HBV THERAPEUTIC VACCINES WEBINAR SUMMARY

TUESDAY JANUARY 18, 2022

10:30am – 1:00pm EST

AGENDA

Moderators: Adam Gehring, *University of Toronto*

Session Title	Speaker
Welcoming Remarks	Veronica Miller, *Forum for Collaborative Research* John Travis, *Saint Louis University*
Overview of Therapeutic Vaccines for HBV • Overview of Therapeutic Vaccines for HBV; Goals of Therapeutic Vaccines moving forward (including a brief discussion on previous strategies)	Ulla Protzer, *Technical University of Munich*
Company Presentations: • Vir Biotechnology Inc. • Virion Therapeutics • VBI Vaccines • GlaxoSmithKline (GSK) • Altimmune	 Michael Schmid Hildegund Ertl Francisco Diaz-Mitoma Ventzi Vassilev Sarah Browne
Discussion & Audience Questions: Potential Topics • Optimal Combinations • Monitoring Response • Stratification/Patient Groups • End Points	Previous Presenters Regulators Patient Representatives
Conclusions and Next Steps	Veronica Miller, *Forum for Collaborative Research*

Summary

Welcoming Remarks:

- This webinar will feature an overview of therapeutic vaccines for HBV, presentations on industry strategies, and an audience q&a with a panel representing academia, industry, regulators, and patient advocates.

Overview of the HBV Forum
Slides: https://bit.ly/3APlRkH

- **What:** a platform for ongoing multi-stakeholder dialogue to identify barriers, prioritize research and identify solutions to accelerate therapeutic development for HBV
- **How:** provide a neutral, independent, safe space for discussion and deliberation across stakeholder groups
    - Focus on developing consensus, increasing synergy and collaboration, and reducing duplication and uncertainty
    - Ongoing working group activity throughout the year anchored by larger project events
    - Active & engaged participation

ICE-HBV: International Coalition to Eliminate HBV
Slides: https://bit.ly/3gc3Bsn

Mission: To fast track the discovery of a safe, effective, affordable and scalable cure to benefit all people living with CHB, including children and people living with HCV, HDV and HIV co-infection. ICE-HBV intends to contribute to the elimination of CHB as a global public health challenge.

Organization:

- Formed from the HBV basic and translational scientific community
- Governing board with world-wide representation by clinicians and basic scientists from academia and governmental research institutes
- Working groups targeting challenges in HBV and HDV biology and cure research
- Work closely with industry

Initiatives:

- Publish HBV/HDV cure strategy white papers
- HBV protocol repository
- HBV reagent repositories (with USA NIAID)
- Define standardized protocols for HBV cccDNA quantification
- Research symposia, think tanks on HBV and HDV cure, and educational materials in many languages
- Patient-focused conferences bringing together community activists and leading HBV researchers

Presentations

Presenter: Ulrike Protzer
Organization: Institute of Virology, Technische Universität München
Title: Therapeutic Vaccines moving forward
Slides: https://bit.ly/3gsTPCt

Controlling HBV infection

- Immune control determines the course of Hepatitis B. With a strong antibody and T cell response there is a self-limiting infection. However, with no neutralizing antibodies, T cells are scarce and this leads to chronic infections. The goal of a therapeutic vaccine is to turn this immune tolerance state into an immune control state.
- Target treatments: Killing infected hepatocytes, inducing cell division to dilute cccDNA overtime, degradation of nuclear cccDNA
- T cell response is important.

Therapeutic Vaccine Strategies

- TherVac B Strategy
    - A heterologous protein-prime with an MVA-boost is superior to single component to create immunity.
    - Antiviral treatment → Particulate protein prime, adjuvanted → MVA vector boost:
        - Reduces inflammation → Induces neutralizing antibodies, prime T cell responses → Expands T cells, controls infection
    - DNA vs adjuvanted protein for prime?
        - Found that protein prime is superior to the DNA prime in producing CD8+, CD4+, and antibody responses
        - C-di-AMP adjuvanted protein induces anti-HBs and primes CD8+ T cells
    - Antiviral effect of DNA vs protein prime
        - PBS does nothing
        - S protein and S & Core proteins reduces the antigen load largely
        - DNA in a low dose does nothing
        - DNA in a high dose sometimes triggered a response
        - Protein prime in TherVacB allows induction of (neutralizing) antibodies and antiviral CD8 T cells and has a superior antiviral effect
    - RNA Prime vs Protein Prime
        - For T-cell priming, protein is superior to DNA or RNA
    - TherVacB in HBe-negative HBV infection
        - TherVacB was able to reduce the HBeAg, induce T cell response, induce AntiS
        - TherVacB is able to "cure" HBV in AAV-HBV infected, HBV-carrier mice
    - Anti-CD4 and -CD8 depletion during prime vaccination
        - Activation of CDD4+ T cells during prime is essential for the success of TherVacB
    - HBV titers influence T-cell response to TherVacB
        - High HBV antigen levels impair the efficacy of therapeutic vaccination

    - HBV Cure by TherVacB if antigen levels are high
        - TherVacB cures high-titer HBV carriers after siRNA pre-treatment

Summary

- HBV is able to avoid and to escape immune responses
- Antivirals control but do not eliminate HBV
- Immune activation will be necessary to clear the virus
- Therapeutic Vaccination activating virus-specific T cells seems most promising
- T cells are scarce in chronic HBV infection – new T cells need to be primed
- Activation of CD4 T cells are important to help B cells and CD8 T cells
- Neutralizing antibodies help to limit further virus spread
- High antigen load (over longer time) will limit vaccine efficacy
- Therapeutic vaccination is safe and can cure HBV in preclinical models

Clinical Translation

- Therapeutic vaccination should activate B-, CD4+ and CD8 + T cells
- Optimal vaccine design: heterologous (protein prime / MVA boost)
- Antigen and vector design should cover HBV genotypes A-E
- In initial trials, a preselection of low HBsAg patients may be necessary
- To treat high-titer infection, a combination with siRNA is promising

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Presenter: Michael A. Schmid
Organization: Vir Biotechnology
Title: VIR-3434, an investigational monoclonal antibody neutralizing Hepatitis B virus and facilitating FcgR-mediated elimination of HBsAg
Slides: https://bit.ly/3octPzq

VIR-3434

- Monoclonal antibody that neutralizes HBV
    - Inhibition of viral entry
    - Presentation to and stimulation of T cells
    - Clearance of HBsAg and delivery to dendritic cells
- Fc-engineered antibody as a potential therapeutic vaccine against HBV
    - Generation of immune complexes → Immune complex binding to FcγRs on Dendritic cells → Phagocytosis, DC maturation and antigen presentation → Generation of effector T cells → Durable HBV specific immunity, potential functional cure
- GAALIE-Fc mutation & mAb:HBsAg ratios are crucial
    - FcgR signaling inducing effector functions that could mediate HBsAg elimination and potentially lead to functional cure
    - GAALIE induces signaling and binding
- VIR-3434 promotes FcγR-mediated association of HBsAg to immune cells in whole blood from HBV+ donors
    - GAALIE-Fc is essential to mediate HBsAg binding to immune cells
    - HBsAg binding is in line with FcgRIIIa (CD16) expression
- VIR-3434 in complex with HBsAg activates moDCs and stimulates antigen-specific reporter CD4+ T cells

    - Significant increase of dendritic cell activation based on the GAALIE-Fc mutation
- Clinical data, phase 1: single dose of VIR-3434: preliminary HBsAg change from baseline
    - Virally suppressed participants with chronic HBV infection
    - Single doses of 6, 18, or 75 mg of VIR-3434 were generally well tolerated
    - Rapid decline in HBsAg ≥ 1 log10 IU/mL within 7 days

Conclusions

- VIR-3434 targets the conserved antigenic loop within HBsAg and mediates pan-genotypic neutralization of HBV in vitro
- In vitro, Fc-engineered VIR-3434 bound and activated FcγRIIa and more efficiently compared to the mAb with wild-type Fc
- VIR-3434 mediated the association of HBsAg to immune cells (neutrophils, monocytes, and NK cells) in whole blood of patients with CHB
- VIR-3434 in complex with HBsAg activated moDCs more efficiently and induced CD4+ reporter T cell responses, in vitro. These results are a first step towards potential long-term immunity and functional cure via a vaccinal effect.
- In patients with CHB, a single low dose of 6, 18 or 75 mg of VIR-3434 resulted in rapid reductions in HBsAg within 1 week.

Presenter: Hildegund Ertl
Organization: Virion Therapeutics
Title: VRON-0200: A pan genotypic therapeutic HBV vaccine containing core and pol coupled with an intrinsic checkpoint inhibitor: Preclinical Summary
Slides: https://bit.ly/32OOzWu

Therapeutic HBV Vaccine approach

- Combine antigen and intrinsic check point inhibitors
- Induce a naïve T cell response to de novo epitopes to restore viral control

A First-in-class Immunotherapy for Chronic HBV

- First selected antigens that were immunogenic parts of HBV core & pol antigens
- Then cloned into an intrinsic checkpoint inhibitor
- Cloned the gene and fused it into a viral vector platform

Antigen Selection:

- Core & Polymerase (Pol) 1-3
    - More conserved, less abundantly expressed so T cells are not exhausted

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
- Stimulation of CD8+ T cells to subdominant epitopes that were not induced by the infection
    - Affected by duration of disease and viral loads

Checkpoint Inhibitor

- Herpes Simplex Virus Glycoprotein D
    - HVEM is a co-inhibitor on T cells that will block BTLA

Methods
- Combination HBV PolN, PolC & Core Studies
  - Observed vectors instigated an T cell response

Candidate Optimization
- Within each target, poor/non immunogenic regions were removed
- Remaining regions were combined, fused into gD (VRON-0200) and compared to gDPolN (most immunogenic initial antigen)
- VRON-0200 vaccine responded to Core as well

Efficacy
- GD enhances antiviral activity, which correlates with CDD8+ T cell responses
- The VRON-0200 vaccinated mice had a steady decline in viral load
- CD8+ T cells affect the clearance of the virus
- Vaccination reduces S-antigen levels even at high AAV doses and without S in vaccine

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

Presenter: Francisco Diaz-Mitoma
Organization: VBI Vaccines
Title: VBI-2601: Immunotherapeutic HBV Program
Slides: https://bit.ly/3Hh0rzz

Vaccines:
- Prophylactic Vaccine (PreHevbrio): recently approved for commercial use
- Immunotherapeutic candidates (VBI-2601 (BRII-179))

PreHevbrio
- Only 3-Antigen HBV Vaccine
- PreHevbrio is scientifically differentiated from other HBV vaccines
  - Expresses the three hepatitis B surface antigens (S, pre-S1, and pre-S2), and manufactured in mammalian cells (vs. yeast)
  - The pre-S1 and pre-S2 regions of the hepatitis B virus contain hepatocyte receptor binding sites

VBI-2601
- Potential to be a Critical Component of a Functional Cure for Chronic HBV Infection
  - Drive down hepatitis B virus (HBV) DNA
  - Drive down immuno-suppressive HBV S-antigen

    - Achieve long-term immunologic control

Development Plan & Status: 3 different clinical programs

- Phase 1b/2a Study- Completed in 2021
    - Two-part, multi-center, controlled, dose-escalation study (n=44)
    - Assessed VBI-2601 safety, tolerability, and immunologic antiviral activity in non-cirrhotic patients with chronic HBV infection
    - Conducted in Australia, New Zealand, Thailand, South Korea, Hong Kong, and China
    - Data demonstrated that VBI-2601 induced both B cell and T cell responses and was well tolerated with no safety signals observed
        - No SAEs, deaths or signs of hepatotoxicity observed
    - Data Demonstrated Significant Restoration of Antibody and T Cell Responses
        - Potent re-stimulation of T cell responses to HBV surface antigens (S, Pre-S1, Pre-S2) seen in 67% (Cohort B n=6/9) and 78% (Cohort C n=7/9) of evaluable patients in the low-dose VBI-2601 unadjuvanted and adjuvanted, respectively
        - Boosting of antibodies to HBV surface antigens observed in 19/43 (44.2%) of evaluable patients
- Phase 2 Combination Study- Initiated April 2021
    - First-in-class study to evaluate safety and efficacy of VBI-2601 in combination with an HBV-targeting siRNA (VIR-2218)
    - Multi-center study to be conducted in Australia, New Zealand, Thailand, South Korea, Hong Kong, China, Singapore, and Taiwan
    - Expected enrollment of ~135 adults aged 18-60 years with chronic HBV infection
    - Interim Phase 2 data expected H2 2022
- Phase 2a/2b "Add-On" Study to Standard-of-Care- Initiated December 2021
    - Two-part Phase 2 study designed to evaluate the clinical effect of adding VBI-2601 to existing standard of care therapy (PEG-IFN-α and Nrtl) in non-cirrhotic HBV patients
    - Expected enrollment of ~600 subjects in China
    - Initial data expected H1 2023

Upcoming Milestones:

- H2 2022: Top-line interim clinical data from Phase 2 combination study of VBI-2601 (BRII-179) and BRII-835 (VIR-2218) expected
- H1 2023: Initial data from Phase 2a/2b "add-on" study of VBI-2601 (BRII-179) + current standard-of-care therapy expected

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Presenter: Ventzi Vassilev
Organization: GSK
Title: Targeted Immunotherapy for Chronic Hepatitis B
Slides: https://bit.ly/3s6LpWt

GSK Hepatology Heritage

- Been developing vaccines for Hepatitis A and B for over 30 years

- Designed therapeutic interventions by understanding how CHB is controlled through immune mechanisms: the immunotherapy design targets simultaneous activation of the cellular (CD8/CD4 T-cells), humoral and innate immune responses.
    - Chimp adenovirus vector (ChAd155-hIi-HBV)
        - hli fusion to MHC class II invariant chain (hli) to enhance CD8 T cell response
        - Clinical research data using HCV antigens encoded by similar vector vaccines shows that inclusion of hli sequence in vaccine significantly improved magnitude HCV-specific T cell responses in humans
    - MVA-HBV booster
        - Boosts a strong T cell response following ChAd priming
    - Inclusion of proteins (Rec proteins HBc + HBs, and Adjuvant AS01)
        - Outcome: Potent humoral and CD4 T-cell response
        - Selective increase of inflammatory cytokines and chemokines in serum induced by AS01B-adjuvanted vaccine suggesting potent innate system activation
- See slides for study design
- Results of *In vivo* testing in HLA.A2 mouse model of chronic HBV infection
    - 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.

Presenter: Sarah K. Browne
Organization: Altimmune
Title: Immunotherapeutics in the Treatment of Chronic Hepatitis B
Slides: https://bit.ly/3odxjBF

HepTcell Vaccine

- In Phase 2, data readout expected H2 2022
- 30 to 40 a.a. long peptides manufactured by solid phase synthesis
- Contain CD4+ and CD8+ T cell epitopes to overcome HLA restriction
- Fluorocarbon moiety promotes micelle formation and improves immunogenicity
- Robust immunogenicity observed with this peptide platform in young and older adults

HepTcell covers 4 predominant HBV genotypes and all other genotypes by homology

- Most individual peptide components of HepTcell can cross-react with multiple HBV genotypes
- Collectively, the peptides in HepTcell cross-react with genotypes A-D
- Based on HBV homology, HepTcell expected to cross-react with all HBV genotypes

See slides for study demographics, methods, and injection site reaction assessments

Immunogenicity Data:

- Looks at robust T cell responses
- Robust IFN-γ ELISpot Responses
- Each peptide and dose influences the change in baseline
- Shows robust responses: Most prominent with low dose peptide and IC31

PHASE 2 CLINICAL TRIAL

- Patients with inactive CHB and HBsAg levels ≤ 100 IU/mL is a subpopulation that might demonstrate a response to immunotherapy
- Virologic response appears to be more likely to occur with a longer duration of immunotherapy
- 80 patients with HBeAg negative inactive CHB and HBsAg ≤ 100 IU/mL randomized 1:1 to HepTcell or placebo administered every 4 weeks for 24 weeks
- Follow-up at 48 weeks after the last dose will assess the safety and durability of response
- Efficacy endpoints
- Primary: proportion of patients with 1.0-log reduction in HBsAg from baseline at Week 24
- Secondary: HBsAg clearance, changes from baseline in HBsAg, HBV DNA, HBcrAg, pg-RNA at Week 24

Goals of treatment:

- Suppress HBV DNA/viral antigens to reduce virus-induced immune dysregulation
- Break T cell tolerance and reprogram HBV-specific immune responses
    - Leads to a functional cure: Loss of HBV DNA and HBsAg

Discussion and Q&A

Moderator: Adam Gehring, *Toronto Centre for Liver Disease, University Health Network*

What is going to be the optimal combination for therapeutic vaccines?

- We can/should look for responses in blood
- But are we looking at the right biomarkers, is it T/B cell magnitude? Specific functionalities?
- Should we be looking at the target organ? T Cell response will likely migrate to the liver

Coming back to the original Question

- SiRNAs? Check point inhibitors?
- Removing/lowering the antigen levels do not restore the T cells in HCV or animal models
- So, will inducing T cells be easier if the antigen levels are lower?
- The amount of antigens and the kind of antigens produced in the liver is important and impacts T cell restoration
- HBsAg levels are clearly associated with responses. Patients with lower HBsAg tend to clear HBsAg more easily…potentially a logical outcome but suggest level of antigen is important.
- Duration of antigen inhibition may play a role for immune restoration
- Age has an impact on immune response
- Immune restoration may depend on the stage the patient is in, how long have they had chronic HBV and how they were originally infected
- AAV-HBV mouse model is not the best model predict what happens in humans.

- Can we give everyone the same regiment?
- Possible mRNA vaccine?

What patients do you enroll in these vaccination trials

- Low surface antigen levels to push into functional cure
- Driving down surface antigen levels with siRNA may not be the same as patients with naturally low surface antigen
- Younger patients potentially have more robust immune responses and could be considered
- We have to think about different HBV genotypes A-E and recognize the mismatches in vaccine antigens and genotypes may occur
- Have variability and diversity in patients and genotypes but understand there is greater burden in Asian and African populations
- Need to consider that patients may be co-infected with other diseases
- The target population should be enrolled in the final phases

Are patients aware of these new technologies?

- COVID-19 vaccines have actually jumpstarted the possibilities of people accepting an HBV vaccines
- Patients want to get off drugs, want to forget about the stigma, want a cure

How do we distribute treatments more widely in places that have more prevalence?

- Sell for $2-3, needs to be affordable
- Simplify vaccine regimens and keep costs down
- Better development of diagnostics

What do regulators think about in order to move vaccines forward

- Safety
- The immune response
- Full characterization of an immune response
- Data on combination therapies
- What is the biological and immunological and virological response?
- Efficacy Data
- Consensus of the endpoints
    - HIV has done this, hopefully HBV will one day
    - Network with other labs and countries
    - Come up with a baseline of T cell analysis assays
        - However, shipping T cells is impossible
        - Finding biomarkers is also difficult