Nomenclature of HBV core protein-targeting antivirals

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Hepatitis B virus (HBV) core protein-targeting compounds are in or entering clinical development without a standardized nomenclature. We propose a naming convention for these core-targeting antiviral products to provide clarity and accelerate HBV drug development.

A greater understanding of the hepatitis B virus (HBV) replication cycle has led to novel antiviral targets, interfering with nucleocapsid assembly and disassembly. In its role as a viral structural protein, the core protein (HBc) forms a capsid of 120 HBc dimers that packages the viral genome. Assembly agonists favour formation of aberrant capsids or morphologically normal capsids devoid of genetic material[1]. A number of such 'capsid assembly modulators' (CAMs) are in clinical development. However, a lack of consistent nomenclature for these drugs has generated confusion. Compounds targeting HBc have been described as CAMs, core protein allosteric modulators (CpAMs), core or capsid inhibitors, core-targeting agents, and as subclasses (with inconsistent use on what is class 1 or 2, CAM-A (aberrant), CAM-E (empty) and CAM-N (normal))[2]. As HBc-targeting compounds are undergoing clinical trials, a consistent classification would improve clarity. To address the need for a convention that appropriately categorizes these molecules and provides clear, precise language to document their development, the HBV Forum and ICE-HBV jointly convened a working group (Supplementary Box 1) to develop a standardized nomenclature that accommodates mechanisms of action (MOAs) whilst being simple, intuitive and accessible.

Current CAMs are agonists that accelerate HBc assembly and can also disrupt HBc capsid behaviour. Both mechanisms take advantage of biological HBc activities, assembly and disassembly. An understanding of the molecular interaction between CAMs and HBc explains these disparate activities and the potential for CAMs to contribute to an HBV cure. CAMs interfere with assembly of new viral nucleocapsids, probably by enhancing spontaneous nucleation, accelerating capsid formation and leading to formation of empty and/or aberrant capsids[2–4] (FIG. 1). Structural studies show that CAMs bind in a hydrophobic pocket at an HBc–HBc interface, increasing interactions between proteins. Some CAMs favour formation of empty particles that resemble normal HBV capsids. Other CAMs can induce aberrant assembly that can lead to hexagonal sheets of HBc, large and incomplete balloon-like structures, and large cylinders (FIG. 1). Aberrant assembly, however, is not general to all CAMs. A subset of CAMs prevents HBV from infecting cells when the cells are treated with the drug before, or shortly after, infection[5]. Suspected mechanisms include capsid dissolution (possibly by favouring an HBc–HBc interaction geometry that is incompatible with icosahedral geometry)[2,4,5]; prevention of newly formed capsids from cycling back to the nucleus; or capsid-stabilizing CAMs inhibiting uncoating at the proper time and place (yet to be demonstrated experimentally).

Preclinical studies have shown that CAMs exhibit antiviral activity across HBV genotypes, and against nucleos(t)ide analogue (NUC)-resistant mutants. Next-generation CAMs have demonstrated improved resistance profiles compared with first-generation CAMs in cell culture models. Next-generation CAMs have in vitro antiviral potency corresponding to 2–3 $\log_{10}$ against covalently closed circular DNA (cccDNA) formation better than earlier CAMs. More than 20 CAMs are in preclinical or clinical development[6,7] (Supplementary Table 1). Several have completed phase Ib studies with 4 weeks of treatment and 8 weeks of follow-up; limited data are available for CAMs given for a longer duration.

In phase II studies, addition of a CAM to a NUC intensified the on-treatment suppression of viral replication, decreased serum HBV DNA and HBV RNA by multiple logs and prevented virological breakthroughs from a selection of CAM-resistant variants. For example, in the phase II JADE study, 148 patients not currently receiving treatment and 84 patients virologically suppressed by NUC therapy were randomly assigned to receive bersacapavir (JNJ-379), a CAM, once daily or placebo with NUC or bersacapavir alone for ≥24 and ≤48 weeks[8]. Bersacapavir with a NUC

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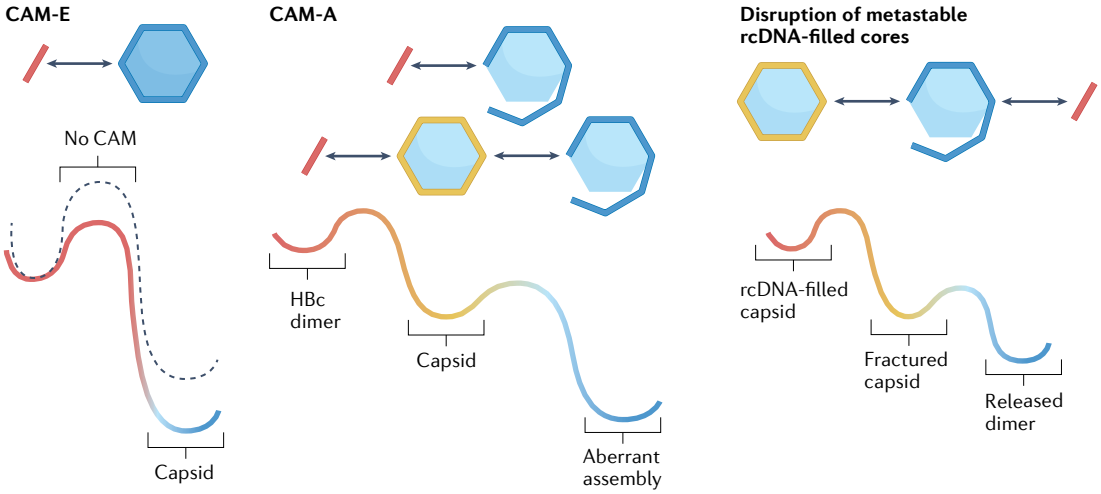

Fig. 1 | **Mode of action of CAMs supporting the proposed nomenclature.** Capsid assembly modulators (CAMs) interfere with assembly of new viral nucleocapsids by enhancing spontaneous nucleation leading to formation of empty (CAM-E) and/or aberrant (CAM-A) capsids. CAMs can also lead to disruption of metastable relaxed circular (rcDNA)-filled capsids (CAM-A). HBc, hepatitis B virus core protein.

showed promising antiviral activity in patients with chronic hepatitis B in preliminary data, with pronounced reductions in both HBV DNA and HBV RNA levels. However, the effects on hepatitis B surface antigen (HBsAg) and hepatitis B e-antigen (HBeAg) levels were small and mainly observed in previously untreated HBeAg-positive patients. This finding suggests a limited effect on the cccDNA template for HBsAg and HBeAg expression. A pilot sub-study of vebicorvir (ABI-H0731) plus NUC evaluated whether intensified virological suppression could allow safe discontinuation of all therapy after 72 weeks with profound viral suppression, defined by HBV total nucleic acid (both HBV DNA and RNA) <20 IU/ml and low or undetectable HBeAg levels[9,10]. However, all patients relapsed, indicating that despite profound viral suppression, cccDNA was not eradicated. Thus, intensified on-treatment virological suppression was not associated with a statistically significant reduction in HBsAg levels.

Ongoing studies are assessing how CAMs can be combined with other antiviral (such as RNA interference) and immunomodulatory approaches. Long-term combination treatment with potent, next-generation CAMs might be required to engage the inhibition of cccDNA formation and contribute to HBsAg loss and a finite therapy resulting in functional cure. Thus, agreeing on a consensus nomenclature is vital given the important part CAMs are expected to play in combination therapy for HBV cure.

The HBV Forum and ICE-HBV led the CAM working group, including scientific experts from regulatory agencies (the FDA and European regulatory system National Competent Authorities), industry developing CAM therapeutics, academia and clinical research. The group was tasked with reviewing nomenclatures in the context of the molecule's MOA and proposing a standardized nomenclature that is simple, easy to remember and scientifically accurate, but will not complicate terminology for core-interacting drugs with other MOAs. Through an evolving consensus, the working group proposes CAM, for capsid assembly modulator. This nomenclature encompasses how the molecules function and indicates that the capsid assembly (and disassembly) is being modulated, describing the MOA (FIG. 1). We propose 'core protein-targeting antivirals' as an overarching classification for drugs interacting with core proteins with other MOAs. Although more information is needed to subcategorize CAMs, we propose CAM-A (aberrant) and CAM-E (empty) as an interim subclassification (FIG. 1).

In summary, CAMs are small molecules with two established MOAs against HBV. They stimulate HBc

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assembly to decrease proper formation of pregenomic RNA-filled capsids, inhibiting production of new infectious virus. CAMs can also bind to mature HBV capsids and prevent them from properly releasing their contents, blocking cccDNA formation in newly infected cells (Supplementary Fig. 1). By inhibiting formation of new virus and new rounds of infection, CAMs offer at least two routes to suppress HBV infection. They might also inhibit cccDNA replenishment in already infected cells by preventing the recycling of capsids to the nucleus and release of relaxed circular DNA to form cccDNA. Our proposed nomenclature emerged from a review of current data and will be updated when more information is available to further distinguish between the chemical classes. This work was undertaken to facilitate clarity in HBV drug development through standardized nomenclature reflecting the science on which drug development is grounded.

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Competing interests

F.Z. has received grants from Assembly Biosciences, Beam, Janssen and Viravaxx and is also a consultant for Assembly, Aligos, Antios, Arbutus, Gilead Sciences, GlaxoSmithKline, Janssen and Vir Biotechnology. A.Z. has equity in Assembly Biosciences and serves on their scientific advisory board. A.Z. is also a founder and Chief Scientific Officer of Door Pharmaceutical. J.F. is an employee of Aligos Therapeutics. A.G. is a former employee and current stakeholder of Gilead Sciences. J.H. has been supported by funding from the National Institute of Allergy and Infectious Disease/NIH and Gilead for work relevant here and has consulted for Arbutus, Bristol Myers Squibb, Gilead, Janssen, Roche and Sanofi. O.L. is an employee of Janssen and is a shareholder of Johnson & Johnson. N.M. is an employee of Arbutus Biopharma. W.D. is an employee at Assembly Biosciences and owns stock in Assembly Biosciences and Gilead. S.W. has received funding from Gilead. V.M. receives grant funding for the HBV Forum from Abbott, Aligos Therapeutis, Altimmune, Antios Therapeutics, Assembly Biosciences, Enanta Pharma, Enyo Pharma, Gilead, GlaxoSmithKline, Immunocore, Janssen, Monogram Biosciences, Quest Diagnostics, RFS Family Foundation, Roche, VenatorX, Vir Biotechnology and Virion. H.L.A.J. has received grants from AbbVie, Gilead, GlaxoSmithKline, Janssen, Roche and Vir Biotechnology, and is also a consultant for Aligos, Antios, Arbutus, Eiger, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche, VBI Vaccines, Vir Biotechnology and Viroclinics. S.B., E.D., M.K., K.L., M.N. and G.W. declare no competing interests.

Supplementary information

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