CURE IN HBV...?

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Manchester, UK

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What is ‘cure’ in HBV?

There are various definitions & meanings of ‘cure’

- “Apparent virologic cure”
  - Sustained off-drug suppression of virologic markers
    - sAg negative, plasma DNA negative
  - Normalization of liver function
- “Functional cure”
  - Returned to state of health prior to illness
  - No more likely to develop cirrhosis/HCC than general population
- “Absolute cure”
  - As for functional **AND** ‘virus-free’

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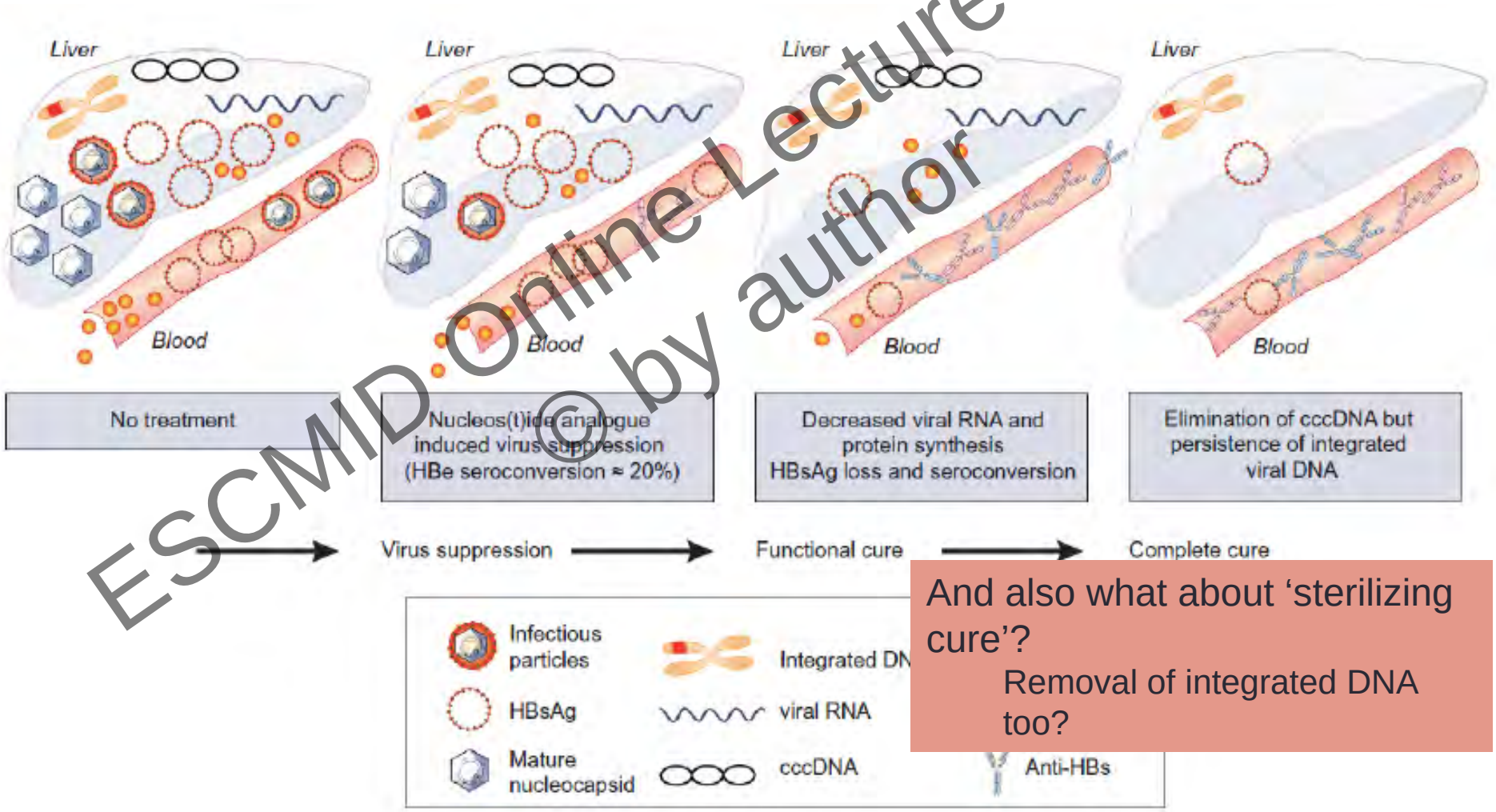
Block et al., 2013

Other definitions….



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And also what about ‘sterilizing cure’?

Removal of integrated DNA too?

Durantel & Zoulim, J Hepatol, 2016

What are the potential advances in the pipeline?

- ‘DAAs’
  - Not officially termed as such
  - Need to understand the lifecycle to understand the potential targets and drugs
- Host-acting agents

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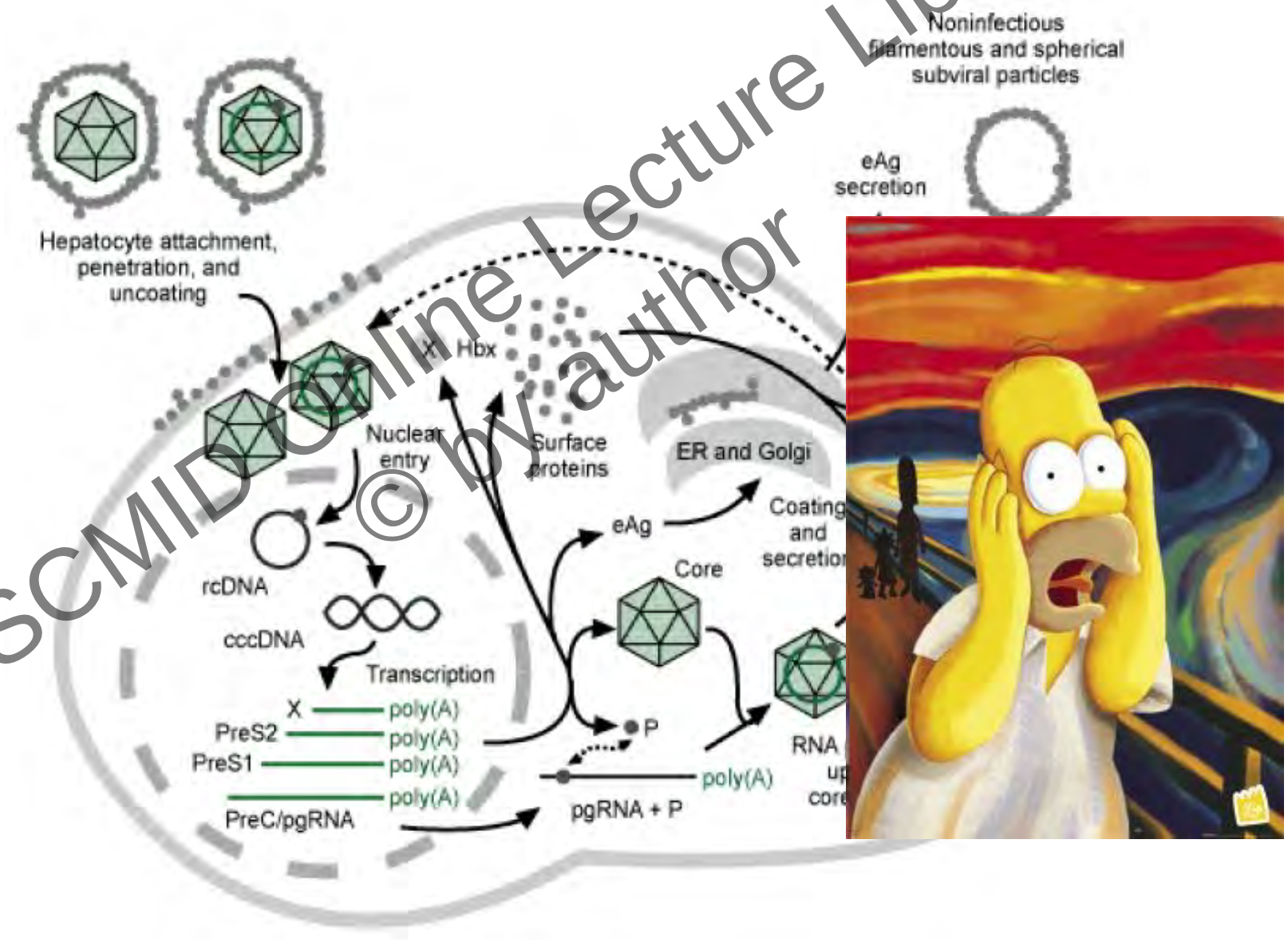
So – lets start with the HBV lifecycle



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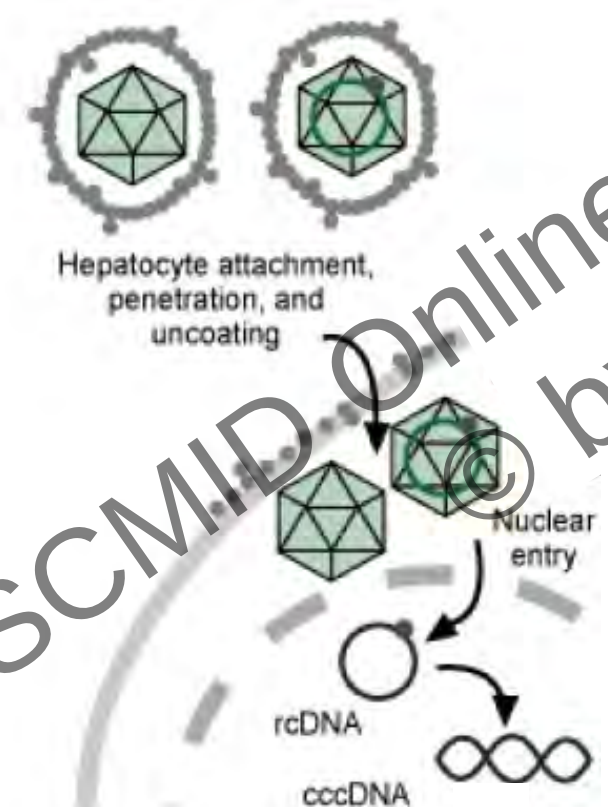
What about viral entry into liver cell and then nucleus?



- Viral envelope binds to cell membrane
  - Receptor = sodium taurocholate co-transporting polypeptide (a bile salt transporter)
- Then it is uncoated and viral DNA enters into cell nucleus…

  …and viral genome is converted to cccDNA

  = “covalently closed circular DNA”

  = HBV ‘mini-chromosome’

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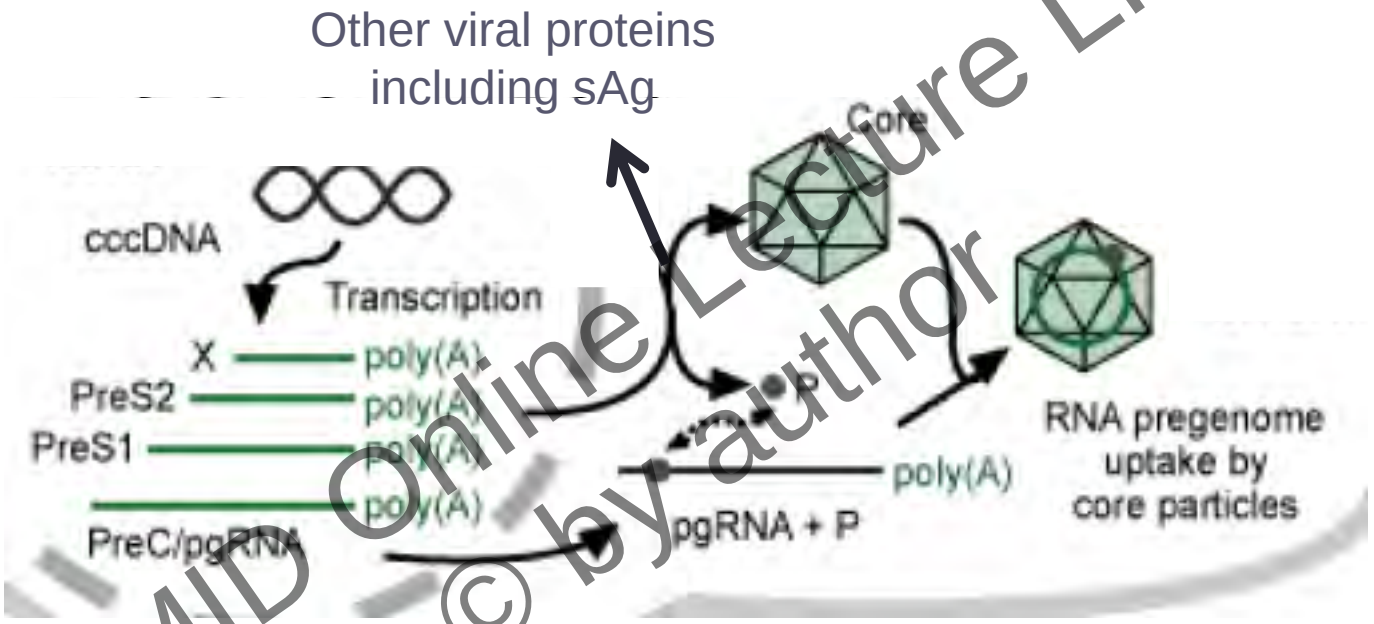
Reverse transcription and translation….



- There is reverse transcription via an RNA intermediate
  - RNA pregenome
- Products then encapsulated within virus core particle
  - RNA pregenome, nucleocapsid & polymerase proteins

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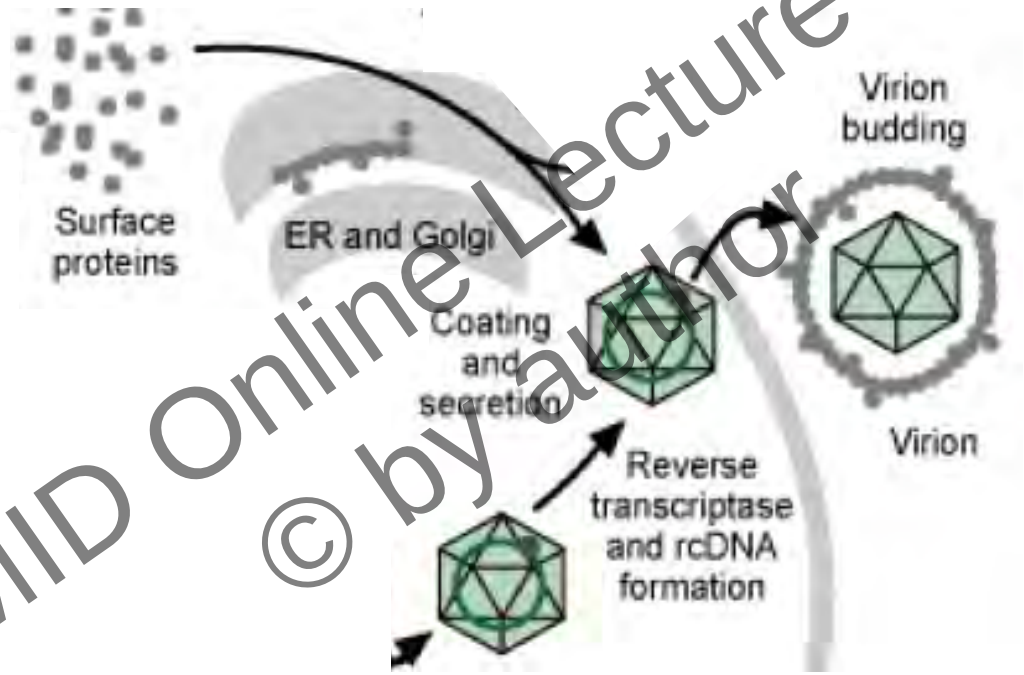
And then it is released



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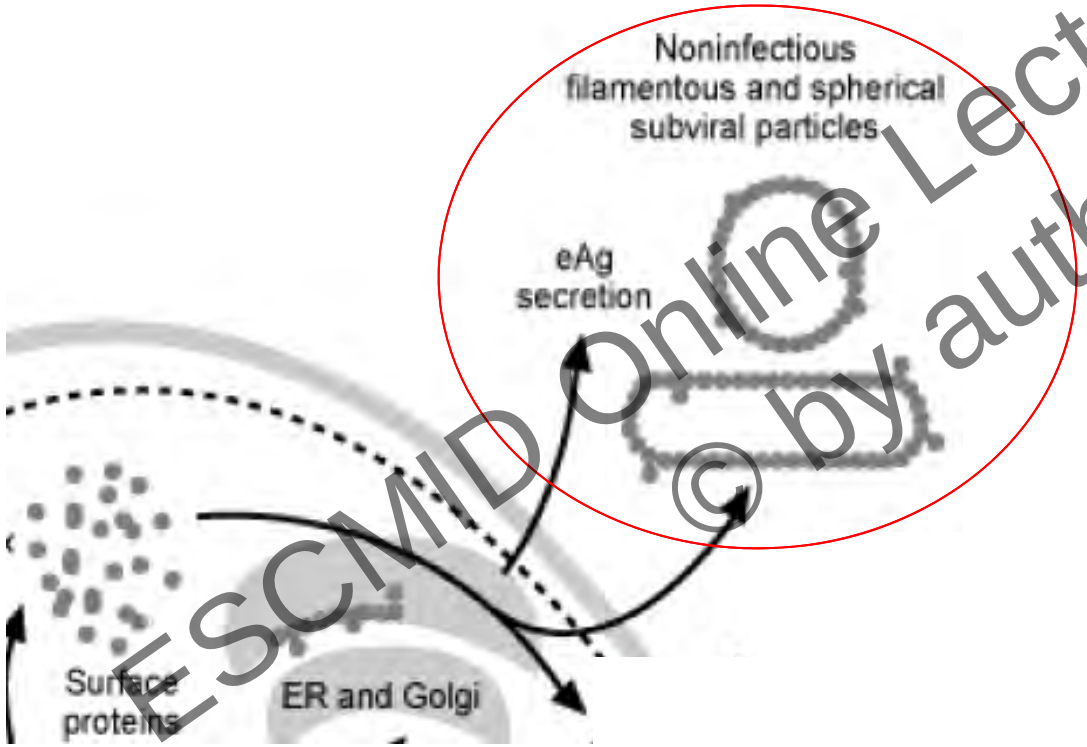
- Virus contains a new negative strand DNA which partially synthesises a positive stand
- Coated by envelope proteins
- ➔ Complete virion ready for release
- But some is also recycled back into the nucleus and replenishes ccc-DNA

Not all the proteins end up in the virus particle….



- Why??

- Immunomodulatory
- Tolerogenic….

- Inflammatory….

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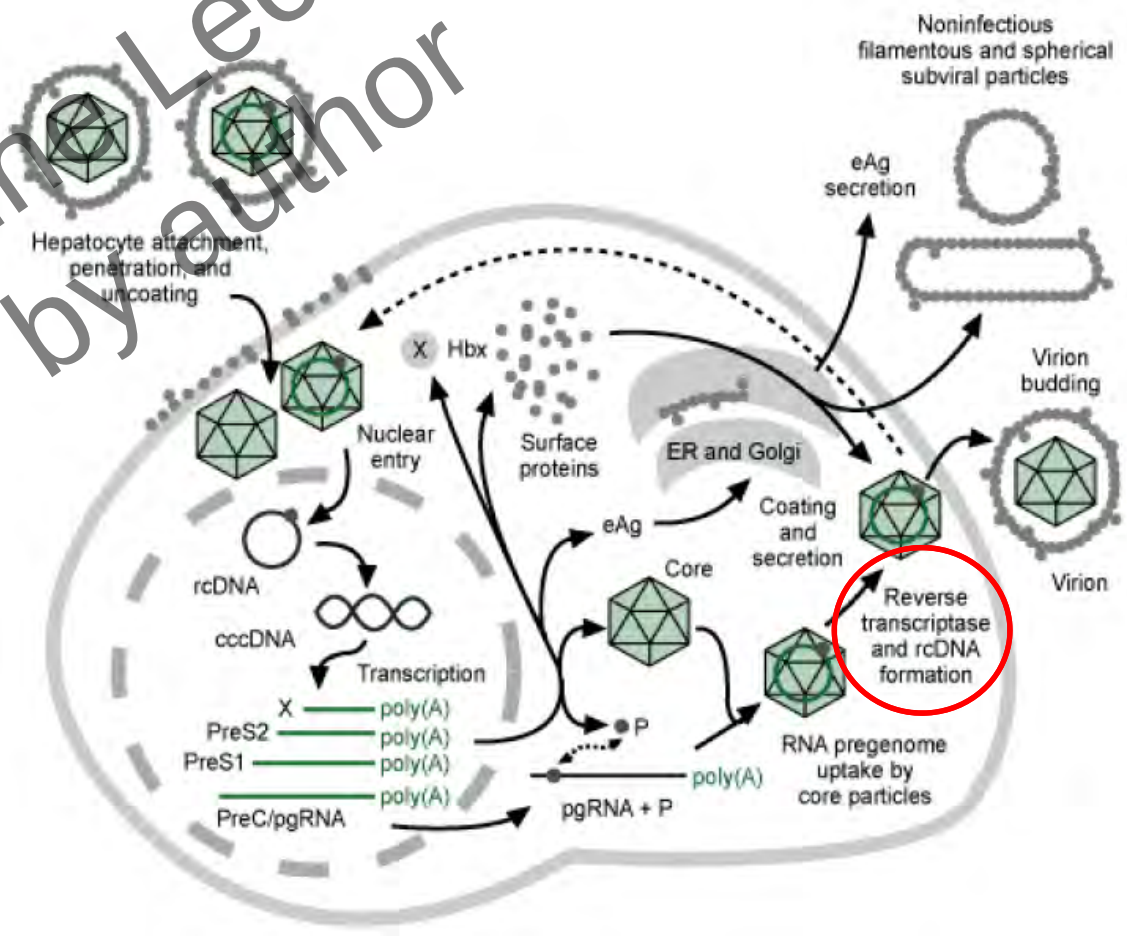
OK.. What drugs do we have at present??

- Nucleos(t)ide analogues
  - Tenofovir disoproxil
  - Adefovir
  - Entecavir
  - Lamivudine
  - Emtricitabine
  - Telbivudine
- Newer Nucs
  - Tenofovir alafenamide
    - (TAF)
  - Besifovir



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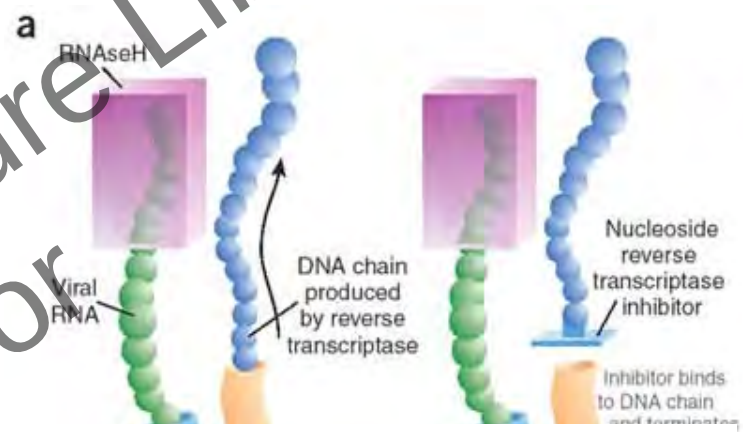

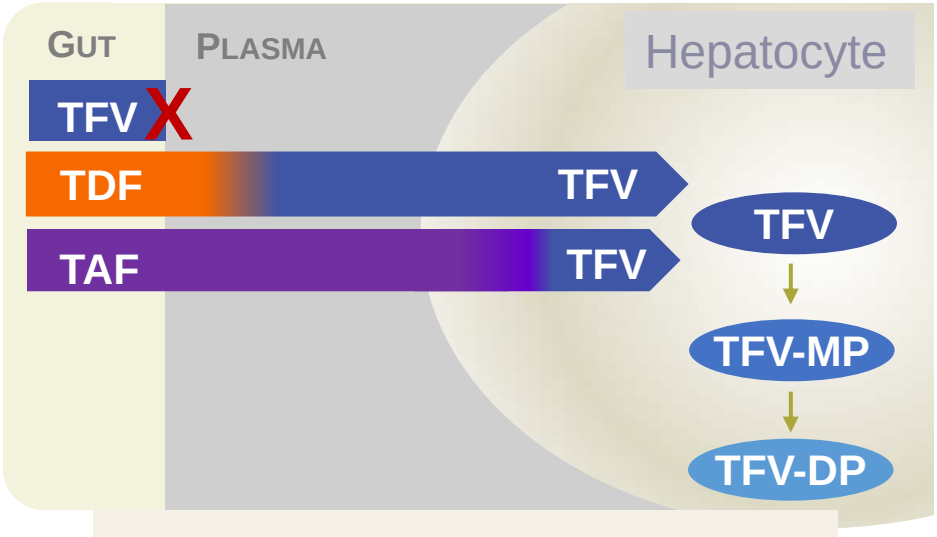

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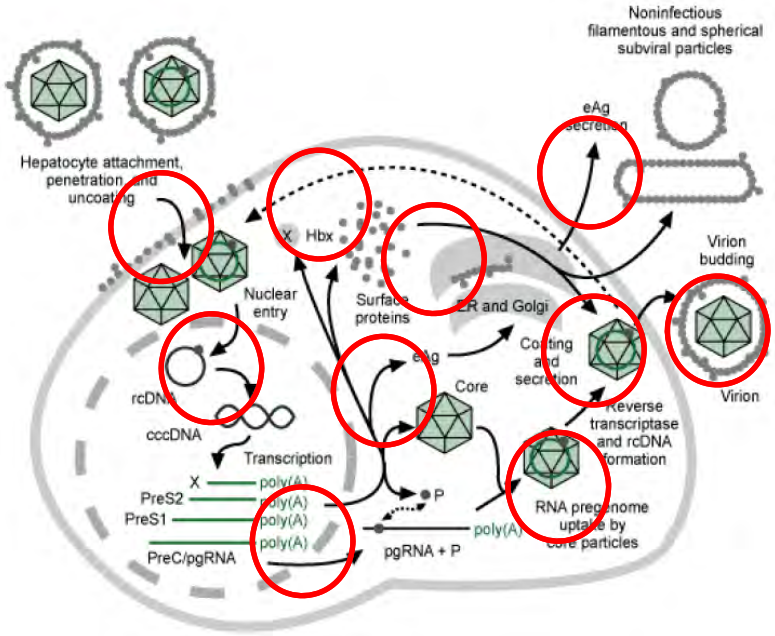
Interferon alpha

- Naturally occurring immunomodulator
  - Multiple activities… not entirely clear which are most important

- Specifically:
  - Induces an antiviral state in cells
    - Induces degradation of nuclear viral DNA
  - Inhibits cellular proliferation
  - Immunomodulates in many ways…



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But we know this usually doesn't result in a proper 'cure'

- There is still active research into combining interferon and nucleos(t)ides…..

- But what are the newer possibilities being actively explored?

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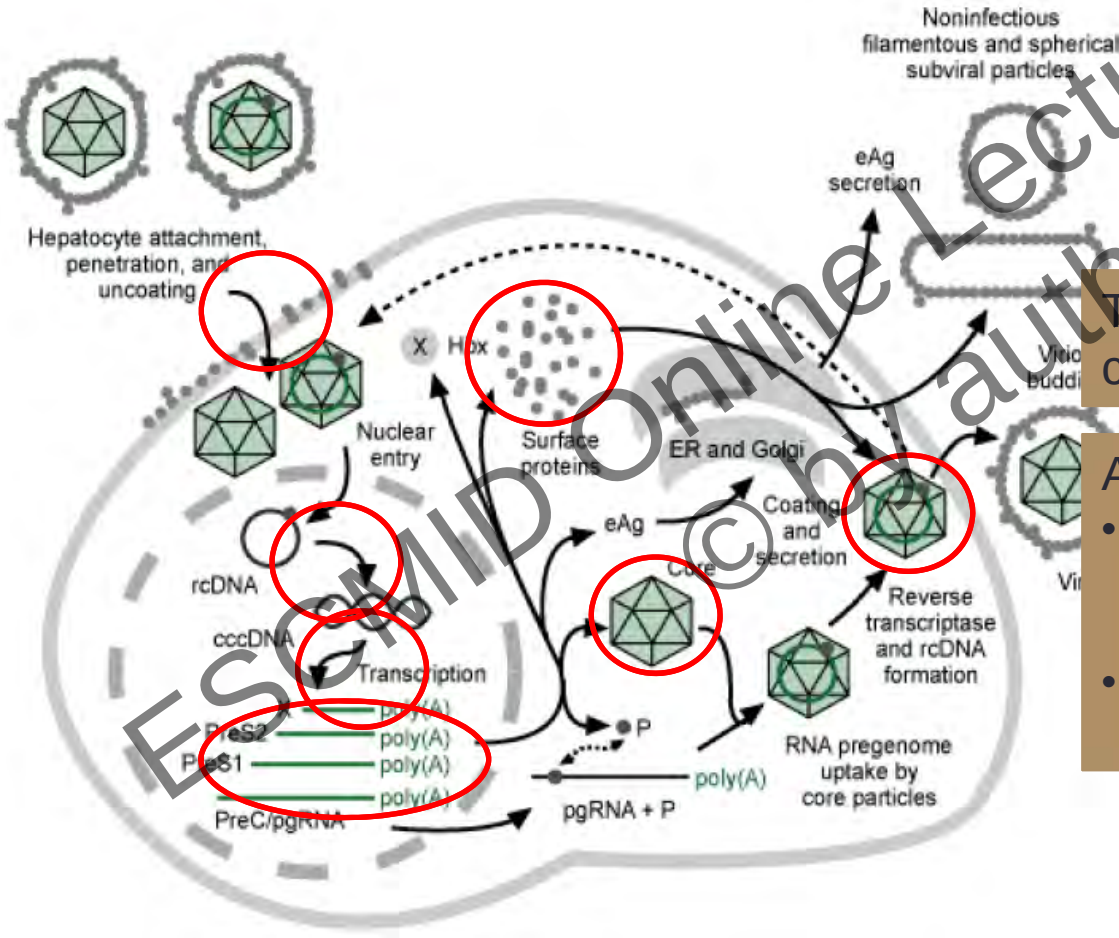
Where else could be targeted??



Target the sodium taurocholate co-transporting polypeptide

Antisense & RNAi approaches:

- Antisense molecules or ribozymes that are complementary to DNA or RNA templates
- Interfere with transcription and translation

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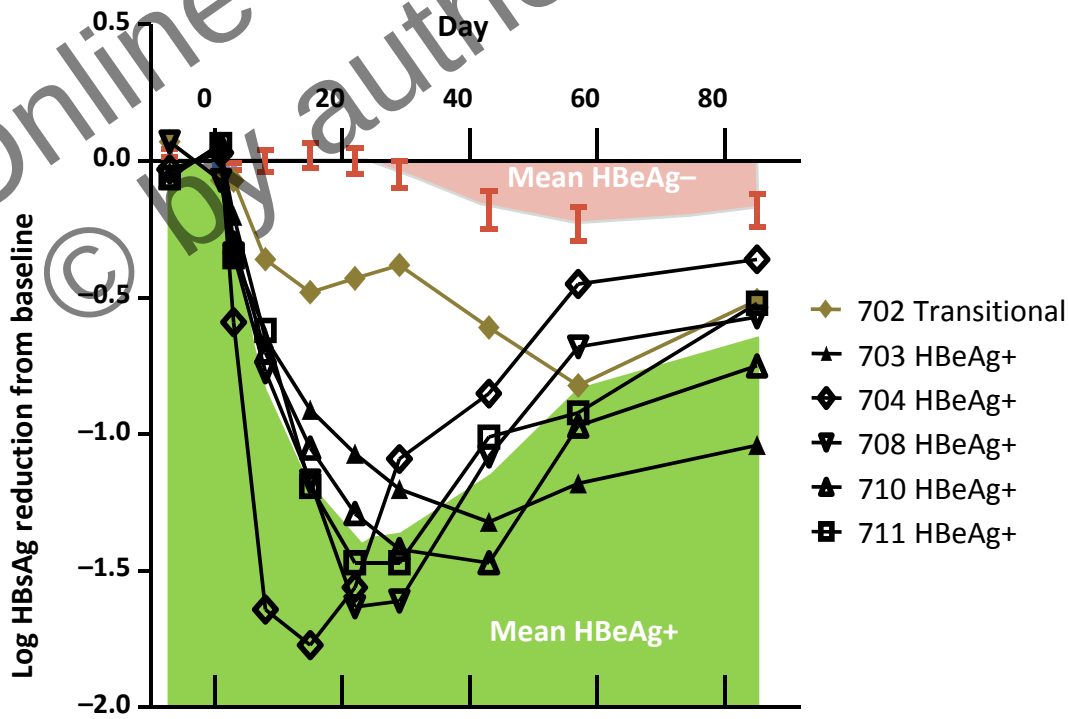
SiRNA: Reductions in viral antigens expressed from cccDNA vs integrated DNA in treatment-naïve HBV after RNA interference therapy with ARC-520

Reduction of HBsAg in treatment-naïve CHB patients after a single dose of 4 mg/kg ARC-520

- 5/6 HBeAg-positive patients showed an immediate, direct antiviral effect; maximum HBsAg reduction was 1.8 log
- 5/6 HBeAg-negative patients showed a delayed response; maximum HBsAg reduction was 0.5 log



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Yuen M-F, et al. EASL 2016, Barcelona. THU-193

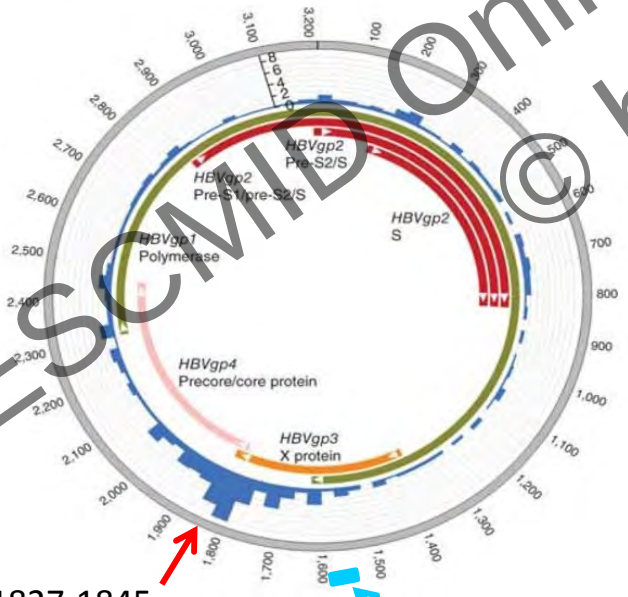
GalNAc-siRNA conjugate ALN-HBV targets a highly conserved, pan-genotypic X-orf viral site and mediates profound and durable HBsAg silencing in vitro and in vivo

Chemically Modified siRNA

- Devoid of innate immune activation
- Metabolically stable
- High intrinsic potency
- Long duration

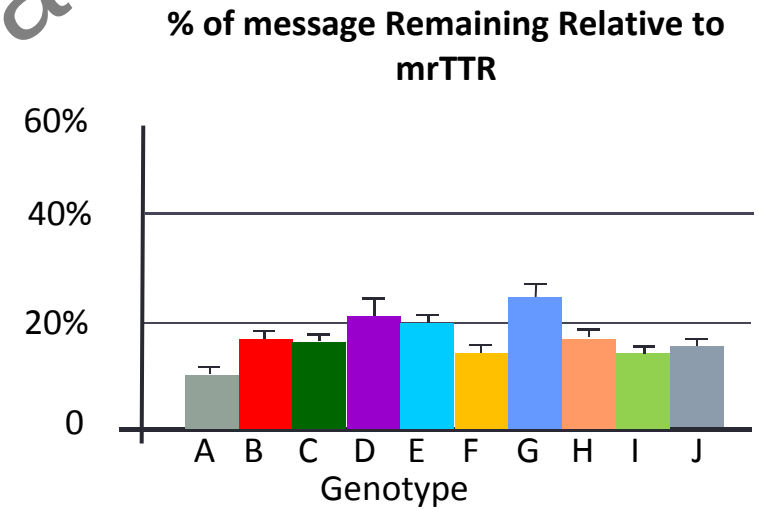
Hepatocyte Targeting

- N-acetyl galactosamine (GalNAc) ligand binds to asialoglycoprotein receptor (ASGPR)
- ASGPR is highly expressed in hepatocytes
- High turnover (recycling time ~15 min)
- Conserved across species



ARWR 77: 1827-1845
ARWR 74: 1781-1799

ALN-HBV



Sepp-Lorenzino L, et al. AASLD 2015, San Francisco. #36

Image from: Wing-Kin Sung, et al., Nature Genetics 44:765 (2012)

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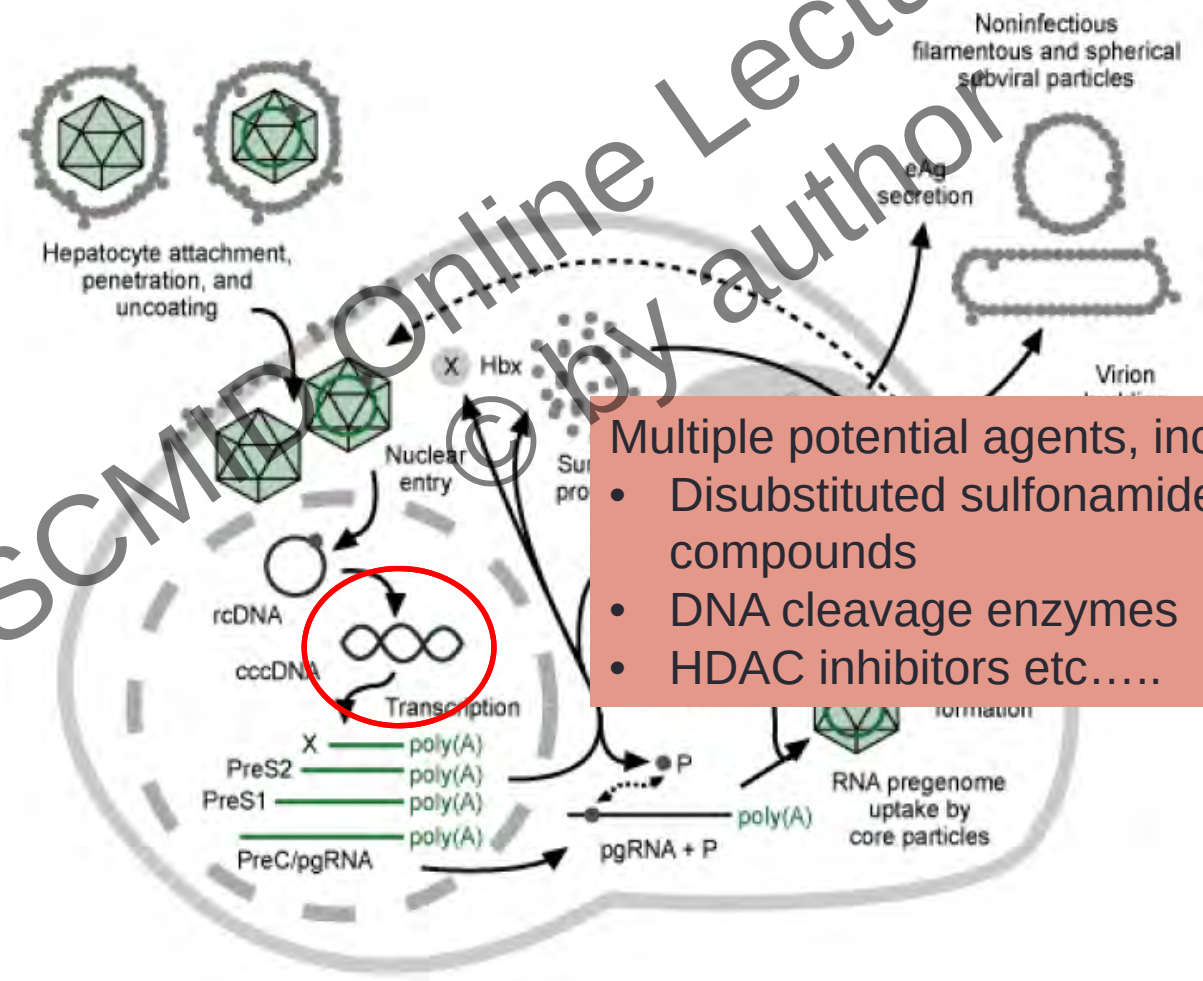
Direct ccc-DNA inhibitors



Multiple potential agents, including:

- Disubstituted sulfonamide (DSS) compounds
- DNA cleavage enzymes
- HDAC inhibitors etc…..

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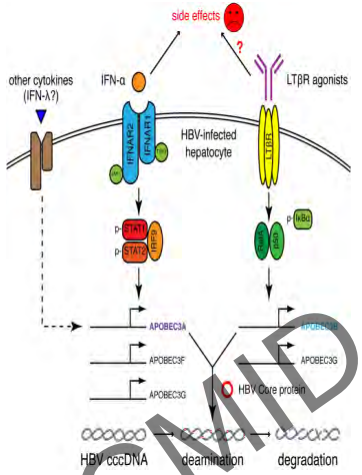
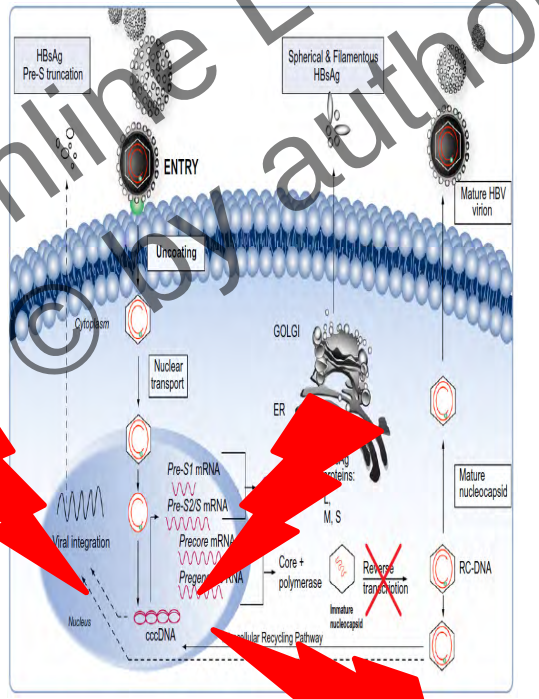
cccDNA inhibitors: Preclinical

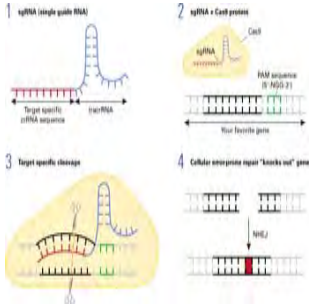
Cytidine deamination and cccDNA degradation
- LT-βR agonists, IFN-α



Lucifora, Science, 2014
Ding and Robek. Hepatology, 2014



CRISPR/CAS9 (DNA nuclease)
- Simple RNA programmable method for seq. specific genome editing. sgRNA directs the CAS9 nuclease to target genomic DNA



Ramanan, Nature Sci Reports, 2015

Epigenetic silencing
- Chromatin-regulating proteins
- Regulate chromatin structures, release DNA from the nucleosome, and activate or suppress gene expression by modifying nucleosome histones or mobilizing DNA-histone structure

Pollicino et al. Gastro 2006

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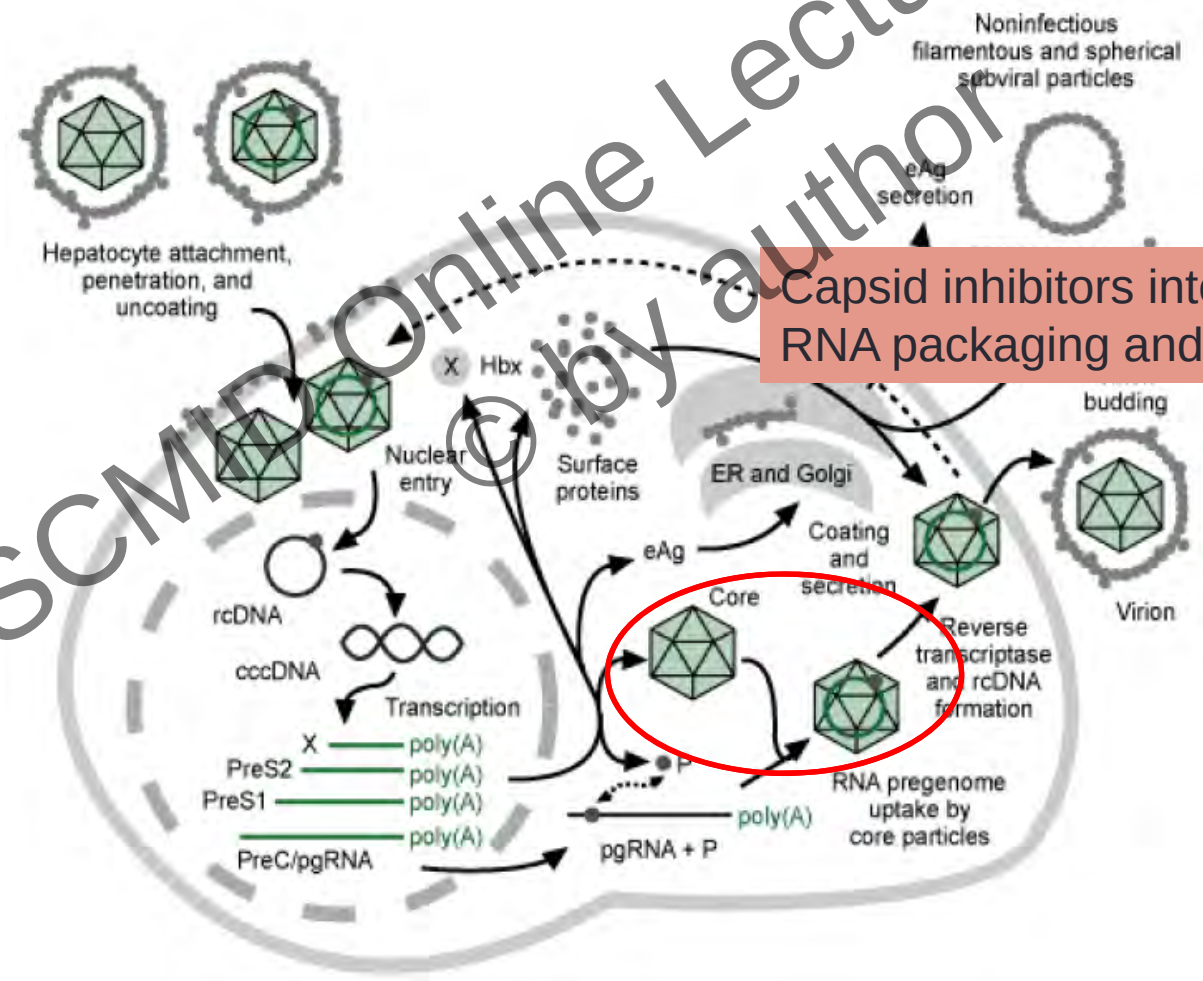
Capsid Inhibitors



Capsid inhibitors interfere with HBV RNA packaging and capsid assembly

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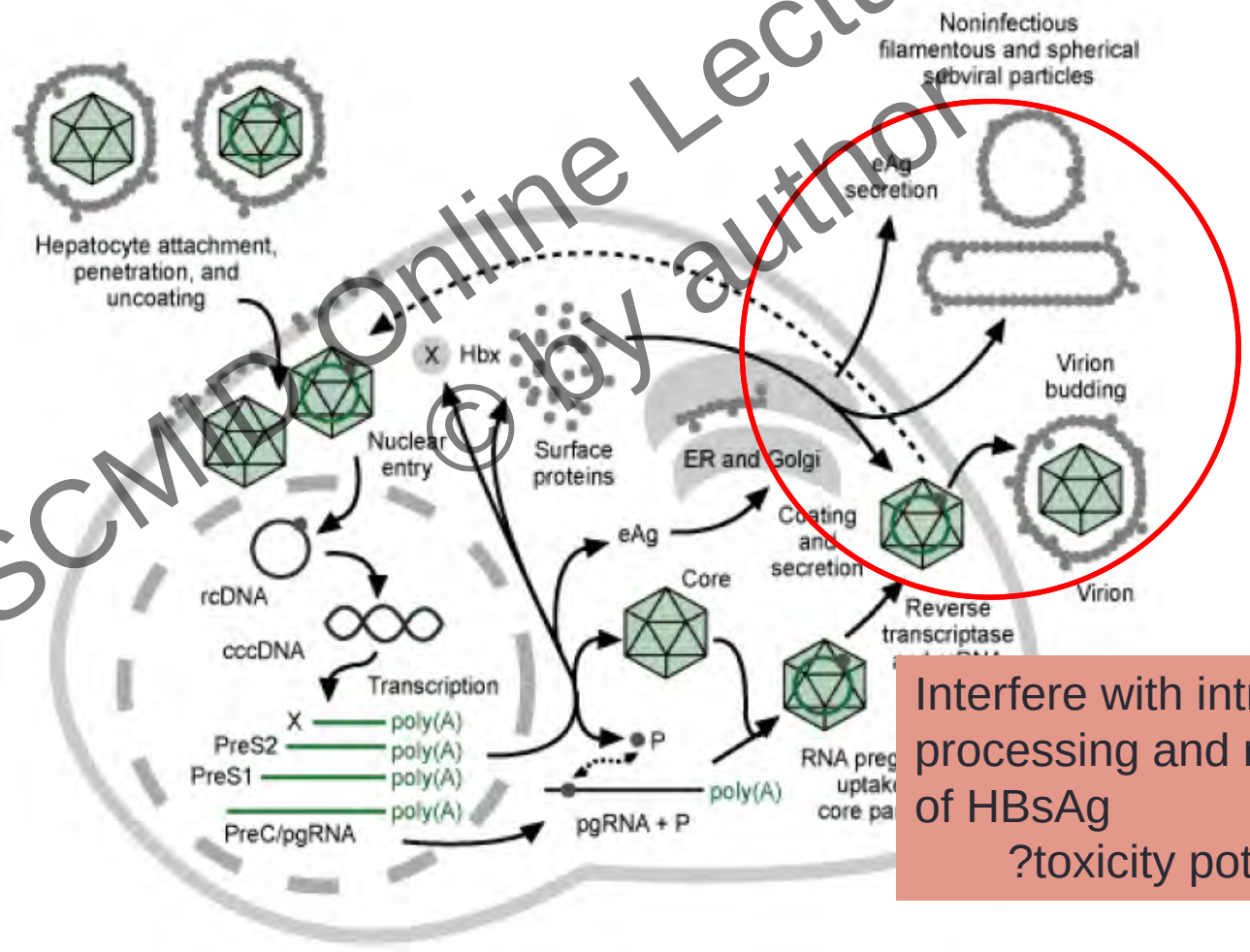
sAg secretion inhibitors



Interfere with intracellular processing and release of HBsAg

?toxicity potential

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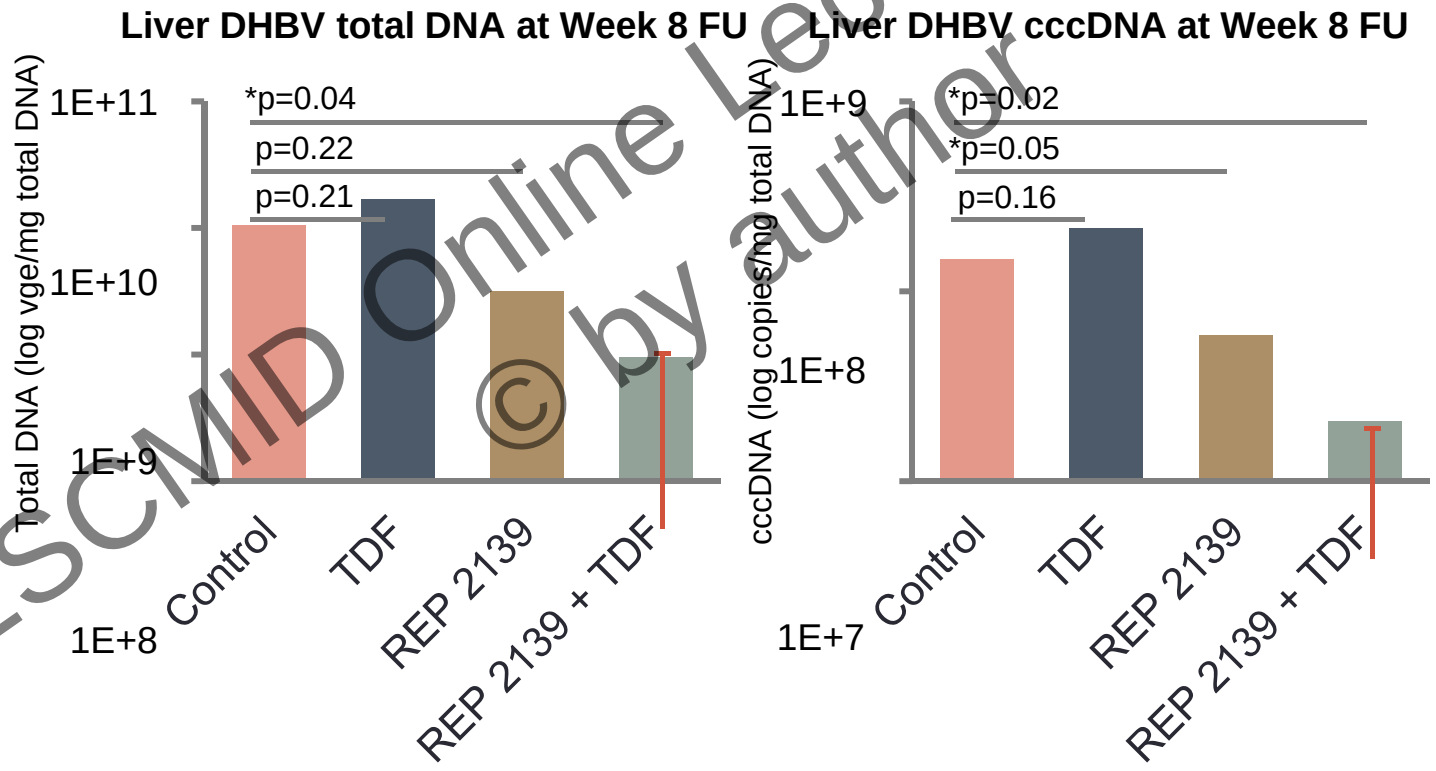
Achievement of surface antigen clearance in the liver by combination therapy with REP 2139-Ca and nucleoside analogues against chronic hepatitis B



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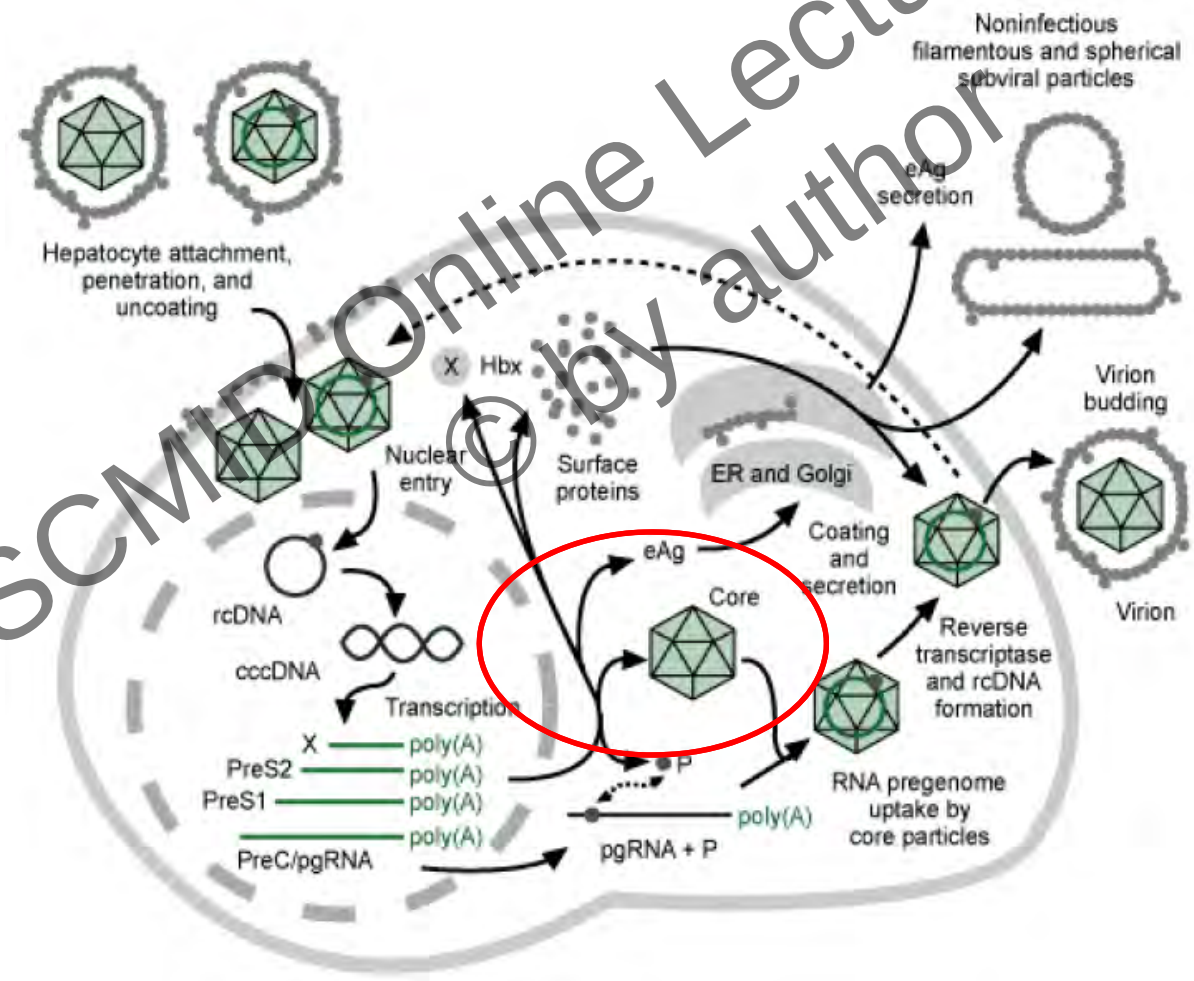
Quinet J, et al. EASL 2016, Barcelona. THU-177

And there are others…..



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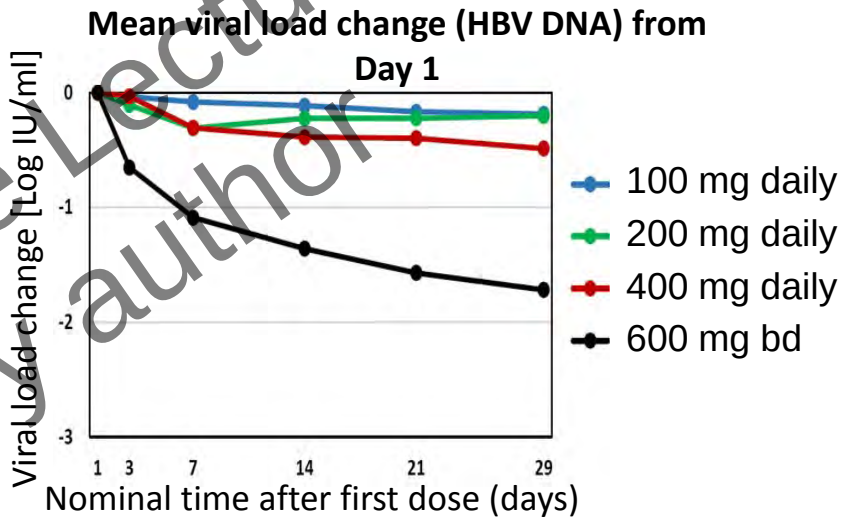
Phase 1b Efficacy and Safety of NVR 3-778, a **HBV Core Inhibitor**, in HBeAg-Positive Patients with Chronic HBV Infection

- HBeAg-positive CHB patients
- Serum HBV DNA >20,000 IU/mL
- ALT levels 1-7 times upper limit of normal
- Randomized to NVR 3-778 capsules at 4 doses (vs placebo) x 28 days



NVR 3-778 600 mg bd associated with mean 1.72 $\log_{10}$ IU/mL HBV DNA reduction in 28 days

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Yuen M-F, et al. AASLD 2015, San Francisco. #LB-10

Host-directed agents?

Immune stimulators:

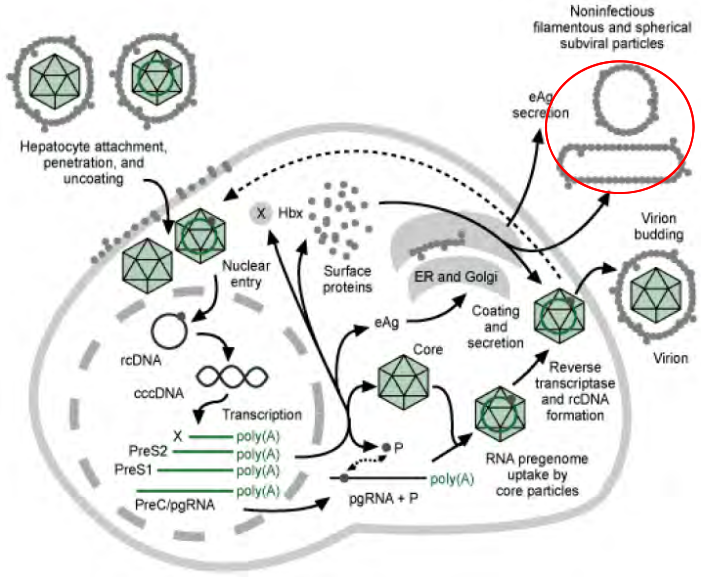
- Toll-like receptor agonists
  - TLR 7 (Lanford et al., 2013; Menne et al., 2015)
  - TLR 9 (Goldstein and Goldstein, 2009)
- Lymphotoxin-b receptor agonists (Lucifora et al., 2014)
- Others….

Checkpoint inhibitors

- PD-, PD-L1, CTL-4 inhibitors etc

Therapeutic vaccines

- S and Pre-S antigen vaccines
- DNA vaccines (especially of S)
- T cell vaccines



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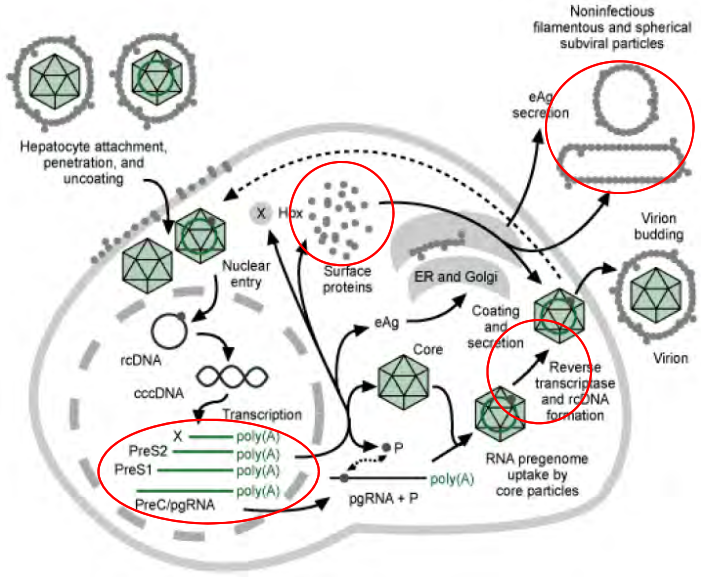
But what are most promising?

- Gilead:
  - GS-9620
    - TLR-7 agonist
      - In phase 2
  - GS-4774
    - Tarmogen T cell immunity stimulator
    - Therapeutic vaccine
      - Phase 2 programme commenced
- Tekmira:
  - TKM HBV
    - siRNA – blocks sAg expression
      - Phase 2 commenced
- Arrowhead:
  - ARC-520
    - siRNA – blocks mRNA translation
      - Multiple dose phase 2 commenced
- Achillion:
  - ACH-126,443
    - L-nucleoside
      - Phase 2



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But there are major issues…

- It is quite likely that a single drug or target will not be sufficient
- Therefore some kind of combination….
  - But how do we decide what to combine with what?

What is our endpoint for studies?

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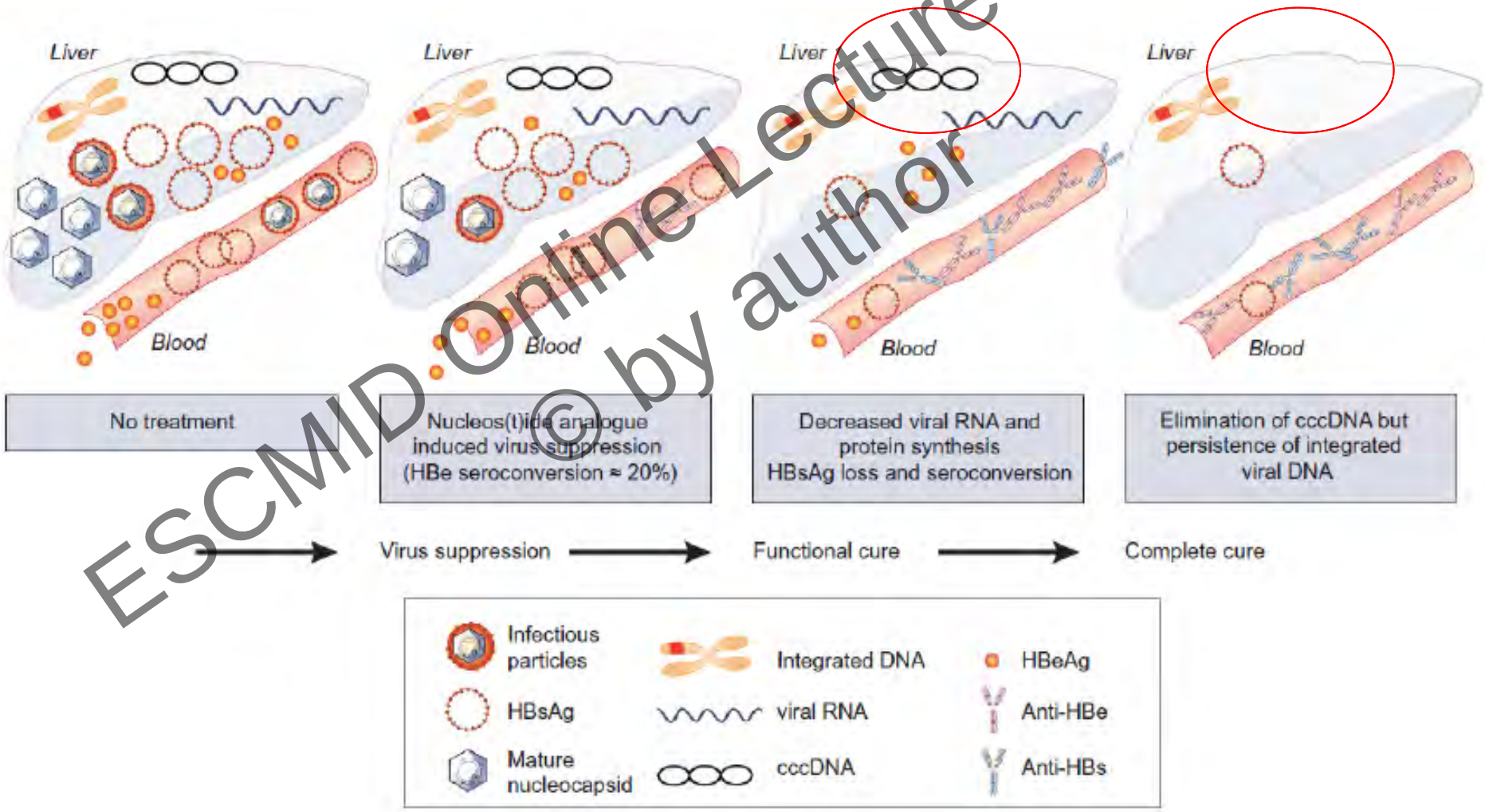
What are we aiming for and how do we know we have got there?



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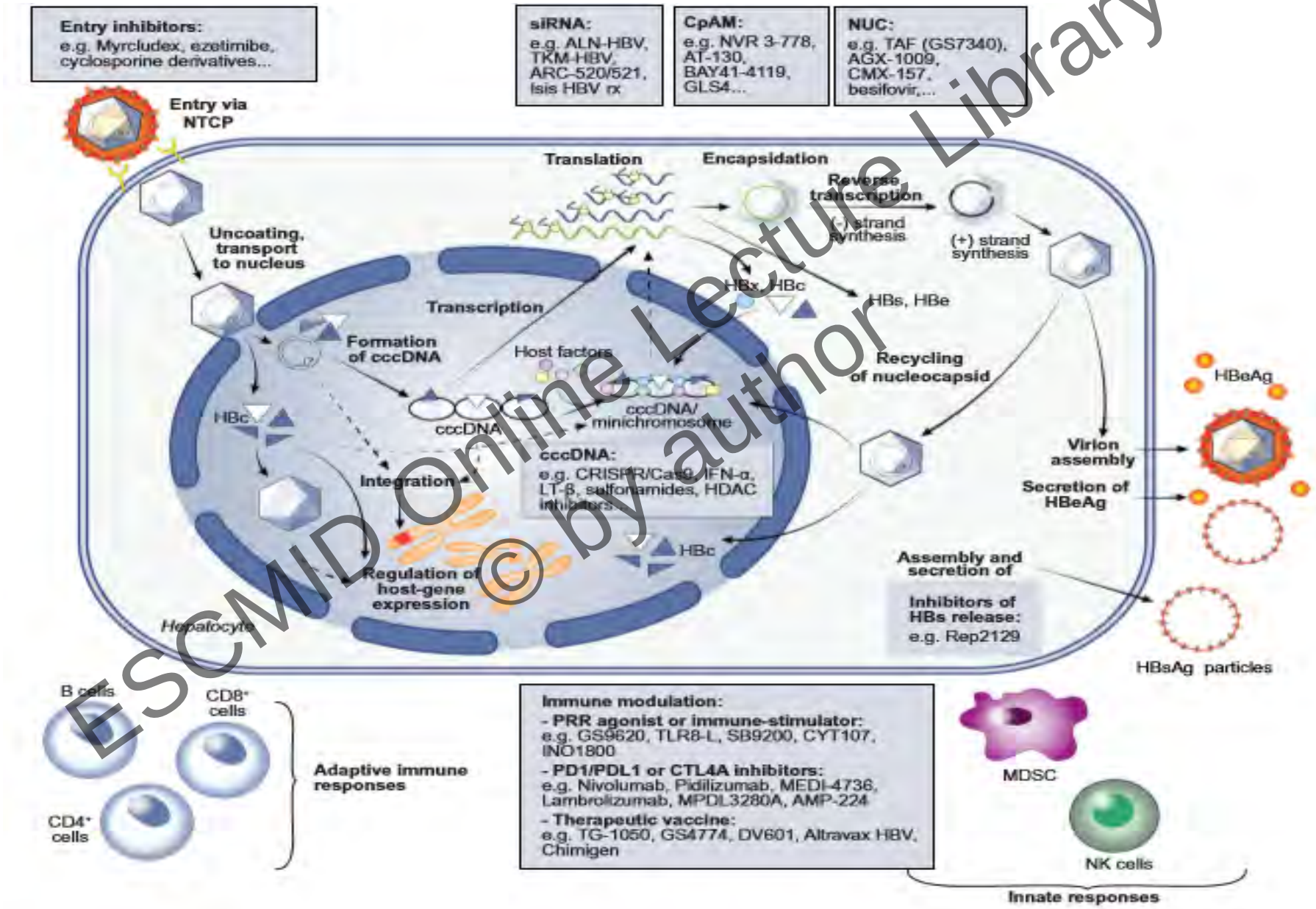

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Durantel et al J Hepatol 64: S117-31 epub 2016/04/17

Conclusions

- There are a variety of definitions of cure
- ‘Proper’ cure is not generally achieved by present regimens
- New agents:
  - There are promising DAAs in development to multiple targets in HBV lifecycle
  - There are host directed therapies to release/improve immune response
- We probably will need a combination approach
- An exciting area, but don’t hold your breath on a particular agent…..

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