Targeted Immunotherapy for Chronic Hepatitis B

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Conflict of interest

- Ventzi Vassilev is an employee of the GSK group of companies.
- This work was sponsored by GlaxoSmithKline Biologicals SA.
Chronic HBV infections represent major and global cause of morbidity and mortality\(^4\)

- 296 million people living with HBV\(^4\)
- 1.25 million new cases in 2019\(^4\)
- 20% of patients with chronic HBV develop cirrhosis and have a 1 in 20 chance of developing HCC\(^1,2\)
- ~60% of hepatocellular carcinoma (HCC) worldwide are caused by HBV\(^3,5\)
- 820,000 worldwide deaths attributed to HBV, majority due to HCC and cirrhosis (~0.3% of chronic cases)\(^4\)

Chronic Hepatitis B is a complex global public health challenge

1. [https://www.nature.com/articles/s41598-017-12005-2](https://www.nature.com/articles/s41598-017-12005-2)
2. [https://www.nhs.uk/conditions/hepatitis-b/complications/](https://www.nhs.uk/conditions/hepatitis-b/complications/)
3. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097640/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097640/)
GSK Hepatology Heritage

Pharmaceuticals
- **1989**: Hepatitis B Vaccine (Recombinant)
  - For children + adults
  - US Approval: 1989
- **1992**: Azathioprine
  - EU Approval: 1992
  - For autoimmune chronic hepatitis and to enhance survival of hepatic transplants
- **1995**: Lamivudine
  - US Approval: 1995
  - EU Approval: 1999
  - For Adults with Chronic Hepatitis B
- **1999**: Lamivudine
- **2001**: Combined hepatitis A and hepatitis B (Recombinant) vaccine
- **2002**: Hepatitis A (Inactivated) Hepatitis B (rDNA)Vaccine (adjuvanted, adsorbed)
- **2005**: Hepatitis B (rDNA)Vaccine (adjuvanted, adsorbed)
- **2012**: Etilomopag
  - US Approval: 2012
  - For thrombocytopenia in PEG-IFN treated patients with chronic hepatitis C

Vaccines
- **1989**: Hepatitis B Vaccine (Recombinant)
  - For children + adults
  - US Approval: 1989
- **1992**: Hepatitis A Vaccine (Inactivated)
  - For children + adults
  - US Approval: 1995
- **1999**: Combined hepatitis A and hepatitis B (Recombinant) vaccine
- **2001**: For adults
  - US Approval: 2001
- **2002**: For children + adults
  - EU Approval: 2002
- **2005**: For children + adults
  - EU Approval: 2005

The dates of licensure/launch may differ per country.
CHB is controlled and resolved through immune mechanisms
Importance of T-cell mediated control

- Viral clearance after acute HBV infection is associated with broad, robust CD4+ and CD8+ T cell response and seroconversion\(^1\)
- HBV is susceptible to immune control after chronicity is established\(^1,6\)
  - HBV cure is underlined with successful long term immune control
  - Strong inverse correlation between HBV-specific functional T-cells and control/cure/suppression of viremia
- However, an insufficient T-cell response to HBV antigens is characteristic of CHB and limits durable viral control and clearance\(^2,3\)
- T-cell exhaustion is a major pathway mediating an impaired response\(^2\)
- CHB patients who recover spontaneously or after interferon-alpha treatment have T-cell responses similar to those of acute HBV patients\(^4\)
- Resolution of chronic Hepatitis B and anti-HBs seroconversion in humans by adoptive (bone marrow) transfer of T-cell immunity\(^5\)

\(^1\)Thimme et al, J. Virol. 2003, 77, 68–76
\(^2\)Bertoletti et al, Gut, 2012, 61:1754
\(^3\)Ye et al, Cell Death Disease, 2015, 6(3):e1694
\(^4\)Rehermann et al, JCI, 1996, 97:1655
\(^5\)Lau et al, Gastroenterology, 2002, 122:614
\(^6\)Yang et al, Gene Therapy, 2006, 13:1110

Adapted from Ye et al., CDD, 2015, 6(3):21694
Immunotherapy for CHB: CD8 T-cell activation

ChAd priming

ChAd155-hli-HBV
(Prime)

Adults with chronic HBV infection
(under NA treatment >24 months)

ChAd155-hli-HBV

HBC-2A°-HBs (adw strain)
° 2A self cleavage peptide
Immunotherapy for CHB: CD8 T-cell activation

MVA boosting

ChAd155-hIi-HBV (Prime)  MVA-HBV (Boost)

Adults with chronic HBV infection (under NA treatment >24 months)
Heterologous prime/boost regimen increased T cell response in humans

Clinical data from HCV-004 study

The vaccination strategy based to use ChAd3 as primer and a modified vaccinia Ankara MVA as booster encoding for HCV NS3-NS5b polyprotein induced high polyfunctional CD4+ and CD8+ specific T cells.
Immunotherapy for CHB: CD8 T-cell activation

Genetic adjuvant

ChAd155-hli-HBV (Prime)  MVA-HBV (Boost)

Adults with chronic HBV infection (under NA treatment >24 months)

ChAd155-hli-HBV

hli: fusion to MHC class II invariant chain (hli) to enhance CD8 T cell response (Borghese, 2011), (Capone, 2014).
Inclusion of hli sequence in vaccine significantly improved magnitude HCV-specific T cell responses in humans

Esposito, Sci Transl Med. 2020 Jun 17;12(548)

**Inclusion of Invariant chain in a viral vaccine induces a greatest and unpresented T cell response.**

**Significantly stronger T cell response compared to ChAd3-NS/MVA-NS vaccination regimen.**
Targeted immunotherapy for CHB: humoral and CD4 T-cell activation

ChAd155-hIi-HBV
(Prime)
MVA-HBV
(Boost)
Rec proteins
(HBc + HBs)
Adjuvant
(AS01)

Sequentially or co-administered

Adults with chronic HBV infection
(under NA treatment >24 months)
Targeted immunotherapy for CHB

ChAd155-hi-HBV (Prime) + MVA-HBV (Boost)

Rec proteins (HBc + HBs) + Adjuvant (AS01)

Sequentially or co-administered

Adults with chronic HBV infection (under NA treatment >24 months)

Functional HBc/HBs-CD4+ and CD8+ T cells + Potent humoral responses

CHB functional cure
Head-to-head comparison of AS in humans

Naive subjects, HBsAg as a model

<table>
<thead>
<tr>
<th>Adjuvants</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS01</td>
<td>MPL, QS21 in liposome</td>
</tr>
<tr>
<td>AS03</td>
<td>o/w emulsion containing α-tocopherol</td>
</tr>
<tr>
<td>AS04</td>
<td>MPL adsorbed on Alum (AlPO4)</td>
</tr>
<tr>
<td>Alum</td>
<td>Al(OH)3 (Engerix)</td>
</tr>
</tbody>
</table>

rHBs Ag
Mulder, 2012

AS01/03/04 is a GSK proprietary adjuvant system

Primary
Vaccine doses
Time (days)
0+3–6h 0 1 14
30+3–6h 30 31 33

Healthy HBs-naive Adults
(N=713)
NCT00805389

Secondary
HBs-specific CD4 T cells and Abs Cytokines and haematology/CRP gene expression

Head-to-head comparison of AS in humans
Abs titers and CD4 T cells

Naïve setting (HBS: ECR-002)

Budroni et al, npj Vaccines (2021) 6:78; https://doi.org/10.1038/s41541-021-00337-0
Selective increase of inflammatory cytokines and chemokines in serum induced by AS01B-adjuvanted vaccine

Burny et al. 2021, Vaccine 37:2004
Targeted immunotherapy for CHB

Adults with chronic HBV infection (under NA treatment >24 months) + Rec proteins (HBc + HBs) + Adjuvant (AS01) + Humoral responses + Innate activation

Sequentially or co-administered

Functional HBc/HBs-CD4+ and CD8+ T cells

CHB functional cure
### HLA.A2 mouse model of chronic hepatitis B virus infection

#### - study design -

**HBV chronic infection mouse model**

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Day 0</th>
<th>Day 30</th>
<th>Day 58</th>
<th>Day 72</th>
<th>Day 86</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/M/P/P HBV+</td>
<td>21</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
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<tr>
<td>AAV2/8-HBV</td>
<td></td>
<td>ChAd155-hIi-HBV</td>
<td>MVA-HBV</td>
<td>MVA-HBV</td>
<td>MVA-HBV</td>
<td>MVA-HBV</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP/MP/MP/MP HBV+</td>
<td>21</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
</tr>
<tr>
<td>AAV2/8-HBV</td>
<td></td>
<td>ChAd155-hIi-HBV + Hbc-HBs /AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
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<tr>
<td>No Vaccine HBV+</td>
<td>21</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
</tr>
<tr>
<td>AAV2/8-HBV</td>
<td></td>
<td>NaCl</td>
<td>NaCl</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP/MP/MP/MP Healthy mice</td>
<td>9</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
<td>HBV+</td>
</tr>
<tr>
<td>AAV2/8-HBV</td>
<td></td>
<td>ChAd155-hIi-HBV + Hbc-HBs /AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
<td>MVA-HBV + Hbc-HBs/AS01</td>
</tr>
</tbody>
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**Ethical statement**

Animal husbandry and experiment were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GlaxoSmithKline Biologicals’ policy on the care, welfare and treatment of animals, in GSK animal facilities located in Rixensart, Belgium (AAALAC accredited). The ethical protocol was approved by the local GSK ethical committee.

HBV mouse model image: (Hwang et al, Lab Anim Res 2018:34(3), 85-91)

Chronic hepatitis B infection model (Don et al, J Virol 2013)
The immune tolerance for HBc-specific CD8\(^+\) T cells and HBs-specific antibody responses have been successfully overcome in AAV-HBV transduced HLA.A2/DR1 mice although levels remain lower than in non-infected mice.

The co-administration vaccine regimen (viral vectors together with adjuvanted proteins) induced higher HBC/HBs-specific antibody and T cell responses compared to the sequential regimen.
The vaccine co-administration regimen induced similar levels of HBs-specific CD4+ T cell responses as those detected in the vaccinated healthy mice group.

Despite the induced HBV specific immunity (notably HBC-specific CD8+ T cells responses) no increase in AST/ALT serum levels was detected → no sign of liver cytotoxicity was observed.

No decrease in circulating HBs antigen titers was detected after vaccination.
Clinical Phase I/II Proof-of-Principle (FTIH) clinical trial
https://clinicaltrials.gov/ct2/show/NCT03866187

- Safety
- Immunogenicity
- Efficacy of vaccine regimens

Loss of HBsAg and or ≥ 10-fold decrease of HBsAg in serum (≥15% patients)
Phase I/II POP efficacy TH HBV VV-001 study (ongoing)

CHB patients (18-65 years old) well controlled under NA therapy (>24m), HBeAg negative

Key treatment regimens assessed

- **Sequential regimen**: ChAd prime+ MVA boost + 2 doses of adjuvanted proteins
- Adjuvanted proteins only (4 doses)
- Sequential ChAd prime+ MVA boost, no adjuvanted proteins

- **Co-administration regimen**: prime with ChAd and adjuvanted proteins + 3 booster doses of MVA with adjuvanted proteins
- Co-administration regimen: prime with ChAd and adjuvanted proteins + booster with MVA and adjuvanted proteins

Follow-up ~72 weeks
Achieving high CHB *Functional Cure* response rates is likely to be achieved through combined mechanisms of action.

Maximizing prospects for achieving CURE

- Inhibition of Viral Replication
- Antigen Reduction
- Immune Stimulation
Summary

- GSK has long-standing heritage for prevention and treatment of hepatic infections

- GSK’s strategy leverages the use of potent technological platforms:
  - Heterologous prime-boost regimens consisting of viral vectors and adjuvanted recombinant proteins, genetic adjuvantation

- The GSK’s targeted immunotherapy is differentiated strategy aiming at induction of immune profile capable of control and resolution of the CHB infection
  - Simultaneous activation of the cellular, humoral and innate arms of the immune system
  - Ph2 clinical study is progressing well and interim immunogenicity data will be reported soon

- GSK’s internal portfolio of CHB assets has a potential to deliver enhanced levels of functional cure through combinations
  - Ph2 combination therapy studies are planned