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# Immunotherapeutics in the Treatment of Chronic Hepatitis B

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World Antiviral Congress
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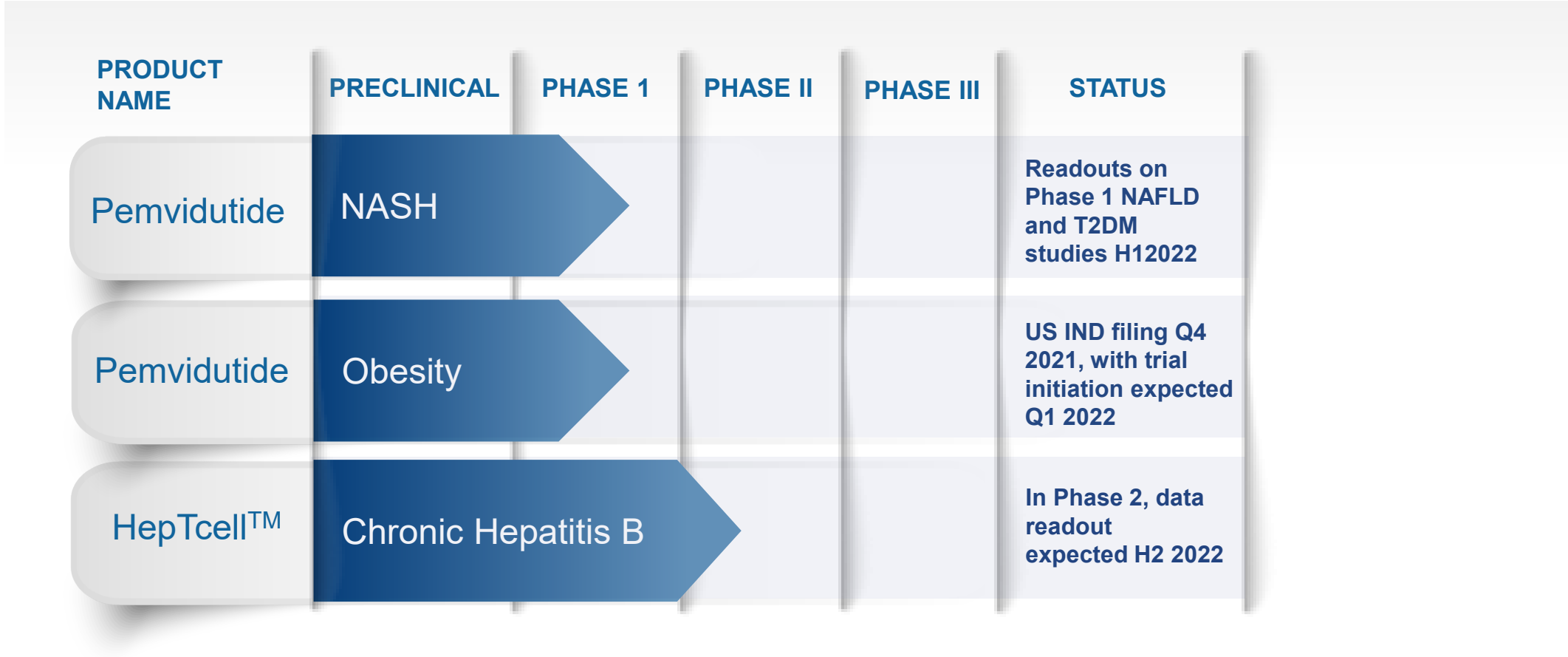
# FOCUS ON LIVER AND METABOLIC DISEASES

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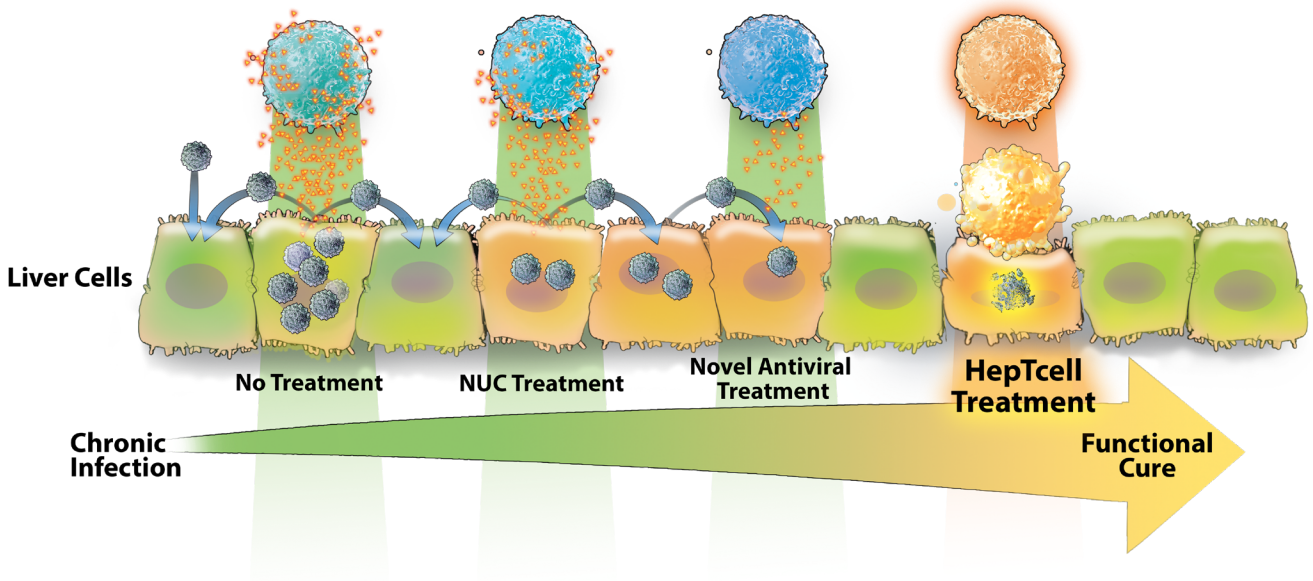
# CURRENT HBV THERAPEUTICS DO NOT LEAD TO FUNCTIONAL CURE

## 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 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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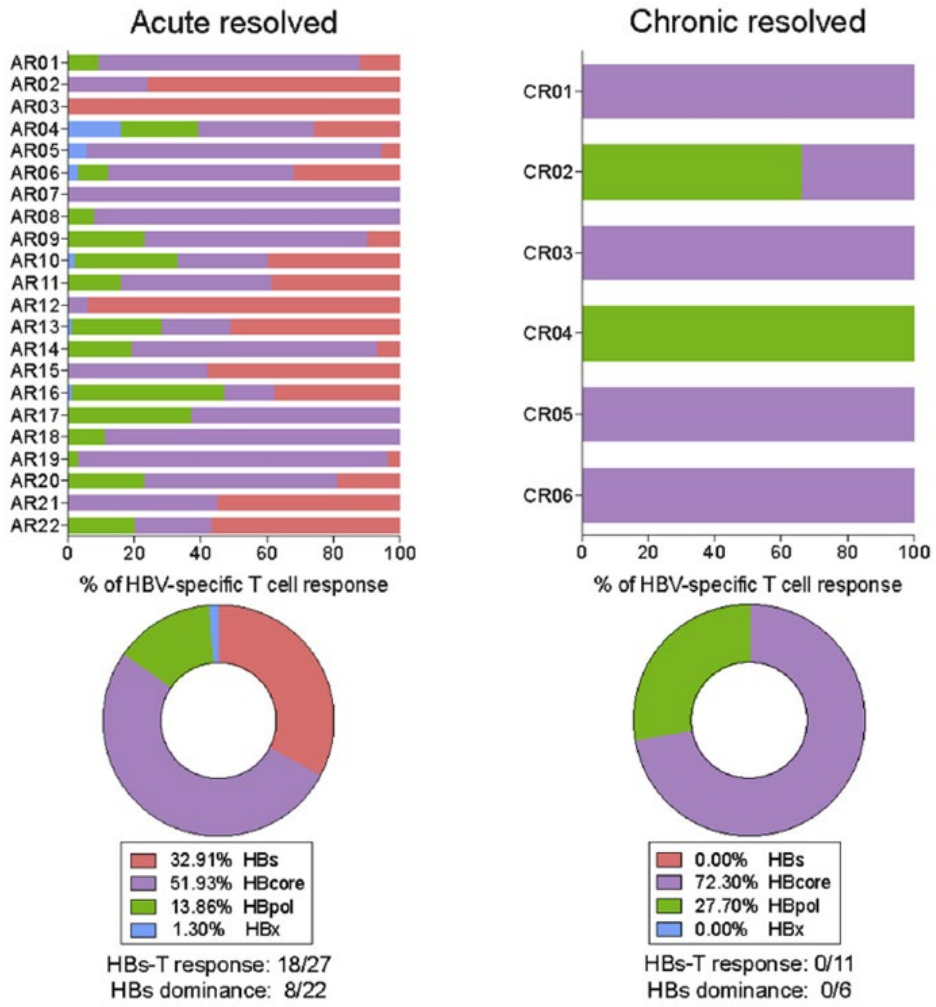
# IMMUNE RESOLUTION OF CHB

## 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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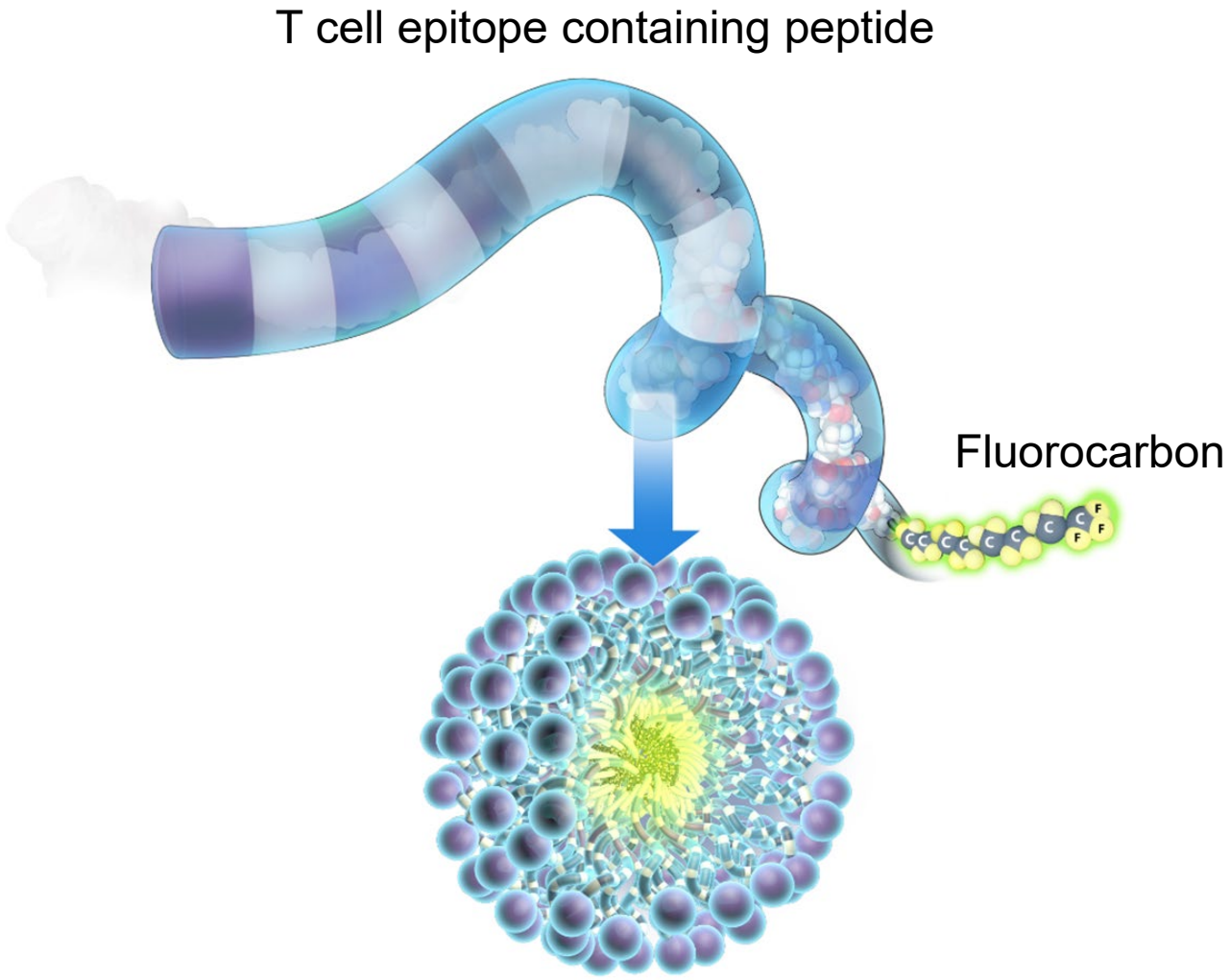
# HEPTCELL IMMUNOTHERAPEUTIC TECHNOLOGY

## 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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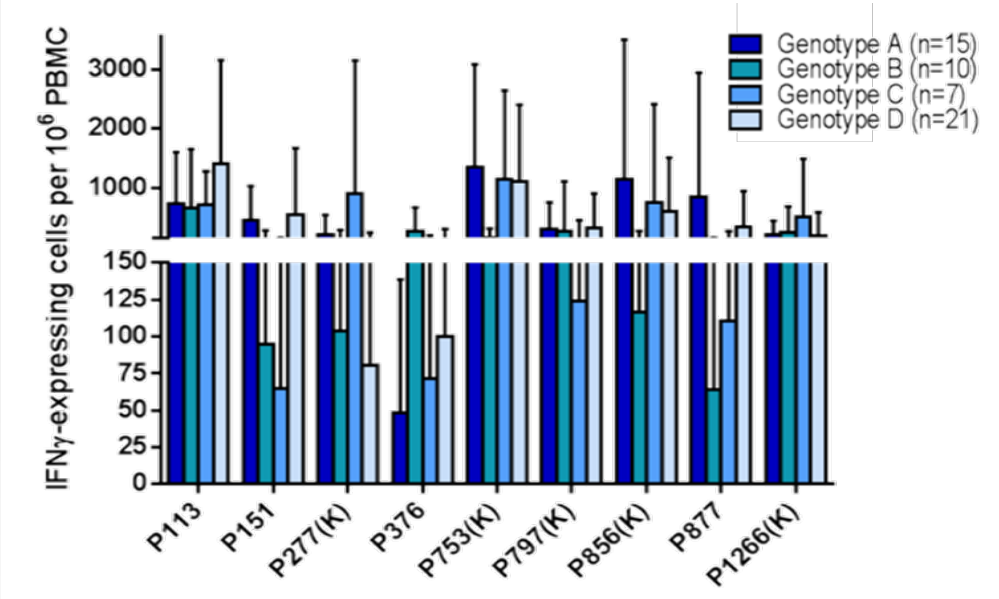
# HEPTCELL PRECLINICAL ACTIVITY

## 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: 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

## 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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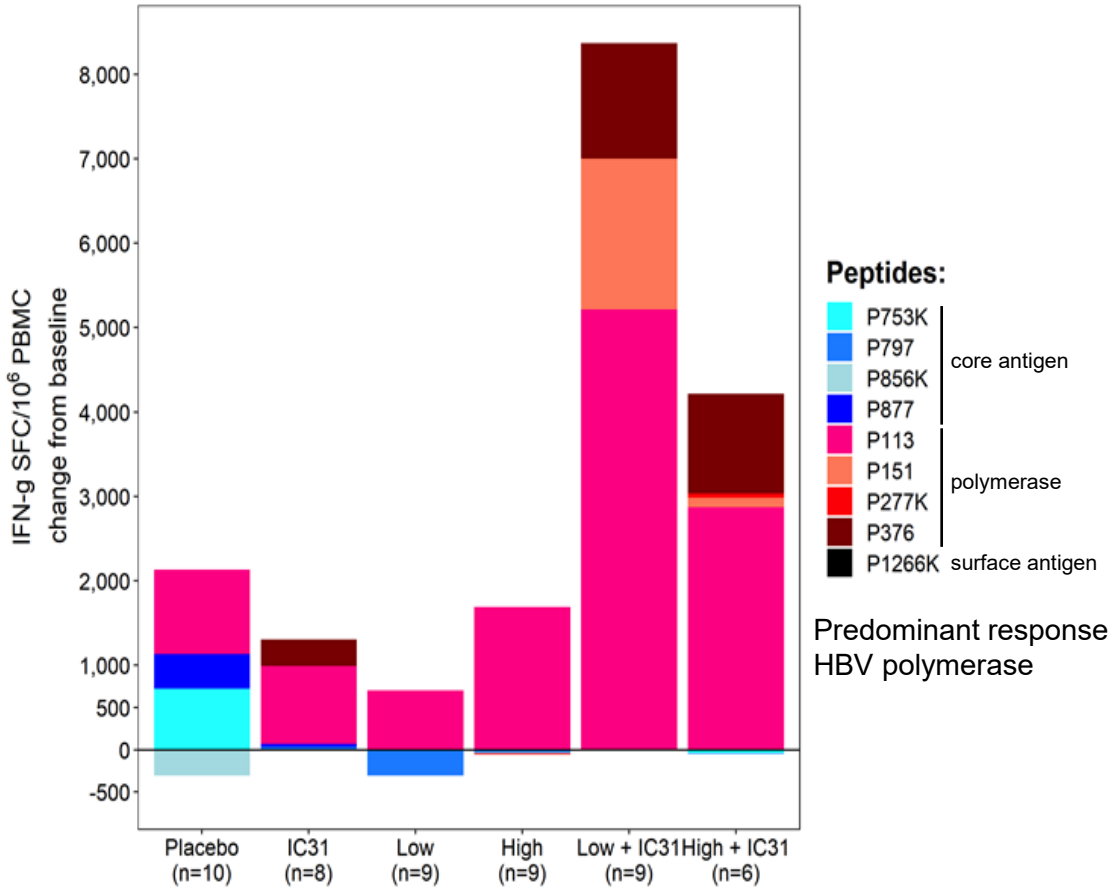
# HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY

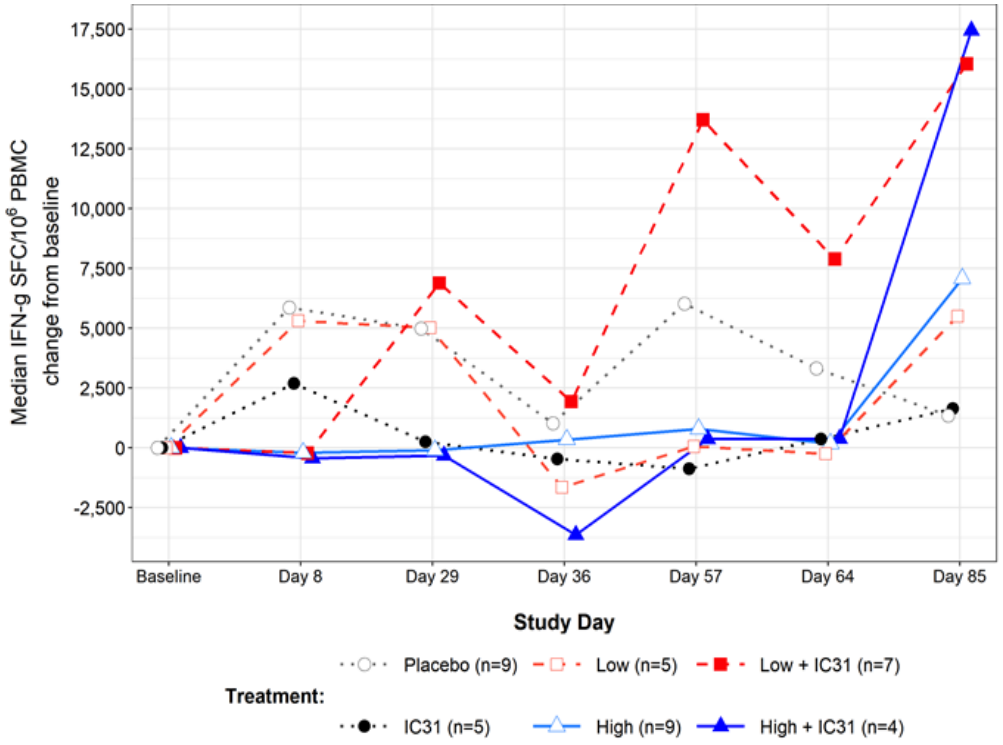
## Robust IFN-γ ELISpot Responses that Increase over Time

### Change from Baseline, Day 85




Predominant response to HBV polymerase

### Change from Baseline over Successive Administrations

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# HEPTCELL – PHASE 2 CLINICAL TRIAL

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

- 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
- Data readout expected in H2 2022

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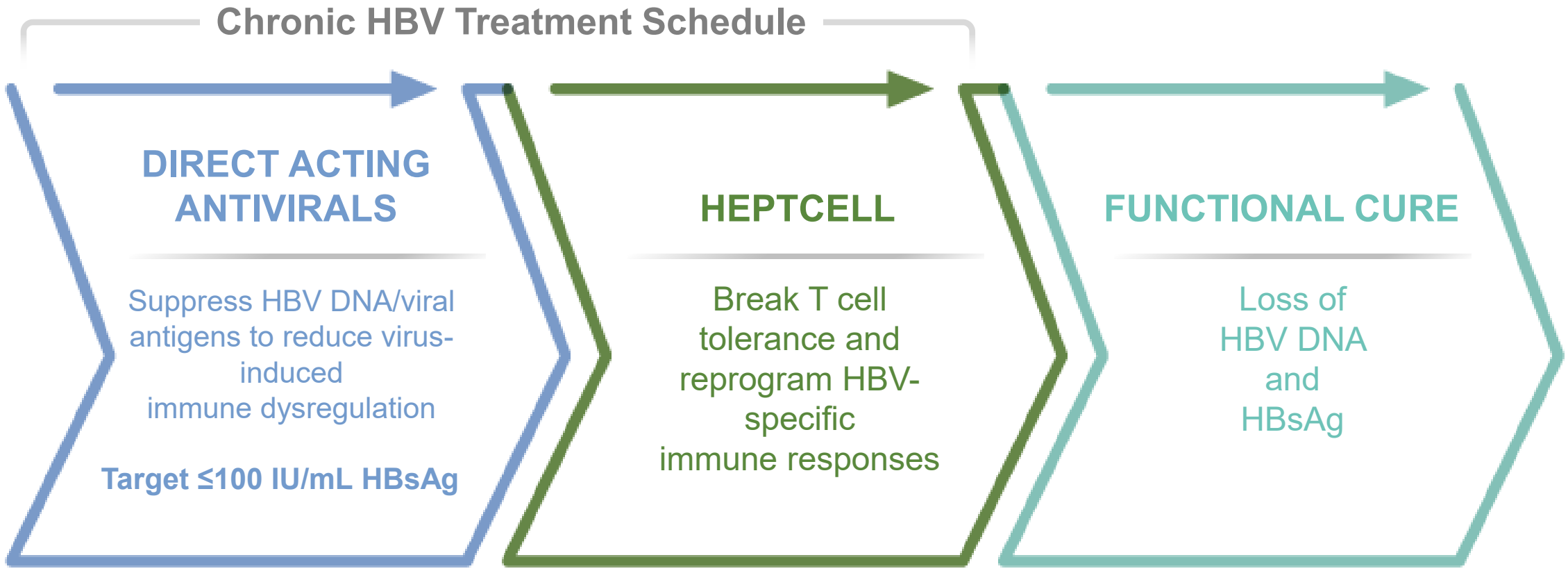
# HEPTCELL – KEY COMPONENT OF COMBINATION APPROACH

Combination with novel direct-acting antivirals for improved activity

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