SESSION III

GENE EDITING & EPIGENETIC APPROACHES TO HBV CURE

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THE FORUM
For Collaborative Research℠

Gene Editing and Epigenetic Approaches for HBV Cure

Therapeutic Endpoints and other issues

1. Is Sterilizing Cure feasible with Gene Therapies?

Modelling by Alexander Ploss, Princetom

a) Total number of hepatocytes in 1.5 kg patient liver

⇨ **1.8×10^{11} cells** (Sohlenius-Sternberg (2006) Toxicol In Vitro , Bayliss et al. (1990) Biochem Soc Trans)

b) Frequency of HBV infected cells: *(Pan et al. (2025) Gut)*

- Untreated: mean=24% ⇨ **4×10^{10} cells**
- NUC suppressed: mean = 3.4% ⇨ **6×10^{9} cells**

c) Total number of cccDNA molecules in the liver

- 2-20 copies of cccDNAs/cell ⇨ **$6 - 60 \times 10^{9}$ ccc DNAcopies**

d) Residual cccDNA molecules according to gene editing efficiency

- 99% hepatocytes edited ⇨ **60,000,000 copies cccDNA**
- 99.999% hepatocytes edited ⇨ **60,000 copies cccDNA**

➡ **Minimum cccDNA to establish infection⇨1-400**

(McCullough et al. (2018) Transfusion, Allain et al. (2013) Transfusion, Komiya et al. (2008) Transfusion; +work by Chisari and Prince groups)

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Gene Editing and Epigenetic Approaches for HBV Cure

Therapeutic Endpoints and other issues

1. Is Sterilizing Cure feasible with Gene Therapies?
2. Will repeated dosing be required – same or higher?
   Will combination therapy be required and what MOA?
3. How will we distinguish cccDNA and integrant editing?
   - Serum and tissue biomarkers?
   - Patient baseline characteristics?
4. Is Partial Cure/Sustained Control an alternative endpoint?
5. When should NUCs be withdrawn
   - What biomarkers could inform who will relapse?

Gene Editing and Epigenetic Approaches for HBV Cure

Therapeutic Endpoints and other issues

1. Will gene-targeting approaches reduce risk of HCC?
2. Could gene-targeting approaches increase risk of HCC through on- and off-target editing ?
3. Are there other safety concerns?
4. How long should participants be followed up for?
   a) Any DNA cutting approach *currently 15 years?*
   b) Epigenetic silencing *currently 5 years?*