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Two novel nonnucleosidic compounds inhibit *hepatitis B virus* replication by inducing genome-free capsid formation

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Hepatitis B infection is a most common chronic viral infection worldwide. It has long been a difficult pathogen because of its unique life cycle and its ability to integrate into host genome. During the hepatitis B virus life cycle, nucleocapsid assembly is essential for HBV replication. Both RNA reverse transcription and DNA replication occur within the HBV nucleocapsid. We have been dedicating to discover non-nucleosidic anti-HBV agents for more than ten years, and found two series of compounds with anti-HBV activity as assembly effectors. Isothiafludine (NZ-4) is a derivative of bis-heterocycle tandem pairs derived from the natural product leucamide A. It inhibit HBV replication both *in vitro* and *in vivo*. NZ-4 is a novel HBV inhibitor with a unique mechanism. Its activity depends on the presence of ARD-I of HBc C-terminal domain. Currently, NZ-4 is being evaluated in phase I clinical trials in China. Another reported nonnucleosidic HBV inhibitor is a Pyridazinone derivative, 3711. It decreases HBV DNA level in cell model system. It interferes with capsid formation by regulating hydrophobic interactions at the interdimer interfaces of HBc N-terminal domain. As assembly effectors, both compounds induce genome-free capsid formation, without changing capsid morphology. They can also inhibit the replication of various NA-resistant HBV mutants and might provide improved choices to eradicate HBV in the future.

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Anti-PLVAP monoclonal antibody derived therapeutics for hepatocellular carcinoma

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To seek new treatment target for hepatocellular carcinoma (HCC), gene expression profiling was conducted on 18 pairs of HCC and adjacent liver. Genes showing extreme differential expression between paired isogenic tumor and liver tissues were investigated. PLVAP was identified as a top gene showing such differential expression. High PLVAP expression was confirmed in 150 HCC. Using laser-captured microdissection and quantitative RT-PCR, PLVAP was found to expressed by tumor vascular endothelial cells and not detectible in tumor cells, hepatocytes and blood vessels of normal liver. To exploit PLVAP as a specific target for treatment, we developed a recombinant anti-mouse PLVAP Fab fragment co-expressing human tissue factor (TF) to induce thrombosis and ischemic necrosis of HCC. Hep3B xenograft in SCID mice was used for the study. Infusion of anti-PLVAP Fab-TF into tumor feeding artery induced tumor vascular thrombosis and extensive tumor necrosis at doses between 2.5 µg and 12 µg. Tumor growth was suppressed for 40 days after one treatment. No systemic toxicity was noted. Systemic IV administration was ineffective. The results indicate that anti-PLVAP Fab-TF should be infused into tumor feeding artery for therapeutic effect, and may be used to treat HCC without chemotherapeutic agents and drawback of high viscosity of emulsion used for TACE. Subsequently, a recombinant anti-human PLVAP Fab-TF was generated and tested pre-clinically in primates at doses from 0.03 to 10 mg/kg. The results showed that hepatic artery administration could be tolerated up to 1 mg/kg. There were transient elevation of ALT, prolonged prothrombin time (<20 seconds), and reduced platelet counts (<50%). There were no significant changes of bilirubin, ALP, aPTT, creatinine and BUN. The preclinical primate study supports feasibility of clinical trial in HCC patients.

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