International Hepatitis B Cure Workshop 2016

New Treatment Options:
Immunomodulatory Agents

**Therapeutic Vaccines**

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Disclosures

- Consulting for:
  - Arbutus
  - Genentech
  - Alnylam
Overview: Therapeutic Vaccine

- Background considerations
  - Goals in HBV therapy
  - Rationale for therapeutic vaccination
    - Immune tolerance/dysfunction in chronic infection
    - Who, when, how to augment?
- Therapeutic vaccine approaches to date
- Conclusion
Goals in HBV therapy

HBV DNA
HBV Ag
cccDNA
ALT

Control vs Cure

Adaptive Immunity

Cirrhosis
HCC
Reactivation
Death
Cost
HBV Pathogenesis
Largely immune-mediated disease (non-cytopathic virus)

Acute

CD4 → CD8 → Cured → Killed

IFNγ, TNFα

Inflammatory Mediators

Chronic

Exhausted T cells

NK, KC, Nφ, PD-1, Bim

DC, γδT, CTLA-4, IL-10

γδT, MDSC, Tim-3, TGFβ

MDSC, Lag-3, IL-17

Tregs, arginase
Antiviral “immunity” in chronic infection

But they are antigen-dependent

And there may be responsive progenitor cells
**Good news:** There is protective immunity in chronic infections

**Caveat:** But it is lost when infection is ‘cured’

- Resistance to *S. mansoni* and *S. japonicum* waned after treatment (Tawfik 1986, Moloney 1987)
- Sterilizing cure of *L. major* led to loss of protective immunity to re-challenge (Belkaid 2002)

Adoptively transferred LCMV-specific CD8 T cells from chronic LCMV animals do not persist in naïve mice (Wherry 2004)

Relevant for therapeutic HBV Ag loss

*Wherry et al, PNAS 2004*
Progenitor pool of more functional CD8 T-cells in chronic viral infection

- Phenotype of potential progenitors:
  - **T cell factor 1**+ memory-like CD8 T cells sustain immune response to chronic viral infection (Utzschneider, Immunity 2016)
  - **Follicular CXCR5**+ CD8 T cells curtail chronic viral infection (He/Hou, Nature 2016)
  - **PD1int**, **Tbet-hi** CD8 T cells with greater renewal capacity and response to PD-1 blockade (Blackburn PNAS 2008, Nakamoto Gastro 2008, Paley Science 2012)

T cell responsiveness after resolution of chronic HBV infection

Rehermann et al, JCI 1996

HLA A2-restricted HBV CTL epitopes
1) Core 18; 2) Env 183; 3) Env 335; 4) Pol 455; 5) Pol 575

Boni Gastro 2012
Therapeutic vaccine: Who should get it?

- Is there specific patient group that may be more responsive with greater long term benefit?
  - ? Clinical stages of chronic hepatitis B
  - ? Available progenitor population?
  - Not yet defined...
Clinical phenotypes in chronic hepatitis B
(confusing immune-based terminologies)

Readout:
- ALT--hepatocellular injury
- HBV DNA--replication, elimination, spread...
- Liver biopsy--inflammation +/- fibrosis (not often)

<table>
<thead>
<tr>
<th>Clinical Phenotype</th>
<th>HBsAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Assumptions about T cells</th>
<th>Response to antiviral therapy</th>
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</thead>
<tbody>
<tr>
<td>Immune Tolerant</td>
<td>+</td>
<td>Low</td>
<td>High</td>
<td>Tolerant</td>
<td>Poor</td>
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<tr>
<td>Immune Active</td>
<td>+</td>
<td>High</td>
<td>High</td>
<td>Actively killing HBV-infected cells</td>
<td>Better</td>
</tr>
<tr>
<td>Inactive “Carrier “</td>
<td>+</td>
<td>Low</td>
<td>Low</td>
<td>Actively Controlling HBV</td>
<td>Greater turnover? New infection?</td>
</tr>
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ALT: ALT--hepatocellular injury
HBV DNA: HBV DNA--replication, elimination, spread...
Liver biopsy: Liver biopsy--inflammation +/- fibrosis (not often)
HBV-specific T cell responses do not distinguish between clinical CHB phenotype groups

![Graph showing % LPR responders for different HBV peptide pools and immune status groups.](Park et al, Gastro 2016)
Clinical phenotypes in chronic hepatitis B (confusing immune-based terminologies)

- Antiviral T cells are largely tolerized in CHB
- ALT represents inflammation and injury (not immunity)
- Need to better define “immunity” vs inflammation/injury

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<th>T cell Tolerance</th>
<th>Inflammation &amp; Injury</th>
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<tbody>
<tr>
<td>Immune Tolerant</td>
<td>+</td>
<td>Low</td>
<td>High</td>
<td>Tolerant</td>
<td>+++</td>
<td>-</td>
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<td>++</td>
<td>-</td>
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</table>
Therapeutic Vaccine: When to give it?

- Lower barriers for immune induction
  - Less virus (e.g. on therapy)
  - Less inflammation
  - Less immune inhibitory mechanisms

- Less risk
  - Less HBV-infected target
  - More preserved liver function

DNA/ALT  HBeAg  HBsAg

Antiviral Therapy
Boosting immune response with immune inhibitory blockade?

In liver and blood

- **Fisicaro Gastro 2010**

With differential impact based on HBeAg status

- **Park Gastro 2016**

* Effective memory T cell response upon immune boosting with PD1 blockade (Pauken/Wherry Science 2016)
Therapeutic approaches to date: Safe, immunogenic but not yet effective

- rHBsAg +/- IFNα, 3TC, rIL2
- rHBsAg/HBIG immune complex
- CTL epitope vaccine (Heathcote 1999)
- Yeast-based T cell vaccine +/- nuc
  - GS-4774
- DNA vaccine (PreS/S, C, P +/- X) +/- nuc, IL12
  - pCMV S2.S, HB-100, HB-110
- Adenoviral vector
  - TG1050
DNA (HBV preS2/S)

- **Phase I study** - pCMV S2.S DNA IM x 3-4 times over 4m in prior treatment nonresponders *(Mancini-Bougine, 2004, 2006)*
  - Safe, well-tolerated transiently immunogenic but without substantial effect in viremia *(Mancini-Bougine, 2004, 2006)*

- **Phase I/II study** - pCMV S2.S DNA over 44w *(Fontaine/Pol 2014)*
  - 70 CHB patients on nuc with HBV DNA-neg > 12m
  - Safe, well-tolerated
  - But 97% reactivation
**pDNA (S/S1/S2/X/P) + rIL12 + NUC**

**Plasmid DNA HB-100 (adr)**

- **S/S1/S2/X/C/P/hIL-12 + 3TC**
  - 12 Caucasians
  - Monthly HB-100 IM + 3TC x 52 wk
  - Safe, well-tolerated, immunogenic
  - 50% with HBV suppression at 1y post treatment cessation

**Plasmid DNA HB-110**

- **S/S1/S2/C/P + hIL-12 + ADV**
  - 27 HBeAg+ Koreans with 90% HBV DNA drop on 8wk ADV
  - 12 IM + ADV x 24wk -> ADV x 24wk
  - Safe, well-tolerated, immunogenic
  - A tendency for greater HBeAg loss and DNA suppression than ADV alone

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Yang, Gene Therapy 2006

Yoon, Liver Int 2014
Yeast-based T-cell vaccine: GS-4774

Heat-killed, whole recombinant Saccharomyces cerevisiae yeast expressing HBV S, C and X as a fusion protein (promotes both CD4 & T cells)

- **Phase I:** 88% HBV-specific T cell response in 60 healthy control (Gaggar, Vaccine 2014)

- **Phase II:** 178 CHB non-cirrhotics >1y HBV suppression on NUCs (Lok, J. Hep 2016)
  - Safe, well-tolerated, 5 HBeAg loss for GS-4774 vs none in control
  - No loss of serum HBsAg

Lok J. Hep 2016
Adenoviral vector: TG1050

- Non-replicative Adenovirus 5 vector encoding a modified HBV C, P, S fusion protein (geno D)
- Immunogenicity with antiviral effects in mouse model of CHB (*Martin, Gut 2016*)
- Phase 1/1b safety, tolerability and dose-finding study in CHB patients on TDF or ETV ongoing
<table>
<thead>
<tr>
<th>Compound</th>
<th>Phase</th>
<th>Available Result</th>
<th>Sponsor</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>ANRS HB02 (naked DNA)</td>
<td>2</td>
<td>Vaccine failed to improve off treatment viral suppression</td>
<td>French National Agency for Research on AIDS and Viral Hepatitis</td>
<td>NCT00536627</td>
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<tr>
<td>FP-02.2 peptide vacc</td>
<td>1</td>
<td>Recruiting HBeAg- on ETV or TFV</td>
<td>Altimmune, Inc.</td>
<td>NCT02496897</td>
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<tr>
<td>HB110E (S) + ETV</td>
<td>2a</td>
<td>Completed</td>
<td>Genexine</td>
<td>NCT01813487, NCT00513968, NCT01641536</td>
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<tr>
<td>Engerix-B + NUC</td>
<td>1</td>
<td>Recruiting</td>
<td>Chang Gung Memorial Hospital</td>
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<tr>
<td>TG1050</td>
<td>1</td>
<td>Recruiting</td>
<td>Transgene</td>
<td>NCT02428400</td>
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<tr>
<td>CVI-HBV-002 (S)</td>
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<td>CHA Vaccine Institute Co., Ltd.</td>
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<tr>
<td>INO-1800 (S, C)</td>
<td>1</td>
<td>Recruiting</td>
<td>Inovio Pharmaceuticals</td>
<td>NCT02431312</td>
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<tr>
<td>Euvax B (S) + PEG IFN + ETV</td>
<td>4</td>
<td>Recruiting</td>
<td>Seoul National University</td>
<td>NCT02097004</td>
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<tr>
<td>GS-4774 (S, C, X)</td>
<td>2</td>
<td>No significant viral decrease in treatment experienced patients, Phase 2 of naive group ongoing.</td>
<td>Gilead</td>
<td>NCT01943799, NCT01779505, NCT0174276</td>
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<tr>
<td>DV-601 (S, C)</td>
<td>1</td>
<td>Well tolerated in small cohort, viral response was observed in all patients.</td>
<td>Dynavax</td>
<td>NCT01023230</td>
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<tr>
<td>ABX203 + NUC</td>
<td>3</td>
<td>Ongoing</td>
<td>Abivax S.A.</td>
<td>NCT02249988</td>
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<tr>
<td>pPDPSC18</td>
<td>1</td>
<td>Completed, result not reported</td>
<td>Powder Med</td>
<td>NCT00277576</td>
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<td>IFN + IL2 + HepB vaccine</td>
<td>4</td>
<td>Recruiting</td>
<td>Tongji Hospital</td>
<td>NCT02360592</td>
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<tr>
<td>HBsAg-activated MoDC</td>
<td>1, 2</td>
<td>Recruiting</td>
<td>Sun Yat-Sen University</td>
<td>NCT01935635</td>
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</tbody>
</table>
Summary & Conclusion

- To date, therapeutic vaccine efforts have not been successful in treating chronic hepatitis B.
- Yet, antigen-dependence of virus-specific CD8 T cells in chronic infection suggests that therapeutic vaccine is needed to promote durable protective immunity in CHB.
- Considerations for further immune augmentation need to be balanced with safety and durability.
Thank you for your attention!

Block HBV life cycle (replication, cccDNA...)

Block viral spread

Therapeutic Vaccine to maintain control