HBV cure: why, how, when?
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Current HBV treatments control replication and liver disease progression in the vast majority of treated patients. However, HBV patients often require lifelong therapies due to the persistence of transcriptionally active viral cccDNA mini-chromosome in the nucleus, which is not directly targeted by current antiviral therapies. A true complete cure of HBV would require clearance of intranuclear cccDNA from all infected hepatocytes. An intermediate but still relevant step forward that would allow treatment cessation would be reaching a functional cure, equivalent to resolved acute infection, with a durable HBsAg loss + anti-HBs seroconversion, undetectable serum DNA and persistence of cccDNA in a transcriptionally inactive status. Recent advances in technologies and pharmaceutical sciences, including the cloning of the major HBV receptor (i.e. the NTCP transporter) and the development in vitro HBV infection models, have heralded a new horizon of innovative antiviral and immune-therapeutic approaches.

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Introduction
Current treatments for chronic hepatitis B (CHB) (see the companion paper by Zoulim et al. [1]) are able to control viral replication and liver disease progression in the vast majority of treated patients. Although these improvements have radically changed the management and outcome of individual CHB patients the global control HBV infection is still a largely unattained goal. Due to the inability of all available treatments to eliminate HBV infected hepatocytes, there is no cure for HBV infection, lifelong therapies are often required and very few patients maintain a sustained viral and clinical remission off-therapy [2]. The persistence of the virus in most patients under treatment also contributes to the substantial residual risk to develop an hepatocellular carcinoma (HCC) [3]. The suboptimal to very low access to anti-HBV therapies and to the HBV prophylactic vaccine in many highly endemic regions, together with the partial effect of treatments on HCC development, concur to explain why still more than 240 million people worldwide are chronically infected with HBV and up to a million patients die every year from HBV-related liver cancer and end stage liver disease [4]. Despite all these limitations, the availability of HBV prophylactic vaccines and the potential of anti-HBV therapies to control HBV transmission make HBV eradication, in principle, a reachable objective. The lack of a cure for chronic HBV is due in part to the continued presence of transcriptionally active cccDNA mini-chromosome in the nucleus, which is not directly targeted by current antiviral therapies, and by the profound depression of both intrahepatic innate immunity and adaptive HBV specific T cell and B responses [2]. Recent advances in understanding the molecular biology and replication cycle of HBV, including the cloning of the major HBV receptor (i.e. the NTCP transporter) and the development of in vitro HBV infection models [5], have provided new insight on potential future targets for drug development and boosted the efforts to develop innovative antiviral and immune-therapeutic approaches.

Targeting the HBV replication cycle
HBV entry into hepatocytes is initiated by the low-affinity interaction between the antigenic loop (‘a’ determinant) of the HBV envelope proteins with heparan sulfate proteoglycans on the hepatocytes surface [6,7*], followed by the high-affinity interaction of the myristoylated pre-S1 domain of the HBV large envelope protein with the liver-specific receptor sodium/taurocholate cotransporter (NTCP) [8*,9], the fusion of HBV particles with the cell membrane mediated by receptor-mediated endocytosis [10,11] and the release of the HBV genome — containing nucleocapsids into the cells. Nucleocapsids transport into the nucleus probably involves microtubules and the nuclear import in machinery [12]. In the nucleus, the relaxed circular, partially double-stranded HBV genome is repaired to a full-length, circular DNA by the covalently attached viral polymerase (P) and still poorly understood cellular factors involving the topoisomerases and DNA
repair pathways. The tyrosyl DNA phosphodiesterase TDP2 mediates the first step of cccDNA formation from incoming rcDNA (i.e. removal of the phosphodiester bond between the viral polymerase and viral minus strand DNA) [13] but its role in the formation of active cccDNA precursors has been challenged [14]. The circularized protein-free genome then complexes with host histone and non-histone proteins including various histone-modifying enzymes into a minichromosome that functions as the template for the transcription of the three classes of HBV RNAs [i.e. genome-length RNAs (pregenomic and precore RNAs coding for c gene products and P protein), S RNAs (S proteins), and X RNA (HBx protein)]. cccDNA transcriptional activity is regulated by epigenetic modifications and specific host transcriptional factors [15*]. The HBV core and X proteins are also present on the minichromosome and HBx play an important role in HBV transcription [16,17,18*]. The pregenomic RNA transcript is reverse-transcribed by the P protein to relaxed circular DNA in the core-containing nucleocapsid. The nucleocapsid can either assemble into an infectious virion with the envelope proteins through the multivesicular body pathway [19] or recycle back to the nucleus [20] to amplify/replenish the cccDNA pool (1–10 molecules for infected hepatocyte) [21].

Defective HBV specific immune responses

Acute HBV infections are cleared by a coordinated activation of innate and adaptive immune responses in about 95% of immune-competent adults but only in 5–10% of children. In acute self-limited infections, HBV replication is suppressed by non-cytopathic mechanisms involving cytokines [22] well before the onset, usually delayed by 4–6 weeks post infection, of the strong polyclonal CD8+ T and CD4+ T cell responses that are thought to be instrumental for the elimination of infected hepatocytes, antibody production and clinical recovery [23]. During chronic HBV infection, the unrestricted viral replication and the ongoing liver damage are accompanied by the accumulation of non HBV-specific T cells in the liver, whereas HBV-specific CD8+ T cells are found at very low frequency and have an exhausted phenotype characterized by over-expression of inhibitory checkpoint molecules such as PD-1, CTLA-4, CD244, and Tim3. CD4+ T cell responses are also affected with an impaired production of IL-2 and low proliferation potential and Treg and IL-10 secreting T cells accumulate in the liver [24]. In keeping with the notion that the HBV viral structures (double strand viral double strand DNA and RNA–DNA hybrids) that are potentially capable to stimulate the innate immunity sensors, are sequestered into the cytoplasmic capsid particles [25] and the lack of intrahepatic gene modulation following the onset of viremia in HBV-infected chimpanzees [26] HBV has been considered as a ‘stealth’ virus. More recent data have challenged this notion suggesting that the virus is detected by the innate immunity sensors but it rapidly blocks innate immunity at several levels in hepatocytes as well as in other liver cells (for review, see [27,28]).

Definition of HBV cure

Although the term cure is being increasingly used in HBV infected patients, several concepts around the definition of a cure of HBV infection need to be clarified.

True complete cure of HBV would require the clearance of intra-nuclear cccDNA from all infected hepatocytes, thereby allowing treatment cessation and preventing the risk of reactivation in case of a loss of immune control [2]. The requirement to eliminate an intranuclear reservoir is a clear distinction from HCV infection, where the entire replication cycle occurs within the cytoplasm. As an intermediate but still relevant step toward HBV cure there is consensus on aiming at reaching a functional cure, equivalent to a resolved acute infection: durable HBsAg loss (with or without anti-HBs seroconversion), undetectable serum DNA, persistence of cccDNA in a transcriptionally inactive status and the absence of spontaneous relapse after treatment cessation [2]. According to this definition functional cure equals the natural condition known as occult HBV infection. Due to the lack of solid data regarding the off therapy stability of viral suppression, patients treated with current anti-viral treatments who reach and maintain low serum HBsAg levels, equivalent to those observed in HBV inactive carriers, are not included in the definition of functional cure. These definitions do not take into account the possible presence and persistence of integrated HBV DNA in the host genome. The integration of viral DNA into the host genome, that occurs randomly in regenerating infected hepatocytes [29], does not contribute to HBV replication but is an important factor in viral pathogenesis both by cis-acting mechanisms (insertional mutagenesis) and by the continuous expression of trans-acting wild type and truncated HBx or truncated pre-S/S polypeptides bearing enhanced transforming properties [3]. Clonal expansions of hepatocytes containing unique virus-cell DNA junctions formed by the integration of HBV DNA can be detected in patients at various stages of chronic infection [30]. Whether these integrants must be eliminated to prevent all HBV-related pathogenicity in the absence of other liver co-morbidities is still debated. Terms like HBV eradicating or sterilizing therapies, although evocative, should be avoided.

Current antiviral therapies for chronic HBV disease is limited to direct acting antivirals (DAAs) that target the viral DNA polymerase, the most efficacious of which are the nucleos(t)ides analogs (NUCs) entecavir and tenofovir, and interferon [namely the long acting pegilated interferon (PEG-IFN)] [31]. DAAs act directly on viral replication by inhibiting the reverse transcription of pre-genomic RNA to DNA and the subsequent replication of the (+) strand of HBV DNA [29]. Interferon up-regulates a range of antiviral ‘interferon stimulated genes’ (ISGs) to modify
the cccDNA epigenome, control viral replication and stimulate NK cell activity with little or no effect on adaptive HBV specific T cell responses [32,33,34*]. The efficacy of interferon therapy is HBV genotype dependent, working best for genotypes A and B and less well in genotypes C and D, and is far from satisfactory, leading to HBsAg clearance only in a minority of patients. Altogether these treatments are not curative, since they do not directly target cccDNA, although it has been recently shown, by us and by others, that interferon treatment diminish cccDNA transcriptional activity [34*,35,36], a property that may explain its ability to lower serum HBsAg levels and to induce HBsAg loss in a proportion of patients. IFNa also induces, at least in some cell culture systems, a partial loss of cccDNA [37*,38].

**Strategies for HBV cure**

Several strategies targeting all steps of the HBV replication cycle (HBV entry, HBV cccDNA production and activity, viral replication and viral proteins expression) and/or aiming at stimulating the intrahepatic innate immune responses or restoring the deficient adaptive HBV specific B and T cell responses are currently being explored (Figure 1). Mechanistically all these different approaches can be classified in 4 functional categories according to their mode of action and their objective or targets (Figure 2):

(a) complete inhibition of HBV replication;
(b) restoration of host innate immunity and adaptive anti-HBV T and B cell responses;
(c) selective sensitization of HBV infected hepatocytes to immune elimination;
(d) direct targeting of cccDNA.

Notably, some compounds or classes of compounds may fit in more than one category (Figure 2).

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**Figure 1**

The landscape of HBV cure efforts. All steps of the HBV replication cycle (viral entry, cccDNA formation, chromatinization and transcription, viral mRNAs, envelope protein secretion, core proteins and the capsid, Pol enzymatic activities), the intrahepatic innate immune responses and the deficient adaptive HBV specific B and T cell responses are currently being explored as potential new therapeutic targets.
HBV cure strategies classification according to their mode of action. The different approaches aiming at ‘HBV cure’ can be classified in 4 functional categories according to their mode of action and intended objective. Some compounds or classes of compounds may fit more than one category. (1) A complete inhibition of HBV replication can be achieved by entry inhibitors, capsid inhibitors, nucleic acids polymers (NAPs), si/shRNAs, small molecules inhibiting the DNA polymerase/reverse transcriptase RNaseH activities of Pol. The aim is to avoid the de-novo infection of uninfected hepatocytes and a complete blockade of the replenishment of the cccDNA pool through the recycling of mature core particles into the nucleus, (2) the restoration of the defective host innate immunity and adaptive anti-HBV T and B cell responses can potentially be achieved by: (a) si/shRNA approaches or NAPs to reduction HBsAg; (b) the anti-PD1/PDL1 or other checkpoint inhibitors; (c) therapeutic vaccines; (d) transfer of engineered TCR bearing CD8 cells; (e) TLRs agonists; (3) a selective sensitization of HBV infected hepatocytes to immune elimination using cIAP inhibitors/Smac agonists, (4) the direct targeting of cccDNA is pursued by multiple approaches aiming to: (a) inhibit cccDNA formation; (b) destroy cccDNA molecules by targeted endonucleases; (c) silence the viral mini-chromosome by targeting the epigenetic control of cccDNA transcription; (d) interfere with the activity of cccDNA bound viral proteins [HBc and HBx].

Complete inhibition of HBV replication

Complete suppression of the HBV polymerase should, in theory, reduce viremia and intrahepatic levels of replicative forms of HBV DNA to zero, and even cccDNA should be eliminated, as the infected cells are eventually replaced. According to this model, people with CHB should be cured with DAAs alone if treated long enough unless, as suggested by some recent observations [39], despite the persistent negativity of serum HBV DNA, a complete inhibition of the HBV polymerase is not achieved. If the degree of suppression of viral replication in infected hepatocytes is not complete new hepatocytes infection and a low level of core particles recycling to the nucleus will occur. In addition to new Pol and RNaseH inhibitors, entry inhibitors, capsid inhibitors, NAPs and si/shRNA-based approaches have all the potential to cooperate with NUCs to achieve a complete inhibition of HBV replication.

(a) Entry inhibitors that target the NTCP receptor prevent the de novo infection of hepatocytes by HBV and HDV as well as viral spreading from infected human hepatocytes.
The most prominent representative of this category is the HBV ’entry inhibitor’ Mycludex B, which is a myristylated PreS1 peptide currently under clinical trial [8].

**b) Anti-capsid inhibitors.** The HBV capsid is essential for HBV genome packaging, reverse transcription, intracellular trafficking and the re-import of encapsidated HBV genomes into the nucleus [41]. Several non-nucleoside analog (NNA) inhibitors of pgRNA packaging and HBV capsid assembly have been identified [41]. HBV capsid proteins (HBV core/HBc) can also traffic to the nucleus of infected cells where they bind the cccDNA mini-chromosome [17] and the regulatory regions of a subset of cellular genes [42]. Compounds that would also target the nuclear functions of HBV core proteins, that is, regulation of cccDNA transcriptional activity [43] and/or regulation of ISGs expression, would have the potential for an enhanced antiviral activity. At least two chemical classes of anti-capsid drugs are in phase I and phase II clinical assays [44].

### Restoration of host innate immunity and adaptive anti-HBV T and B cell responses

The key challenge for all immunomodulatory strategies will be to stimulate antiviral immuno-mediated pathways without triggering detrimental anti-HBV flares.

Two main approaches have been developed to inhibit HBV gene expression at the post-transcriptional level in order to reduce the excess production of sub-viral particles and, by relieving HBsAg-mediated immunosuppression, restore antiviral immunity:

**a) RNA interference.** RNA interference (RNAi) are increasingly considered as a realistic new therapy for chronic HBV, with recent clinical studies showing liver-specific knockdown of HBV replication and protein expression [45–48]. Their potential effect on immune restoration by decreasing viral antigen load is actively investigated.

**b) Nucleic acid polymers** (NAPs) are sequence-independent phosphoro-thioated oligonucleotides that display a broad spectrum of antiviral activity against several enveloped viruses, including HBV. REP9-AC (REP 2055), a 40-nucleotide poly-cytidine amphipathic DNA polymer, inhibits both HBV entry and HBsAg release from infected hepatocytes. REP 2139 in combination therapy with PEG-IFN alpha-2a is in clinical trial for both in chronic HBV and HDV co-infection [49,50].

**Check-point inhibitors.** The exhausted HBV-specific CD8+ T cells in CHB patients express high levels of inhibitory molecules including programmed cell death protein 1 (PD-1), cytotoxic T lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene 3 (LAG-3), T cell membrane 3 (Tim-3) and CD244 (2B4) [24]. Inhibitors of these checkpoint molecules have a potent immunostimulatory effect by rescuing virus specific CD8+ T cells [51–53]. Nivolumab (BMS-936558) and pembrolizumab (MK-3475) are both anti-PD-1 monoclonal antibodies that have progressed through phase 3 development in oncology. Phase 1 studies of anti-PD-1 therapies for the treatment of CHB patients with HCC have just started [54].

**T-cell therapies.** Engineering HBV-specific T cells through transfer of HBV-specific T cell receptor or HBV-specific chimeric antigen receptors represent promising alternative strategies to construct an HBV-specific T-cell immunity in CHB patients [55]. Their potential is supported by preclinical data and one patient case report [56,57].

**Therapeutic vaccines.** Attempt to break T cell tolerance to HBV proteins (HBsAg, HBcAg) and stimulate HBV-specific T cell immunity in patients chronically infected with HBV. Historical studies of therapeutic vaccination for HBV have been disappointing but this approach is being pursued with new vaccine candidates [58,59].

**Innate immunity ligands.** Toll-like Receptors (TLRs) are pattern recognition receptors that play a key role in the recognition of bacteria and viruses as part of the innate immune response and are involved in the pathogenesis of HBV. The TLR7 agonist GS-9620 is in clinical development. In pre-clinical in vivo models it has been shown to stimulate production of interferon-alpha as well as other cytokines and to activate interferon-stimulated genes, natural killer cells, and lymphocyte subsets, to suppress serum and liver HBV DNA and to reduce HBsAg serum levels [60,61,62]. RIG-I, a member of the Retinoic acid-inducible gene (RIG-I)-like RNA helicases (RLHs) class of innate pattern recognition receptors, has dual antiviral effect against HBV by inducing a type III interferon response and by blocking the interaction of the HBV polymerase with pgRNA to directly suppress viral replication [63]. The SB-9200 an oral dinucleotide prodrug has shown activity against both HCV and HBV in preclinical models [64] and clinical trials in HBV populations are planned to start in 2016.

### Selective sensitization of HBV infected hepatocytes to immune elimination

Cellular inhibitor of apoptosis proteins (cIAPs) have recently been shown to attenuate TNF signaling during HBV infection and restrict the death of infected hepatocytes, promoting viral persistence [65]. Birinapant, a Smac mimetic that antagonizes cIAP, has shown anti-HBV activity in preclinical models [66] and a phase 1 study was initiated in 2015.

### Direct targeting of cccDNA

Strategies targeting the cccDNA for HBV cure aim at preventing cccDNA formation, eliminating existing
cccDNA or silencing cccDNA transcription. These aims can be achieved by direct-acting antivirals (DAAs), host-targeting agents (HTAs) [that inhibit key host factors required for the viral replication cycle] and immune-modulatory agents that elicit signals converging on the cccDNA mini-chromosome. Mechanistically, control of cccDNA can be obtained by inhibition of rcDNA entry into nucleus, inhibition of conversion of rcDNA to cccDNA, physical elimination of cccDNA, inhibition of cccDNA transcription (epigenetic control), or inhibition of viral/cellular factors contributing to cccDNA stability/formation. All these approaches are currently at the preclinical stage.

**cccDNA formation.** Di-substituted sulfonamide (DSS) compounds have been identified as inhibitors of de novo cccDNA formation in unbiased screenings [67] but their molecular target is still unknown.

**cccDNA destruction** approaches include two different approaches. The first, direct, approach makes use of transcription activator-like effector nucleases (TALENs) [68] and the clustered regularly interspaced short palindromic repeats (CRISPR) strategies [69–73]. The possibility of targeting viral sequences integrated in the host genome is obviously a plus but the open issue of potential off-target effects induces some caution. The second is based upon the ability, apparently shared by members of the IFN and TNF family of cytokines, to decrease cccDNA stability via the induction of deamination and apurinic/apyrimidic site formation in the cccDNA and the up-regulation of nuclear APOBEC3 deaminases [37*,38*]. These results await confirmation and the safety and therapeutic index of lymphotixin-β receptor (LTBR) agonists in patients with chronic HBV infection and liver disease remains to be explored.

**Functional silencing of cccDNA.** These strategies are intended to target histones modifying enzymes that have been shown to bind to the cccDNA (including the inhibition of histone acetyl-transferases [HATs] and the activation of histone de-acetylases [HDACs] and histone methyl-transferases [HMTs]) to induce a permanent/stable epigenetic inactivation of the cccDNA. Modulation of these enzymatic activities with small compounds has been shown to induce the expected PMTs on cccDNA bound histones, to reduce cccDNA transcription and to inhibition viral replication in cell systems, providing the proof of concept for an epigenetic silencing of cccDNA [74,75*]. However, efficacy must be confirmed *in vivo*. The functional redundancy between the members of the different classes of chromatin modifiers and the possible off-target effects on the host genome should be carefully considered.

**cccDNA bound viral proteins.** The role of the viral proteins HBx and HBc in cccDNA transcription and/or stability [16,17,18*] has led to the development of drug discovery programs targeting the cellular proteins [76] that are bound and mediate the activities of HBx and HBc on the cccDNA.

**Conclusive remarks**

The complexity of HBV replication cycle and virus–host interactions that ensure HBV persistence represent a formidable obstacle to a cure. Nevertheless the hunt for new molecules and therapeutic strategies acting on novel targets with the aim to set true combination therapies is clearly on. Strategies targeting directly or indirectly the cccDNA as well as the restoration of the immune response against HBV infected cells will likely need to be combined to reach at least a virological and immune functional cure status similar to that observed in HBsAg sero-converters, if not a complete cure. A major effort must be dedicated to define the clinical, immunological and virological endpoint that should be used to measure the impact of the new treatments in future clinical trials. Similarly, regulatory agencies (FDA, EMEA) must be made aware of the strong need for early combination trials. Clinical trial design will need to take into account the clinical complexity of CHB and the need for selection of homogeneous and well characterized CHB patients to be included in the different trials. Whereas is not possible to predict when a cure for HBV will be available, the magnitude of the academic and industry-based research and R&D efforts makes a breakthrough possible within a time frame much shorter than initially expected. Working to find a cure for CHB does not negate the need to further implement mass HBV vaccination and increase the access to existing DAAs in highly endemic areas in the South of the world.

**Conflict of interest**

FZ received research grants through INSERM from Roche, Gilead Sciences, Novira, Janssen and Assembly Bioscience, and consulting honoraria from Roche, Gilead Sciences, Novira, Arbutus and Janssen.

ML participates to advisory boards of BMS, Assembly Biosciences Gilead, Arbutus, Janssen, Galapagos, Medimmune.

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**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest


Using an RNA interference (RNAi) — based loss-of-function screen in a new NTCP-expressing HuH7 cell line that does not require the use of infection-enhancing treatments the AA identify glypican 5 (GPC5) as a new HBV and HDV entry factor and potential antiviral target.


The AA shows, using near zero distance photo-cross-linking and tandem affinity purification, that the receptor-binding domain of pre-S1 specifically interacts with the sodium taurocholate co-transporting polypeptide (NTCP), a transmembrane transporter predominantly expressed in the liver. This is the first demonstration that NTCP is a functional receptor for both HBV and HDV.


The AA introduce the cccDNA-ChIP, a chromat-innunoprecipitation (ChIP)-based assay, to analyze, in vitro and ex vivo, the transcriptional regulation of HBV cccDNA minichromosome. First demonstration that cccDNA transcription and HBV replication are regulated by epigenetic modifications of cccDNA-bound histones.


Using primary human hepatocytes and differentiated HepaRG cells allowing conditional trans complementation of HBxs, the AA show that HBx is required to initiate and maintain cccDNA transcription and HBV replication and highlight HBx as the key regulator during the natural infection process.


45. Belloni L, Allweiss L, Guerrieri F, Pediconi N, Voz T, Pollicino T, Petersen J, Raimondo G, Dandri M, Levreiro M: IFN-α inhibits HBV transcription and replication in cell culture and in humanized mice by targeting the epigenetic regulation of the
The AA show that IFN-α inhibits HBV replication by decreasing the transcription of pregenomic RNA (pgRNA) and subgenomic RNA from the HBV covalently closed circular DNA (cccDNA) minichromosome, both in cultured cells replicating HBV and in human liver chimeric-mice infected with HBV. Mechanistically, IFN-α induces the epigenetic repression of HBV cccDNA transcriptional activity by the active recruitment to the cccDNA of transcriptional corepressors.


First demonstration that autologous T cells genetically modified to express an HBsAg specific T cell receptor can survive, expand, recognize tumor cells in vivo and mediate a reduction in HBsAg levels without exacerbation of liver inflammation or other toxicity.


The result of this double-blind, phase 1b trials with the GS-9620 oral agonist of toll-like receptor-7 show that GS-9620 is safe, well tolerated,
and associated with induction of peripheral ISG15 production in the absence of significant systemic IFN-alpha levels or related symptoms.


The AA show that the retinoic acid-inducible gene-I (RIG-I) senses the 5′-U region of the HBV pre-genomic RNA and prevents the interaction of the HBV polymerase with the 5′-U region to suppress viral replication. Lipo- some-mediated delivery and vector-based expression of the 5′-U region-derived RNA in the liver abolished the HBV replication in human hepatocyte-chimeric mice.


Cellular inhibitor of apoptosis proteins (cIAPs) impair the clearance of HBV by preventing TNF-mediated killing/death of infected cells. Using an immuno-competent mouse model of chronic HBV infection the AA show that bimarapant and other Smac mimetics are able to rapidly reduce serum HBV DNA and serum HBV surface antigen, and they promote the elimination of hepatocytes containing HBV core antigen Smac mimetics.


Using a new cccDNA ChIP-Seq approach the AA generate the first genome-wide maps of cccDNA-bound histone post-translational modifications (PTMs) in de novo infected HepG2 cells, primary human hepatocytes and HBV-infected liver tissue. Transcription and active PTMs in HBV chromatin are reduced by the activation of the IFNα innate immunity pathway, and this effect can be recapitulated with a small molecule epigenetic modifying agent.


In this landmark paper, the AA show that the structural maintenance of chromosomes (Smc) complex Smc5/6 act as a host restriction factor for HBV and that HBx relieves the inhibition to allow productive hepatitis B virus gene expression by hijacking the cellular DDB1-containing E3 ubiquitin ligase.