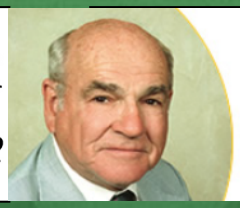
Hepatitis B Foundation
Cause for a Cure



Baruch S. BLUMBERG INSTITUTE
Living Science

Understanding new medicines to treat chronic hepatitis B: toward a cure

October 26, 2016

Define an HBV cure

Functionally (practical):

- Sustained, off drug response (loss of viremia and antigenemia

Clinically:

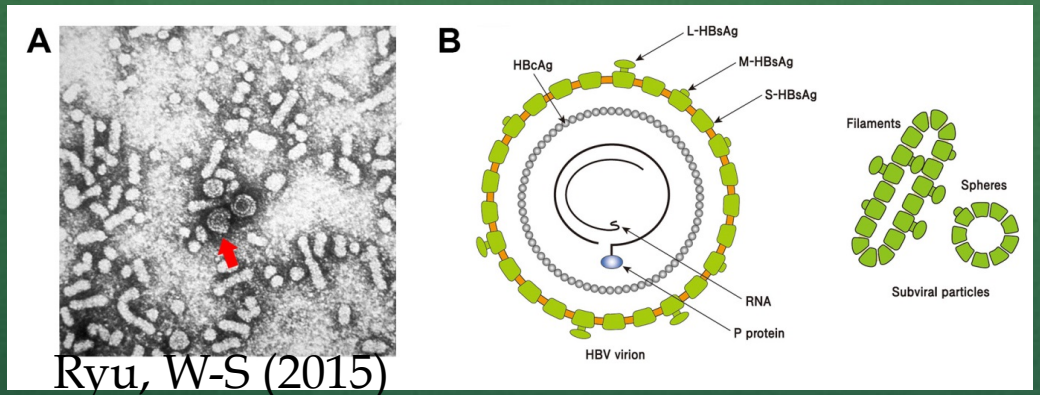
- Return an individual to the risk of death and disease due to liver disease to that of an age and gender adjusted uninfected individual

- *Block, Gish et al, AVR, 2015*
- *Liang, Block et al, Hepatology, 2016*

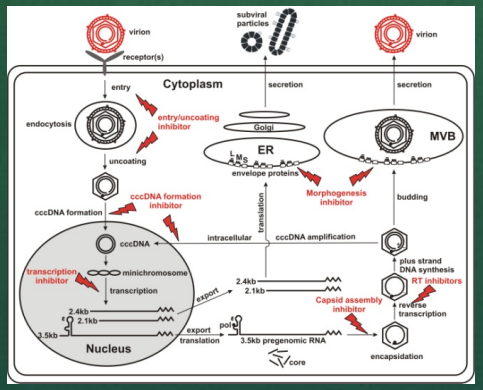
Categories of HBV therapeutics

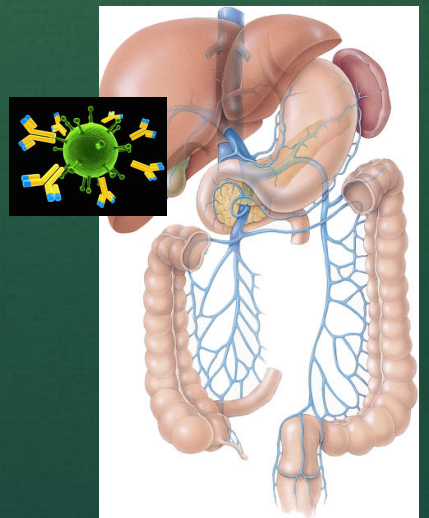
Direct Acting Antivirals (DAA)

Indirect (Host) Acting Antivirals (Hos

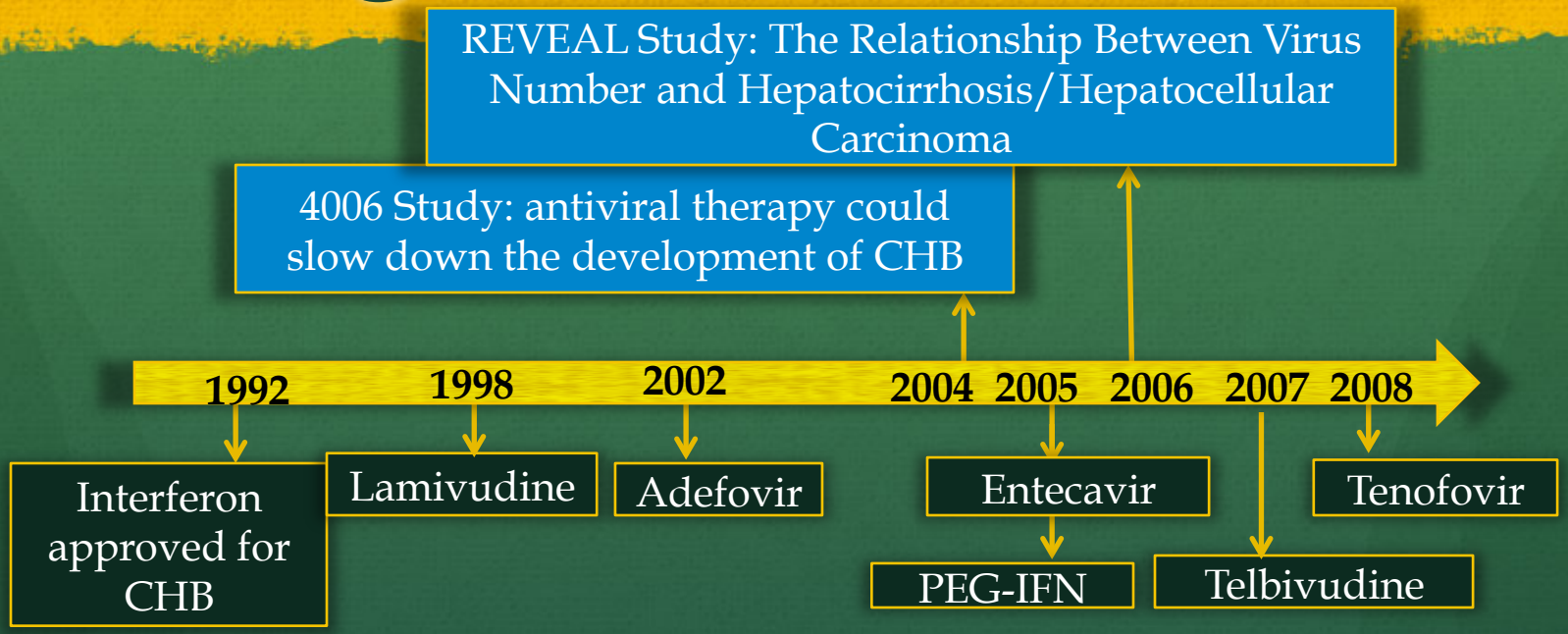


Ryu, W-S (2015)





Timeline of Approved Drugs for Chronic HBV



Tenofovir approved in US for HBV, in 2008, but not yet approved in China for HBV

All are Direct Acting Antivirals (DAA)

Functional cures do occur with current therapeutics, although rarely

JOURNAL OF **HEPATOLOGY**

Table 2. Results of main studies for the treatment of HBeAg-positive chronic hepatitis B at 6 months following 12 months (48 or 52 weeks) of pegylated interferon alpha (PEG-IFN) and at 12 months (48 or 52 weeks) of nucleos(t)ide analogue therapy.

	PEG-IFN		Nucleoside analogues			Nucleotide analogues	
	PEG-IFN-2a	PEG-IFN-2b	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Dose*	180 µg	100 µg	100 mg	600 mg	0.5 mg	10 mg	245 mg
[Ref.]	[63]	[64]	[63, 65-68]	[68]	[67]	[69, 70]	[70]
Anti-HBe seroconversion (%)	32	29	16-18	22	21	12-18	21
HBV DNA <60-80 IU/ml (%)	14	7	36-44	60	67	13-21	76
ALT normalisation# (%)	41	32	41-72	77	68	48-54	68
HBsAg loss (%)	3	7	0-1	0.5	2	0	3

*PEG-IFN were given as percutaneous injections once weekly and nucleos(t)ide analogues as oral tablets once daily.

#The definition of ALT normalisation varied among different trials (i.e. decrease of ALT to ⩽1.25-times the upper limit of normal (ULN) in the entecavir or ⩽1.3-times the ULN in the telbivudine trial).

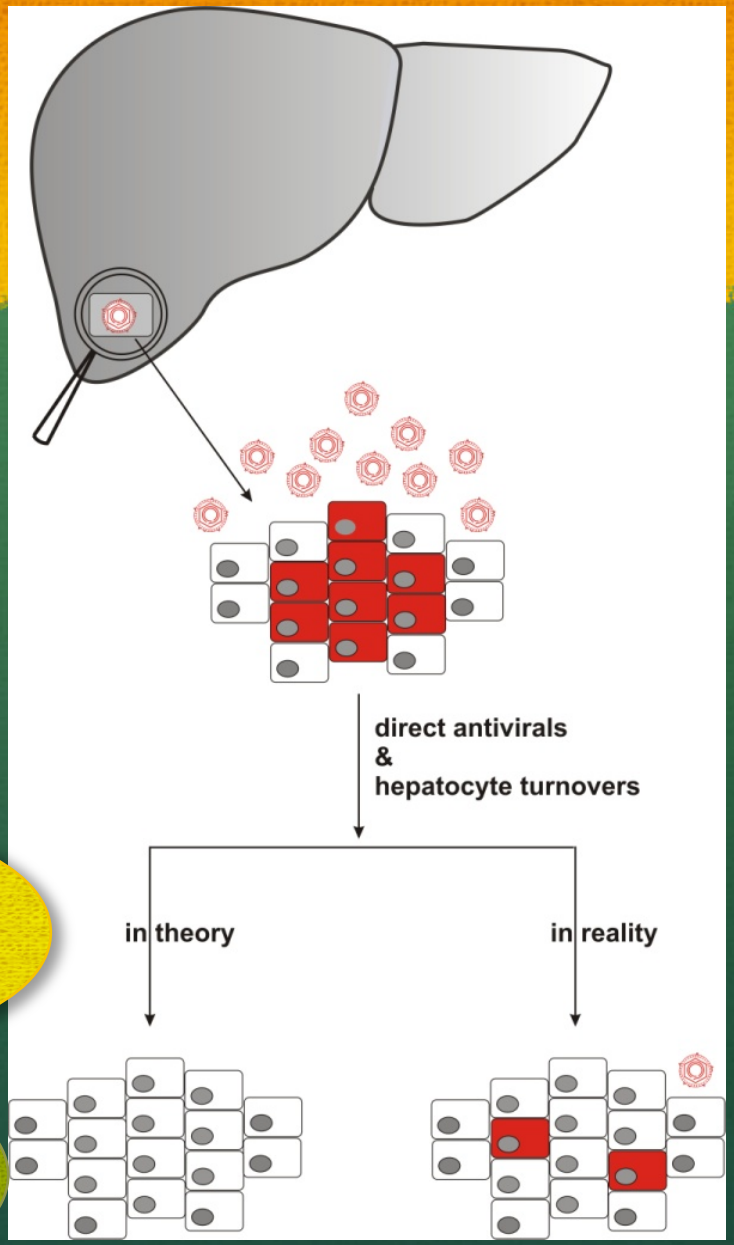
Journal of Hepatology **2012** vol. 57 | 167–185

Failure to cure with NUCs is because

Nests of infected cells (cccDNA containing) remain; HBsAg continues to be made:
T cells exhausted
B cells: no detectable HBsAb

T cells (exhausted)

B cells (No detectable Antibody to HBs)



Need

- Something new that complements current compounds
- *Different mechanism DAA*

+

- *An immuno-enhancer*

Categories of Anti-HBV Strategies

Direct Acting Antivirals

- In Use
  - Polymerase
- Potential
  - RNaseH
  - RNAi
  - Capsid inhibitors
  - sAg
  - eAg
  - Virus attachment
  - CRISPR/CAS

In-Direct Acting Antivirals

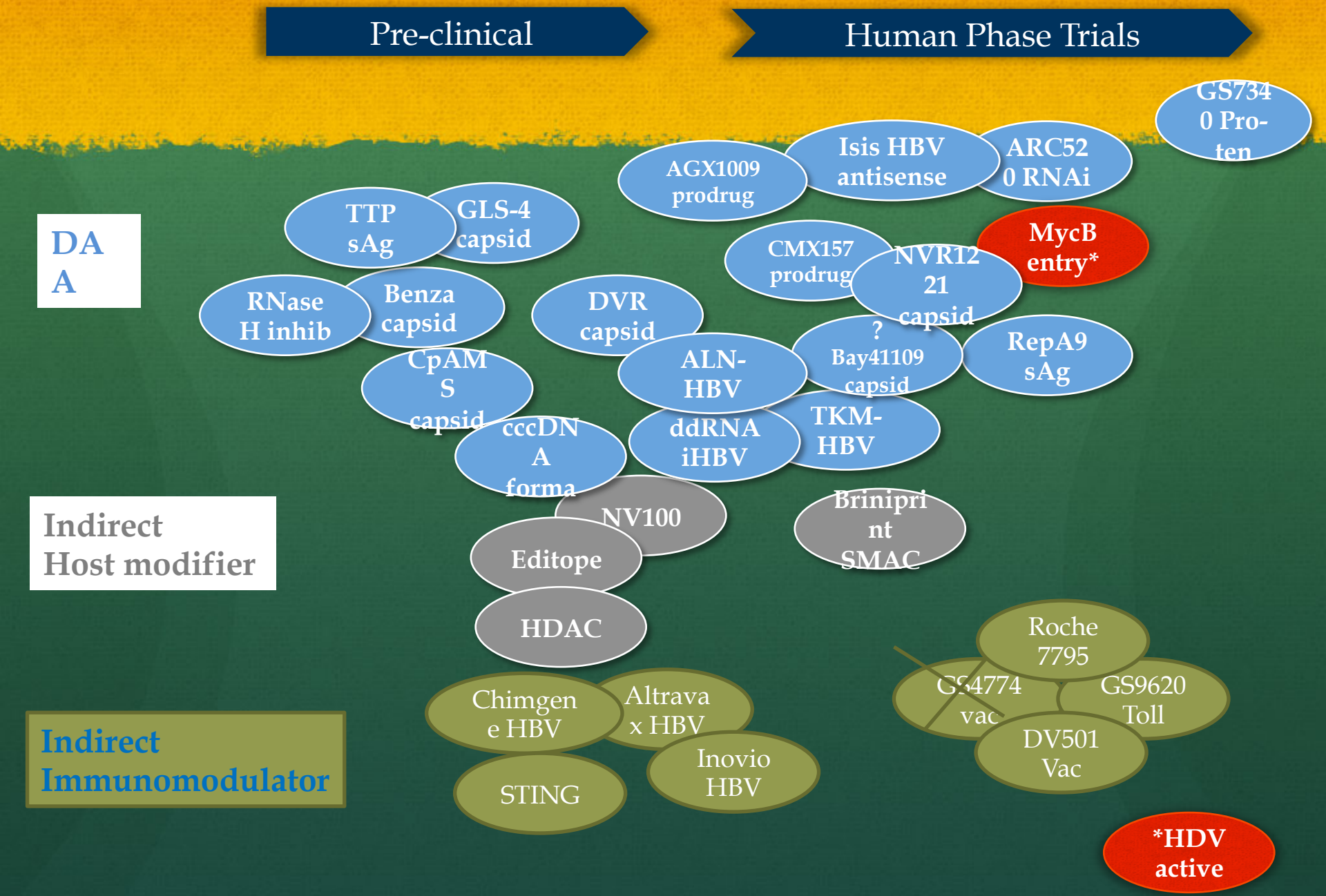
Immuno-modulatory

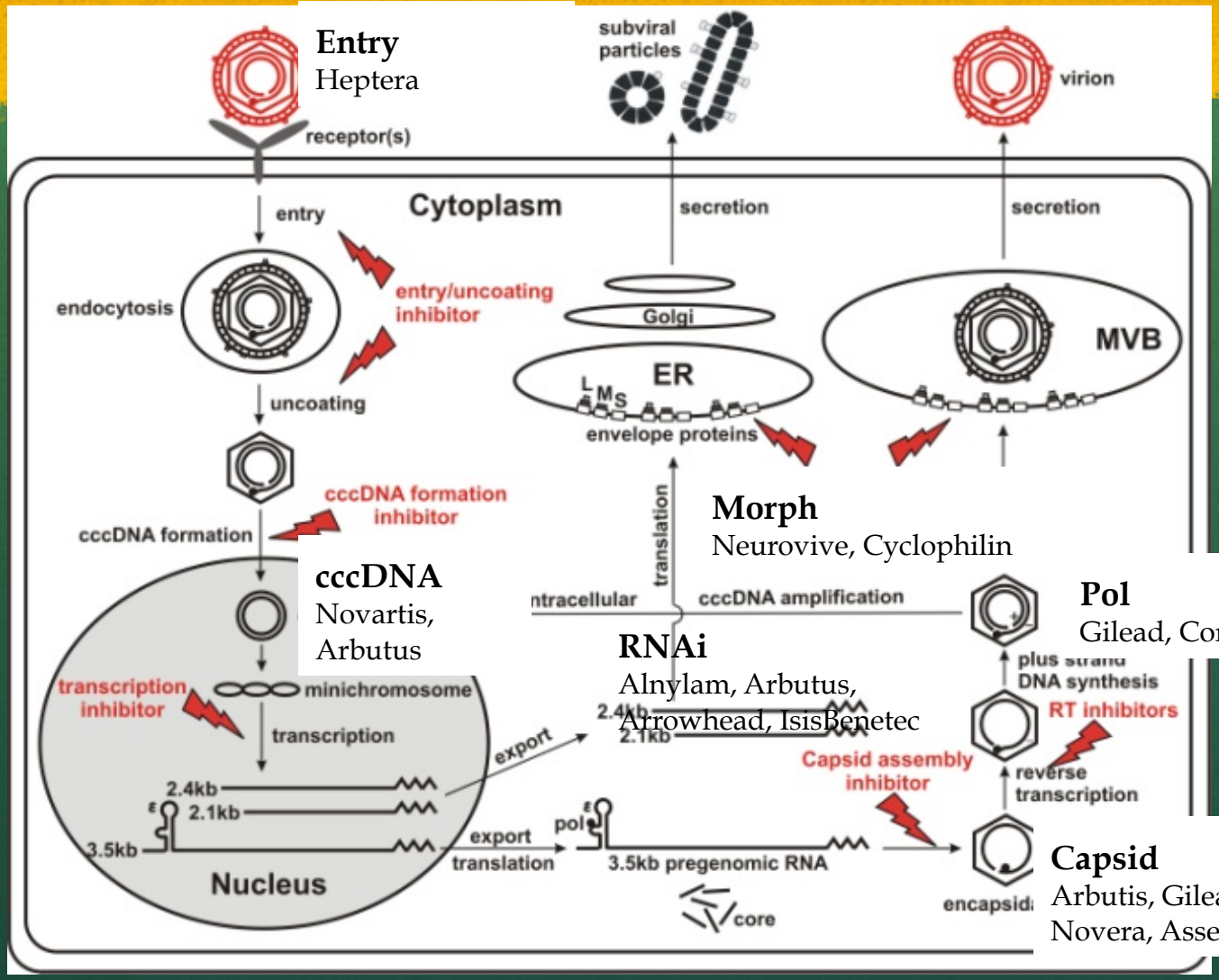
- In Use
  - Interferons
- Potential
  - Therapeutic vaccines
  - PD-1 blockade
  - Toll R agonists
  - STING, other innate defense
  - Interleukins, other cytokines

Essential host functions

- In Use
  - None for HBV
- Potential
  - Epigentic modifiers
  - Entry
  - Morphogenesis
  - Exit
  - Glycan processing

The HBV Therapeutic Development Landscape as of Jan, 2016

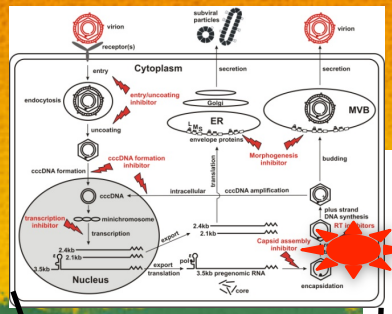


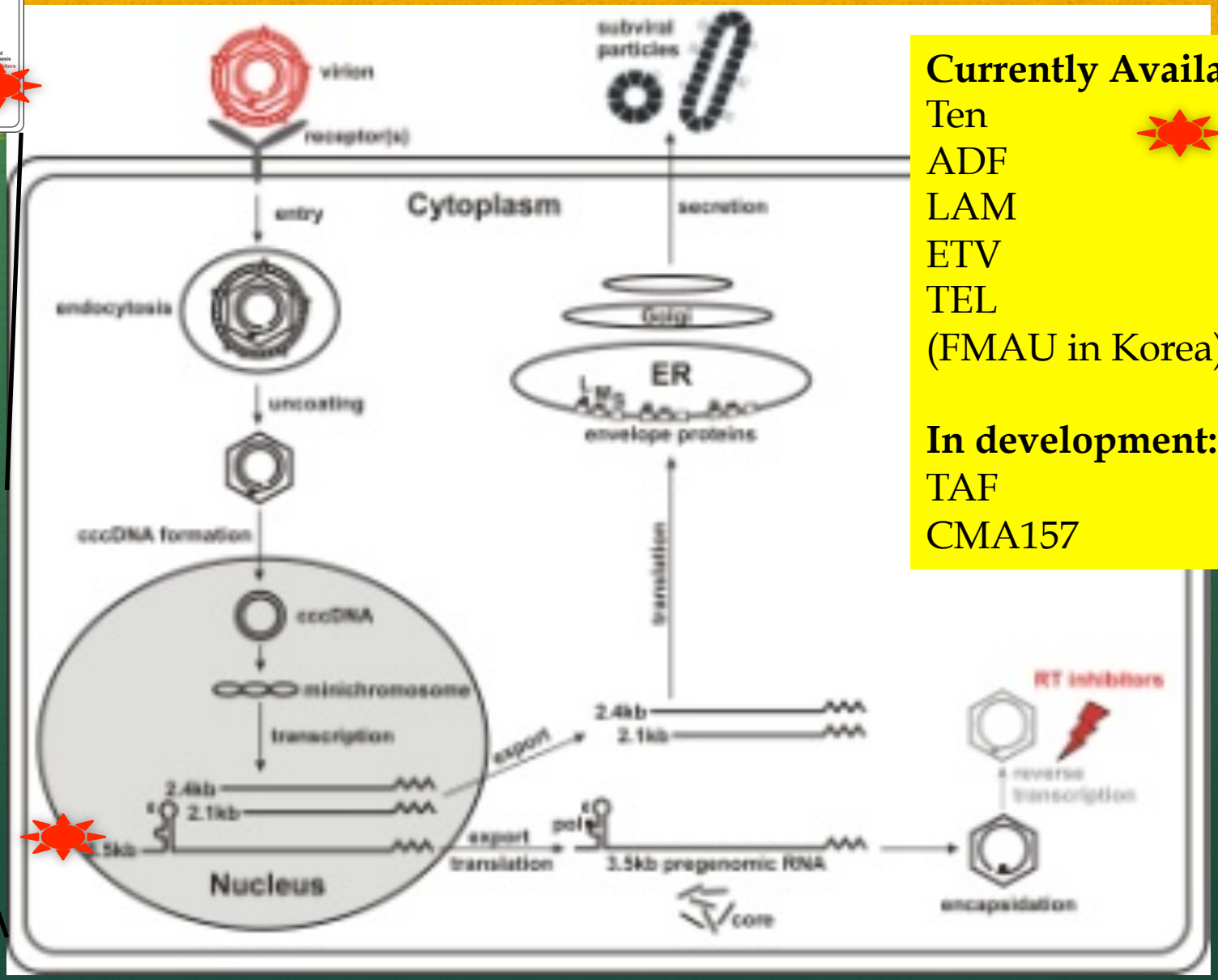


Immuno
Gilead, Arbutus, Roche,Inovio, Akshaya, Springbank

Block & Liang, 2016

Pol inhibitors:

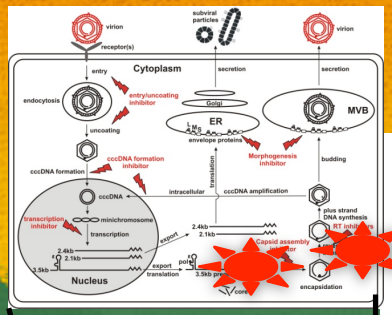


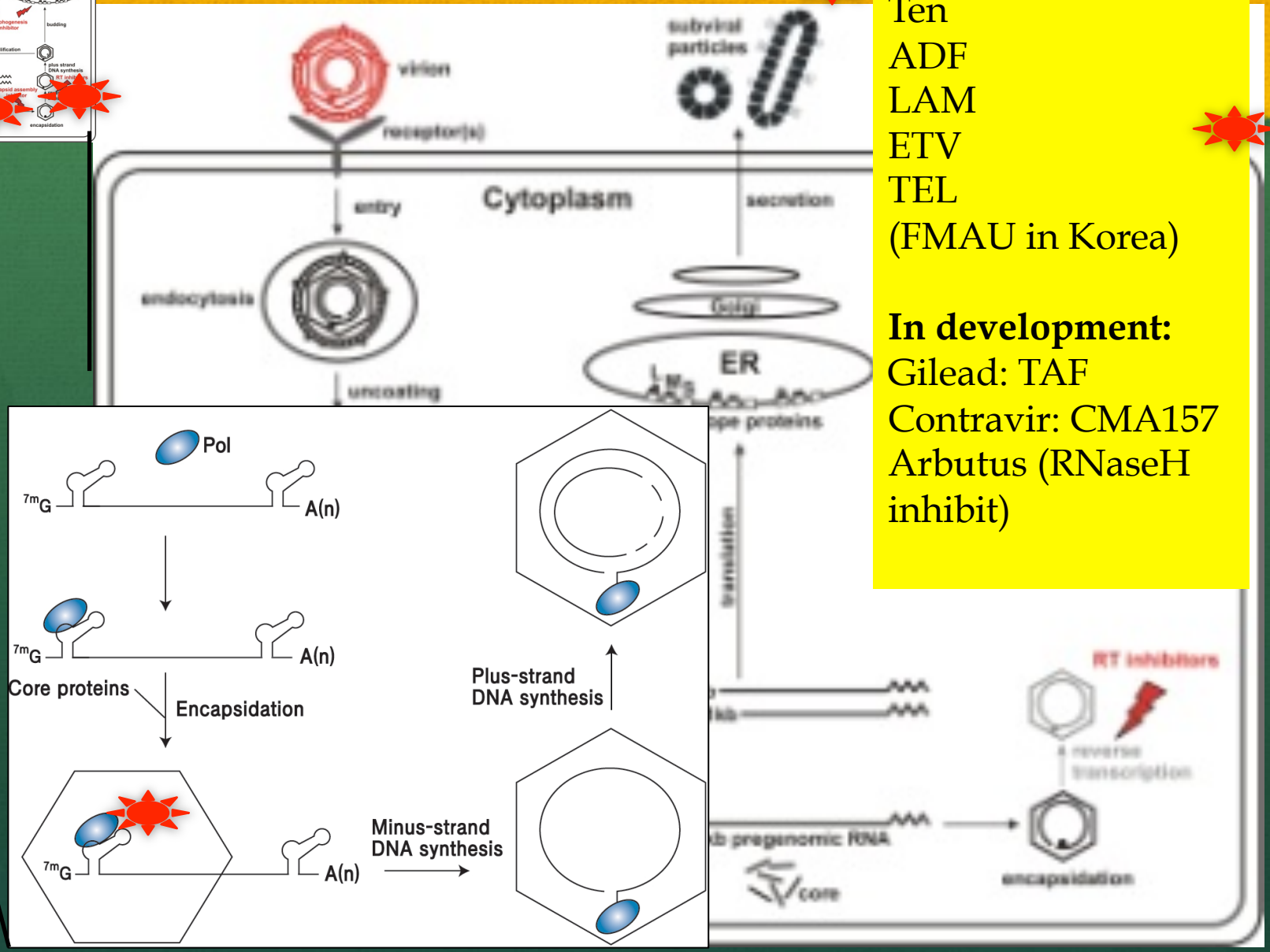


Currently Availabl
Ten
ADF
LAM
ETV
TEL
(FMAU in Korea)

In development:
TAF
CMA157

Pol inhibitors:

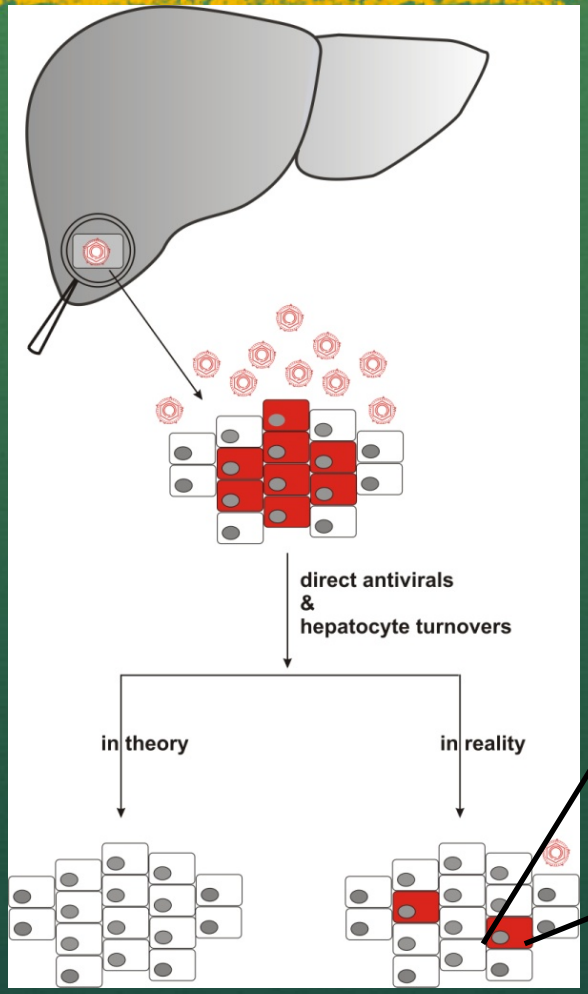


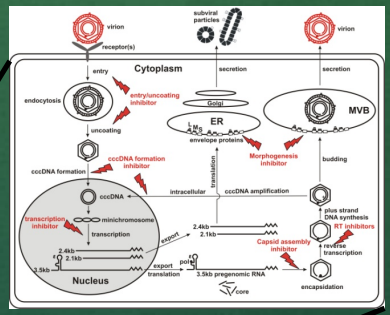


Currently Available
Ten
ADF
LAM
ETV
TEL
(FMAU in Korea)

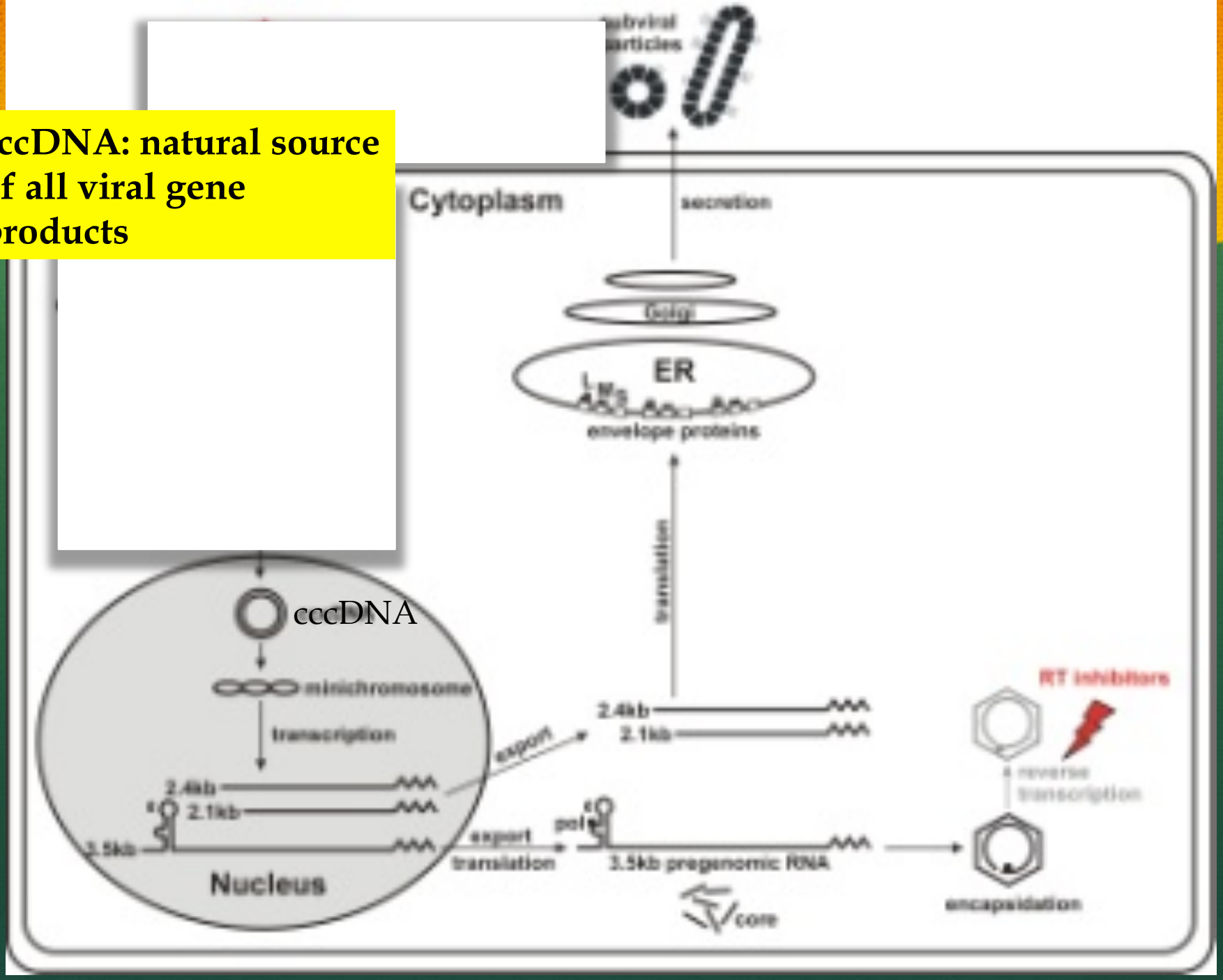
In development:
Gilead: TAF
Contravir: CMA157
Arbutus (RNaseH inhibit)

cccDNA: "natural" source of all viral gene products

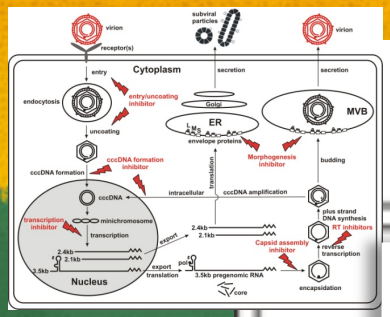


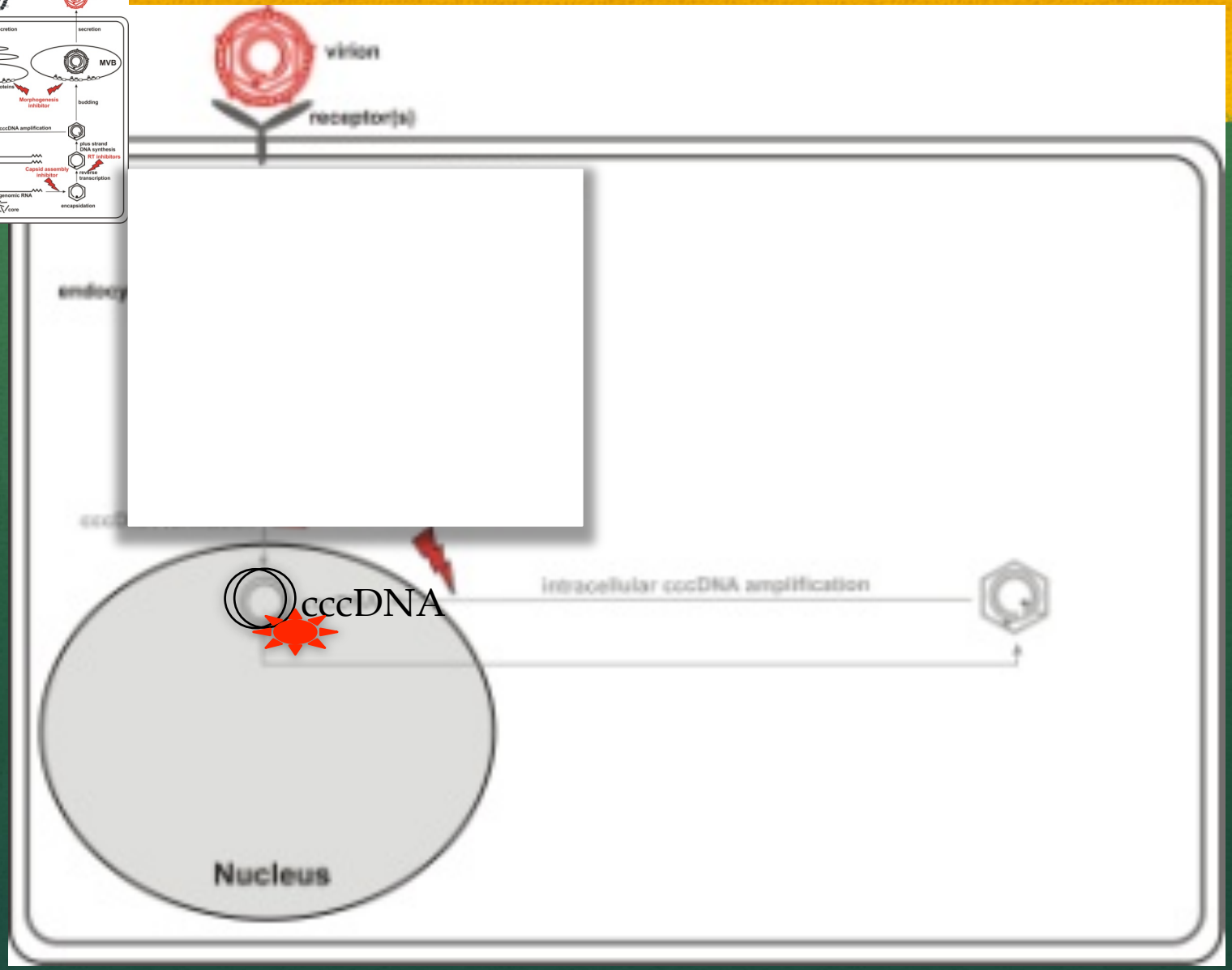


cccDNA: natural source of all viral gene products



Repress cccDNA, and repress all natural gene product





But cccDNA is a small, tough target

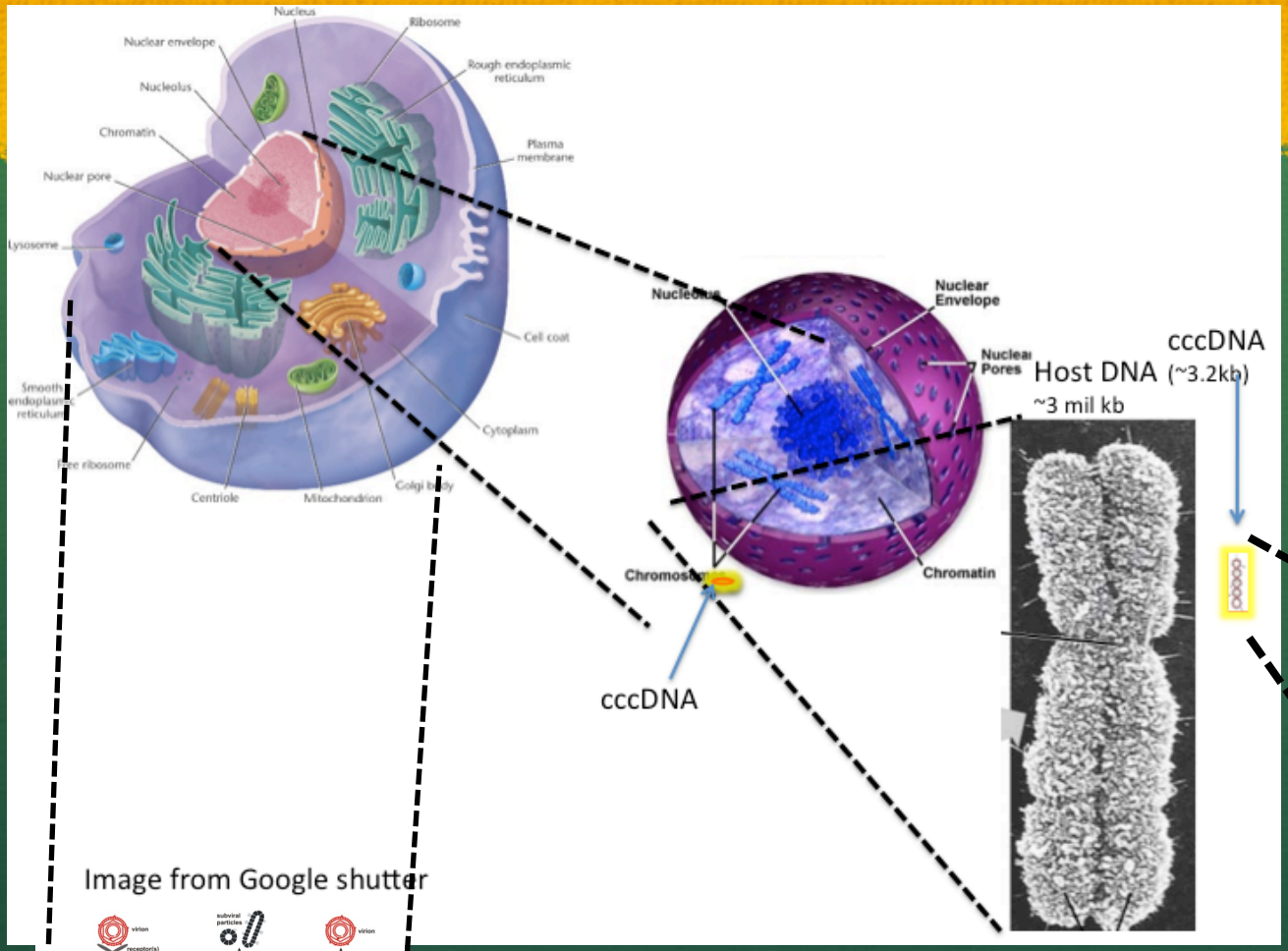
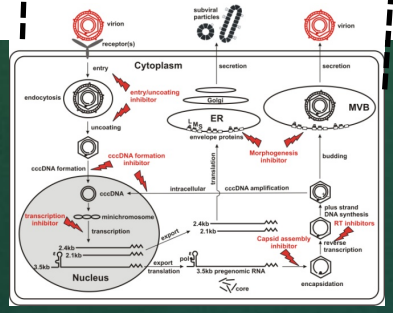
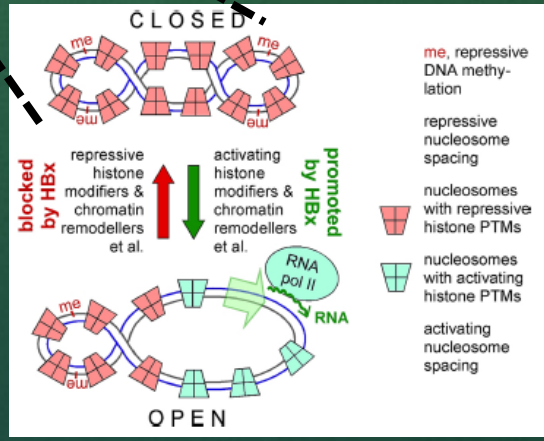


Image from Google shutter



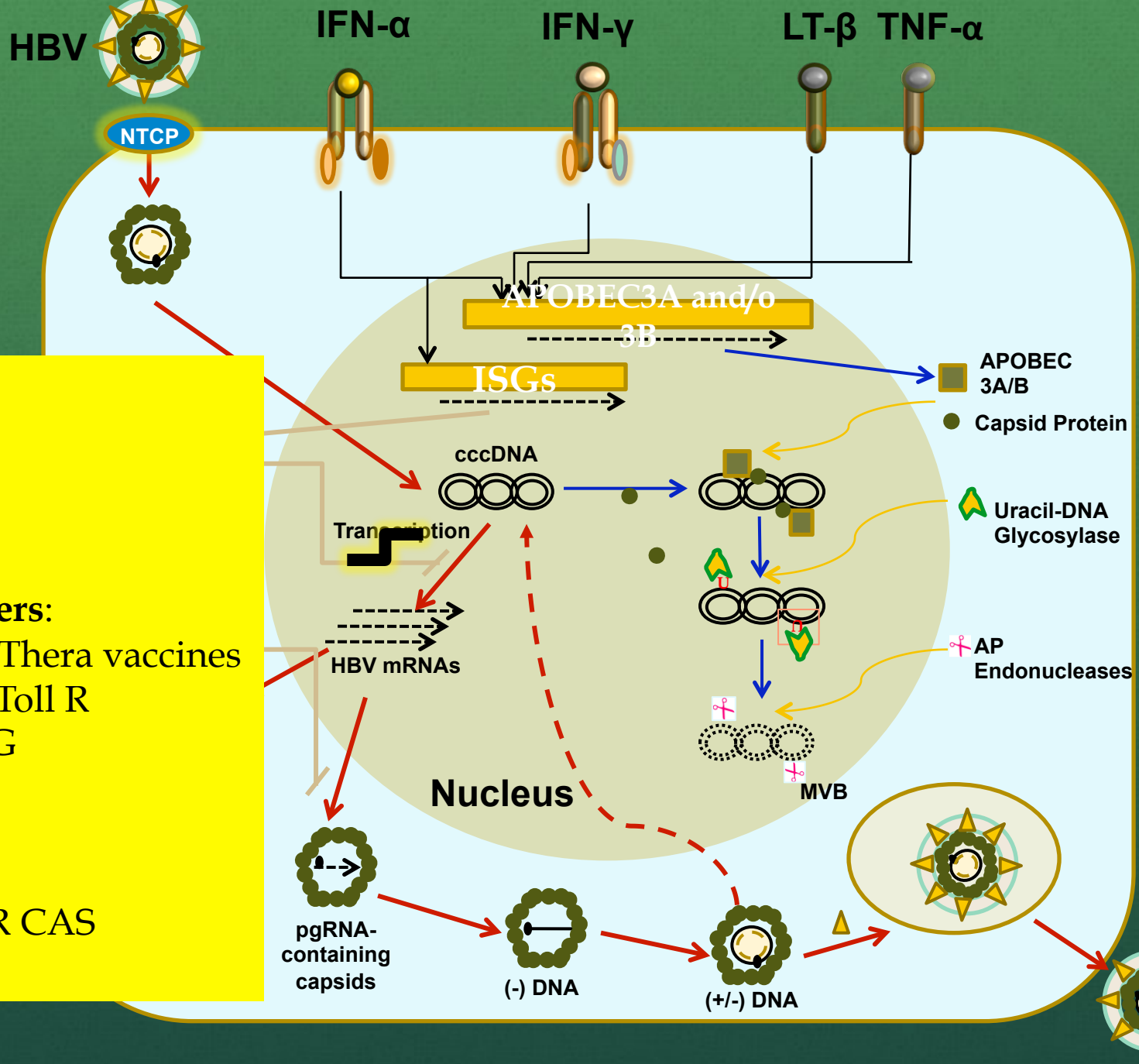


Nassal et al, Gut 2015 from Gut

Biologicals"
Approved:
IFNs

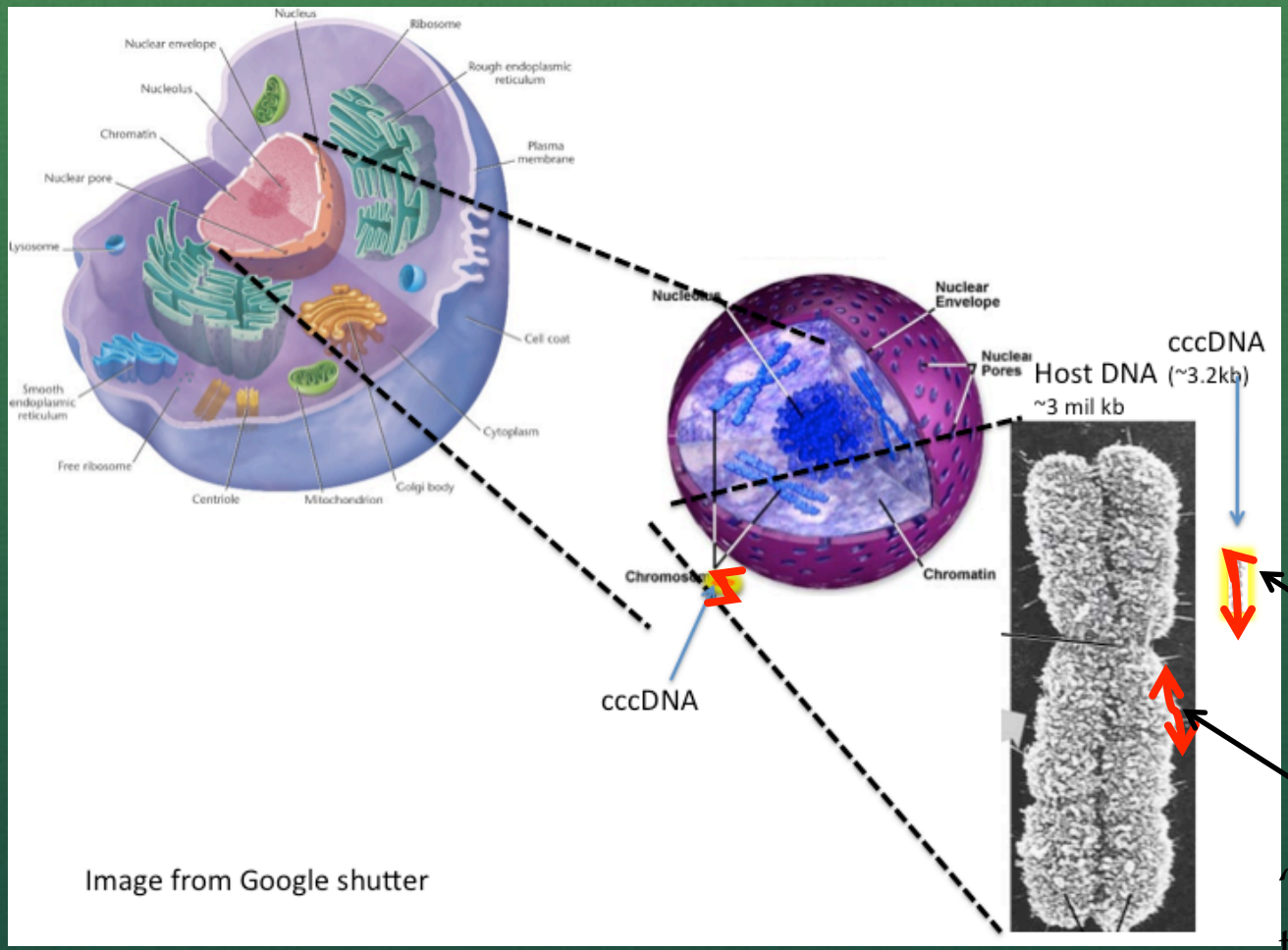
New:
Immunenhancers:
Inovia, Gilead: Thera vaccines
Gilead, Roche: Toll R
Arbutus: STING

Other:
Arbutus (ARB)
Intellia: CRISPR CAS



Block & Guo, 2015, Gastroeneterology

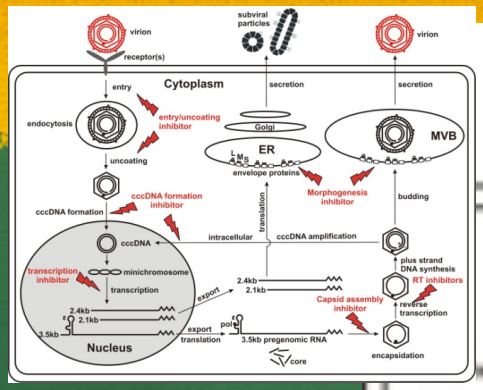
But some HBV DNA is "integrated" and not free cccDNA, and thus might be missed by drugs acting on cccDNA

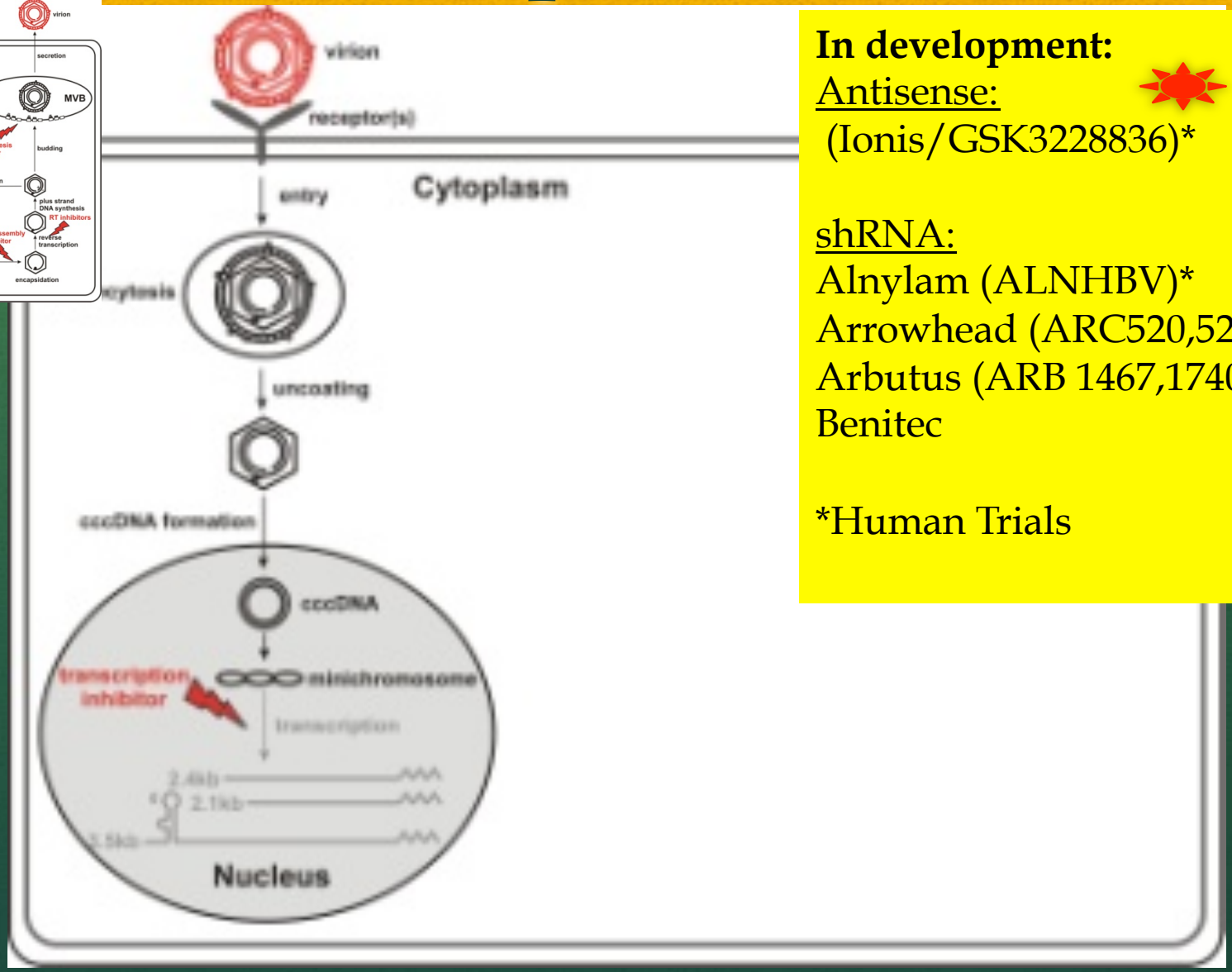


"free" cccDNA

cccDNA "integrated" in to the host chromosomes

RNAi transcript inhibition





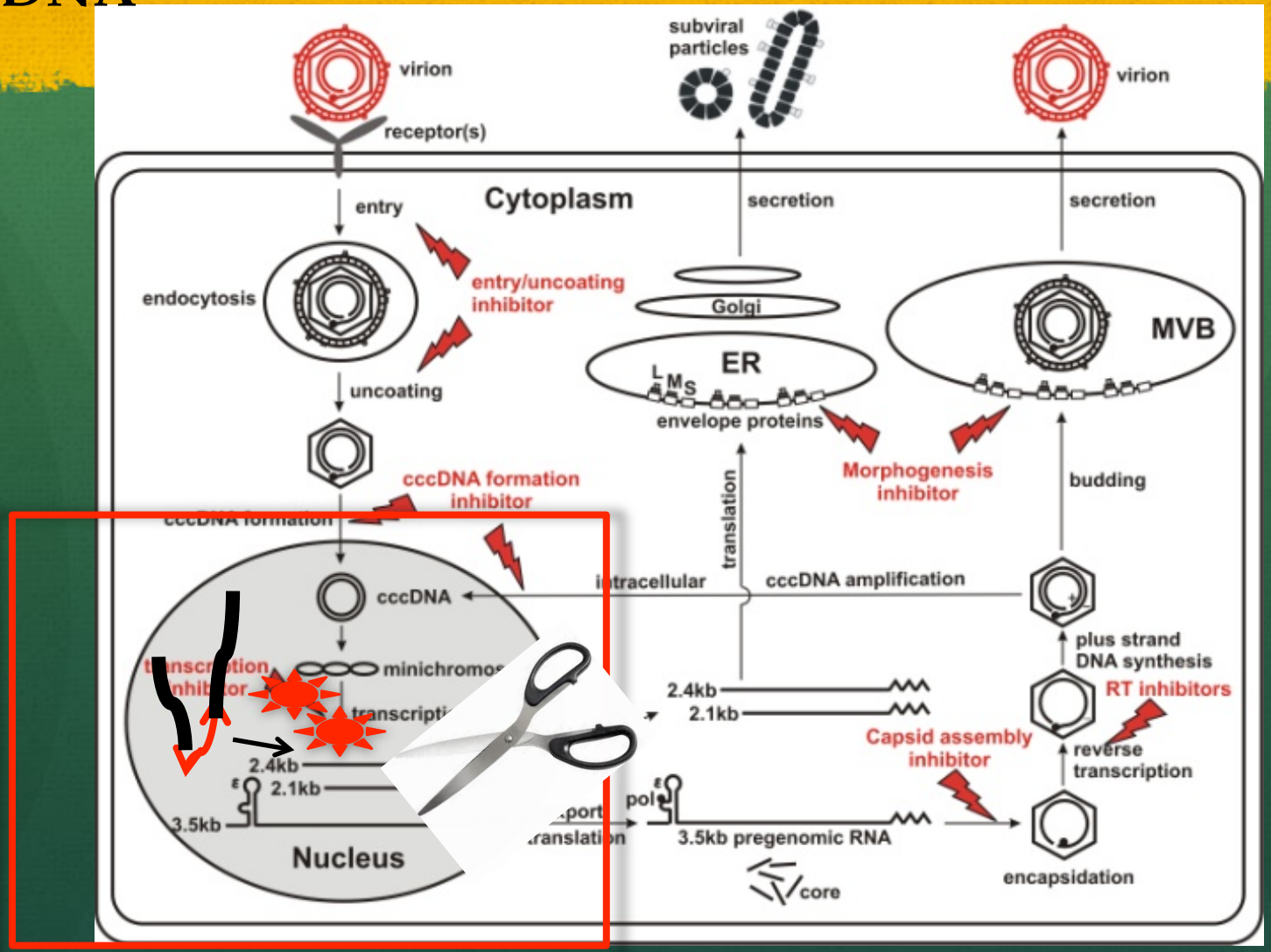
In development:

<u>Antisense:</u>
(Ionis/GSK3228836)*

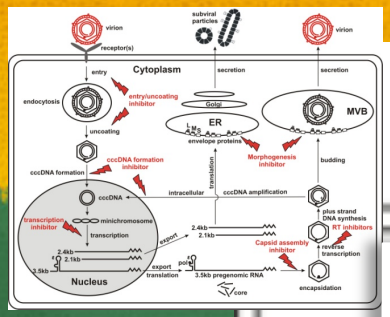
<u>shRNA:</u>
Alnylam (ALNHBV)*
Arrowhead (ARC520,521)*
Arbutus (ARB 1467,1740)*
Benitec

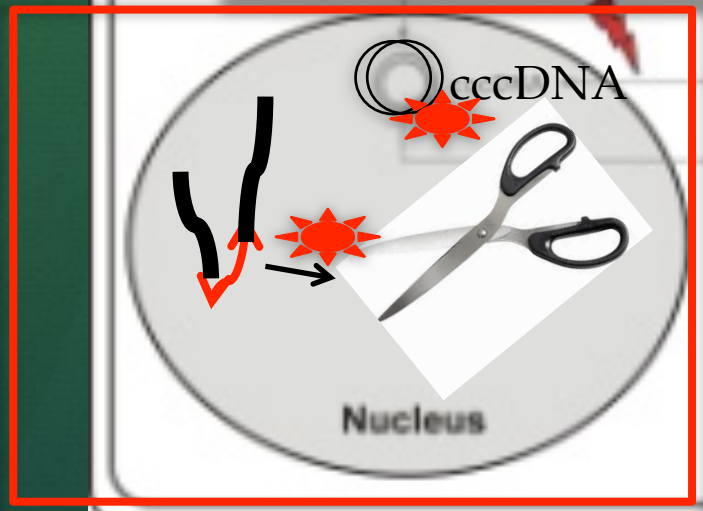
*Human Trials

RNAi / sh RNA leads to degradation of HBV RNA transcripts from cccDNA and integrated DNA



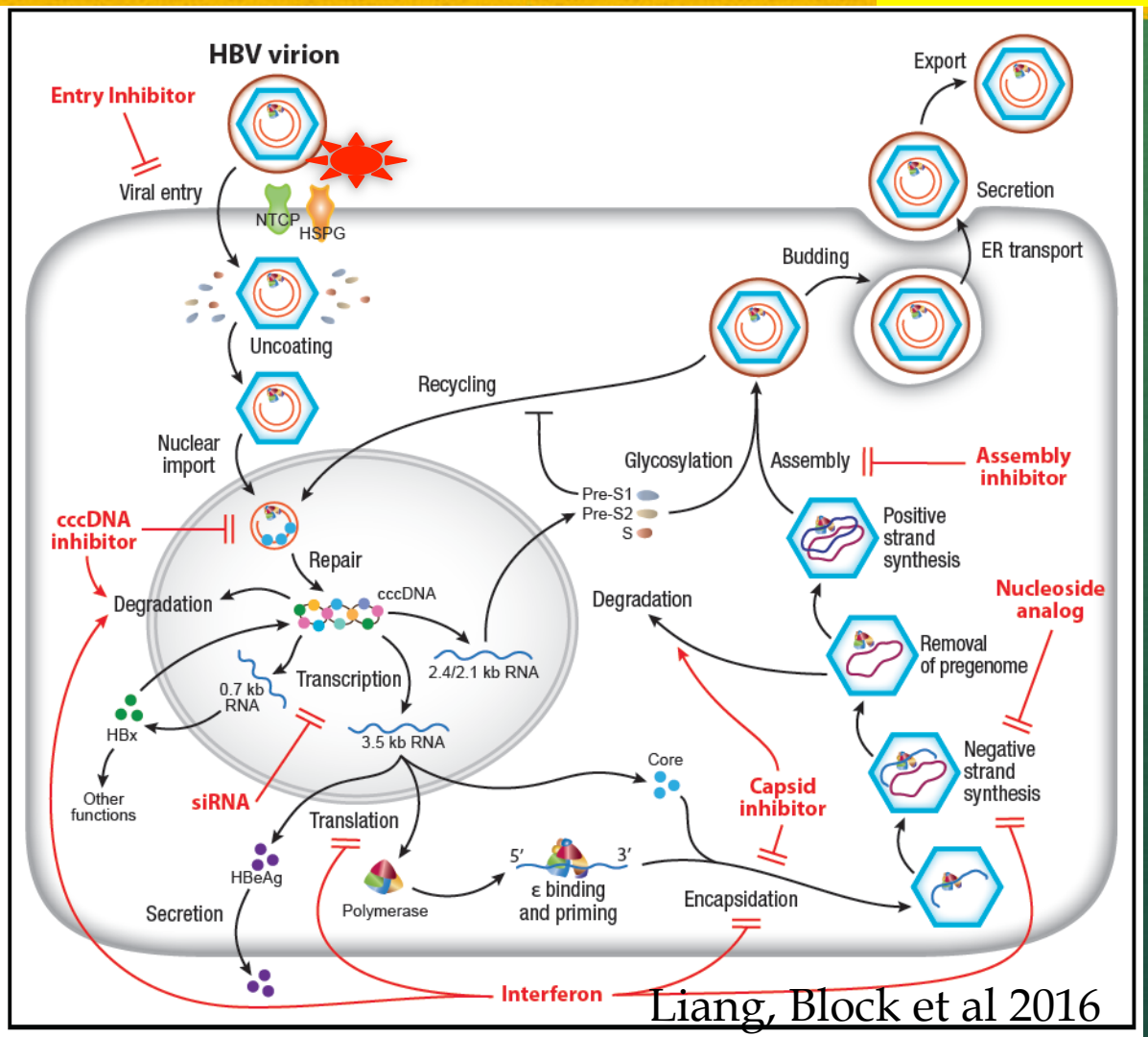
RNAi: Complete shut down:





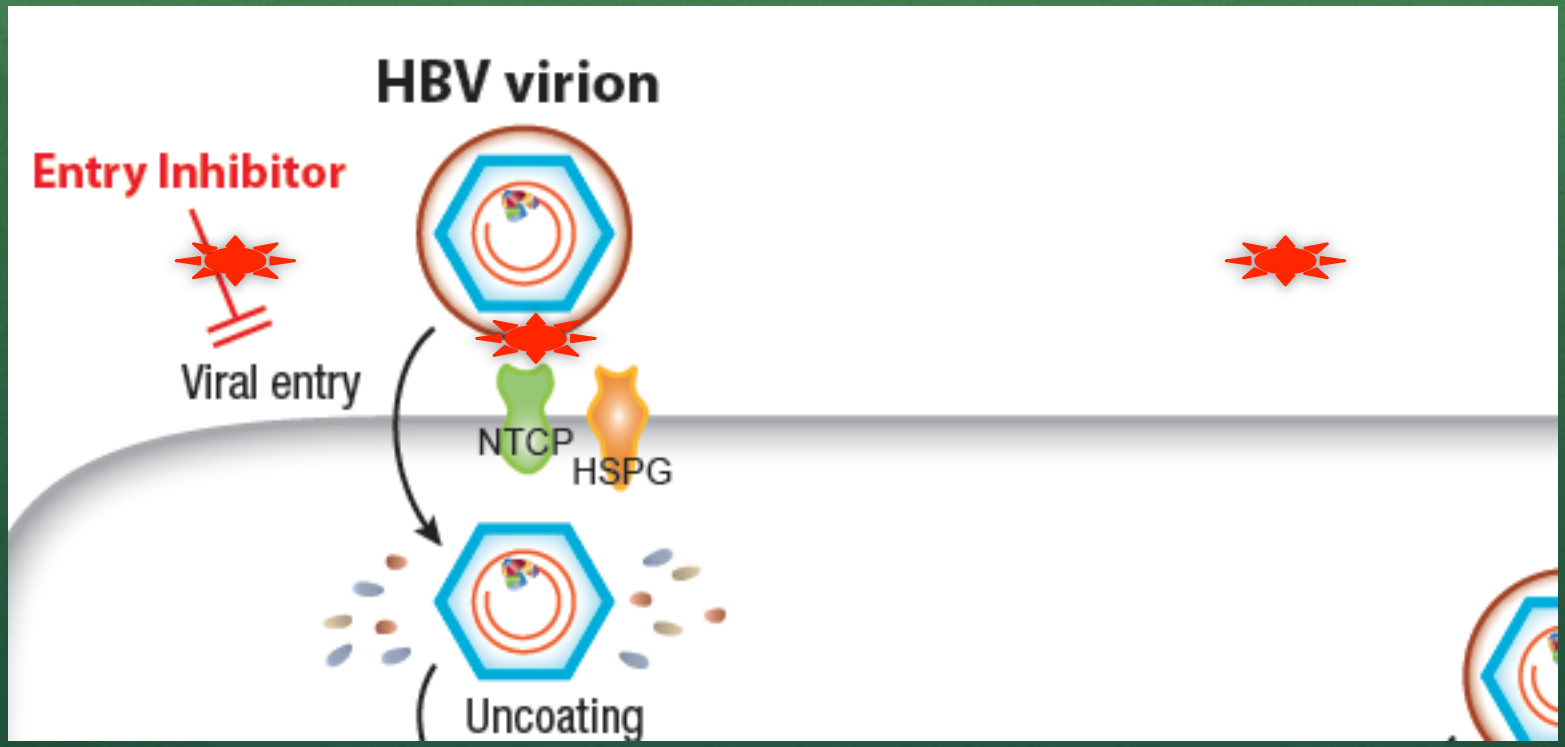
Entry Inhibitors

Entry Inhibitor (oilgopeptide)
MyrcludexB*
Human Trials



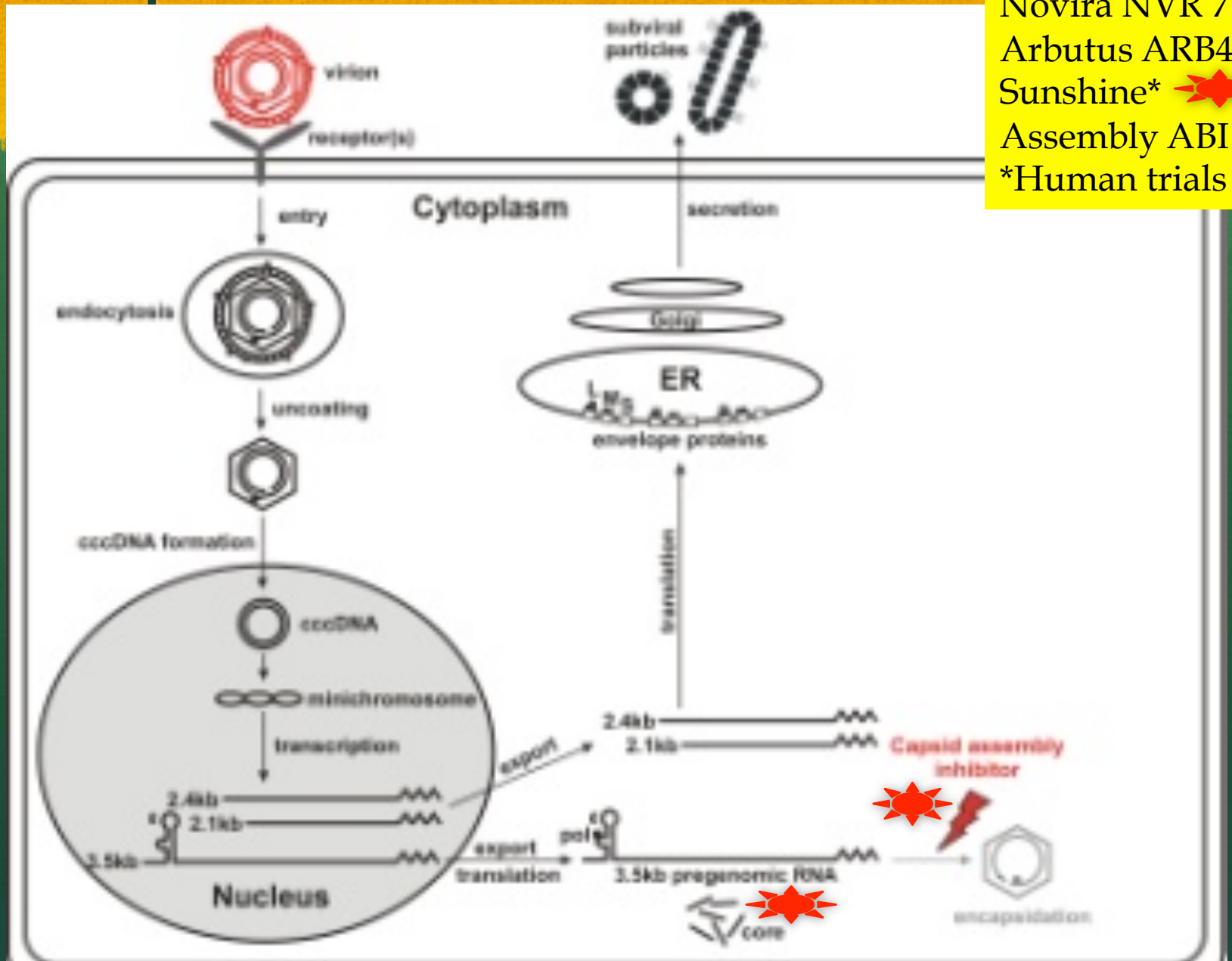
Liang, Block et al 2016

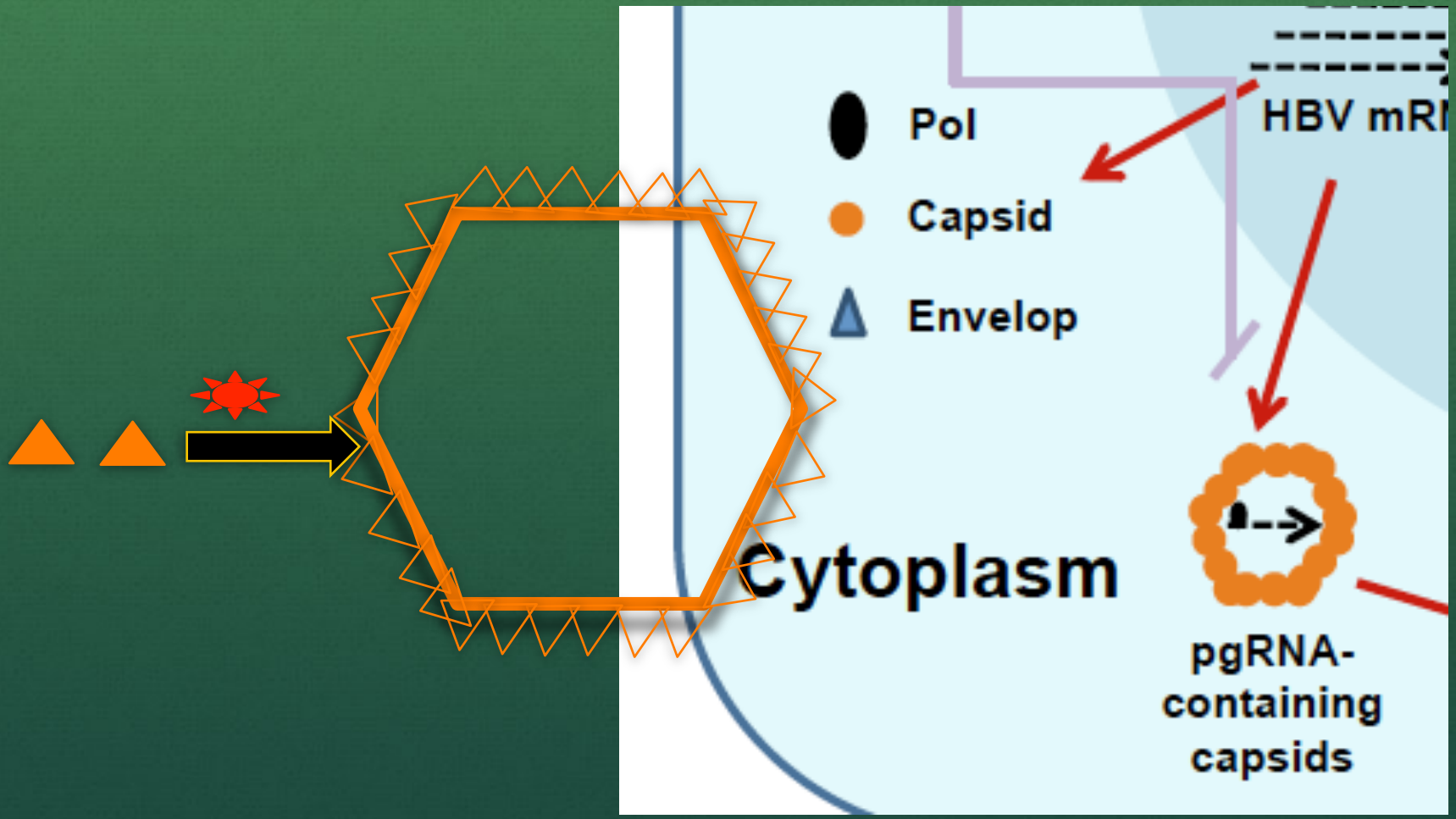
Entry Inhibitors



Capsid inhibition

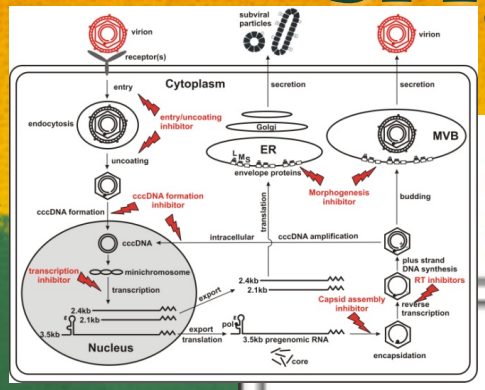
Capsid Inhibitors
Novira NVR 778*
Arbutus ARB423
Sunshine*
Assembly ABI H101
*Human trials

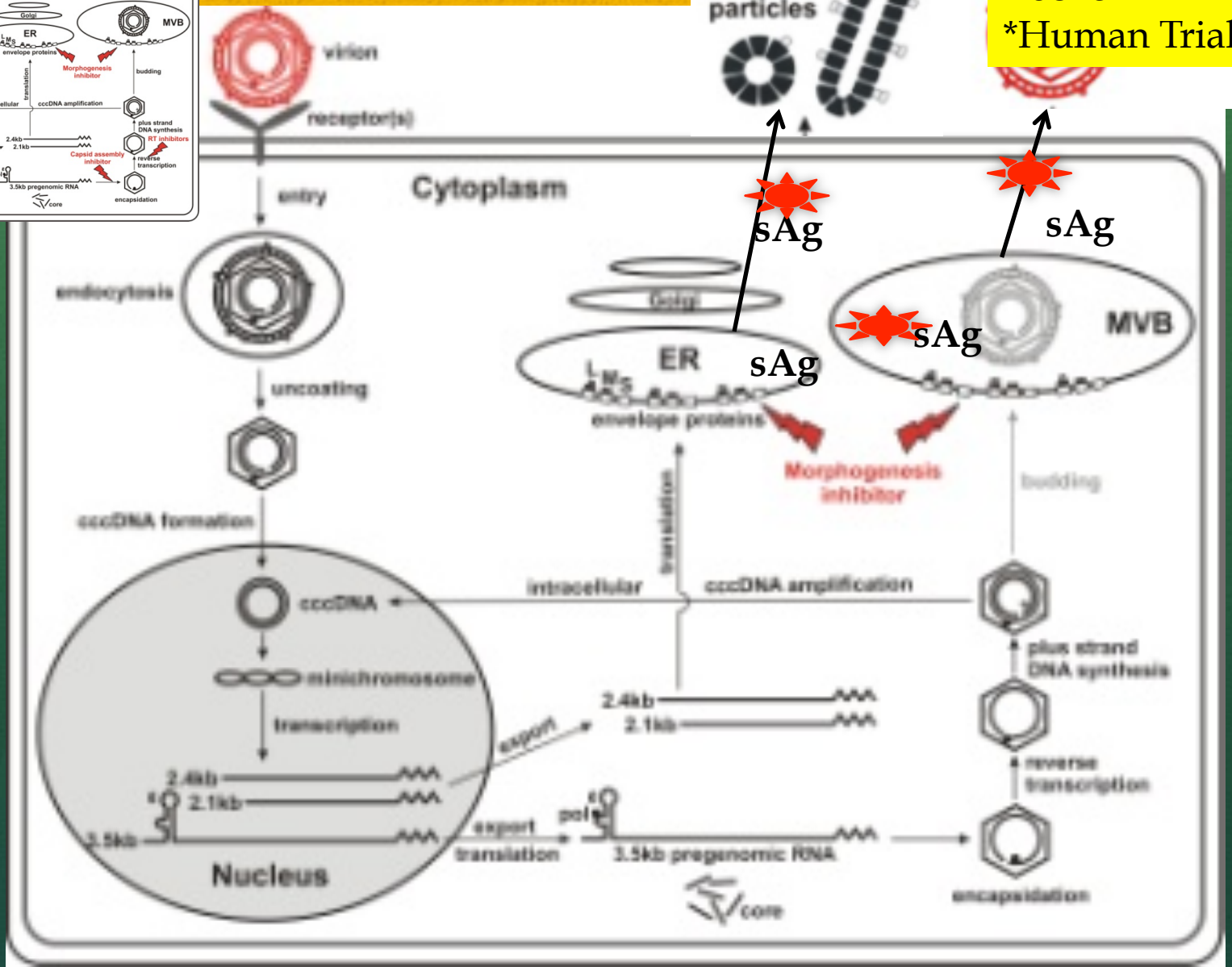



Pol
Capsid
Envelop
HBV mRI
Cytoplasm
pgRNA-
containing
capsids

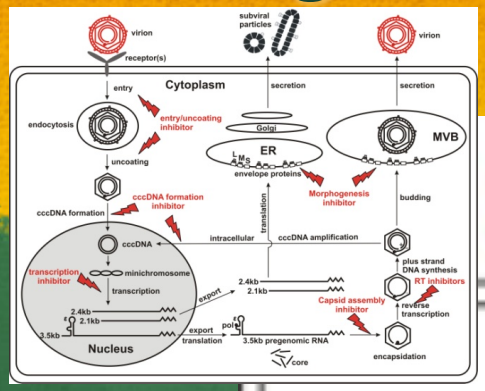
sAg inhibition

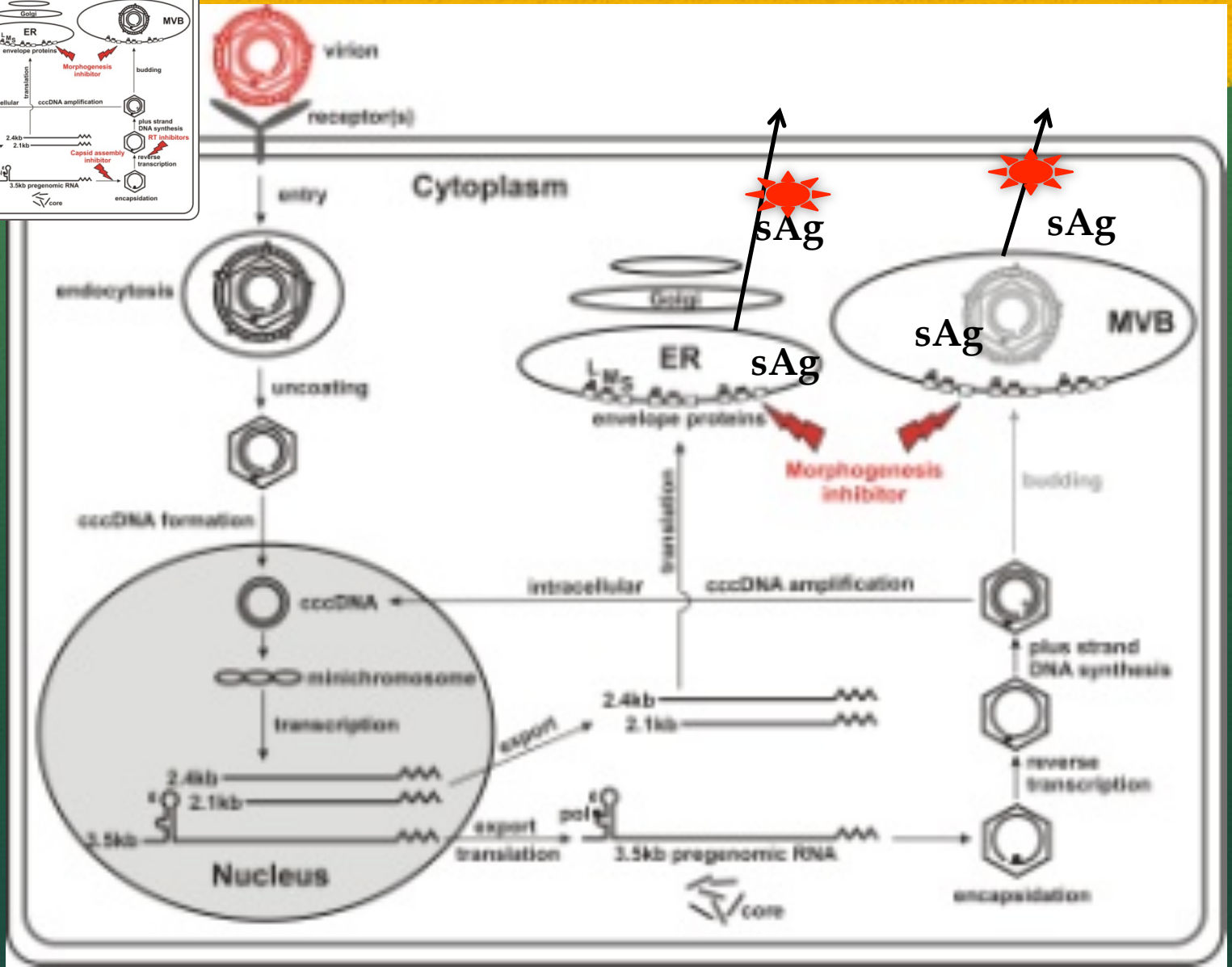
sAg Inhibitor
Replicor Rep2165
Arbutus ARB
Roche*
*Human Trials





sAg inhibition: antiviral, anti-antigenemic, and ?immuno restoration





Hepatitis Delta Virus

- Needs co-infecetion with HBV
- Mycludex B and Eiger's Lornafarnib in human trials for HDV

Adaptive & Innate host defense

Adaptive
Gilead GS4774*
Inovio Roche INO1800*
Altimmune*
Transgene TG1050*

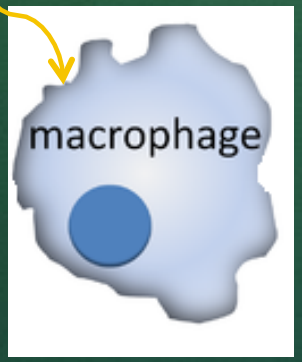
Innate
Gilead Toll GS9620*
Roche Toll RO6884018*
SpringBank RIGI SB9200*
Arbutus STING A
Contravir Cyclophil CPI421

*Human Trials

T cells (exhausted)

B cells (No detectable Antibody to HBs)

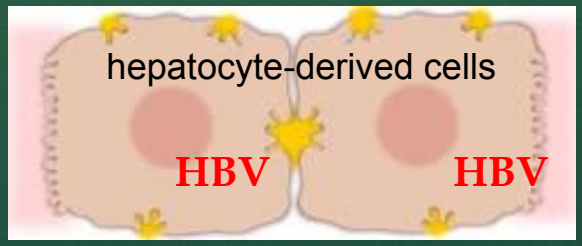
Indirect treatment



RAW 264.7 cells

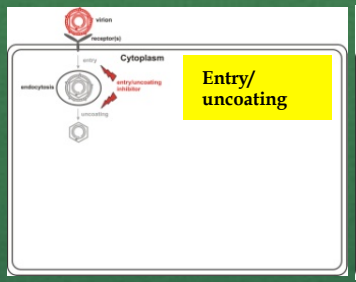
Two cell chamber transfer

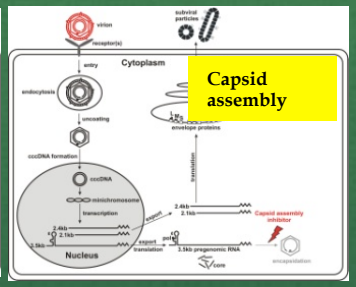
Awaken, stimulate

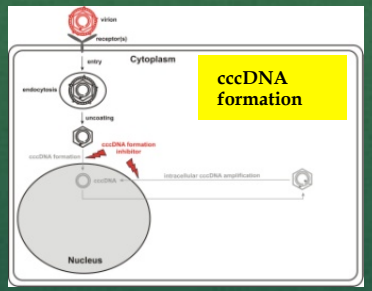


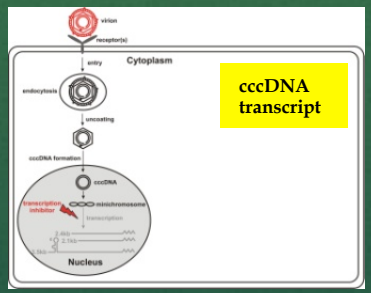
Inhibiting the virus life cycle at any step should be equal in eliminating infection

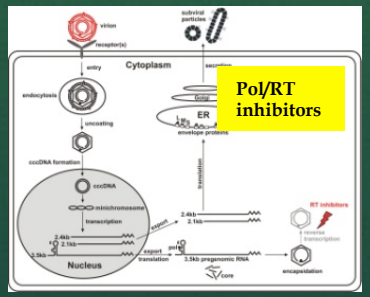
Break HBV down in to at least 12 different “assayable”, “targetable” steps
Grouped in to 6, here…

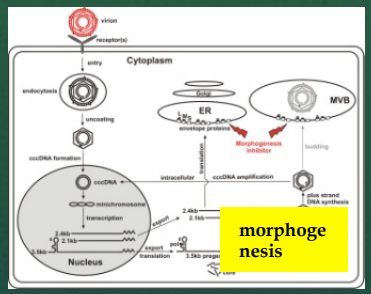




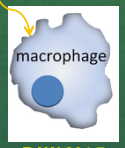








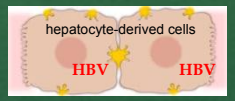
Indirect treatment



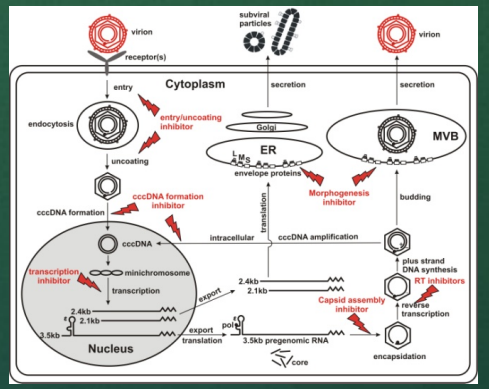
RAW 264.7 cells

Two cell chamber transfer

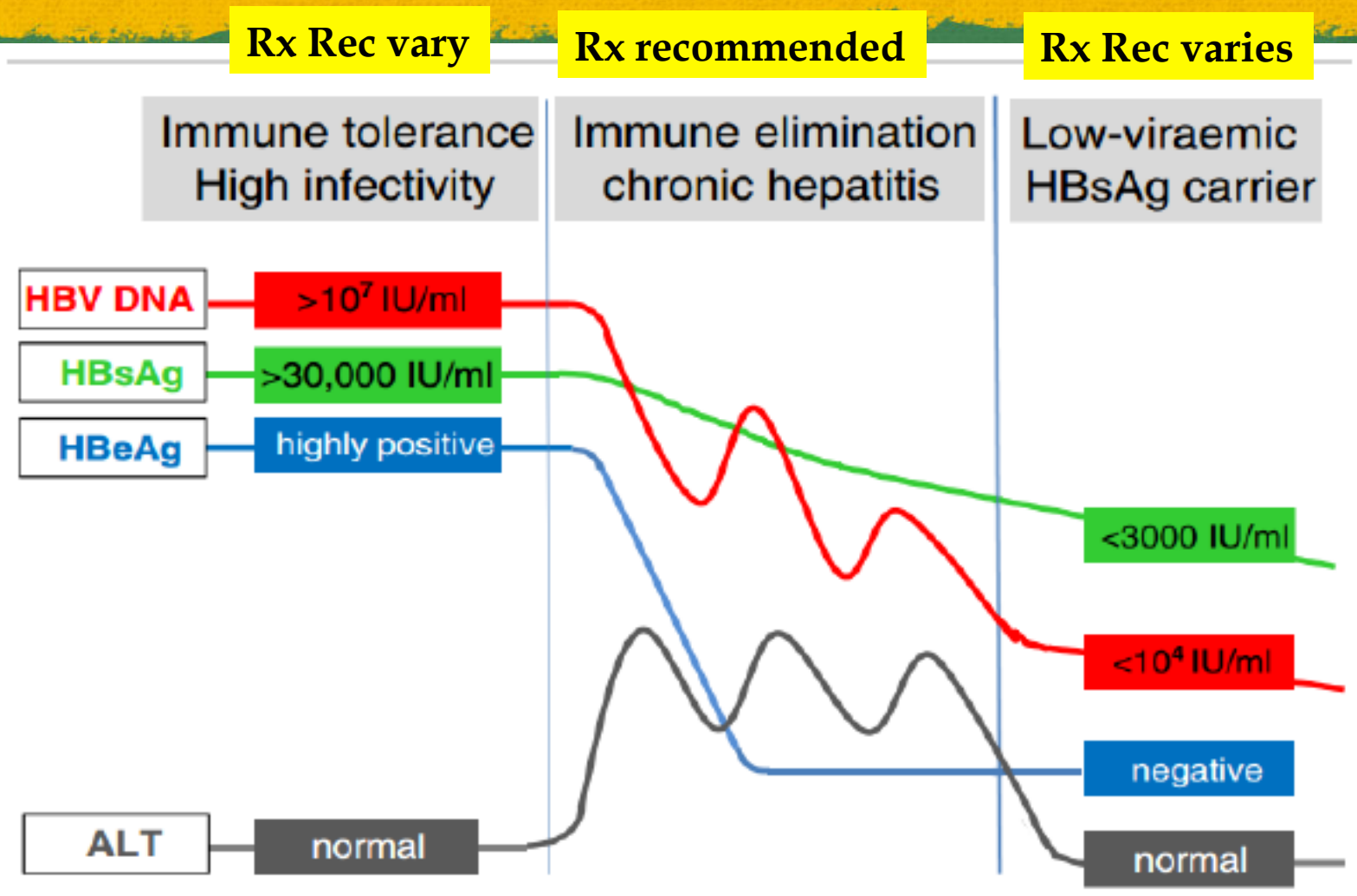
Innate host



Selective
elimination



Current Guidelines

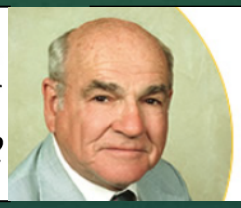


Source: Gerlich, W. 2013. *Virology Journal*, 10:239

Hepatitis B Foundation Goal

- No one will die from HBV by 2030
- A cure is possible, necessary, and expected

Hepatitis B Foundation
Cause for a Cure



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