Targeted Immunotherapy for Chronic Hepatitis B

Ventzi Vassilev

Program Development Lead, GSK Vaccines

Hep B foundation webinar, 18th Jan 2022

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

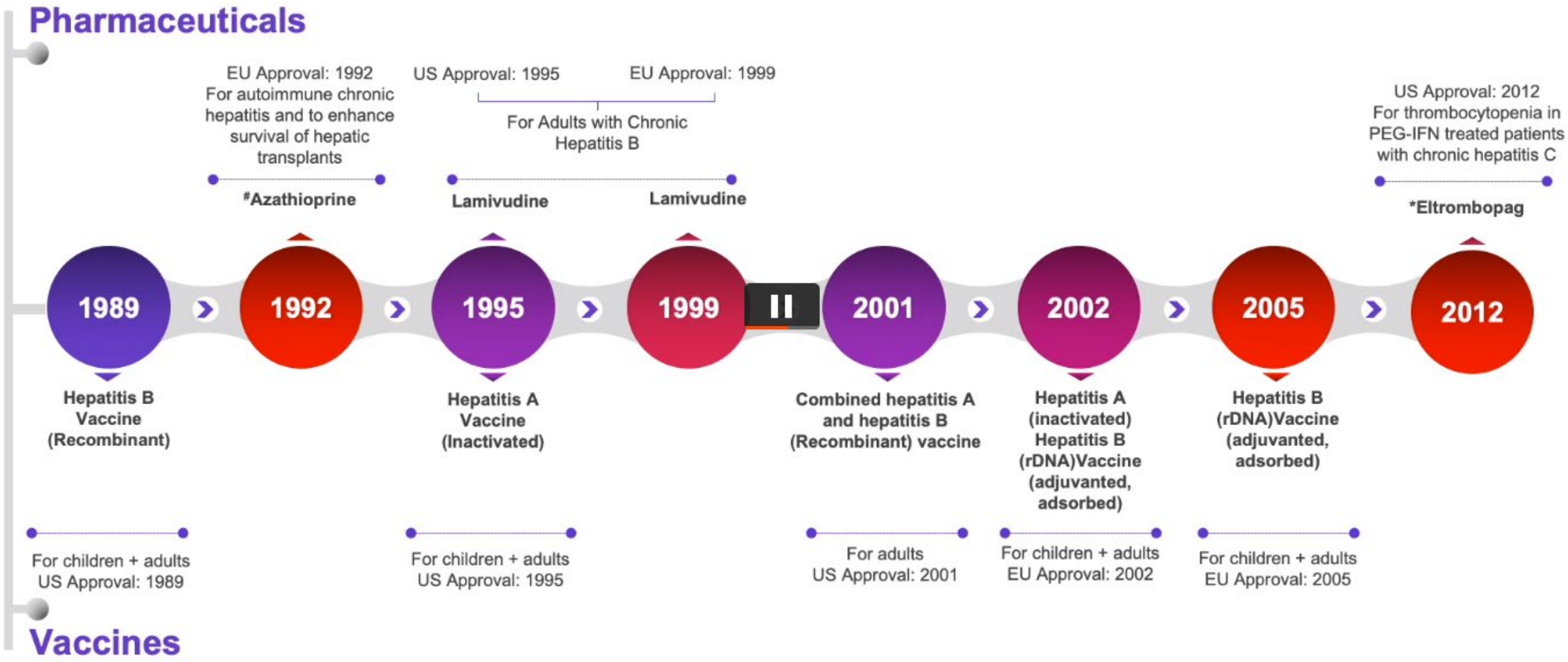
worldwide deaths attributed to HBV, majority due to HCC and cirrhosis

(~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
[2] https://www.nhs.uk/conditions/hepatitis-b/complications/
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097640/
[4] WHO 2019 Global Hepatitis Report (2017)
[5] Yim, HJ. & Lok, A. (2006)

GSK Hepatology Heritage

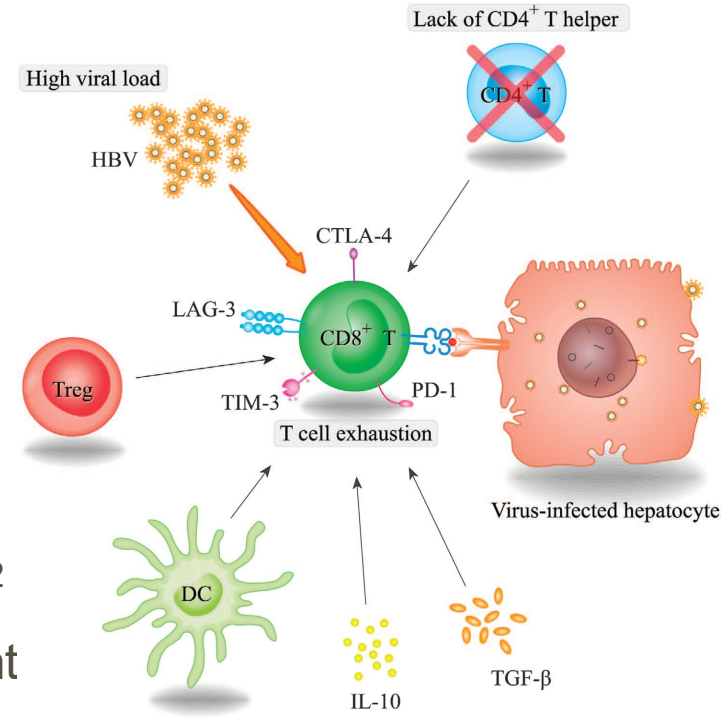


The dates of licensure/launch may differ per country.

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]

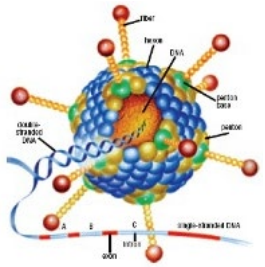


Adapted from Ye et al., CDD, 2015, 6(3):21694

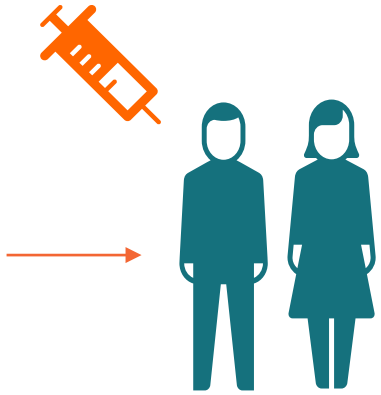
[1]Thimme et al, *J. Virol. 2003,* 77, 68–76
[2]Bertoletti et al, Gut, 2012, 61:1754
[3]Ye at al, Cell Death Disease, 2015, 6(3):e1694
[4]Rehermann et al, JCI, 1996, 97:1655
[5]Lau et al, Gastroenterology, 2002, 122:614
[6]Yang et al, Gene Therapy, 2006, 13:1110

Immunotherapy for CHB: CD8 T-cell activation

ChAd priming



ChAd155-hli-HBV
(Prime)



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

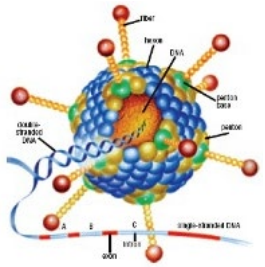
ChAd155-hli-HBV

HBc-2A°-**HBs** (*adw strain*)

° 2A self cleavage peptide

Immunotherapy for CHB: CD8 T-cell activation

MVA boosting



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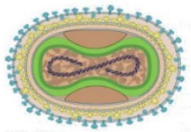
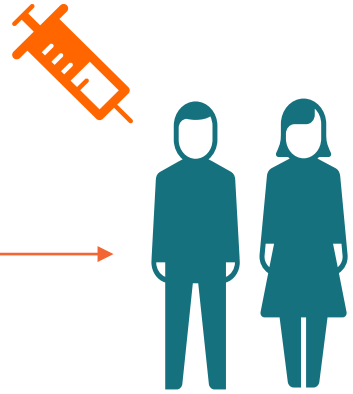


MVA-HBV
(Boost)



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

Heterologous prime/boost regimen increased T cell response in humans

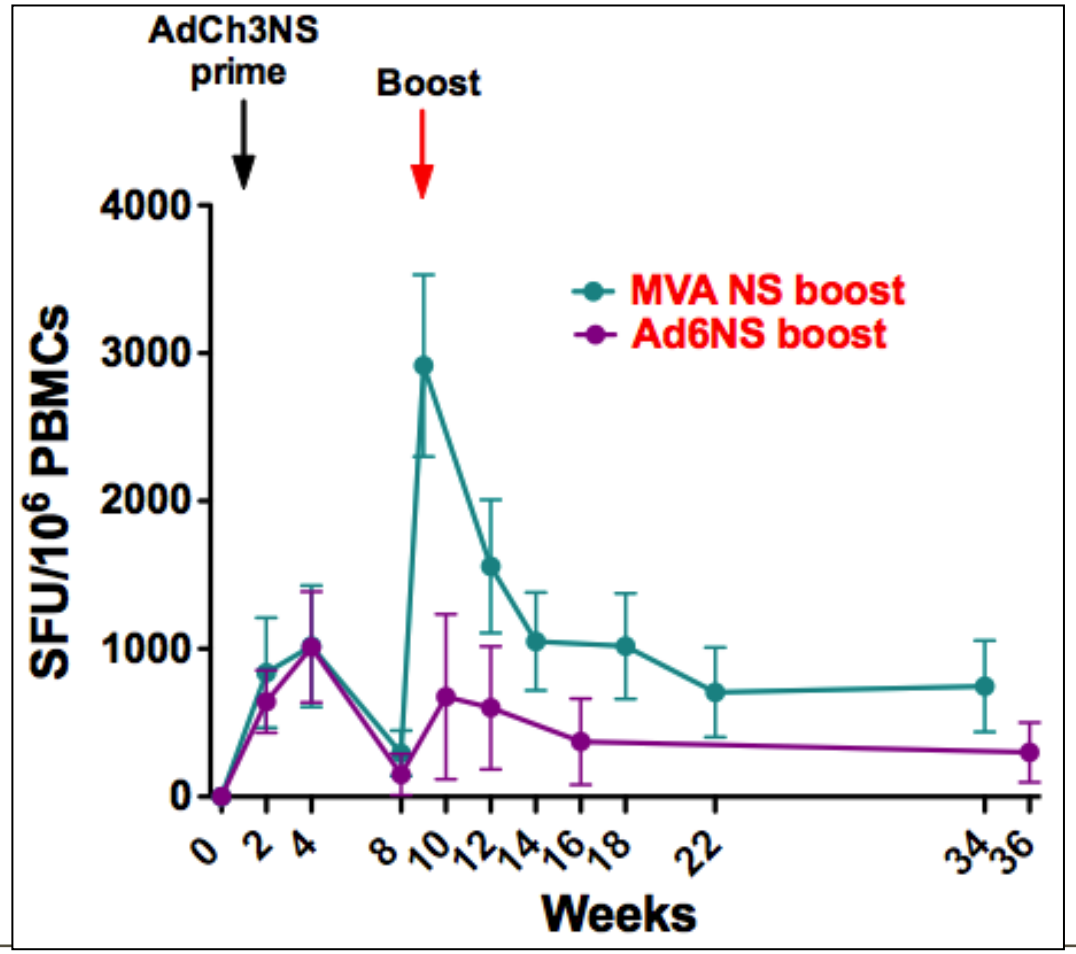
Clinical data from HCV-004 study

ChAd3-NS PRIME

MVA-NS BOOST

NS= Nonstructural region of HCV virus

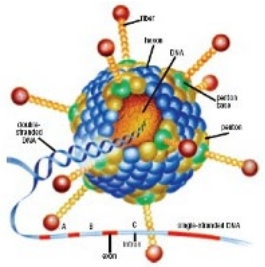
Swadling et al.,2014



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



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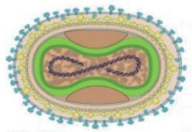

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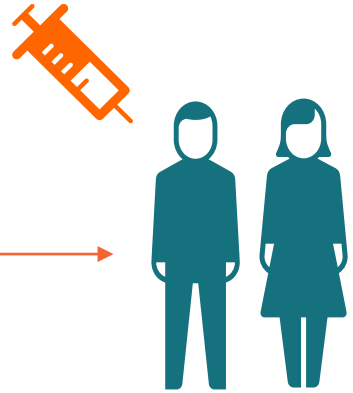

Adults with chronic HBV infection
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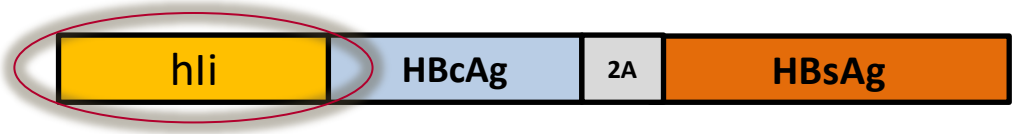


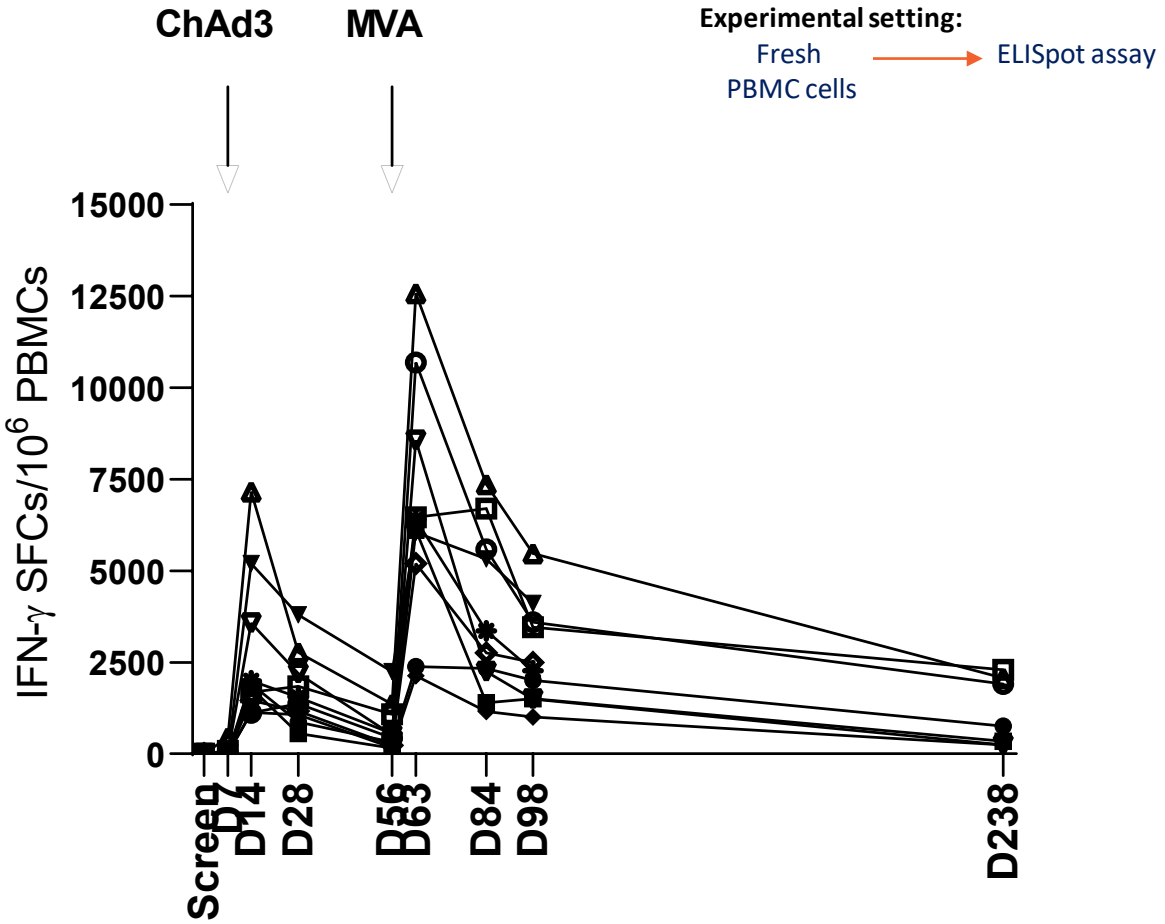
ChAd155-hli-HBV

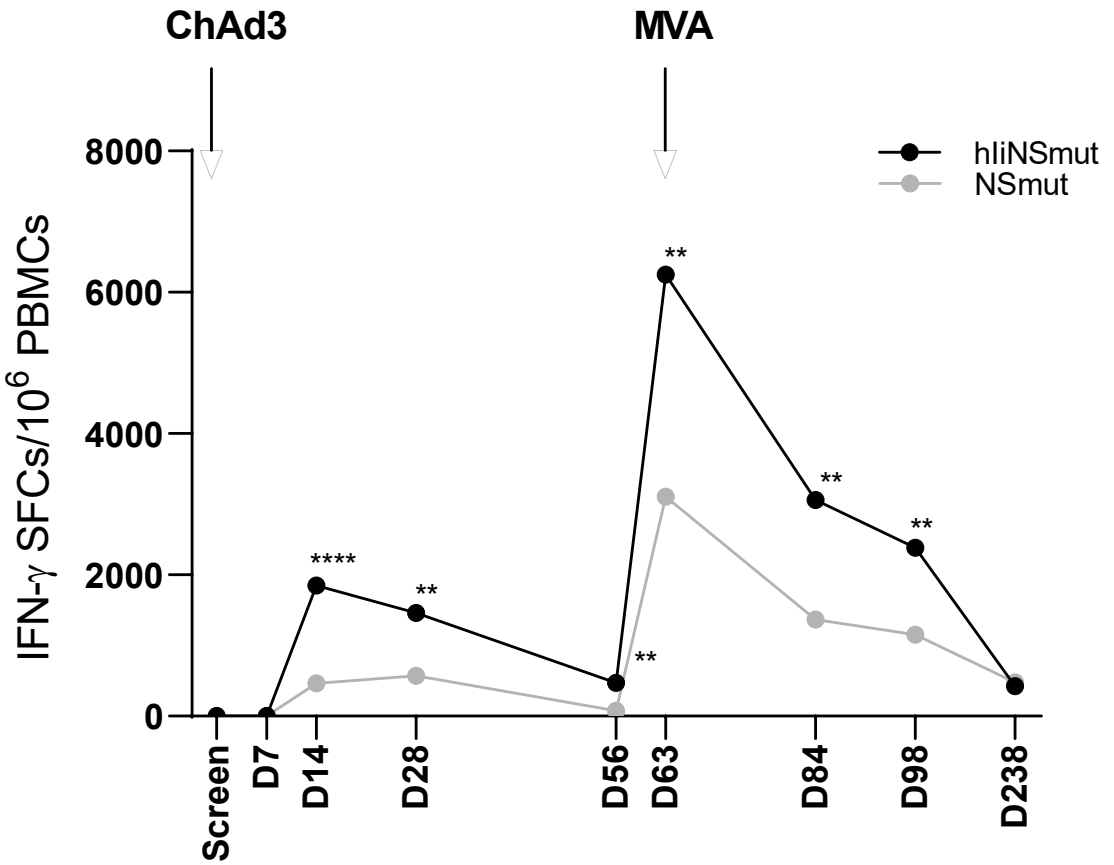
hli: fusion to MHC class II invariant chain (hli) to enhance CD8 T cell response

(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)

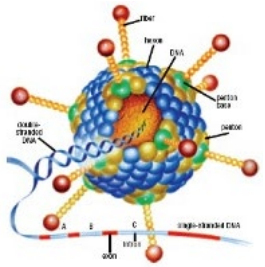




Inclusion of Invariant chain in a viral vaccine induces a greatest and unpresented T cell response.

Significantly stronger T cell response compared to ChAd3-NS/MVA-NS vaccination regimen.

Targeted immunotherapy for CHB: humoral and CD4 T-cell activation



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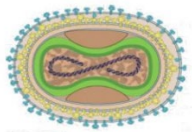


MVA-HBV
(Boost)

+

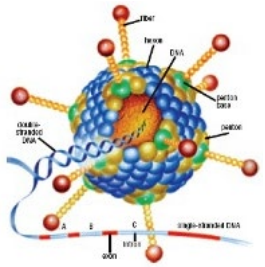
Rec proteins (HBc + HBs)

Adjuvant (AS01)

Sequentially or co-administered

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

Targeted immunotherapy for CHB



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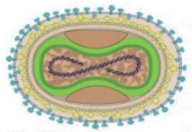

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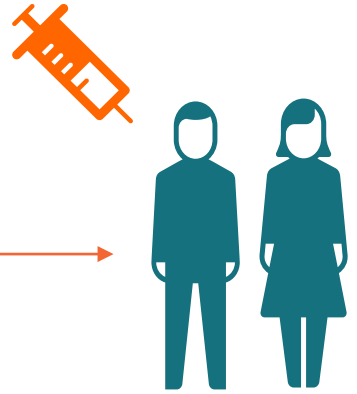


Adults with chronic HBV infection
(under NA treatment >24 months)

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

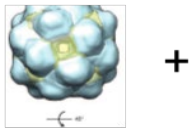
+

Potent humoral responses

CHB functional cure

Head-to-head comparison of AS in humans

Naive subjects, HBsAg as a model



rHBs Ag
Mulder, 2012

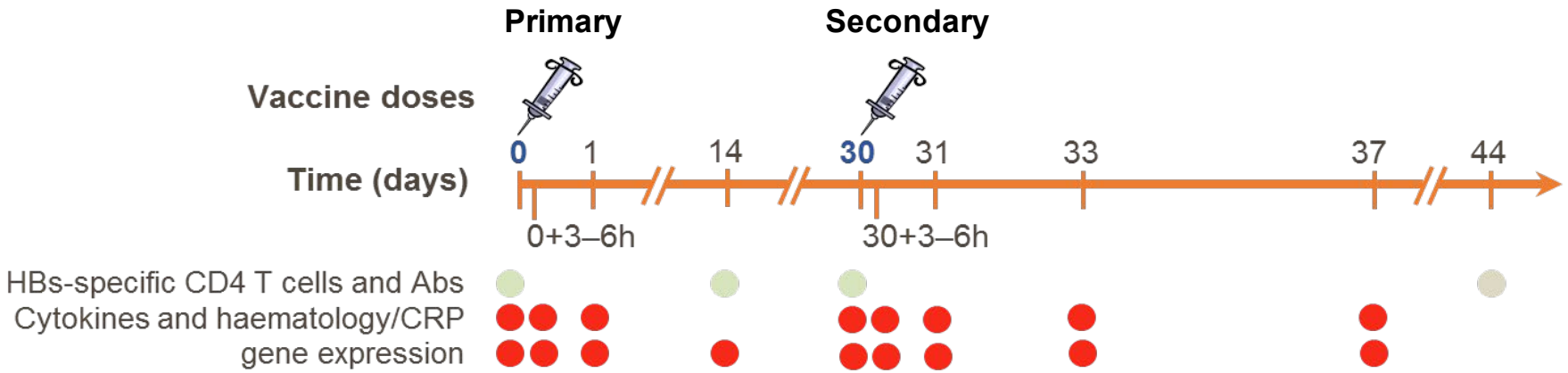
+

Adjuvants	Composition
AS01	**MPL, QS21** in liposome
AS03	**o/w emulsion** containing α-tocopherol
AS04	**MPL** adsorbed on Alum (AlPO4)
Alum	Al(OH)3 (Engerix)

Healthy HBs-naive Adults

(N=713)

NCT00805389



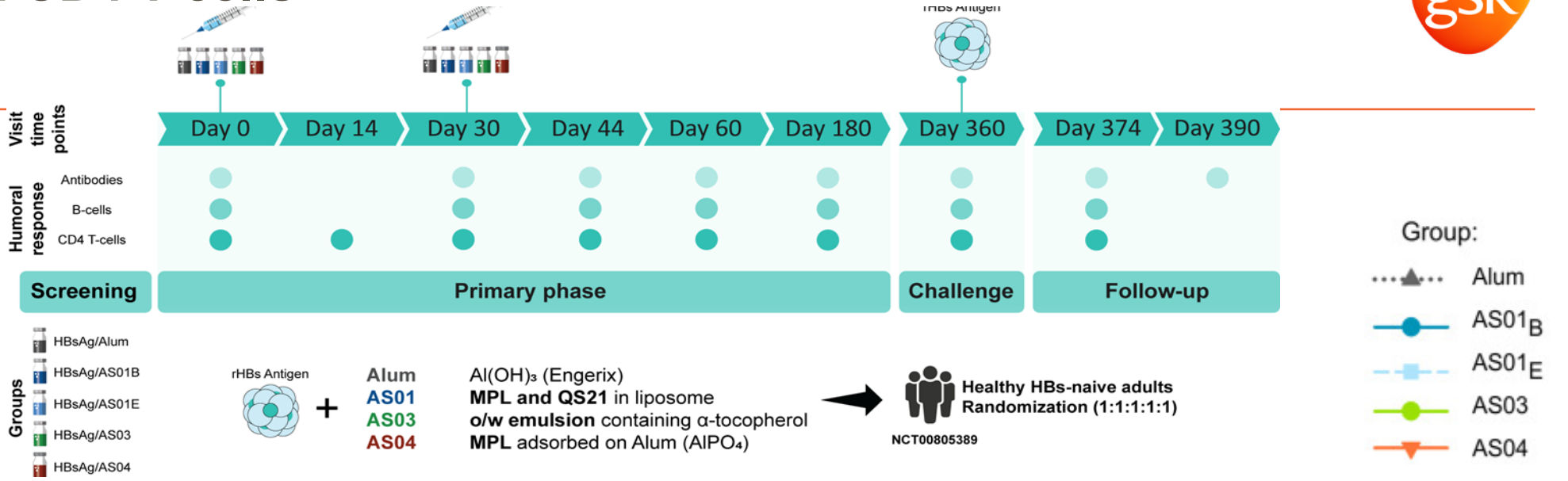
Leroux-Roels et al. Clin Immunol 169:16-27 (2016)

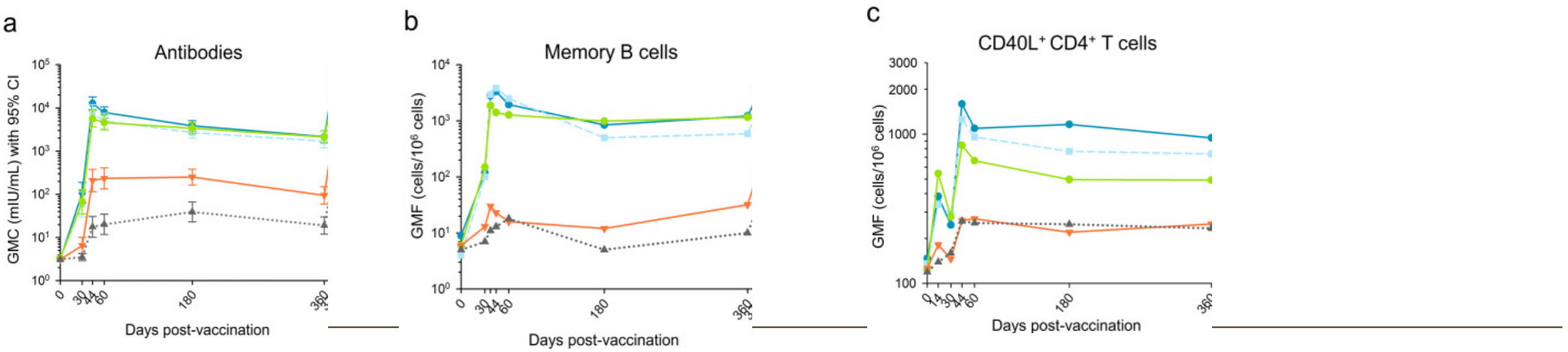
AS01/03/04 is a GSK proprietary adjuvant system
AS, adjuvant system; (r)HBs, (recombinant) Hepatitis B virus surface antigen; MPL, 3-O-desacyl-4'-monophosphoryl lipid A; QS21, Quillaja Saponaria Molina, fraction 21; o/w, oil-in-water; Abs, antibodies; CRP, C-Reactive Protein.

Head-to-head comparison of AS in humans

Abs titers and CD4 T cells

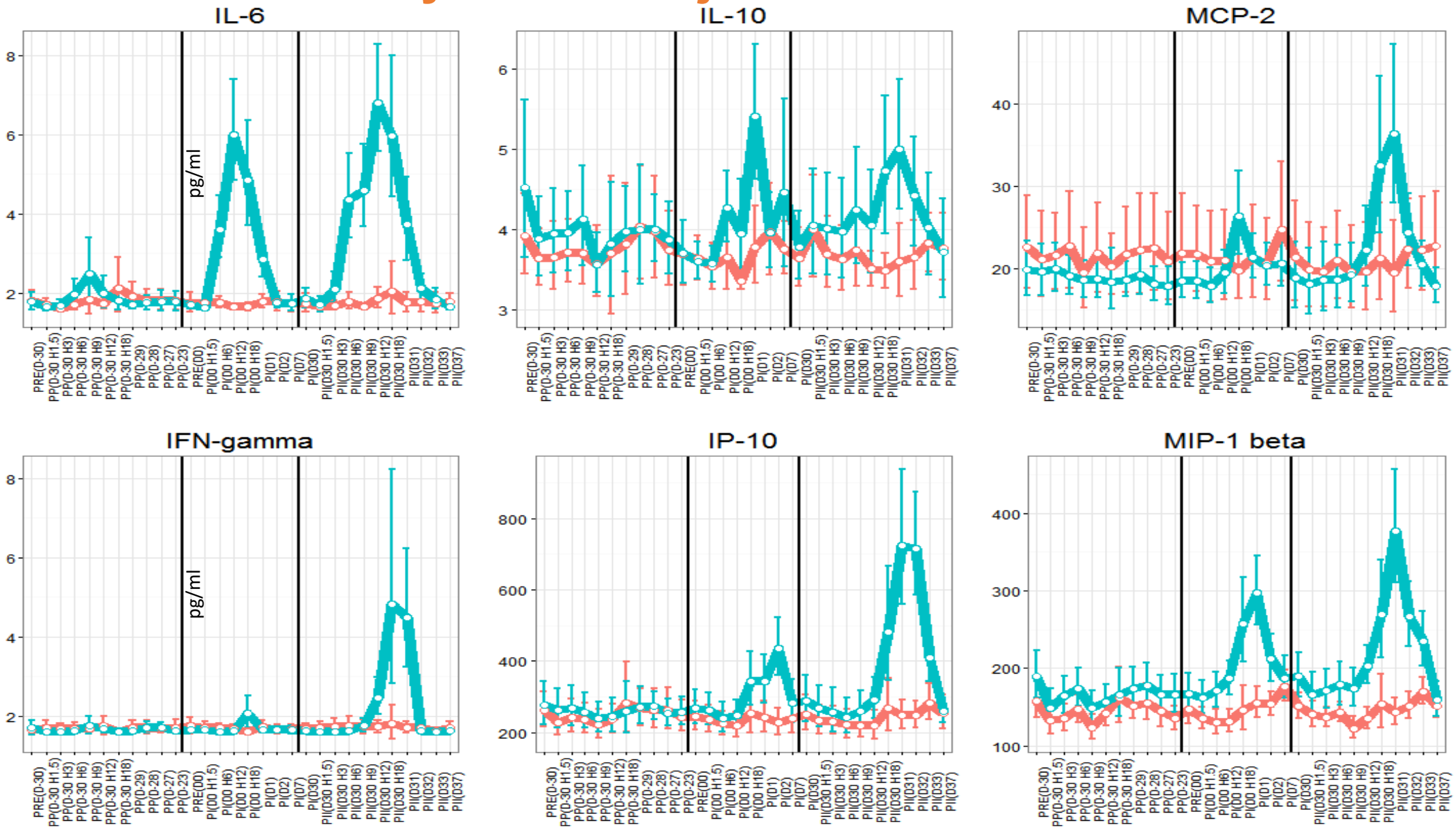
Naïve setting (HBS: ECR-002)





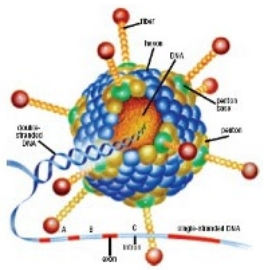
Budroni et al, npj Vaccines (2021) 6:78 ; https://doi.org/10.1038/s41541-021-00337-0

Selective increase of inflammatory cytokines and chemokines in serum induced by AS01B-adjuvanted vaccine

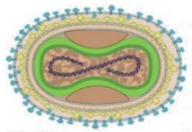


Burny et al 2021, Vaccine 37:2004

Targeted immunotherapy for CHB



ChAd155-hli-HBV
(Prime)



MVA-HBV
(Boost)

+

Rec proteins (HBc + HBs)

Adjuvant (AS01)

Sequentially or co-administered

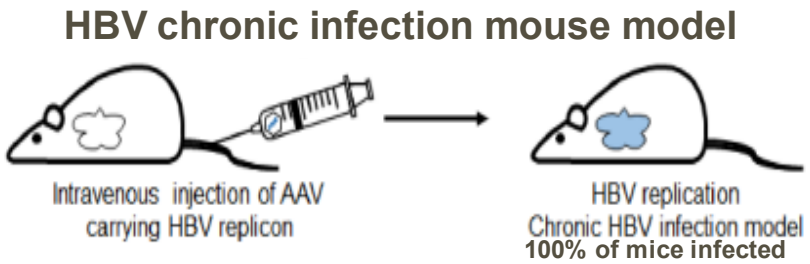
Adults with chronic HBV infection
(under NA treatment >24 months)

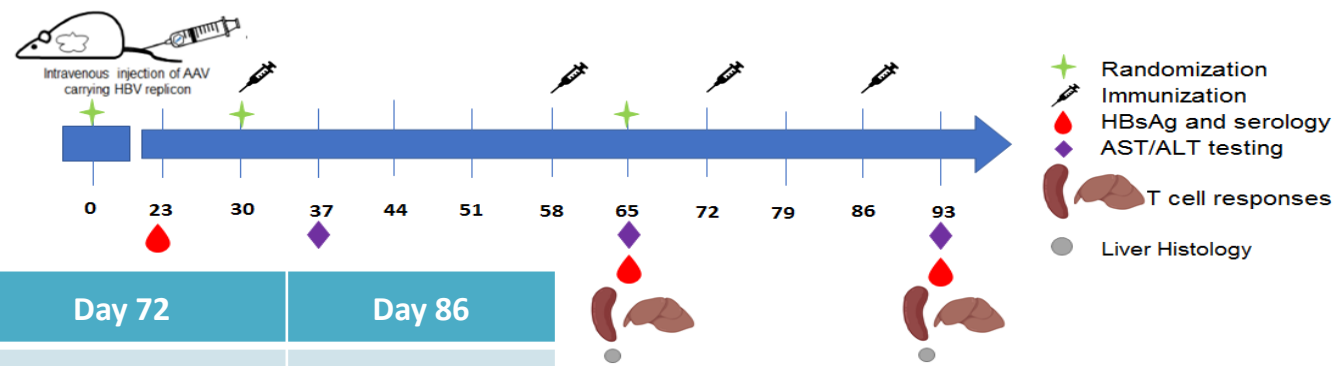
Functional HBc/HBs-CD4+ and CD8+ T cells

Humoral responses
+
innate activation

CHB functional cure

HLA.A2 mouse model of chronic hepatitis B virus infection - study design -





Groups	N	Day 0	Day 30	Day 58	Day 72	Day 86
A/M/P/P HBV+	21	AAV2/8-HBV	ChAd155-hIi-HBV	MVA-HBV	HBc-HBs /AS01	HBc-HBs /AS01
AP/MP/MP/MP HBV+	21	AAV2/8-HBV	ChAd155-hIi-HBV + HBc-HBs /AS01	MVA-HBV + HBc-HBs/AS01	MVA-HBV + HBc-HBs/AS01	MVA-HBV + HBc-HBs/AS01
No Vaccine HBV+	21	AAV2/8-HBV	NaCl	NaCl	NaCl	NaCl
AP/MP/MP/MP Healthy mice	9	-	ChAd155-hIi-HBV + HBc-HBs /AS01	MVA-HBV + HBc-HBs/AS01	MVA-HBV + HBc-HBs/AS01	MVA-HBV + HBc-HBs/AS01

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

Chronic hepatitis B infection model (Dion et al., J Virol 2013)

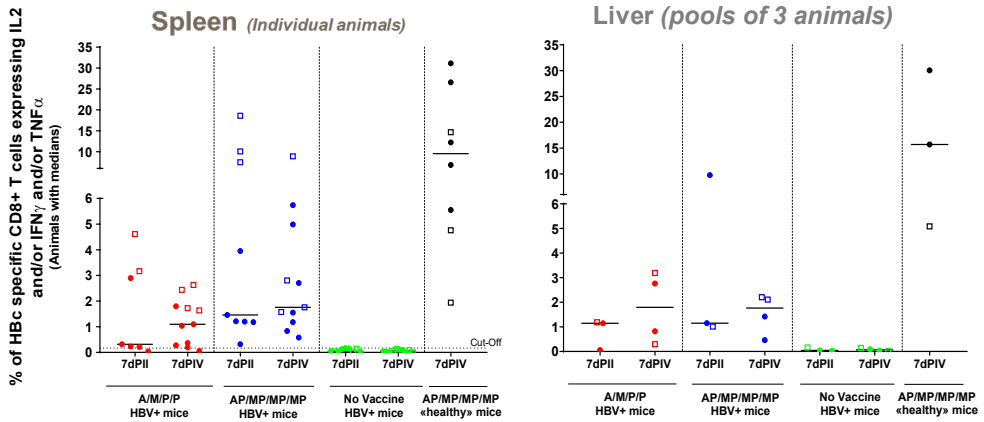
Ethical statement

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.

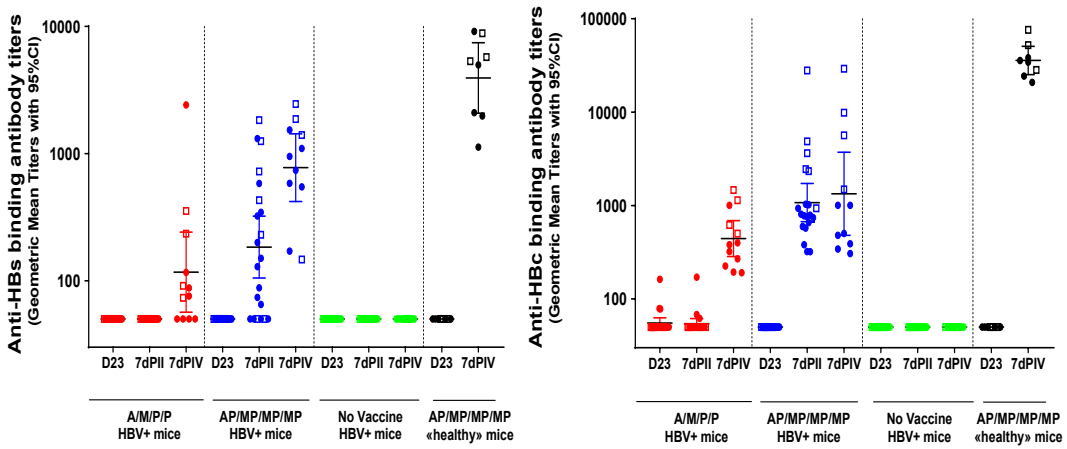
Results of *In vivo* testing in HLA.A2 mouse model of chronic HBV infection

HBc-specific

CD8+ T cell

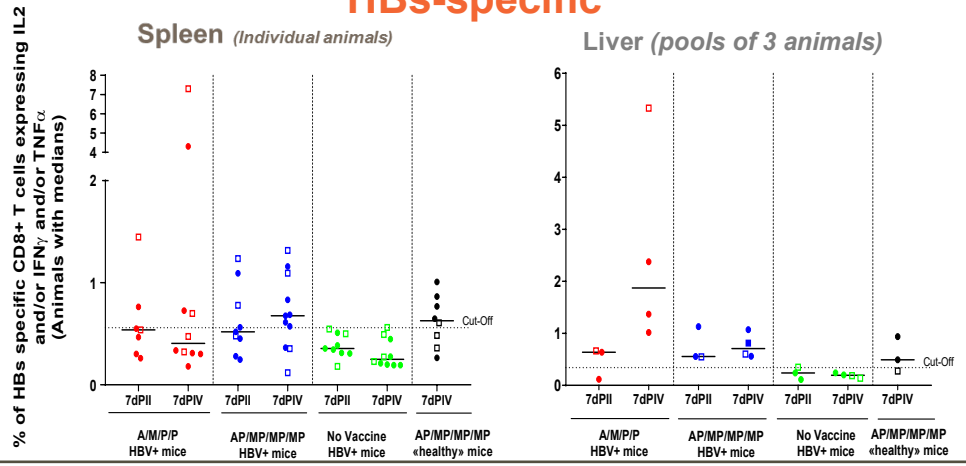


HBs- and HBc-specific antibody responses induced



HBs-specific

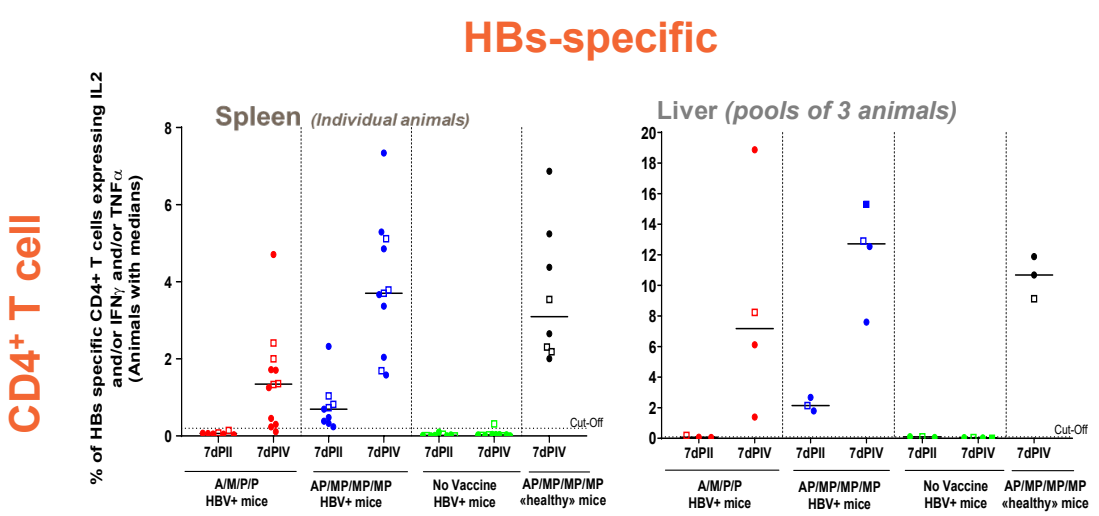
CD8+ T cell

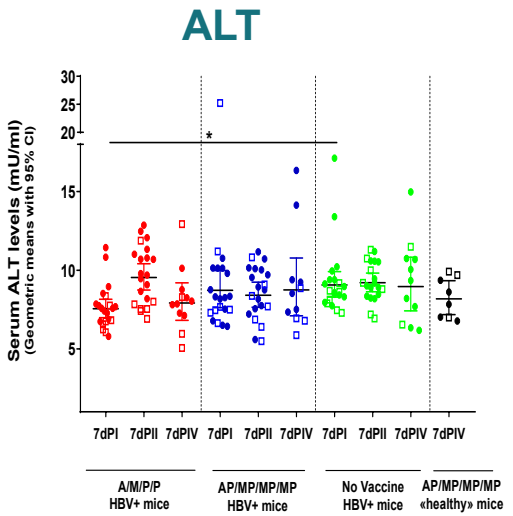


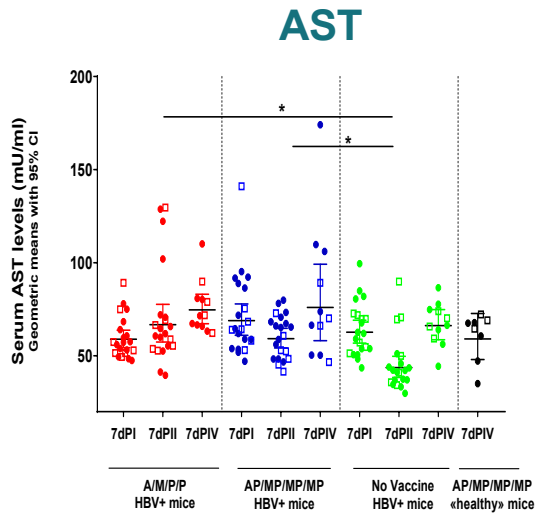
- The immune tolerance for **HBc-specific CD8+ T cells** and **HBs-specific antibody responses** have been successfully overcome in AAV-HBV transduced HLA.A2/DR1 mice although levels remain lower than in non-infected mice.
- The **co-administration vaccine regimen** (viral vectors together with adjuvanted proteins) induced **higher HBc/HBs-specific antibody** and **T cell responses** compared to the sequential regimen.

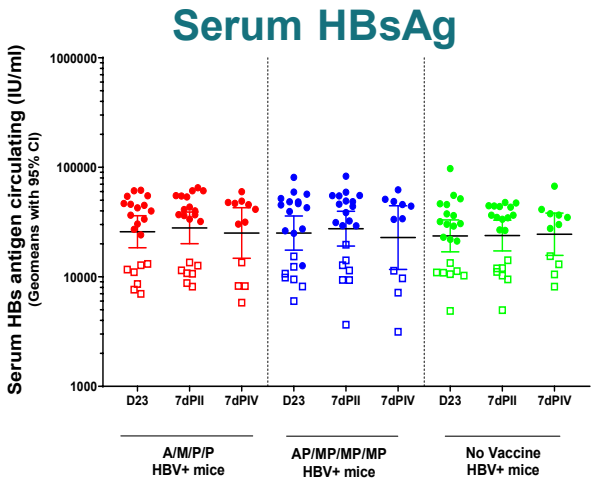
Group legend:
HLA.A2 mice Sequential ThHBV
HLA.A2 mice Co-administration ThHBV
HLA.A2 mice Control (placebo)
healthy mice Co-administration ThHBV

Results of *In vivo* testing in HLA.A2 mouse model of chronic HBV infection









- 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.

Group legend:
HLA.A2 mice Sequential ThHBV
HLA.A2 mice Co-administration ThHBV
HLA.A2 mice Control (placebo)
healthy mice Co-administration ThHBV

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

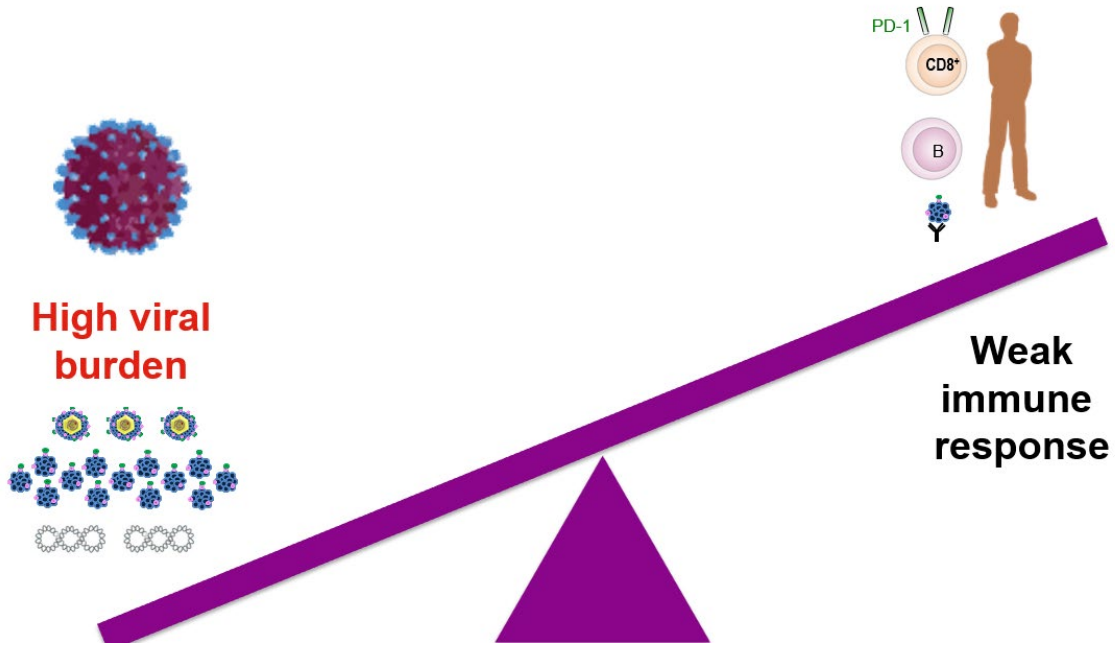
– **Co-administration regimen**: prime with ChAd and adjuvanted proteins + 3 booster doses of MVA with adjuvanted proteins

– Co-administration regimen: prime with ChAd and adjuvanted proteins + booster with MVA and adjuvanted proteins

ChAd-hli-HBV MVA-HBV HBc-HBs AS01 Control (placebo)

Achieving high CHB *Functional Cure* response rates is likely to be achieved trough 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