Challenges and Approaches for Virological Cure of Hepatitis B

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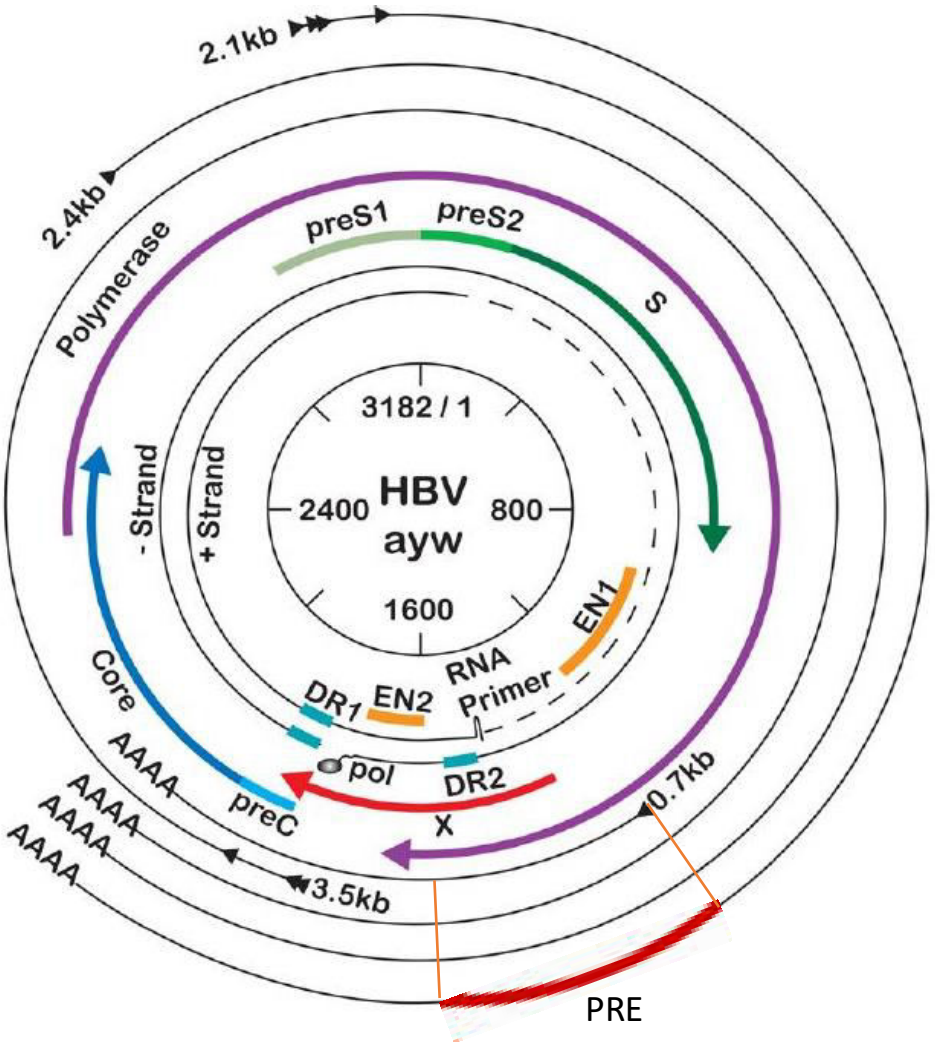
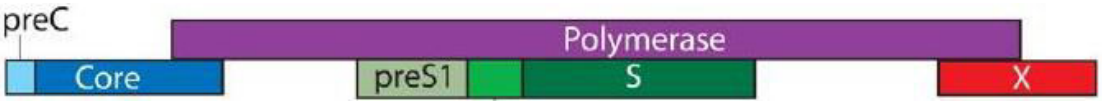
The Approaches for a HBV Cure

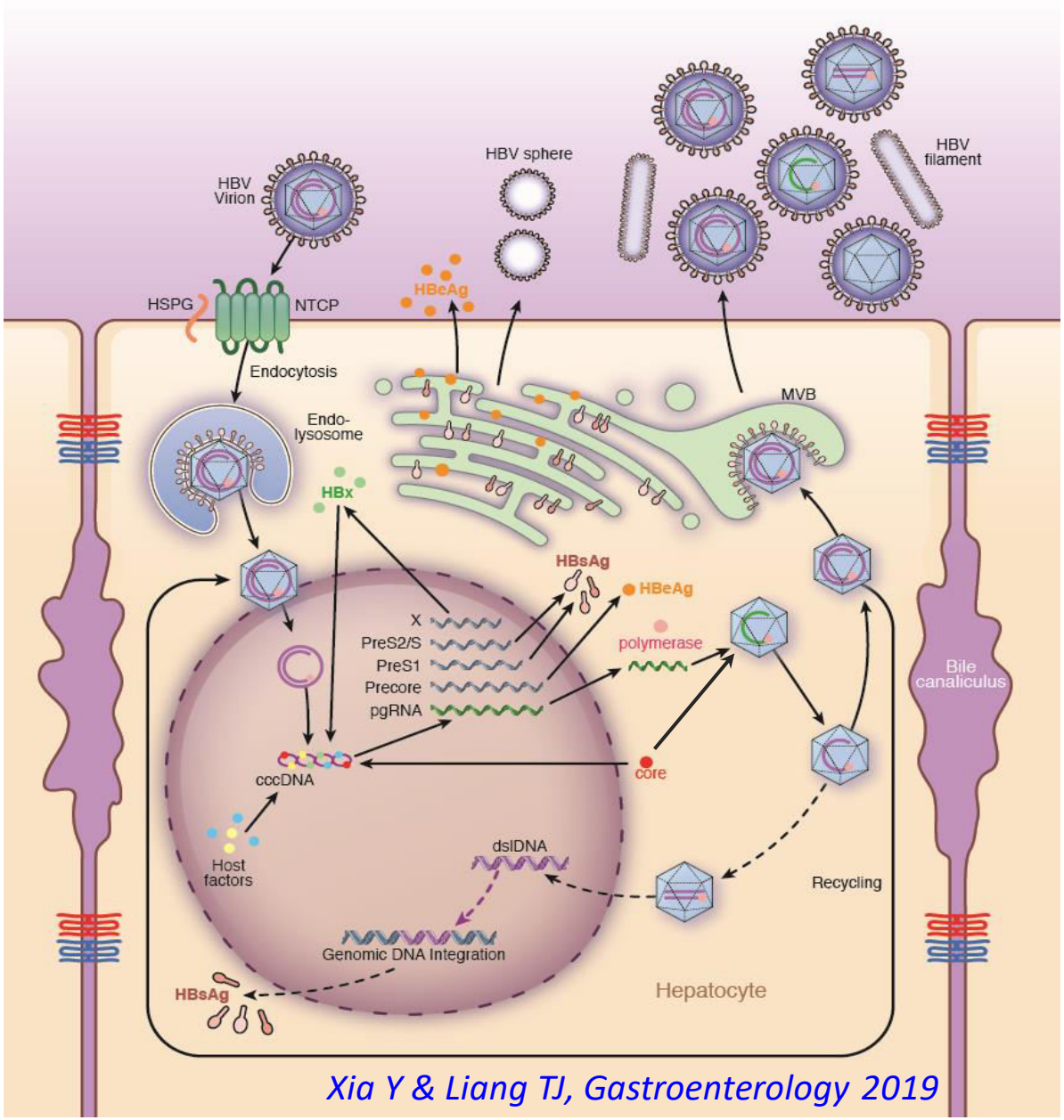
- HBV genome, gene products and life cycle
- Current therapies
- Approaches to virological cure: viral vs host targets
- Immunotherapy

HBV Genome and Gene Products





HBV Life Cycle



Xia Y & Liang TJ, Gastroenterology 2019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NEW WEAPONS AGAINST
HIV
Breakthrough of the Year

Approved HBV Therapies

- Six nucleoside analogs: NRTIs
  - Lamivudine (1998)
  - Adefovir (2002)
  - Entecavir (2005)
  - Telbivudine (2006)
  - Tenofovir disoproxil fumarate (2008)
  - Tenofovir alafenimide fumarate (2016)
- Two forms of interferon:
  - Interferon-alfa-2 (early 1990s)
  - Peginterferon-alfa-2 (early 2000s)

Why New Therapies?

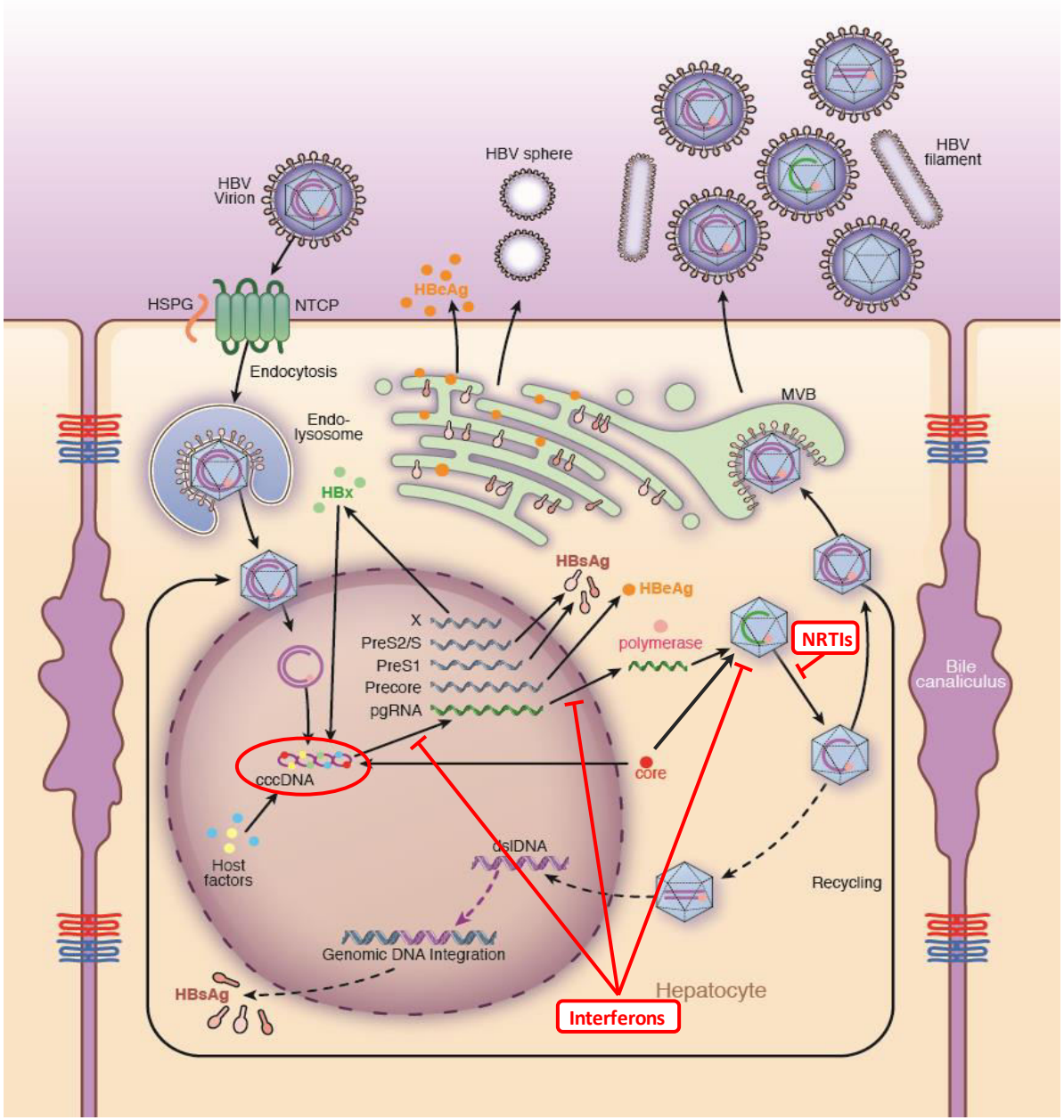
Ultimate goals of HBV treatment

- Eradicate HBV
- Reverse liver damage
- Prevent cirrhosis and HCC

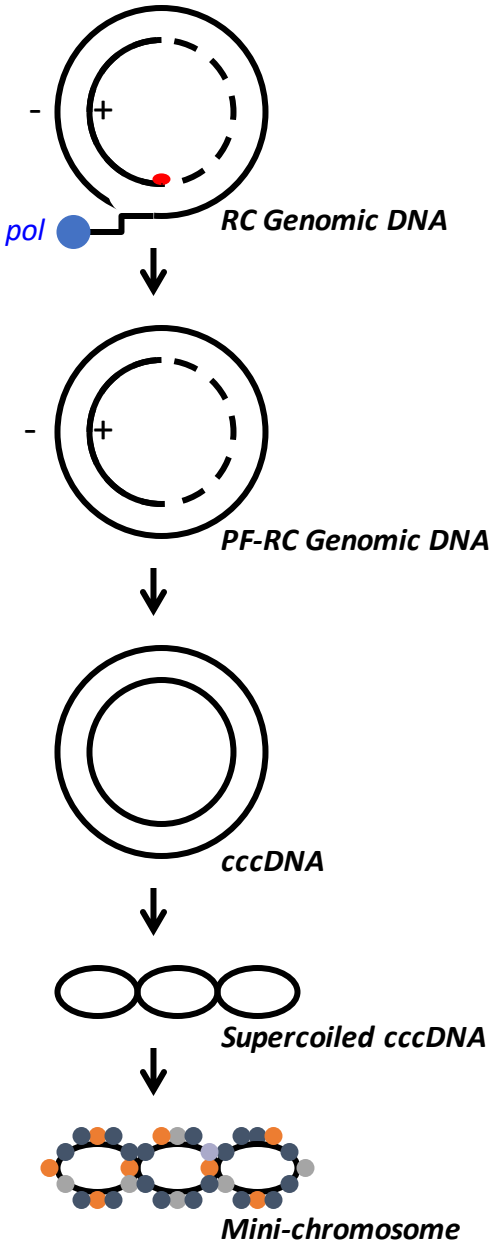
Efficacy of existing treatment

- Suppress but not eradicate HBV
- Low rate of HBsAg loss
- Partial reversal of inflammation and fibrosis
- Decrease but not eliminate risk of HCC
- Prolonged therapy, side effect & cost

HBV Life Cycle



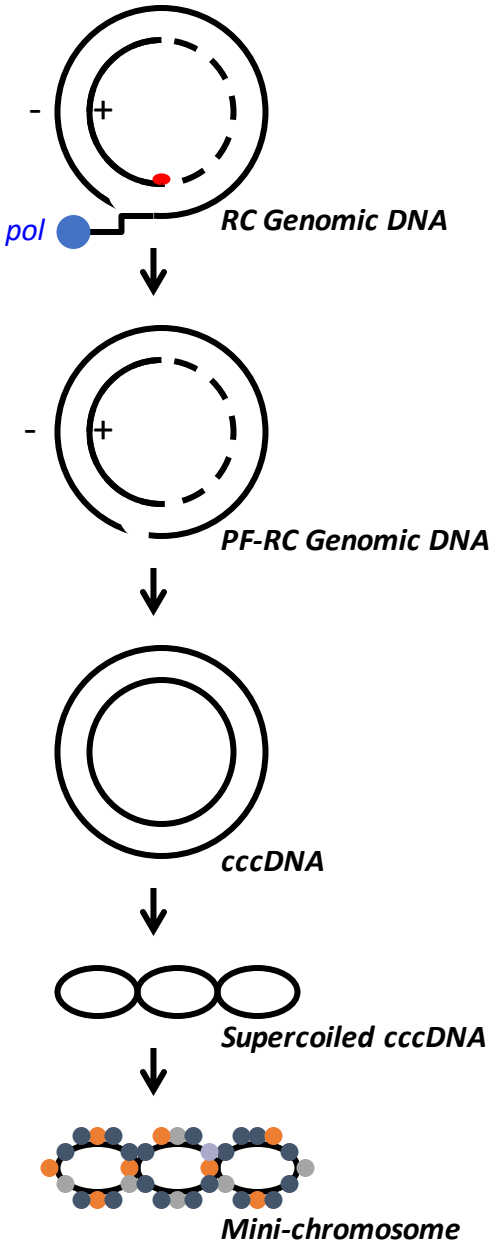
HBV cccDNA



- Viral replication: 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, nonhistone proteins and viral proteins (core, HBx)

Levrero et al, J Hepatol 2009; Koniger et al, PNAS 2014

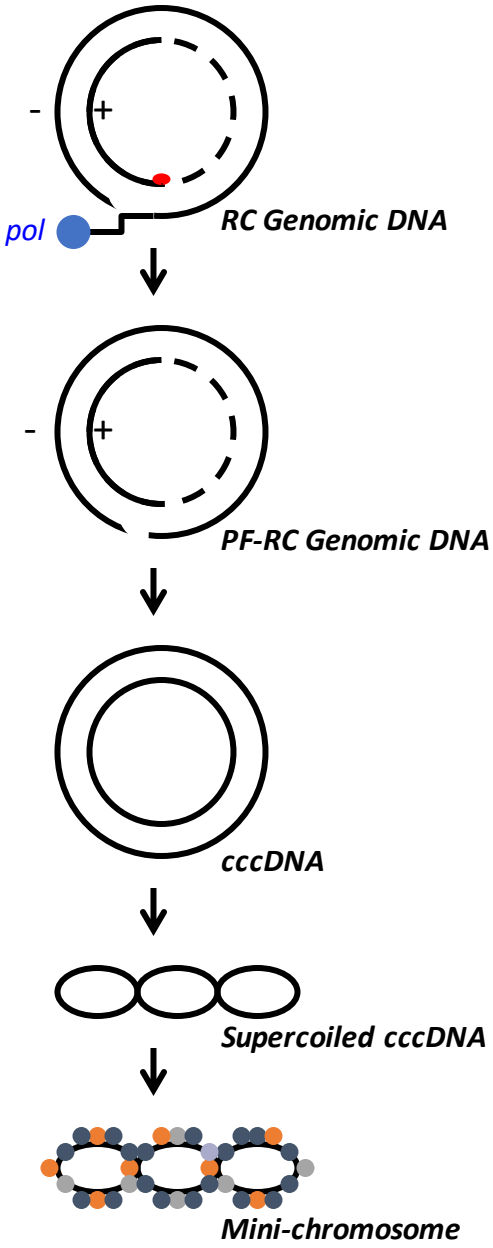
HBV cccDNA



- 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 and TNF-α induce APOBEC3A to degrade cccDNA
- HBx exerts an epigenetic regulation of cccDNA transcription by targeting degradation of viral restriction factor SMC5/6

Levrero et al, J Hepatol 2009; Lucifora et al, Science 2014; Tropberger et al, PNAS 2015; Riviere et al, J Hepatol Decorsiere et al, Nature 2015

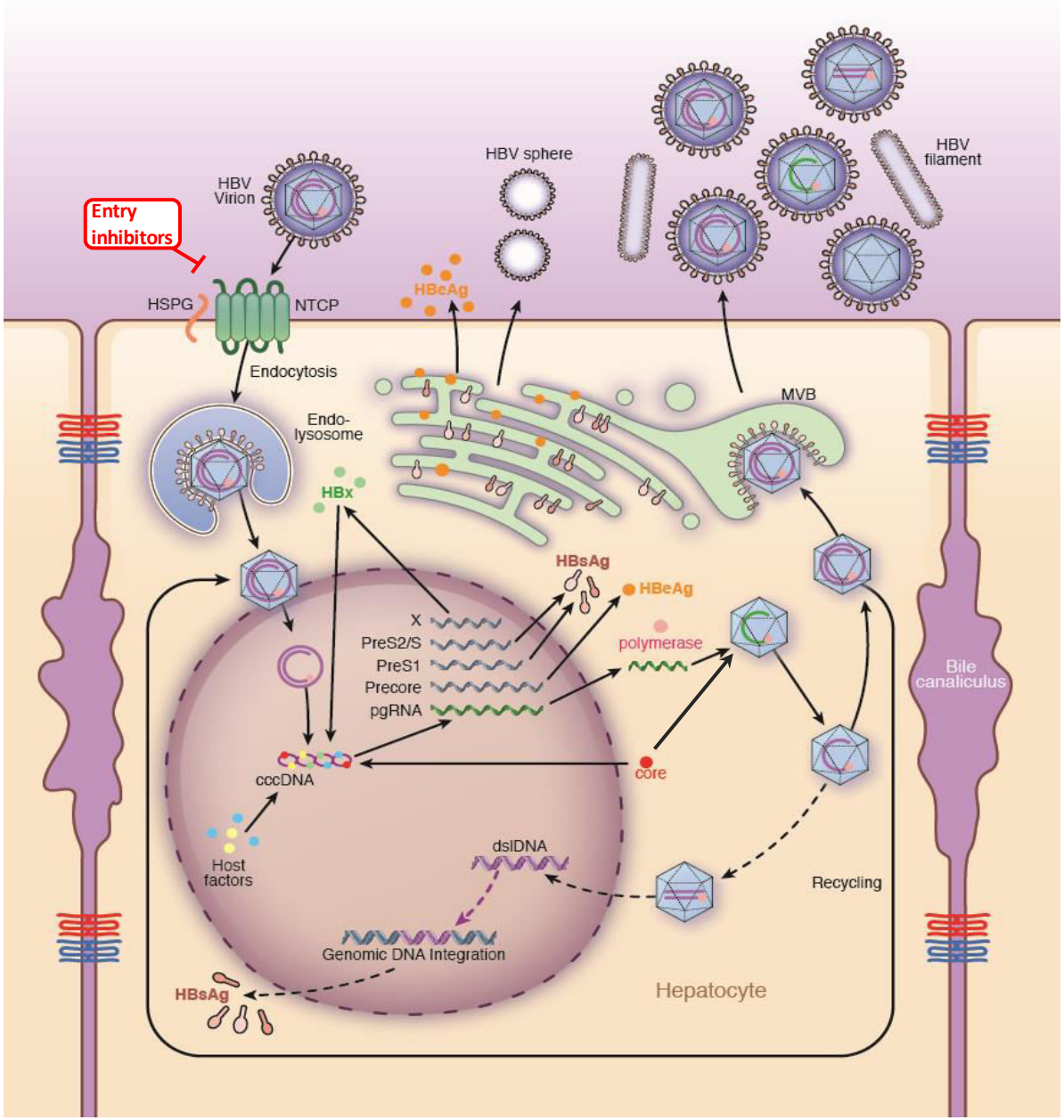
HBV cccDNA



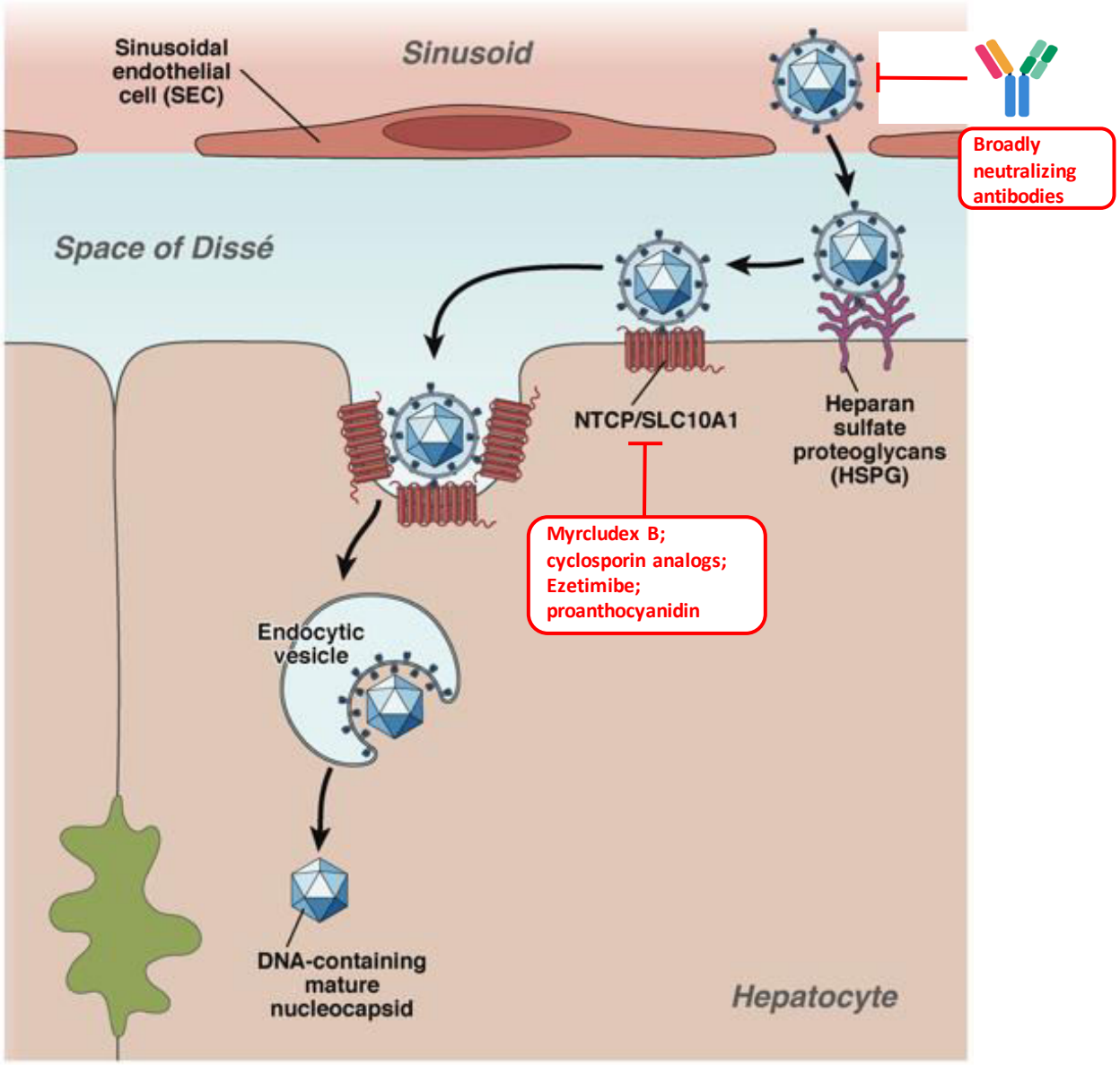
- Long half-life, stable in quiescent cells; mechanism of turn-over unknown
- Loss of cccDNA controlled by
  - Cell death: immune cytolytic mechanism
  - Dilution by cell proliferation: liver regeneration
  - Cell cure: immune non-cytolytic mechanism, IFNs & other cytokines
- Persistence of low-level cccDNA in hepatocytes, even in long-term treated patients

Guidotti et al, Science 1999; Summers et al, PNAS 2003; Mason et al, J Virol 2009

HBV Life Cycle

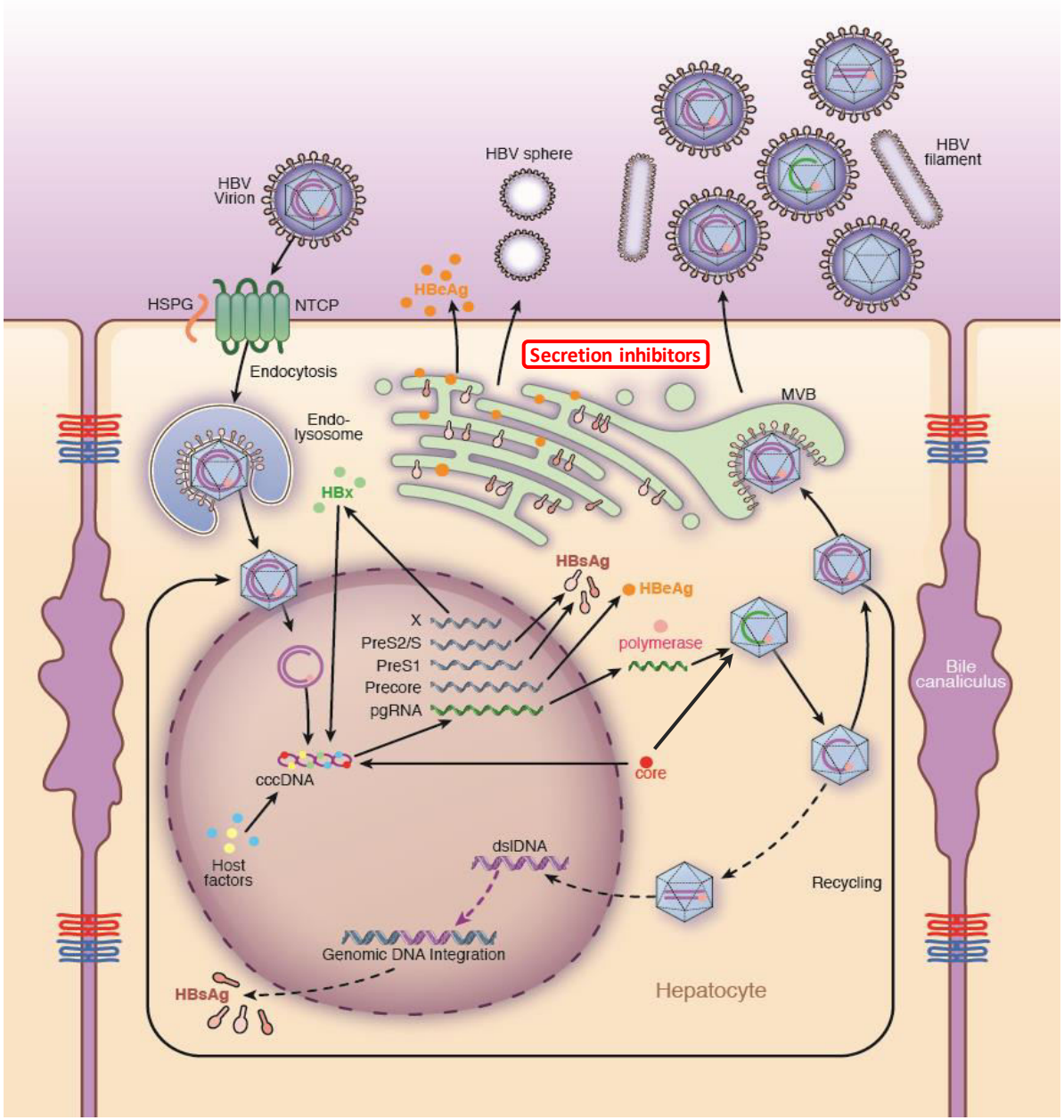


HBV Entry Inhibitors



Urban et al, Gastroenterology 2014

HBV Life Cycle



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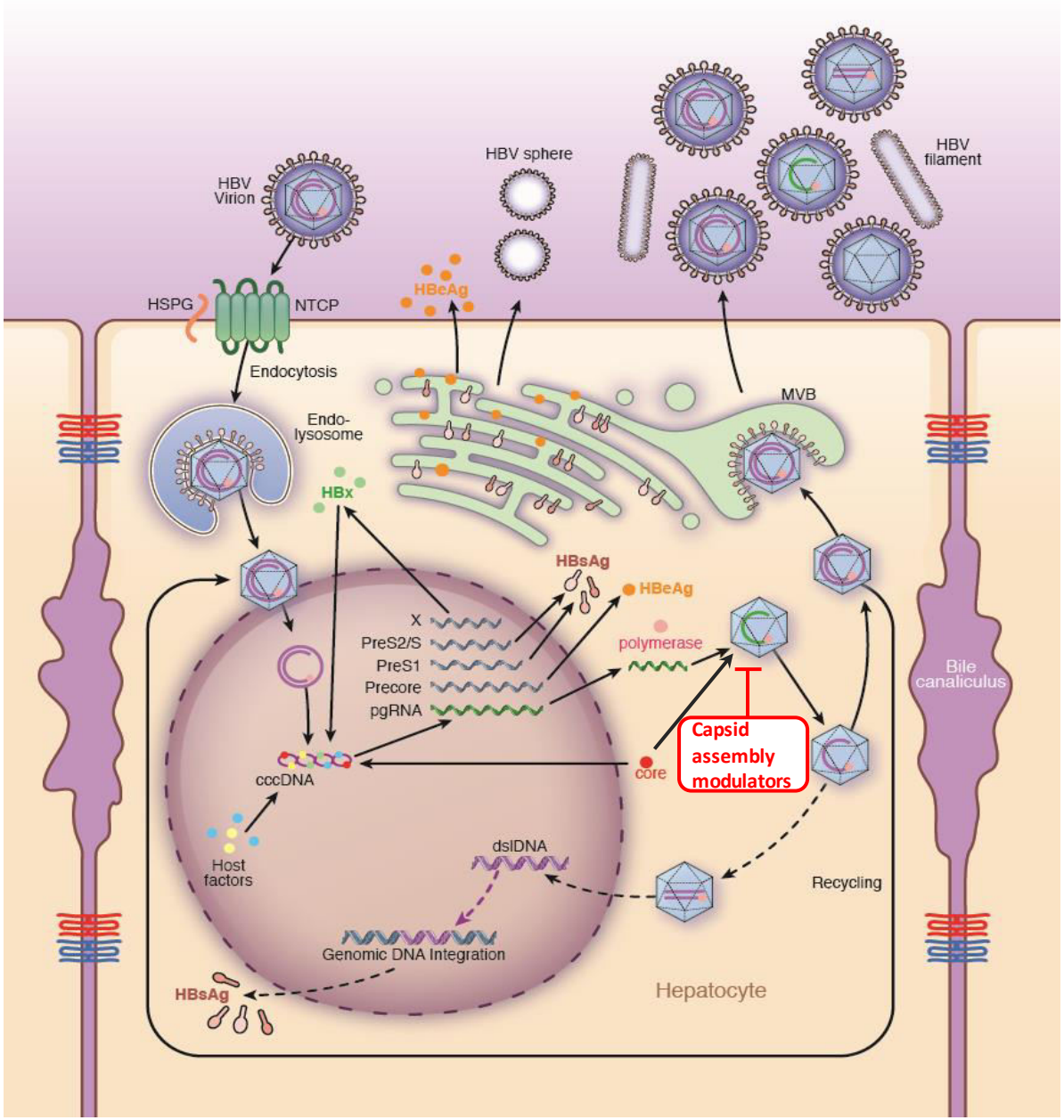

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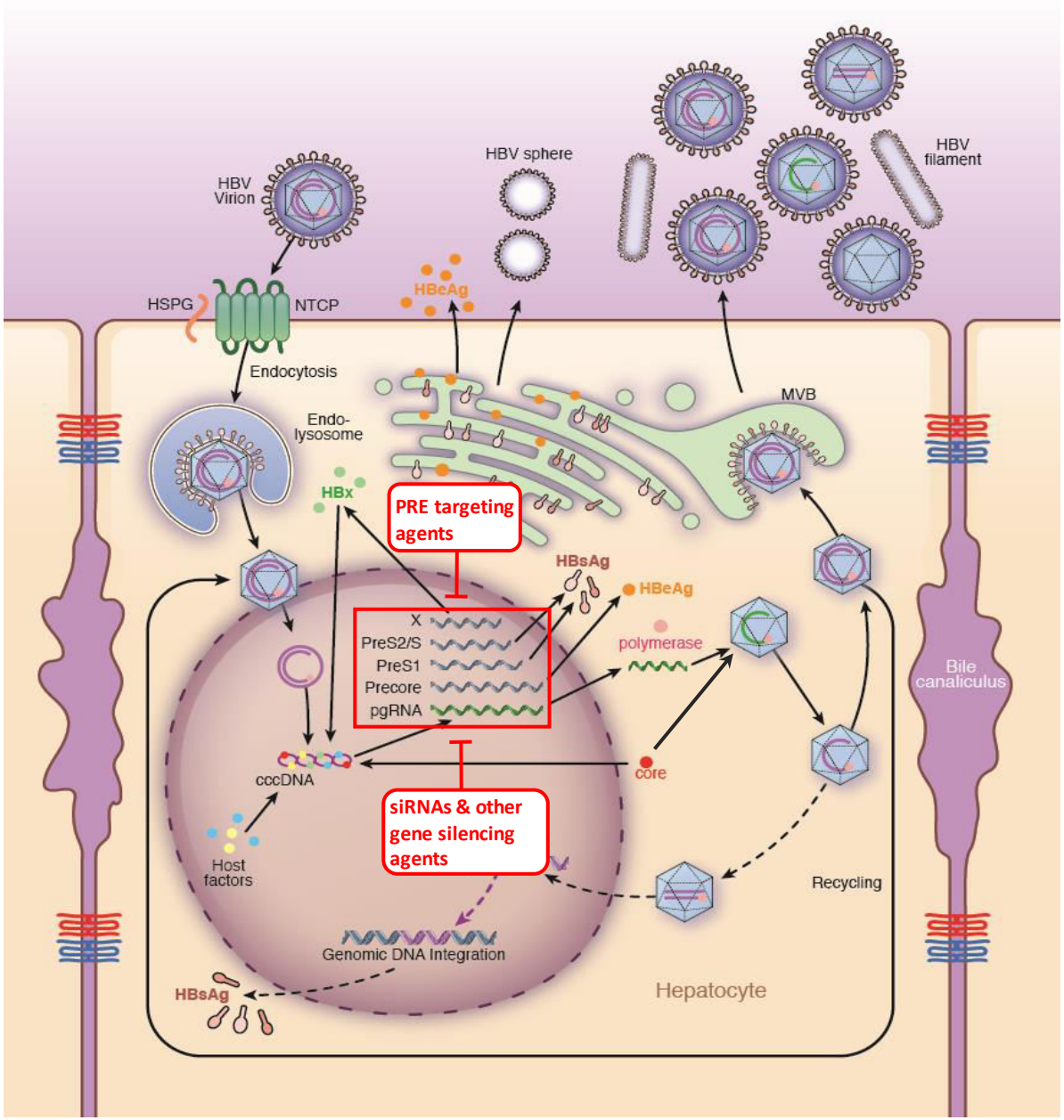

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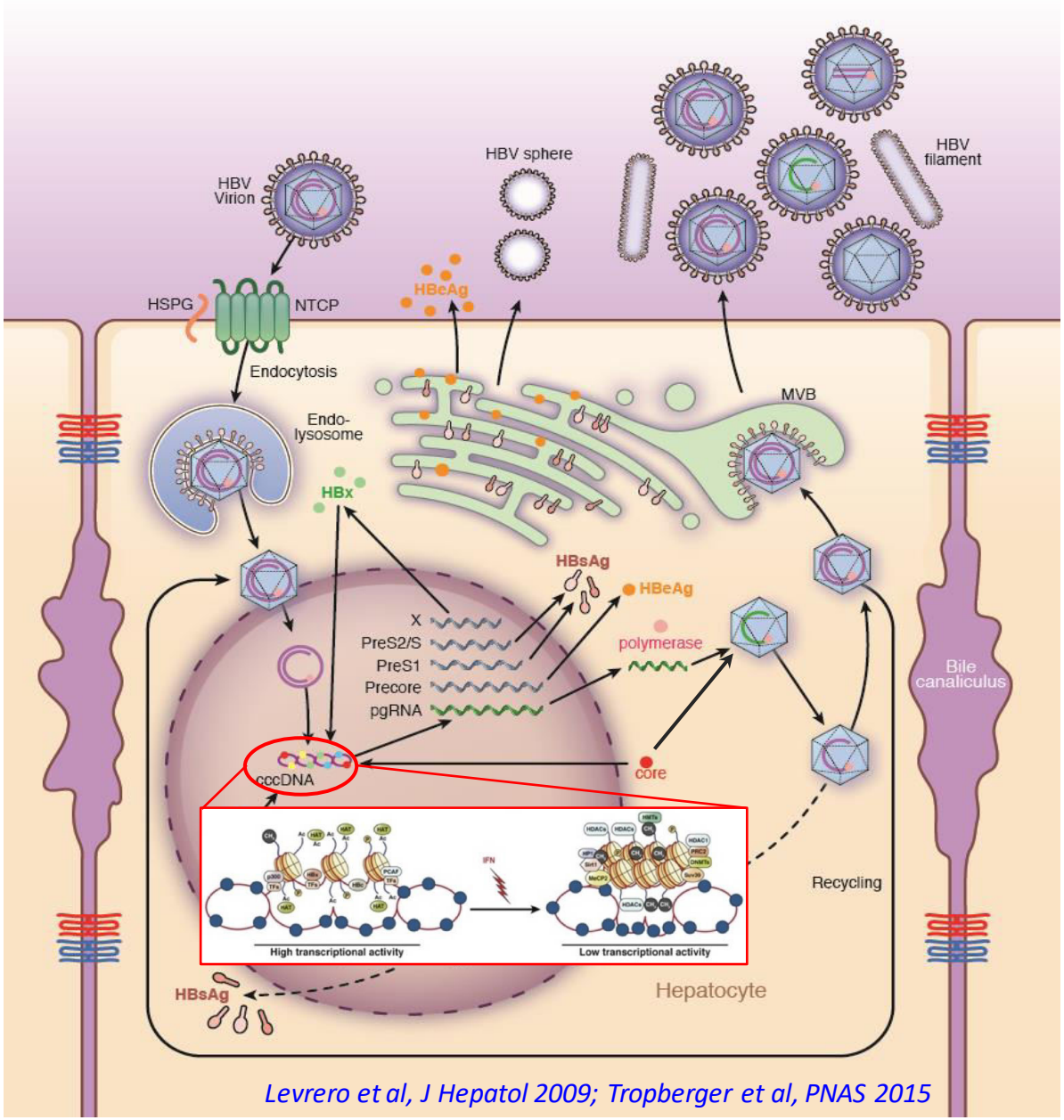
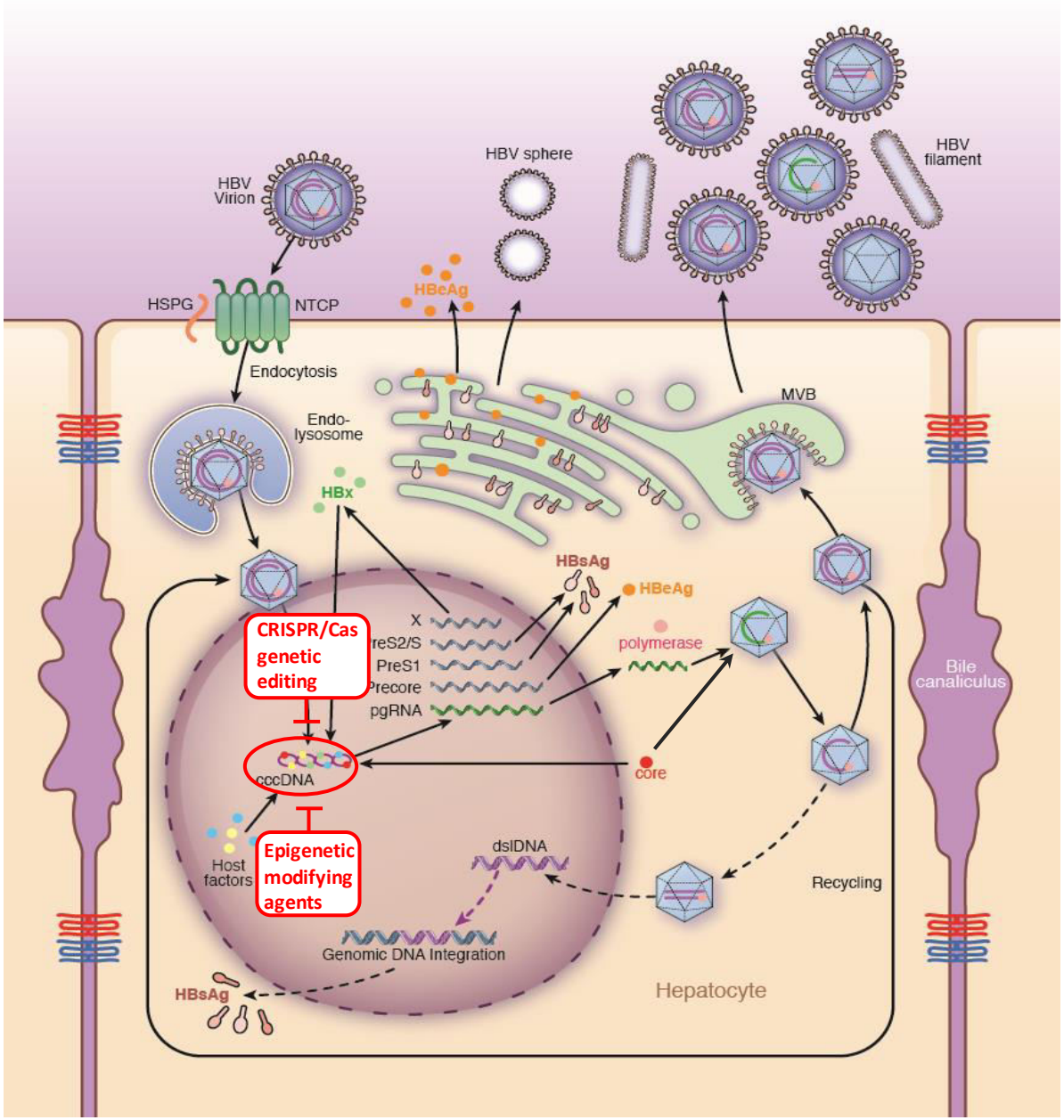


Levrero et al, J Hepatol 2009; Tropberger et al, PNAS 2015

HBV Life Cycle



Host Targeting Antivirals

- Limited viral targets
- Host factors requisite for productive viral infection
- High barrier for drug resistance
- Potential toxicity
  - Redundancy
  - Differential sensitivity

Targeting cccDNA?

- Prevent cccDNA formation: NRTIs, CAMs, TP/RNase/TDP2 inhibitors
- Silence cccDNA activity: Epigenetic modifying agents; anti-HBx; HBV-specific transcription inhibitors
- Accelerate cccDNA degradation: APOBEC3A activator?
- High-throughput screen of large diverse compound libraries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