Is There a Best Host Targeting Antiviral in HBV Therapeutic Development?

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Host Targeting Antivirals

- Non-immune based
- Host factors requisite for productive viral infection
- High barrier for drug resistance
  - Viral mutations result in reduced interaction with host factors
- Potential toxicity
  - Redundancy
  - Differential sensitivity
Host Targeting Antivirals: Examples

- HIV: Maraviroc, CCR5 entry inhibitor
- Other viruses
  - Ribavirin: IFN potentiator
  - Kinase inhibitors (sunitinib, erlotinib): entry
- HBV
  - Entry (NTCP): myrcludex B, cyclosporin A
  - Assembly & release: glucosidase inhibitors, nucleic acid polymers
  - cccDNA biogenesis and turnover
**HBV cccDNA**

- Initial formation after entry; recycling of rcDNA-containing nucleocapsid for amplification
- Conversion of rc to cccDNA mediated by host proteins (removal of pol by TDP2)
- Negatively regulated by LHBsAg
- 1-10 copies/cell
- Mini-chromosomes: histones, histone enzymes, nonhistone proteins and viral proteins (core, HBx)

*Levrero et al, J Hepatol 2009; Koniger et al, PNAS 2014*
**HBV cccDNA**

- Transcriptional regulation by hepatocyte-specific factors (HNF1, 3 & 4) and other transcriptional factors (RXR, PPAR-α, etc)

- Epigenetic regulation: histone (H3 and H4) acetylation (↑) and methylation (↓)

- IFN-α recruits histone deacetylase 1 to suppresses transcription and induces ISG20 to degrade HBV RNA

- IFN induces APOBEC3A to degrade cccDNA

- HBx regulates cccDNA transcription by targeting degradation of viral restriction factor SMC5/6

Host Targeting Antivirals: Strategies

• Genome-wide siRNA or CRISPR/Cas9 screen to identify host factors

• Repurposing or repositioning of approved drugs targeting these host factors

• High-throughput screen of library of known pharmaceutical collections (approved or late preclinical)
Host Targeting Antivirals: Potential Target

Retinoid X Receptor α Transactivates the Hepatitis B Virus Enhancer 1 Element by Forming a Heterodimeric Complex with the Peroxisome Proliferator-Activated Receptor

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Not Yet!