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HepTcell as Immunotherapy to Achieve Functional Cure for Chronic HBV

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Chronic HBV Drug Development
April 2022

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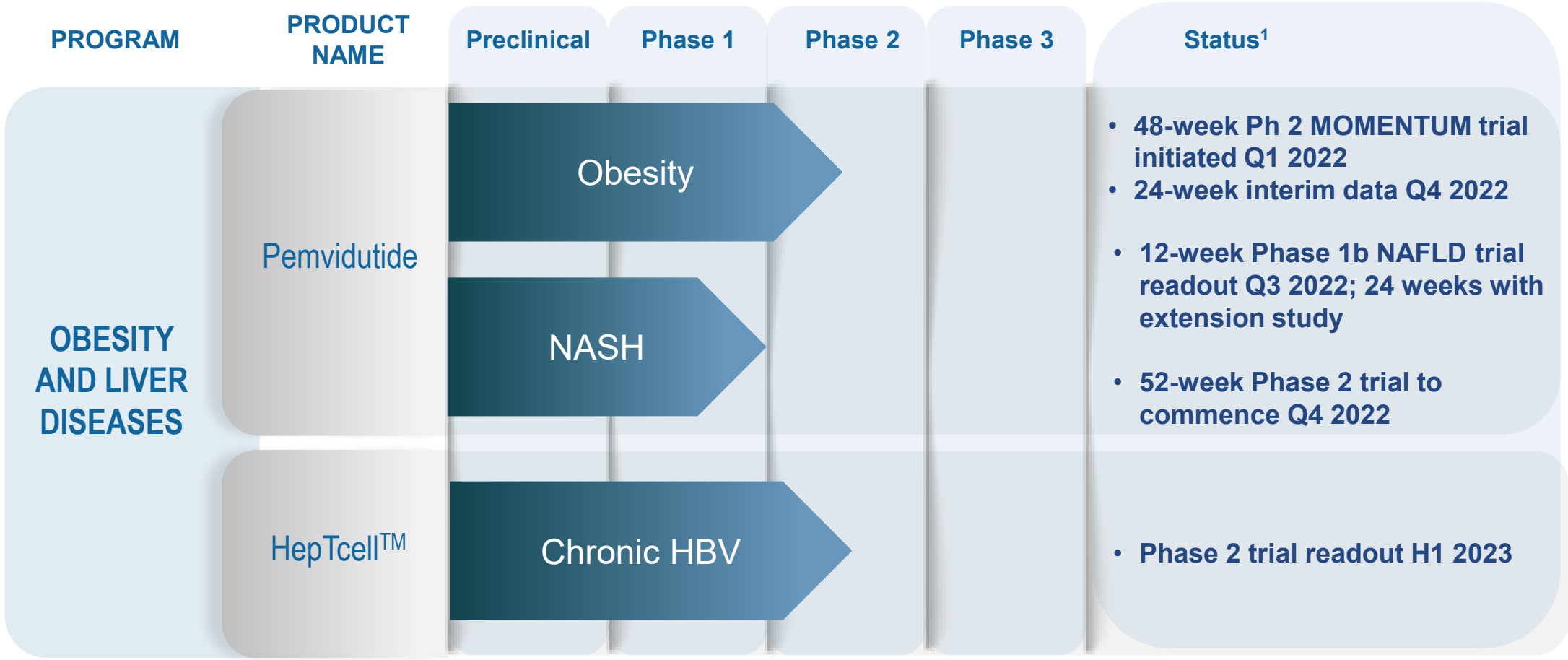
ALTIMMUNE - FOCUS ON LIVER AND METABOLIC DISEASES



[1] *expected dates*

CURRENTLY APPROVED HBV THERAPEUTICS DO NOT LEAD TO A CURE

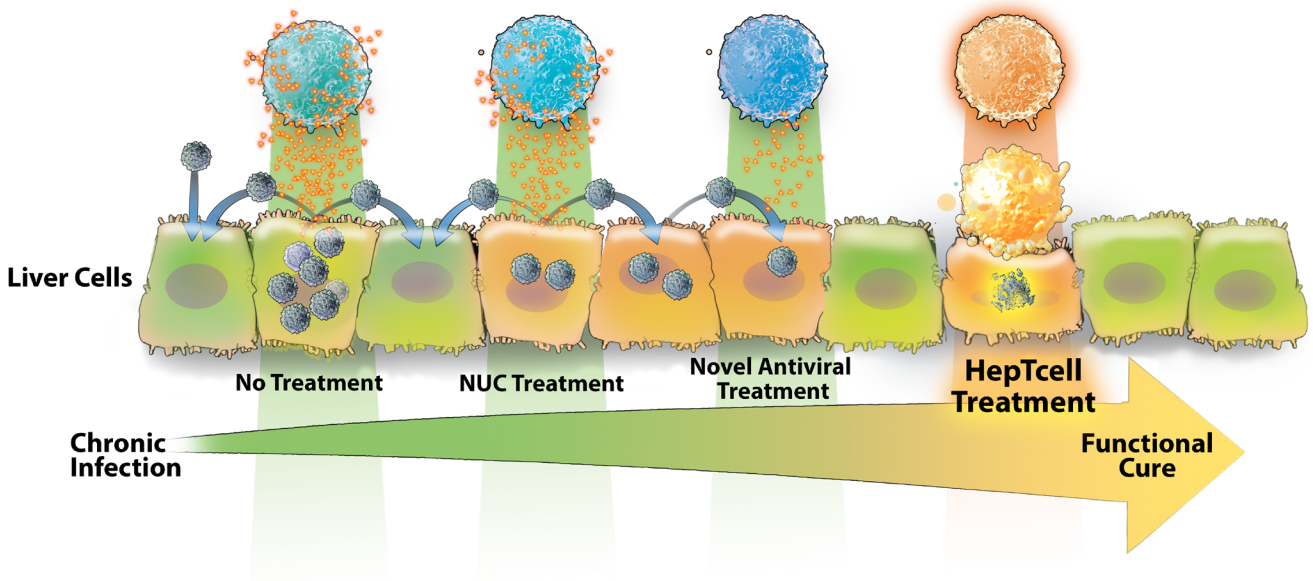
Immune activation will be required for significant impact

Current antivirals prevent disease progression but **rarely clear chronic infection**

Breaking T cell immune tolerance is key to functional cure

Antigen-reduction strategies with newer direct-acting antivirals **unlikely to result in immune reactivation alone**

HepTcell is designed to "wake up" dormant T-cells to eliminate infection



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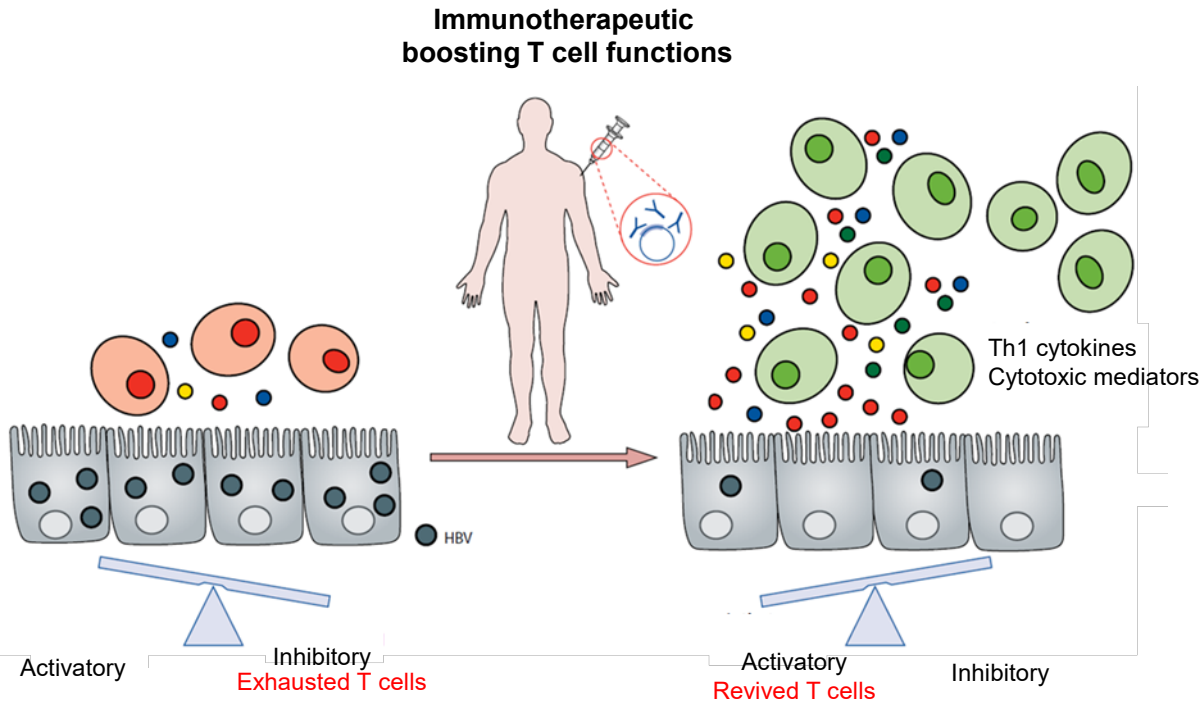
GOAL OF IMMUNOTHERAPY IN CHRONIC HEPATITIS B (CHB)

Restore immune control and mimic spontaneous resolution



- CHB is characterized by a profound immune exhaustion driven by decades of persistent viral antigen presentation
- Spontaneous loss of HBsAg is associated with improved HBV-specific CD4+ and CD8+ T-cell responses
- Resolution of CHB in recipients of bone marrow transplants from donors with HBV immunity

Figure adapted from 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
  - Focus towards surface antigen-specific tolerance barrier
  - Vaccine based on full length antigens - T cell responses biased towards less-conserved domains
  - Weak immunogens/suboptimal 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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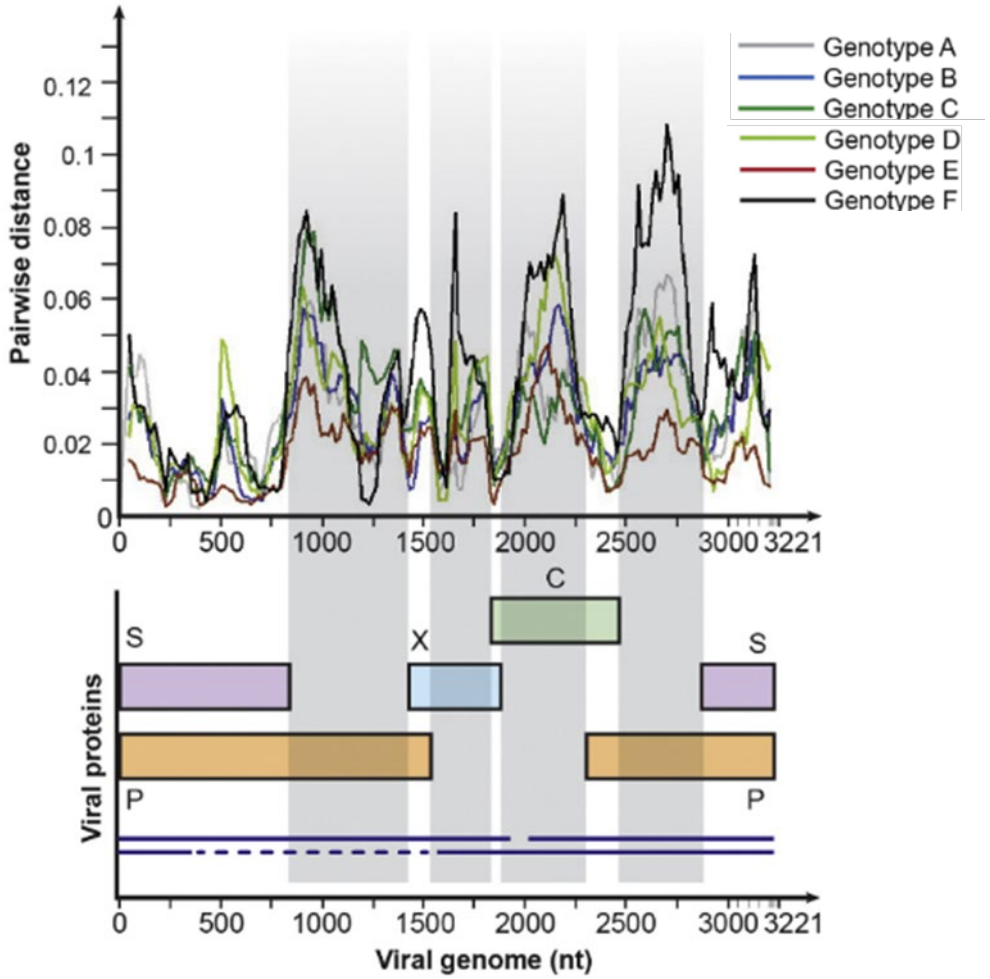
IMMUNE RESOLUTION OF CHB

Importance of targeting conserved regions across the HBV proteome



- Intra- & inter-genotypic variability across the HBV proteome poses challenges to therapeutic vaccination
- HBV utilizes an error-prone reverse transcriptase and T-cell escape mutations have been observed in HBV carriers
- Immunotherapy targeting conserved regions across the HBV proteome is anticipated to provide cross-reactive T-cell responses

Figure adapted from 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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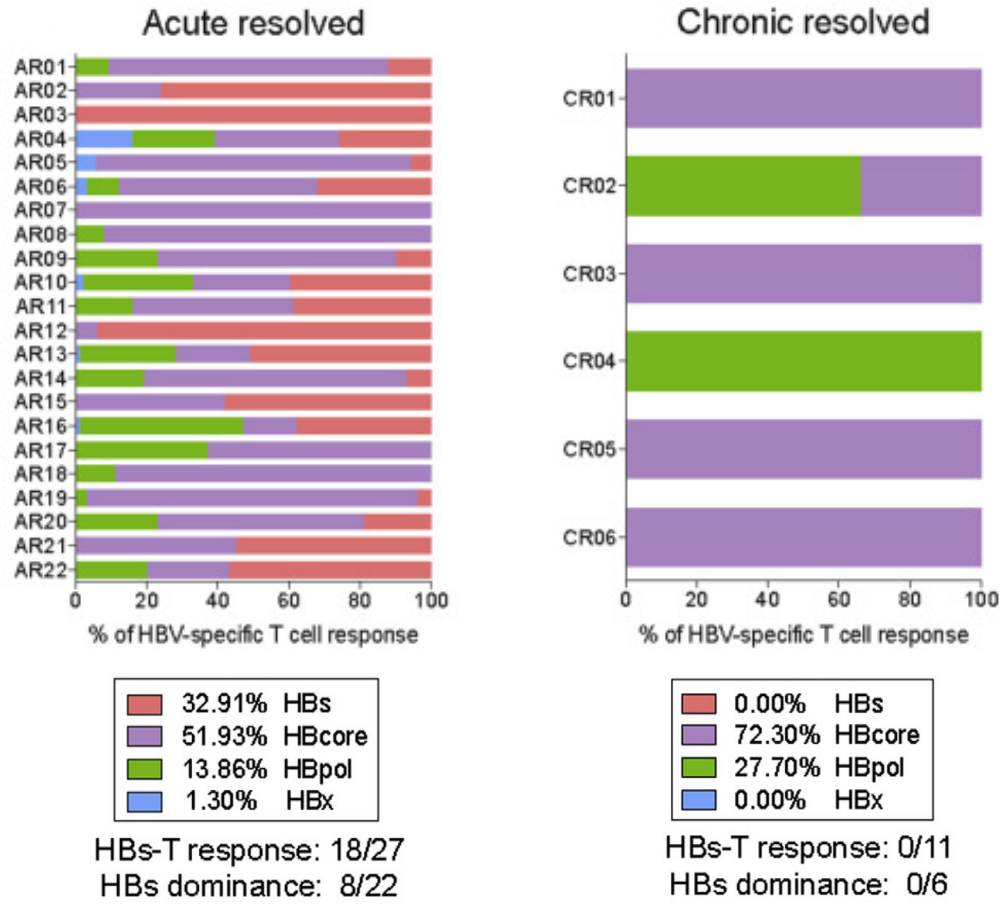
IMMUNE RESOLUTION OF CHB

Importance of core and polymerase as target antigens



- 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
- Ideal HBV therapeutic vaccine should include broad coverage of potentially relevant immunogens

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

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IMMUNE RESOLUTION OF CHB

Indicators of immune potential

- Duration of infection and antigen levels appear to drive peripheral HBV-specific T cell exhaustion
- Lower HBcrAg and/or HBsAg levels are associated with core & pol-specific T cell responses, regardless of age
- In inactive carriers, leukocyte related genes were inversely correlated with liver HBsAg levels
- Reduction of HBsAg by RNAi increased the efficacy of therapeutic vaccines in a mouse model
- Overall, this suggests that antigen-reduction strategies in combination with immunotherapy may improve HBV-specific T cell functions, especially in younger patients

Le Bert Gastroenterology 2020. Aliabadi Gut 2021. Montanari J Infect Dis. 2022. Michler Gastroenterology 2020

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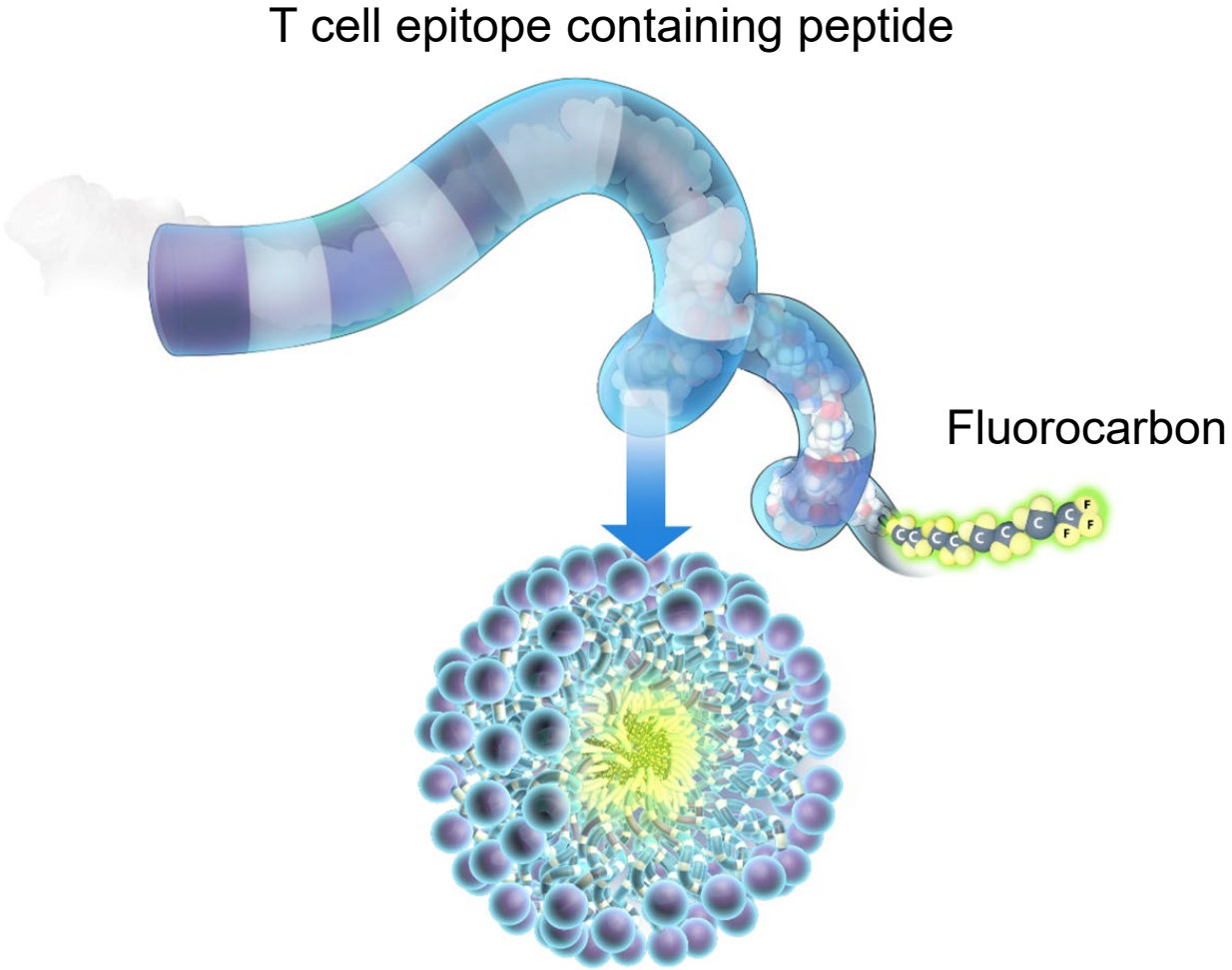
HEPTCELL IMMUNOTHERAPEUTIC TECHNOLOGY

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



- 30 to 40 a.a. long peptides manufactured by solid phase synthesis
- Proprietary bioinformatic platform predicts natural clusters of 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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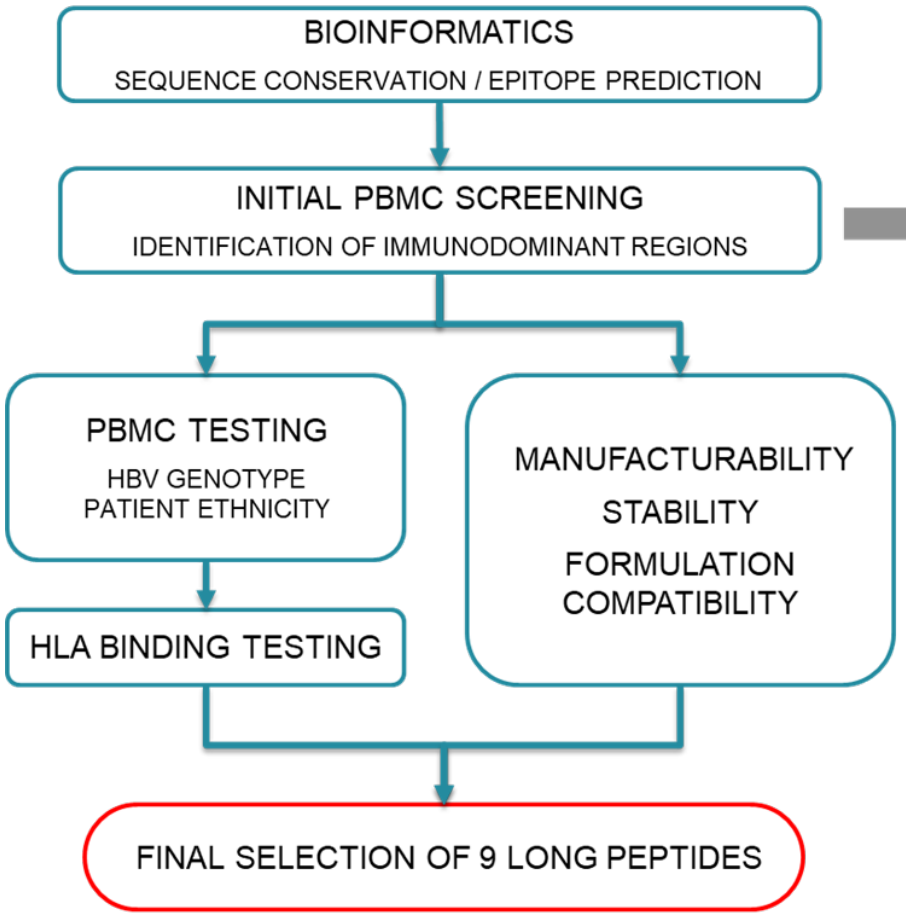
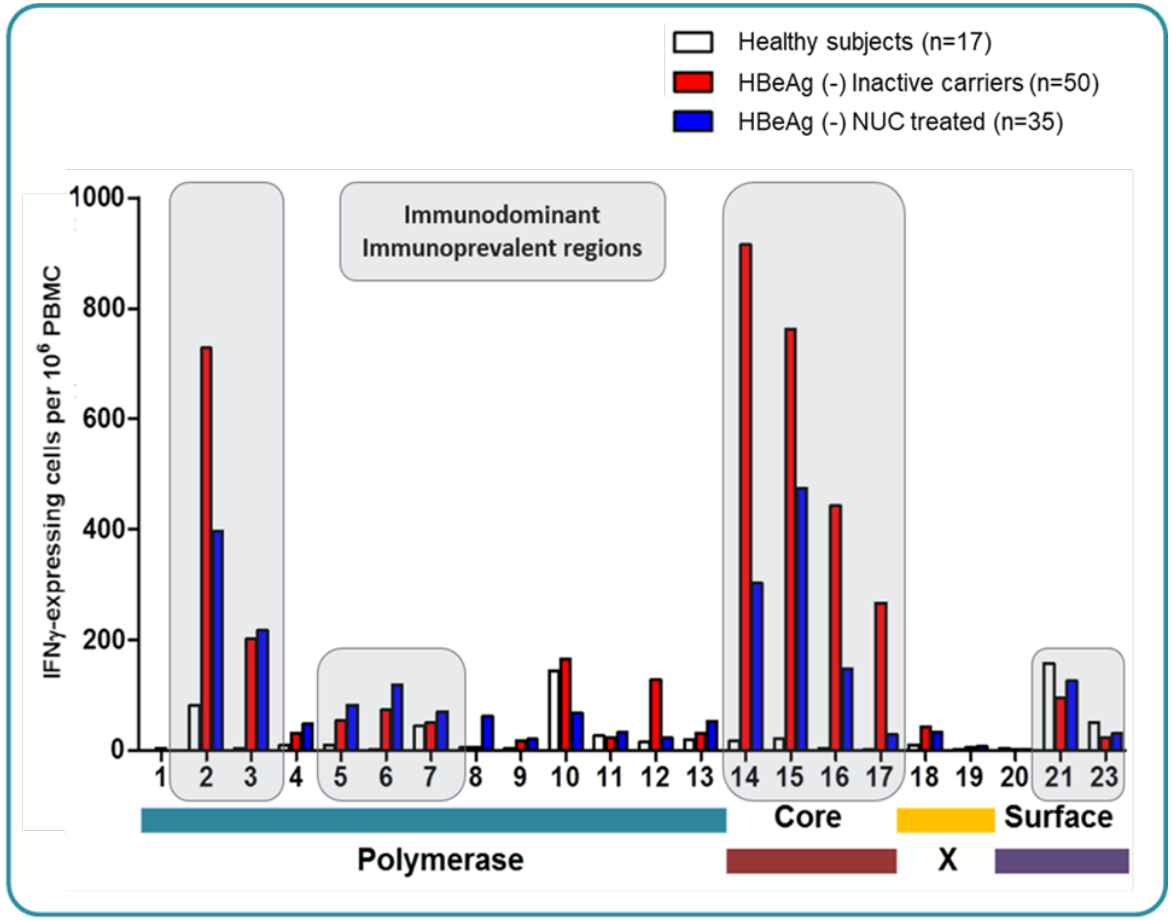
HEPTCELL VACCINE DESIGN

Selection process combining *in silico* and *in vitro* methodologies





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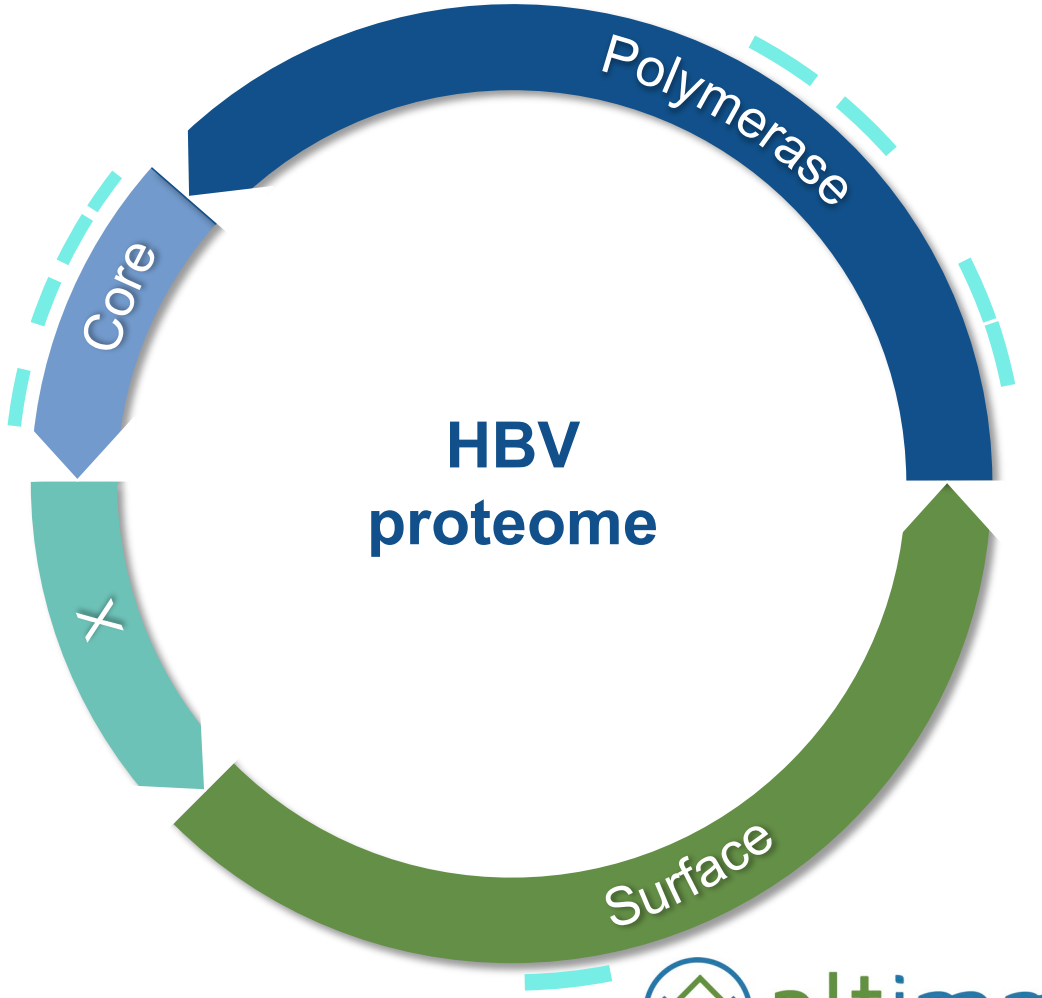
HEPTCELL TECHNOLOGY

Extensive coverage of HBV proteome targets multiple conserved targets

HepTcell comprises 9 peptides
representing ~20% of the HBV proteome

Focused on key conserved domains
within the HBV proteome, primarily in polymerase and core proteins

Immunogenicity of peptides validated in preclinical studies using samples from chronic-infected subjects



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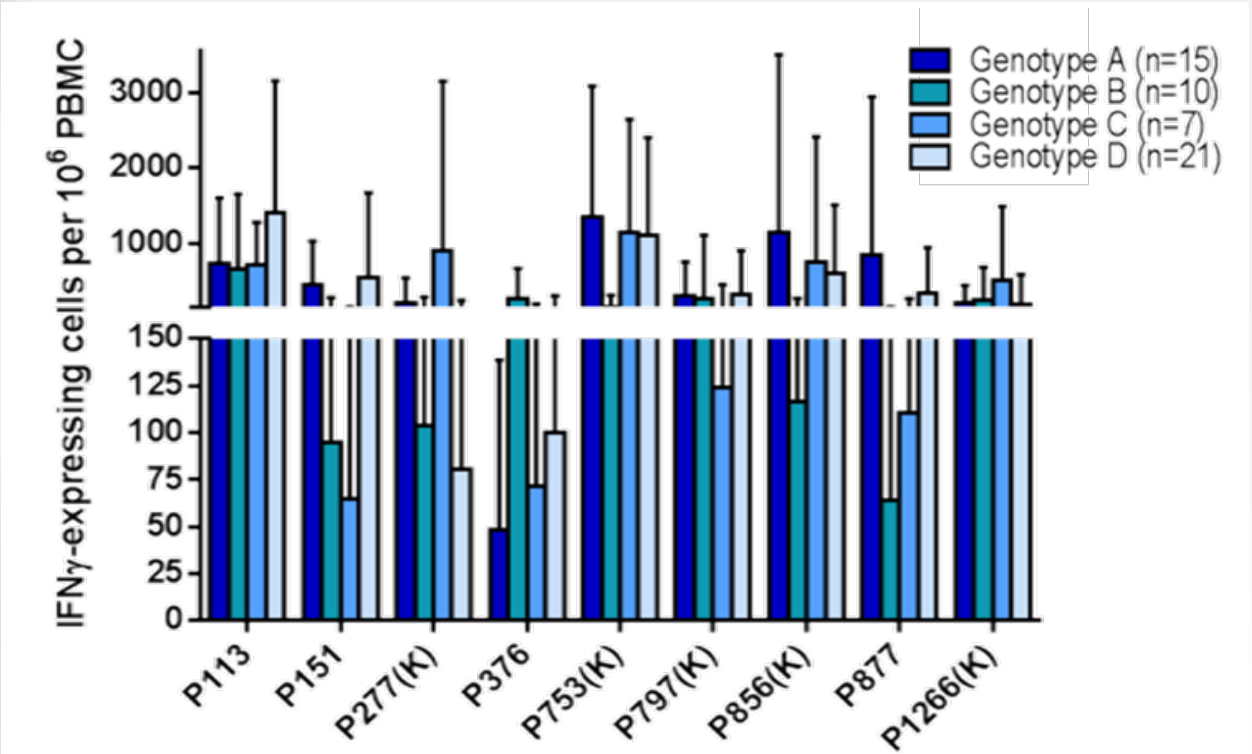
HEPTCELL PRECLINICAL ACTIVITY

Broad cross-genotype coverage

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



- Collectively, HepTcell peptides cross-react with genotypes A-D
- Based on HBV homology, HepTcell expected to cross-react with all HBV genotypes
- Immune responses stimulated irrespective of ethnic background
- Flow cytometry analyses demonstrate polyfunctional CD4+ and CD8+ T cell responses

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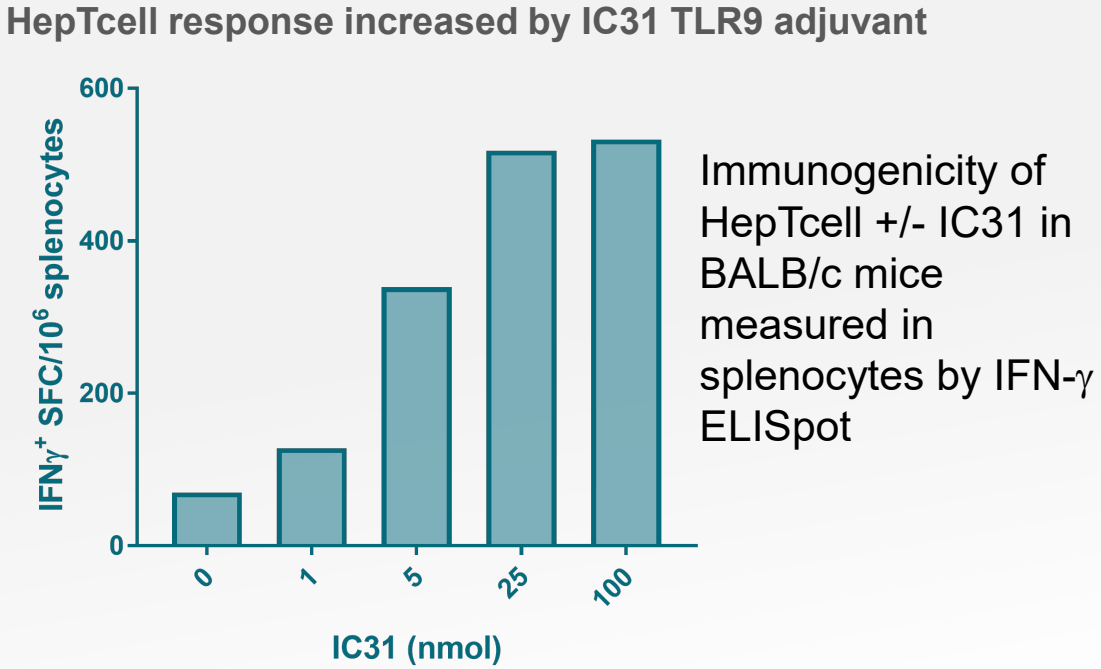
HEPTCELL PRECLINICAL ACTIVITY

Co-formulation with IC31 (TLR9 agonist) adjuvant

Improved immune responses in combination with TLR9 adjuvant



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

- IC31® adjuvant is a strong inducer of interferon, which boosts the immunogenicity of HepTcell
- Clinical responses with IC31 consistent with preclinical data

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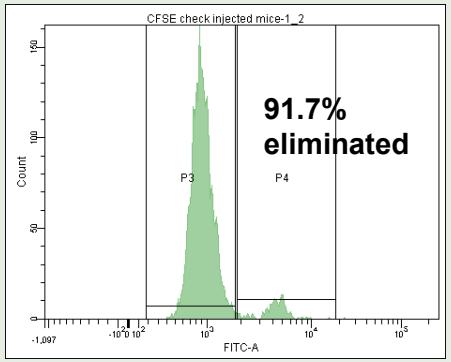
HEPTCELL PRECLINICAL ACTIVITY

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

In vivo killing assay

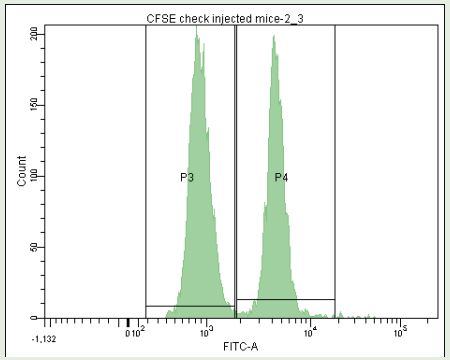
HepTcell + IC31® stimulates T cell responses that clear over 90% of cells loaded with HBV antigens in one day

VACCINATED ANIMAL



cell+flu | cell+HBV

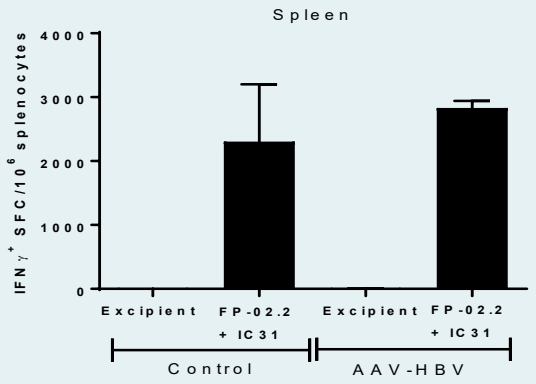
CONTROL ANIMAL

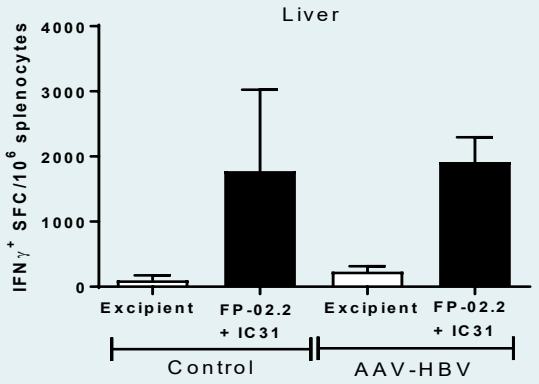


cell+flu | cell+HBV

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

60 HBeAg- chronic HBV patients

Well controlled on licensed antivirals (entecavir or tenofovir)

DESIGN

3 injections 28 days apart

4 different regimens vs placebo and adjuvant alone

RESULTS

All regimens well tolerated

No liver flares or autoimmune events

Increased T cell response to HBV peptides in adjuvanted regimens

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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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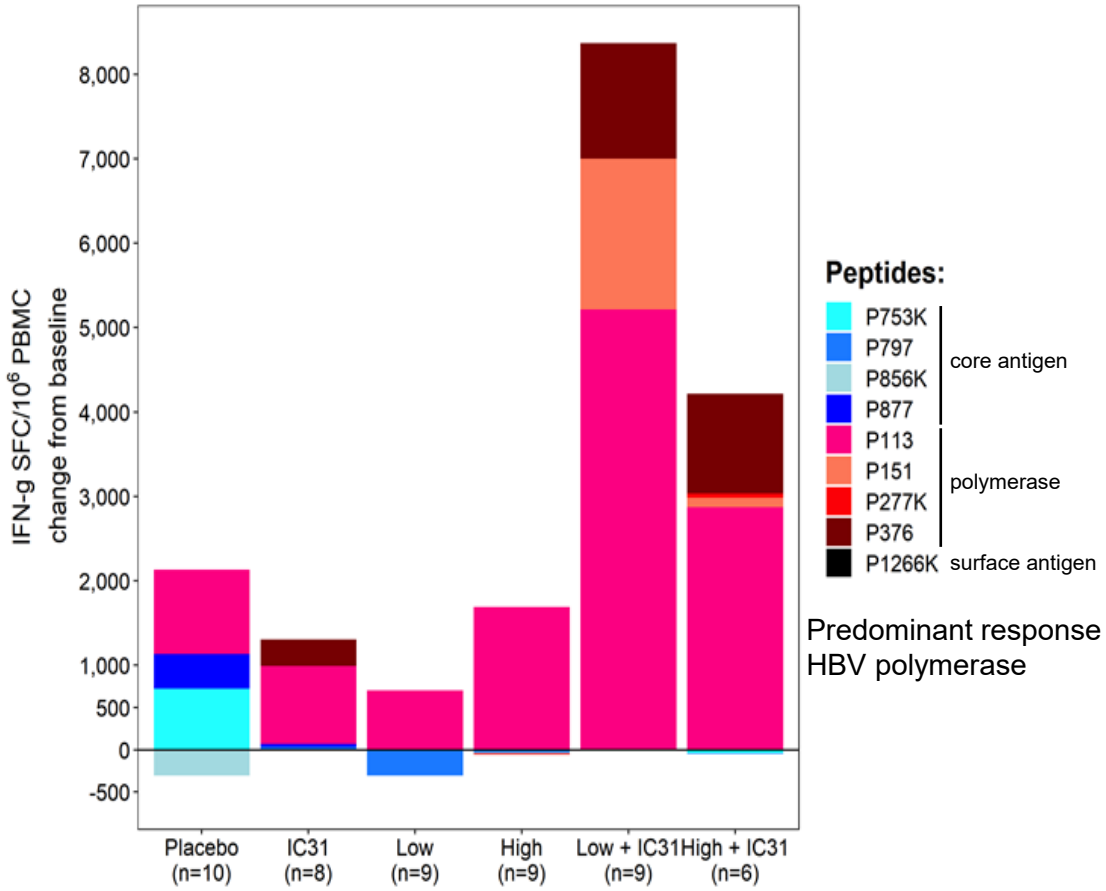
HEPTCELL PHASE 1 SAFETY AND IMMUNOGENICITY STUDY

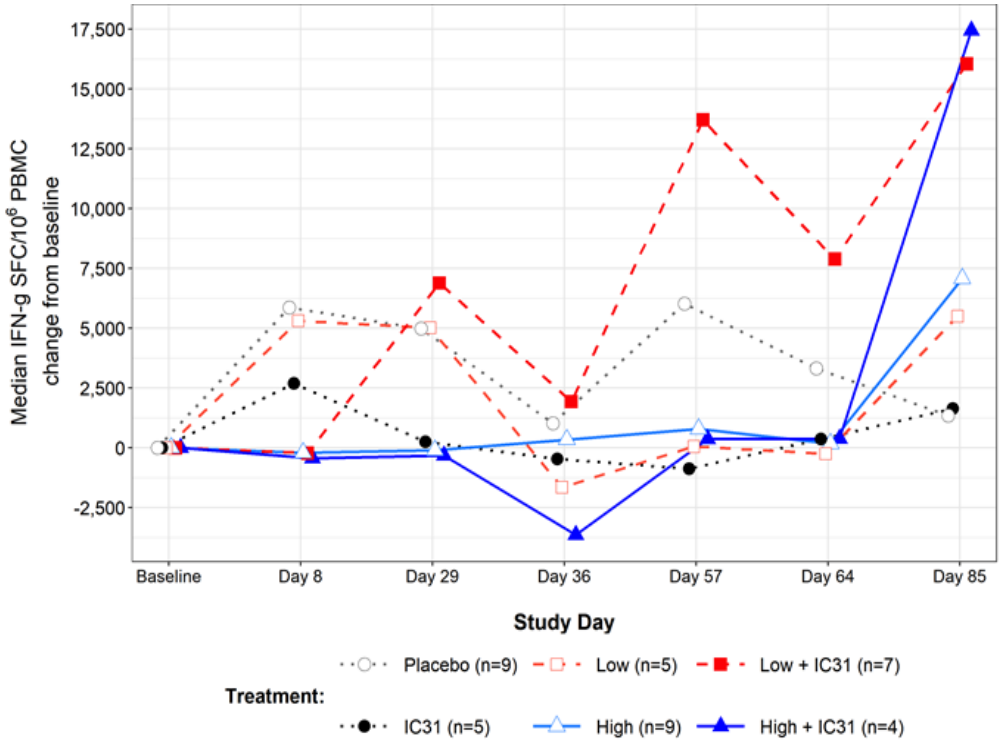
Robust IFN-γ ELISpot Responses that Increase over Time

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 better responses to immunotherapy
  - Patients with high levels of serum HBsAg are known to rarely achieve spontaneous or treatment-induced HBsAg decline or loss
  - Inactive carriers with low HBsAg levels have been shown to achieve higher rate of HBsAg loss and seroconversion with IFN-α treatment
- 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 HBV antigens to levels sufficient to generate immunogenicity

Cao *et al* Hepatology 2017

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HEPTCELL PHASE 2 CLINICAL TRIAL

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

- 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 study phase of 48 weeks after the last dose will assess the safety and durability of response of treatment
- 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
- 23 sites in the US, Canada and Europe
- Data readout expected in H1 2023

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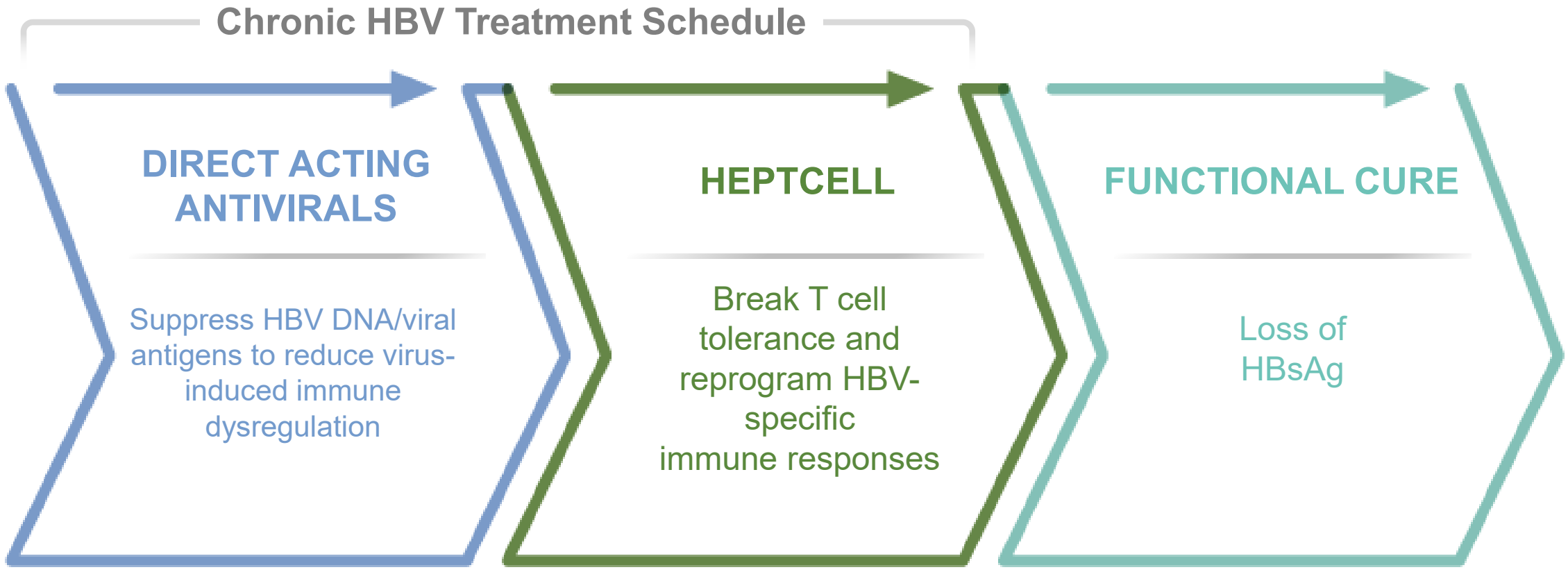
HEPTCELL – KEY COMPONENT OF COMBINATION APPROACH

Combination with novel direct-acting antivirals for improved activity



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Chronic HBV Drug Development
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