Pre-Clinical Anti-HBV Activity with a Passively Targeted, Multi-TLR, NOD and STING Agonist

HansonWade STING & TLR-Targeting Therapies Summit 2023

Indaptus THERAPEUTICS

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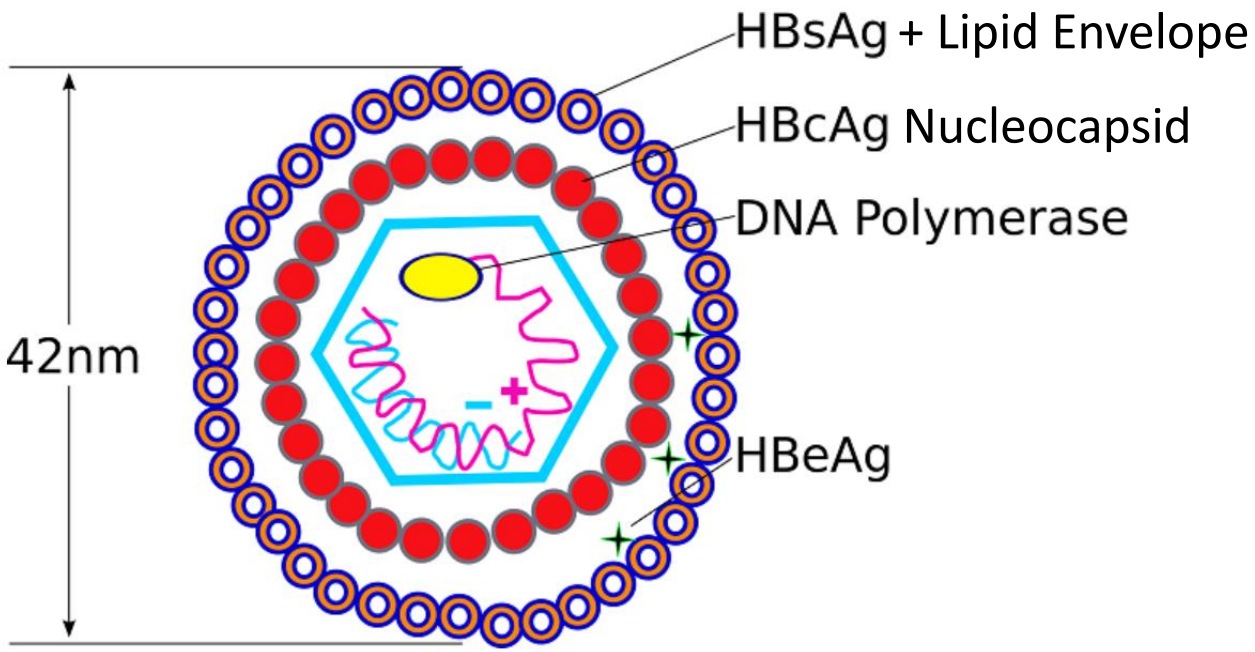
Disclosure – Michael J. Newman is an employee, director and stockholder of Indaptus Therapeutics.

Hepatitis B Virus (HBV)

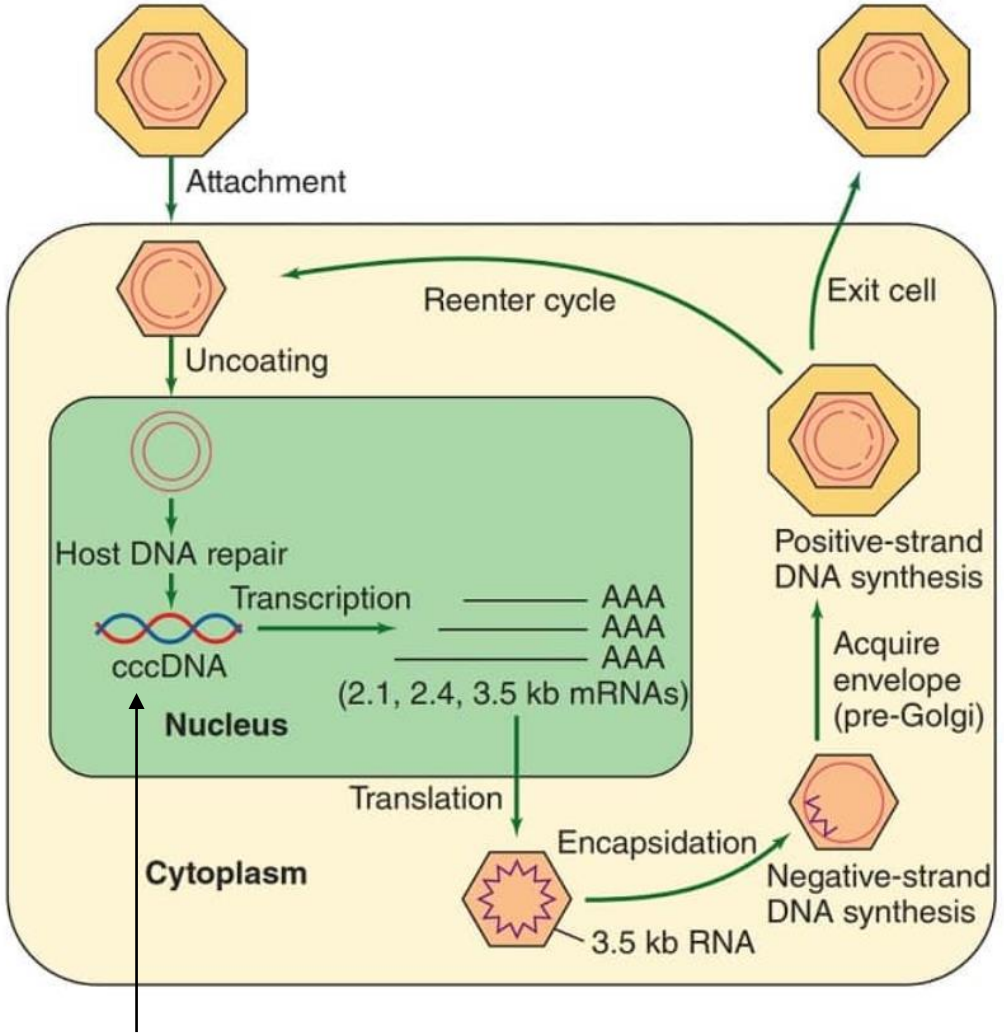
- **Partially double-stranded DNA virus**
  - Family *Hepadnaviridae*, 4 serotypes, 10 genotypes, 40 sub-genotypes
- **Transmitted by body fluids - Infects hepatocytes producing a chronic liver infection**
  - ~300 million people infected world-wide (>3% of population)
  - Effective vaccines, but no curative treatment (IFN-α & DNA analogues reduce viral load)
  - Only 2% of cases treated with current therapies
  - Major cause of fibrosis, cirrhosis and liver cancer (HCC)
  - ~1 million deaths per year world-wide

HBV Structure, Life Cycle and Key Diagnostic/Prognostic Markers



- **Key Diagnostic and Prognostic Markers**
  - Plasma - viral DNA, HBsAg, HBeAg
  - Liver - viral DNA, HBcAg, cccDNA

Adapted from https://microbiologyinfo.com/hepatitis-b-virus

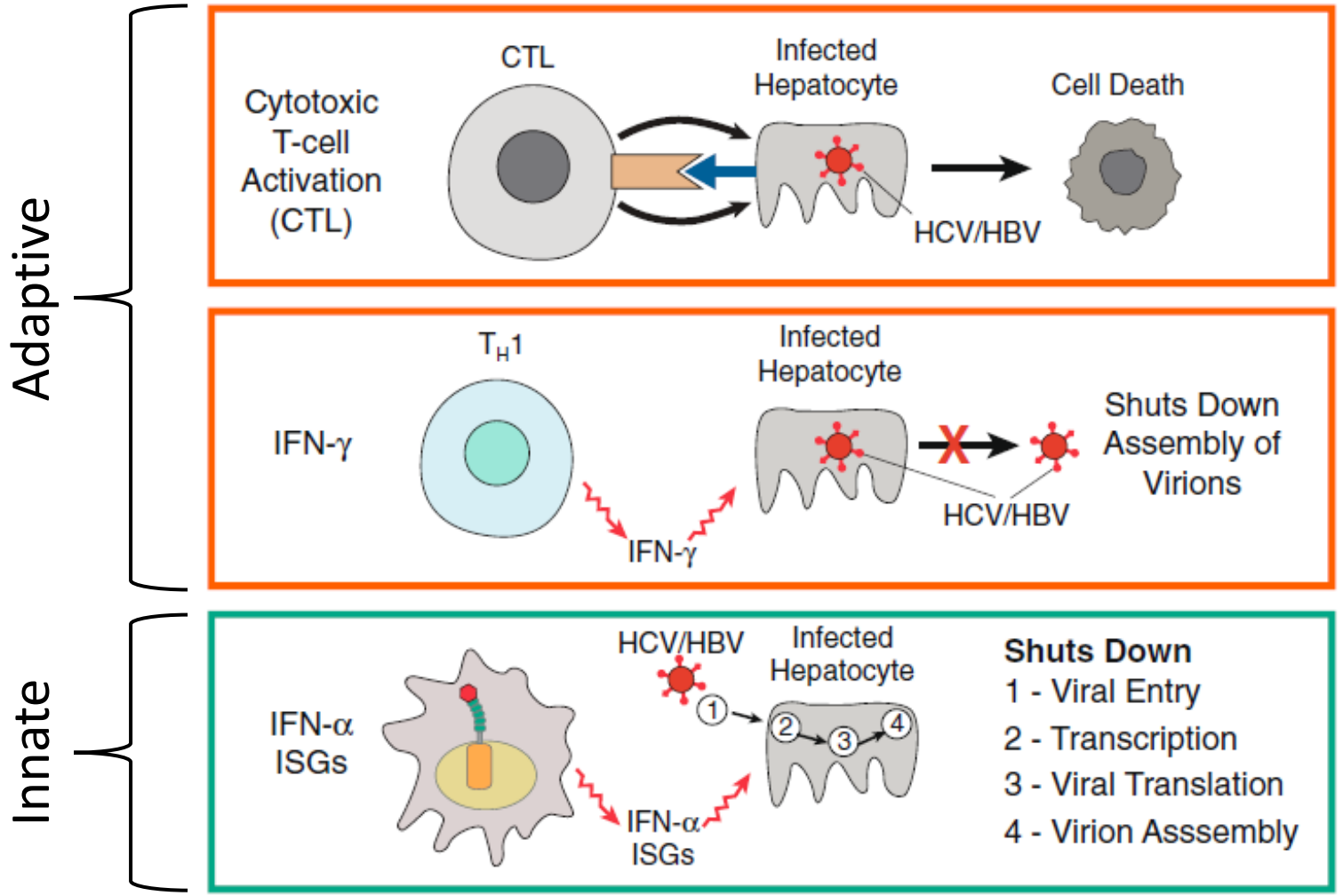


cccDNA = covalently closed circular DNA

Immune-Mediated "Functional" Cure of cHBV is Possible

- **~1% of cHBV patients per year mount an effective immune response and this can be "transferred"**
  - Revill et al., Lancet Gastroenterol Hepatol v4 p545 2019
  - Ablation of Persistent Hepatitis B by Bone Marrow Transplantation From a Hepatitis B-Immune Donor
    Ilan et al., Gastroenterology v104 p1818 1993
- **~6% of genotype A cHBV patients achieve functional cure with pegIFN (9% with pegIFN + tenofovir)**
- **Relevant mechanism of action observations**
  - Intracellular Inactivation of the Hepatitis B Virus by Cytotoxic T Lymphocytes
    Guidotti et al., Immunity v4 p25 1996
  - Toll-Like Receptor Signaling Inhibits Hepatitis B Virus Replication In Vivo
    Isogawa et al., J Virology v79 p7269 2005 (activity via activation of TLR3, 4, 5, 7 and 9)
  - Interferon-γ and Tumor Necrosis Factor-α Produced by T Cells Reduce the HBV Persistence Form, cccDNA, Without Cytolysis
    Xia et al., Gastroenterology v150 p194 2016

Immune-Mediated Mechanisms Involved in cHBV Clearance: Innate Cells + Adaptive Cells / Antibodies + Cytokines



Innate and adaptive immune cells, cytokines released from immune cells (hepatocytes?) and interferon-stimulated gene (ISG) products are all major contributors to potential clearance and functional cure of cHBV

B/Plasma cell derived antibodies (e.g. anti-HBsAg) also likely to be important

cccDNA Silencing/Degradation

Cytokines (IFN-α/β, IL-6, IL-1β) induce epigenetic silencing and APOBEC3-mediated degradation of cccDNA

Funk et al., J Translational Medicine v12 p129 2014
Also - Kim et al., Clin Mol Hepatol v28 p17 2022

Martinez et al., J Hepatology v75 p706 2021

A multi-targeted approach will be essential!

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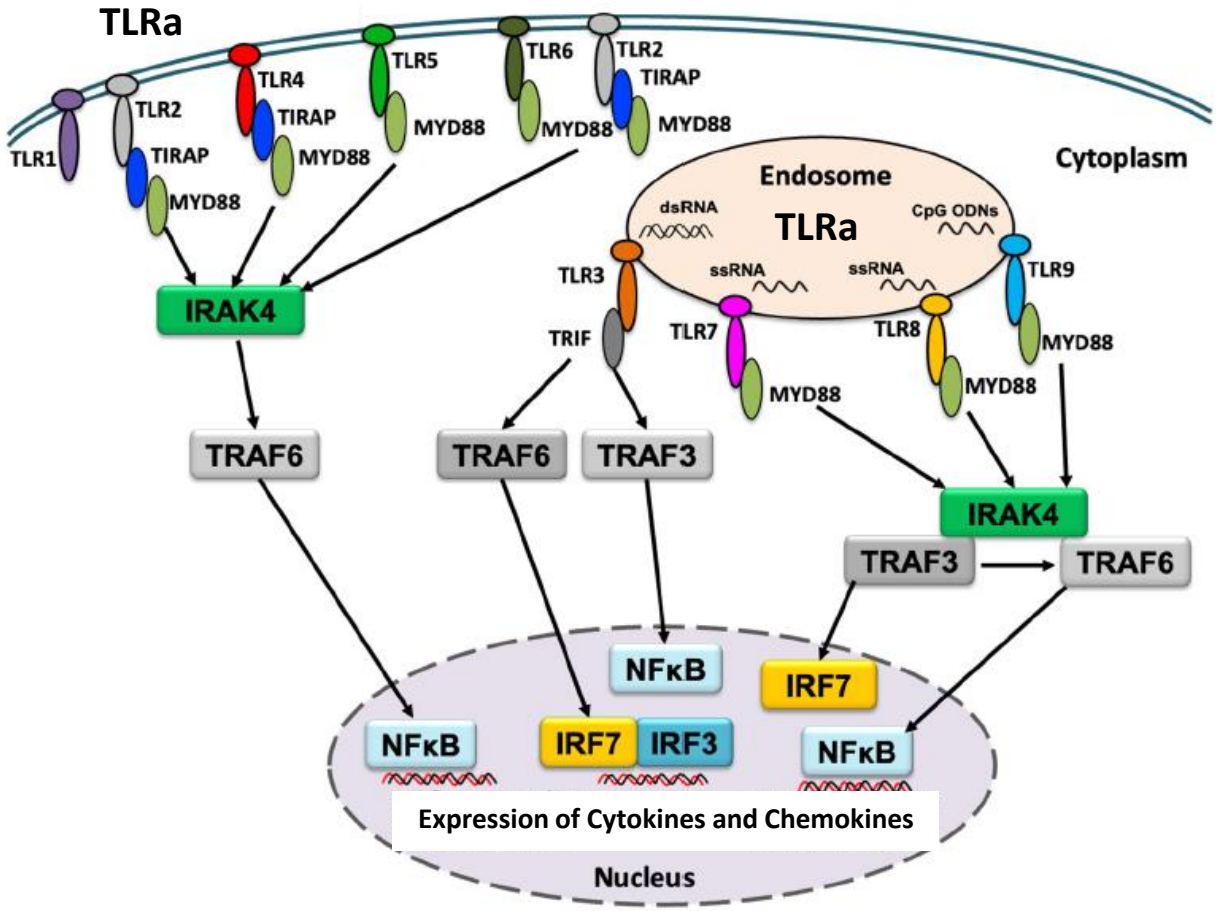
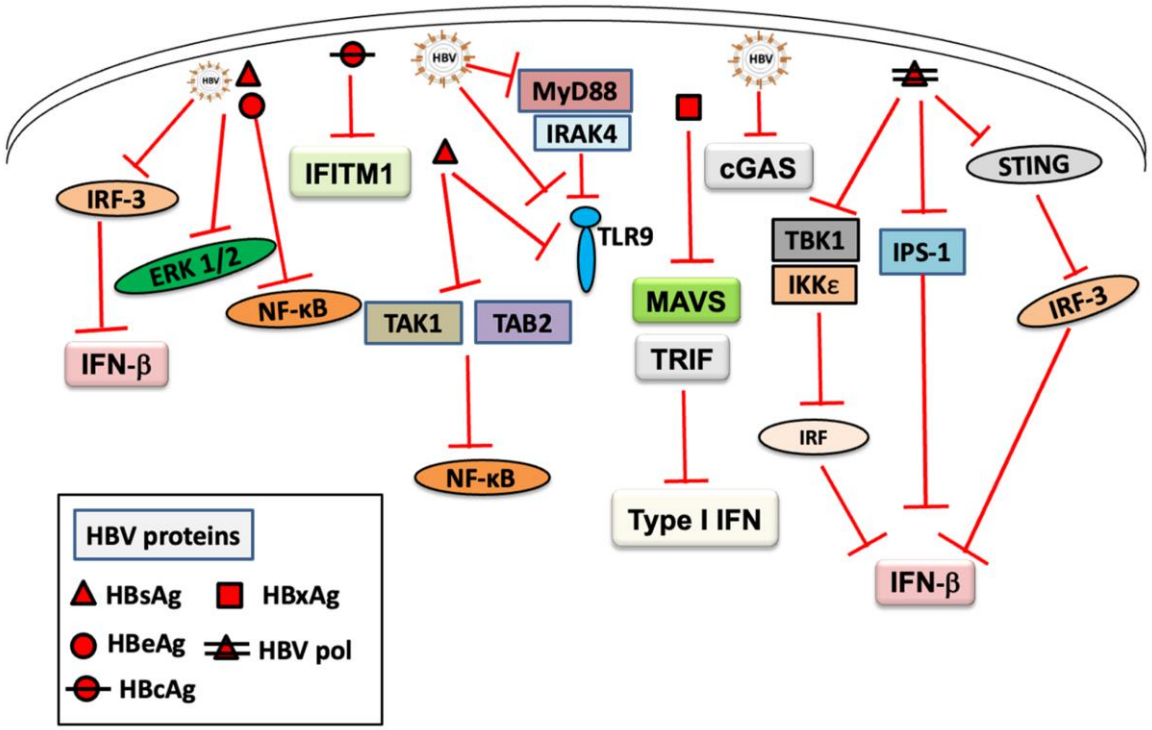
Activation of Toll-Like Receptors (TLRs) on Immune Cells (and Hepatocytes?) by TLR Agonists (TLRa) is Critical for Innate and Adaptive Anti-cHBV Immunity

Essentially all Immune Cells and Hepatocytes



Immune cell membrane/endosomal TLRs are activated by "Danger Signals" (TLRa) from pathogens, triggering immune cell activation and secretion of anti-viral cytokines and chemokines

HBV-Infected Hepatocyte



In cHBV, insufficient HBV "Danger Signals" (TLRa) are released
Also, HBV proteins inhibit cytokine/chemokine (TLR) induction pathways in infected hepatocytes + lymphocytes

We need to overcome this multi-cell/pathway blockade
Single TLRa approaches have not been successful
Can this be done with a multi-TLRa approach?

Adapted from Kayesh et al., Int J Mol Sci v22 p10462 2021

TLR/NOD Agonist-Related Products Approved to Treat Early-Stage Cancer or Prevent Infections: No Products for Advanced Cancer or Chronic Infections

- **Bacillus Calmette-Guérin (BCG) (Sanofi/Merck)**
  - Tuberculosis vaccine (1921) made from live, attenuated *Mycobacterium bovis* (TLR2,4,9 agonists?)
  - Standard of care for superficial bladder cancer via local (intravesical) administration
- **Picibanil™ (OK-432) (Chugai)**
  - Locally-administered, killed, Gram-positive component of Coley's Toxins - approved in Japan/Taiwan
  - Used mainly to treat lymphangiomas and vascular malformations
- **Mifamurtide (Mepact®) (Millennium/Takeda)**
  - Synthetic derivative of Mycobacterium cell wall muramyl dipeptide (NOD2/TLR2 agonist)
  - Approved in EU for non-metastatic osteosarcoma (i.v.)
- **Imiquimod (Aldara®) (Taro Pharmaceutical Industries/3M)**
  - Topical TLR7 agonist approved for superficial basal cell carcinoma, genital warts and actinic keratosis
- **Monophosphoryl lipid A (MPL) (GSK)**
  - LPS analogue (TLR4 agonist) approved as adjuvant in Allergic Rhinitis, HPV, Shingles, HBV vaccines (i.m.)
- **CpG DNAs (1018, 7909) (Dynavax, Merck)**
  - TLR9 agonists approved as adjuvants in HBV vaccines (i.m.)

Reminder of Indaptus' "Decoy" Technology from Cancer Presentation

Multi-TLR, NOD and STING agonist Decoy bacteria

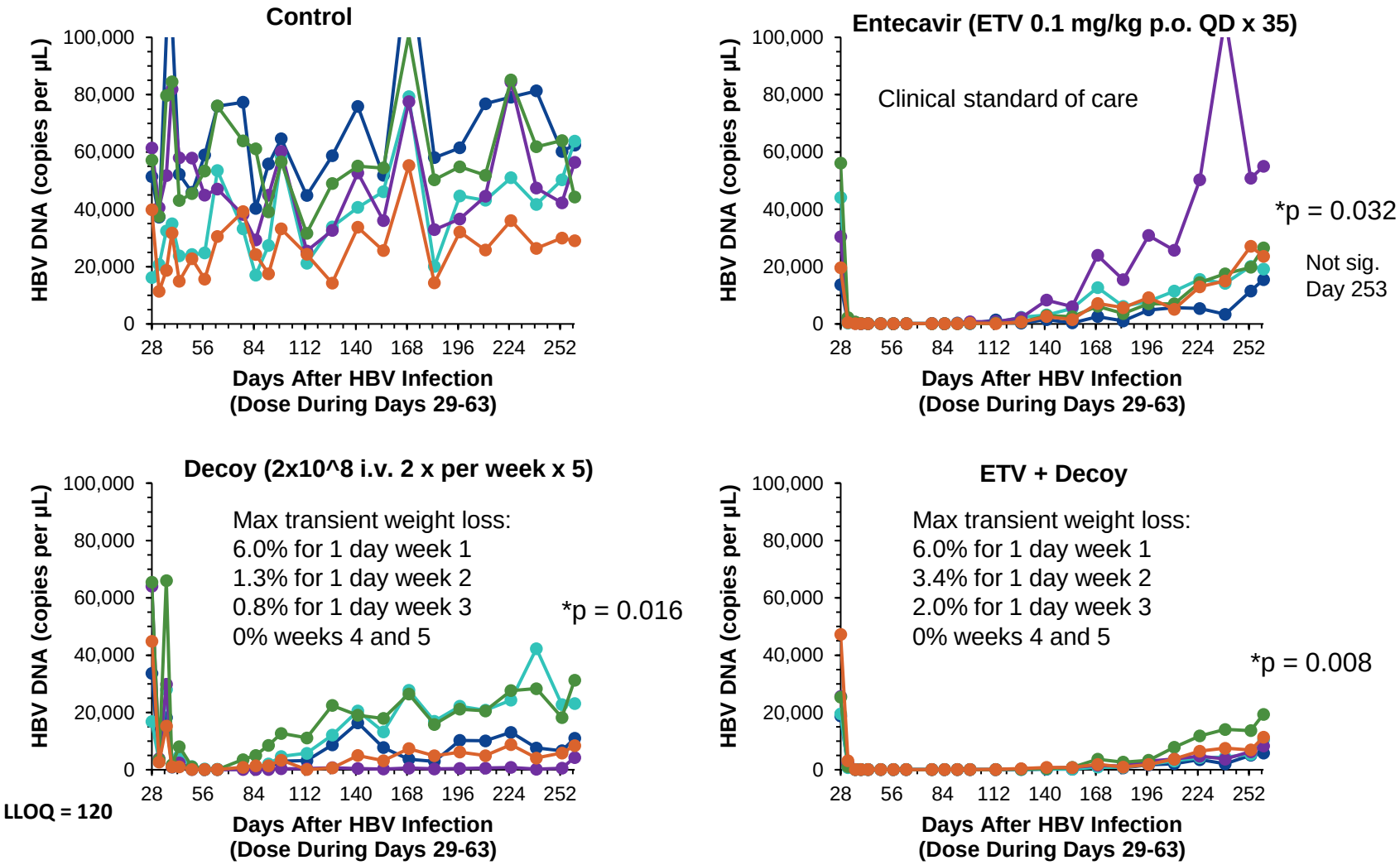
- Contain TLR1,2,4,6,8,9, NOD2 and STING agonists
- Induce anti-tumor and anti-viral cytokine and chemokine secretion from PBMCs
- Safely prime or activate both innate and adaptive immune pathways in mice
- Induce targeted, non-adverse immune infiltration/activation in liver and spleen (rabbits)
- Rationale to test Decoy bacteria in a chronic HBV model

Mouse AAV-HBV Model of Chronic Hepatitis B Virus (HBV) Infection

- Mouse liver cells are not infected by human HBV, but placement of the human HBV genome into a related adeno-associated virus (AAV) produces a virus that can chronically infect mouse liver
- Mice infected with AAV-HBV chronically produce high plasma/liver levels of HBV, HBsAg and HBe/cAg
- A cccDNA-like molecule is also found in mouse livers infected with AAV-HBV
  (Correlation with human cHBV cccDNA has not been fully established)
- Human standard of care Entecavir produces similar results in humans and the mouse model:
  Transient reduction in plasma HBV DNA, without inhibitory effects on plasma/liver HBsAg, HBe/cAg or cccDNA-like molecule in liver

IV Decoy Bacteria Reduce Plasma HBV DNA Levels in the Mouse AAV-HBV Model of Chronic HBV Infection

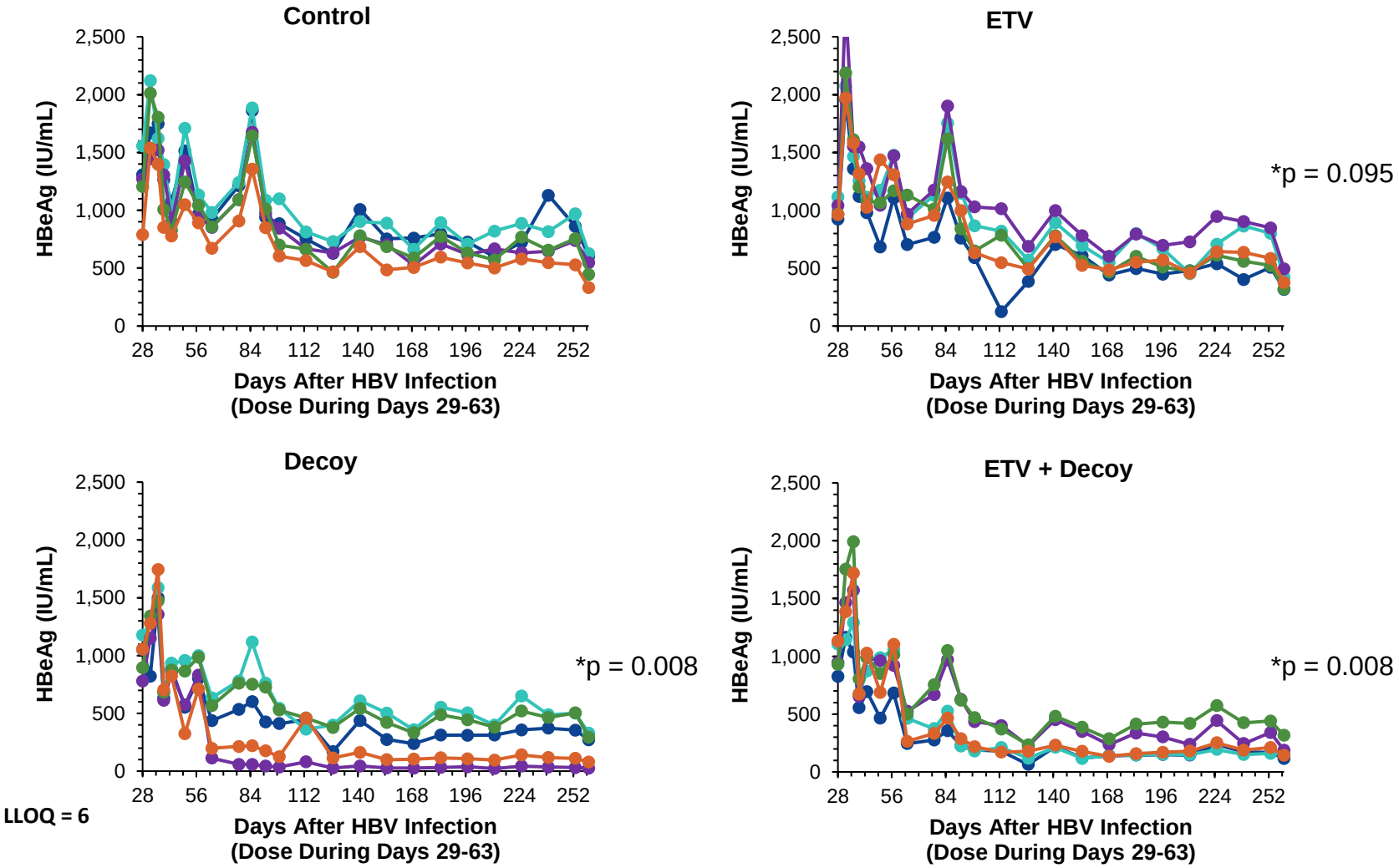
Dose during days 29-63 (5 weeks) / All groups received indomethacin in drinking water (no effect of indomethacin alone)



*Unpaired, non-parametric, Mann-Whitney U-test compared to Control at last data-point (Day 260) 28 weeks after EOT

IV Decoy Bacteria Reduce Plasma HBeAg Levels in the Mouse AAV-HBV Model of Chronic HBV Infection (no activity with standard of care)

Dose during days 29-63 (5 weeks) / All groups received indomethacin in drinking water (no effect of indomethacin alone)



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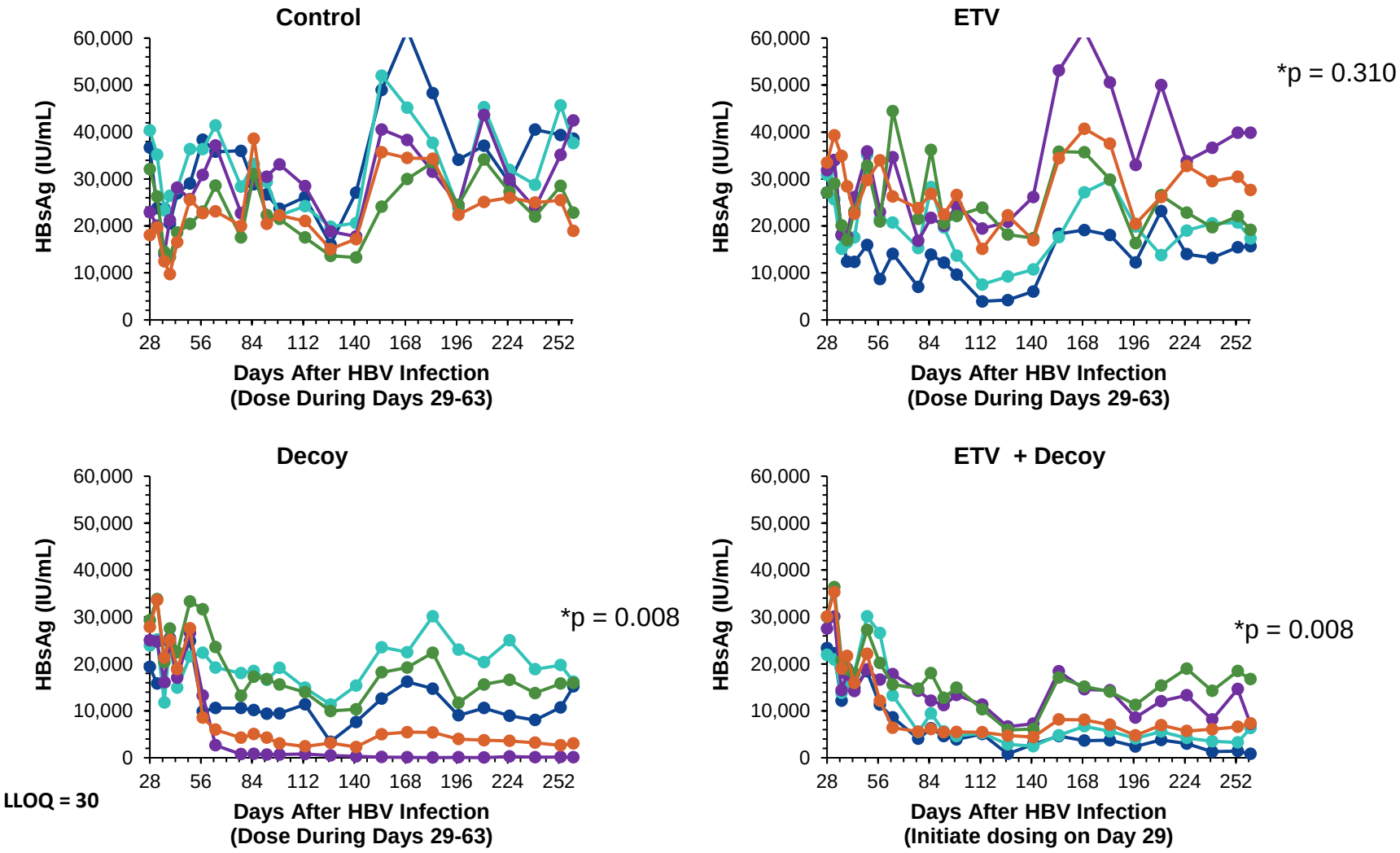
IV Decoy Bacteria Reduce Plasma HBsAg Levels in the Mouse AAV-HBV Model of Chronic HBV Infection (no activity with standard of care)

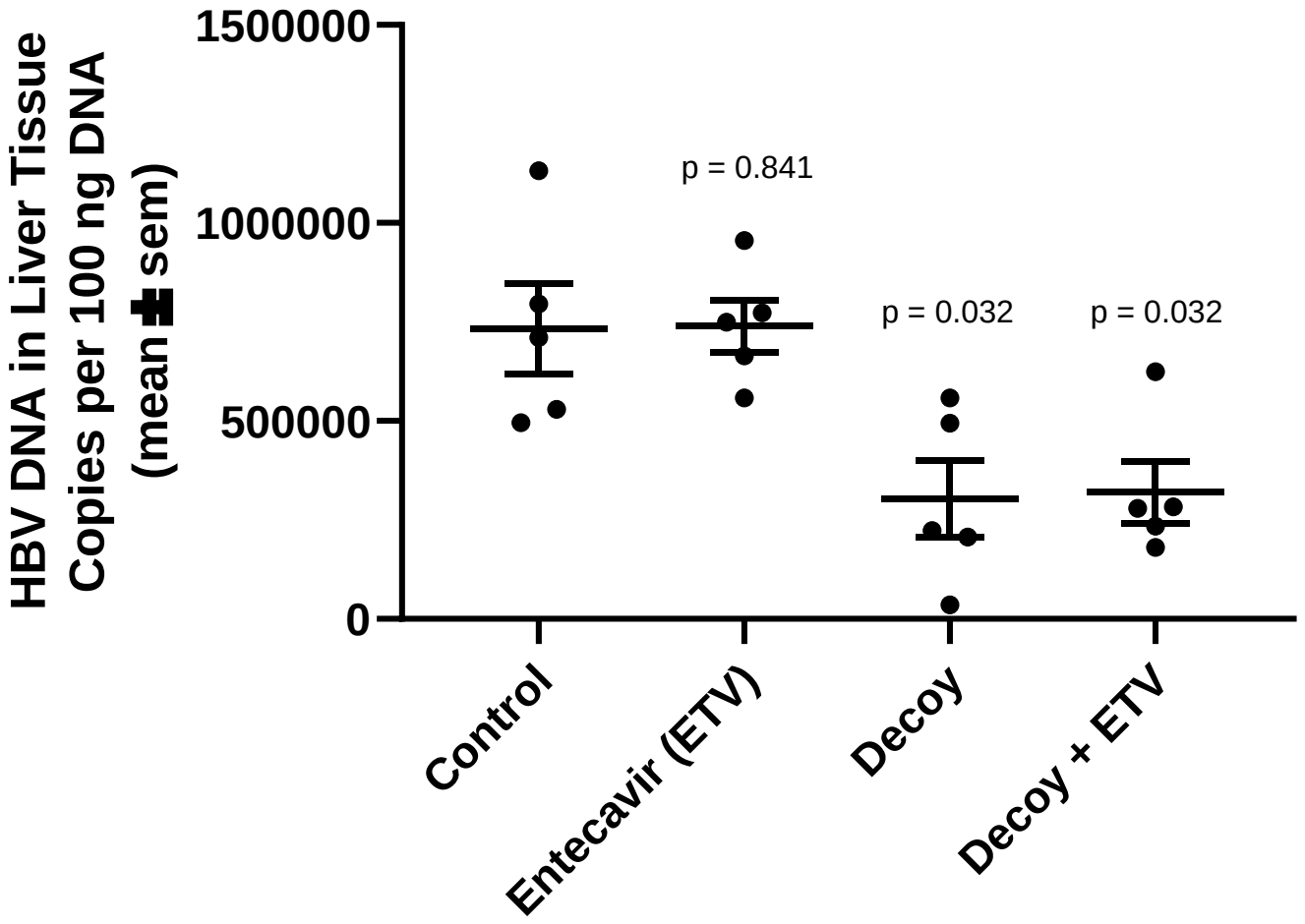
Dose during days 29-63 (5 weeks) / All groups received indomethacin in drinking water (no effect of indomethacin alone)



*Unpaired, non-parametric, Mann-Whitney U-test compared to Control at last data-point (Day 260) 28 weeks after EOT

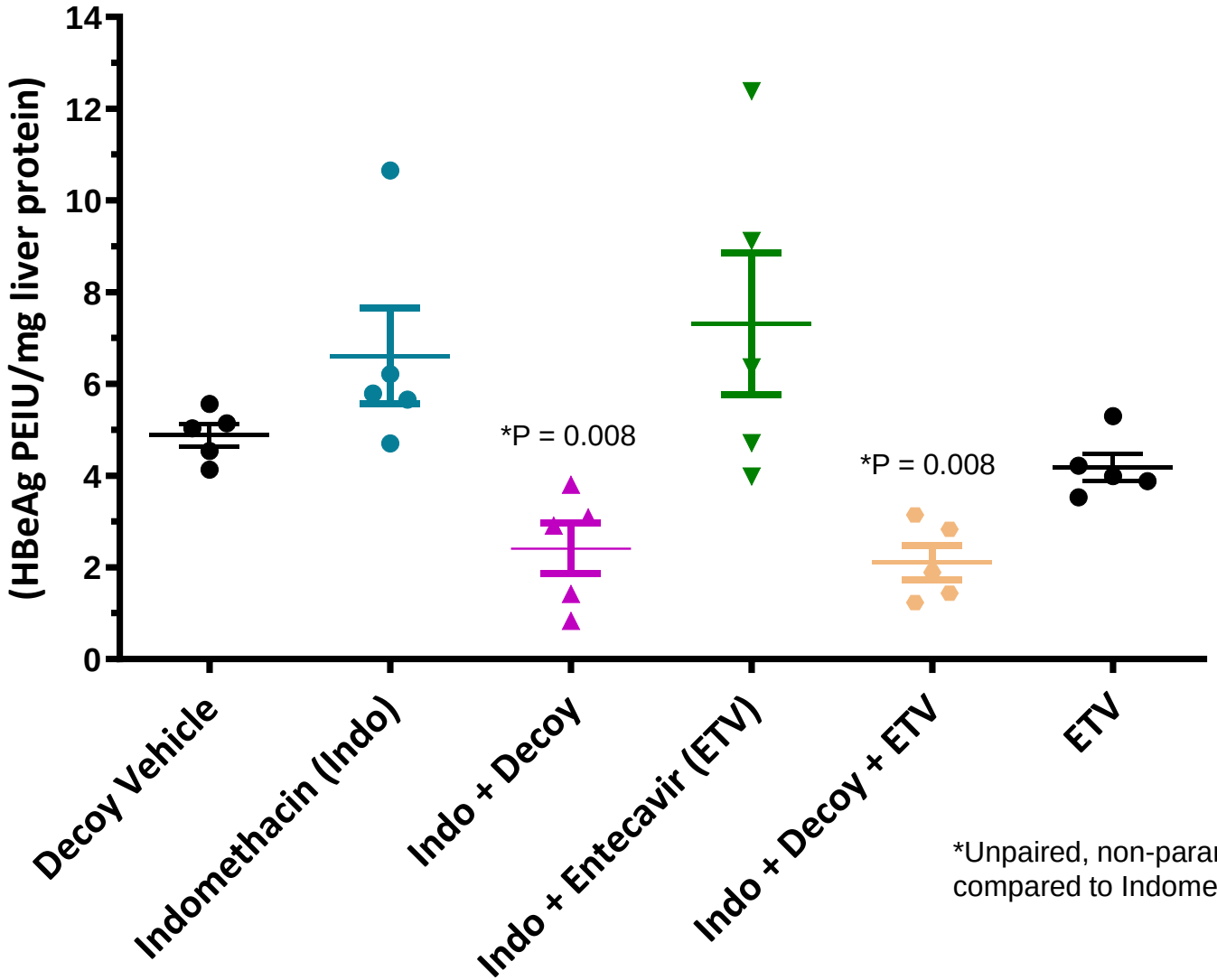
IV Decoy Bacteria Reduce HBV DNA Levels in the Livers of Mice Infected with AAV-HBV (no activity with standard of care)

Dose during days 29-63 (5 weeks) / All groups received indomethacin in drinking water
Terminate Day 260 28 weeks after EOT



IV Decoy Bacteria Reduce HBcAg Levels in the Livers of Mice Infected with HBV (no activity with standard of care)

Dose during days 29-63 (5 weeks) / Terminate Day 260 28 weeks after EOT



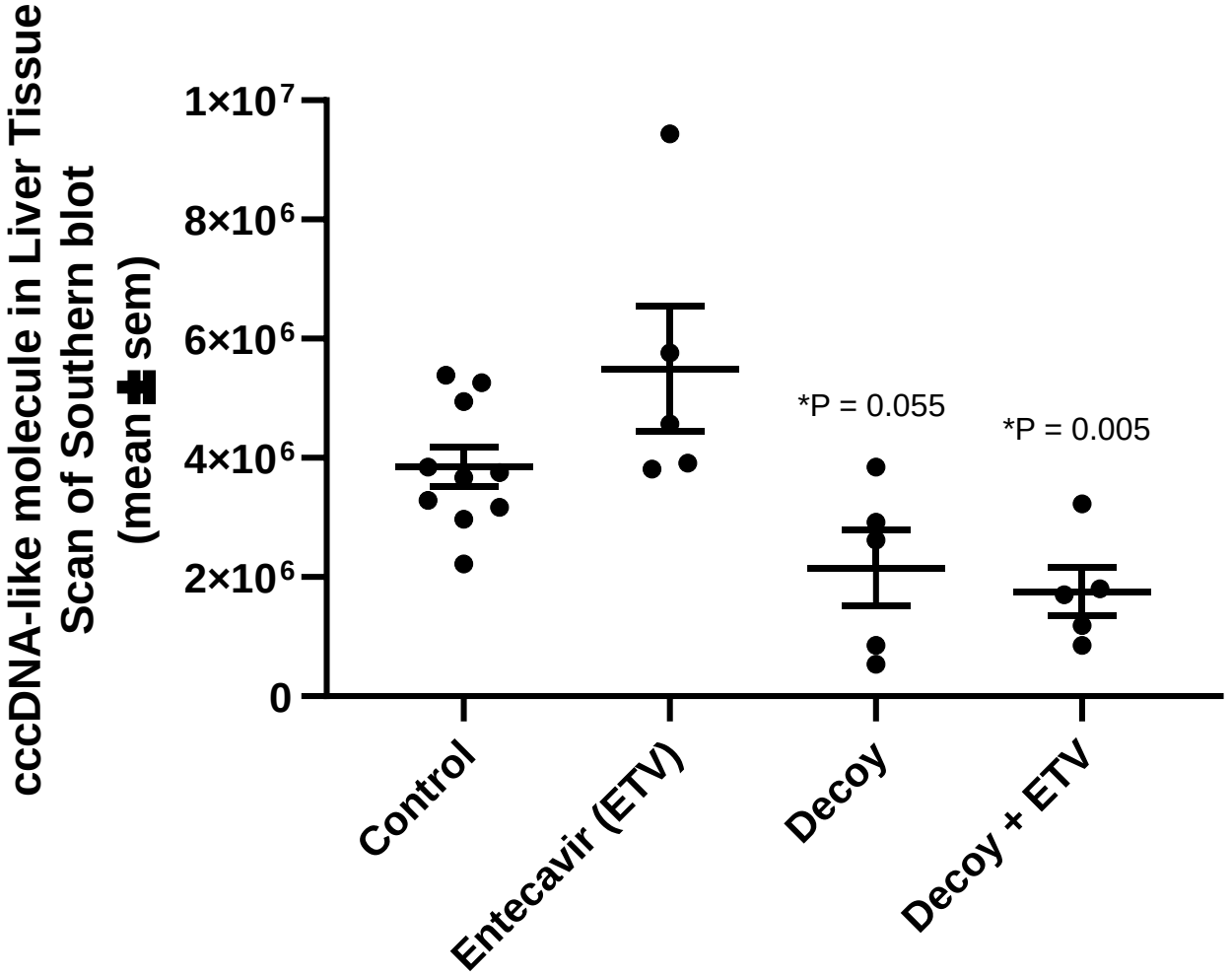
*Unpaired, non-parametric, Mann-Whitney U-test compared to Indomethacin alone

IV Decoy Bacteria Reduce Levels of cccDNA-Like Molecule in the Livers of Mice Infected with AAV-HBV (no activity with standard of care)

Dose during days 29-63 (5 weeks) / All groups received indomethacin in drinking water
Terminate Day 260 28 weeks after EOT

Isolation and identification was carried out by Hirt DNA extraction and Southern Blot

Correlation of AAV-HBV cccDNA-like molecule with cccDNA target in human infection is not fully established



*Unpaired, non-parametric, Mann-Whitney U-test compared to Control

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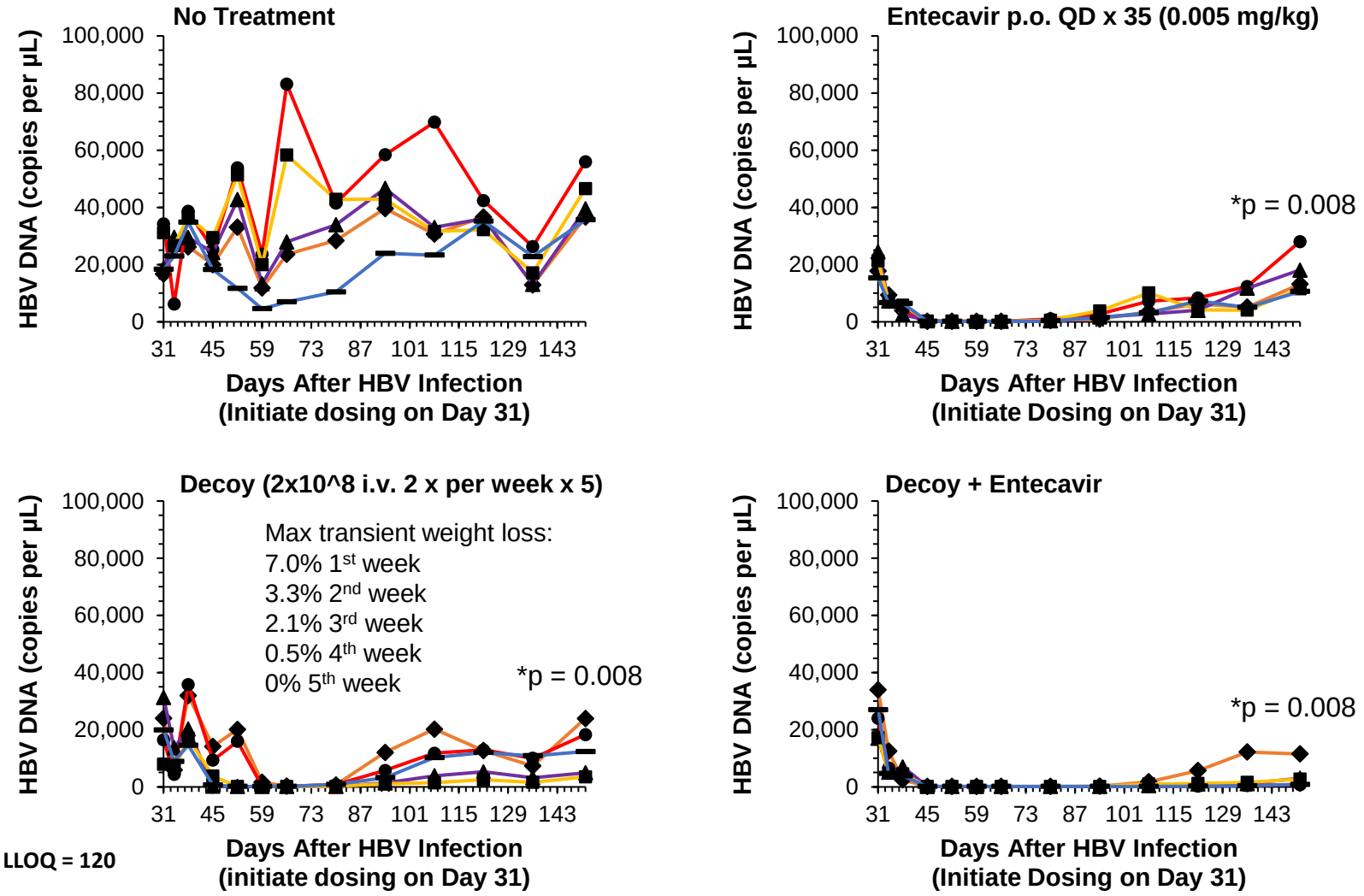
Side-Effects/Toxicity of IV Decoy Bacteria in the AAV-HBV Model

- Decoy bacteria produced mild, transient body weight loss of ~6% for 1-2 days in the 1st week of treatment, with little or no body weight loss after subsequent treatments
- Three mice in the Decoy group and two mice in the Decoy + ETV group exhibited transient elevated plasma ALT levels on 1-3 occasions during days 28-56, which resolved after Day 56
- At termination, H&E liver histopathology revealed no Decoy treatment-related changes

IV Decoy Bacteria Reduce Plasma HBV DNA Levels in the Mouse AAV-HBV Model of Chronic HBV Infection (Exp. #2 / No Indomethacin)

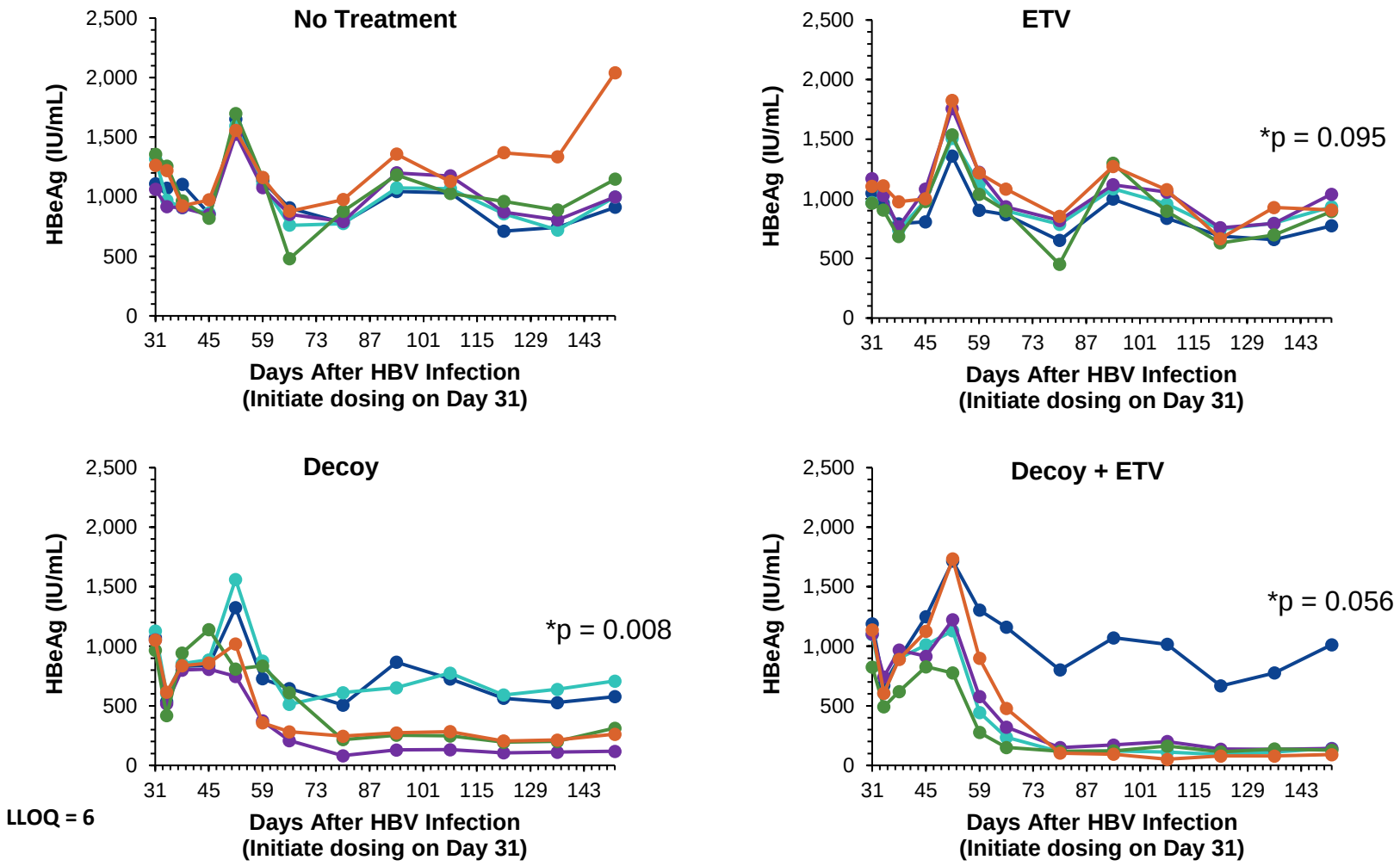
Dose during days 31-66 (5 weeks) / No indomethacin



*Unpaired, non-parametric, Mann-Whitney U-test compared to Control at last data-point (Day 151) 12 weeks after EOT

IV Decoy Bacteria Reduce Plasma HBeAg Levels in the Mouse AAV-HBV Model of Chronic HBV Infection (Exp. #2 / No Indomethacin)

Dose during days 31-66 (5 weeks) / No indomethacin

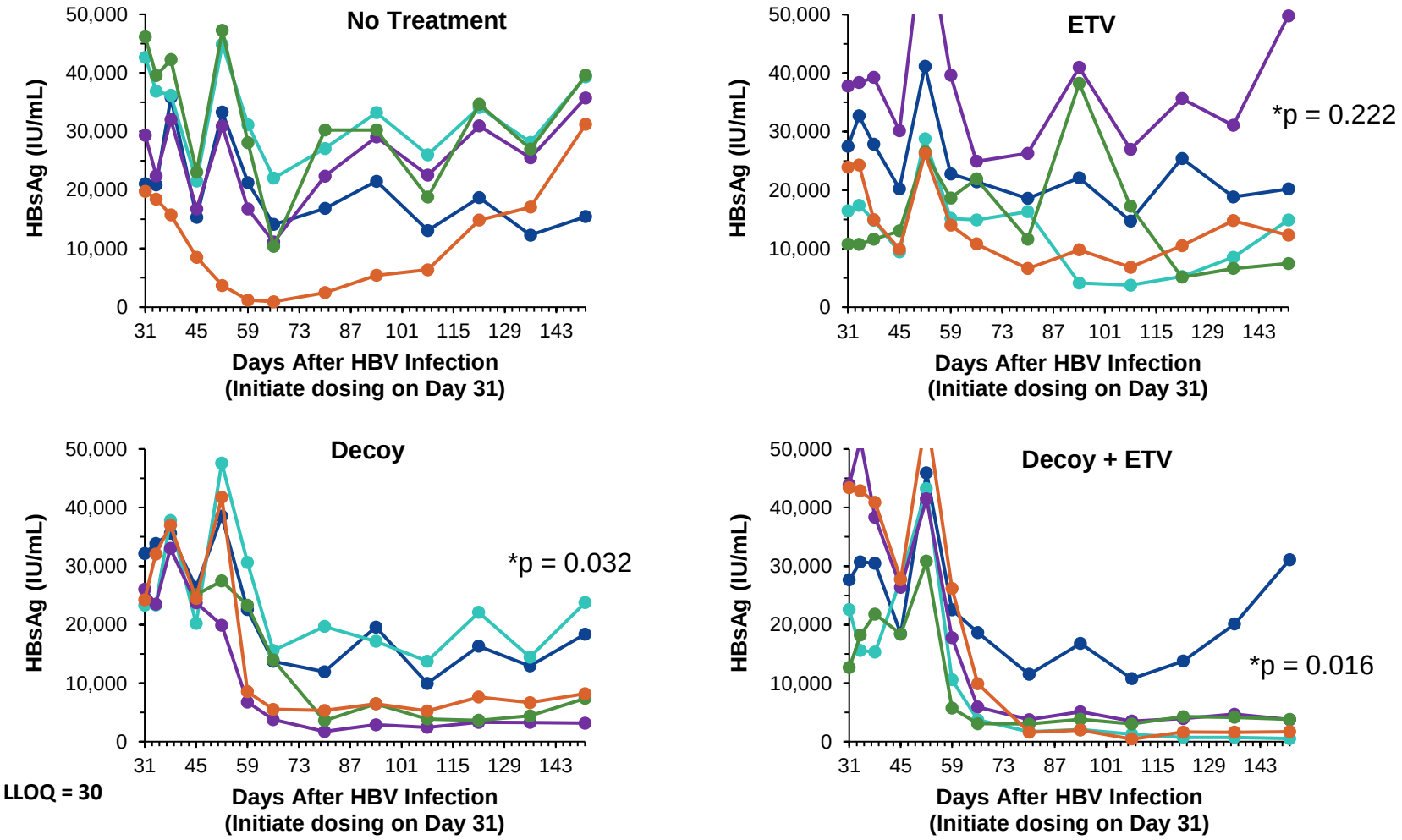


LLOQ = 6

*Unpaired, non-parametric, Mann-Whitney U-test compared to Control at last data-point (Day 151) 12 weeks after EOT

IV Decoy Bacteria Reduce Plasma HBsAg Levels in the Mouse AAV-HBV Model of Chronic HBV Infection (Exp. #2 / No Indomethacin)

Dose during days 31-66 (5 weeks) / No indomethacin



*Unpaired, non-parametric, Mann-Whitney U-test compared to Control at last data-point (Day 151) 12 weeks after EOT

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AAV-HBV Experiment #2 Summary (No Indomethacin)

- Efficacy and toxicity similar to experiment #1 (indomethacin not required for efficacy)
- Decoy bacteria induced long-lasting production of T-cell mediated anti-HBsAg activity (T cell ELISpot), but did not produce B-cell anti-HBsAg activity (B cell ELISpot)

Indaptus' Decoy Platform - Infectious Diseases Summary

- We have invented a systemically administered, toxicity attenuated, multi-TLR, NOD, STING agonist product that produces safe, single agent anti-cHBV activity in a pre-clinical *in vivo* model
- Single agent Decoy activity has also been observed with a humanized mouse model of human HIV
- Indaptus technology does not require targeting with or to a specific viral antigen
- Decoy toxicology studies have demonstrated targeted, non-adverse immune activation in liver and spleen without sustained hallmarks of cytokine release syndromes
- A Phase 1 clinical trial in Oncology has been initiated with potential to test in HCC patients with HBV
- Acknowledgements:
  - AntiCancer, Crown Biosciences, Eurofins Panlabs, InvivoGen, Molecular Diagnostic Services, Pacific BioLabs, Transcure, WuXi AppTec