HDV therapy problems

Hepatitis D results from a double viral infection. The evaluation of therapeutic goals requires consideration and targeting of two viral infections, adding complexity to the management of the HDV patient

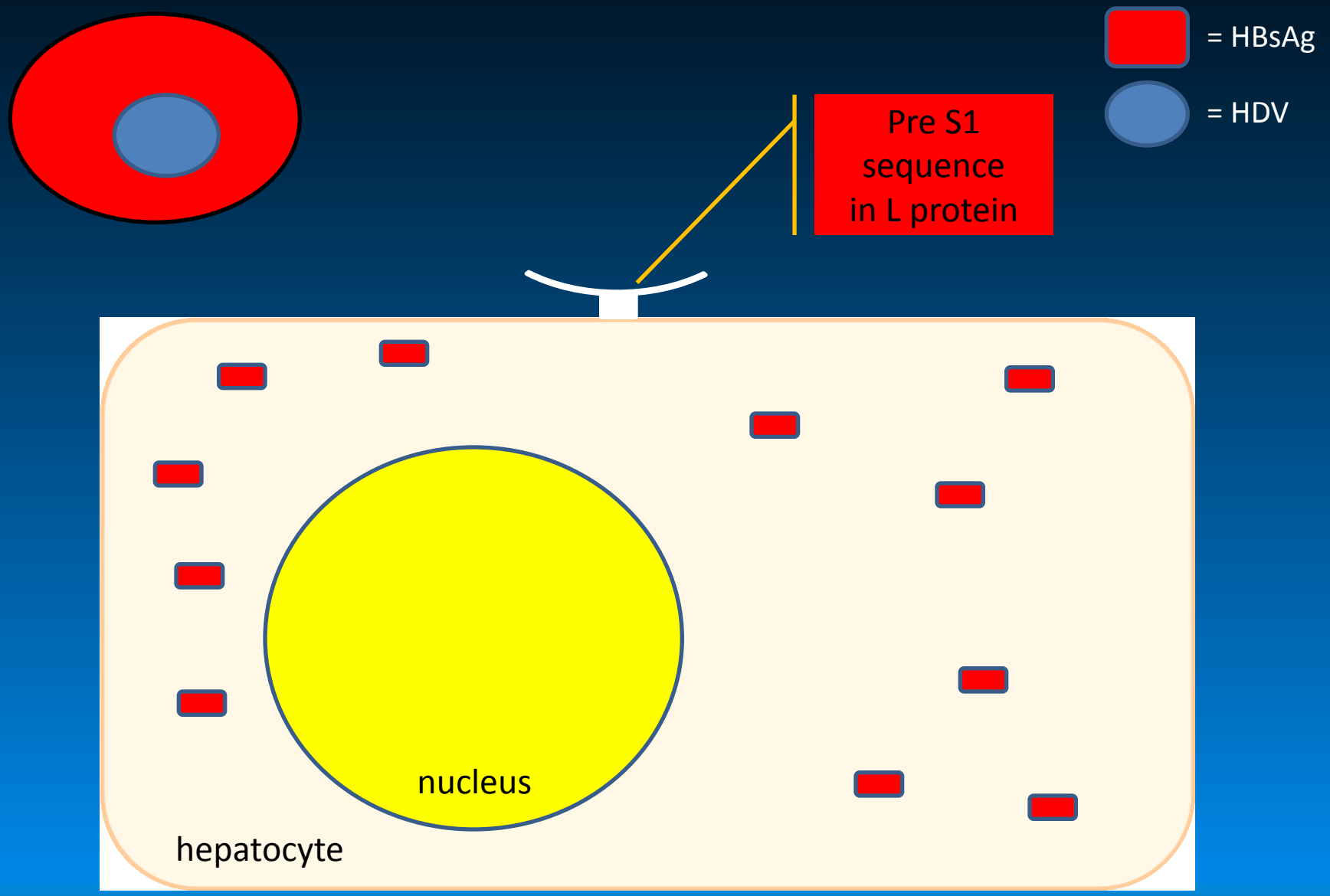
Therapy targets:

- the HDV
- the HBV
- both

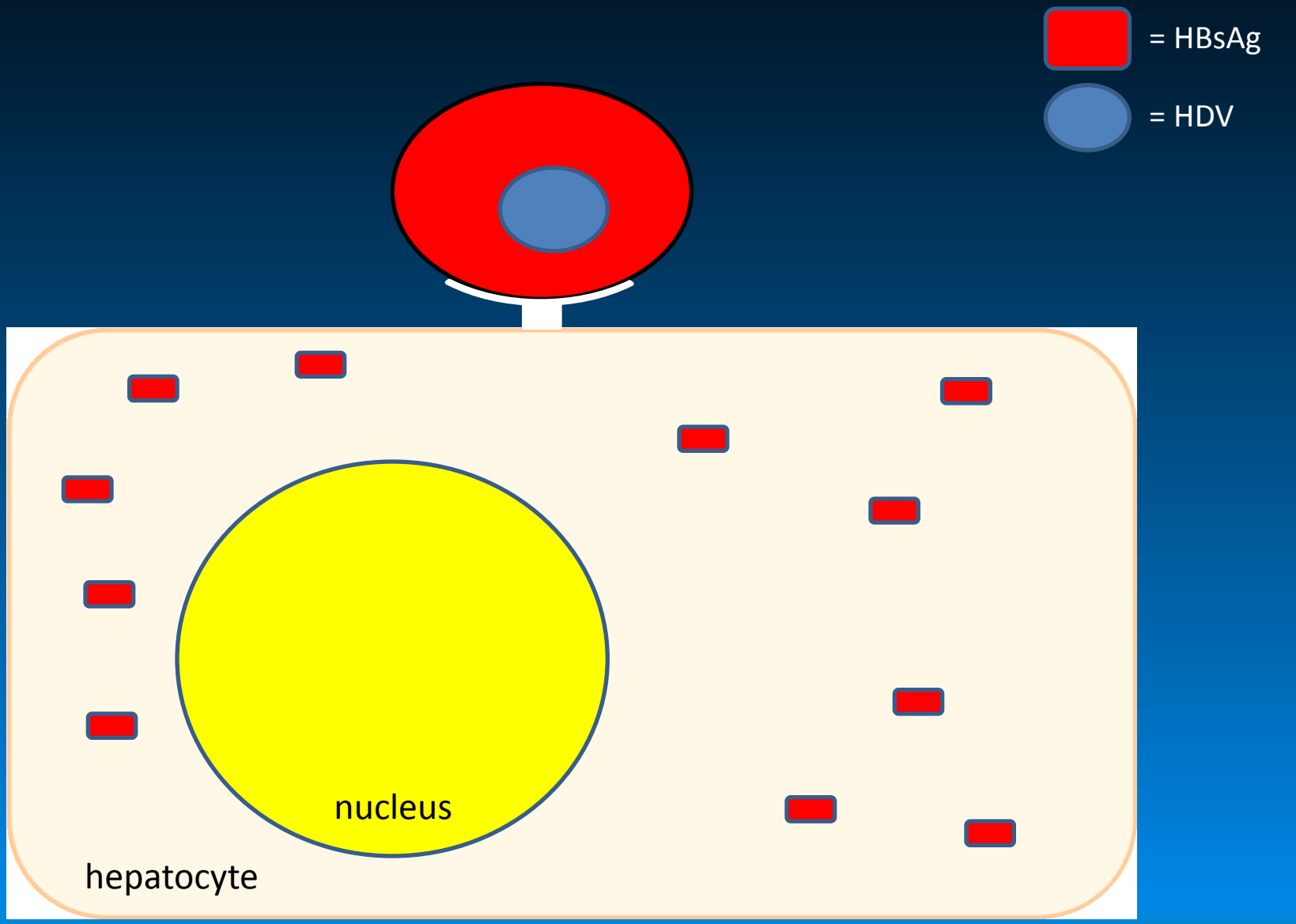
THE LIFE CYCLE OF HDV

IMPLICATIONS FOR THERAPY

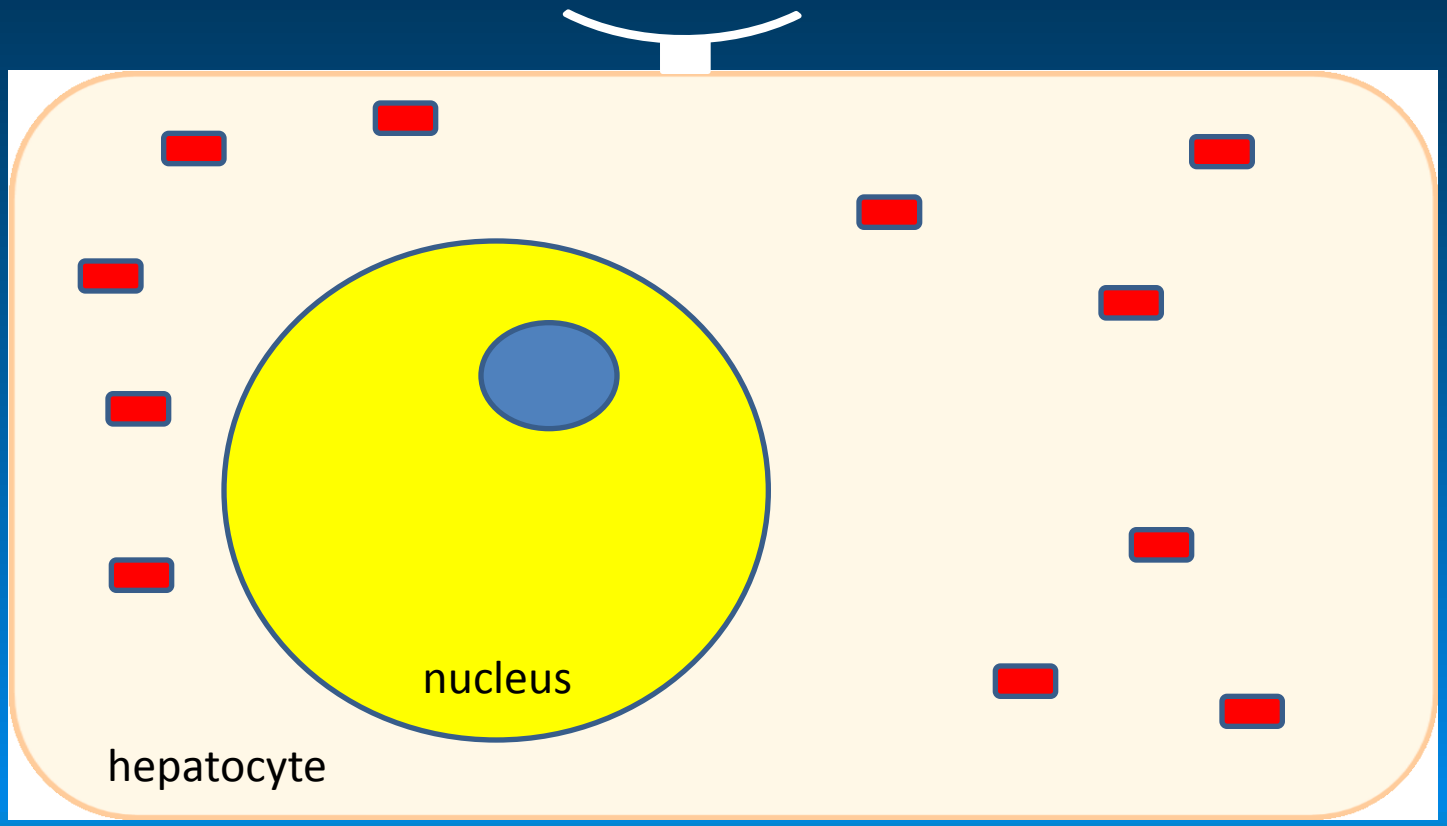
Attachment of HDV through HBsAg



HDV transferred to nucleus



HDV transferred to nucleus



Replication of HDV-RNA

Cell Ligase
HDV Ribozyme?

+

+

- = genomic HDV-RNA

+ = antigenomic HDV-RNA

HOST
RNA polymerase II, I, III

HDV Ribozyme

-

Replication of HDV-RNA

Cell Ligase
HDV Ribozyme?

= genomic HDV-RNA

= antigenomic HDV-RNA

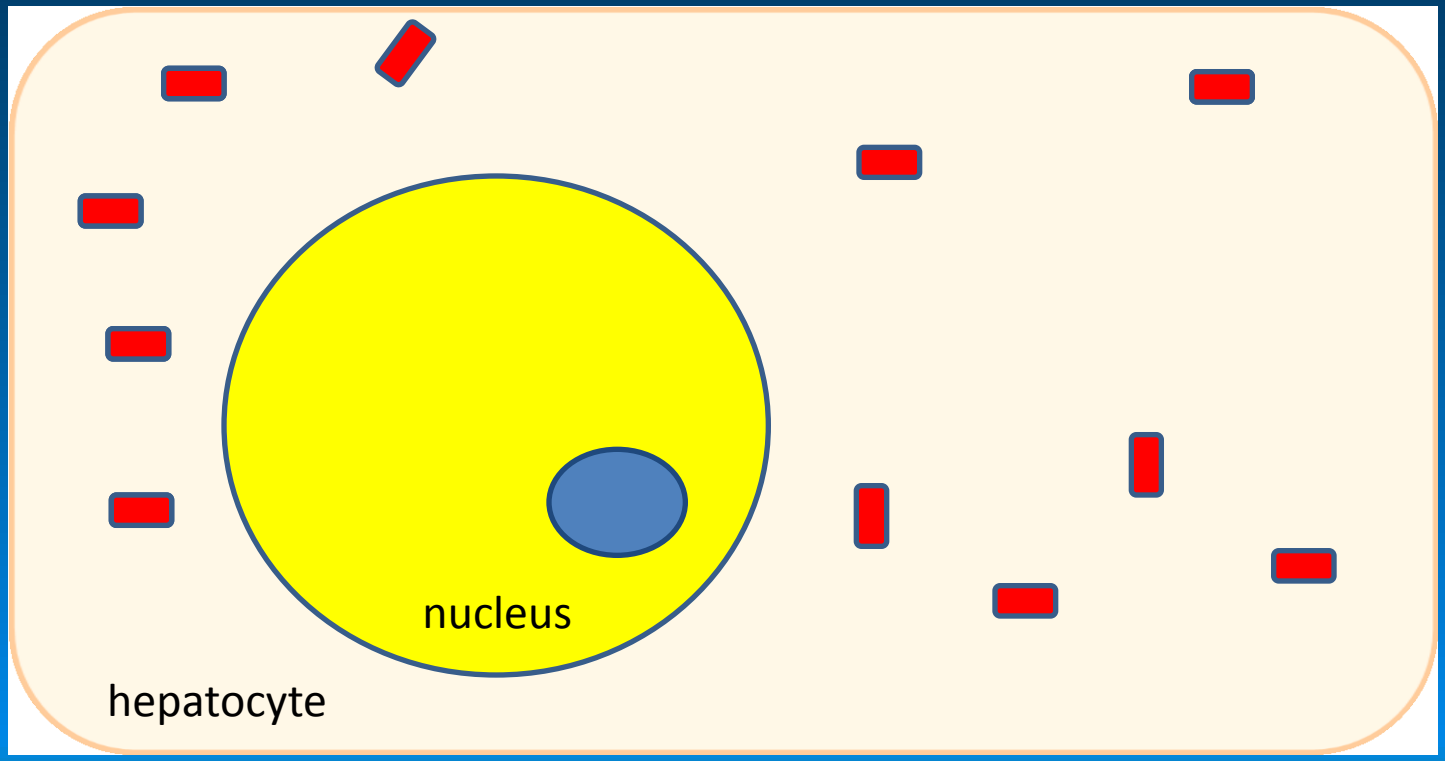
HOST
RNA polymerase II, I, III

HDV Ribozyme

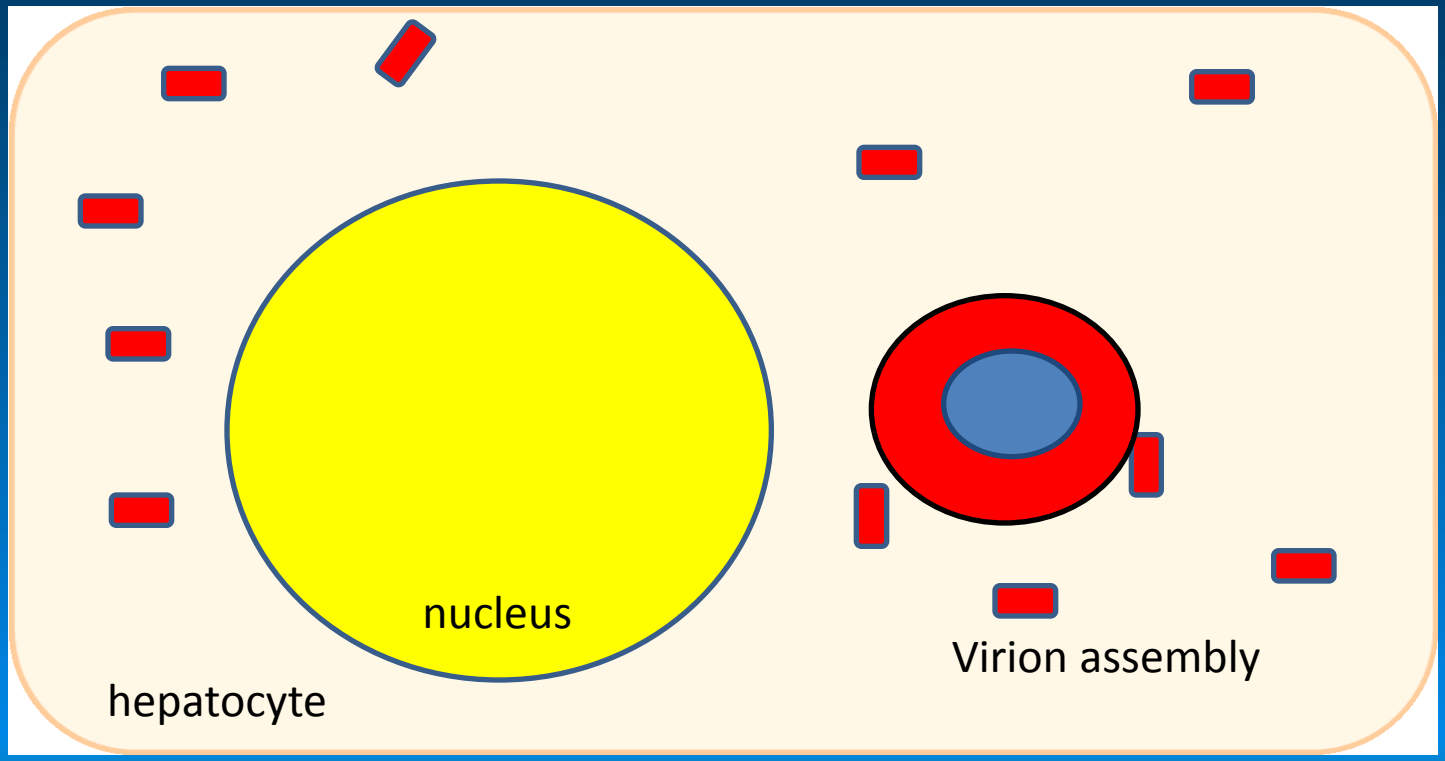
Assembly of HDV virions

= HBsAg

= HDV-RNA



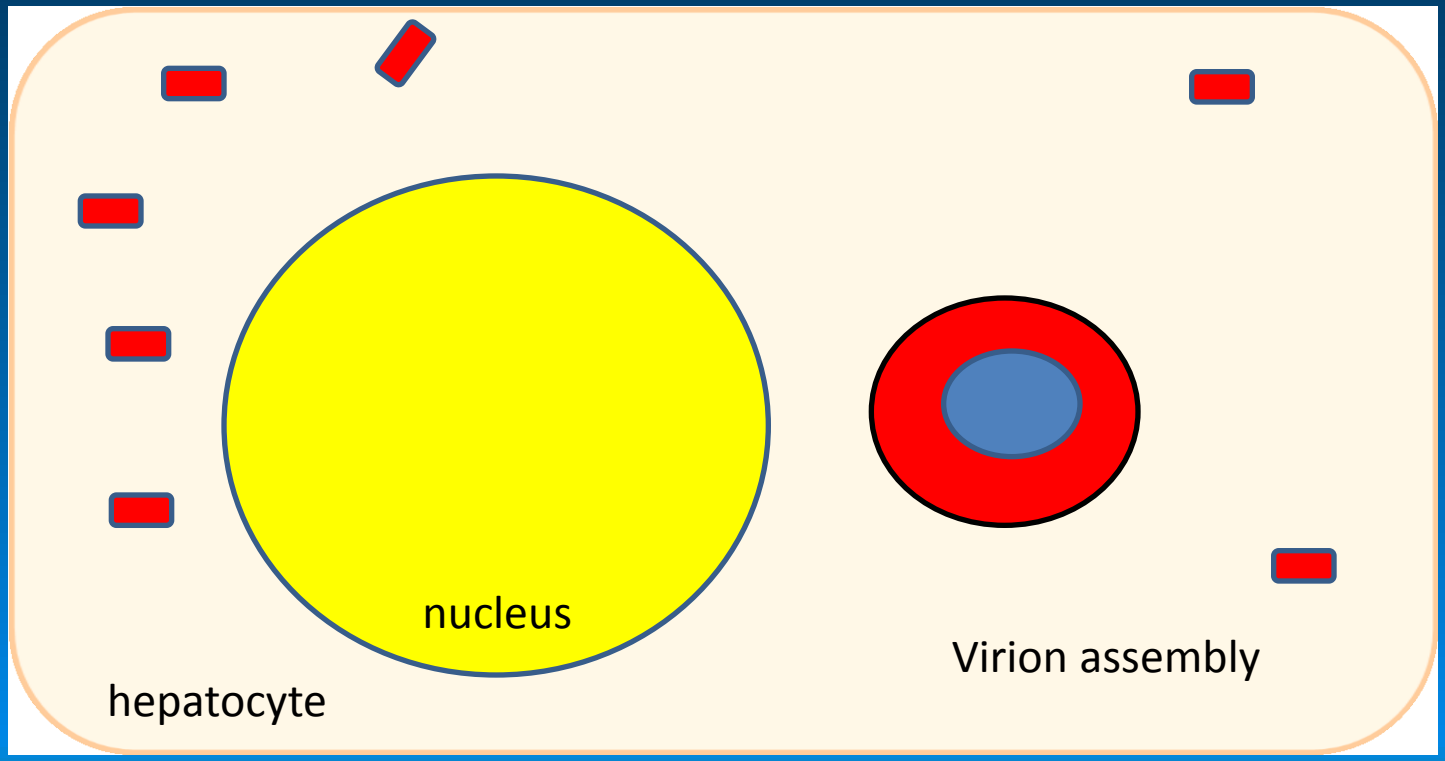
Assembly of HDV virions



Assembly of HDV virions

= HBsAg

= HDV



HDV therapy problems

- HBV required only to provide the HBsAg capsid
- replication of HDV indipendent from HBV replication (i.e. from HBV-DNA levels)
- NO OWN REPLICATION FUNCTION OF HDV to be targeted by antivirals

HDV therapy problems

HDV-RNA: not standardized, need for an international reference

Regional references:

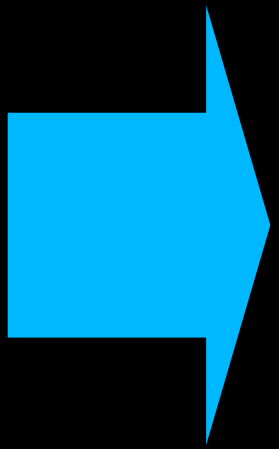
- Paul Erlich (Germany)
- National Reference Center for Viral Hepatitis (France)
- Centers for Disease Control (USA)
- National Institute for Viral Disease (China)

IgM anti-HD: surrogate marker of disease activity

HDV:
Antiviral Therapy

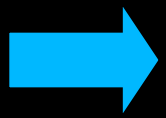
Drugs Evaluated for the Treatment of Chronic Hepatitis D

- Thymosin
- Ribavirin
- Lamivudine
- Famciclovir
- Adefovir
- Entecavir



No Efficacy

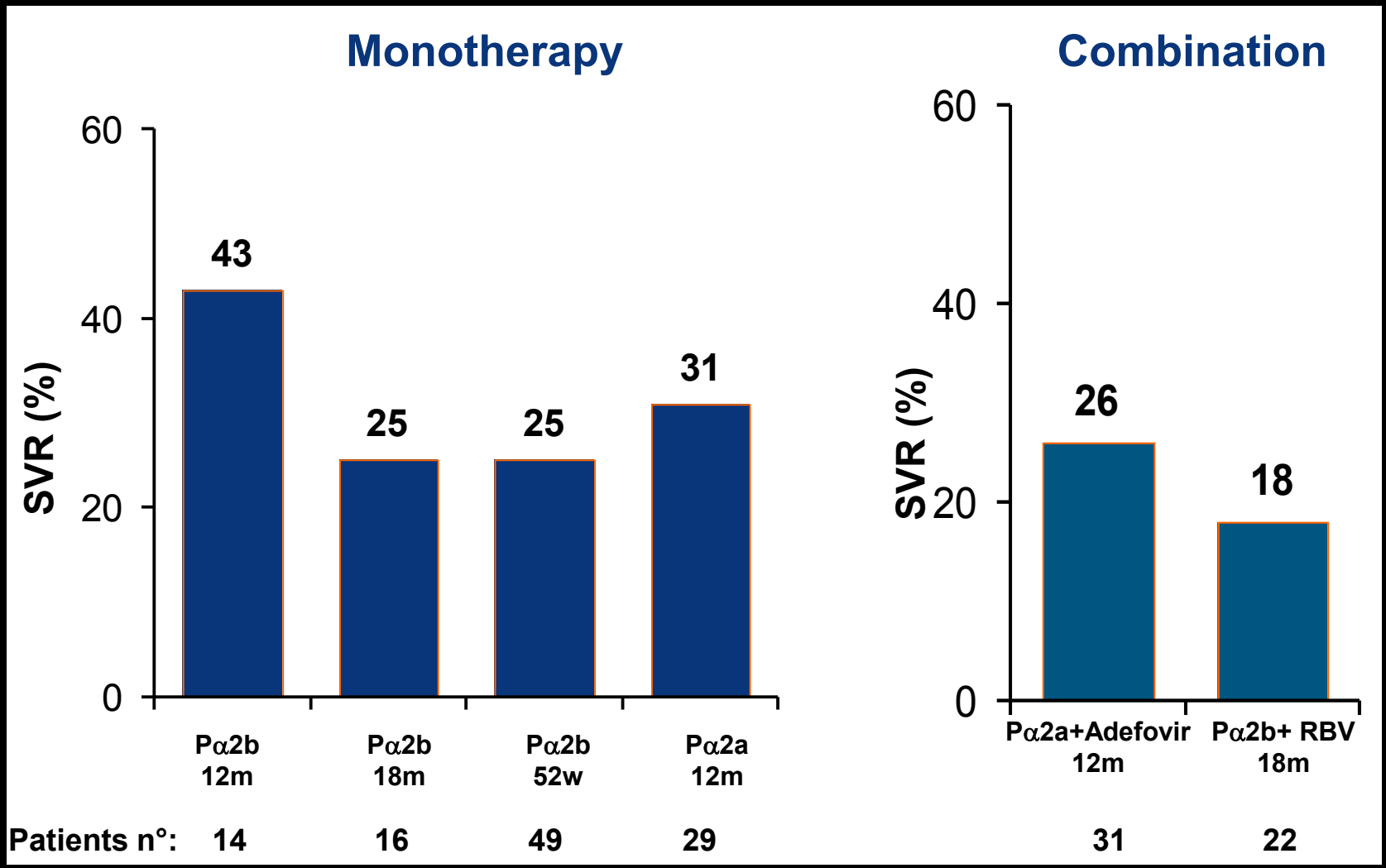
- IFN/Peg IFN



Limited Efficacy

Therapy of chronic hepatitis D with Peg-IFN

Sustained virologic response (SVR)



m = months w = weeks P = Peg-IFN RBV = ribavirin

HDV therapy problems

- small series of patients
- different designs and protocols
- ↓ ALT vs clearance HDV-RNA not always consistent
- clearance of HDV-RNA vs histology not always consistent
- no advantage to treat up to 24 vs 12 months in controlled series

Therapy – conclusions

The current recommendation is pegylated Interferon-alfa weekly for 12 to 18 months

20%-25% of the patients respond; HDV may relapse as long as HBsAg is around

Only reliable end-point of therapy is the clearance of the HBsAg

The SVR paradigm does not apply to hepatitis D (as long as HBsAg persists)

In the HBsAg setting, HDV may remain infectious at 10^{-11} serum dilutions, i.e. at titers far below the sensitivity threshold of current HDV-RNA assays (10 cp/ml)

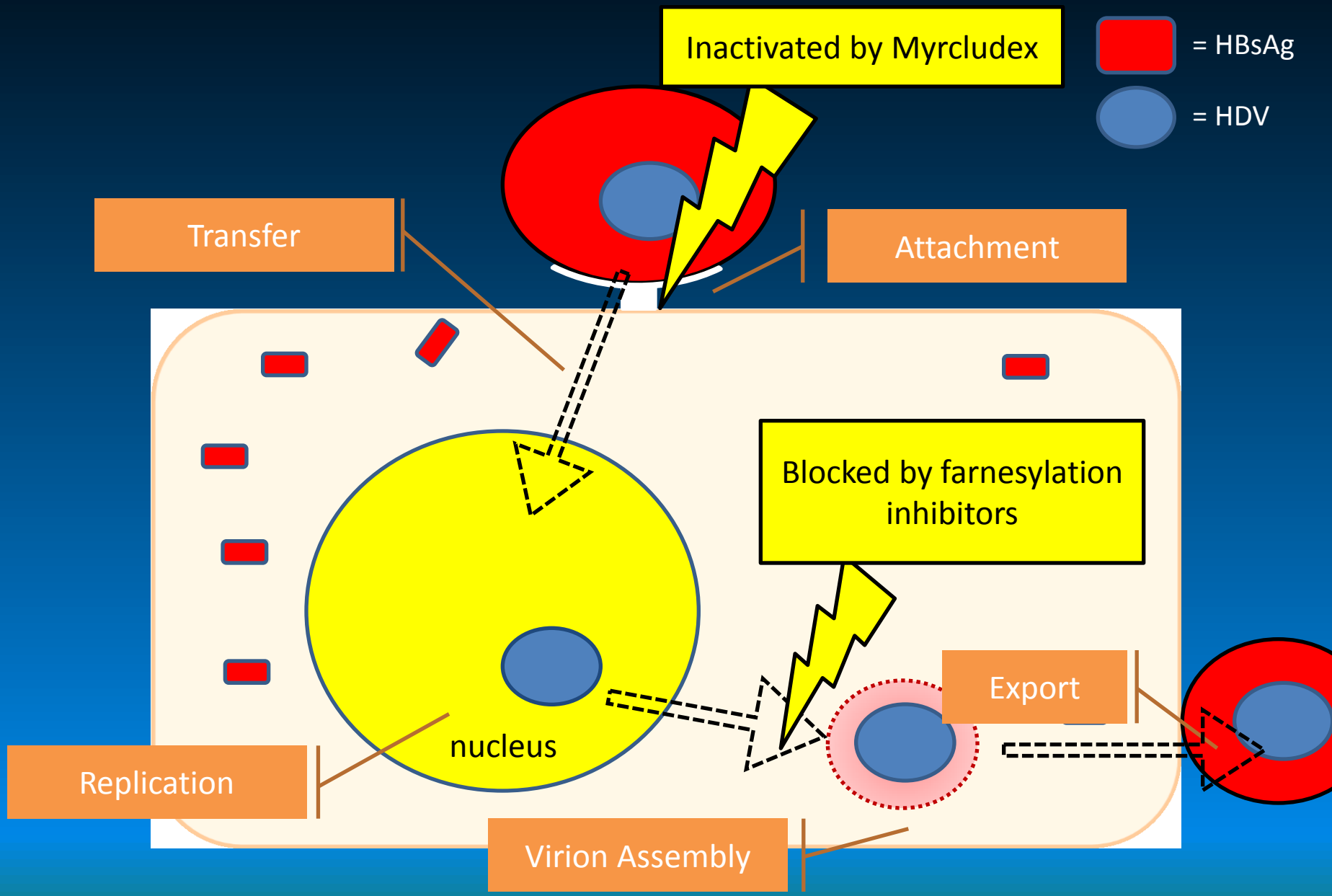
Possible factors predicting response to therapy

- HDV genotype: non 1 > 1
- low HDV-RNA at baseline and decline during therapy
- low HBsAg at baseline and decline during therapy ?

Therapy of chronic hepatitis D conclusions

- The current management of HDV patients is based on accepted common practice rather than on evidence from trials. Therefore therapy should be pragmatic and individualized
- Therapy protocols should be determined on the clinical and virologic evolution during therapy
- Therapy extended over 12 months may be of benefit in patients with partial responses. Therapy extended over years may be of benefit in the individual patient with rapidly advancing disease who responds to Peg-IFN but relapses on its withdrawal

Therapeutic targets?

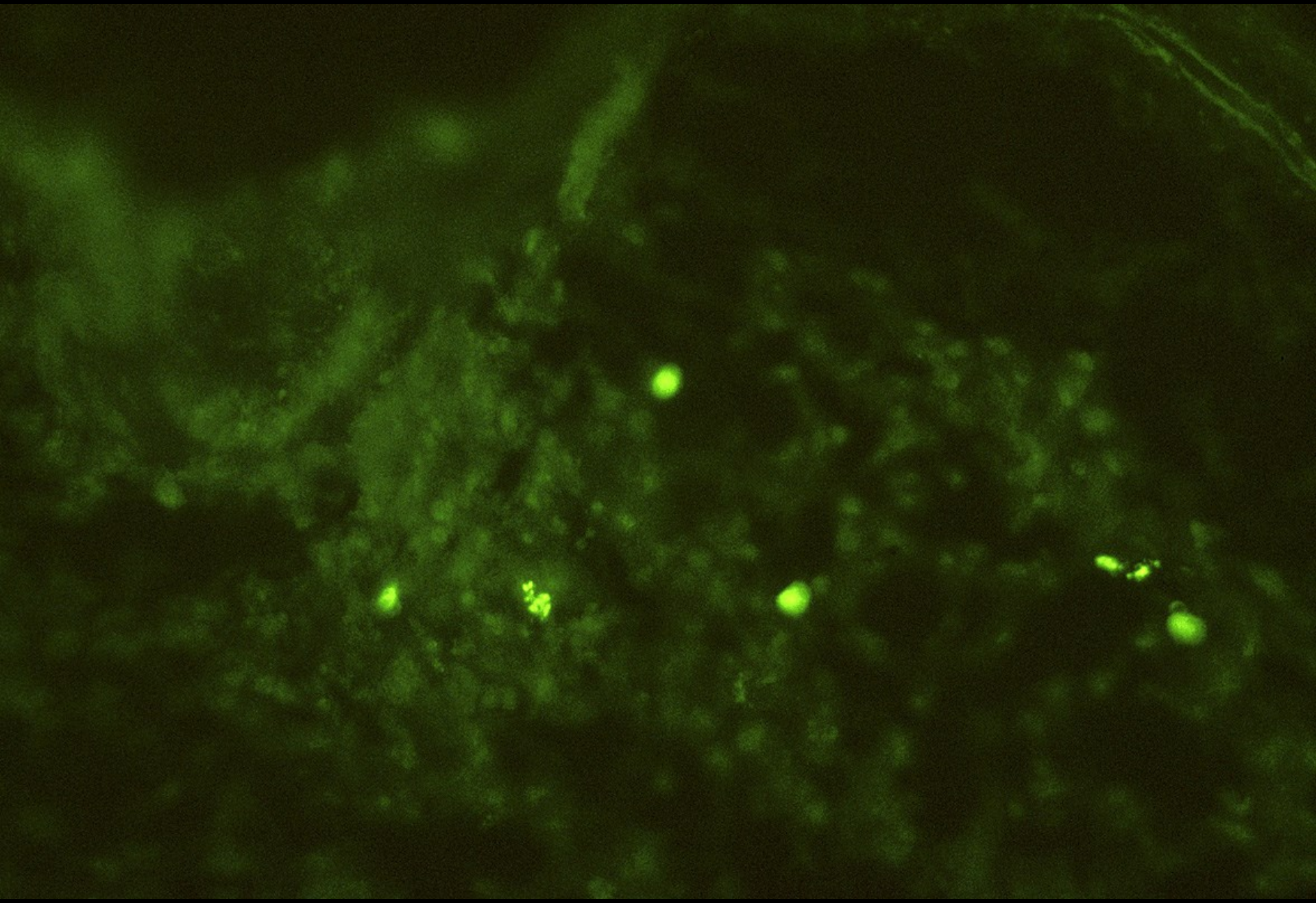


HDV: Therapy

Liver Transplantation

Liver transplantation for end-stage HDV disease

- Valid treatment, survival good
- Risk of graft reinfection distinctly lower than HBV
- HBIG with antivirals protect virtually every transplant



Latent HDV infection in liver

How long does it persist?

Up to 3 years in human liver grafts

Rizzetto, 2006; Moderacke, 2011

Even six weeks after initiating HDV infection, HBV can be used to superinfect, with assembly and release of infectious HDV

Lugehetmann, Hepatology, 2011

THE FUTURE

- Improved control (eradication?) of HDV through increased control of HBV
- Efficacious therapies in particular for residual difficult-to-treat disease
- HDV-RNA as a biological tool for developing therapeutic ribozymes