hansonwade
Chronic HBV Drug Development
April 25-27, 2022

Indaptus THERAPEUTICS

April 27, 2022

Driving Pre-Clinical Anti-HBV Activity With a Novel Multi-TLR Agonist Therapeutic Vaccine

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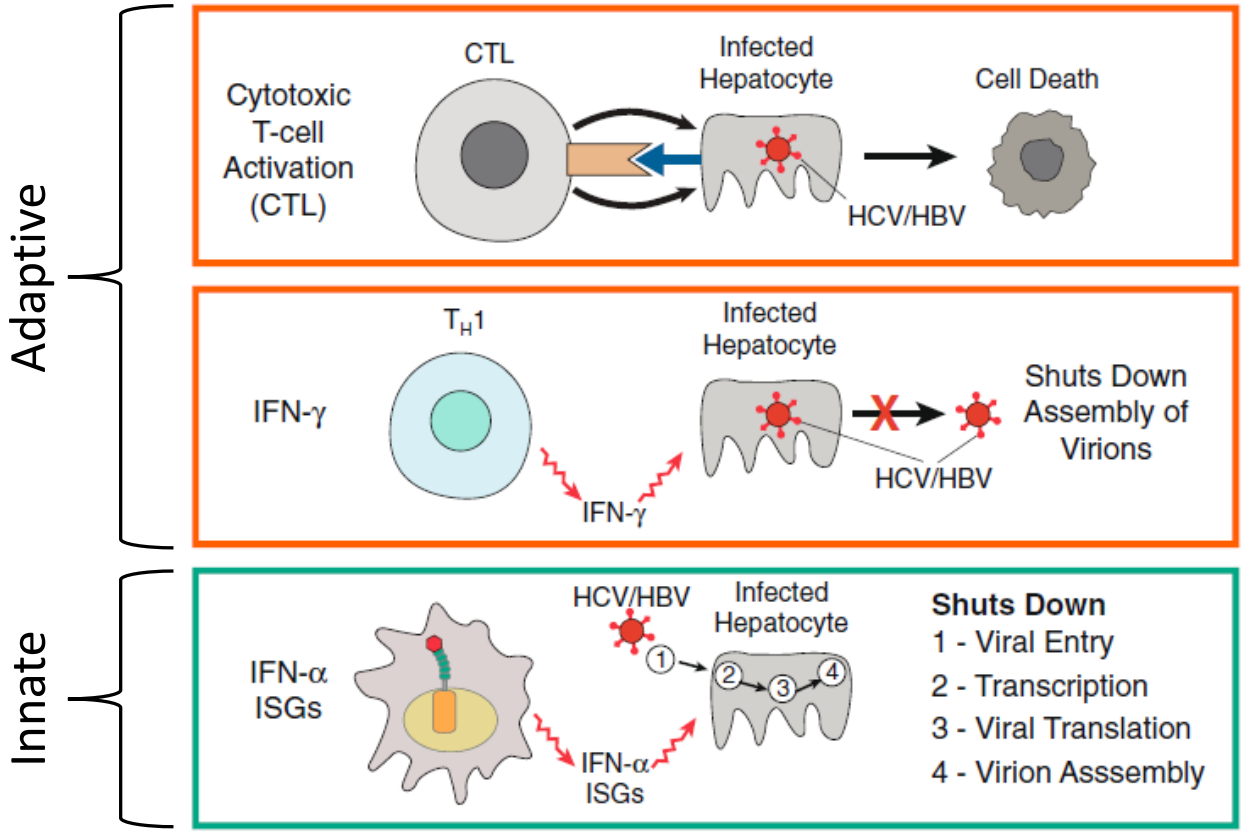
Michael J. Newman is an employee of Indaptus Therapeutics

Achieving Functional Cure of Chronic HBV (cHBV)

- **Approximately 1% of chronically infected individuals per year mount an effective immune response to control chronic hepatitis B infection**
  - Revill et al., Lancet Gastroenterol Hepatol v4 p545 2019

- **Relevant clinical, pre-clinical in vivo and in vitro observations**
  - Ablation of Persistent Hepatitis B by Bone Marrow Transplantation From a Hepatitis B-Immune Donor
    Ilan et al., Gastroenterology v104 p1818 1993
  - Intracellular Inactivation of the Hepatitis B Virus by Cytotoxic T Lymphocytes
    Guidotti et al., Immunity v4 p25 1996
  - 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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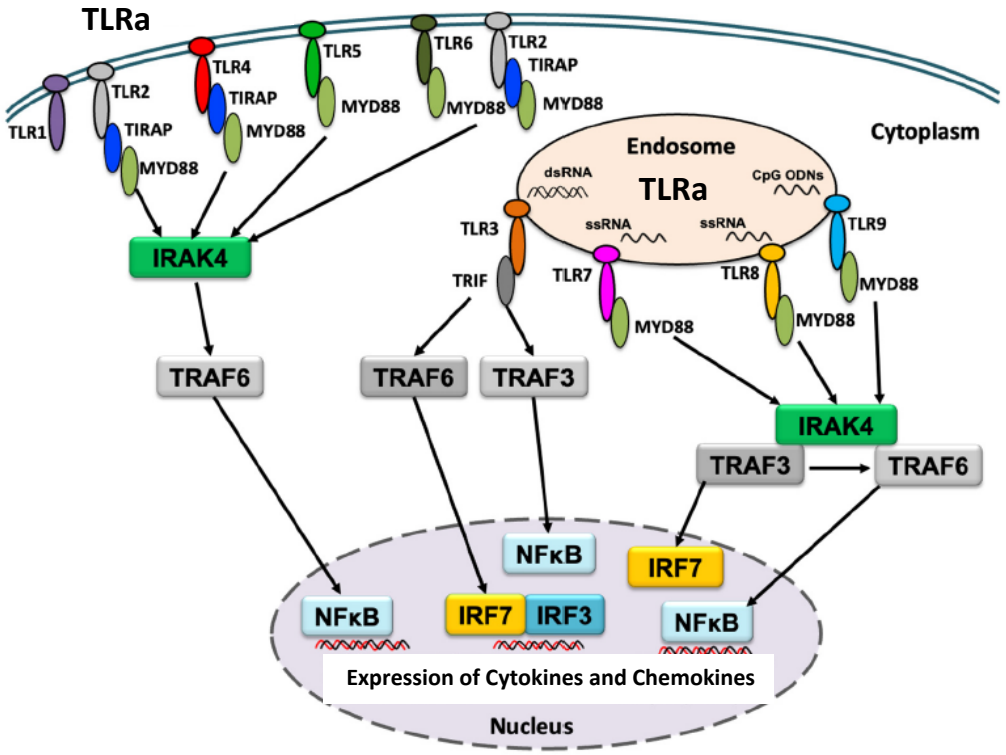
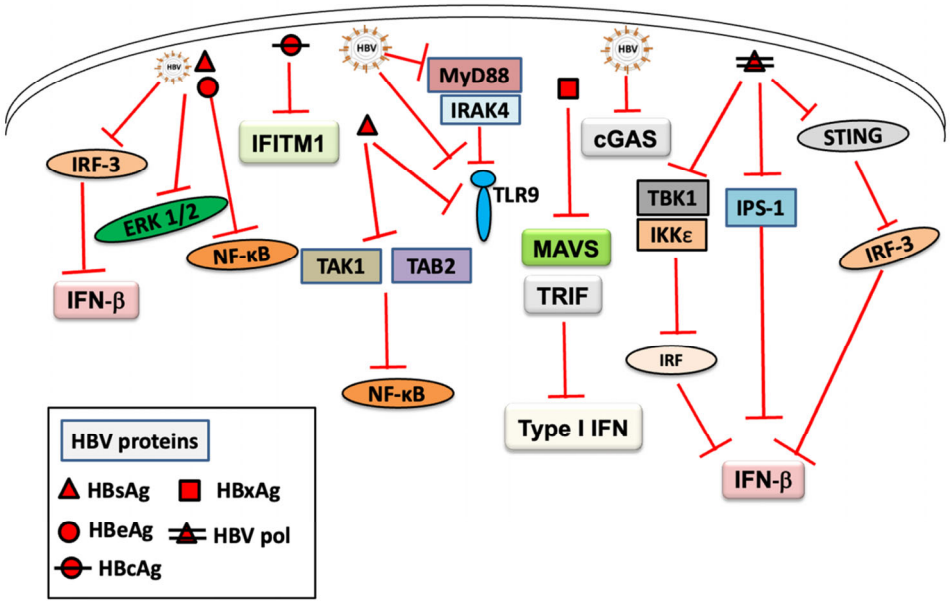
Activation of Toll-Like Receptors (TLRs) on Immune Cells (and Hepatocytes?) by TLR Agonists (TLRa) is Critical for Innate and Adaptive Anti-cHBV Immunity

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

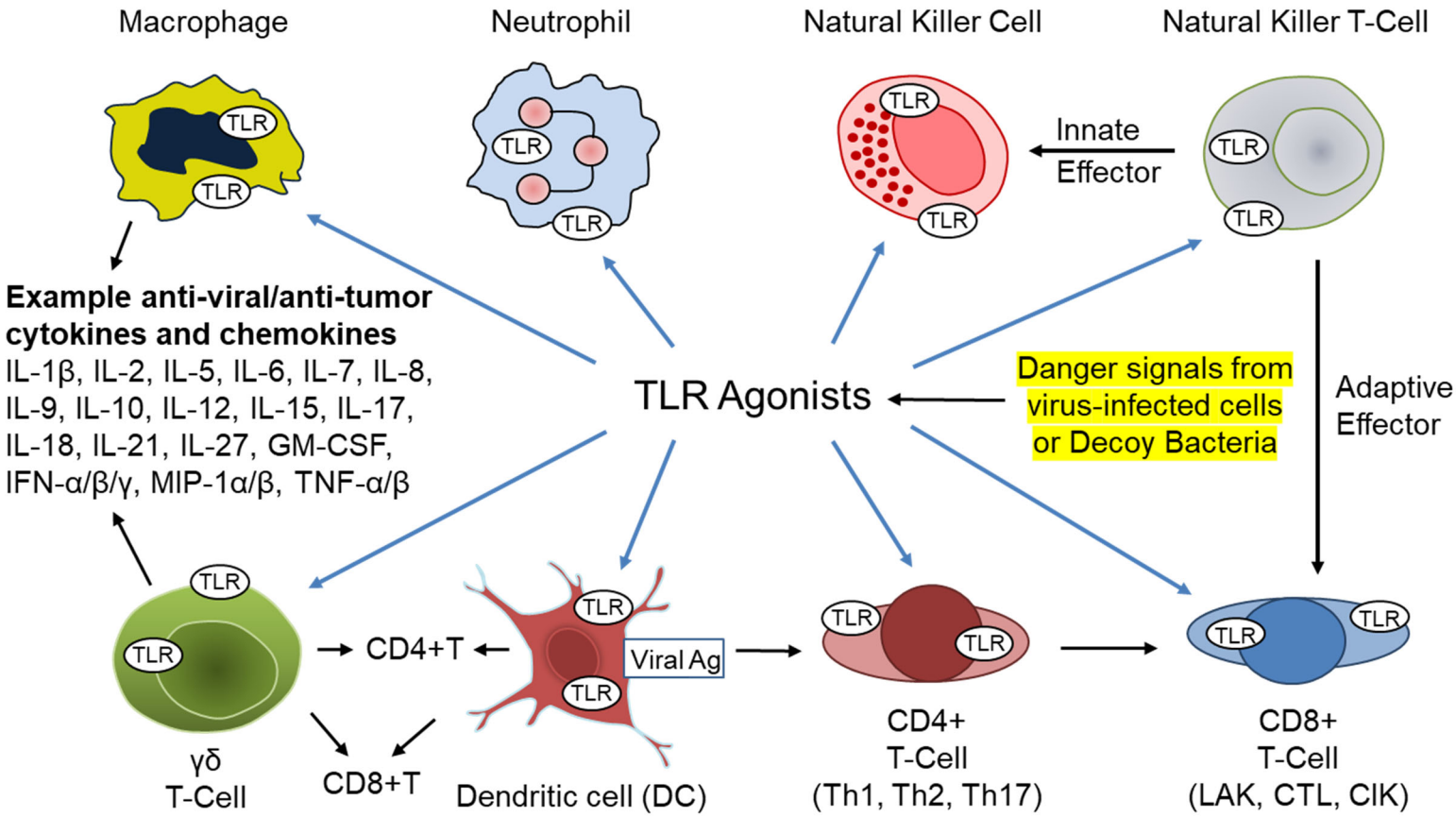


In cHBV, insufficient HBV "Danger Signals" (TLRa) are released
Also, HBV proteins may inhibit cytokine/chemokine (TLR) induction pathways in infected hepatocytes

We need to overcome this multi-cell/pathway blockade

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

Overcoming Immune Suppression in cHBV (and Cancer)
Indaptus Concept: Multi-TLR Agonist Decoy Bacteria



Cytokines secreted by immune cells produce autocrine/paracrine activation and have direct anti-viral and anti-tumor activity

Rationale and Potential Source for a Multi-TLR Agonist (TLRa) Product

- **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 or 9)

- **Gram-negative bacteria contain multiple TLR agonists (+ NODa & STINGa)**

Maltose-binding protein, Outer membrane protein	TLR2a
Double stranded RNA	TLR3a
Lipopolysaccharide (LPS)-endotoxin	TLR4a
Flagellin	TLR5a
Single stranded RNA	TLR7/8a
Unmethylated CpG DNA	TLR9a

- **TLRs directly or indirectly activate essentially all immune cells (innate & adaptive)**
  - Indirect activation occurs via induction of secretion of cytokines and chemokines

- **Cytokines and chemokines are principal inducers of anti-viral immune responses**

Problem – Systemic Administration Required: IV Administered Gram-Negative Bacteria are Toxic

- **TLR4a LPS-endotoxin constitutes ~75% of the Gram-negative outer cell membrane**
- **LPS is one of the most potent and broadly acting immune system danger signals**
- **Limits the number of bacteria (and other danger signals) that can be administered i.v.**
  - Can't provide optimal amount of other TLRa needed for activation of immune pathways
- **Two options – eliminate or reduce LPS**
  - Elimination of LPS was tried for cancer (Vion Pharma) – no anti-tumor activity in Phase 1
  - LPS/TLR4 anti-HBV activity + used in HBV vaccines (Luchner et al., Pharmaceutics v13 p142 2021) LPS stimulates NK cells, induces maturation of APC/Dendritic cells, primes and amplifies T and B-cell function and enhances T-helper Th1 responses (Arenas Drug Targets v12 p221 2012)
  - Better bet – reduce LPS by ~90%
    Remaining 10% might be enough and allow i.v. administration of more of everything else

Indaptus Solution

- **Hypothesis to produce an i.v.-safe and effective product**
  - Use a single, pure strain of non-pathogenic, Gram-negative bacteria
  - Selectively reduce LPS-endotoxin activity by ~90%
  - Kill and stabilize the bacteria so that they don't fall apart prior to immune cell clearance
- **Potential advantages of approach**
  - IV-administered bacteria are passively targeted to the liver and spleen and rapidly cleared from blood in mice, rabbits and humans (within ~15 minutes)
  - Passive targeting to liver and spleen should produce innate and adaptive immune system priming or activation at site of infection and key lymphoid organ
  - Rapid clearance should reduce potential for systemic toxicities common with small molecule and protein-based immunotherapies that depend on continuous exposure

Patented Decoy Treatment Kills Bacteria and Significantly Reduces LPS-Endotoxin Activity and *In Vivo* Toxicity (Including *In Vivo* Pyrogenicity)

Treatment	Live Bacteria	LPS Endotoxin Activity (LAL Assay)	Pyrogenicity Threshold (Rabbit Assay)
No Treatment	100%	44.7 Units / 10^6 Bacteria	$3x10^4$ Bacteria
Decoy Manufacturing Process	0	3.6 Units / 10^6 Bacteria (92% reduction)	$9x10^5$ Bacteria (97% reduction) (requires more bacteria to increase rabbit temperature)

Decoy bacteria are also 100 to 2,500-fold less toxic in mice (LD_{50}) than some live, attenuated bacterial products

Despite Reduced Toxicity, Decoy Treatment Does Not Significantly Compromise Induction of Anti-HBV Cytokine Secretion by Human PBMCs

Secretion by Human PBMCs *In Vitro*	**Untreated Bacteria**	**Decoy-Treated Bacteria (Decoy10)**	**Decoy-Treated Bacteria (Decoy20)**
Anti-Viral Cytokine	**pg/mL (mean of triplicate determinations ± %CV at same bacterial dose for each cytokine)**		
GM-CSF	1,094 ± 22	1,197 ± 2	1,695 ± 23
IFNγ	175,866 ± 7	47,488 ± 3	55,321 ± 10
IL-12p70	176 ± 14	528 ± 7	428 ± 37
TNFα	49,782 ± 11	77,919 ± 13	99,247 ± 16

Results suggest that we have (partly) dissociated toxicity from anti-viral cytokine induction

Multiple TLR Agonist Decoy Bacteria Induce Higher Levels of Anti-Viral Cytokine/Chemokine Secretion by PBMCs than Mono-Specific TLR Agonists

Secretion by Human PBMCs *In Vitro*	CpG (TLR9)	Poly(I:C) (TLR3)	R848 (TLR7/8)	LPS (TLR4)	Decoy10 (Multi-TLR)
Anti-Viral Cytokine	**pg/mL (triplicate full titration peak average from two exp)**				
GM-CSF	0	2	136	276	1,246
IFNγ	7	248	61,914	33,293	171,284
IL-12p70	4	15	205	84	375
TNFα	65	334	36,663	24,944	73,069
MIP-1α*	0	272	17,866	19,278	29,942

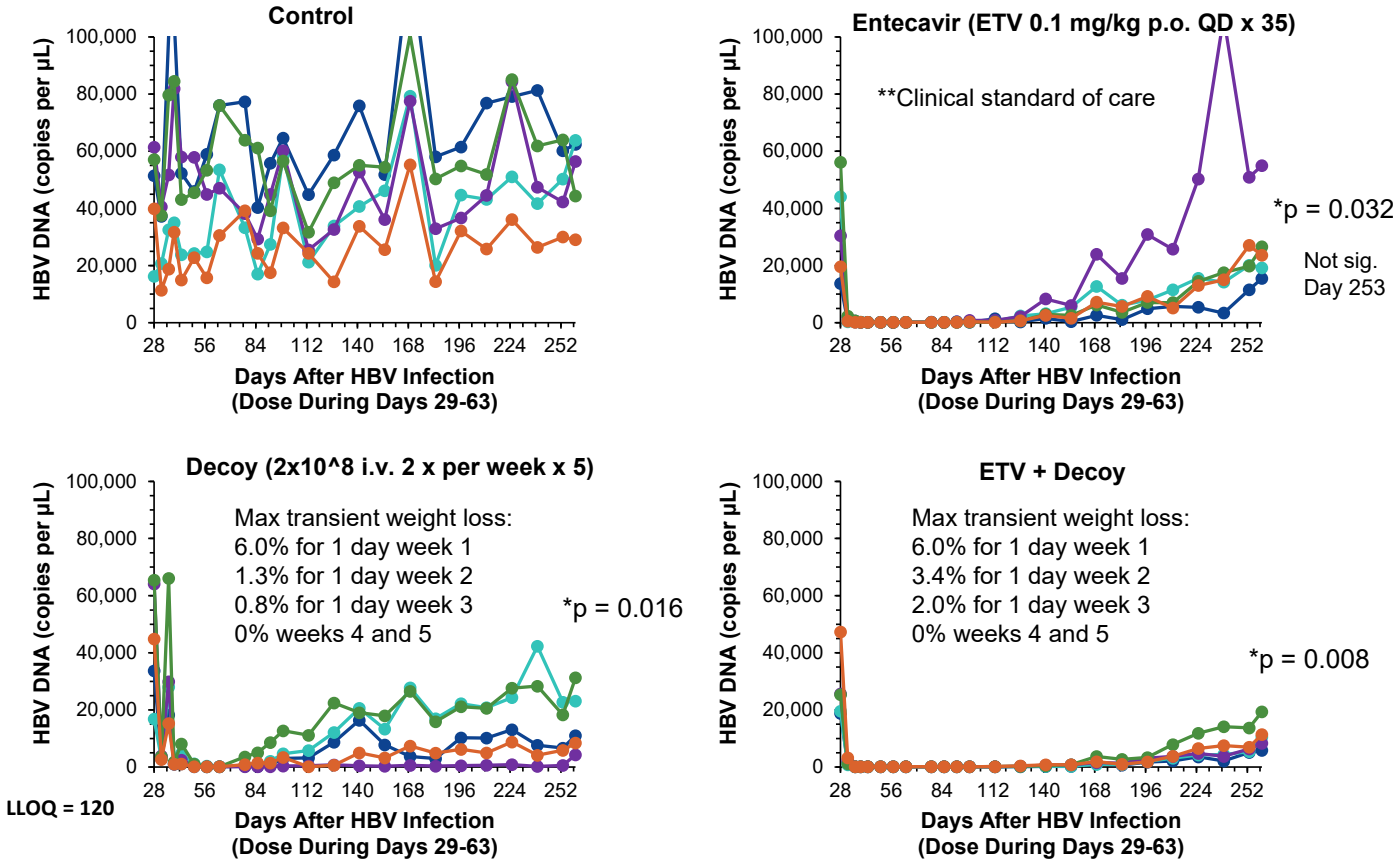
*One experiment

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

- Mouse liver cells are not infected by human HBV virus, 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 blood levels of HBV virus, as well as the important HBV markers plasma HBsAg and HBeAg
- HBV DNA, HBe(c)Ag, HBsAg and a cccDNA-like molecule are also found in mouse livers infected with AAV-HBV (AAV-HBV cccDNA-like molecule correlation with cHBV cccDNA has not been fully established)
- Entecavir produces similar results in humans and the mouse model - reduction in plasma HBV DNA during treatment, without inhibitory effects on plasma HBsAg/HBeAg, or liver HBV DNA, HBe(c)Ag, HBsAg or cccDNA-like molecule

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

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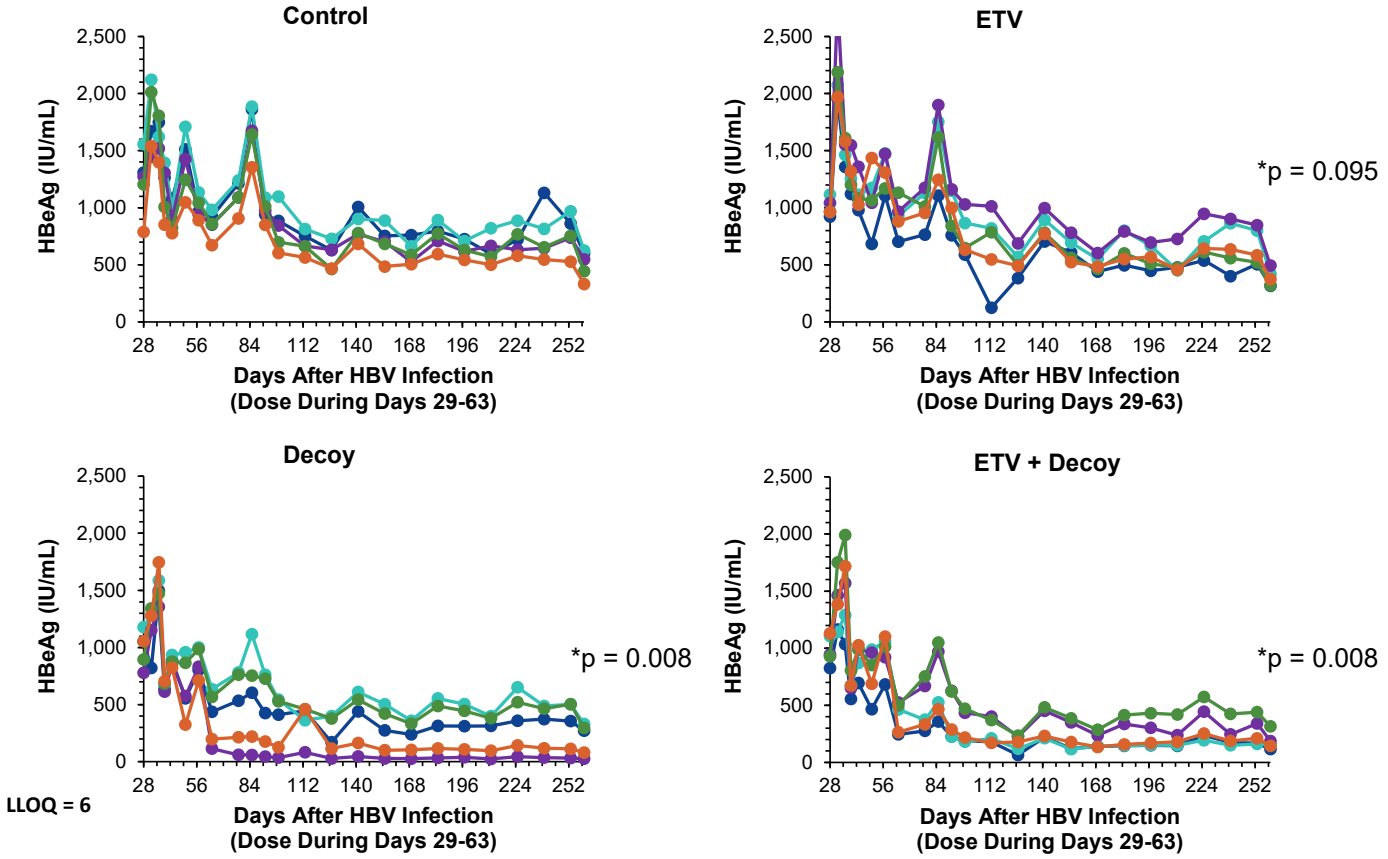
IV Decoy Bacteria Reduce Plasma HBeAg Levels in the Mouse AAV-HBV Model of Chronic HBV Infection

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



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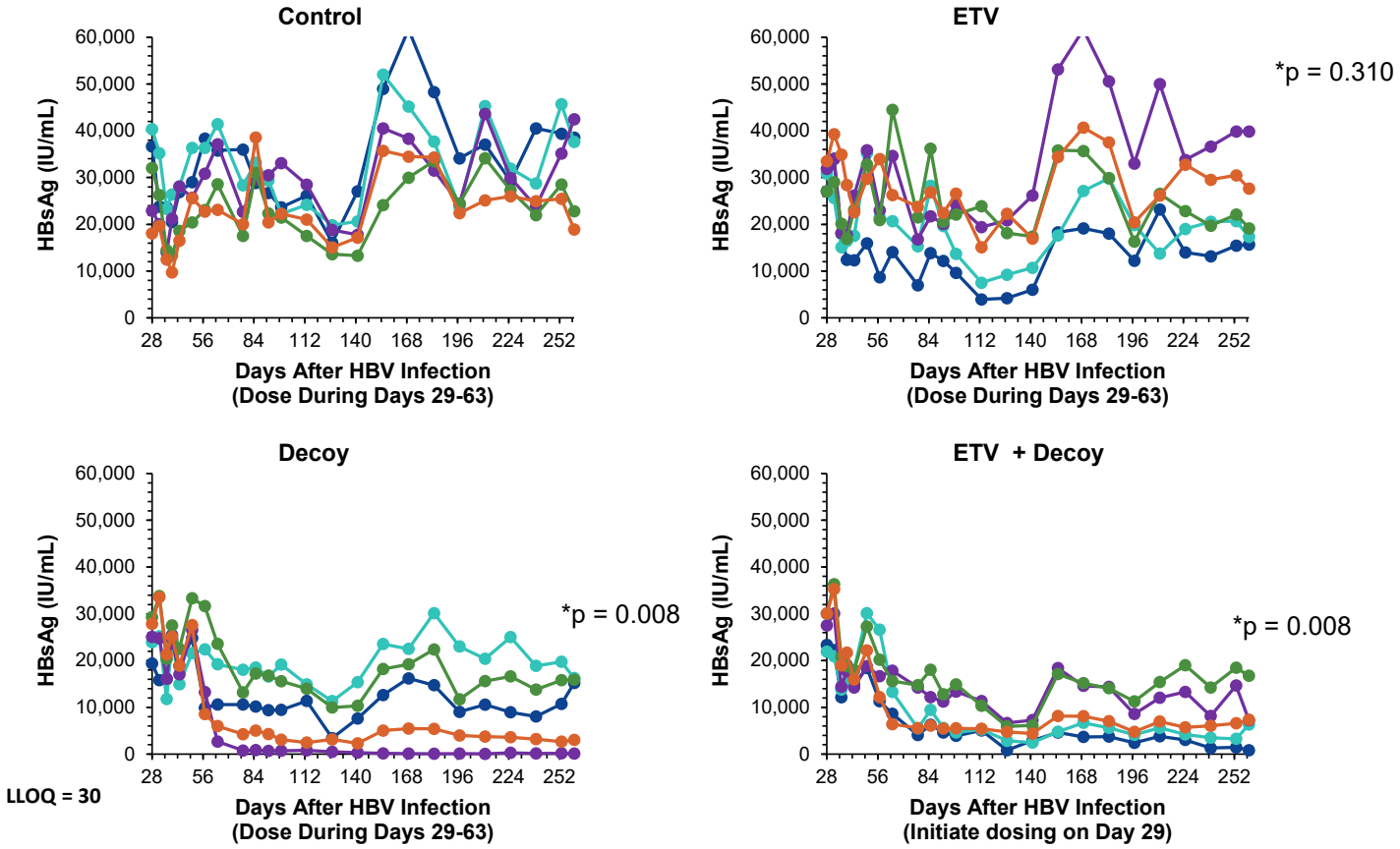

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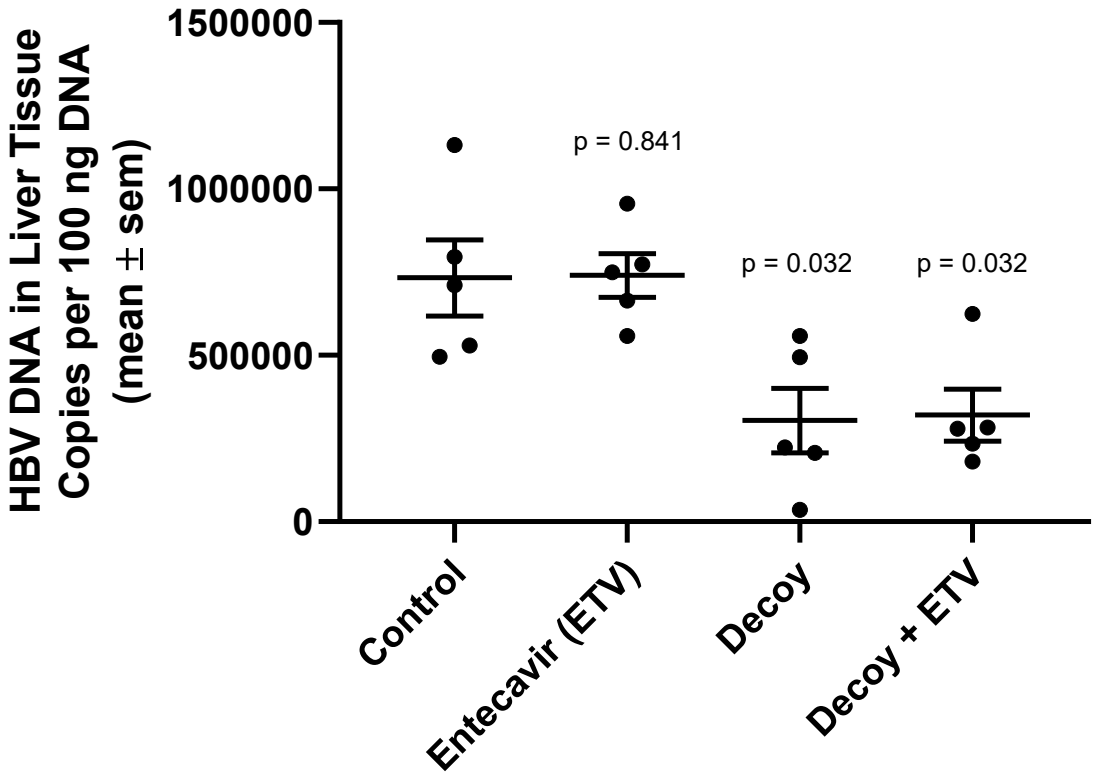
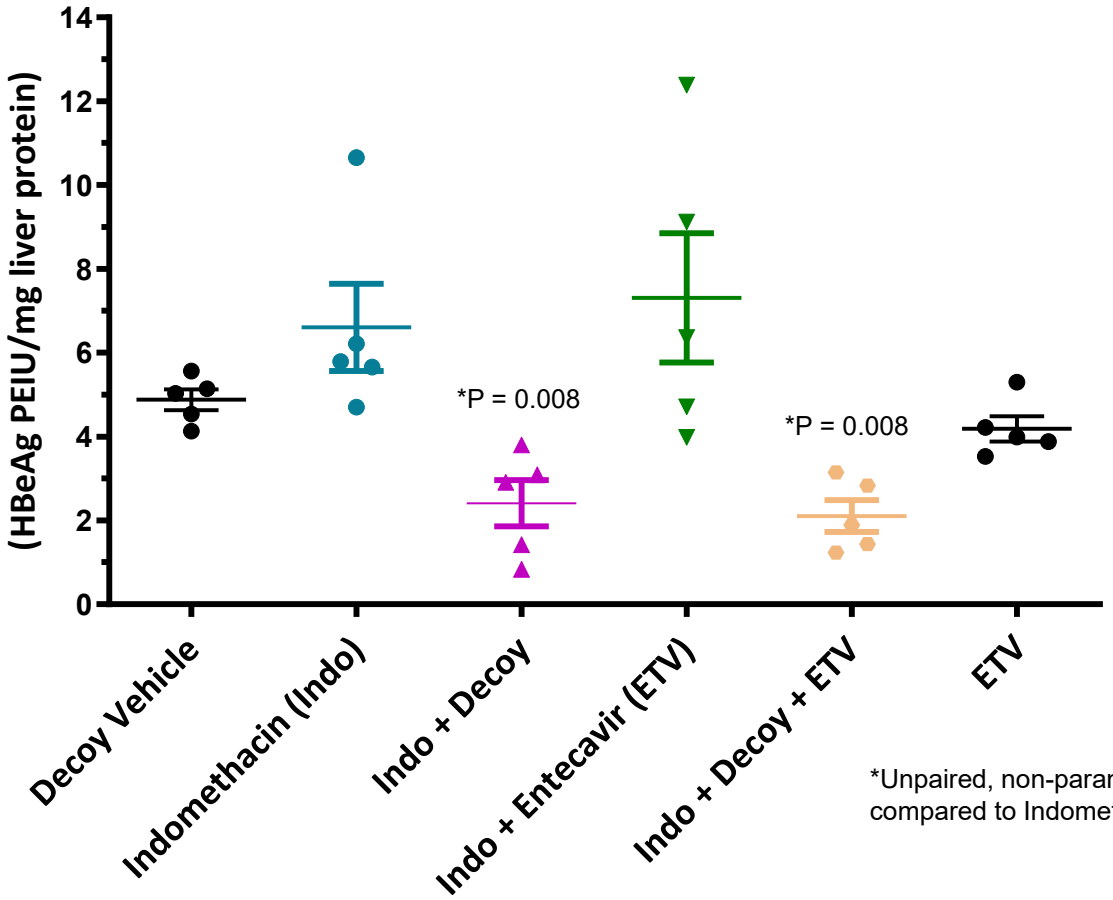
IV Decoy Bacteria Reduce HBV DNA Levels in the Livers of Mice Infected with HBV (AAV-HBV Model)

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 HBe(c)Ag Levels in the Livers of Mice Infected with HBV (AAV-HBV Model)

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

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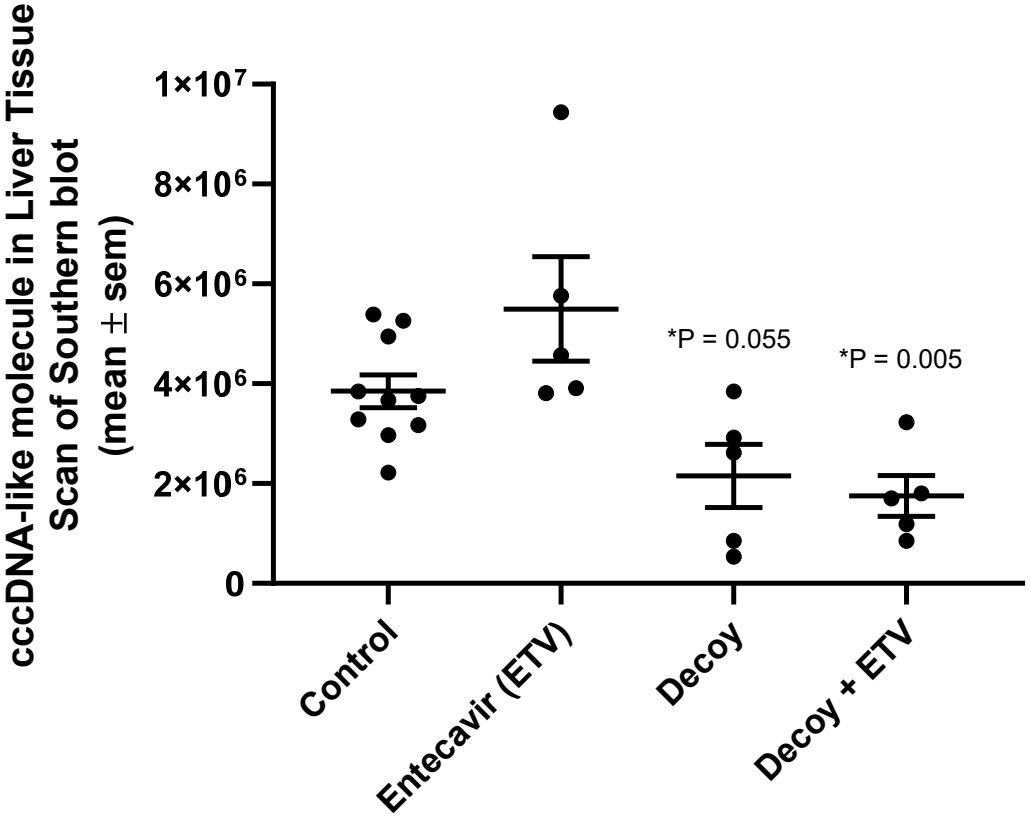
IV Decoy Bacteria Reduce Levels of cccDNA-Like Molecule in the Livers of Mice Infected with HBV (AAV-HBV Model)

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

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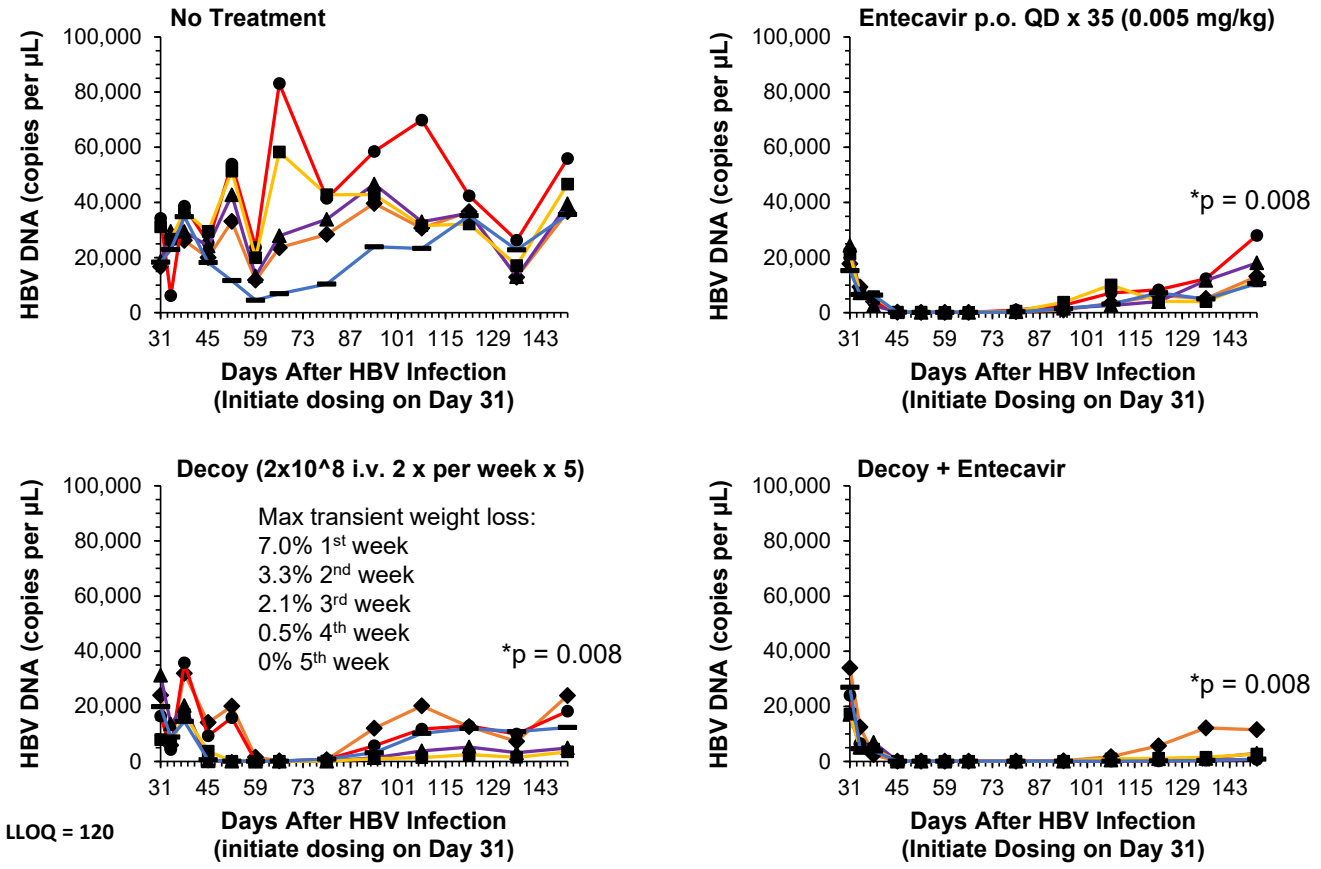
Side-Effects/Toxicity of IV Decoy Bacteria in the AAV-HBV Model

- 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

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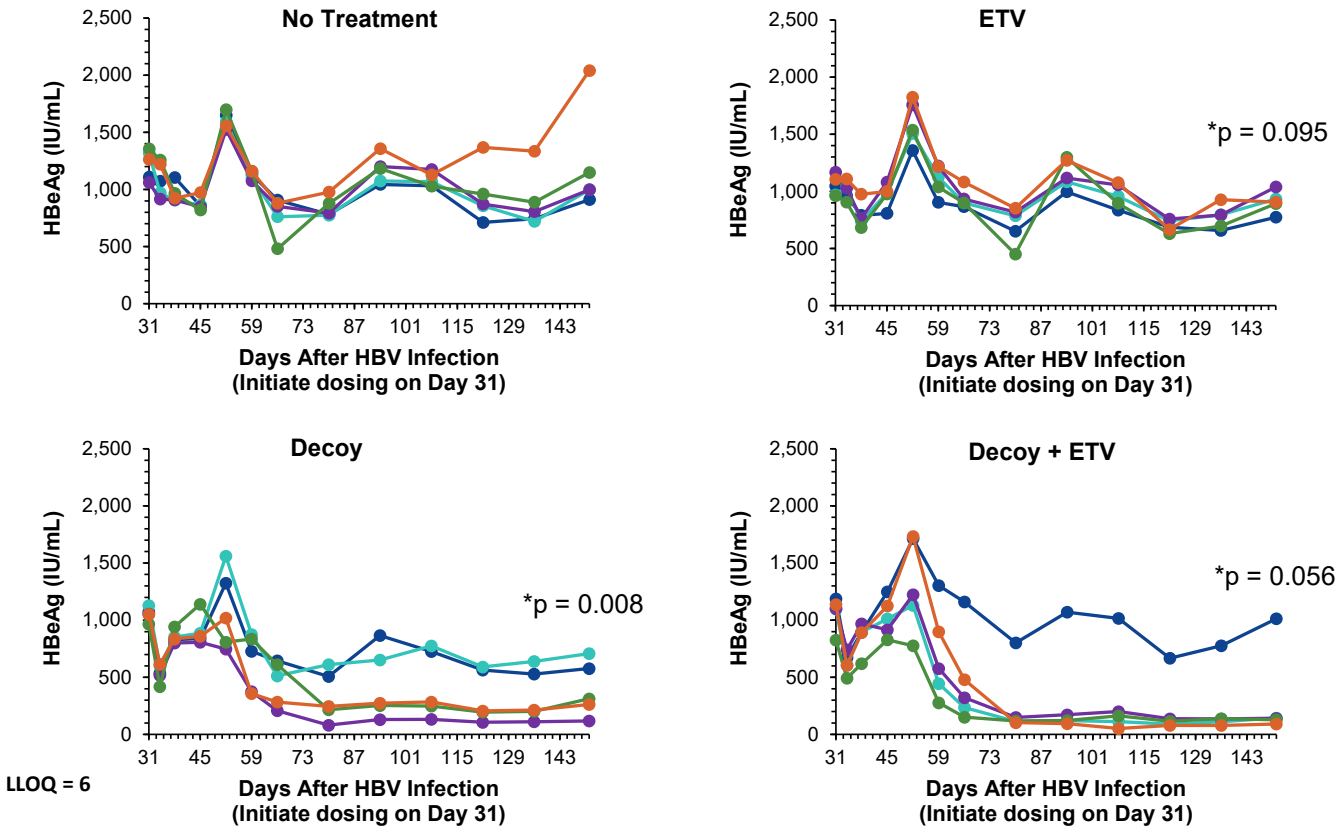
IV Decoy Bacteria Reduce Plasma HBeAg Levels in the Mouse AAV-HBV Model of Chronic HBV Infection (Exp. #2 / No Indomethacin)

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



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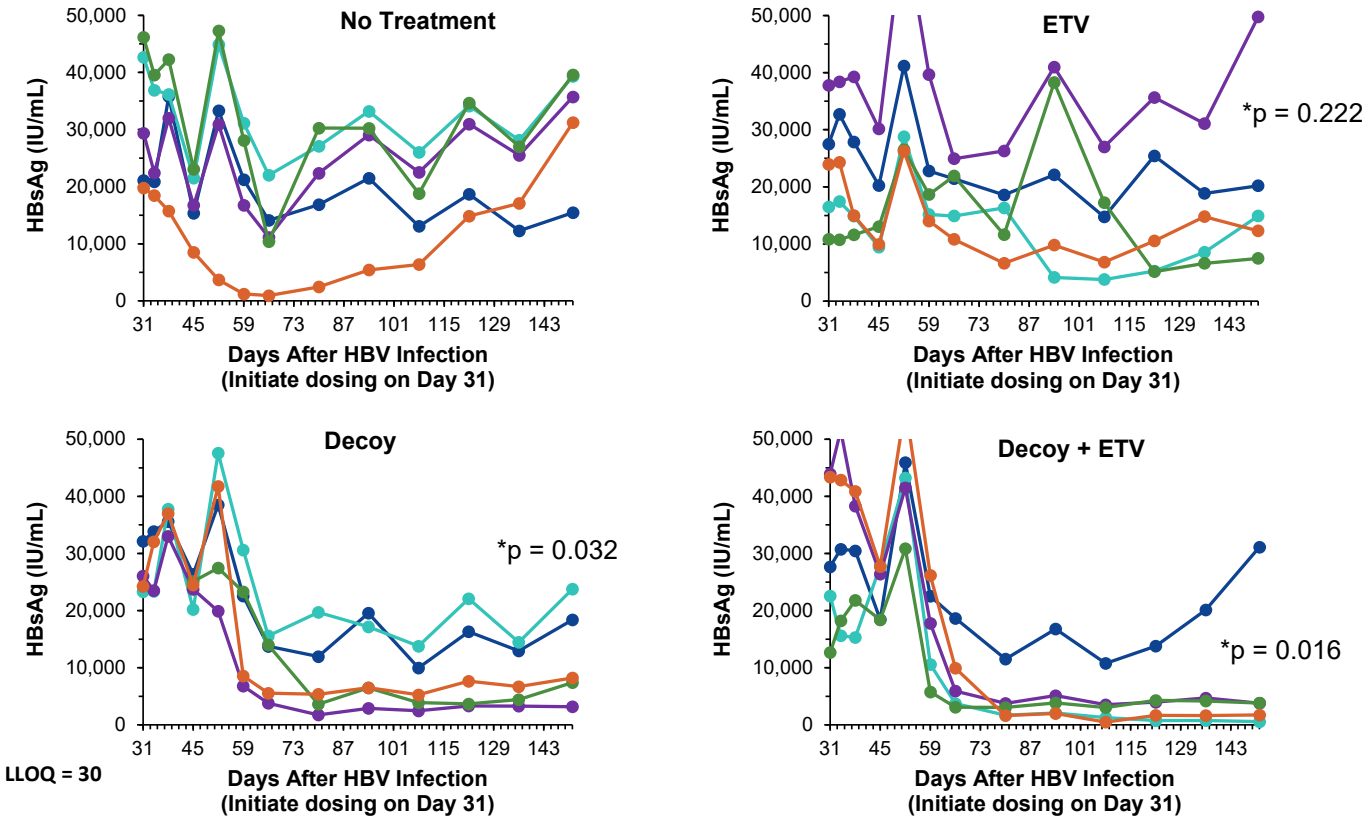
IV Decoy Bacteria Reduce Plasma HBsAg Levels in the Mouse AAV-HBV Model of Chronic HBV Infection (Exp. #2 / No Indomethacin)

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



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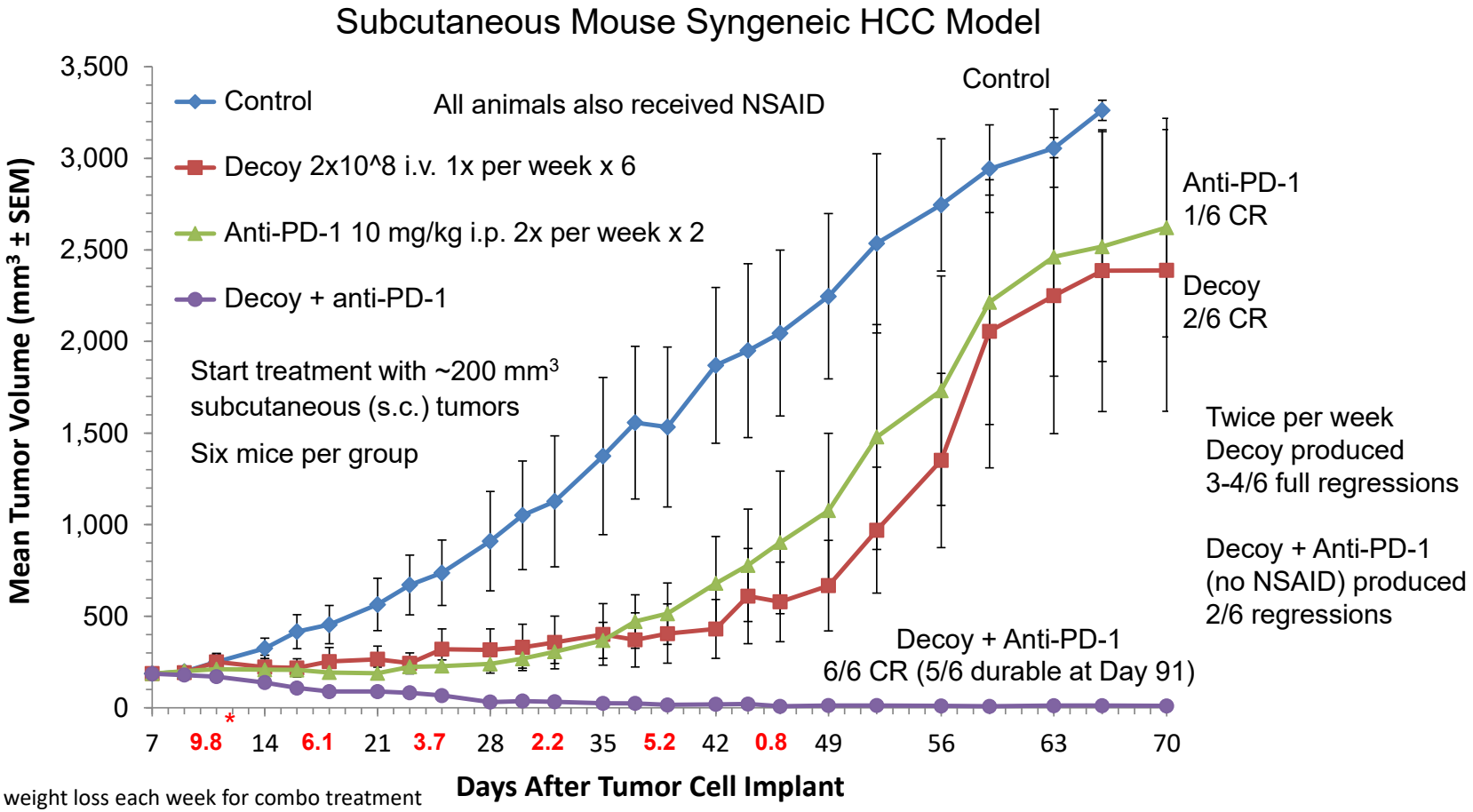
AAV-HBV Experiment #2 Summary (No Indomethacin)

- 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)

Do Decoy Bacteria Prime or Activate Both Innate and Adaptive Immune Pathways? Positive Results in Oncology Models

- Rationale for use of Decoy bacteria platform is the same for anti-viral and anti-tumor immunotherapy
- Decoy bacteria produce single agent activity and/or combination therapy-mediated tumor eradication in multiple pre-clinical models, including hepatocellular carcinoma (~44% of HCC cases caused by cHBV)
- Tumor eradication by Indaptus technology in pre-clinical models is mediated by activation of innate and adaptive pathways and produces innate and adaptive immunological memory (resistance to tumor re-challenge)

Combination of Decoy Bacteria With Anti-PD-1 Checkpoint Therapy Produces Complete Responses With Established Hepatocellular Carcinoma (Pre-Clinical)



* Max % transient weight loss each week for combo treatment
No increase in toxicity with triple combo

Anti-PD-1 active pre-clinical and in clinical trials for HBV

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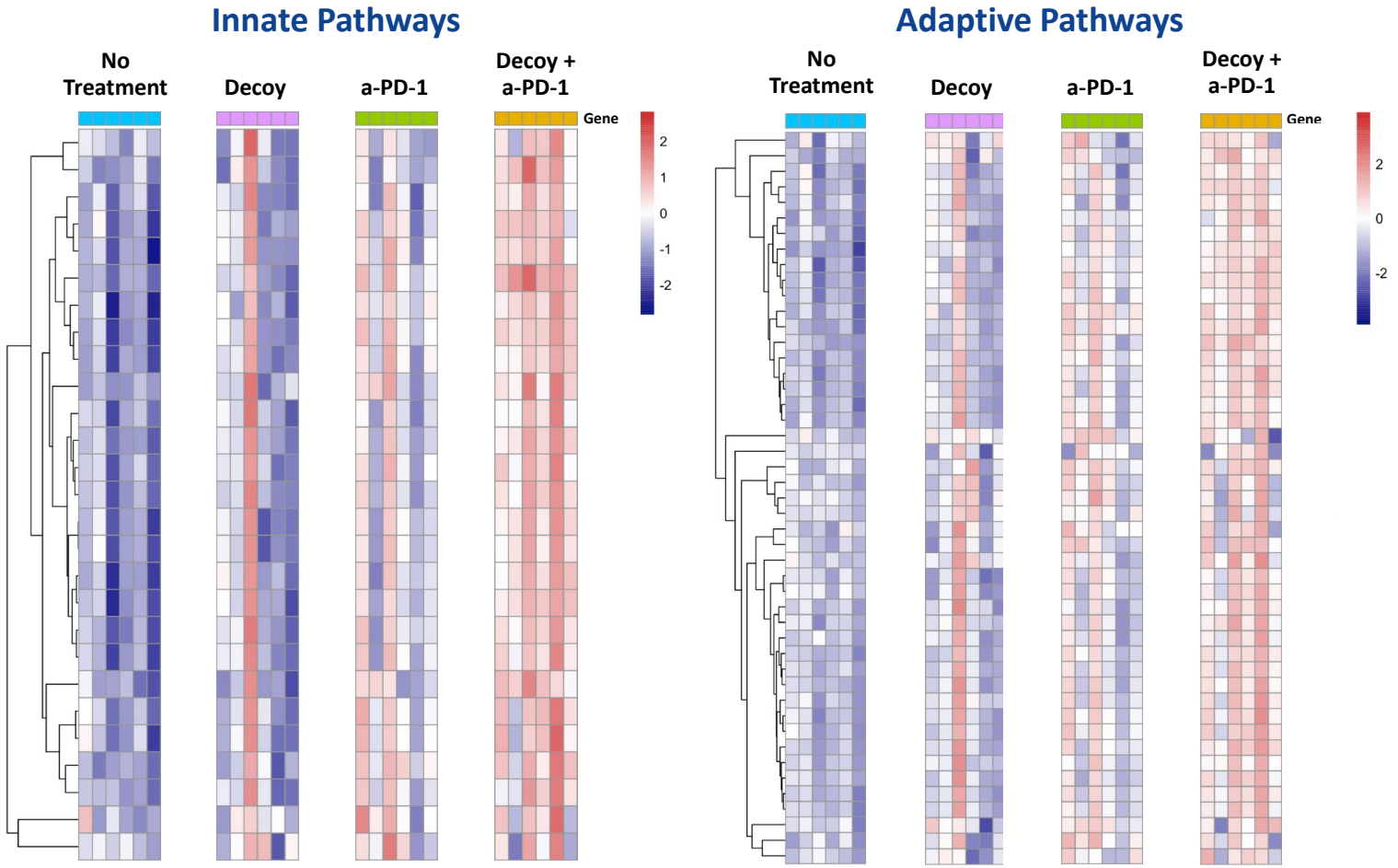
IV Decoy Bacteria Synergize with Anti-PD-1 to Activate Innate and Adaptive Immune Pathways / Associated With Eradication of Murine HCC Tumors

NanoString 770 gene expression analysis: Innate or Adaptive Immune response in tumors

Mice with 200 mm^3 s.c. HCC tumors were treated 1x with Decoy and/or 2x with anti-PD-1 over 1 week (6 mice/group)

"Cold" tumors are turned into "Hot" tumors (inflammation score)

Decoy induces mild, transient weight loss and there was no increase in toxicity with combination treatment



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Indaptus Summary and Next Steps

- We have invented a systemically administered, toxicity attenuated, multi-TLR agonist product that produces safe single agent anti-cHBV activity in a pre-clinical *in vivo* model
- Toxicology studies have demonstrated targeted, non-adverse immune activation in liver and spleen without sustained hallmarks of cytokine release syndromes
- Indaptus technology does not require targeting with or to a specific viral antigen, but has the potential for significant improvement via viral antigen provision or targeting – next step for anti-viral platform
- Phase 1 initiation in Oncology is planned in 2022
- Acknowledgements:
  - Crown Biosciences, Eurofins Panlabs, Molecular Diagnostic Services, Pacific BioLabs, WuXi AppTec