VRON-0200:
A pan genotypic therapeutic HBV vaccine containing core and pol coupled with an intrinsic checkpoint inhibitor: Preclinical Summary

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Background
CD8+ T Cell Impairment and Chronic HBV Infection

- **CD8+ T cells become impaired during chronic HBV infections, resulting in loss of viral control**
- **Immune modulators & therapeutic vaccines for chronic HBV have shown limited clinical benefits[1–5]**
  - "Rescue" of T cells with PD-1 checkpoint blockade is limited by:
    - ✓ Irreversible epigenetic changes in most HBV-specific T cells
    - ✓ Serious "off target" side effects in an otherwise healthy population
- **Stimulation of naïve HBV-specific T cells by traditional therapeutic vaccines**
  - Likely ineffective as most T cells to immunodominant HBV-specific epitopes are already activated
  - Optimized vaccine approaches that induce a response of naïve T cells to *de novo* epitopes may be able to restore viral control

CD, cluster of differentiation; HBV, hepatitis B virus; PD-1, programmed cell death protein 1.

1. Boni C, et al. *Gastroenterology.* 2019;157:227-41; 2. Gane E, et al. *J Hepatol.* 2019;71:900-7; 3. Janssen H, et al. AASLD. 2020. Abstract 0829; 4. Zoulim F, et al. *Hum Vaccin Immunother.* 2020;16:388-399; 5. Jansen D, et al. *Clin Trans Immunology.* 2021;10:e1232. doi: 10.1002/cti2.1232.

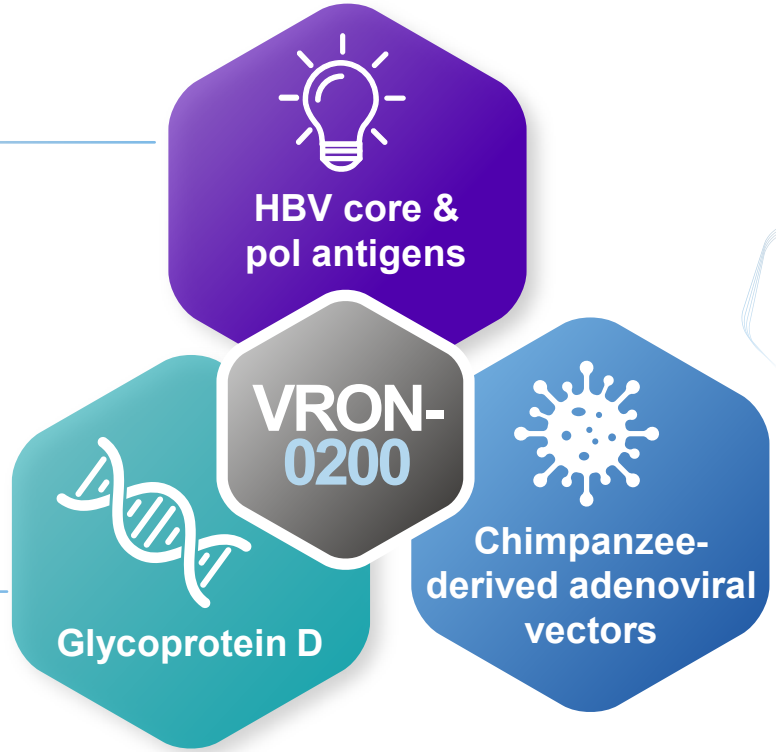
VRON-0200: A First-in-class Immunotherapy for Chronic HBV

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

HBV, hepatitis B virus; pol, polymerase.

VRON-0200: Antigen Selection

Goal: Functional cure of chronic HBV infection

- Expansion of HBV-specific CD8+ T cells induced by the viral infection
  - Limited by $CD8^+$ T cell exhaustion
- De novo stimulation of $CD8^+$ T cells to subdominant epitopes that were not induced by the infection
  - Affected by duration of disease and viral loads

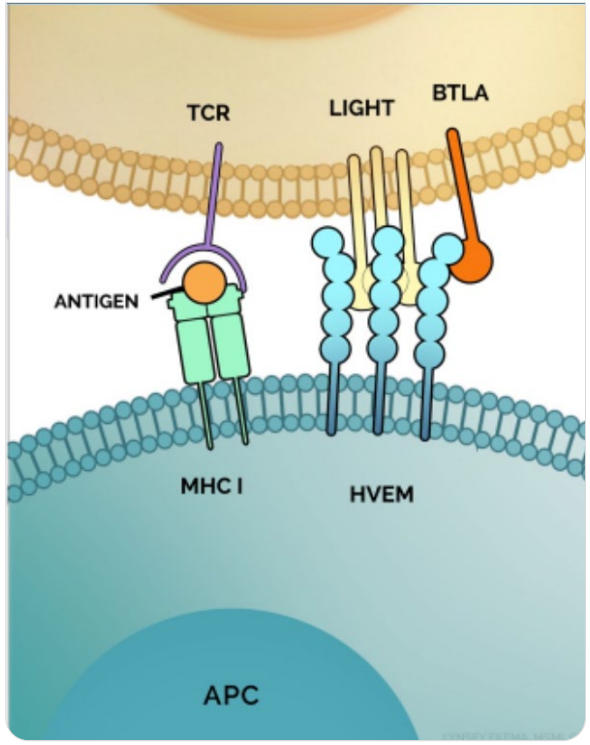
Core & Polymerase (Pol) [1-3]		Surface (env, S) [1-3]	
Produced at low levels throughout disease; T cells directed to core/pol are potentially more "rescuable"	✓	Secreted at high levels throughout course of disease; T cells directed to S have a low likelihood of being rescued	✗
Antigens directly involved with viral replication	✓	Immune decoy; not directly involved in viral replication/ cccDNA proliferation	✗
T cells to core & pol associated with:		**T cells to S:**	
• Prevention of viral breakthrough/flares upon NRTI discontinuation	✓	• High variability across genotypes	✗
• Disease clearance in chronic HBV-infected patients	✓	• Absent in chronic HBV-infected patients	✗
INCLUDED		**NOT INCLUDED**	

1. Le Bert, N et al. Gastroenterology 2020;159;2:652-664; 2. Rivino L., et al. J Clin Invest 2018;128(2):668-681; 3. Cornberg M, et al. J Hepatol 2017;66:398-411.
pol, polymerase; NF, no flare; F, flare; NRTI, nucleos(t)ide reverse transcriptase inhibitor.

Herpes Simplex Virus Glycoprotein D
The Genetically Encoded Checkpoint Inhibitor Adjuvant in VRON-0200

VIRION THERAPEUTICS

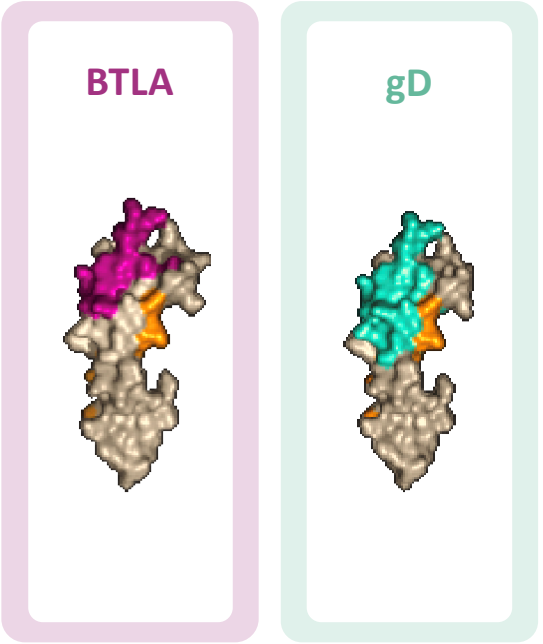
HVEM Complex in Regulating T cell Activation



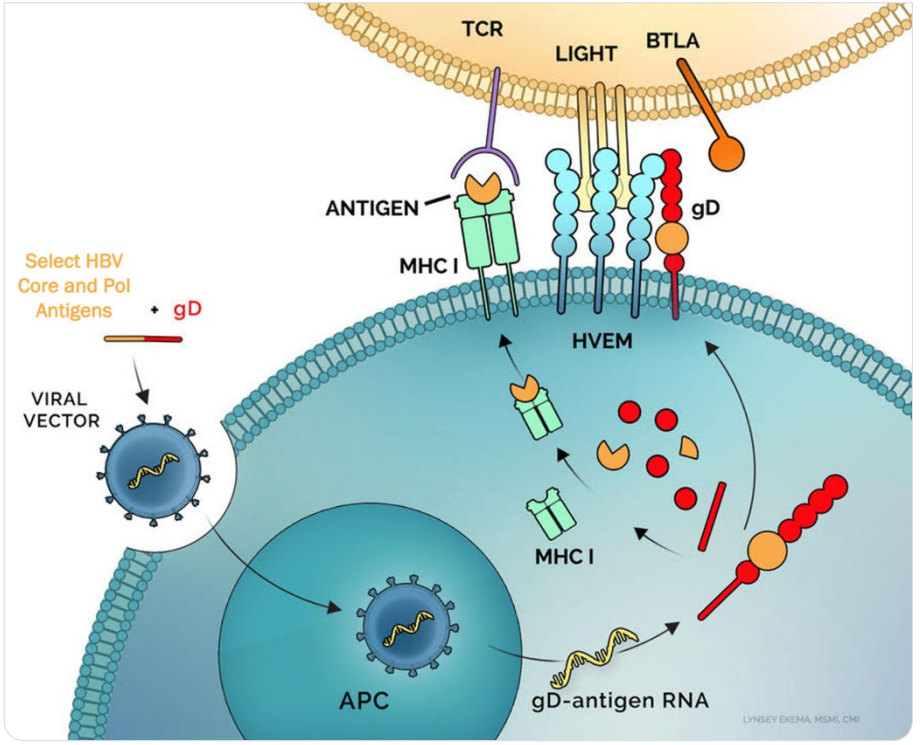
BTLA-HVEM – inhibition
LIGHT-HVEM – stimulation
BTLA-HVEM-LIGHT - inhibition

gD & BTLA Share HVEM Binding Site

HVEM crystal structure[1]



gD BTLA-HVEM Blockade Enhances and Broadens T cell Activation



APC, antigen presenting cell; BTLA, B- and T-lymphocyte attenuator; HVEM, herpes virus entry mediator; pol, polymerase; TCR, T cell receptor.

1. 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

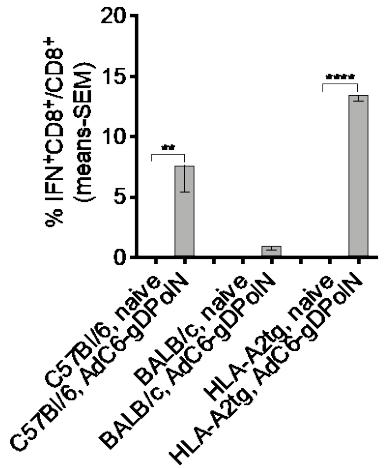
Vaccine vectors – Single IM dose of 1 x 10^{10} vp

- Administered 4 weeks after AAV8-1.3HBV injection

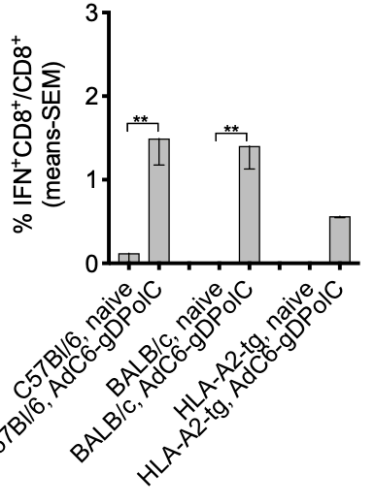
*AdC6 and AdC7 are heterologous chimpanzee adenoviral viral vectors of serotype 6 and 7.
^gDHBVsd also referred to as AdC6-gDHBV3 and AdC7-gDHBV3 when combined with AdC6 and AdC7 vectors, respectively.
ICS, intracellular cytokine staining; IV, intravenous; sd, subdominant; vg, viral genome; vp, virus particles.

Breadth of CD8⁺ T Cell Responses in Several Mouse Strains

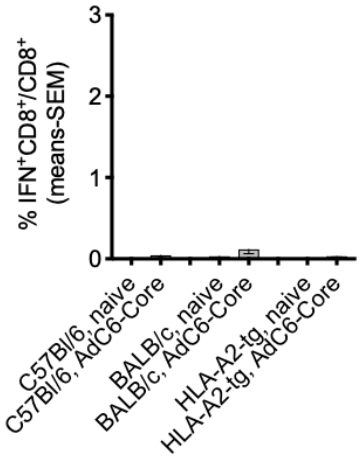
gDPolN

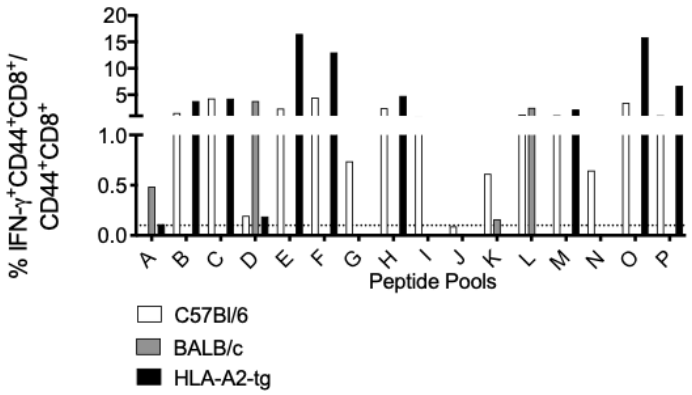


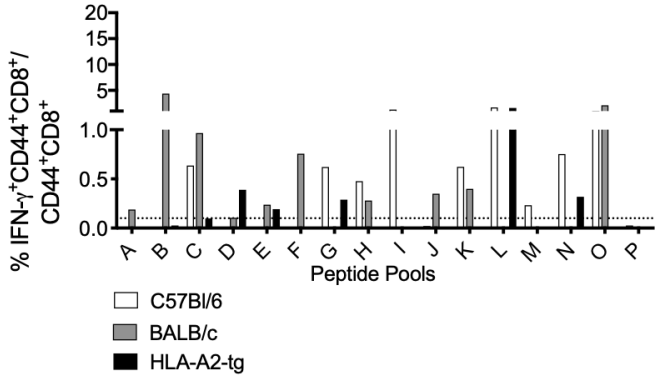
gDPolC

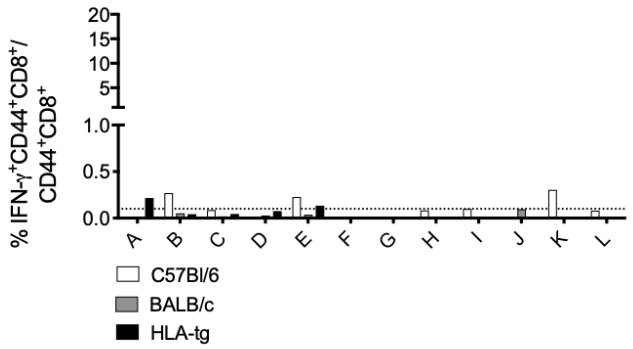


gDCore









** *P*-value between 0.001–0.01 ; **** *P*-value between 0.0001-0.001 via ordinary one-way ANOVA.

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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