HDV Epidemiology, Life Cycle and Targets of Therapeutic Interference

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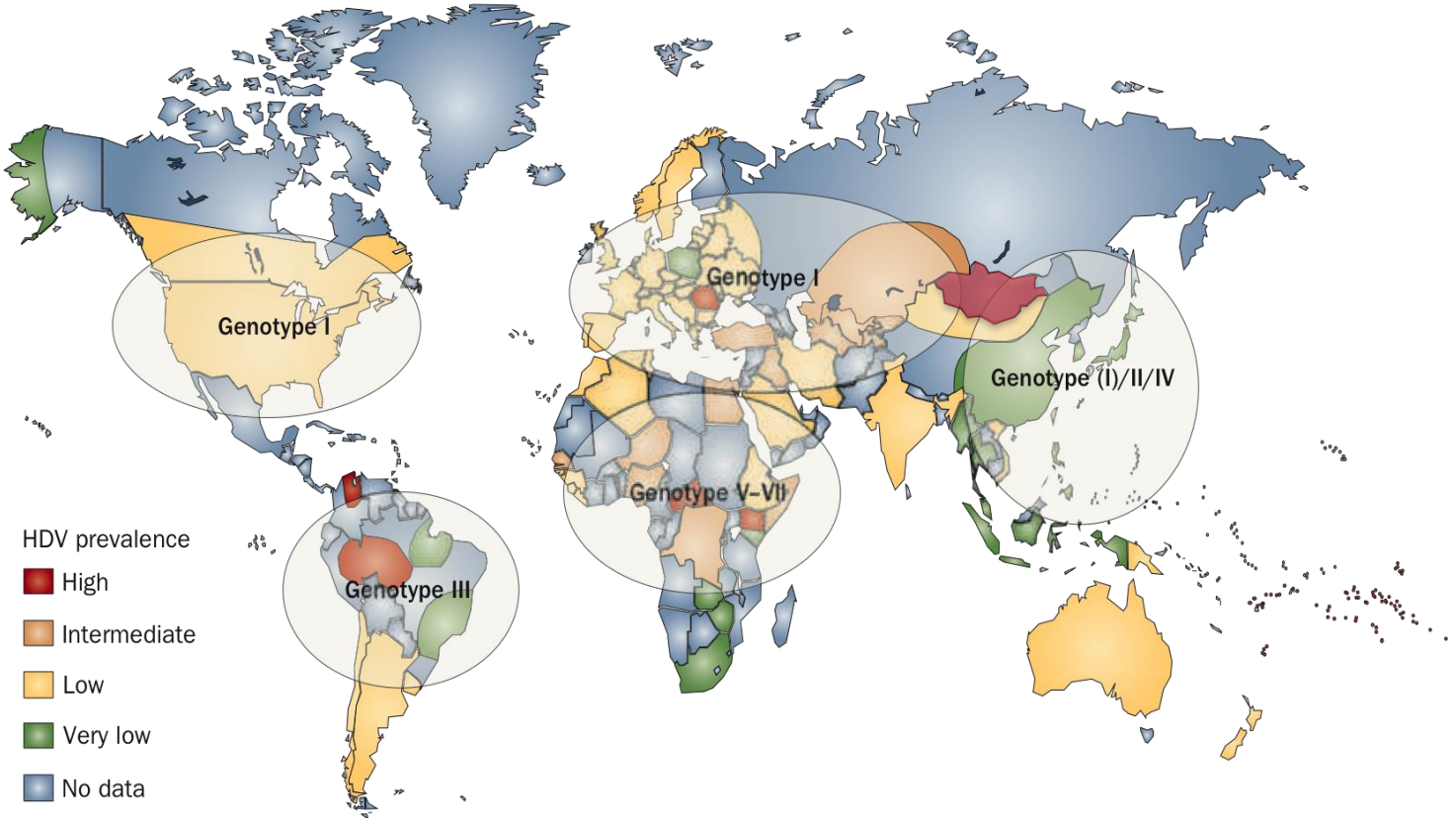
Outline

- Brief overview of:
  - HDV epidemiology
  - HDV life cycle
  - preclinical potential targets for future therapeutic interference
- Highlight targets of agents in clinical development

Hepatitis delta virus (HDV)

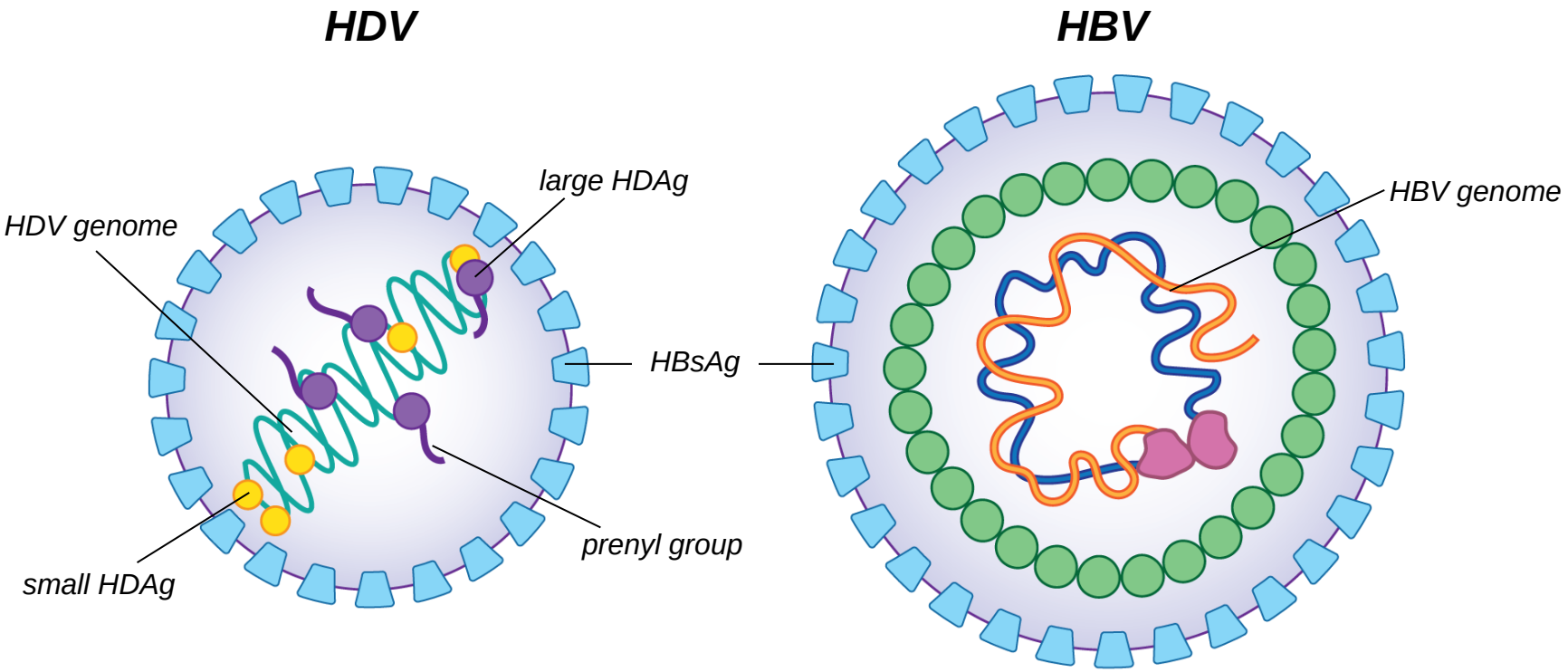


Wedemeyer, H. & Manns, M. P. 2010. *Nat. Rev. Gastroenterol. Hepatol*. 7, 31–40.

- HDV is found in every country except:
  -- where people don't test for HDV, or
  -- their anti-HDV tests don't work

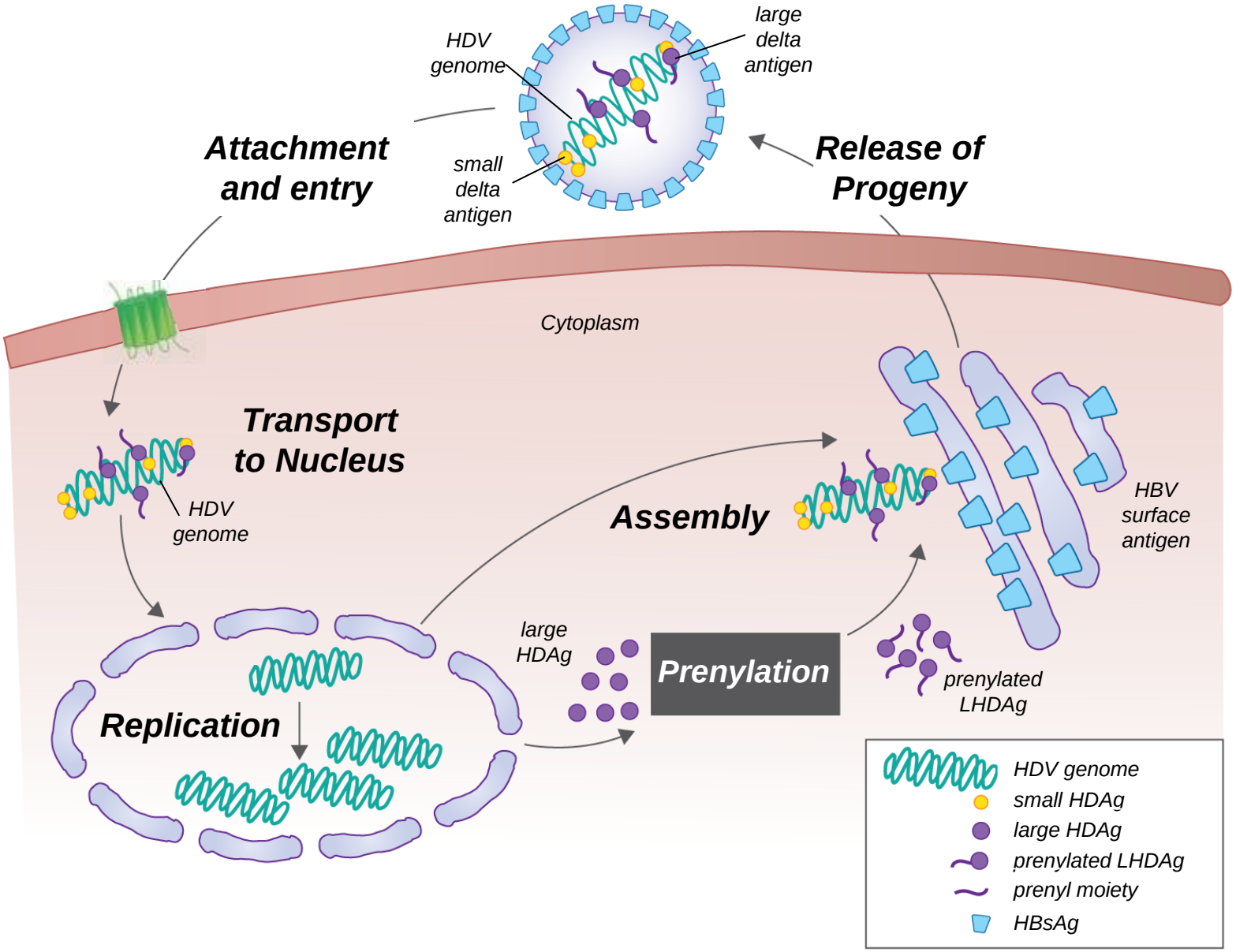
Hepatitis Delta Virus

Requires HBsAg from HBV for Viral Assembly / Packaging



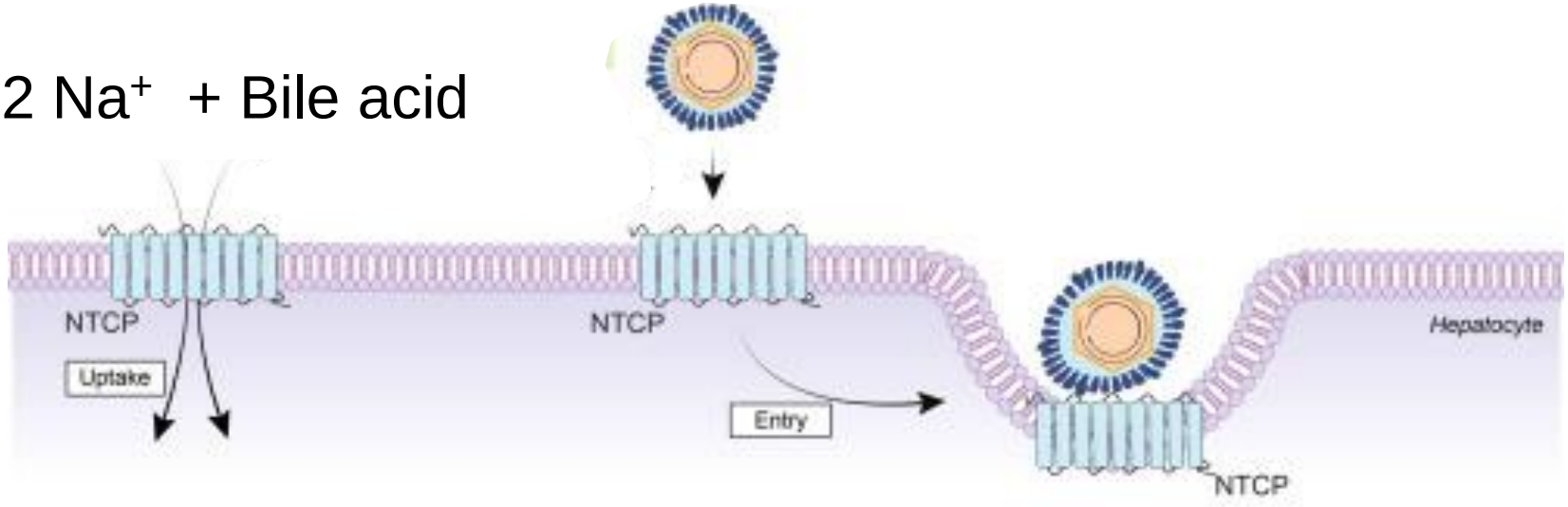
- HDV makes HBV disease worse
- HDV is worst form of human viral hepatitis
- Rapid progression to cirrhosis; HCC; ↓ survival
- ~ 15-20 million world-wide; ~ 100K in U.S.
- No FDA-approved therapy

The HDV Life Cycle



HBV/HDV entry

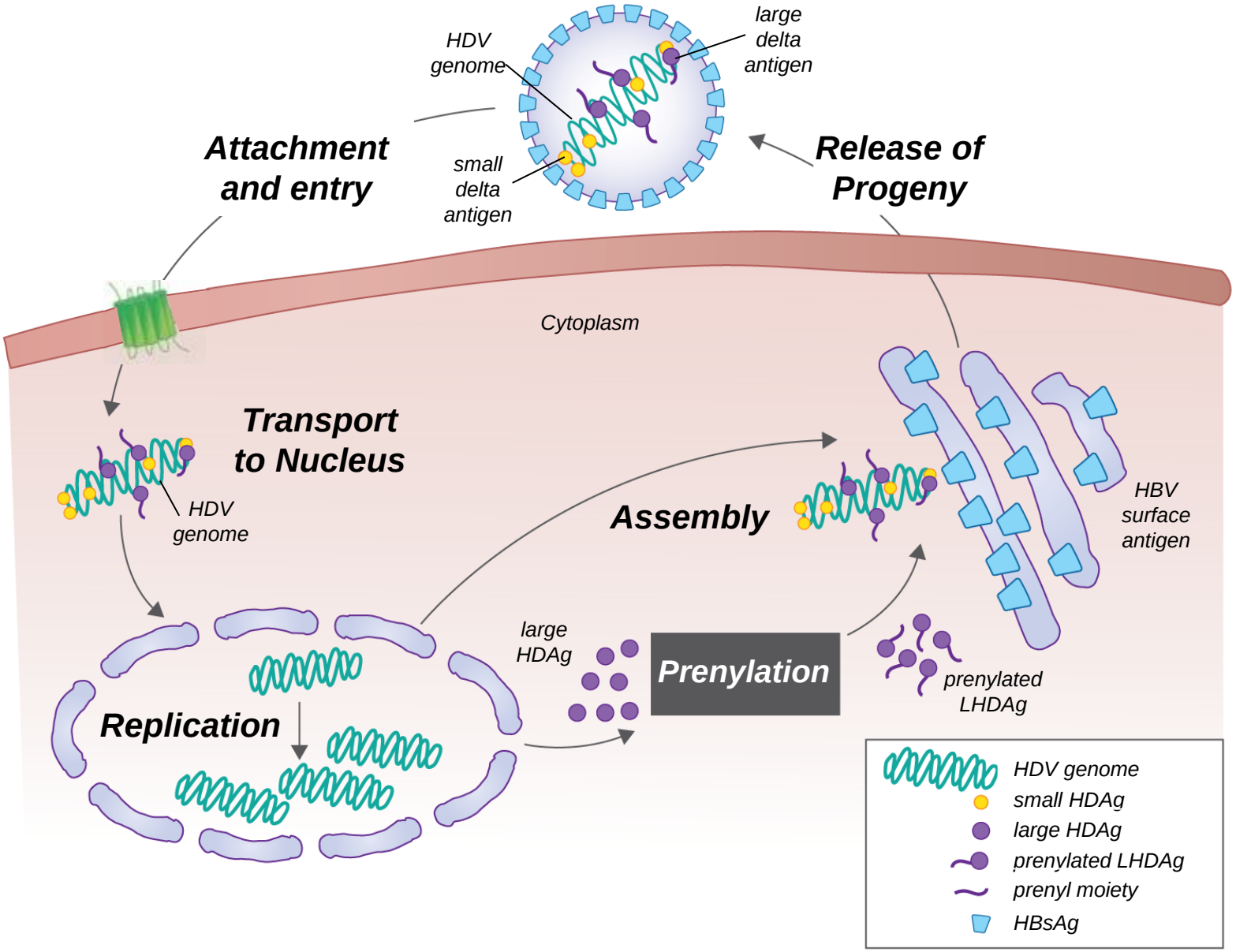
2 Na^+ + Bile acid



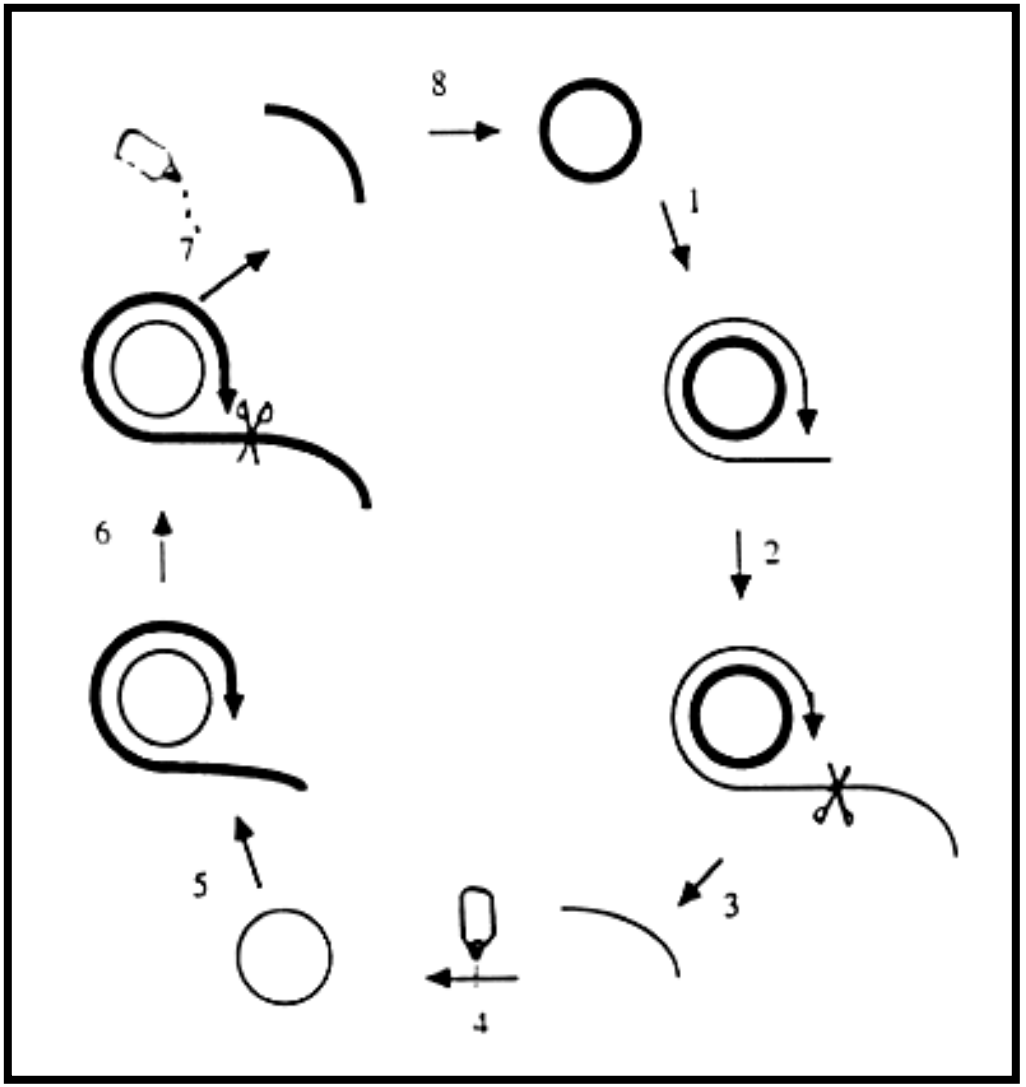
- Na-taurocholate cotransporting polypeptide (NTCP)
  - On surface of hepatocytes
- Receptor for bile acids and HBV/HDV virus entry

Shimura et al. J. Hepatol. 2017 66:4, 685-92

The HDV Life Cycle

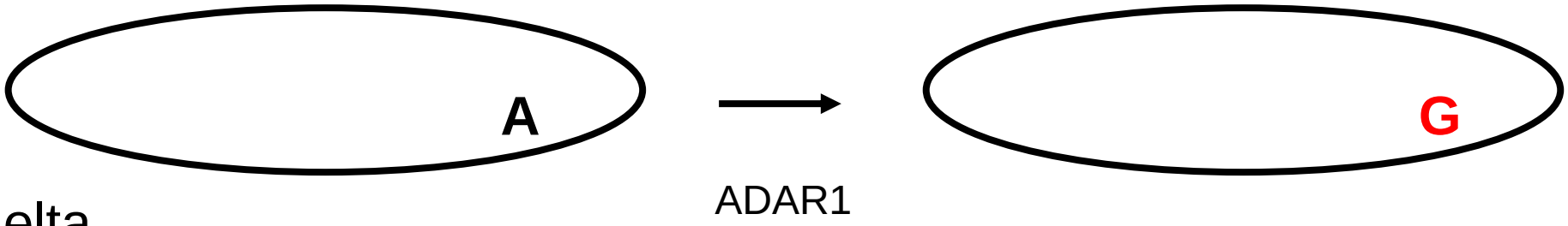


Double rolling circle model of HDV genome replication

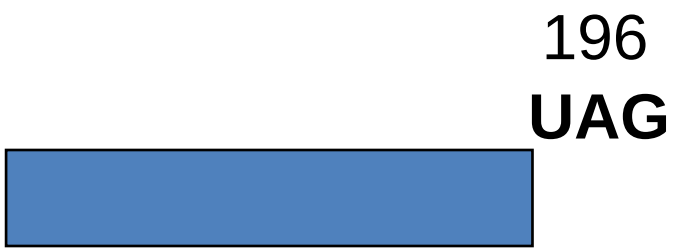


→ Multiple potential host cell targets

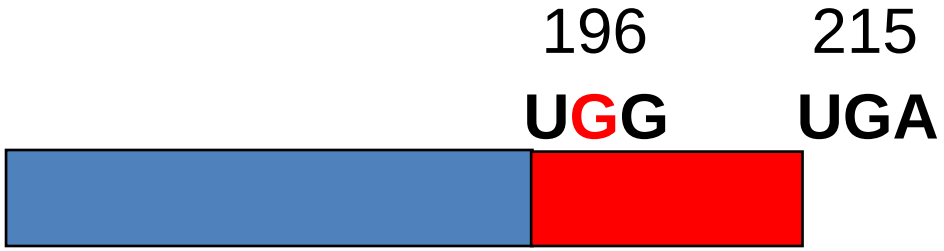
RNA editing generates two types of delta antigen



delta antigen isoform : small large



195 a.a.



195 + 19 a.a.

required for replication

inhibits replication

required for packaging with HBsAg

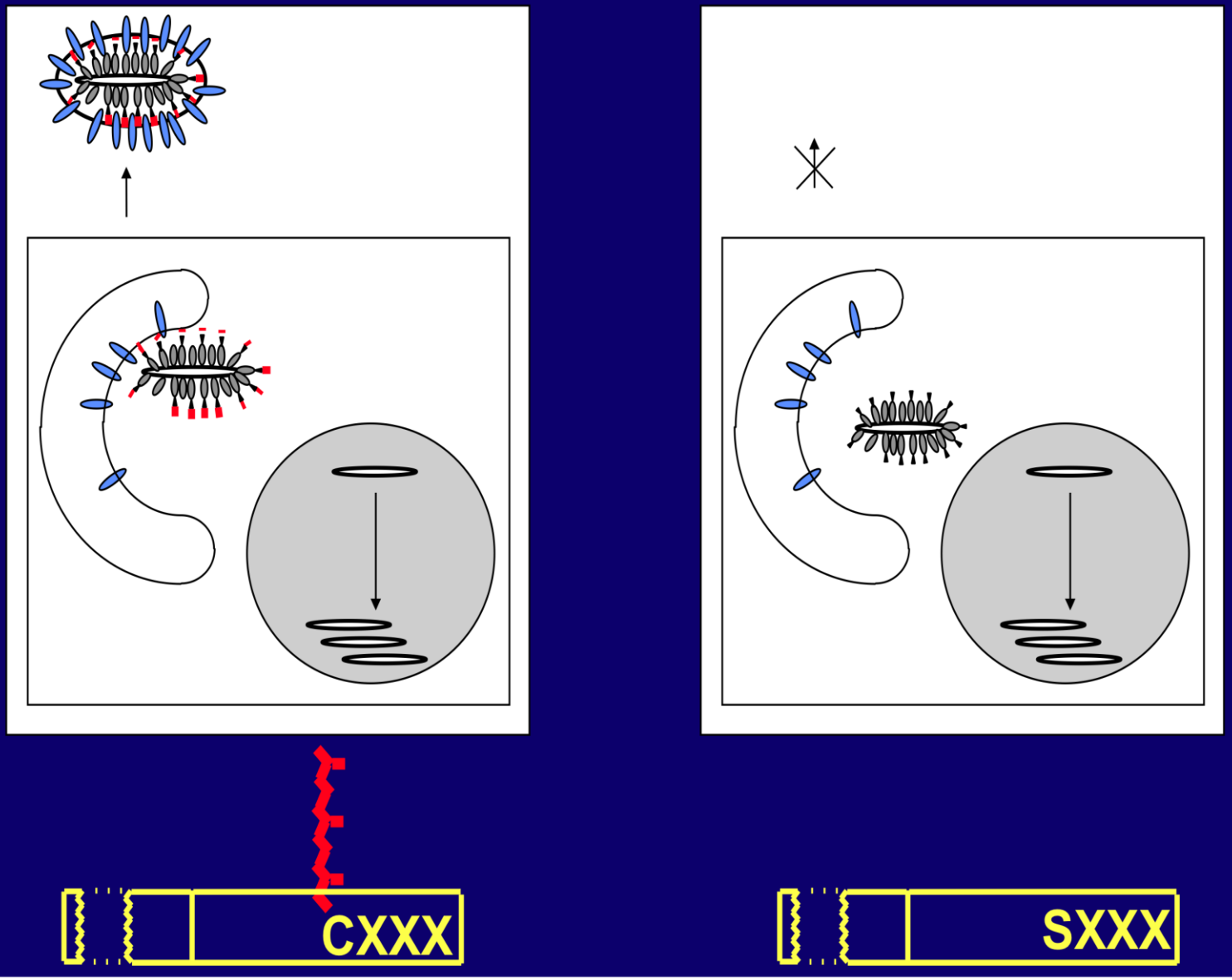
Prenylation of large delta antigen is required for HDV assembly

cys arg pro gln

prenylation site = "CXXX box"

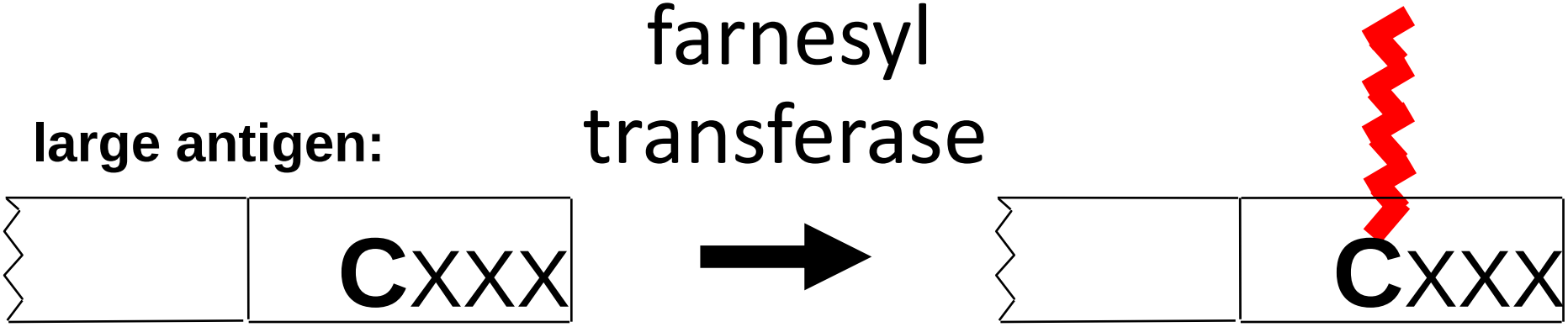
prenylation -- site-specific lipid modification of proteins

mevalonate → → isoprenoids (prenyl lipids)
-farnesyl (C15)
-geranylgeranyl (C20)


CXXX
SXXX

farnesyl transferase

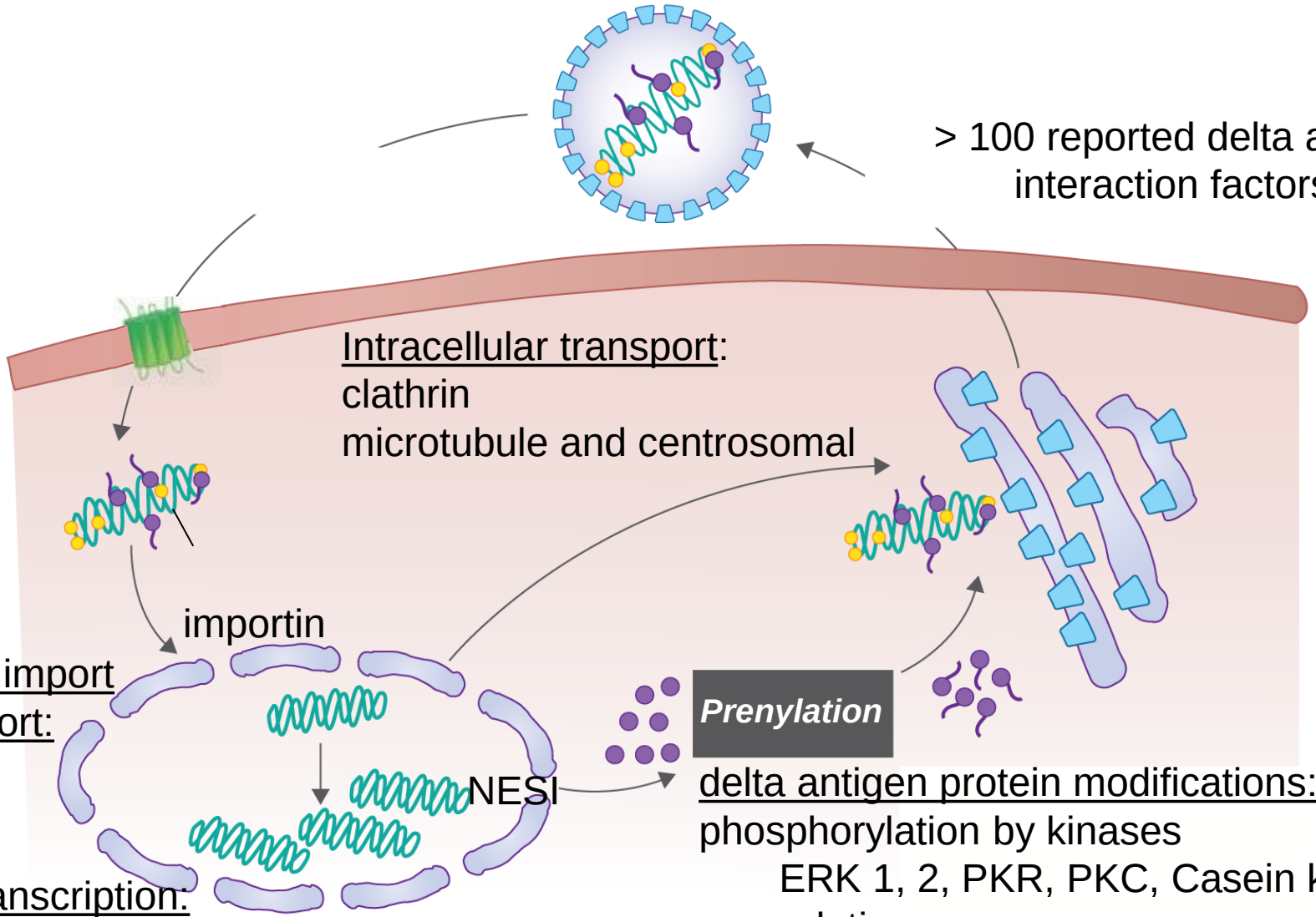
large antigen:



Ser 211 large antigen:
(Cys-->Ser)

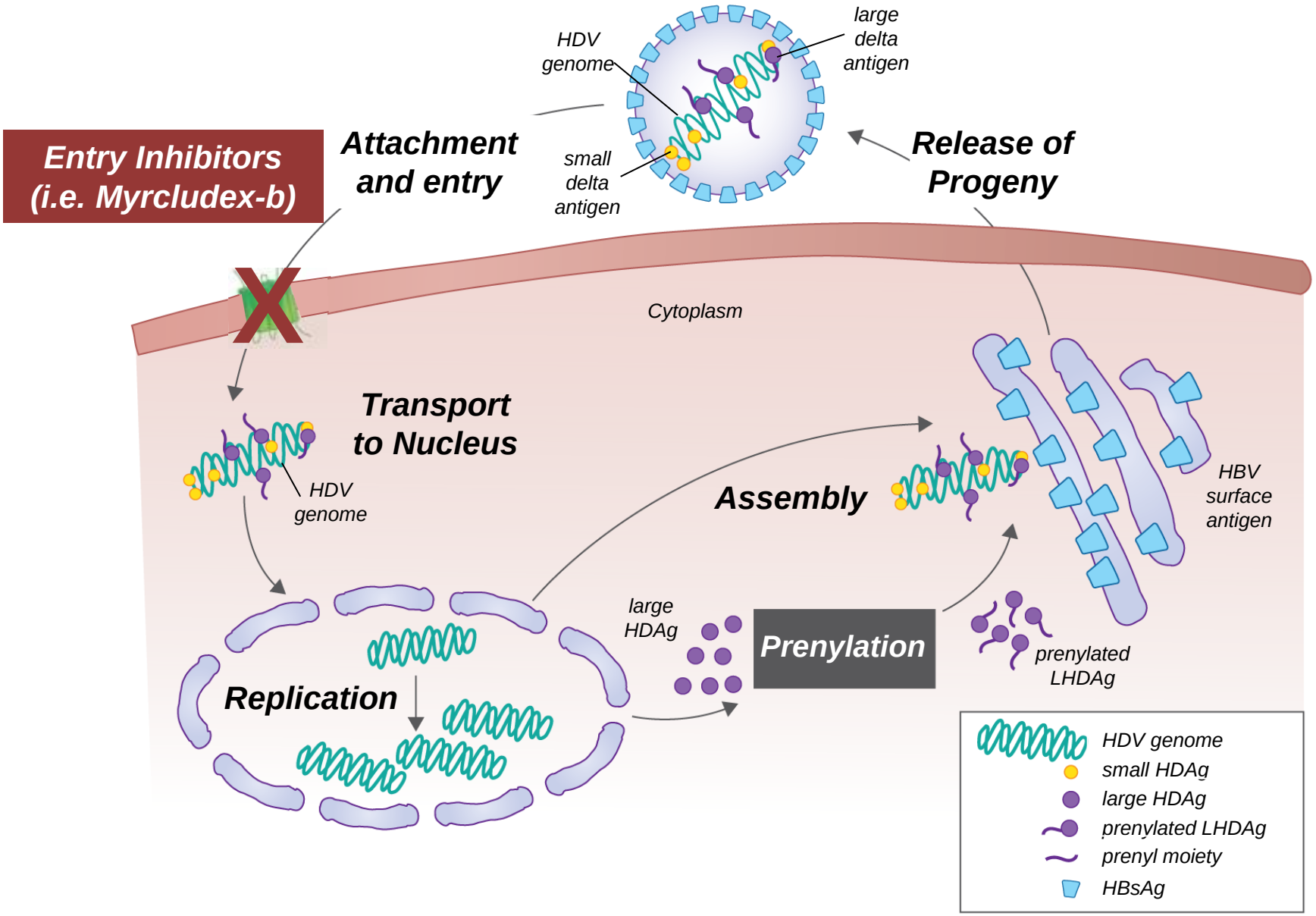
Multiple potential preclinical targets

Caveat: require further confirmation of druggability and acceptable therapeutic index

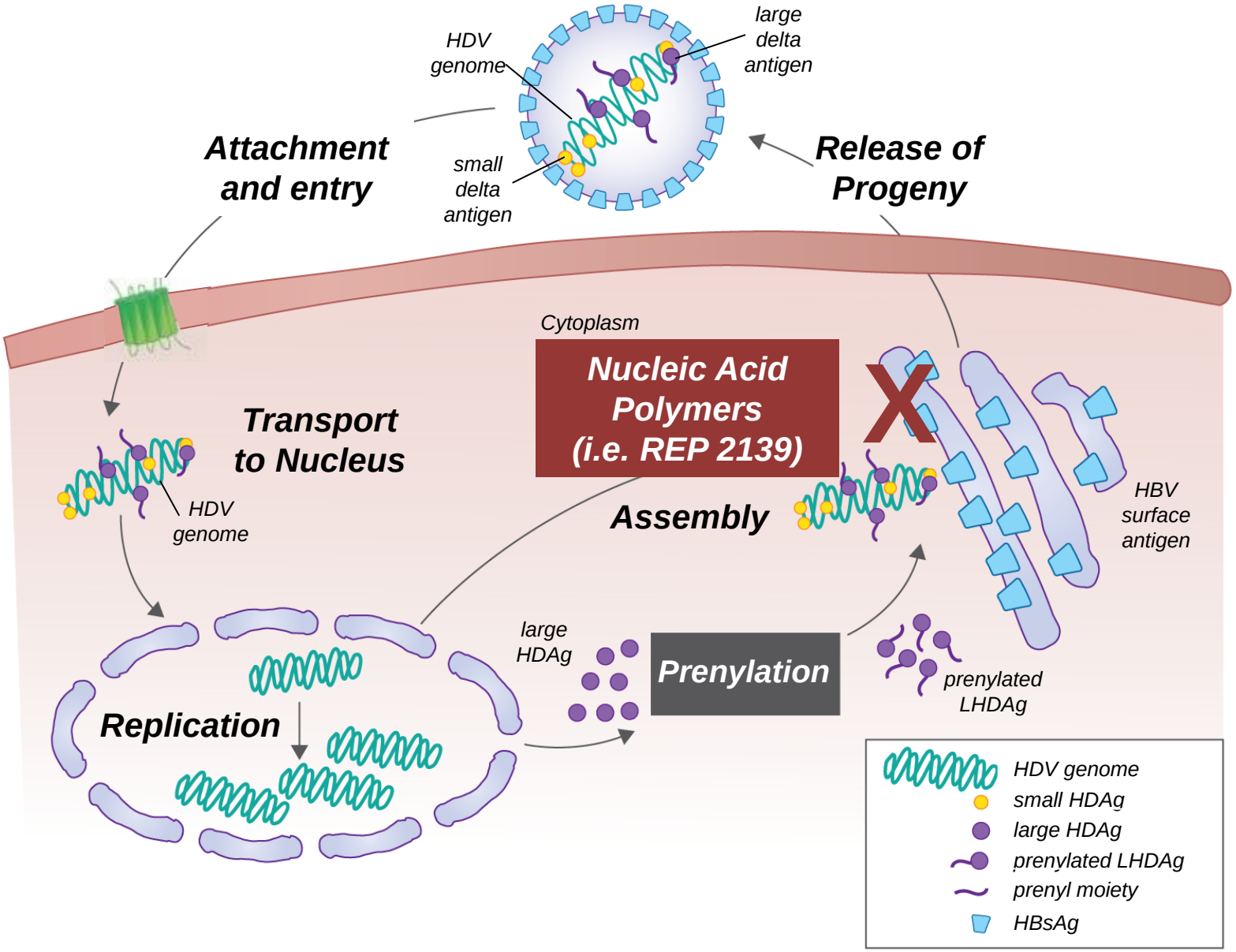


Targets of therapies in advanced clinical development

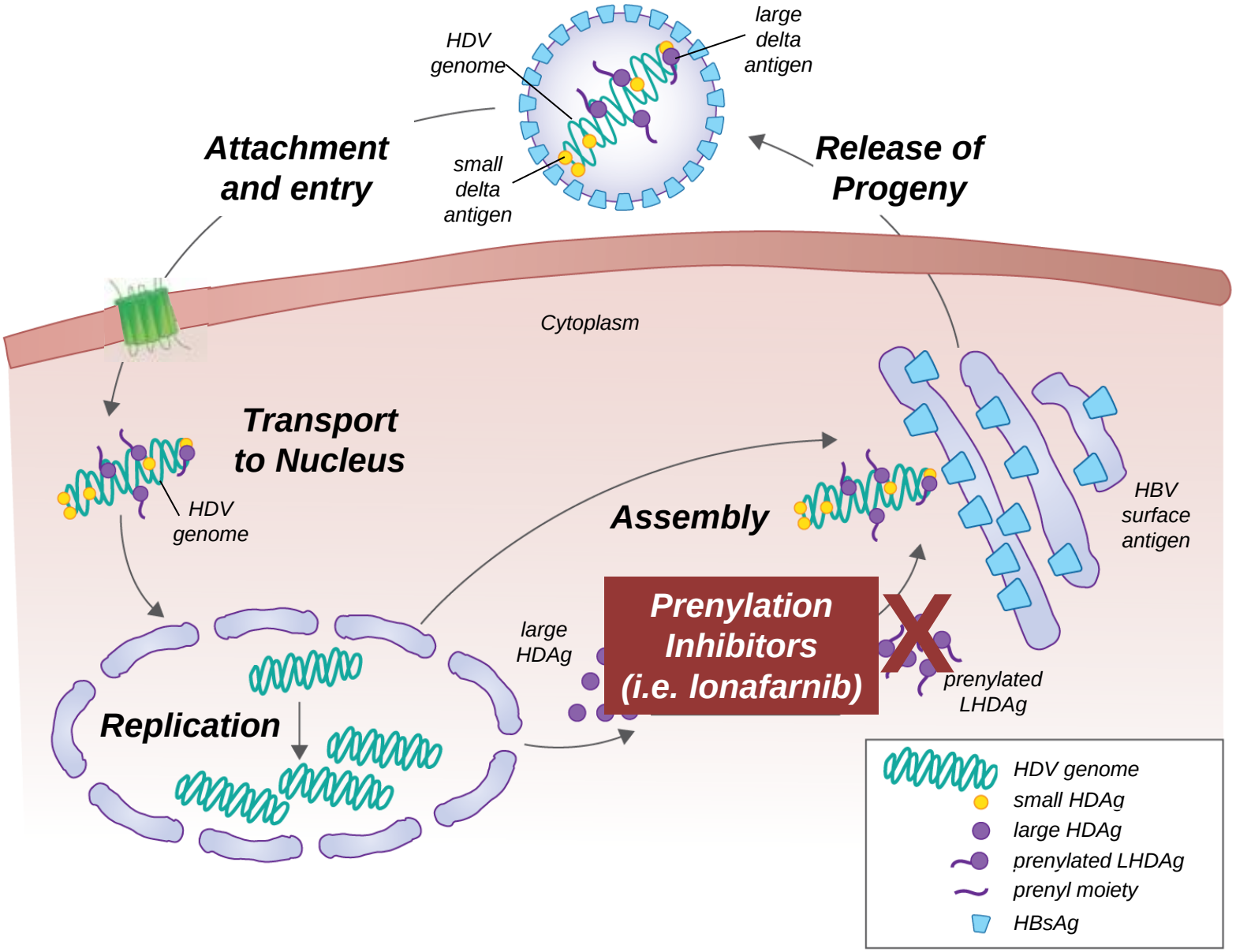
The HDV Life Cycle



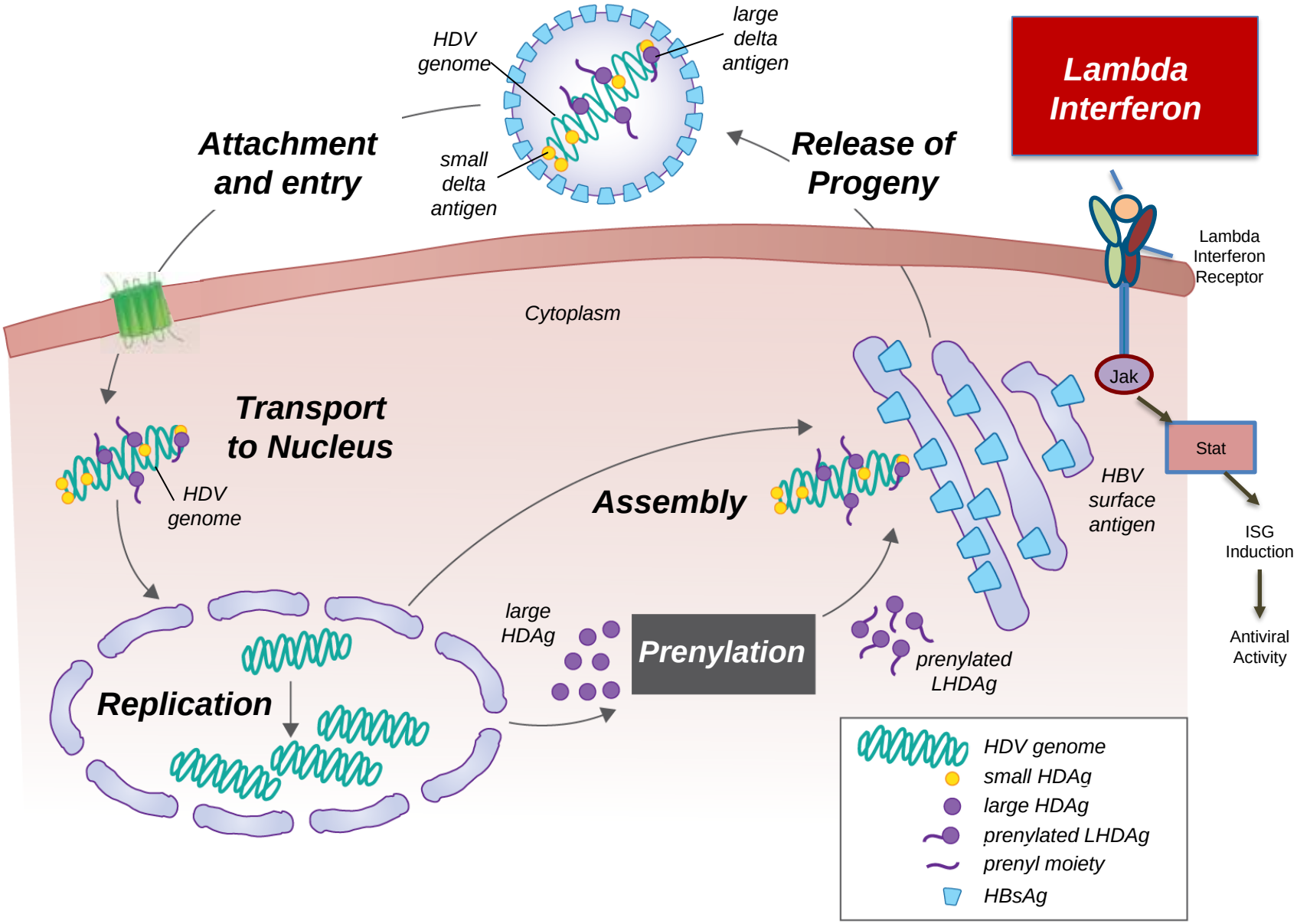
The HDV Life Cycle



The HDV Life Cycle



The HDV Life Cycle



Conclusions

- HDV—found everywhere; % of HBV patients co-infected with HDV varies by country
- HDV--fascinating collection of biology and important cause of human viral hepatitis; most severe form
- Study of HDV life cycle has identified many potential host targets for antiviral intervention; several form the basis for drugs in clinical development (entry, prenylation, HBsAg secretion, IFN lambda signaling)
- Complementary mechanisms of action offer potential for combination therapy