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Diet Congress 2018 & Gastroenterologists 2018: Hepatitis B in focus: New biology, new targets and real hope for finite therapy- Bruce D Given- Arrowhead Pharmaceuticals Inc.

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Drug development work in Chronic Hepatitis B (CHB) has been largely stagnant for the last decade or more. While solid epidemiology work has demonstrated that sero clearance of HbsAg (functional cure) is associated with greatly reduced risk of cirrhosis or HCC, neither interferon therapy nor long-term nucleus(t)ide therapy are associated with meaningful rates of functional cure. With the recent successes achieved in curative treatment of Hepatitis C, the field has returned to curative efforts in CHB and there has been an explosion of pre-clinical drug development against novel targets. As part of this process, new insights have been gained regarding the biology of CHB. This talk will focus on how these new biological insights are translating into new drug discovery efforts, how these new drug classes are performing in the clinic, and the more expected role for combining these drugs is to achieve meaningful rates and functional cure with finite therapy. With a high morbidity and mortality worldwide, And there is great interest in effective therapies for chronic hepatitis B (CHB) virus.

There are several dozen investigational agents being developed for treatment of CHB. Direct-acting antivirals that interfere with a specific step in viral replication host-targeting agents that inhibit viral replication by modifying host cell function, DAAs being developed are RNA interference therapies, covalently closed circular DNA (cccDNA) formation and transcription inhibitors, core/capsid inhibitors, reverse transcriptase inhibitors, hepatitis B surface antigen (HBsAg) release inhibitors, antisense oligonucleotides including Toll-like receptor agonists, immune checkpoint inhibitors interferon.

In this we discuss the agent's clinical stage of development for CHB treatment as well the strategies and agents which are currently at the evaluation and discovery phase for potential future targets and Effective approaches to CHB may require the suppression of viral replication. Some are the recent research advances have led the hope with such a combined approach that may have a functional cure for CHB in the not distant future. Hepatitis B virus is a small, enveloped which partially double-stranded DNA virus that belongs to the *Hepadnaviridae* family. It is estimated that 240 million people are chronically infected with HBV worldwide approximately 75% of who reside in Asia and 12% in Africa.

Although the overall prevalence of chronic hepatitis B (CHB) is substantially lower in Western countries, even in the USA it is estimated that the CHB population may be as high as 2.2 million people. Although not all CHB patients develop complications, it is among the leading causes of liver disease, cirrhosis, and hepatocellular carcinoma (HCC) worldwide, with an estimated 15-40% of CHB patients developing serious sequelae during their lifetimes. Although these therapies can decrease the risks of liver decompensation and HCC and improve survival. They do not commonly yield clearance of hepatitis B surface (HBs) antigen (HBsAg). Loss of HBsAg has been referred to as a "functional cure" because it is associated with reduced liver necro inflammation, increased liver fibrosis regression, normalization of alanine aminotransferase (ALT) levels, reduced risk of liver cirrhosis, decompensation and HCC, and increased survival. Because IFN is associated with substantial adverse effects in many patients and requires parenteral delivery, it is only used in a small percentage of CHB patients. HBsAg loss is even lower in patients receiving NUC therapy; even with long-term therapy for 5-7 years, HBsAg loss has only been seen in 0.3–5% of HBeAg-negative patients and 0–11.8% of HBeAg-positive patients has been largely stagnant for the last decade or more. While solid epidemiology work has demonstrated that seroclearance of HbsAg (functional cure) is associated with greatly reduced risk of cirrhosis or HCC, neither interferon therapy nor long-term nucleos(t)ide therapy are associated with meaningful rates of functional cure. With the recent successes achieved in curative treatment of Hepatitis C, the field has returned to curative efforts in CHB and there has been an explosion of pre-clinical drug development against novel targets. As part of this process, new insights have been gained regarding the biology of CHB.

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