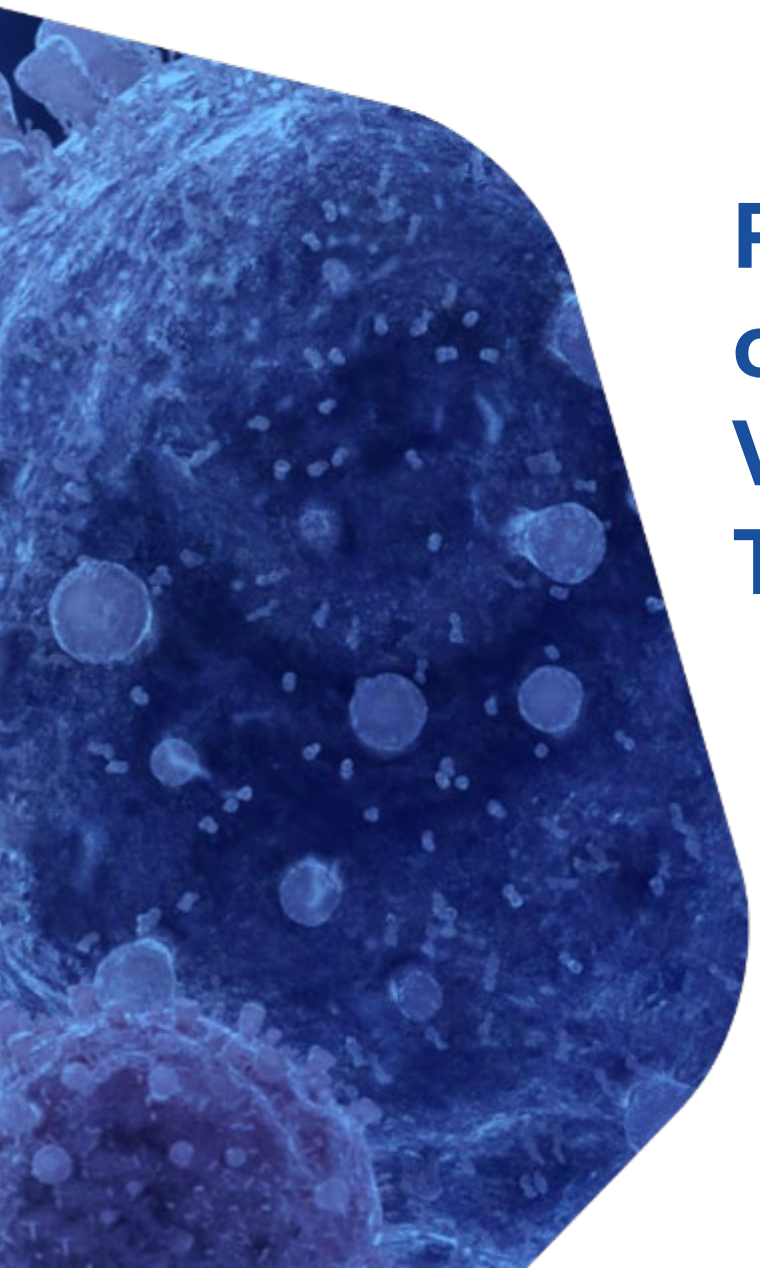

Preclinical Immunogenicity and Efficacy of VRON-0200: A Novel Therapeutic Vaccine for Potential Functional Cure Therapies in Patients with Chronic HBV

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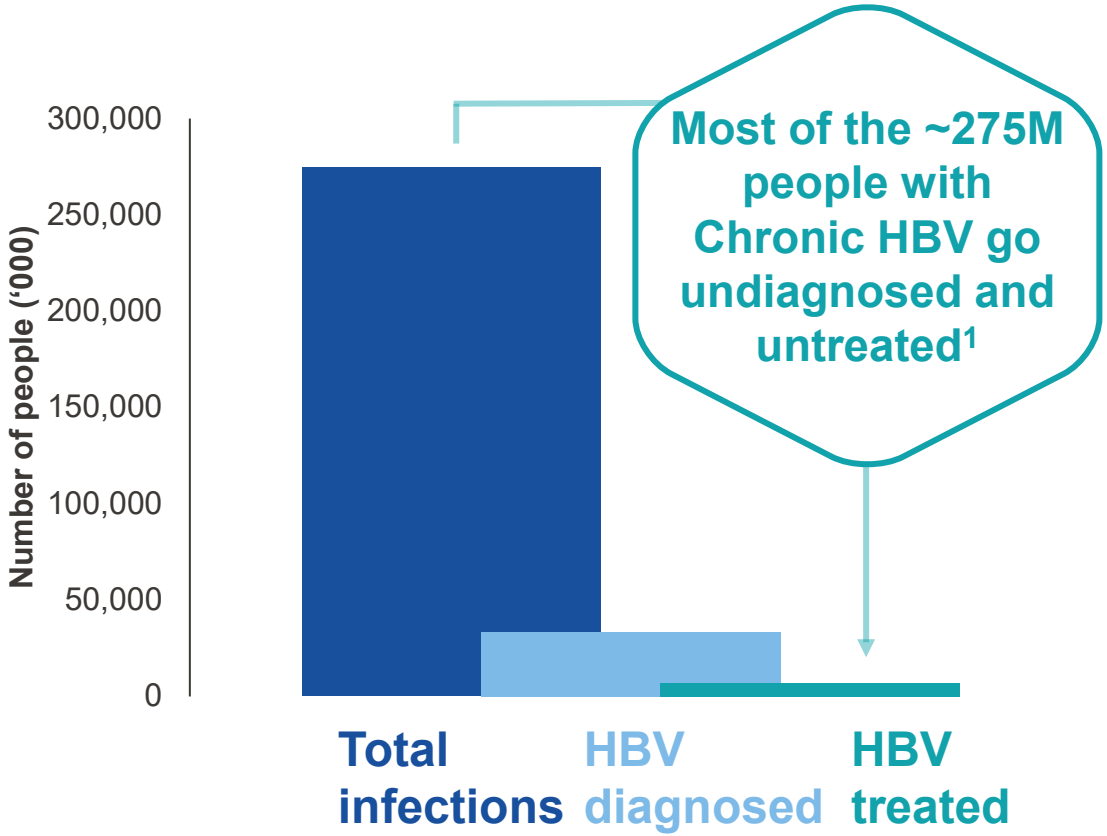
Author Disclosures

- **Co-founder of Virion Therapeutics**
- **Advisor roles with:**
  - Freelance, Inc
  - Takeda
  - Biogen (board)
  - Regenxbio
  - Ring Therapeutics (board)
  - Canine Rabies Treatment Initiative (board)

Despite HBV Preventative Vaccines, Chronic Infection is a High Unmet Need



Chronic HBV remains a **global public health problem** despite vaccination[2]

1 in 4 people with chronic HBV will **die prematurely** from liver cirrhosis, HCC, or liver failure[3]

Antivirals **rarely achieve functional cure** and **require lifelong drug therapy**[4]

HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

1. Razavi-Shearer D, et al. AASLD 2021; 2. Bertoletti A, et al. J Hepatol 2016; 64(1 Suppl):S71–S83; 3. Lok ASF, McMahon BJ. Hepatology 2009;50:661–2;
4. Tsounis EP, et al. World J Gastroenterol 2021;27:2727–57.

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Functional Cure for Chronic HBV Requires a New Therapeutic Approach

CD8⁺ T cells become impaired during chronic HBV infections, resulting in loss of viral control

Immune modulators for chronic HBV have shown limited clinical benefits[1–5]

Novel treatments needed to stimulate new functional CD8⁺ T cells

- Vaccine approaches that stimulate naïve T cells to de novo epitopes may restore viral control[6]

VIRION'S APPROACH FOR CHRONIC HBV FUNCTIONAL CURE	**ELIMINATE** cccDNA-infected hepatocytes	**STIMULATE & EXPAND** **NEW** HBV-specific CD8⁺ T cells to **RESTORE** immune control

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4. Zoulim F, et al. Hum Vaccin Immunother 2020;16:388–99; 5. Jansen D, et al. Clin Trans Immunology 2021;10:e1232;
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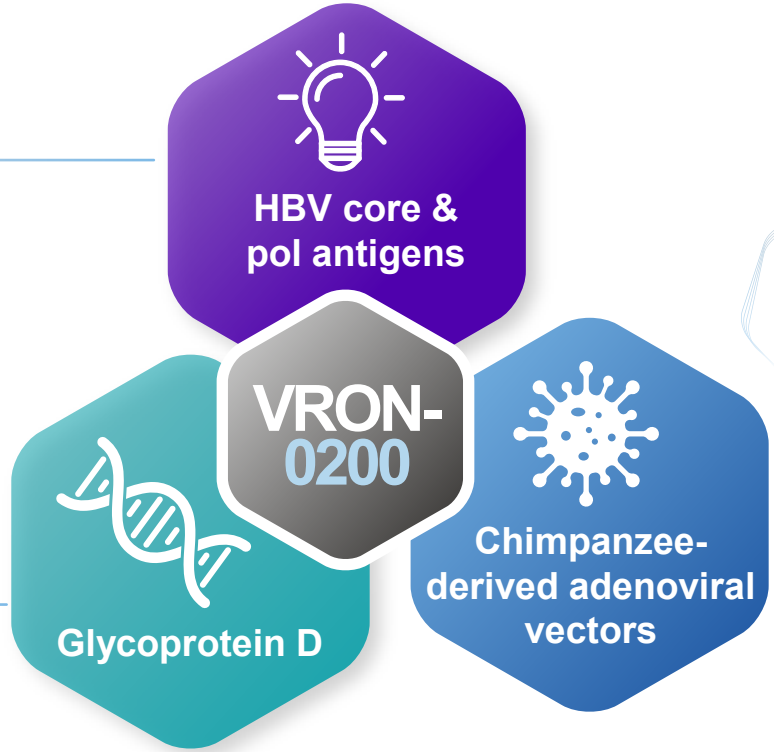
VRON-0200: A First-in-Class Immunotherapy for Chronic HBV

Antigen selection

- Immunogenic parts of **HBV core & pol antigens** selected

Genetically encoded checkpoint modifier

- Checkpoint modification enhances $CD8^+$ T cells response to the target antigen
- Broadens T cell responses
- Locally acting and cleared within 2-3 weeks, with a lower risk for “off target” toxicity



Viral vector platform

- Limited pre-existing vector immunity
- Limited cross-vector immunity
- Allows for prime & boost administration

Challenge model: AAV8-1.3HBV

Liver trophic AAV resulting in high loads of HBV in serum

Pol, polymerase.

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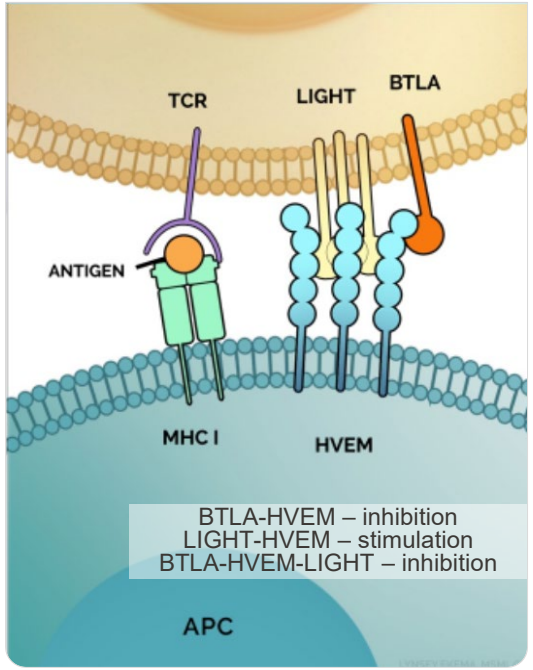
Herpes Simplex Virus Glycoprotein D

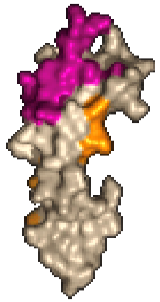
The Genetically Encoded Checkpoint Modifier Adjuvant[1–3]

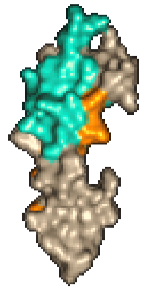
HVEM Complex in Regulating T cell Activation



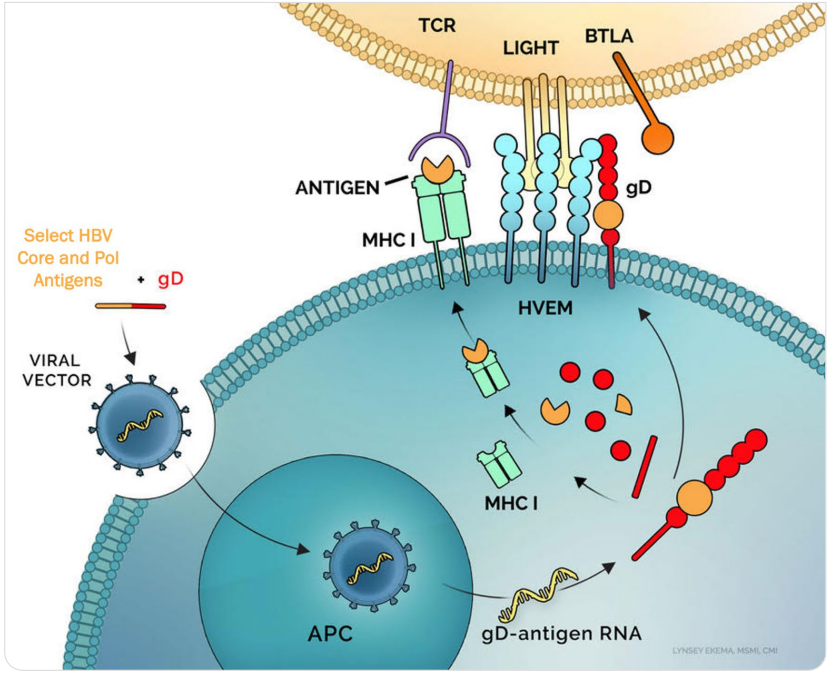
gD & BTLA Share HVEM Binding Site

HVEM crystal structure





gD BTLA-HVEM Blockade Enhances and Broadens T cell Activation



Following IM injection, VRON-infected APCs travel to regional draining lymph nodes

Within APCs, Ad vector produces the fusion protein of gD+ antigen of choice

Degradation of incorrectly produced fusion protein releases peptides from the antigen, which, upon binding to MHC class I, are recognized by CD8+ T cells

The gD fusion protein translocates to the cell surface, where it blocks BTLA-HVEM interaction, thereby increasing TcR signaling and allowing for co-stimulation through LIGHT

APC, antigen presenting cell; BTLA, B-and T-lymphocyte attenuator; gD, glycoprotein D; HVEM, herpes virus entry mediator; IM, intramuscular; LIGHT, lymphotoxin-like, exhibits inducible expression, and competes with herpes simplex virus glycoprotein D for HVEM, a receptor expressed by T lymphocytes; MHC, major histocompatibility complex; pol, polymerase; TCR, T cell receptor; VRON, Virion specific I/O therapy. 1. Xiang ZQ, et al. ASCO-SITC Clinical Immuno-Oncology Symposium 2020; Abstract No. 71; 2. Virion Therapeutics, September 2021. data on file; 3. Stiles KM, et al. J Virol. 2010;84:11646–60.

Methods
Combination HBV PolN, PolC & Core Studies

Vectors investigated*

AdC(6/7)-gDPolN, -gDPolC, -gDCore

- N- or C-terminal part of polymerase or core within gD

AdC(6/7)-gDHBV2 (VRON-0200)

- Polymerase + core within gD

AdC(6/7)-HBV2

- Polymerase + core without gD

Analyses of T cell responses

Post-vaccination analyses of T cell responses in blood, spleen, and liver

- Intracellular cytokine staining (ICS) for IFNγ
- MHC I tetramer staining combined with phenotypic analyses
- Epitope mapping of HBV-specific CD8+ T cells by ICS

Challenge experiment

AAV8-1.3HBV AAV vector model – 1 x 10^9 – 1 x 10^{11} vg IV

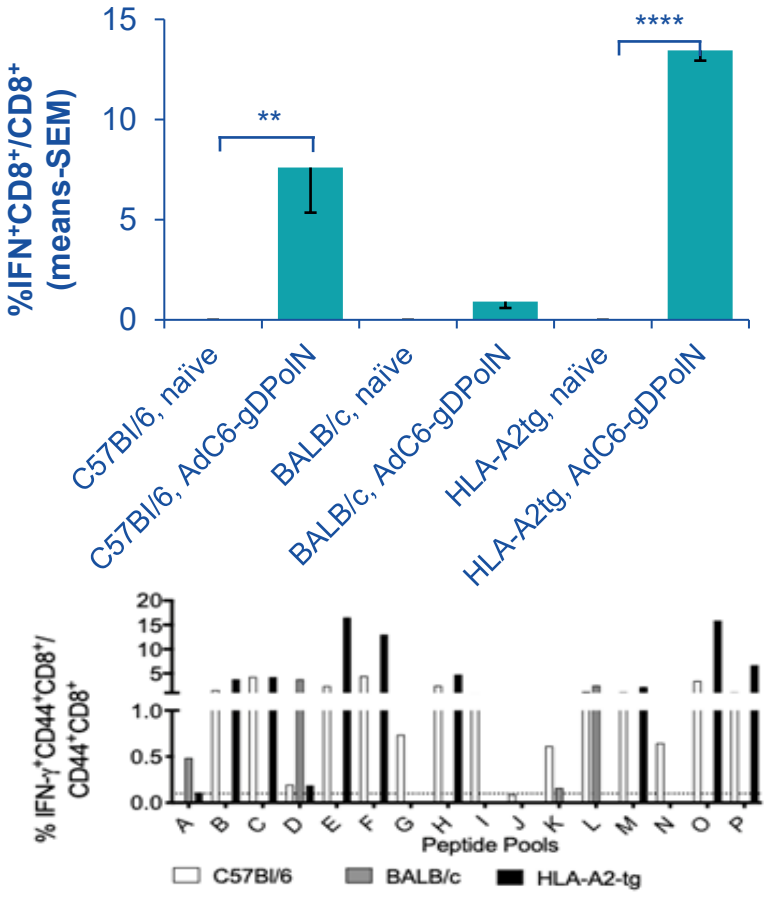
Vaccine vectors – Single IM dose of 1 x 10^{10} vp

- Administered 4 weeks after AAV8-1.3HBV injection

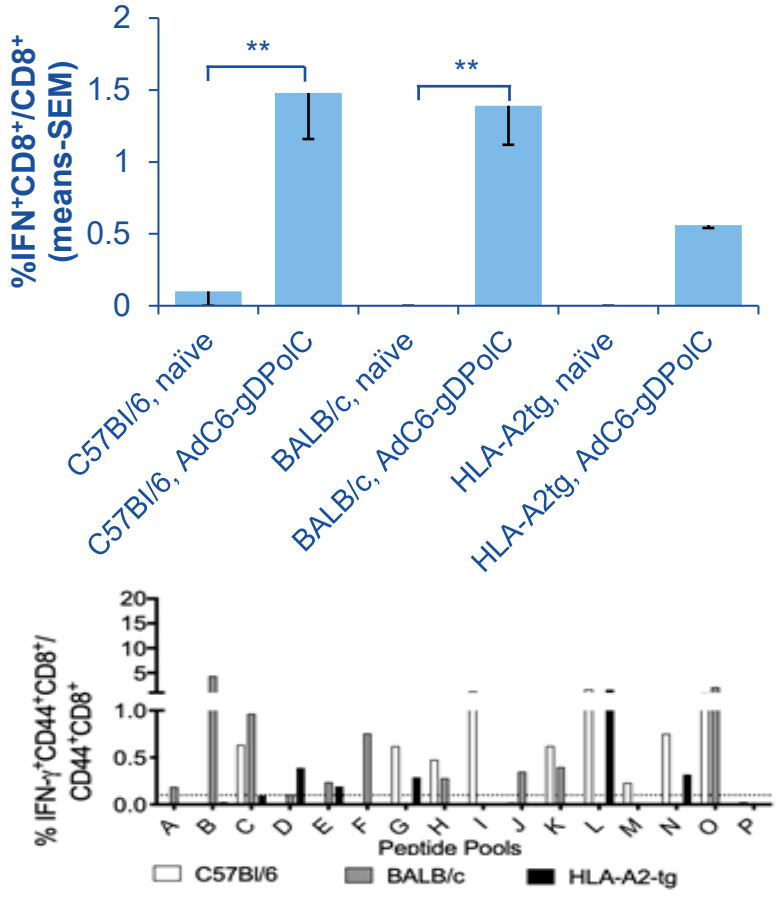
*AdC6 and AdC7 are heterologous chimpanzee adenoviral viral vectors of serotype 6 and 7.
ICS, intracellular cytokine staining; IFN, interferon; IV, intravenous; PolC, C terminus of HBV polymerase; PolN, N terminus of HBV polymerase;sd, subdominant; vg, viral genome; vp, virus particles.

Breadth of CD8+ T Cell Responses Observed in Several Mouse Strains

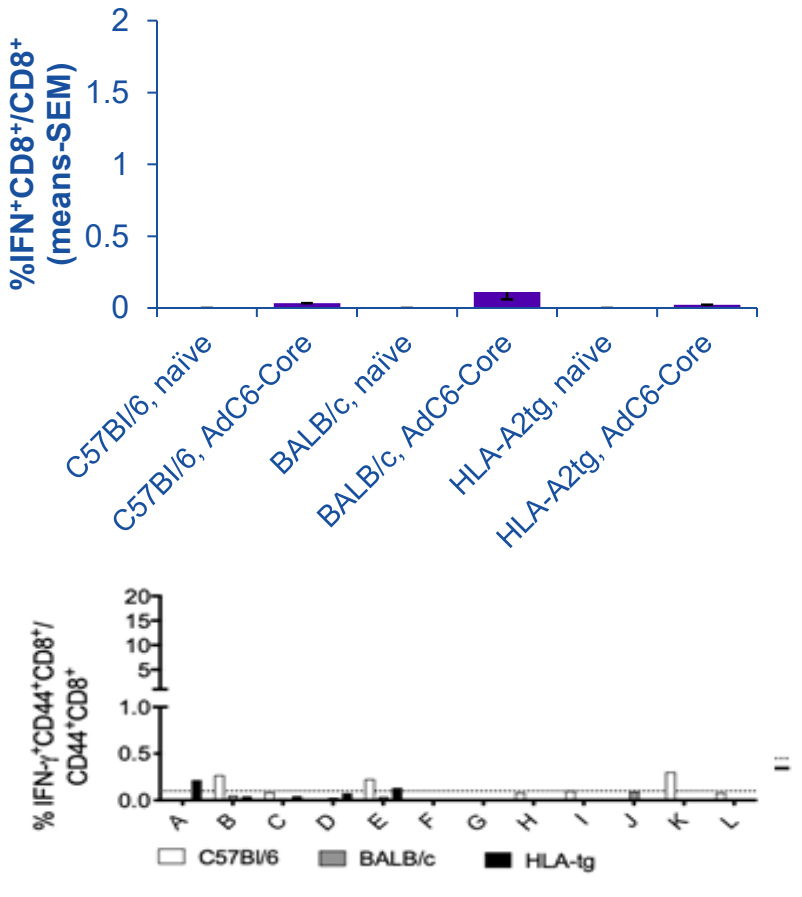
gDPolN



gDPolC



gDCore



HLA, human leukocyte antigen.
P-value between 0.001–0.01 ;**P-value between 0.0001-0.001 via ordinary one-way ANOVA.

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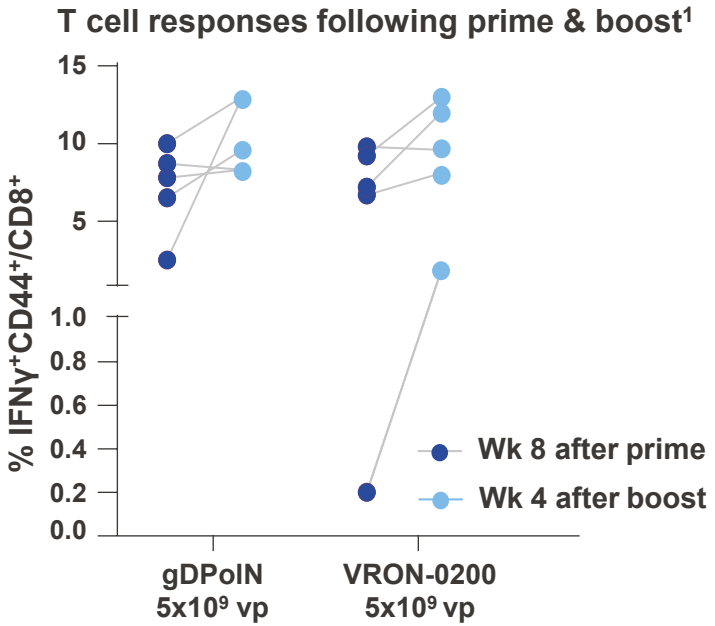
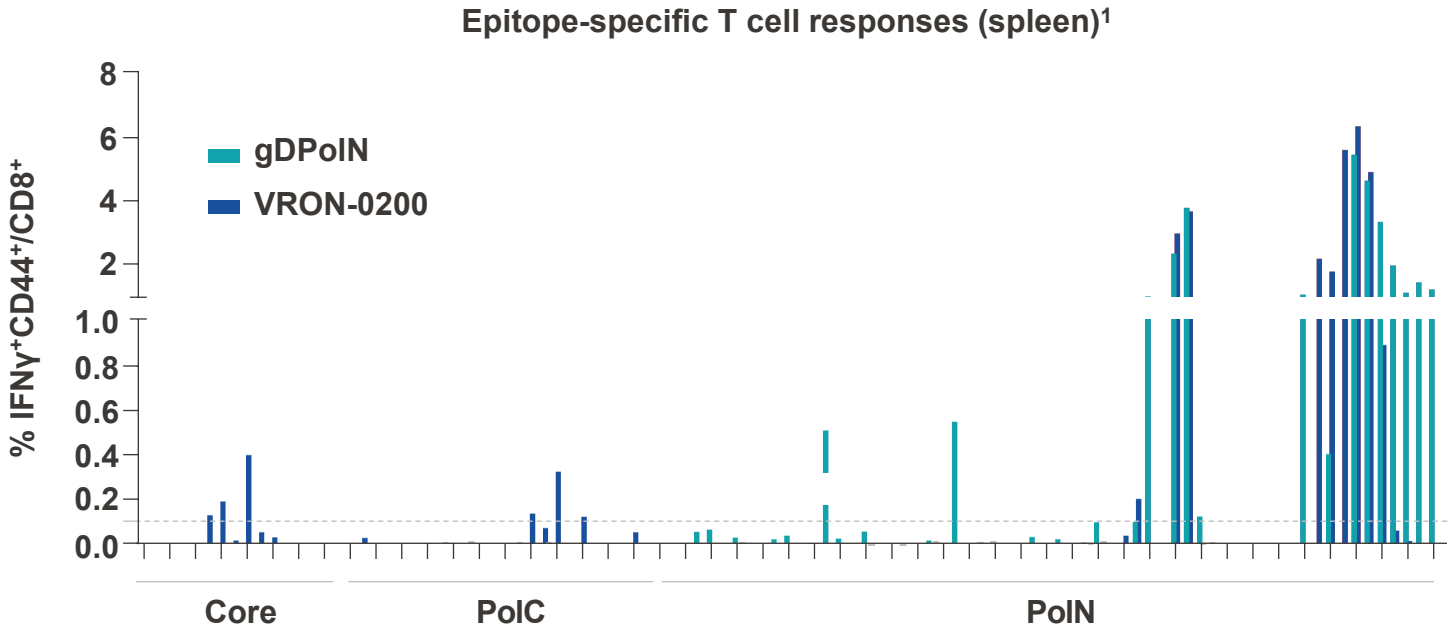
VRON-0200: Candidate Optimization

- Antigenic regions, with no immunity, within each target, were removed
- Remaining antigenic regions were combined, fused to gD (VRON-0200) and compared to gDPolN (most immunogenic region)

Similar Magnitude of Response



CD8+ T Cell Responses to Core & Polymerase



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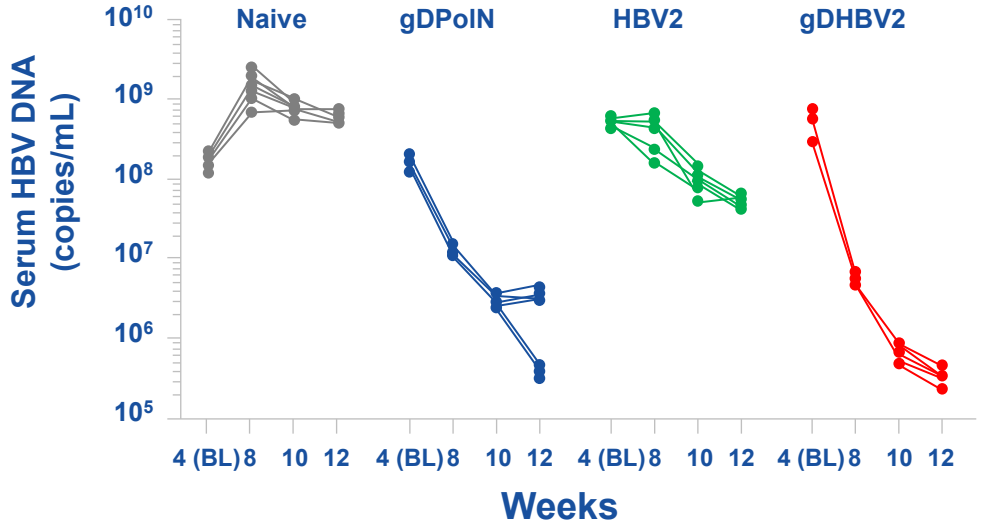
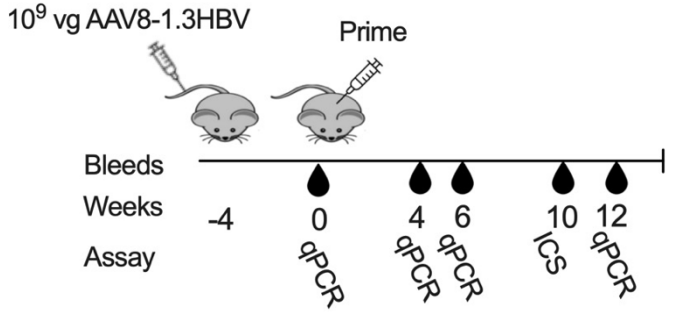
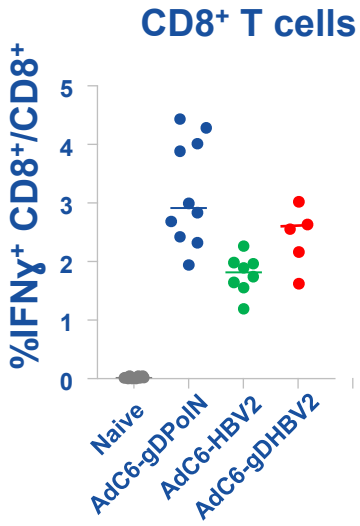
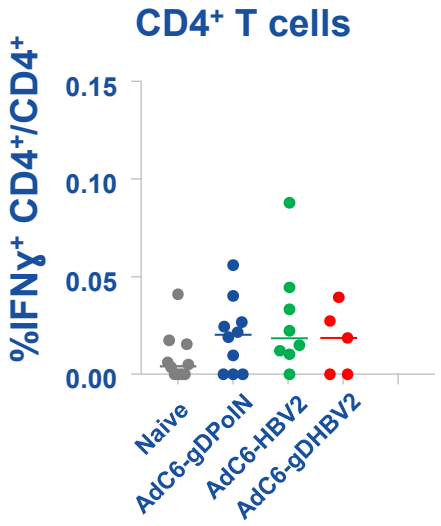
gD Enhances Antiviral Activity, which Correlates with CD8⁺ T Cell Responses

1 x 10^9 vg AAV8-1.3HBV









Correlations

	r-values		
	CD8	CD4	vgc
CD8		-0.020	-0.491
CD4	-0.020		0.157
vgc	-0.491	0.157	

	P-values		
	CD8	CD4	vgc
CD8		0.914	0.004
CD4	0.914		0.389
vgc	0.004	0.389	

Spearman Rank Correlation

*AAV8-1.3HBV mouse model (C57Bl/6 mice).
Hasanpourghadi M, et al. EASL 2021. Abstract OS-2478.

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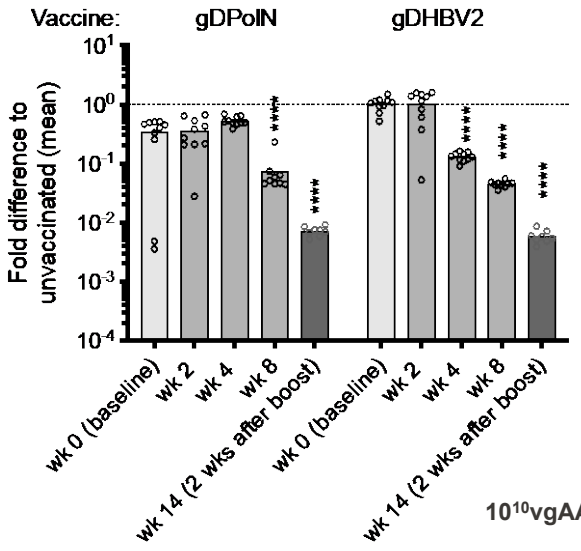
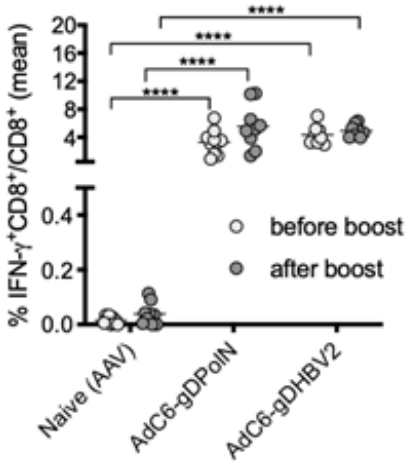
Impact of Increased AAV Doses on Viral Declines AAV8-1.3HBV: 10^{10} and 10^{11} vgc

$1x10^{10}$ vgc AAV8-1.3HBV

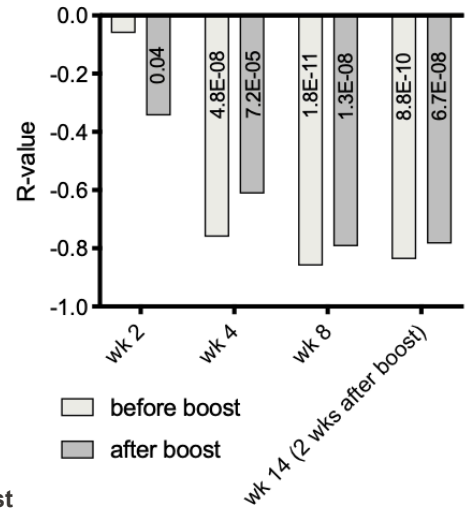
HBV DNA Viral Load Reductions

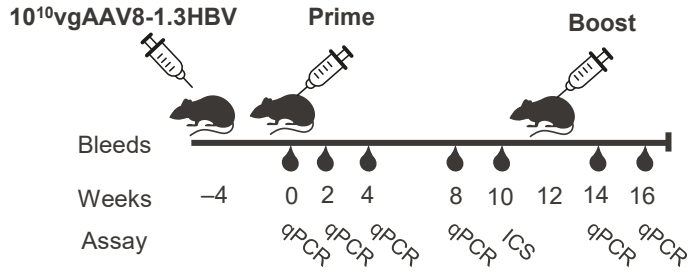


CD8⁺ T Cell Responses



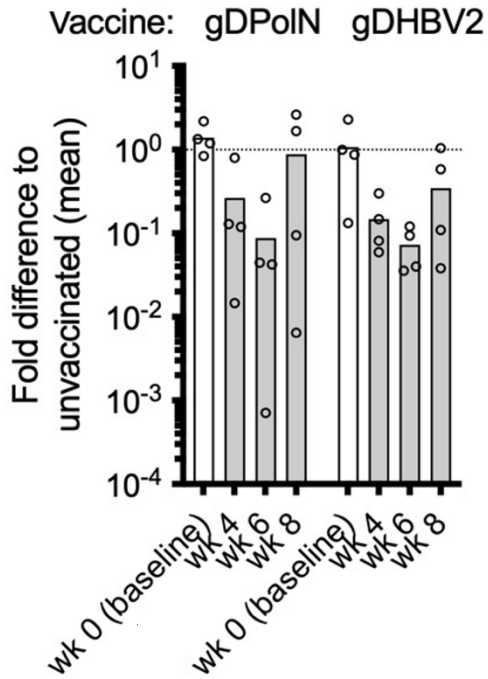
Correlations: CD8⁺ T Cells & Viral Load[a]





$1x10^{11}$ vgc AAV8-1.3HBV

HBV DNA Viral Load Reductions



[a]R values for correlation by Spearman for CD8+ T cells frequencies compared to viral genome copy numbers. Numbers within the bars reflect significant p-values.
****p<0.0001.

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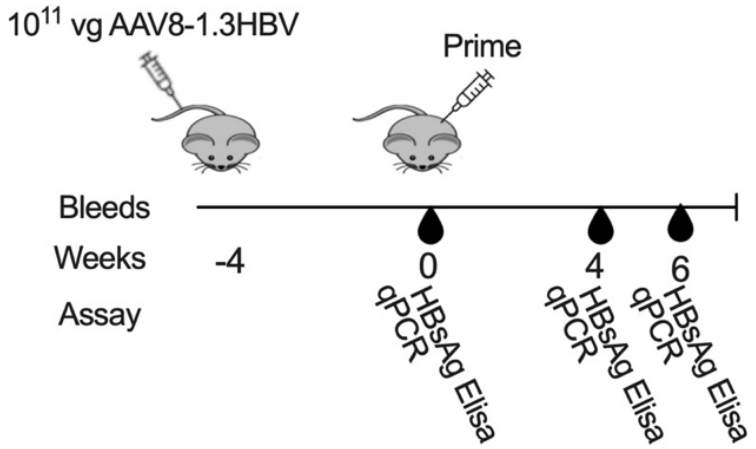
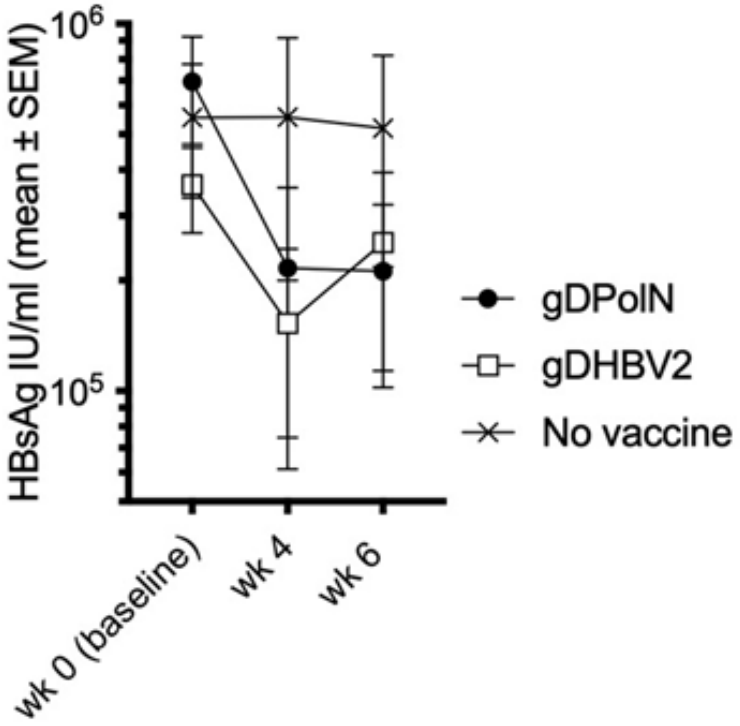
Vaccination Reduces S-antigen Levels Even at High AAV Doses and Without S in Vaccine

Experimental Outline

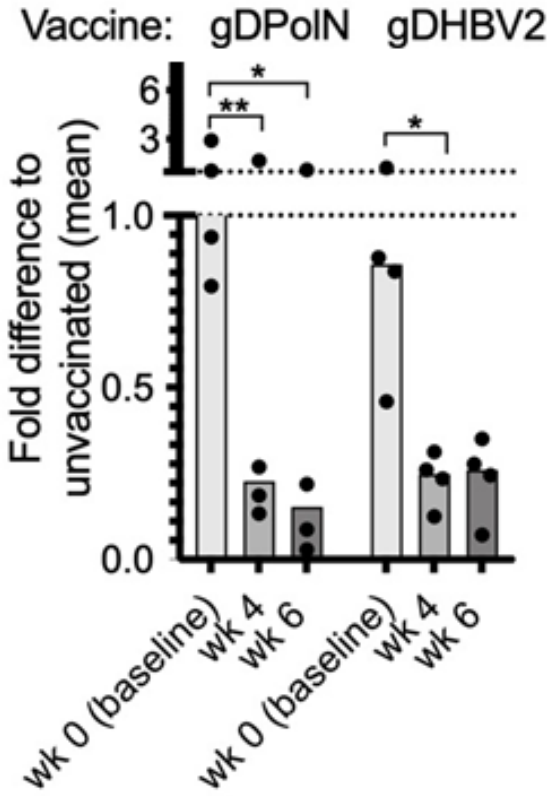


$1x10^{11}$ vgc AAV8-1.3HBV

HBsAg



HBsAg reduction



*p-value between 0.01–0.05; **p-value between 0.001–0.01.

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Conclusions

- **VRON-0200 vaccination**
  - Vaccination elicits potent and broad $CD8^+$ T cell responses to HBV core & polymerase
  - Vaccine-induced $CD8^+$ T cells traffic to the liver
  - Multi-log HBV DNA viral load declines after a single IM injection
    - gD required for optimal antiviral activity
    - Level of vaccine-induced viral declines depend on AAV challenge dose
    - Vaccine-induced $CD8^+$, but not $CD4^+$ T cell responses correlate with antiviral activity
    - S-antigen declines observed despite lack of S in the vaccine construct
- **A Phase 1b clinical study is planned (Q4 2022)**
  - Prime only and prime & boost regimens

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FOR MORE INFORMATION

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