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# How We Can Achieve Success with Immunotherapeutics in the Treatment of Chronic Hepatitis B

Scott Harris, M.D.
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Chronic Hepatitis B Drug Development Summit
May 5, 2021

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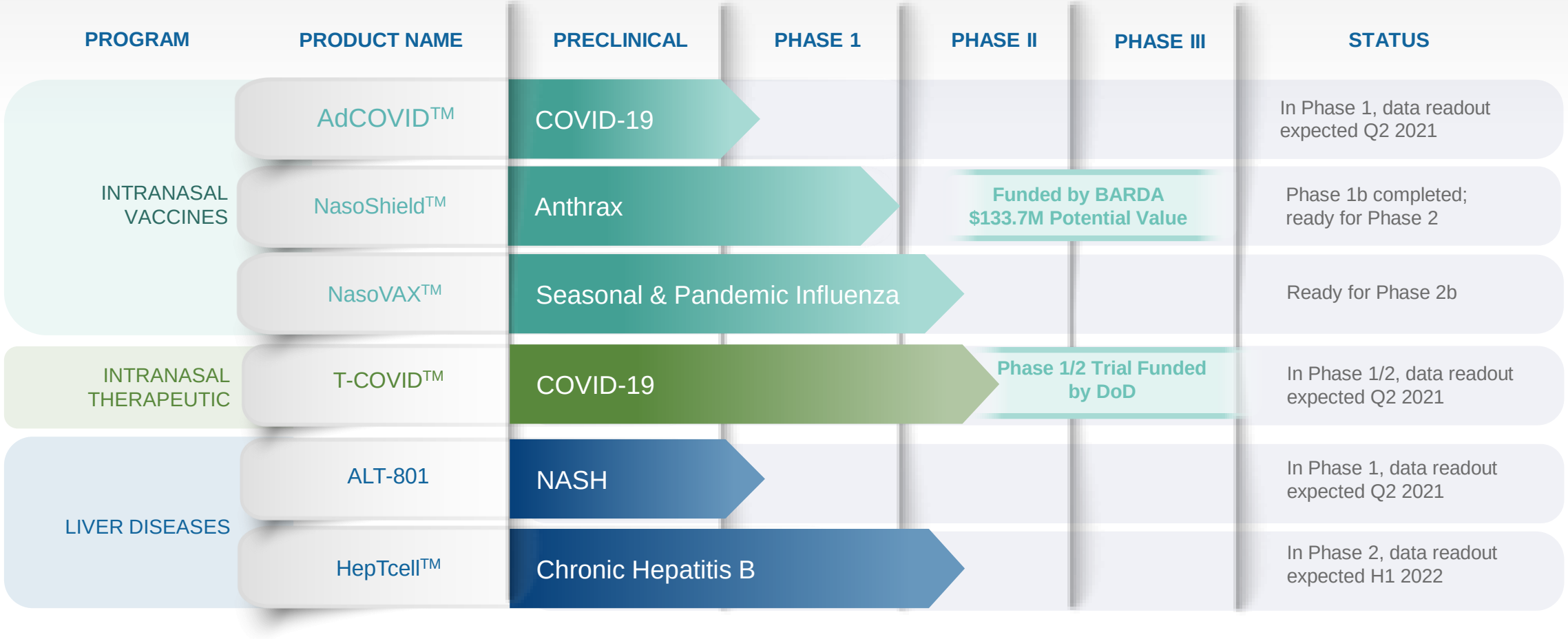
# ADVANCING STRONG DEVELOPMENT PIPELINE

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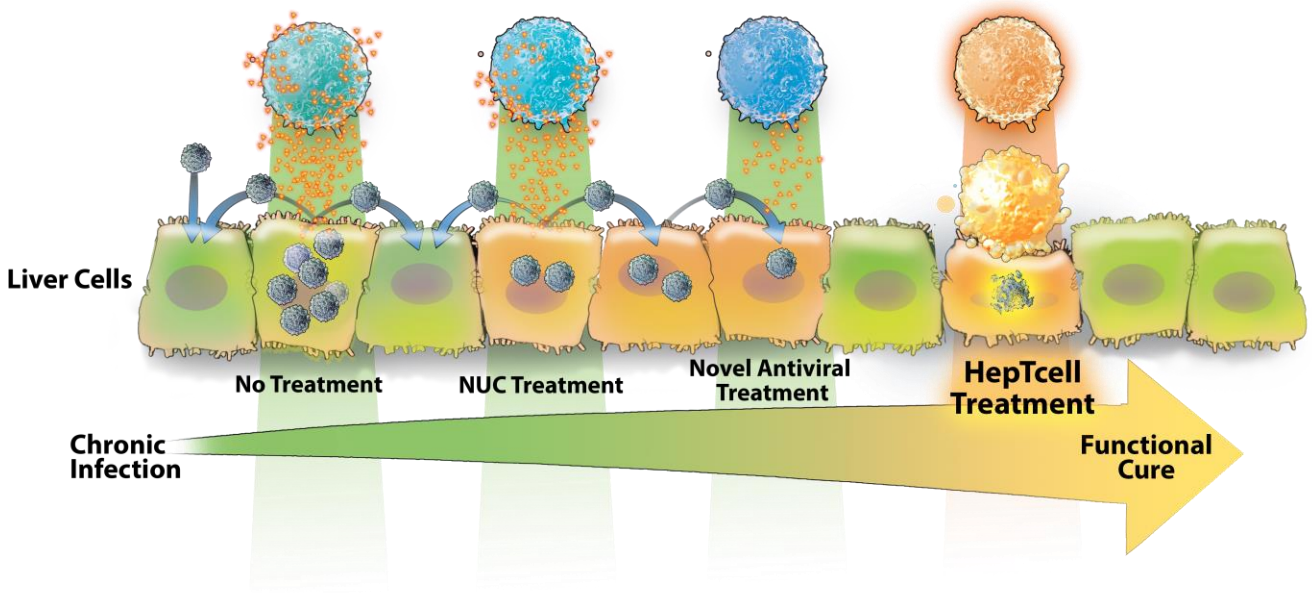
# CURRENT HBV THERAPEUTICS DO NOT LEAD TO FUNCTIONAL CURE

## Immune activation will be required for significant impact

- Current antivirals prevent disease progression but rarely clear chronic infection
- Newer direct-acting antivirals unlikely to result in immune reactivation alone
- Breaking T cell immune tolerance is key to functional cure
- Immunotherapy is designed to “wake up” dormant T-cells to eliminate infection

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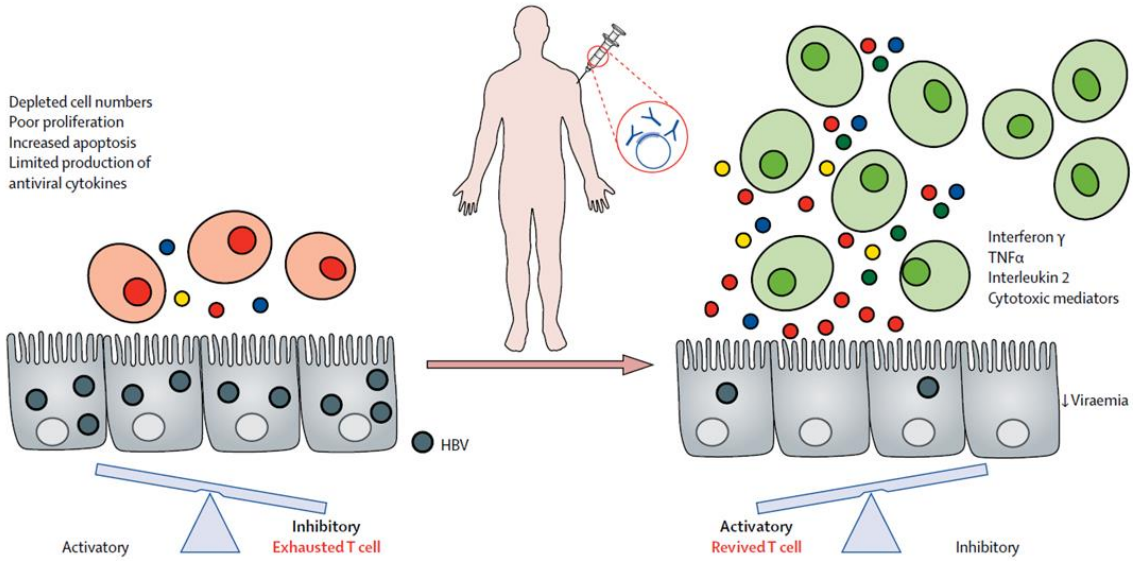
# GOAL OF IMMUNOTHERAPY IN CHRONIC HEPATITIS B (CHB)

## Restore immune control and mimic spontaneous resolution




- CHB is characterized by a profound immune exhaustion driven by decades of high dose antigenic stimulation
- Spontaneous loss of HBsAg is associated with HBV-specific CD4+ and CD8+ T-cells responses
- Resolution of CHB in recipients of bone marrow transplants from donors with HBV immunity

Maini et al. Lancet Gastroenterol Hepatol. 2018 Mar;3(3):192-202.

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# GOAL OF IMMUNOTHERAPY IN CHB

## Limitations of prior immunotherapeutic approaches

- Many therapeutic vaccines have failed
  - Limited to or biased towards Surface Antigen-specific tolerance barrier
  - Vaccine based on full length antigens - T cell responses bias towards less-conserved domains
  - Weak immunogens/vaccine formulation
- Non-specific immunomodulators (checkpoint inhibitors or TLR agonists) carry risk of off-target effects

Li et al PLoS One. 2011;6(6):e20479.

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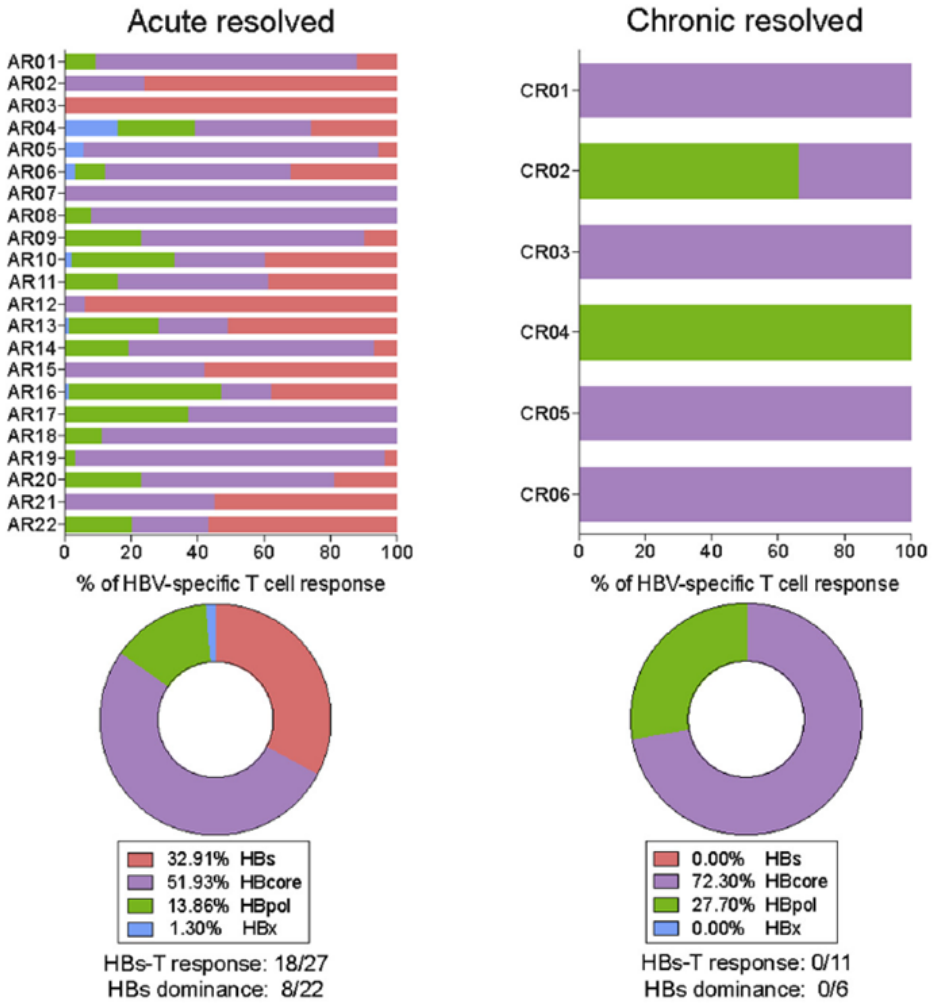
# IMMUNE RESOLUTION OF CHB

## Importance of core and polymerase as target antigens




- T cell responses against HBsAg are strongly affected by duration of exposure
- T cell responses against core and polymerase are dominant in chronic resolved infection
- Baseline T cell responses against core and polymerase are associated with virological control following NA discontinuation

Le Bert Gastroenterology 2020; García-López J Hepatol. 2021, Rivino J Clin Invest. 2018

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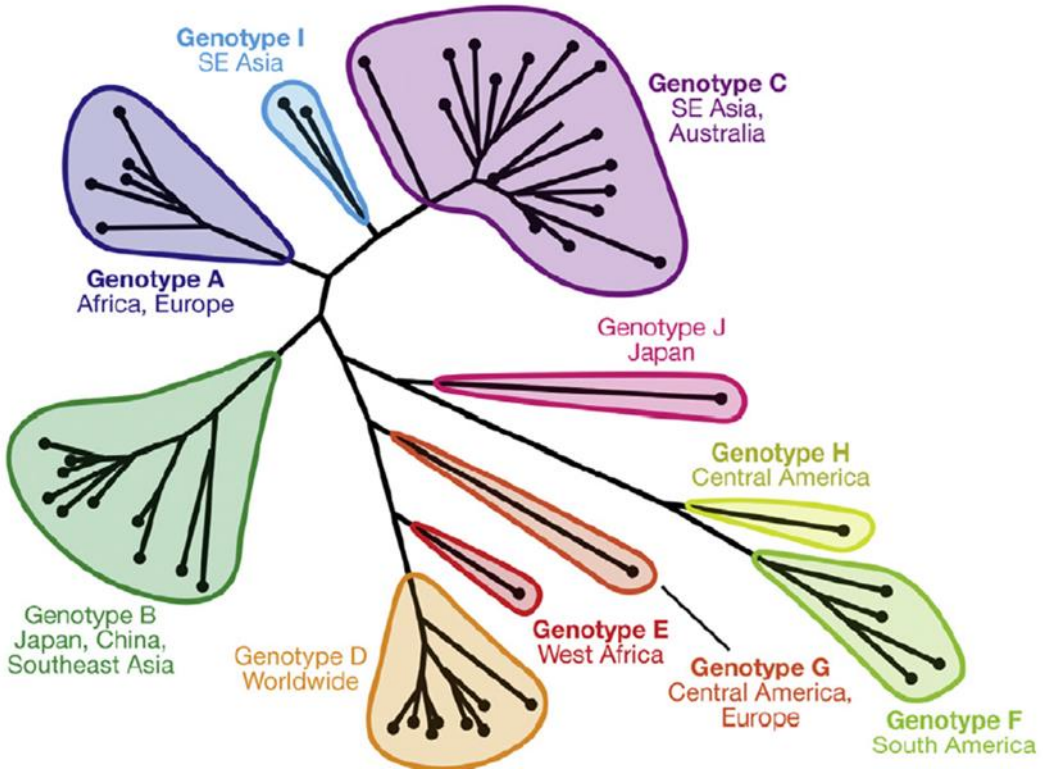
# IMMUNE RESOLUTION OF CHB

## Importance of targeting conserved regions across the HBV proteome




- The intra- and inter-genotypic diversity of HBV poses challenges to therapeutic vaccination
- HBV utilizes an error-prone reverse transcriptase and T-cell escape mutations have been observed
- Targeting conserved regions across the HBV proteome is anticipated to provide cross-genotype protection and a multi-specific T-cell response

McNaughton et al. Gastroenterology. 2019 Jan;156(2):384-399, Bertoletti et al. J Exp Med. 1994 Sep 1;180(3):933-43.

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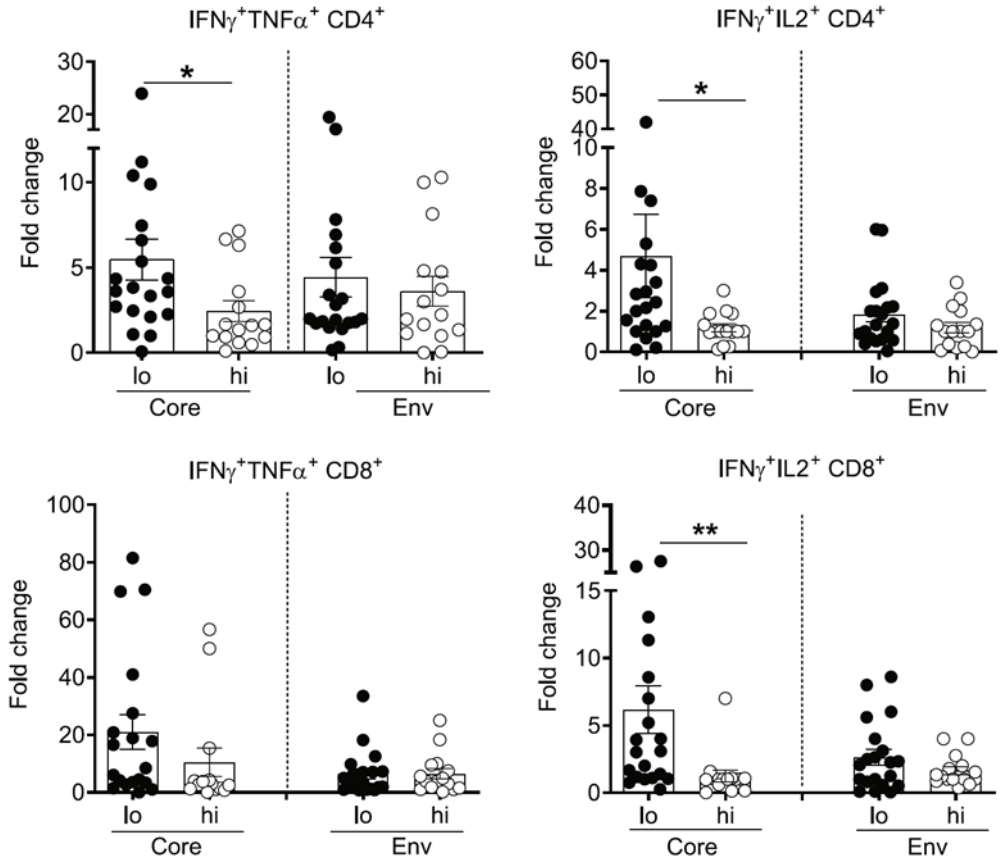
# IMMUNE RESOLUTION OF CHB

## HBsAg levels as an indicator of HBV immune potential




Lo=HBsAg levels <500 IU/ml
Hi = HBsAg levels >50,000 IU/ml

- Persistent high HBsAg levels has a tolerizing effect on HBV-specific immune cells
- Reducing the serum HBsAg in CHB by pharmacological agents could relieve immune cells from functional exhaustion and confer immune control

Kim et al Sci Rep. 2020 Mar 31;10(1):5947

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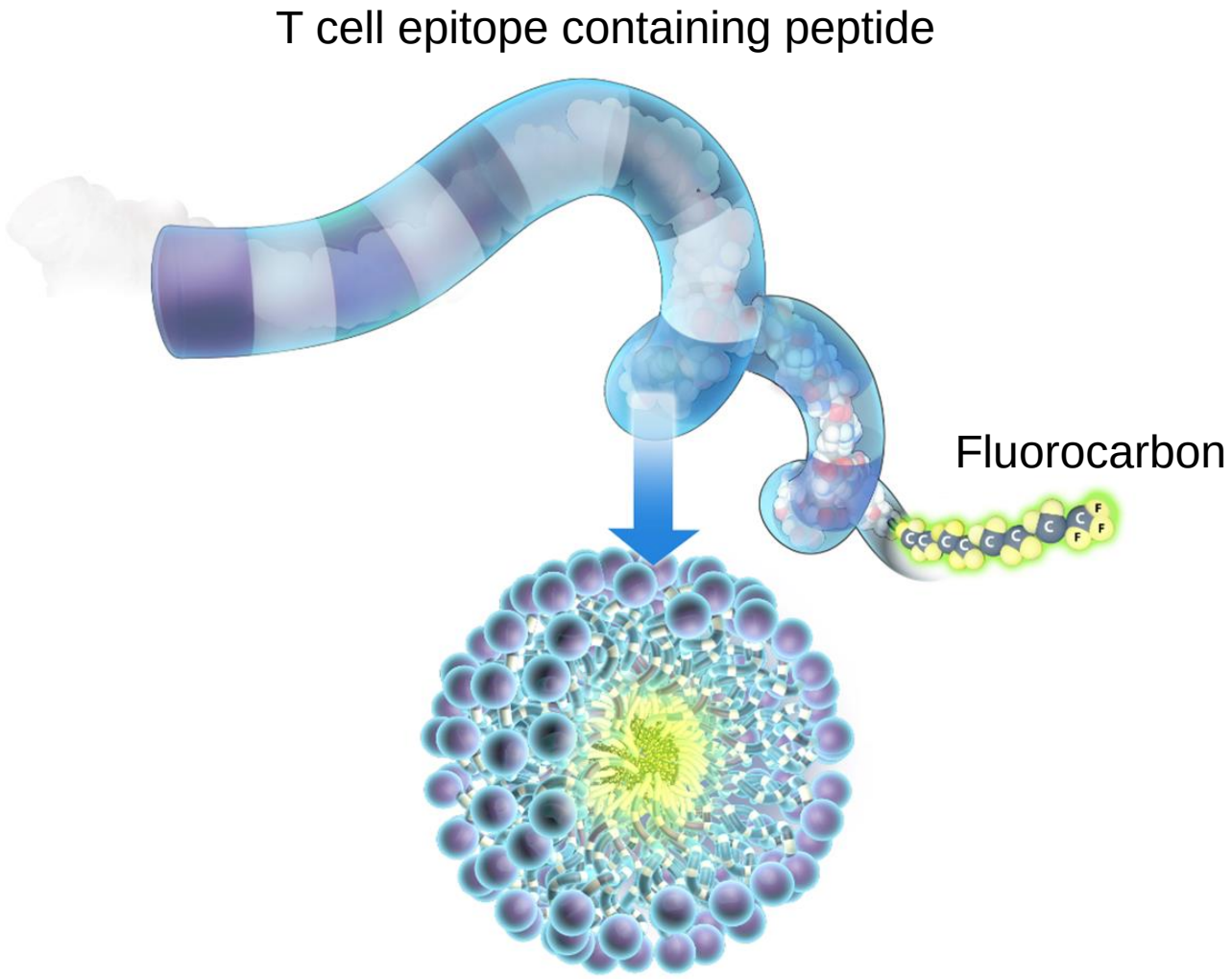
# HEPTCELL IMMUNOTHERAPEUTIC TECHNOLOGY

## Long synthetic peptides to promote CD4+ and CD8+ T cell responses




- 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

Francis et al. Vaccine. 2015 Jan 3;33(2):396-402.

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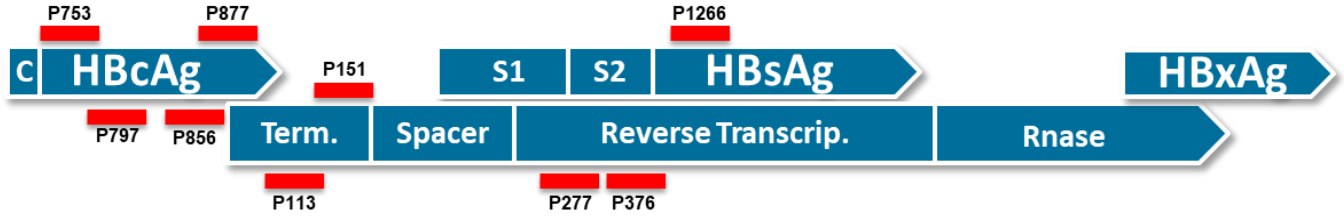
# HEPTCELL IMMUNOTHERAPEUTIC TECHNOLOGY

## Extensive coverage of HBV proteome targets multiple conserved targets




- HepTcell comprises 9 peptides representing 18% of the HBV proteome
- Focuses on key conserved epitope-rich domains within the HBV proteome, mainly polymerase and core protein
- Freeze-dried product, highly stable product at -20°C and 2-8°C
- No homology with human proteins

| Peptides | Length | Proteome Coverage | HBV Genotype | API Stability | Co-formulation Compatibility | Human protein Homology |
|---|---|---|---|---|---|---|
| P113 | 35 | Polymerase | A, B, C, D | >3 years | Yes | No |
| P151 | 35 | Polymerase | A, D | >3 years | Yes | No |
| P277(K) | 39 | Polymerase | A, C | >3 years | Yes | No |
| P376 | 40 | Polymerase | B, D | >3 years | Yes | No |
| P753(K) | 38 | Core | A, B, C, D | >3 years | Yes | No |
| P797(K) | 38 | Core | A, B, D | >3 years | Yes | No |
| P856(K) | 38 | Core | A, B, C, D | >3 years | Yes | No |
| P877 | 31 | Core | A, C, D | >3 years | Yes | No |
| P1266(K) | 39 | Surface | A, B, C, D | >3 years | Yes | No |

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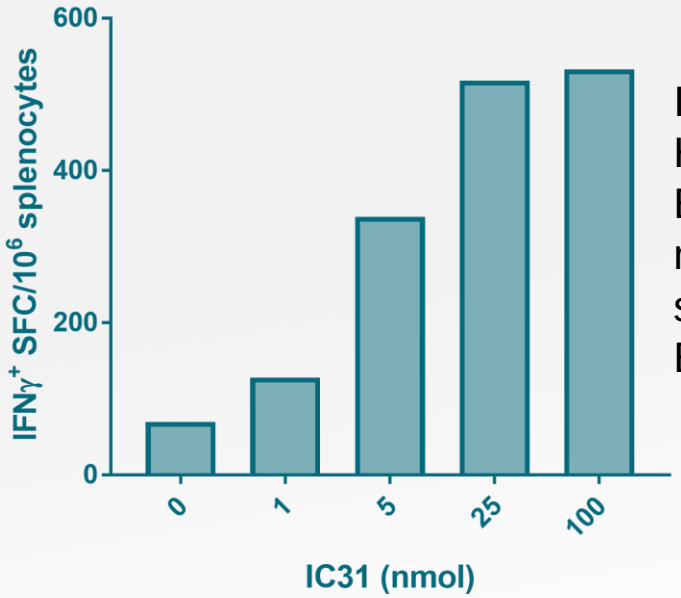
# HEPTCELL PRECLINICAL ACTIVITY

## Adjuvanticity provided by IC31

Improved immune responses in combination with TLR9 adjuvant

**HepTcell response increased by IC31® TLR9 adjuvant**

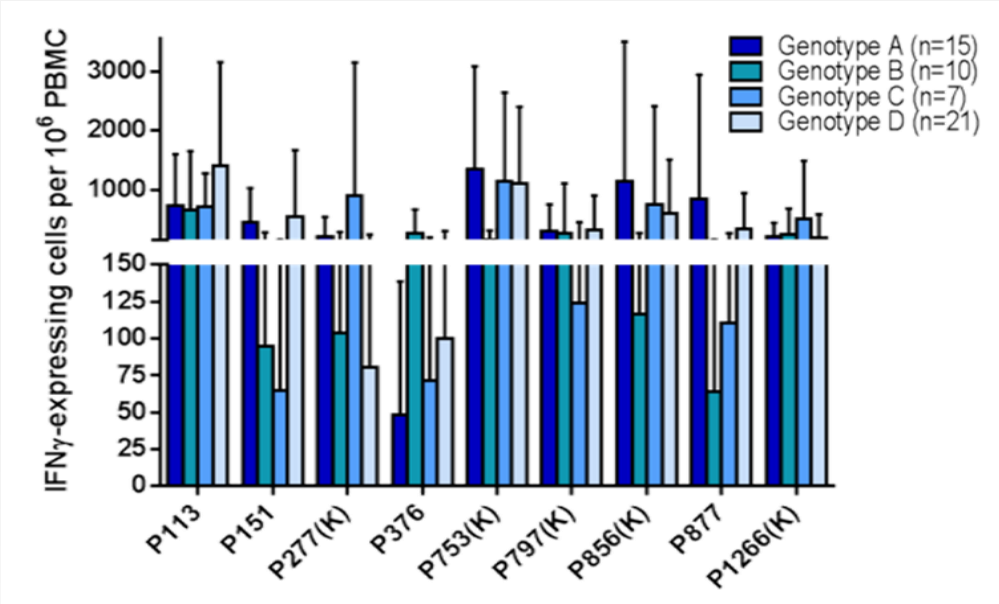



Immunogenicity of HepTcell +/- IC31® in BALB/c mice measured in splenocytes by IFN-γ ELISpot

# HEPTCELL PRECLINICAL ACTIVITY

## Broad cross-genotype coverage

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

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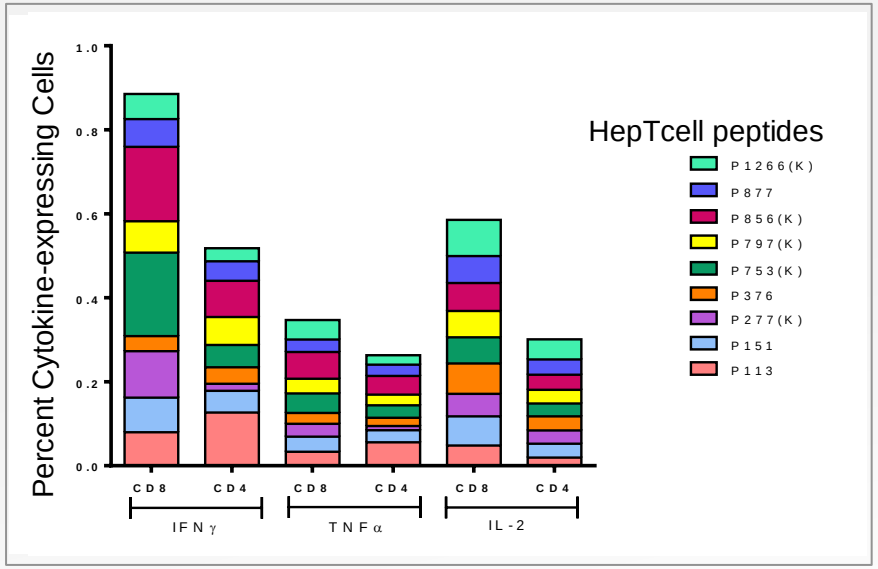
# HEPTCELL PRECLINICAL ACTIVITY

## Potent T cell stimulation

HepTcell stimulates polyfunctional CD4+ and CD8+ T cells from chronically infected subjects




- All peptides show response
- Activation of HBV helper and cytotoxic T cells
- Th1 cytokine profile for cell-mediated killing

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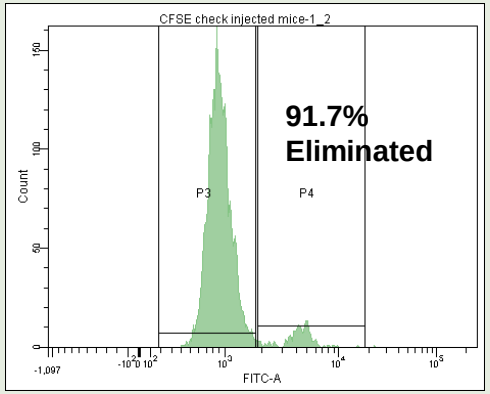
# HepTcell PRECLINICAL ACTIVITY

## Animal models demonstrate clearing of HBV loaded cells and breaking of immune tolerance

*In vivo* killing assay

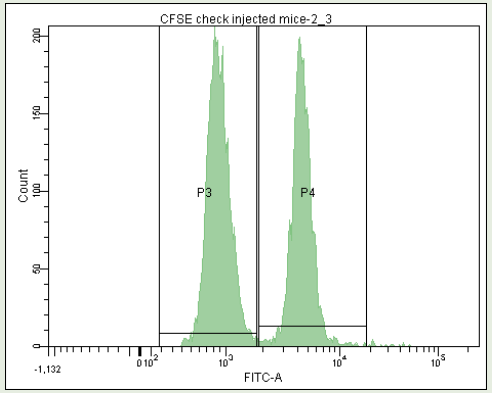
HepTcell + IC31® stimulates T cell responses that clear over 90% of cells loaded with HBV antigens in one day

VACCINATED ANIMAL




cell+flu | cell+HBV

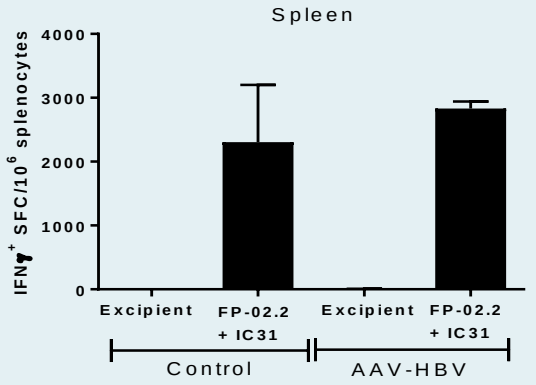
CONTROL ANIMAL

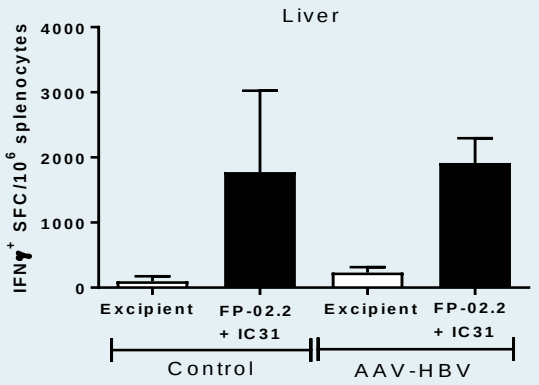



cell+flu | cell+HBV

AAV-HBV mouse model

HepTcell + IC31® breaks tolerance and stimulate strong T cell responses in the spleen and liver



# HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY

## Study in subjects chronically infected with HBV

**Population (n=60)**

- 18-65 yo with eAg negative chronic HBV for ≥ 2 years
- Tenofovir or entecavir for ≥ 2 years
- HBV DNA <50 IU/ml for ≥ 1year
- No history of cirrhosis and current Fibroscan < 11.5 kPa

**Treatment**

- 3 double blind dose escalating cohorts enrolled from sites in UK and Korea
- Low (150 µg) or high dose (500 µg) peptides, with or without IC31, c/w IC31 or saline
- 3 IM injections 28 days apart, followed by 6-month observation

**Endpoints**

- Safety:  Routine labs, AEs, injection site assessment
- Cultured IFN-ɣ Elispot
- qHBsAg

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# HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY

## Baseline characteristics

| | Low (N=10) | Low+IC31 (N=10) | High (N=10) | High+IC31 (N=11) | IC31 (N=10) | Placebo (N =10) |
|---|---|---|---|---|---|---|
| Sex (%male) | 90 | 100 | 70 | 73 | 50 | 90 |
| Race (% white) | 10 | 10 | 0 | 0 | 0 | 10 |
| % black | 30 | 30 | 10 | 0 | 0 | 10 |
| % Asian | 50 | 50 | 70 | 100 | 90 | 30 |
| % other/multiracial | 10 | 10 | 20 | 0 | 10 | 50 |
| Age: (median, min-max) | 39.5 (33-53) | 50 (40-63) | 45.5 (41-65) | 47 (34-64) | 49.5 (40-65) | 47.5 (38-57) |
| Fibroscan (median, min-max) | 4.80 (3.3-6.9) | 5.15 (3.5-7.3) | 6.10 (3.3-10.0) | 4.80 (3.0-6.3) | 3.90 (2.6-7.2) | 5.80 (3.8-8.2) |
| $Log_{10}$ qHBsAg IU/ml (median, min-max) | 2.88 (1.16-3.53) | 2.99 (1.56-3.98) | 2.80 (-0.49-4.14) | 3.02 (2.32-3.75) | 3.22 (-1.52 -3.51) | 3.77 (1.51-4.24) |
| ALT (median, min-max) | 22 (12-33) | 30 (14-46) | 23 (16-38) | 17 (14-25) | 15 (11-39) | 26 (17-37) |

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# HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY

## Safety

- 1 SAE (infectious colitis between dose 2 and 3) in High + IC31 subject
- No autoimmune events
- No hepatitis flares
- No trends in other AEs
- Injection site reactions were self-limited and mild-moderate except for one patient with severe tenderness in the low + IC31 group

**Investigator Assessed Injection Site Reactions**

| | Low (N=10) | Low + IC31 (N=10) | High (N=10) | High + IC31 (N=11) | IC31 (N=10) | Placebo (N =10) |
|---|---|---|---|---|---|---|
| Any Reaction (%) | 60 | 60 | 50 | 46 | 10 | 20 |
| Burning (%) | 0 | 30 | 20 | 0 | 0 | 10 |
| Erythema (%) | 0 | 10 | 0 | 9 | 0 | 20 |
| Induration (%) | 0 | 0 | 10 | 0 | 10 | 20 |
| Swelling (%) | 20 | 0 | 0 | 0 | 0 | 20 |
| Pain (%) | 60 | 30 | 30 | 36 | 0 | 10 |
| Tenderness (%) | 50 | 40 | 50 | 10 | 0 | 20 |

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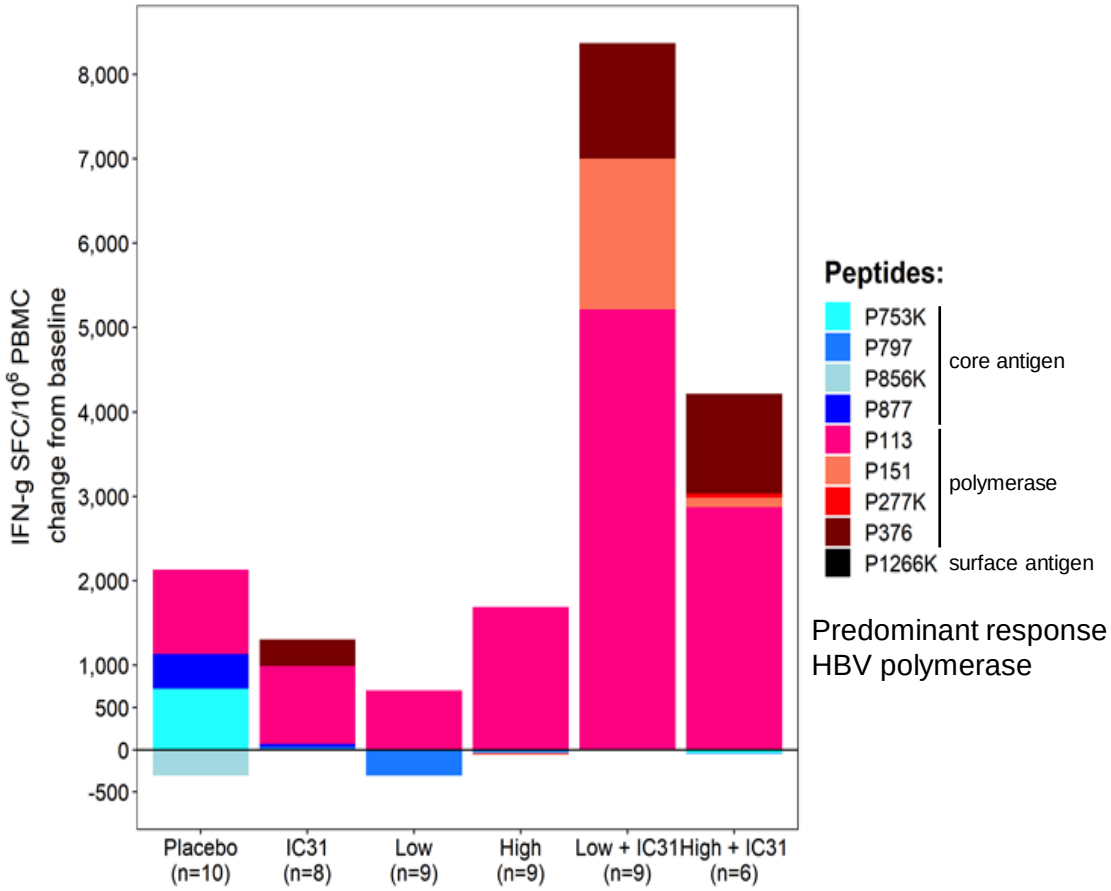
# HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY

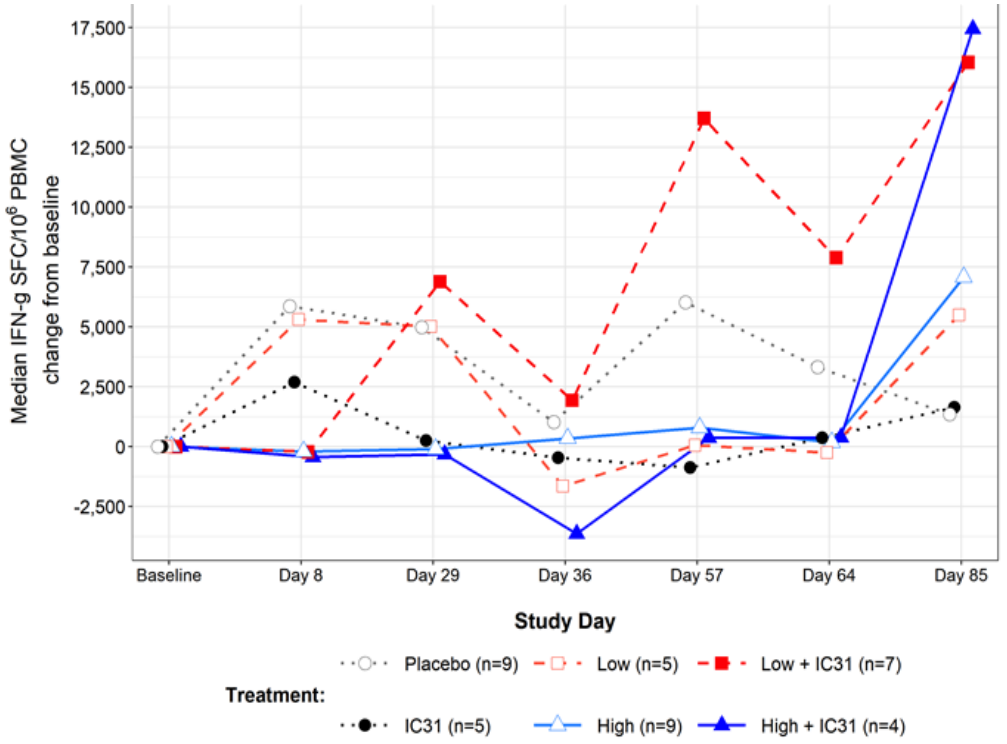
## Robust IFN-γ ELISpot Responses that Increase over Time

### Change from Baseline, Day 85




Predominant response to HBV polymerase

### Change from Baseline over Successive Administrations

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# HEPTCELL: PHASE 2 IMMUNOGENICITY AND EFFICACY TRIAL

## Rationale for the study design

- Patients with inactive chronic infection with HBsAg levels ≤ 100 IU/mL is a subpopulation that might demonstrate a response to immunotherapy
  - Patients with high levels of serum HBsAg and unfavorable immunological status are known to rarely achieve spontaneous or treatment-induced HBsAg decline or loss
    - T cell responses in chronically HBV infected subjects, especially against core antigen, are inversely associated with serum HBsAg concentration [Loggi 2013]
  - Inactive carriers with low HBsAg levels have been shown to achieve higher rate of HBsAg loss and seroconversion with IFN-α treatment [Cao 2017]
- Virologic response appears to be more likely to occur with a longer duration of immunotherapy
- HepTcell could be used in combination with one of the newer direct acting agents in active HBV to drive down HBsAg to levels sufficient to generate immunogenicity

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# HEPTCELL – PHASE 2 CLINICAL TRIAL

Multinational, multicenter trial of HepTcell in inactive chronic hepatitis B (CHB)

- 80 patients with hepatitis B e-antigen negative inactive CHB and HBsAg ≤ 100 IU/mL randomized 1:1 to HepTcell or placebo administered every 4 weeks for 24 weeks
- Follow-up study phase of 48 weeks after the last dose will assess the safety and durability of response of treatment
- 20 sites in the US, Canada and Europe
- Efficacy endpoints
  - Primary endpoint: proportion of patients with 1.0-log reduction in HBsAg from baseline at Week 24
  - Secondary endpoints: HBsAg clearance, changes from baseline in HBsAg, HBV DNA, HBcrAg, pg-RNA at Week 24
- Data readout expected in Q2 2022

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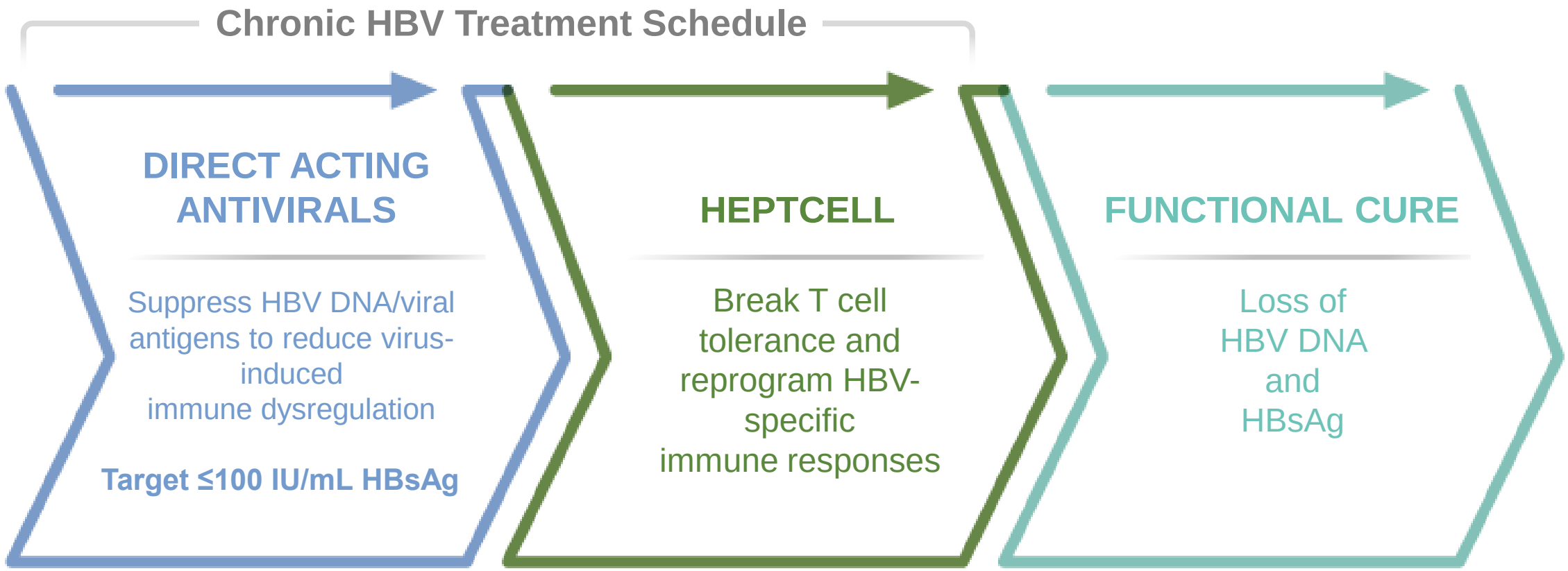
# HEPTCELL – KEY COMPONENT OF COMBINATION APPROACH

Combination with novel direct-acting antivirals for improved activity

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# How We Can Achieve Success with Immunotherapeutics in the Treatment of Chronic Hepatitis B

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