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

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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
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

<table>
<thead>
<tr>
<th>Core &amp; Polymerase (Pol) 1-3</th>
<th>Surface (env, S) 1-3</th>
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</thead>
<tbody>
<tr>
<td>Produced at low levels throughout disease; T cells directed to core/pol are potentially more “rescuable”</td>
<td>Secreted at high levels throughout course of disease; T cells directed to S have a low likelihood of being rescued</td>
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<td>Antigens directly involved with viral replication</td>
<td>Immune decoy; not directly involved in viral replication/cccDNA proliferation</td>
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<td><strong>T cells to core &amp; pol associated with:</strong></td>
<td></td>
</tr>
<tr>
<td>• Prevention of viral breakthrough/flares upon NRTI discontinuation</td>
<td>✓</td>
</tr>
<tr>
<td>• Disease clearance in chronic HBV-infected patients</td>
<td>✓</td>
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</tbody>
</table>

**INCLUDED**
- T cells to core & pol associated with:
  - Prevention of viral breakthrough/flares upon NRTI discontinuation
  - Disease clearance in chronic HBV-infected patients

**NOT INCLUDED**
- T cells to S:
  - High variability across genotypes
  - Absent in chronic HBV-infected patients

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

HVEM Complex in Regulating T cell Activation

HVEM crystal structure<sup>1</sup>

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

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

Methods
Combination HBV PolN, PolC & Core Studies

Vectors investigated*

AdC(6/7)-gDPoIN, -gDPoIC, -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 10⁹–1 x 10¹¹ vg IV

Vaccine vectors – Single IM dose of 1 x 10¹⁰ 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-gDHVB3 and AdC7-gDHVB3 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

**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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