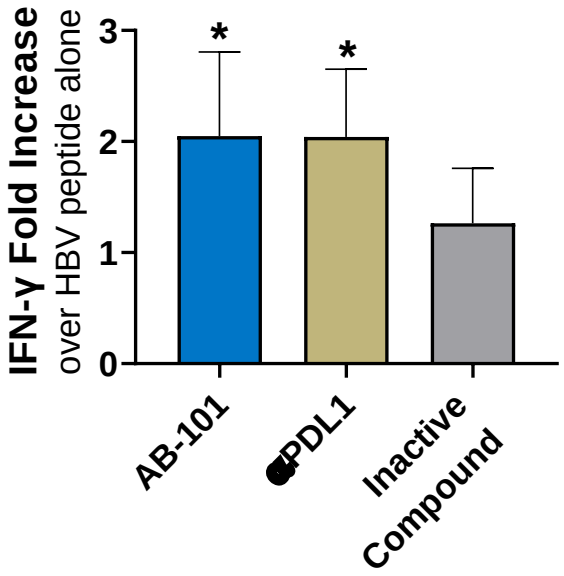
PD-L1 Inhibitor Treatment Reinvigorates HBV-Specific T Cell Responses



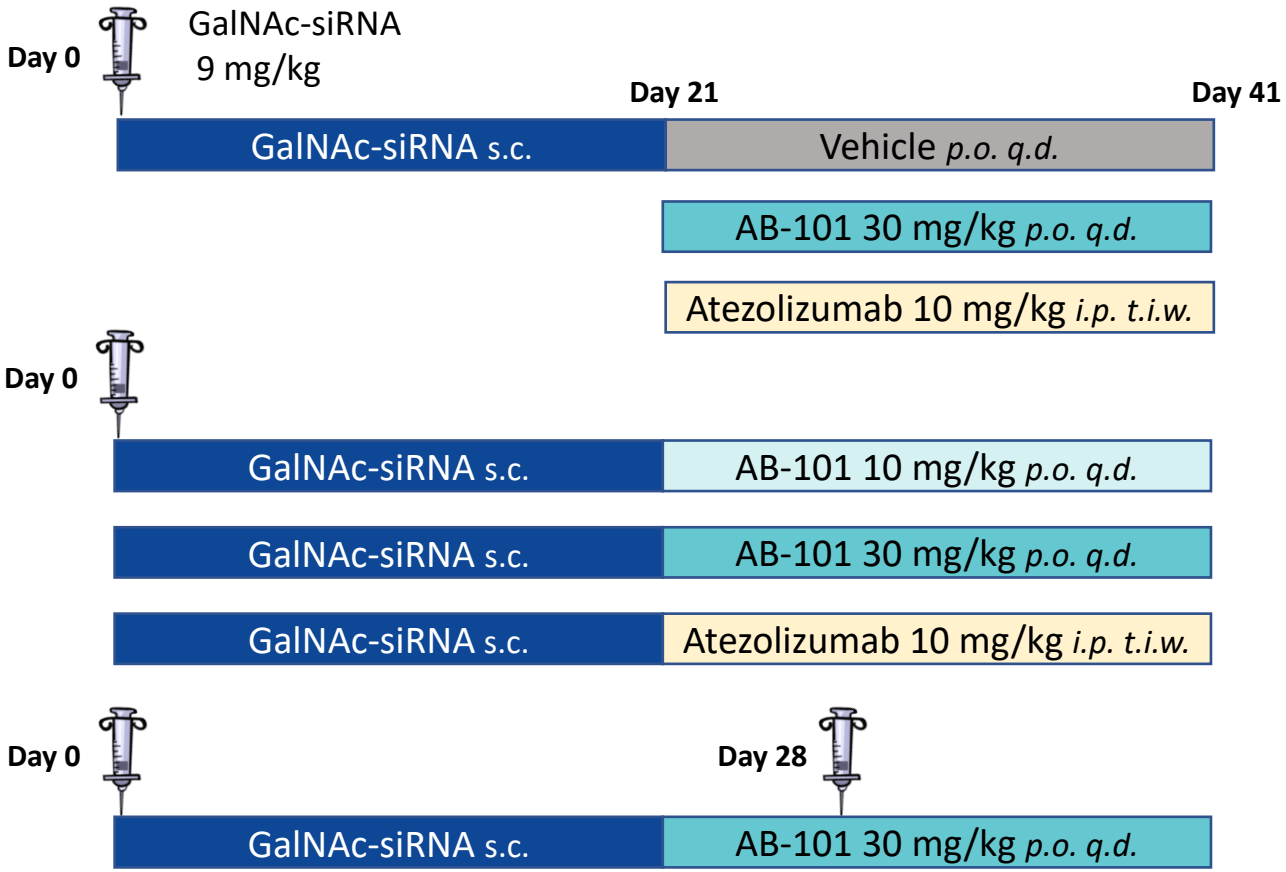


- AB-101 reinvigorates HBV-specific T cell responses *ex vivo*
- Effect is comparable to anti-PD-L1 antibody

N = 9 CHB patient donors
*p<0.05 by One-Way ANOVA with Dunnett's multiple comparisons test

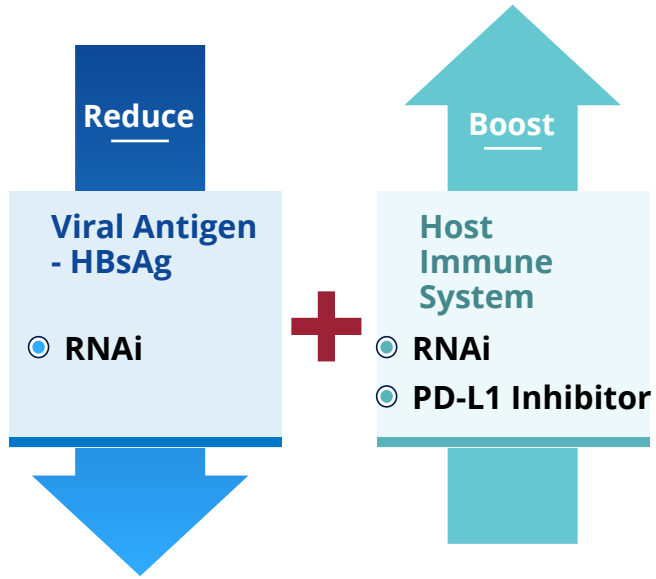
Combination Treatment of PD-L1 Inhibitor + HBV-siRNA

AAV-HBV hPD-L1/hPD-1 Mouse, 28 days post-AAV



+ Vehicle, Naïve and positive immune response control (pHBV1.3 HDI C57BL/6) groups

- Effect of mono- or combination treatment was assessed in an AAV-HBV mouse model
- Sequential treatment was evaluated



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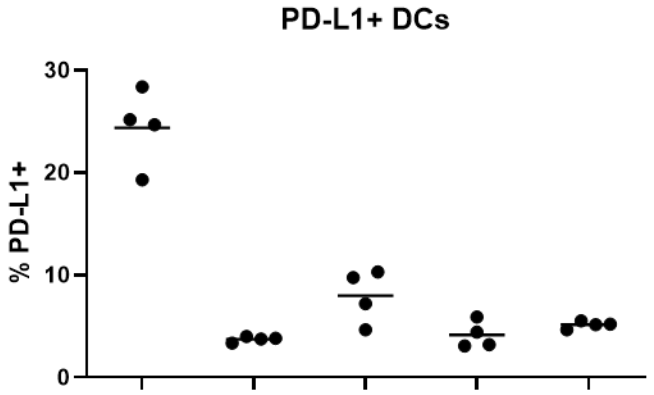
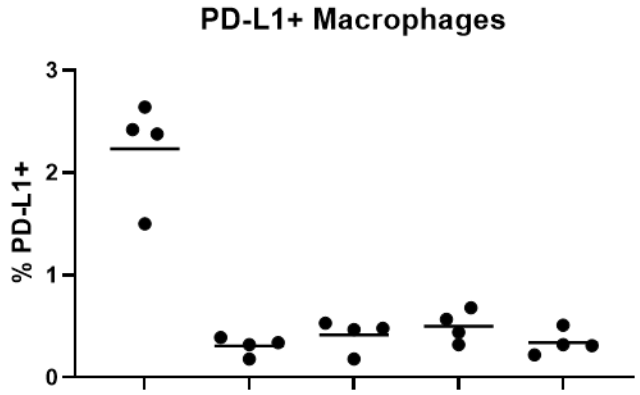
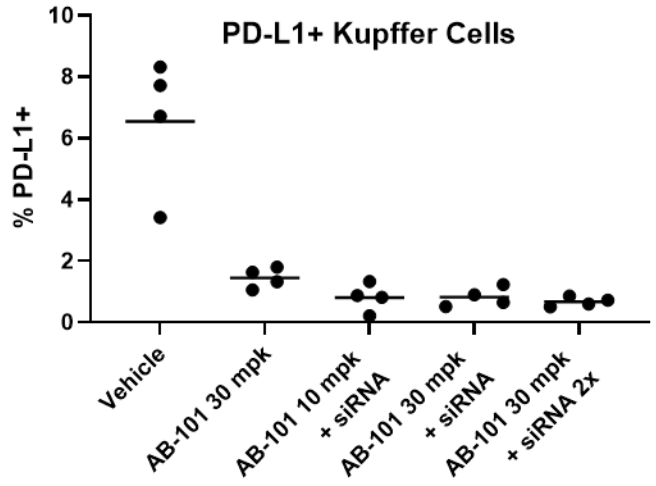
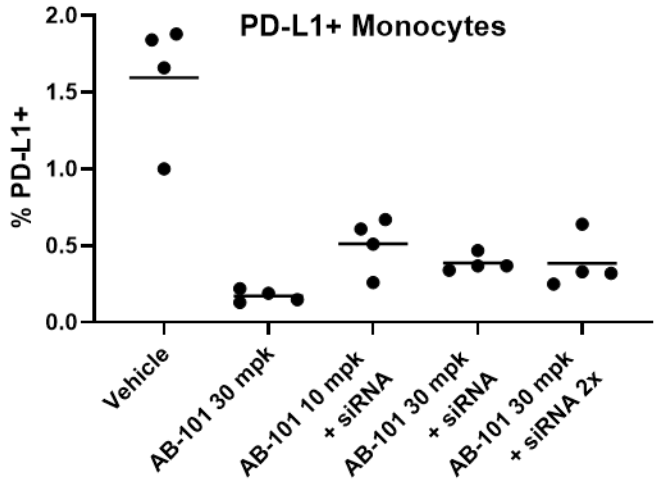
PD-L1 Inhibitor Treatment Reduces PD-L1 in Liver

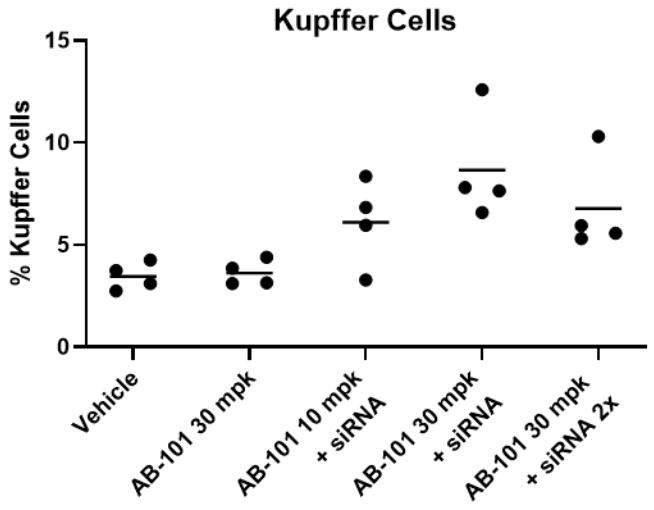








- Target engagement confirmed in liver; reduction of PD-L1 expression in liver immune cells following AB-101 treatment
- Increased frequencies of Kupffer cells also observed in combination treatment groups



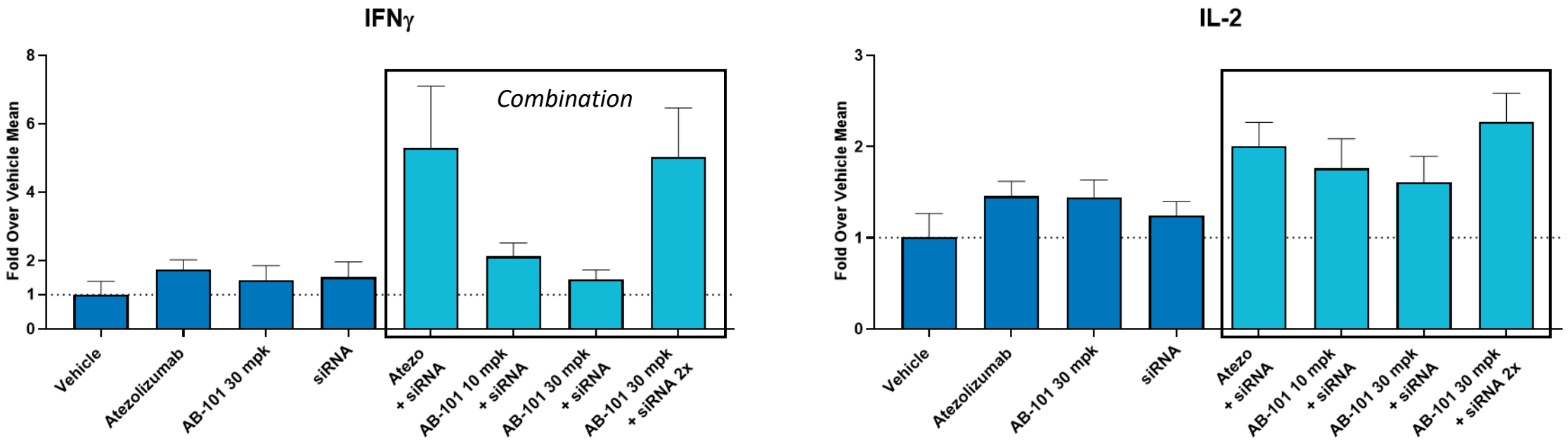
PD-L1 reduction statistically significant in all AB-101 treatment groups
% Kupffer cell increase statistically significant in AB-101 30 mpk + siRNA groups

Day 42

PD-L1 Inhibitor + siRNA Combination Increases HBV-Specific T Cell Activity in Liver

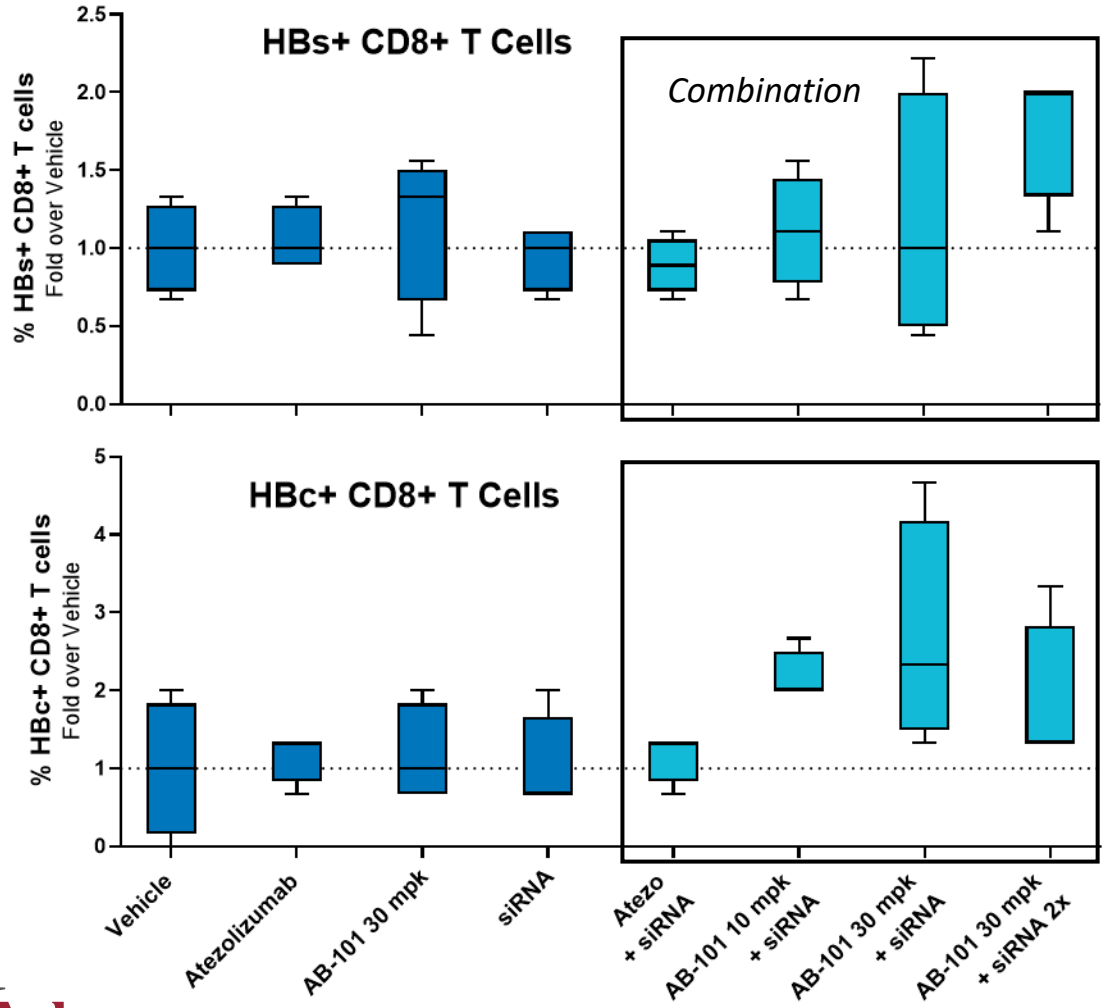
- PD-L1 inhibitor + siRNA combination associated with greater IFNγ and IL-2 production from HBV-specific T cells

Liver HBV-Specific T Cells

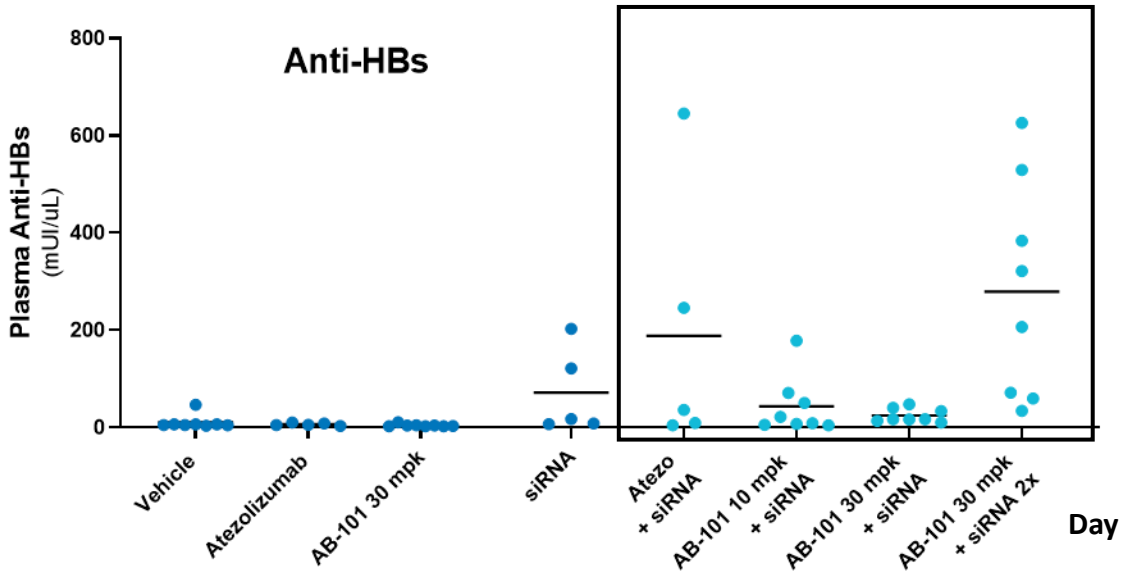


Ex vivo Fluorospot **Day 42**

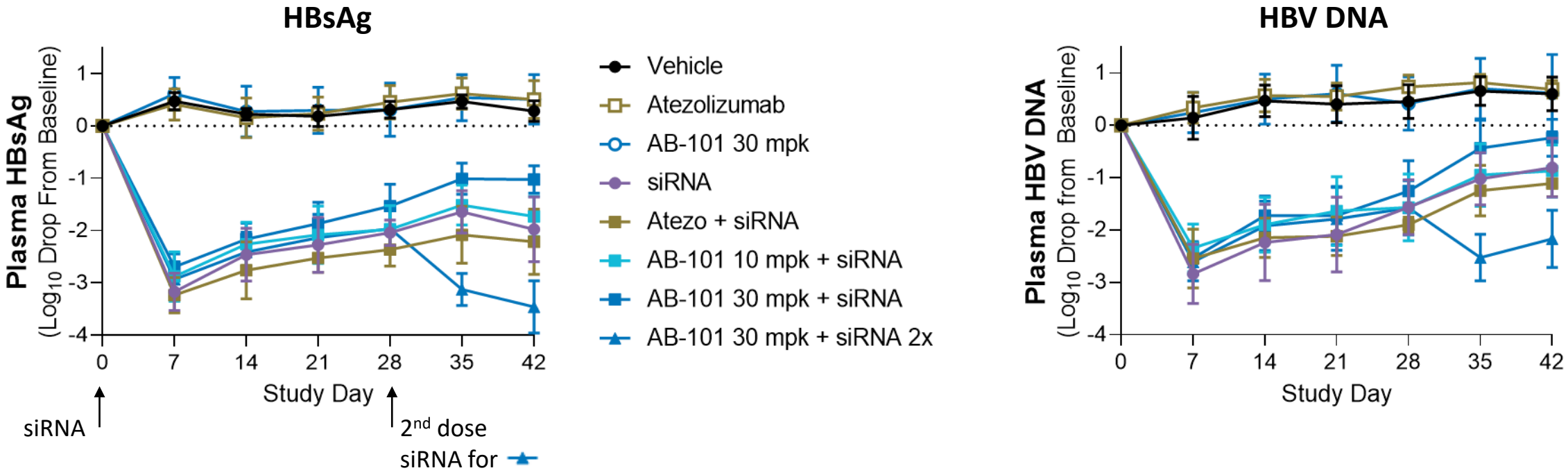
PD-L1 Inhibitor + siRNA Combination Increases HBV-Specific T Cells and Anti-HBs Antibodies



- Greater increase in HBc+ *vs* HBs+ CD8+ T cells
- Greater anti-HBs antibody production in combination with repeat siRNA dosing



siRNA Mediated Reductions in HBsAg and HBV DNA



- PD-L1 inhibitor treatment alone did not result in viral marker reductions
- 2nd dose of siRNA at Day 28 resulted in additional viral marker declines
- Long term follow-up of combination groups off treatment is of interest, to assess whether the observed increased HBV immune response will lead to new virological setpoints

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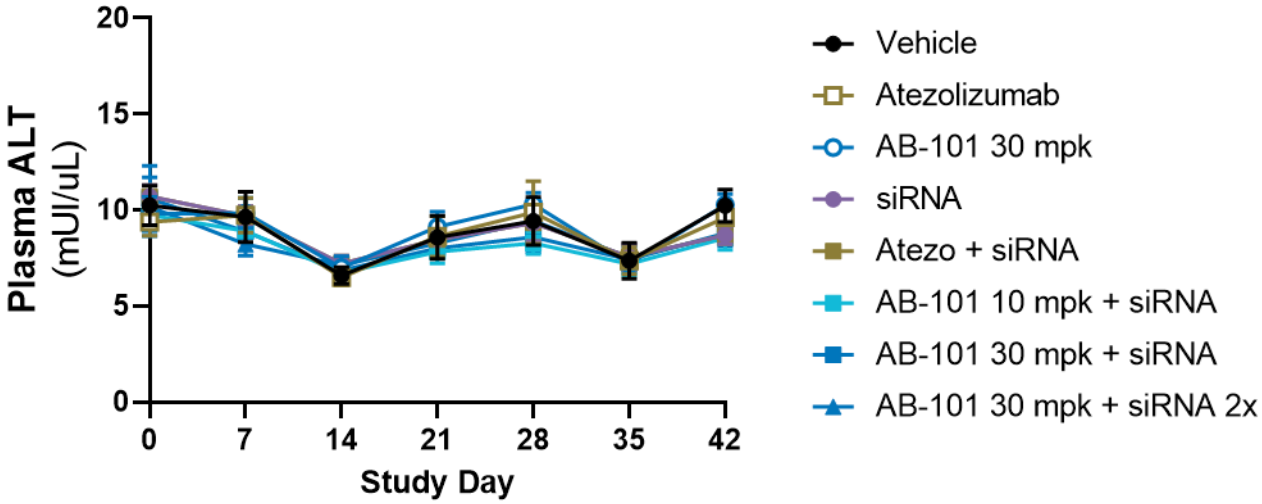
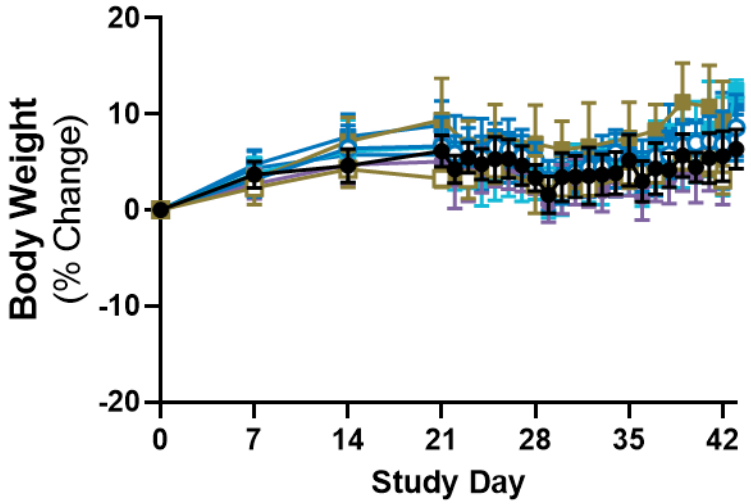
PD-L1 Inhibitor Treatment Alone or in Combination with siRNA Was Not Associated with ALT Elevation





- Treatments were well-tolerated; no changes in liver function markers or decreases in body weight observed

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Summary

- Small-molecule PD-L1 inhibitors have comparable preclinical profiles as antibodies
- Oral small-molecule PD-L1 inhibitors may provide potential advantages over antibodies
  - AB-101 is currently in IND-enabling studies
- Combination treatment of PD-L1 inhibitor + HBV-targeting siRNA reinvigorates HBV immune responses in an AAV-HBV mouse model
  - ➢ Reduced PD-L1 expression in antigen-presenting cells in liver
  - ➢ Increased HBV-specific T cell frequency and activity
  - ➢ Increased anti-HBs antibody production

Combination treatment of HBV-targeting GalNAc-siRNA and small-molecule PD-L1 inhibitor may be a promising strategy for reawakening HBV immune responses

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