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Engineering sequence-specific transcriptional repressors to disable replication of hepatitis B virus

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Chronic infection with hepatitis B virus (HBV) remains and is an important global health problem. Carriers of the virus are at high risk for cirrhosis and liver cancer. Available treatment only has modest curative efficacy and improved therapy is a priority to prevent the life-threatening complications that accompany the infection. The viral replication intermediate comprising covalently closed circular DNA (cccDNA) exists as a stable mini-chromosome in infected hepatocytes. Licensed treatment has no effect on cccDNA and devising methods based on gene therapy to disable this replication intermediate has considerable potential. Previous work from our laboratory demonstrated effective inhibition of HBV replication and targeted disruption of cccDNA by Transcription Activator-Like Effector Nucleases (TALENs). Although this approach is promising, unintended mutagenesis may occur in chronic carriers because of TALEN activity at HBV sequences that are integrated into the host genome. To circumvent this problem, we have produced repressor TALEs (rTALEs) that were designed to induce transcriptional repression at essential HBV transcriptional regulatory elements: the basic core promoter/enhancer II and preS2 promoter sequences. KRAB-encoding sequences were fused to the N-terminal regions of TALEs contain sequence-specific DNA binding domains derived from the AvrBs4 N1 Xanthomas TALE. Each rTALE was expressed from the CMV promoter and engineered to interact with an HBV-specific 18bp target. The repressors were incorporated into recombinant adeno-associated viral vectors which were used to deliver the antiviral elements. Inhibition of HBV replication was observed in cell culture models of HBV replication and in vivo. No evidence of toxicity was detected and inhibitory effects were sustained over a period of at least 2 months. Collectively these data indicate that rTALEs are effective against HBV and provide an efficient means of disabling HBV cccDNA without causing mutations that result from target DNA cleavage.

Biography

Patrick Arbuthnot is currently a Personal Professor and Director of the Wits/SAMRC Antiviral Gene Therapy Research Unit at the University of the Witwatersrand in South Africa. After graduating with a Medical degree, he has completed his PhD in 1992 then carried out his Post-Doctoral work at Necker Hospital in Paris, France. On returning to South Africa, he established the Antiviral Gene Therapy Research Unit, which has now published widely on HBV infection, liver cancer, HIV-1 infection and developing new methods of treating these diseases. His main research interest is in advancing use of biological and synthetic nanoparticles to carry potentially therapeutic nucleic acids (DNA or RNA) that are capable of permanently disabling HBV.

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