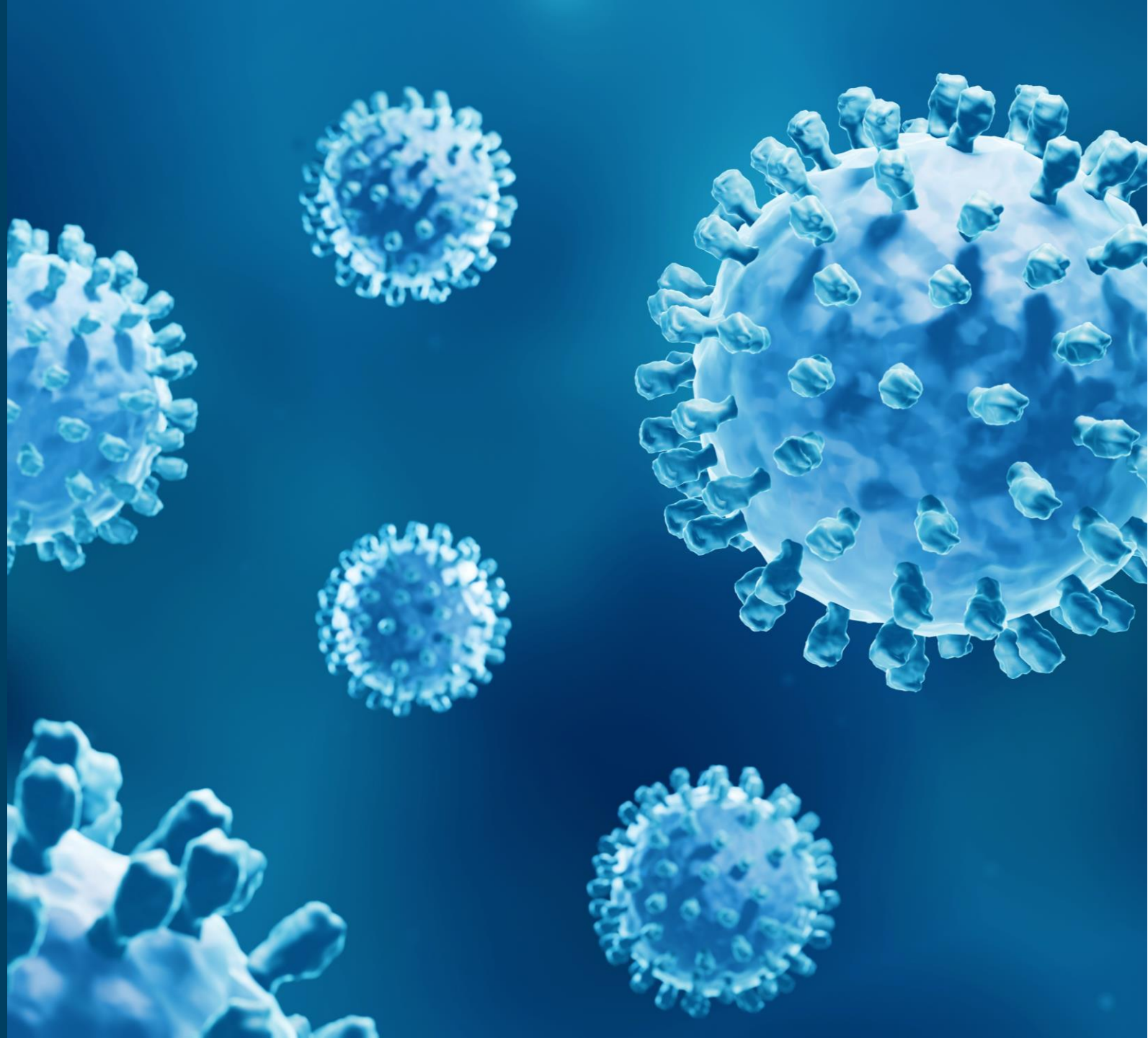
AiCuris

Anti-infective Cures

A novel HBV Capsid Assembly Modulator



AiCuris Anti-infectives-Cures

Sep. 2023

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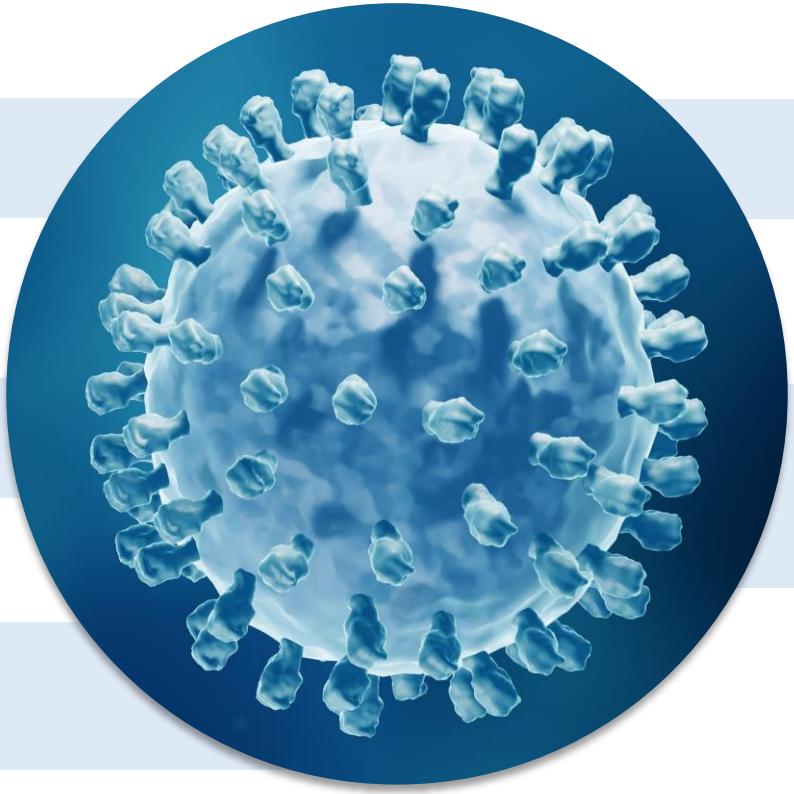
CAM Introduction

- Hepatitis B is a global public health threat and the world's most common serious liver infection.
- Hepatitis B infection cause both acute and chronic liver disease.
- Although there is an effective vaccine, 2 billion people have been affected by HBV infection in their lifetime.
- Globally almost 300 million people are chronically infected.
- Only about 10% of chronically infected people are diagnosed.
- It is the primary cause of hepatocellular carcinoma (HCC), which is the second-leading cause of cancer deaths.



- An estimated 820,000 people die each year from hepatitis B mostly from cirrhosis and HCC.
- Approximately 1.5 million people become newly infected each year.
- Current SOC treatments improve long-term survival, slow the progression of liver diseases and reduce cases of HCC.
- Current SOC requires lifelong treatment and cannot eradicate the virus from the system and cannot cure hepatitis B.
- **There is an urgent need to develop new potent drugs with novel mechanisms and the potential to cure!**

https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
https://www.hepb.org/what-is-hepatitis-b/what-is-hepb/facts-and-figures/

All data included in this presentation are preliminary unless explicitly stated otherwise

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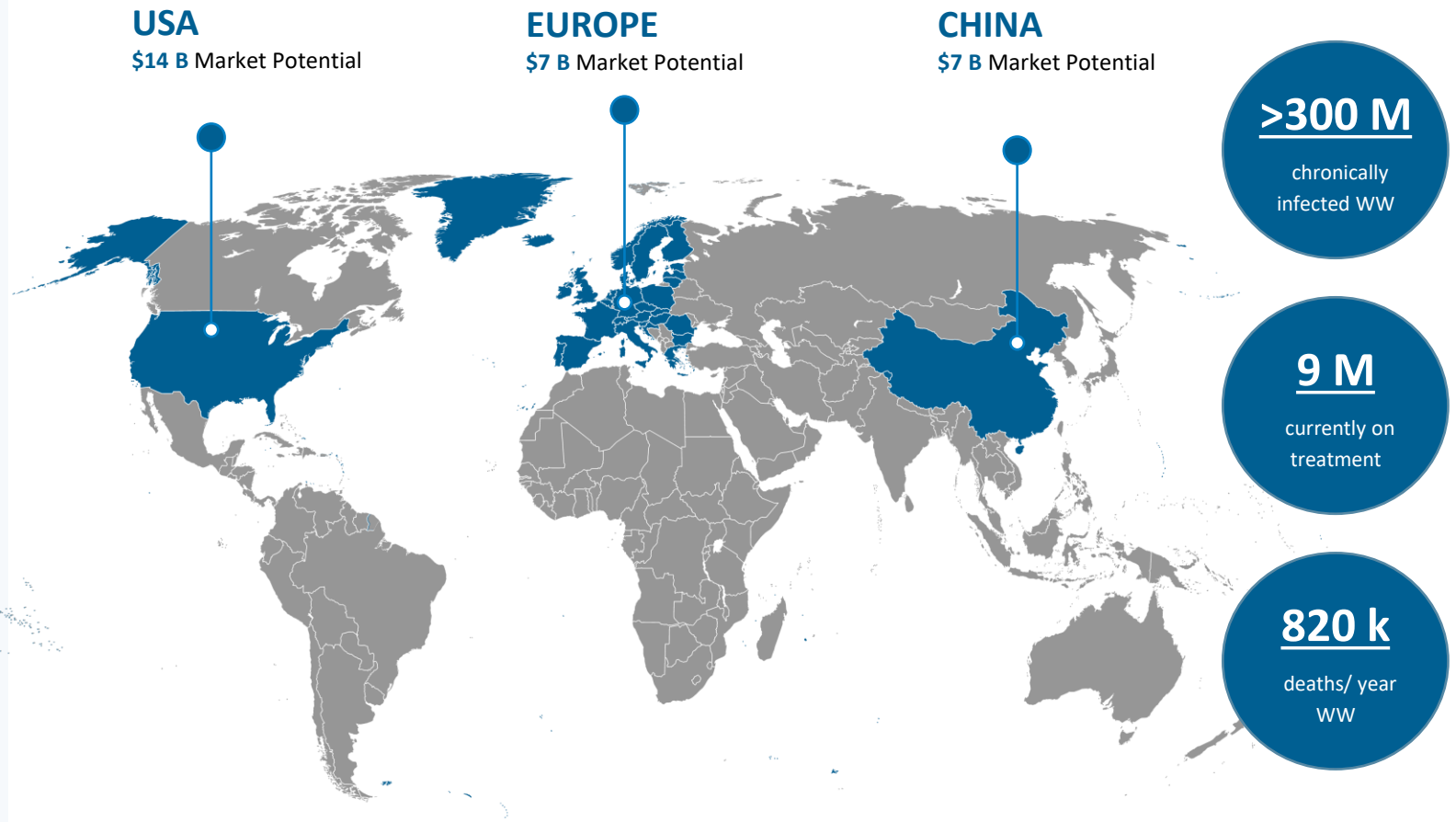
The HBV Market

HBV Global Market:

- Estimated is $28+ billion in 2030 (key driver is US sales and new curative drugs)

HBV in the US:

- Up to 2.4 M people chronically infected.
- Rates of acute hepatitis B infection have risen 50%-450% impacted by the opioid crisis.
- Hepatitis B and the resulting liver cancer are among the greatest health inequalities for people of Asian, Pacific or African descent.
- Only 25% of infected individuals are diagnosed.
- Thousands of people die each year from hepatitis B.



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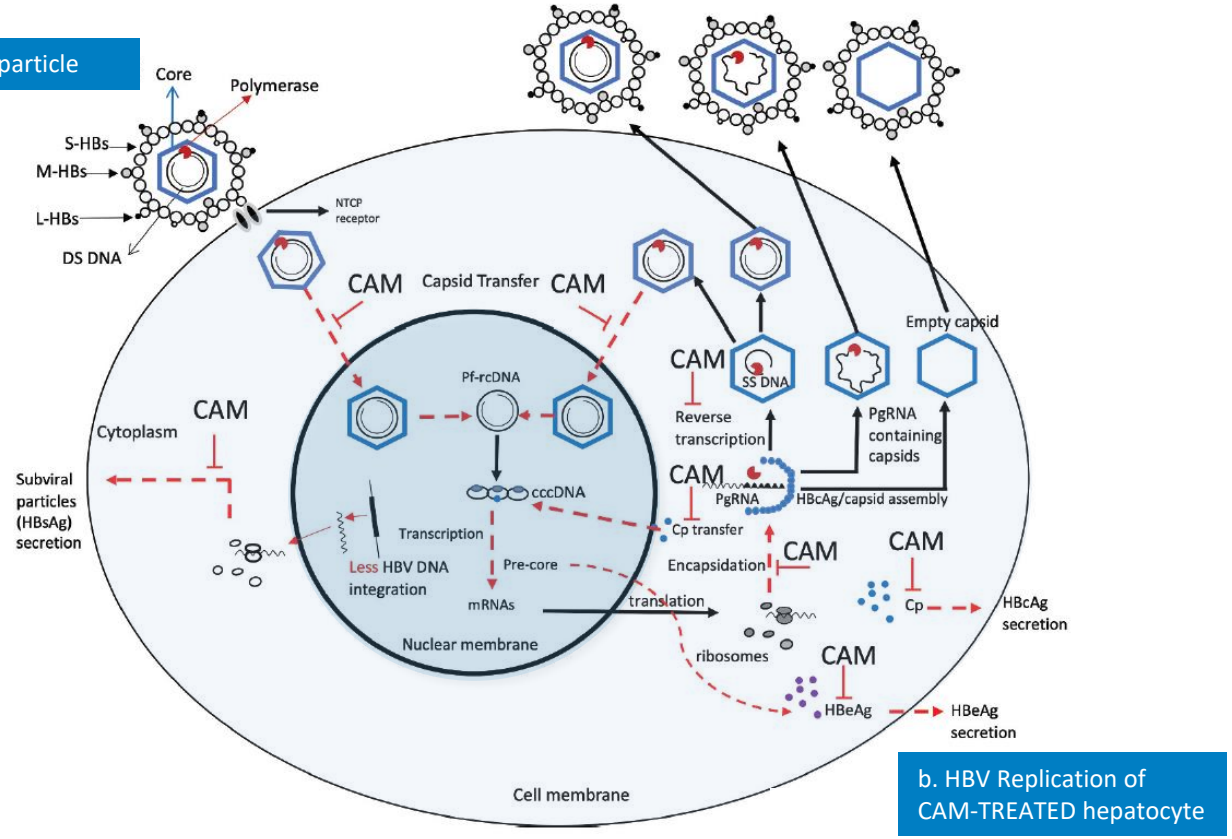
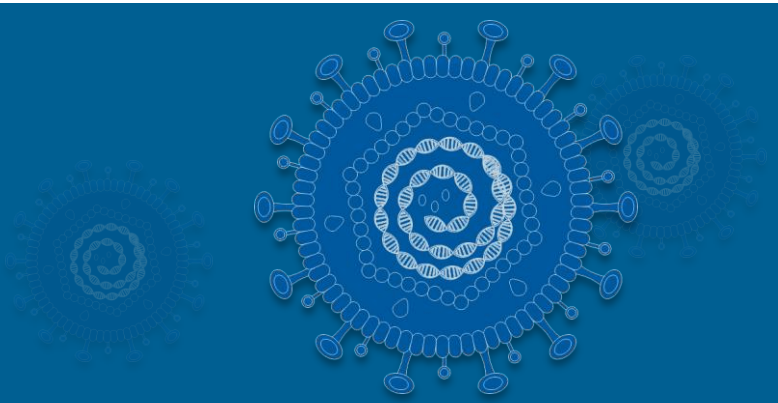


Figure 1. (a & b). HBV replication mechanism and schematic representation of CAM-modulations sites. Panel a represents the HBV particle, and panel b represents the different steps of the HBV replication being affected by CAMs. The dotted arrows in red represent the effects of CAMs on (i) the nuclear transfer of relaxed circular (RC) DNA containing nucleocapsid for covalently closed circular DNA (cccDNA) synthesis and cccDNA recycling/amplification, (ii) core protein (Cp) secretion on plasma or cytoplasm for nucleocapsid assembly, and nuclear transfer for cccDNA formation, (iii) capsid assembly for pre-genomic RNA (pgRNA) encapsidation, (iv) inhibition of reverse transcription to single-stranded (SS) DNA, (v) HBeAg secretion, and (vi) exposure of HBV DNA for integration in the host genome with low levels of HBsAg production. S, small, M, medium, L, large hepatitis B surface (HBs); DS, double stranded; NTCP, sodium taurocholate co-transporting polypeptide; CAM, capsid assembly modulator.

Bassit et al., 2023 Expert Opinion on Drug Discovery 18, 1031-1041



CAMs are novel HBV inhibitors with great potential since they target multiple steps of the virus replication cycle

- Capsid disassembly and nuclear import
- Capsid formation
- pgRNA encapsidation
- cccDNA formation and amplification

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Pharmacology Profile

- Strong antiviral activity with EC_{50} of 5 nM in HepAD38 or HepG2.2.15 cells
- CC_{50} >100 µM in 7 different human cell lines

- Specified mode of action belongs to the CAM-E class (IF with anti-HBV cp staining, Size exclusion chromatography)
- Reduction of HBV DNA, HBV RNA, and surface antigen in HBV infected primary human hepatocytes (PHHs)
- The EC_{50} in HBV infected PHH ranges from 8 to 35 nM (HBV DNA)
- Inhibition of *de novo* formation of cccDNA in HBV infected PHH (EC_{50} 180 nM; southern blot)

- Favourable ADME profile with low protein binding over relevant species (8-15% free)
- PK profiles in mouse, rat and dog allow prediction of human PK
- BID Dosing covers the $paEC_{90}$ (HepAD38) over 24h
- Once daily could be achieved by formulation
- Good preliminary safety profile. No observations in rats up to 1000 mg/kg

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Perspective for the AiCuris CAM

- Current US FDA-approved anti-HBV drugs are safe and effective in supressing viral replication. But fail to eliminate the persisting cccDNA from the liver.

- First CAMs were disappointing in the clinic regarding their cure potential (HBs loss). However, these CAMs were neither potent enough (CAMs of the 1st to 2nd gen.) nor safe and well-tolerated. In addition, study designs were often not suitable for showing a curative effect because the dosage and observation periods were too short.
- Recently, however, clinical trials have shown for the first time that a CAM molecule in combination with entecavir leads to a continual reduction in HBsAg over time.[1]
- In addition to the cccDNA, the integrated viral DNA is also an important factor for the ongoing production of viral antigens and persistence. HBV integration is also a driving mechanism of oncogenesis. Recently it was shown *in vitro* that a CAM molecule can also prevent integration and therefore, may also have the potential to eliminate the virus from the reservoirs and reduce the long-term risk of developing HCC.[2.]
- The half-life of cccDNA in clinical samples was recently calculated to be several months and not decades as previously believed. Clearing the cccDNA reservoirs will therefore be faster than anticipated but will still take time![3]
- It is anticipated that CAMs could be the backbone of a curative combination regimens together with other drugs of different moa like siRNA, ASOs and/ or immunomodulators.[4]

[1]www.aligos.com; [2]www.assemblybio.com; [3]Huang et al., 2021 Hepatology 73, 41-52; [2]Bassit et al., 2023 Expert Opinion on Drug Discovery 18, 1031-1041