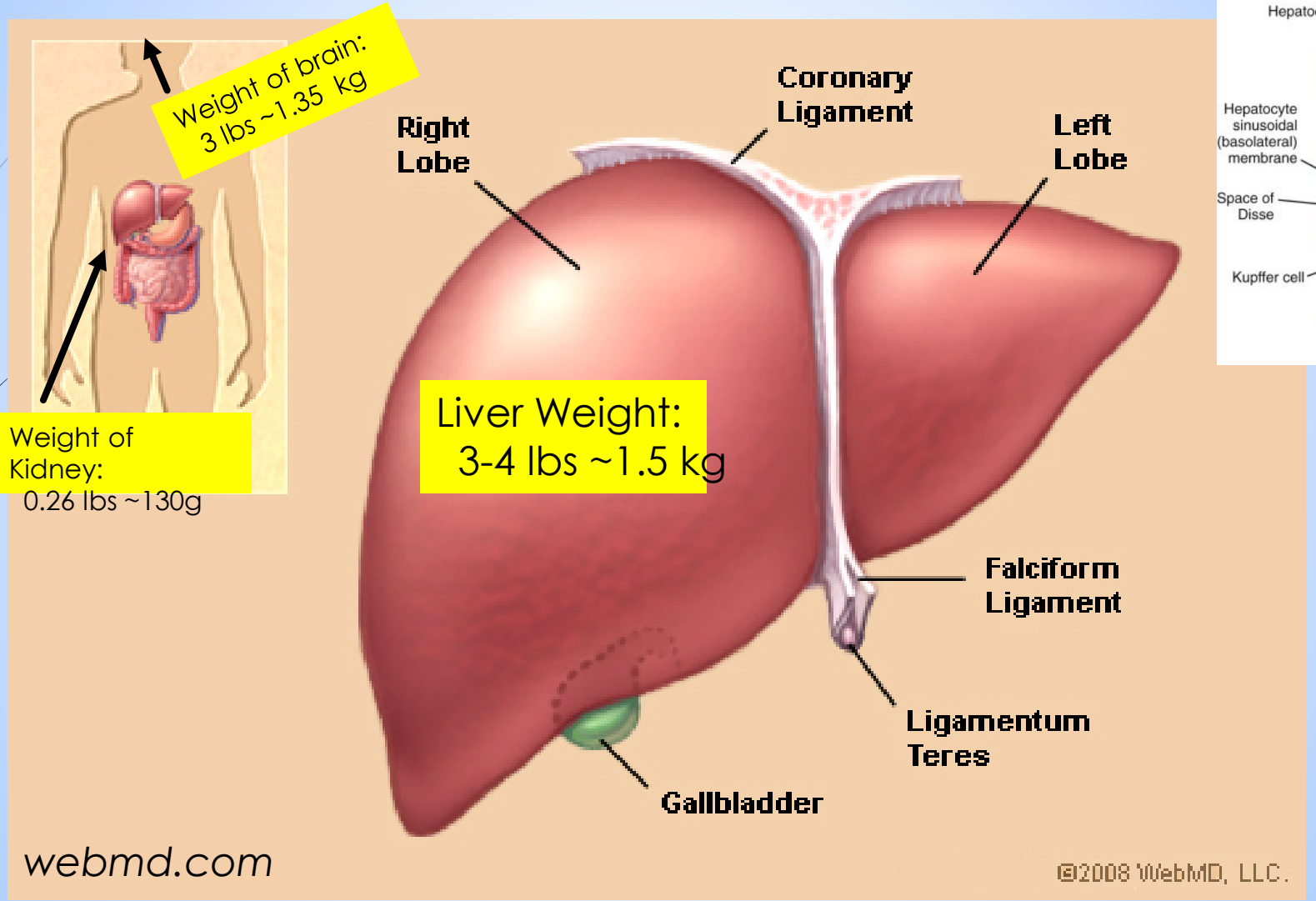
Investigational therapies for chronic hepatitis B : will anything really work?

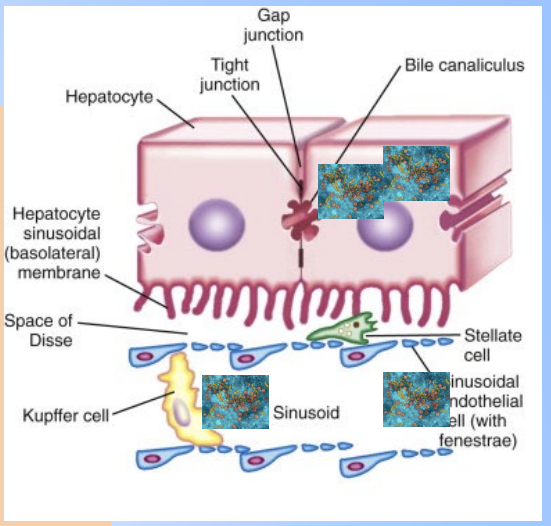
- This presentation will:
  - Describe the basis of therapies for chronic HBV
  - Describe the new therapies in the pipeline for HBV

- Conflicts:
  - Arbutus BioPharma (grant)
  - Contravir Pharma (Board Member)

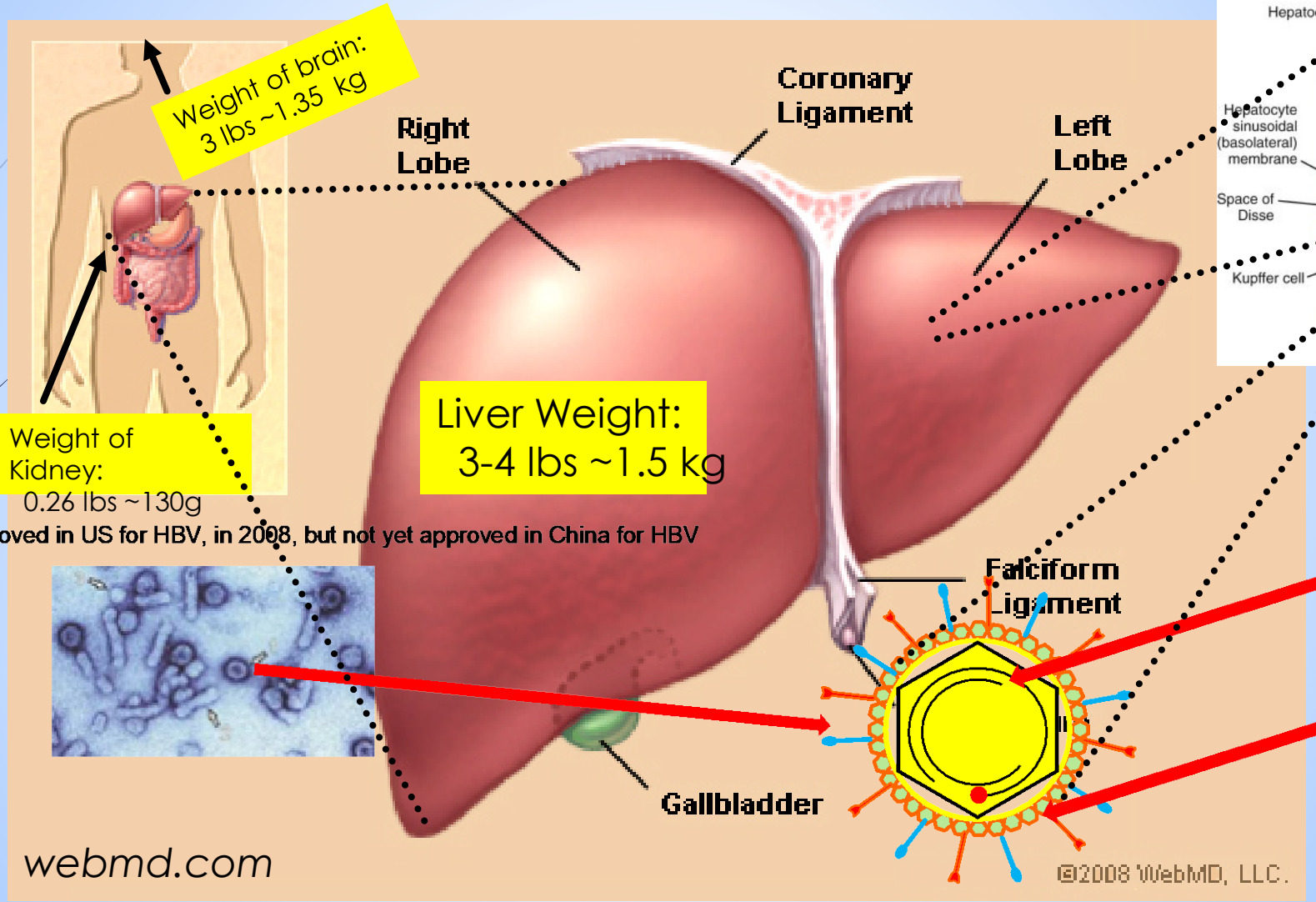
The secret lives of the hepatitis virus and hepatitis!

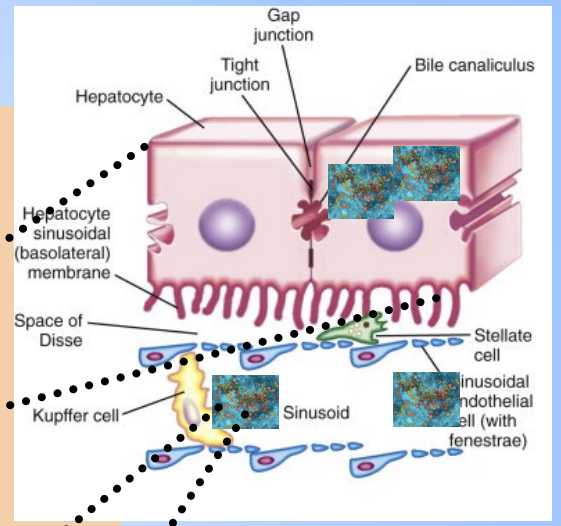
The Liver and hepatitis B





The Liver and hepatitis B





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

HBc / Core

S / Envelope

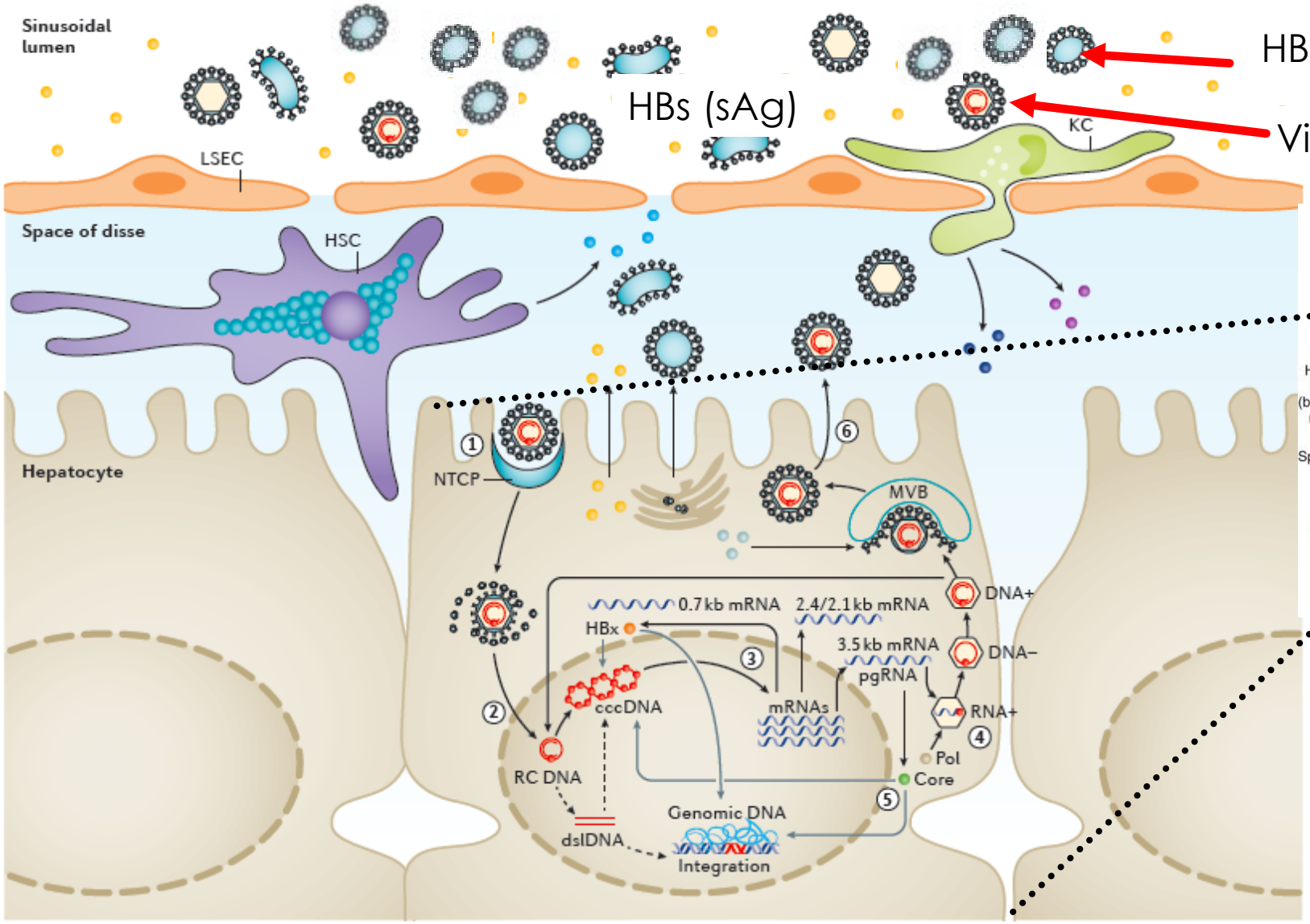
X, Other

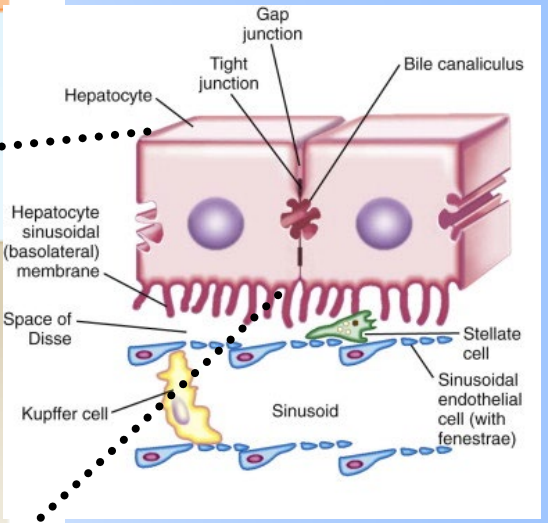
All DAAs act on the polymerase (POL)

Revill, Testoni, Zoulim, Locarnini (2016) Nat Revs Gast&Hep

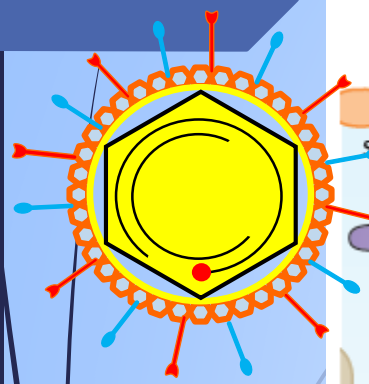
HBs (sAg)

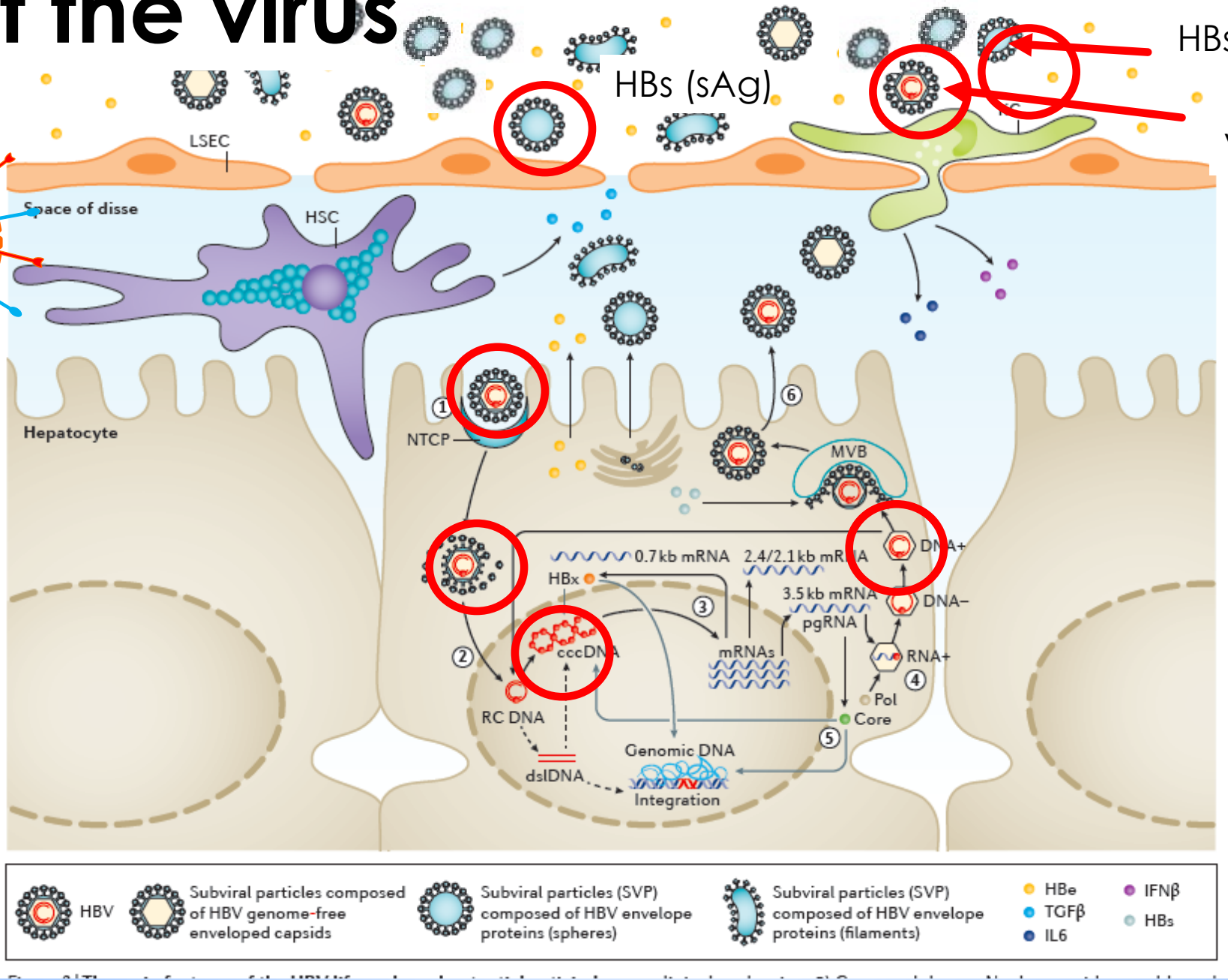
Virions (DNA containing)





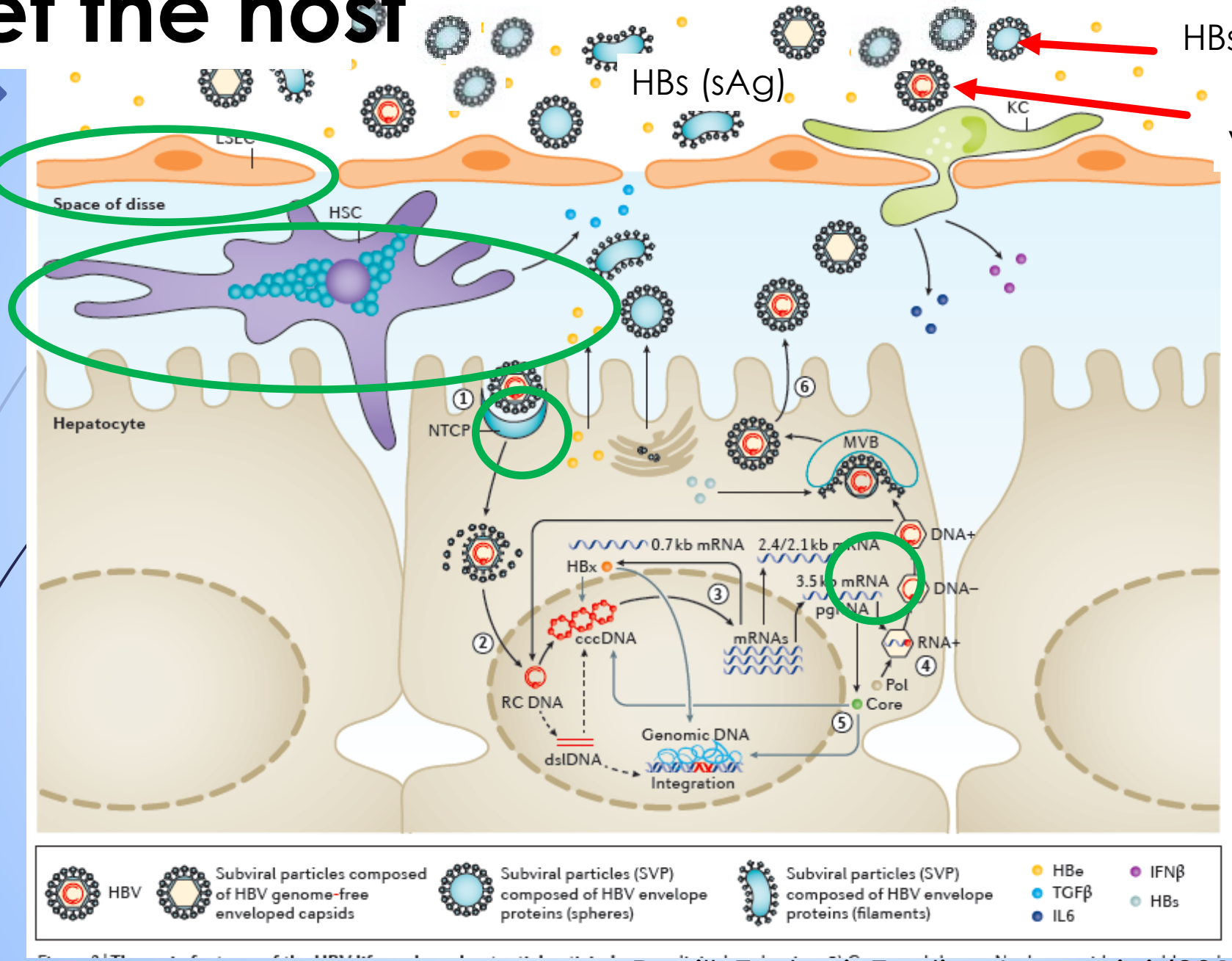
Target the virus





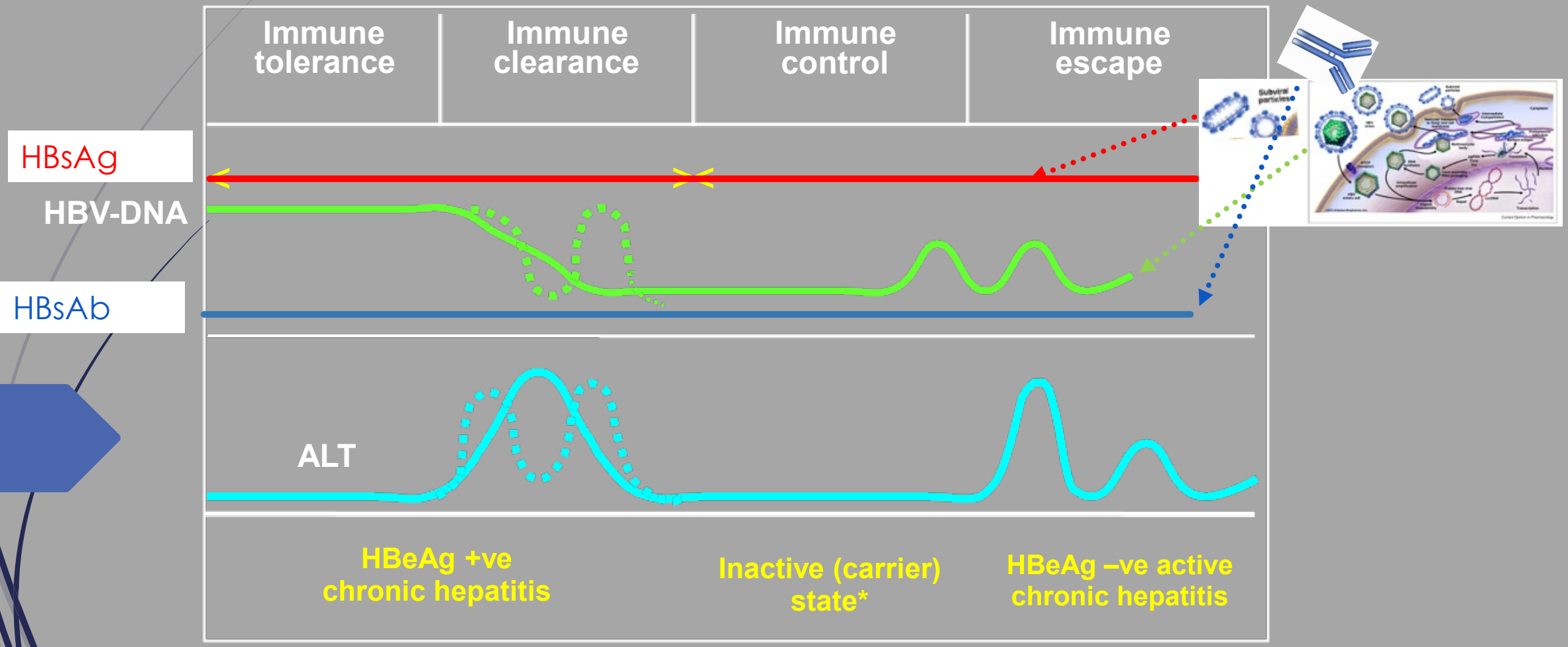
Revill, Testoni, Zoulim, Locarnini (2016) Nat Revs Gast&Hep

Target the host



Revill, Testoni, Zoulim, Locarnini (2016) Nat Revs Gast&Hep

The phases of chronic hepatitis B

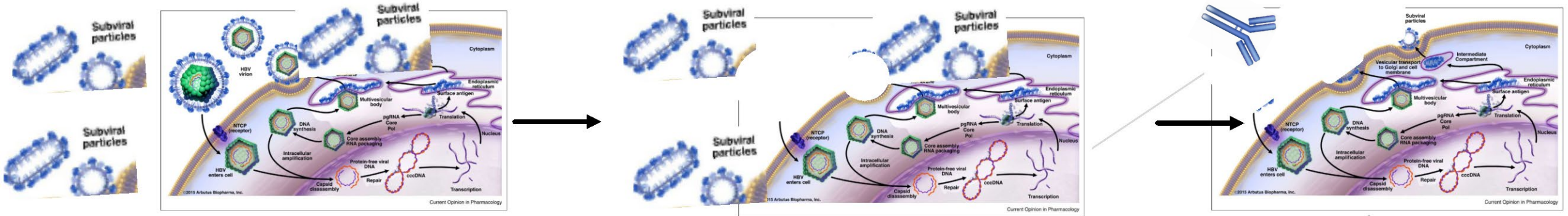


*Previously considered to be ‘healthy carriers’

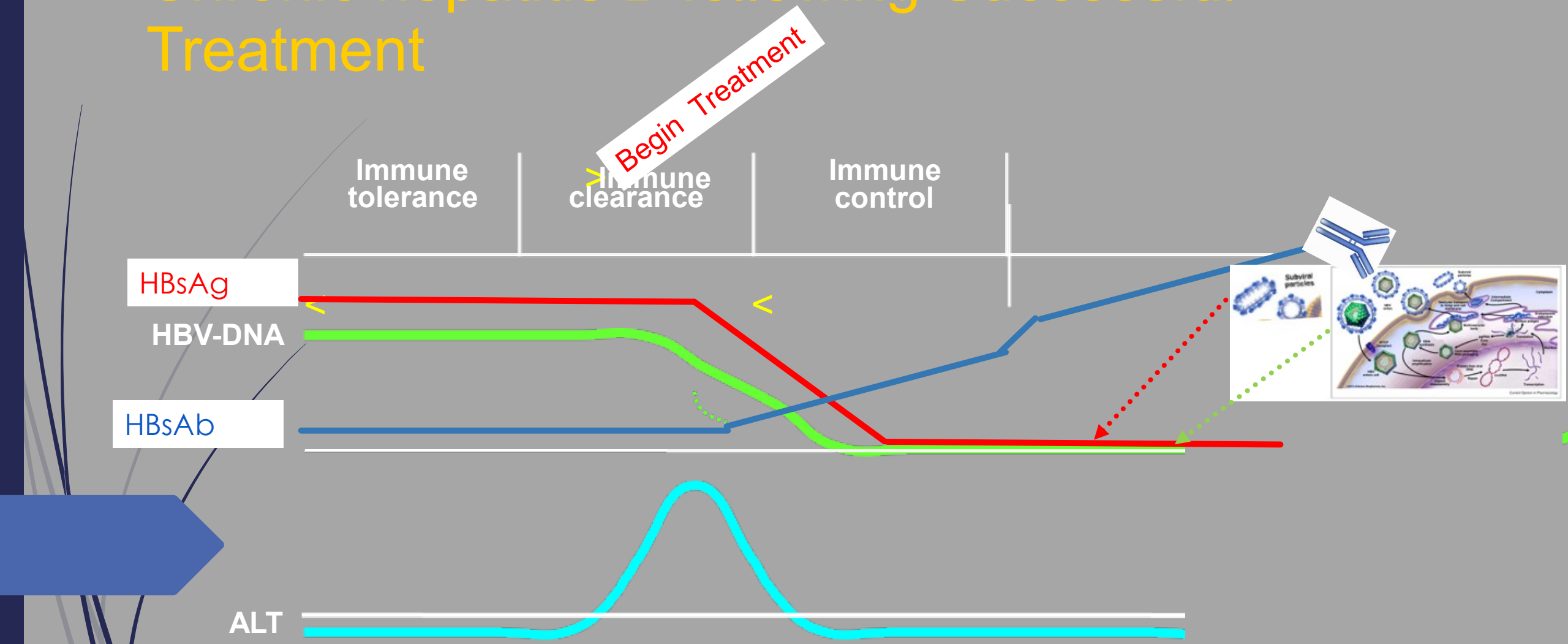
Treatment goals

- Clinically: reduce (eliminate) the clinical consequences of chronic hepatitis B
- Surrogate end points:
  - Eliminate detectable viremia
  - Normalize circulating levels of liver derived enzymes (ALT, AST)
  - Reduce HBs antigenemia
  - Sustained, off drug, beneficial antiviral affect

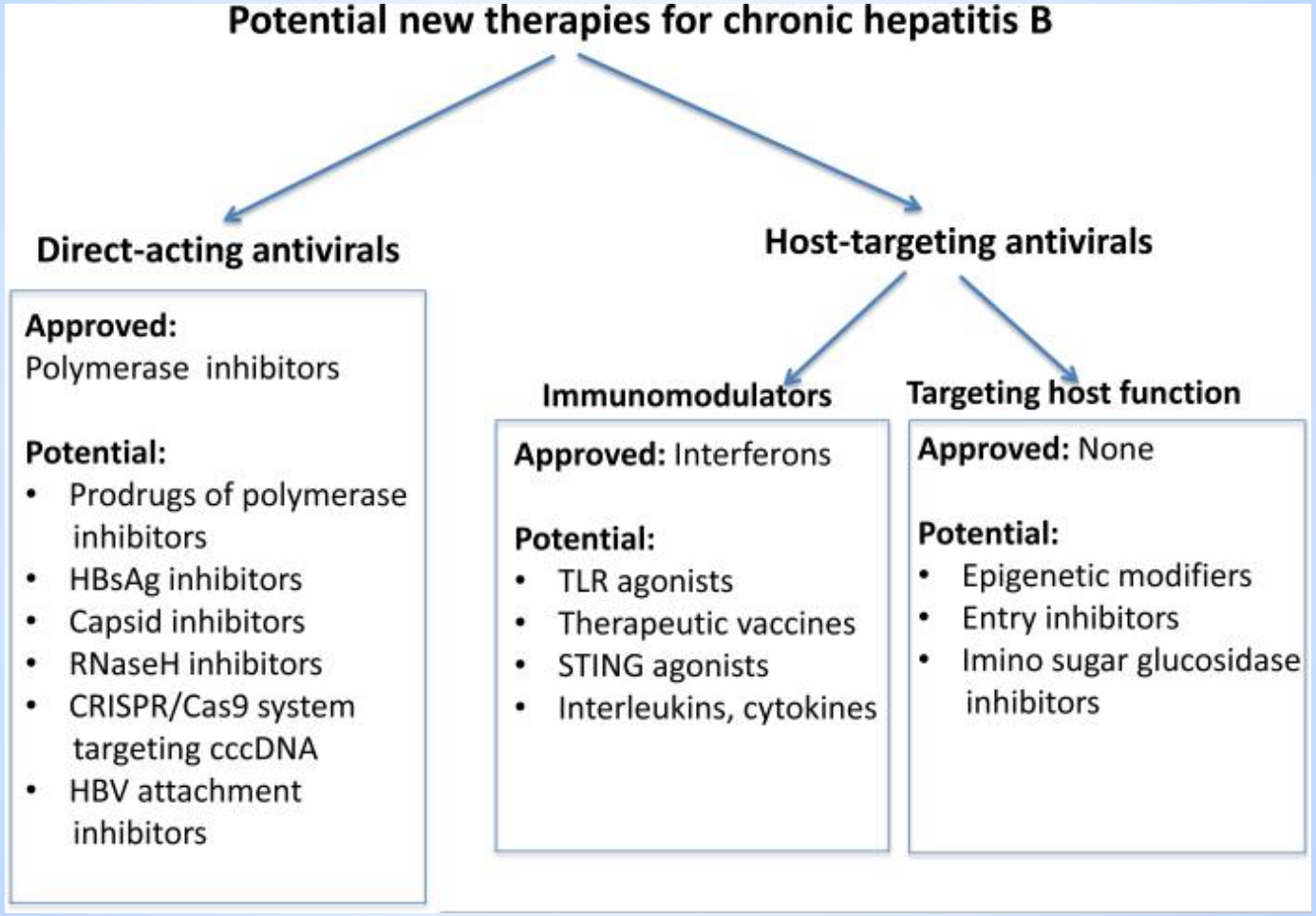
New DAAs: HBs suppressed



Chronic hepatitis B following Successful Treatment



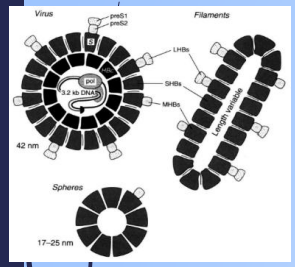
*Previously considered to be ‘healthy carriers’


Potential new therapies for chronic hepatitis B
Direct-acting antivirals
Approved:
Polymerase inhibitors
Potential:
• Prodrugs of polymerase inhibitors
• HBsAg inhibitors
• Capsid inhibitors
• RNaseH inhibitors
• CRISPR/Cas9 system targeting cccDNA
• HBV attachment inhibitors
Host-targeting antivirals
Immunomodulators
Approved: Interferons
Potential:
• TLR agonists
• Therapeutic vaccines
• STING agonists
• Interleukins, cytokines
Targeting host function
Approved: None
Potential:
• Epigenetic modifiers
• Entry inhibitors
• Imino sugar glucosidase inhibitors

The HBV Investigational Development Landscape as of 4. 2005

Pre-clinical

Human Phase Trials



DAA

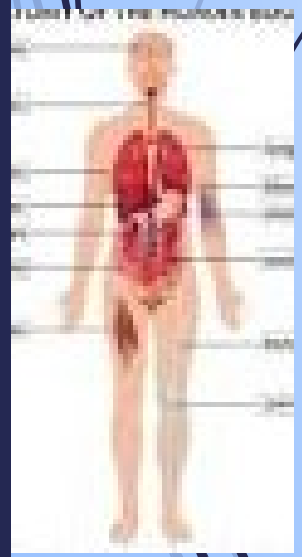
Isis HBV antisense

ARC520 RNAi

Rep2139 sAg

TTP sAg

?Bay41109 capsid



Indirect Host modifier

Editope

DV501 Vac

Indirect Immunomodulator

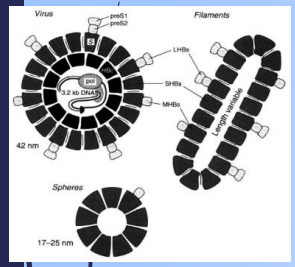
Chimgene HBV

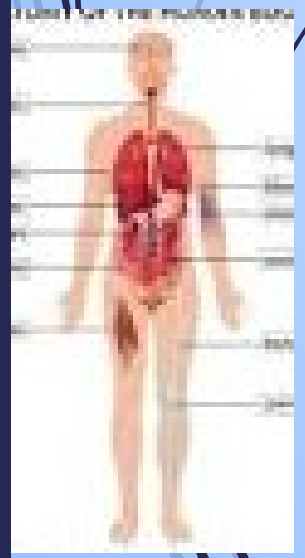
GS4774 vac

Inovio HBV

*HDV active

The HBV Investigational Development Landscape as of 4. 2010





Pre-clinical

Human Phase Trials

TAF

DAA

ARB-423 capsid

Roche 7834 (sAg)

Isis HB antisense

ARC520 RNAi

Rep2139 sAg

TTP sAg

NV100

?Bay41109 capsid

Benza capsid

CpAMS capsid

ALN-HBV

Indirect Host modifier

Lonafarnib*

Editope

DV501 Vac

HDAC

Brinipri nt SMAC

HepTcell

CAR

Indirect Immunomodulator

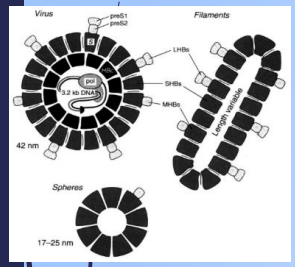
Chimgene HBV

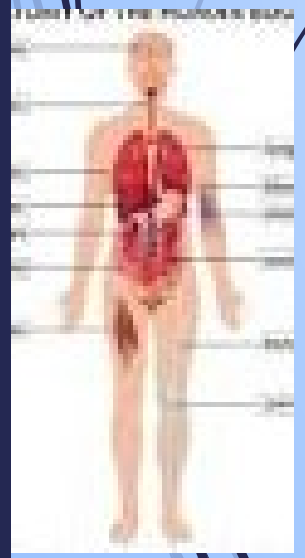
GS4774 vac

Inovio HBV

*HDV active

The HBV Therapeutic Development Landscape as of 4. 2015





Pre-clinical

Human Phase Trials

DAA

Indirect Host modifier

Indirect Immunomodulato

RNase Hi

Roche 7834 (sAg)

ARC520 RNAi

TAF

Isis HBV antisens

ARB-423 capsid

GLS-4 capsid

TTP sAg

ABI 7031 capsid

TLX prodrug

VR1221 capsid

DVR capsid

Benza capsid

?Bay41109 capsid

Rep2139 sAg

ALN-HBV

CpAMS capsid

AGX100

CRISPCAS (intel)

cccDNA forma

ddRNAi HBV

Roche 7834

ARB1740,&1467

MycB entry*

NV100

Brinipri nt SMAC

Edito

CTR431

SB920

Lonafarnib*

HDAC

Roche 7795

HepTcell

CAR

Chimgene HBV

GS4774 vac

GS9620 TLR7

TG1050

Tomega vax

DV501 Vac

STING

Inovio HBV

*HDV active

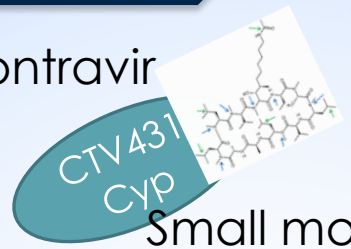
Entry

- Pros:
- Clinical validation
- Anti-HDV
- Stops life cycle from the beginning

Pre-clinical

Human Phase Trials

Contravir

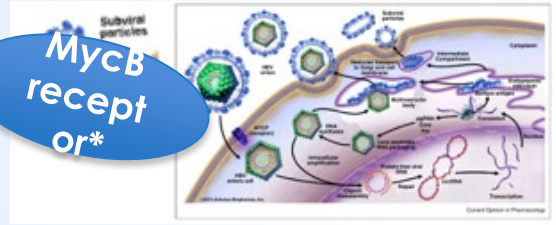


Small mol, oral

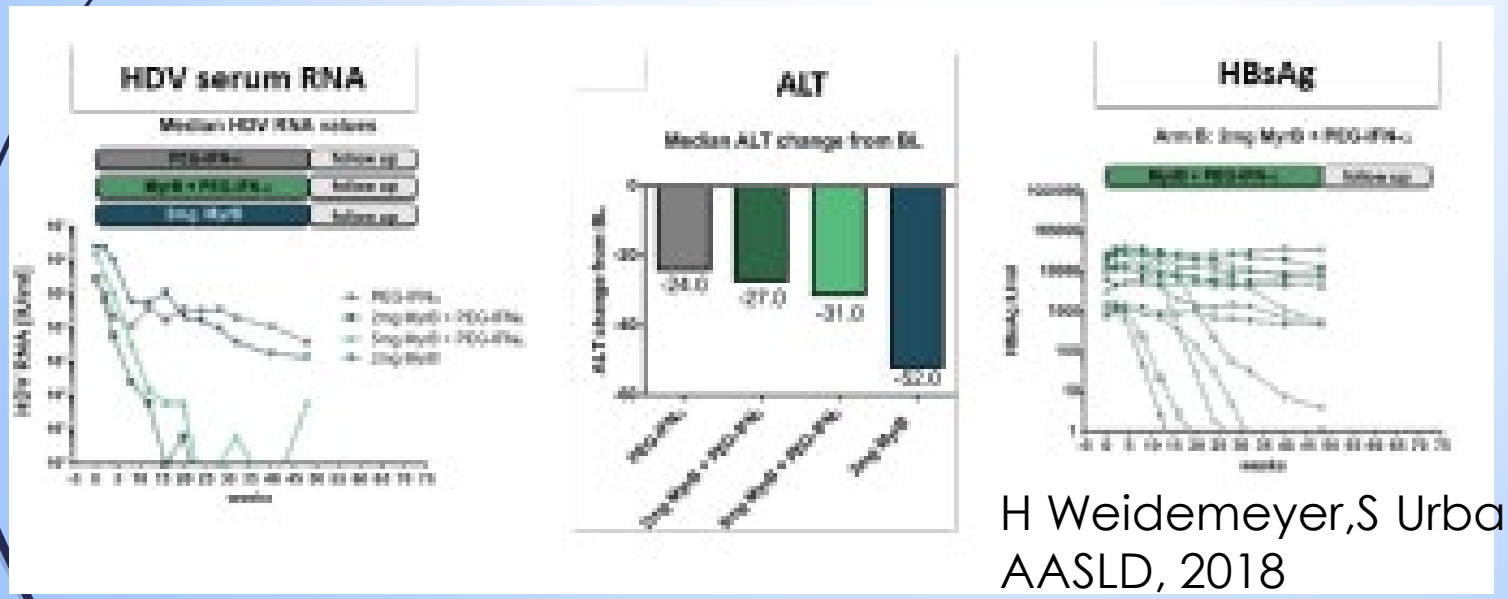
Heptera

MycB entry*

Peptide, iv



- Cons:
- Doesn't affect established infection
- MyrB: NTCP receptor targeted (?affect on bile)
- CTR432: cell chaperons affected (tox?)

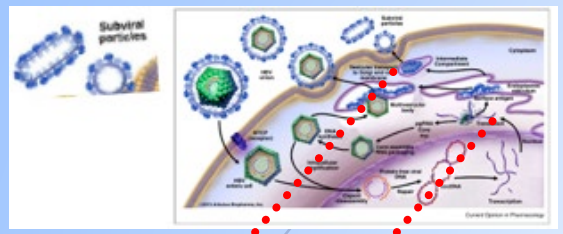


H Weidemeyer,S Urban
AASLD, 2018

Capsid/Core modifiers/uncoating

Pre-clinical

Human Phase Trials



Benza capsid

CpAMS capsid

Novartis

Roche

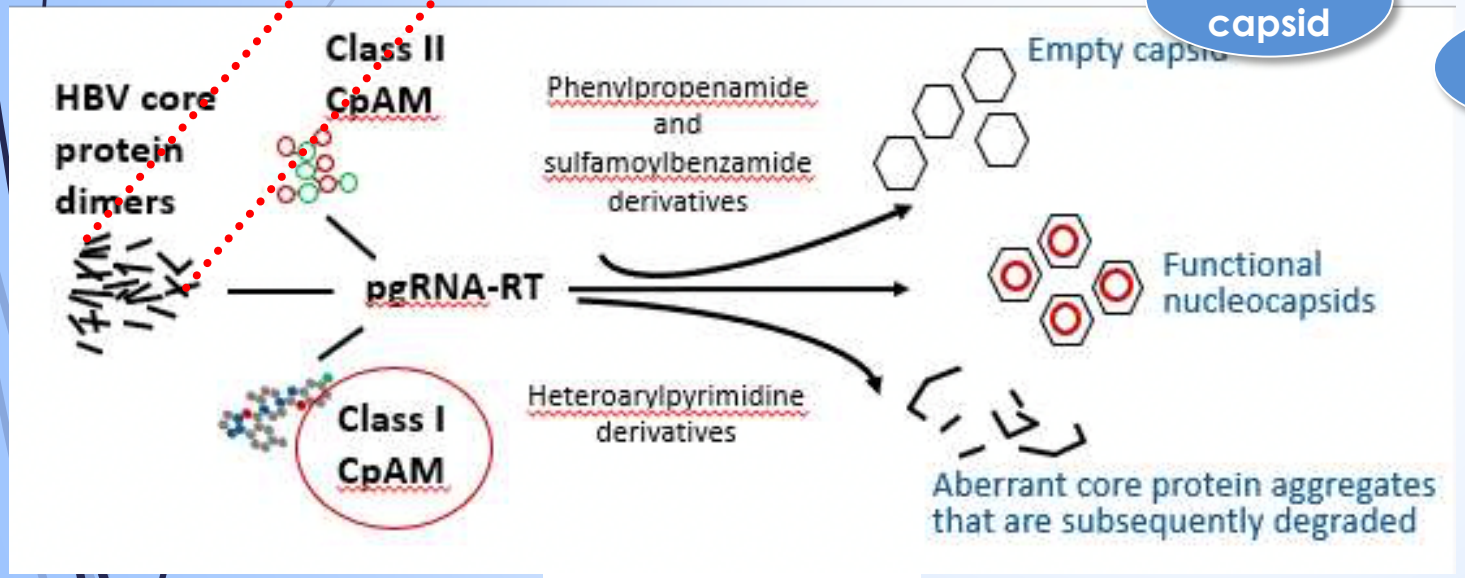
ARB-423 capsid

ABI 7031 capsid

GLS-4 capsid

J&J capsid

?Bay411 0? capsid

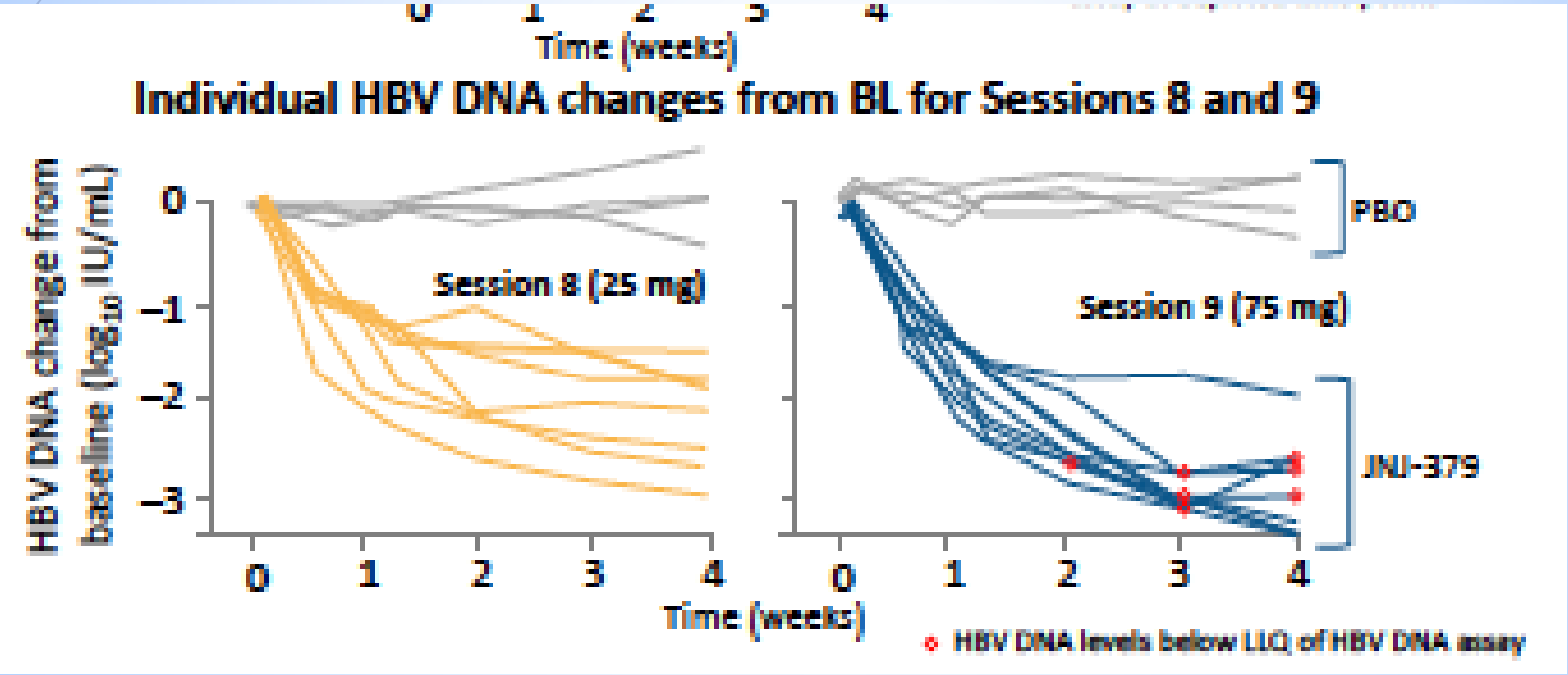


Programs:
Assembly
Blumberg/Arbutus,
Novartis
Novira
Roche
Sunshine

Pros
Multiple, Essential viral function
Validated clinically
Extra-virological affects?
Escape mutants rare

Cons
?replication inhibitor
Resistance possible

Capsid/Core modifiers/uncoating



Wang J, et al. AASLD 2018, Washington DC. #937

HBs Ag inhibitors

Pre-clinical → Human Phase Trials

DAA

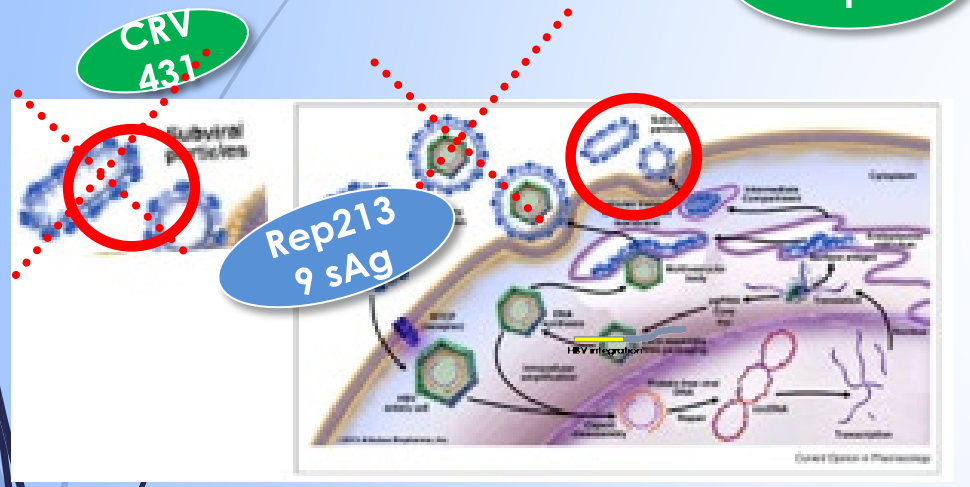
TTP sAg

BSBI 259 sAg

CRV431

CRV431

Rep2139 sAg

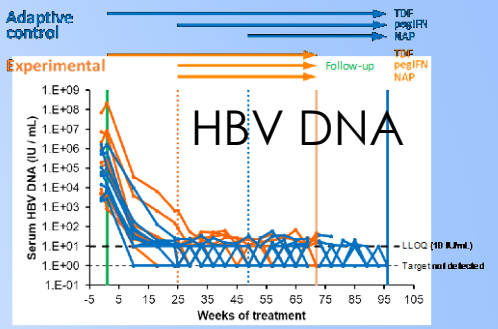


Rep2139 sAg

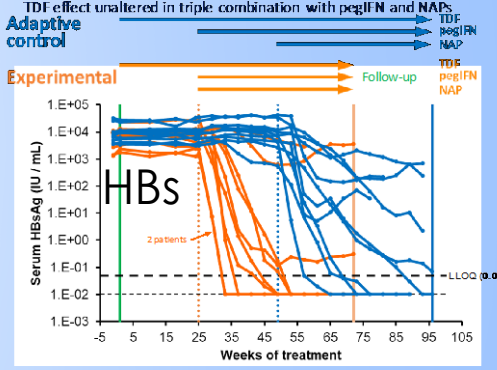
Programs:
Blumberg/ Arbutus,
Contravir
Replicor

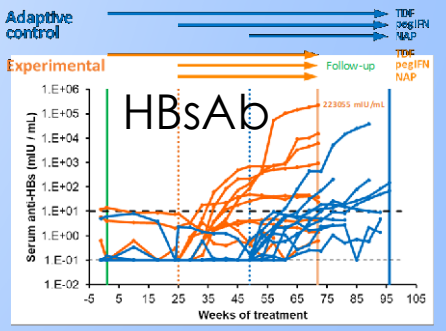
REP 2139 on-treatment antiviral response

Courtesy: A Vailliant



TDF effect unaltered in triple combination with pegIFN and NAPs



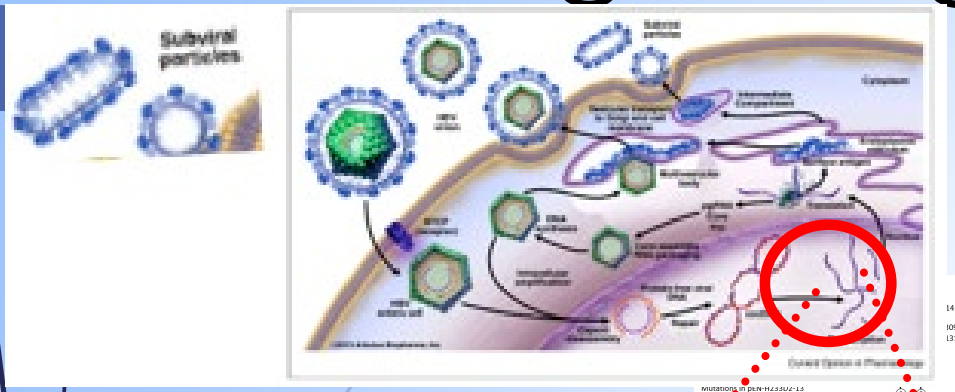


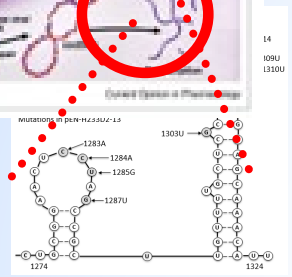
Elevation in serum anti-HBs correlated with extent of HBsAg reduction

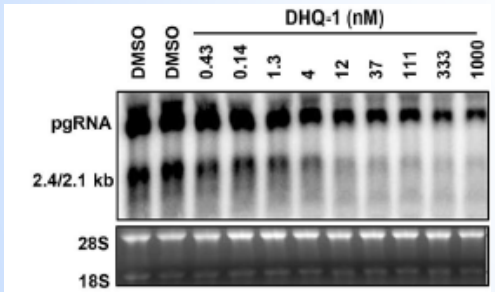
See: Al-Mahtab M, Bazinet M, Vaillant A (2016) PLoS ONE 11(6):e0156667

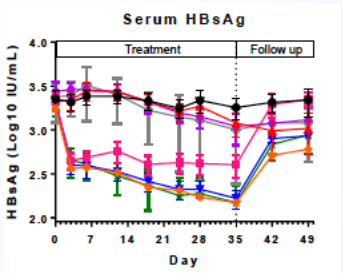
RNA Degrading

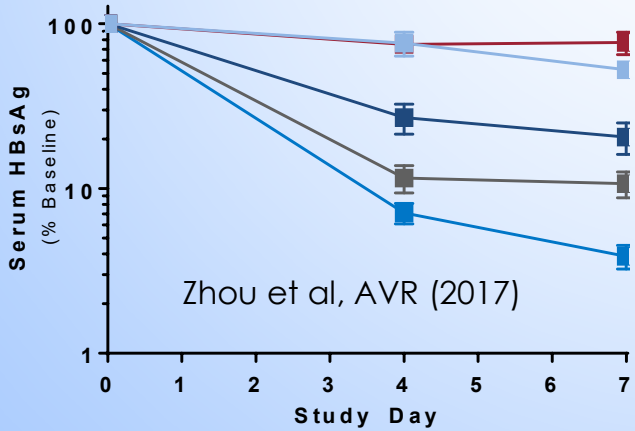
Pre-clinical



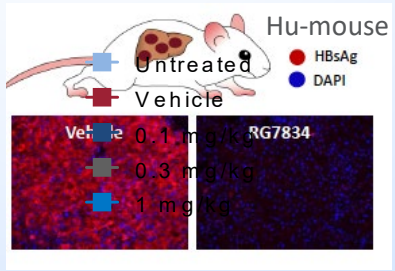




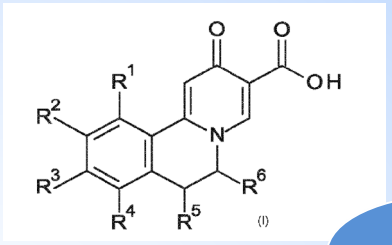




Zhou et al, AVR (2017)



Mueller et al, , J.Hep (2017)



Roche DHQ

AB452

Arbutus

siRNA

Pre-clinical

Human Phase Trials

DAA

ARC RNAi

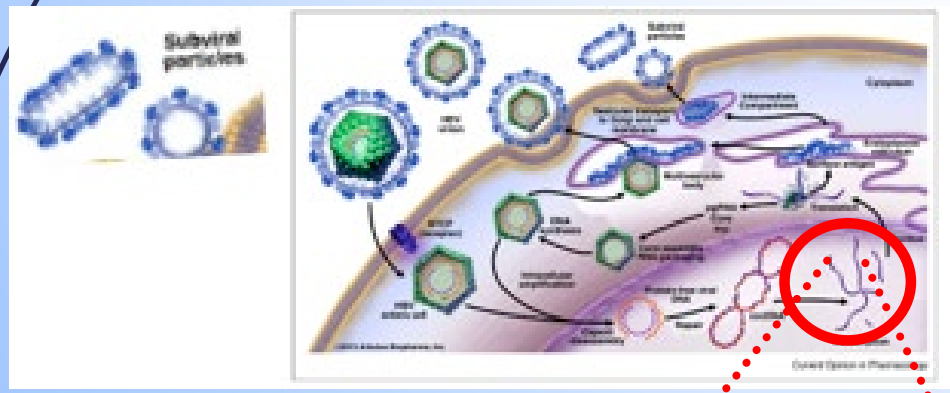
ALN-HBV

CRISPCAS (intel)

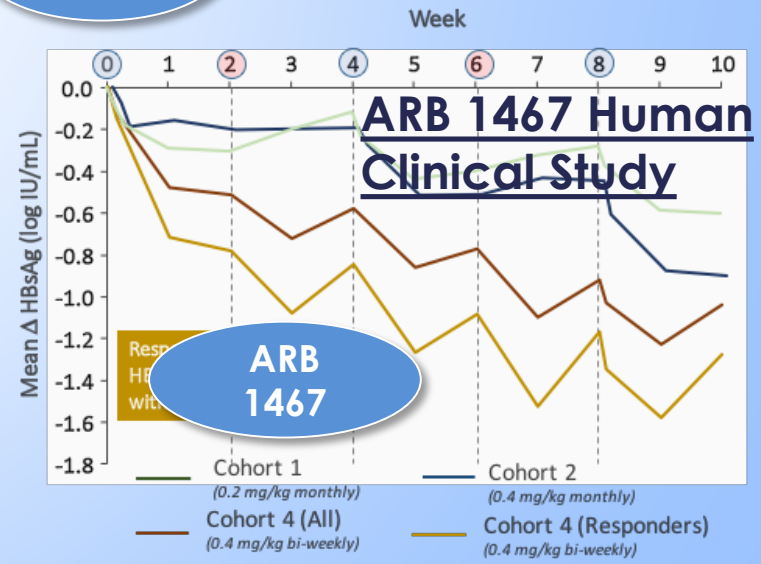
cccDNA forma

ARB 1467

ARC RNAi

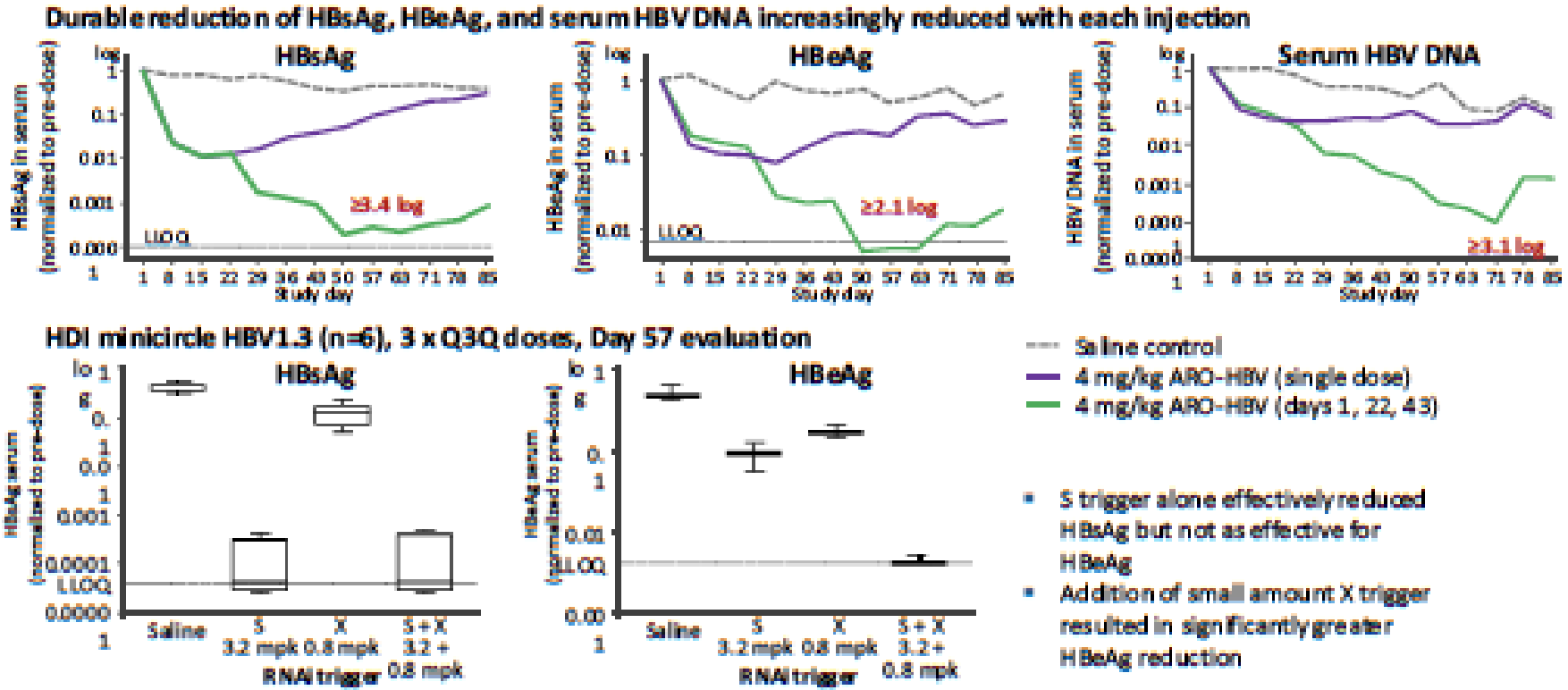


siRNA



Development of subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection

Arrowhead Human Clinical Study



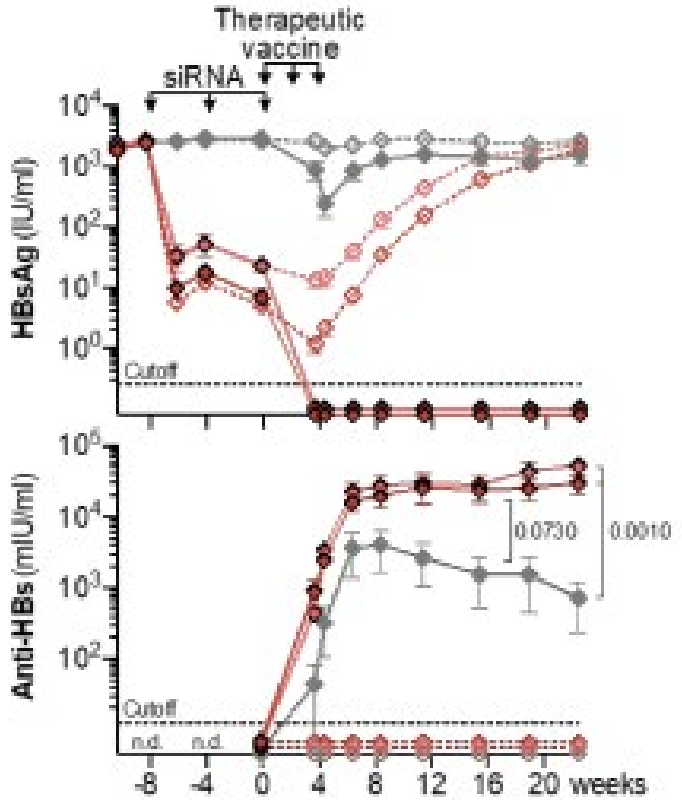
Wooddell C, et al. EASL 2018, Paris. #PS030

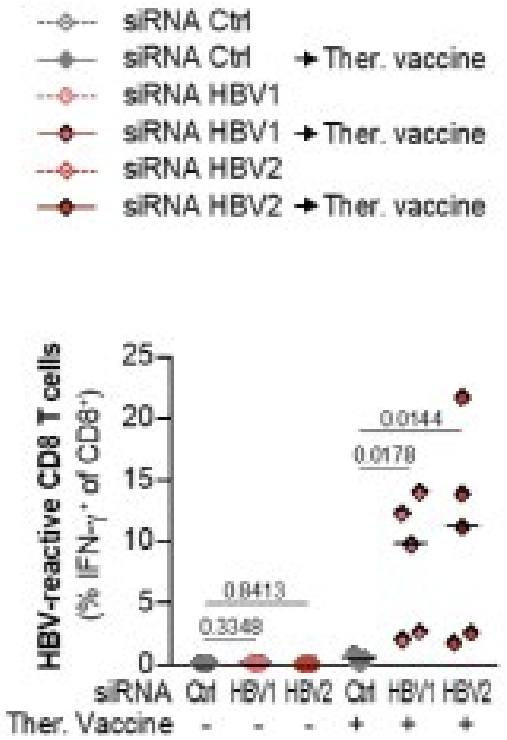
Acknowledgement: IHEP group

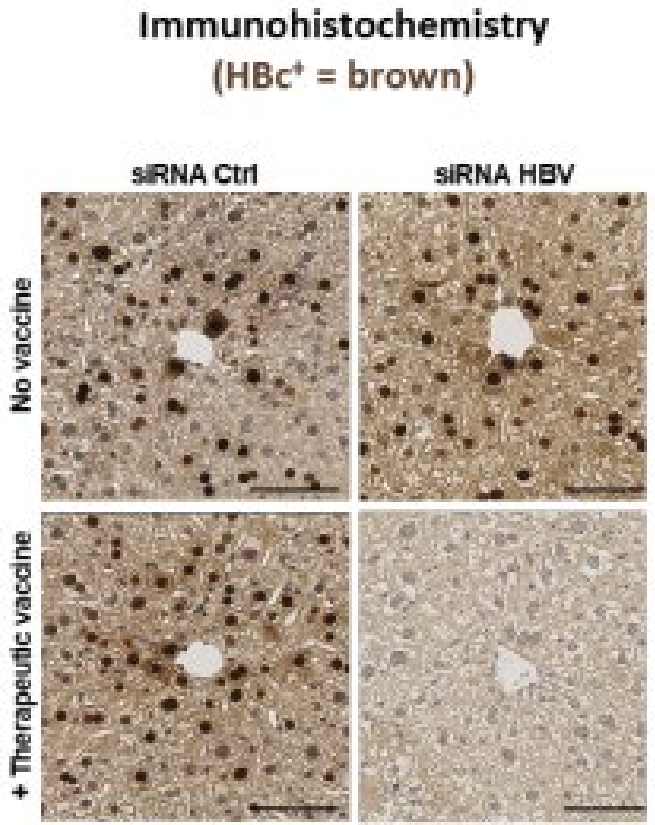
RNAi + Therapeutic vaccination (AAV model)

Arrowhead Pharma

reduces HBs







T. Michler AASLD 2018

Pre-clinical

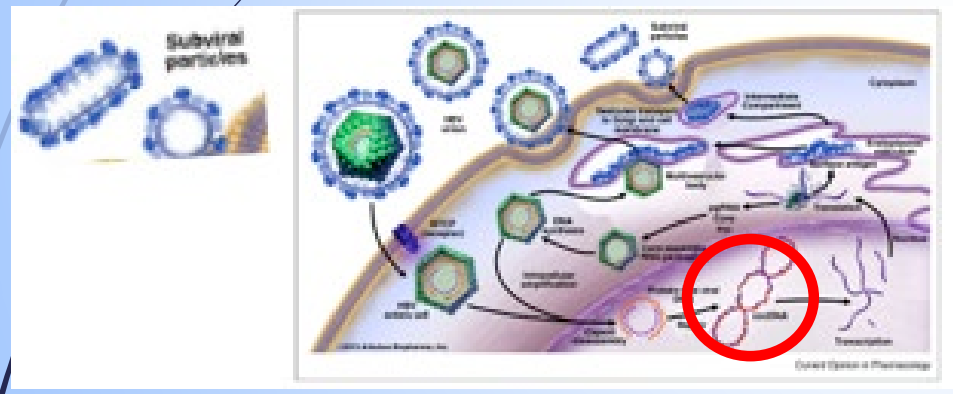
Human Phase Trials

cccDNA

CRISPCAS (intel)ia

CRISPR CoCrystal

BSBI (JT Guo)



Programs:

?Gilead, ?Arbutus, Assembly, ?Others

Blumberg, Fox Chase, Duke, Rockefeller

Immune Modulators as of Jan, 2017

Pre-clinical

Human Phase Trials

Programs:
Akshaya
Arbutus/Blumberg
BMS
Dynavax
Gilead
HepTcell
Inovio
Roche
Springbank
Tomegvax

Opdivo + GS4774

CAR

Chimgene HBV

Tomegavax

STING

SB9200

Roche 7795

HepTcell

GS4774 vac

GS9620 TLR7

TG1050

DV501 Vac

Inovio HBV

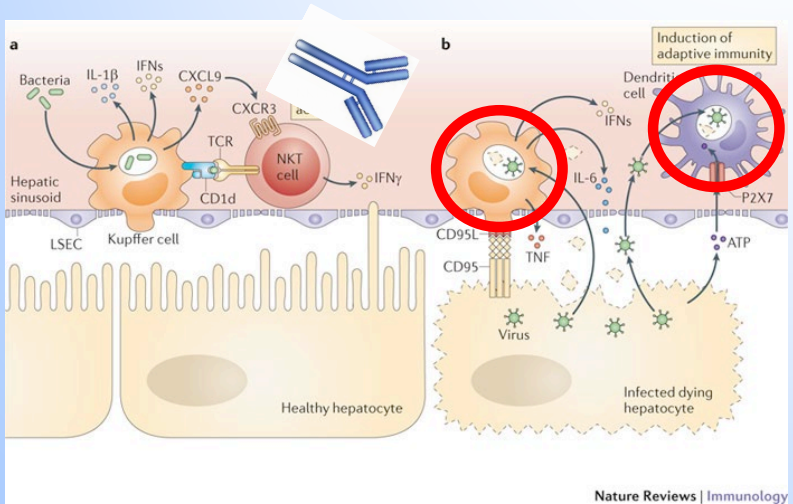


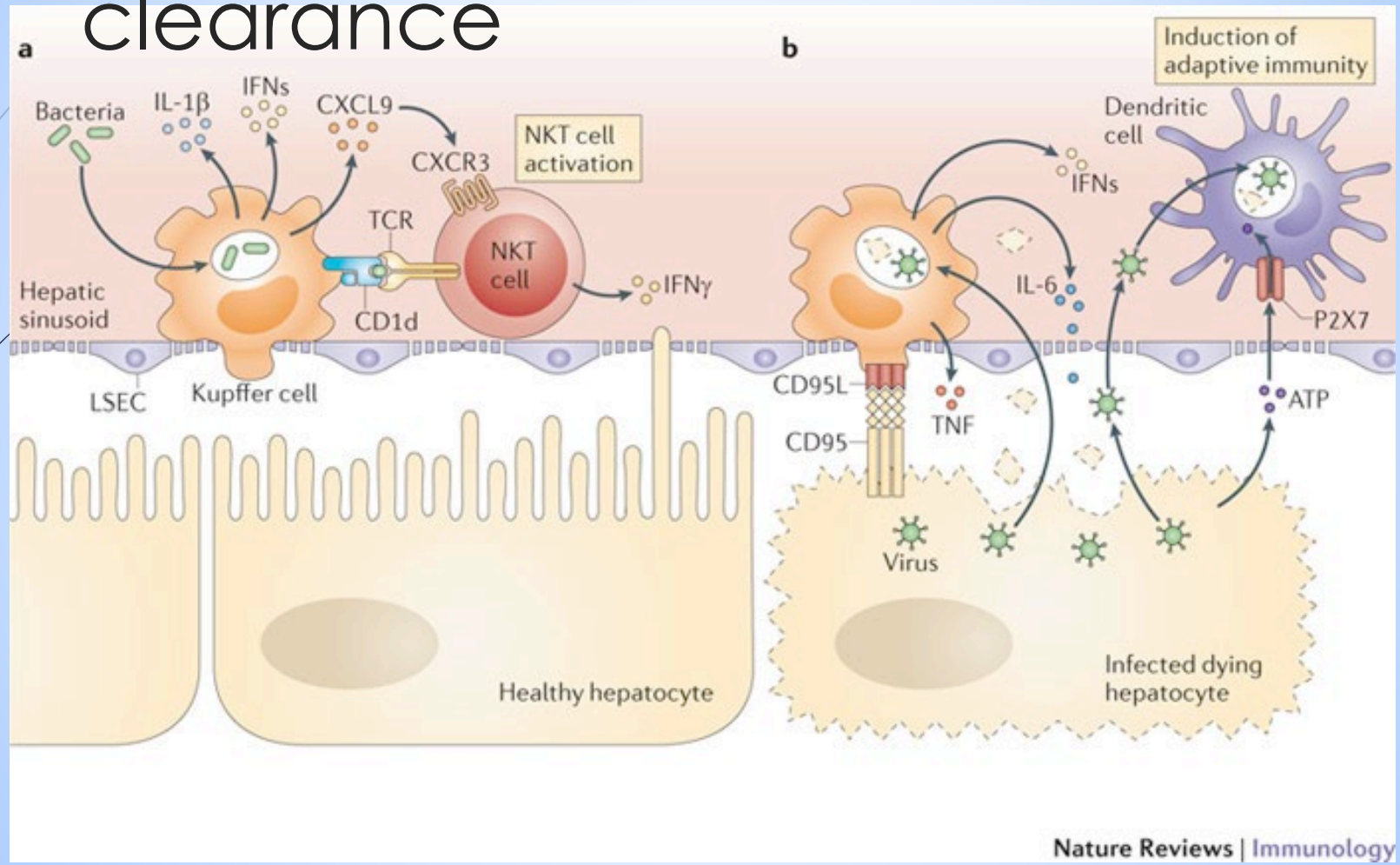
Table 1

Novel immunomodulatory therapies in clinical trials

Compound	Target mechanism	Phase	Available result	Sponsor	Reference
GS-9620	TLR-7 agonist	2	Well tolerated, peripheral ISG response but no detectable IFN, Phase 2 trial ongoing	Gilead Sciences	NCT02579382, NCT01590641, NCT01590654, NCT02166047 [56,59,60,61**,92,93,94]
Nivolumab (HCC and HBV)	PD-1 inhibitor	2	Recruiting	Bristol Myers Squibb	NCT01658878 [76]
SB 9200	RIG-1 and NOD2 activation	2	Recruiting	INC/Springbank	NCT02751996 [67,68]
KRN7000	NK activation	2	No clinically significant viral response, poorly tolerated	Foundation for Liver Research	NCT00363155 [82,88**]
Poly IC	TLR activator	4	Recruiting	Wuhan Union Hospital, China	NCT02532413 [85]
Thymosin + IFN	T cell, NK activator, cytokine production	4	Thymosin + IFN is not superior to IFN alone	Seoul National University Hospital	NCT00291616 [83,84]
GMCSF + IFN + Entecavir/Adefovir activated [illegible] cells	Enhance Ab response and T cell proliferation	3	Recruiting	Tongju Hospital	NCT02327416 [95]
[illegible]B02	Improved antigen presentation	2	Recruiting	Third Affiliated Hospital, Sun Yat-Sen University	NCT01935635, NCT02615639 [91]
	Therapeutic vaccine	2	Vaccine failed to improve off treatment viral suppression	French National Agency for Research on AIDS and Viral Hepatitis	NCT00988767, NCT00536627 [87,96**]
FP-02.2	Therapeutic vaccine	1	Recruiting	Altimmune, Inc.	NCT02496897 [97]
HB110E	Therapeutic vaccine	2a	Recruiting	Genexine	NCT01813487, NCT00513968, NCT01641536 [89]
Engerix-B	Therapeutic vaccine	1, 4	Recruiting	Chang Gung Memorial Hospital	NCT02505009, NCT01817725 [98,99]
TG1050	Therapeutic vaccine	1	Recruiting	Transgene	NCT02428400 [86*]
CVI-HBV-002	Therapeutic vaccine	2	Recruiting	CHA Vaccine Institute Co., Ltd.	NCT02693652 [100]
INO-1800	Therapeutic vaccine	1	Recruiting	Inovio Pharmaceuticals	NCT02431312 [101]
GS-4774	Therapeutic vaccine	2	No significant viral decrease in treatment experienced patients, Phase 2 trial of naïve group ongoing.	Gilead	NCT01943799, NCT01779505, NCT02174276 [83*,84*,102]
DV-601	Therapeutic vaccine	1	Well tolerated in small cohort, viral response was observed in all patients.	Dynavax	NCT01023230 [103,104,105**]
GC1102	Therapeutic vaccine	1	Recruiting	Green Cross Corporation	NCT02569372 [106]
ABX203	Therapeutic vaccine	3	Ongoing	Abivax S.A.	NCT02249988 [85*]
pPDPSC18	Therapeutic vaccine	1	Completed, result not reported	Powder Med	NCT00277576 [107]
IFN + IL2 + HepB vaccine	Vaccine with IFN and IL2	4	Recruiting	Tongji Hospital	NCT02360592 [82]

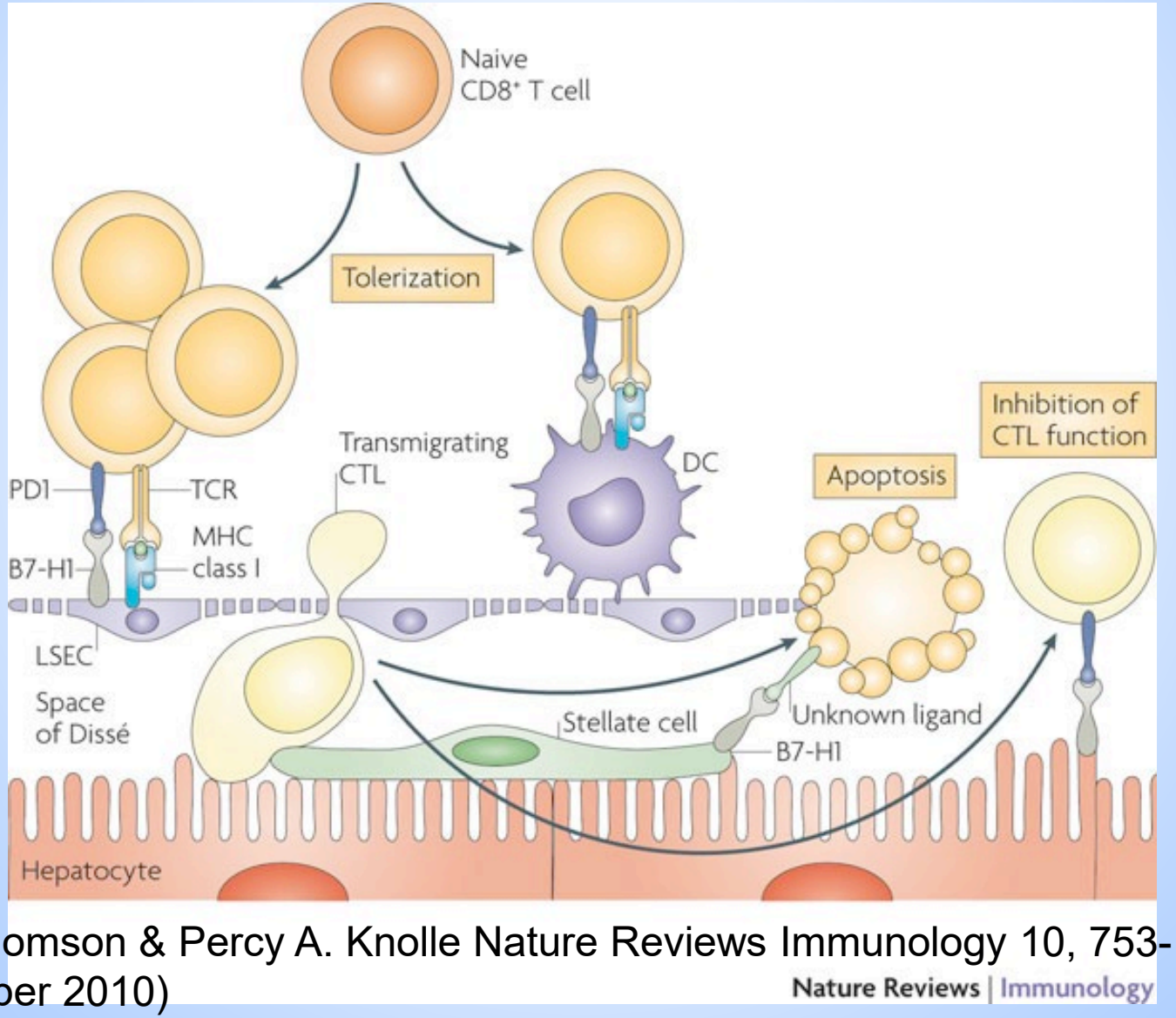
Chang & Liu, 2016

Normal induction of immune clearance



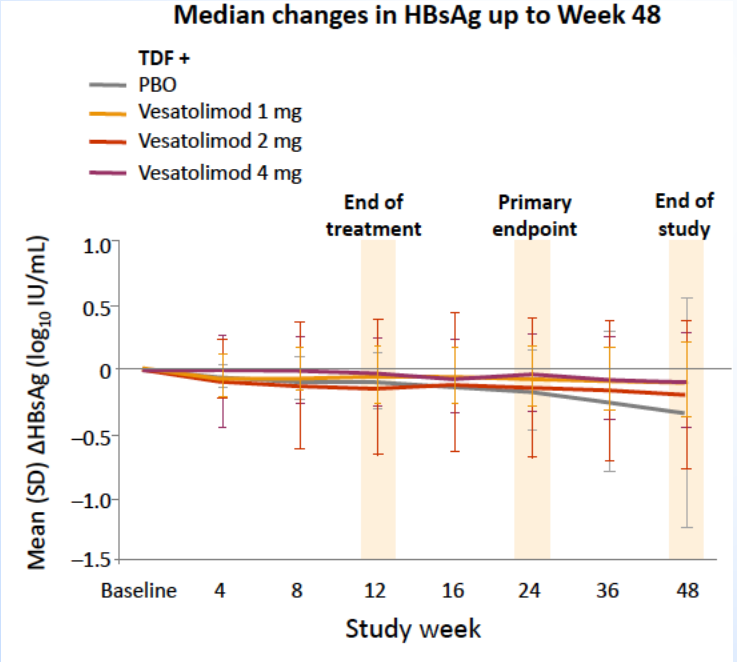
Ulrike Protzer, Mala K. Maini & Percy A. Knolle Nature Reviews Immunology 12, 201-213 (March 2012)

Homeostatic Tolerance



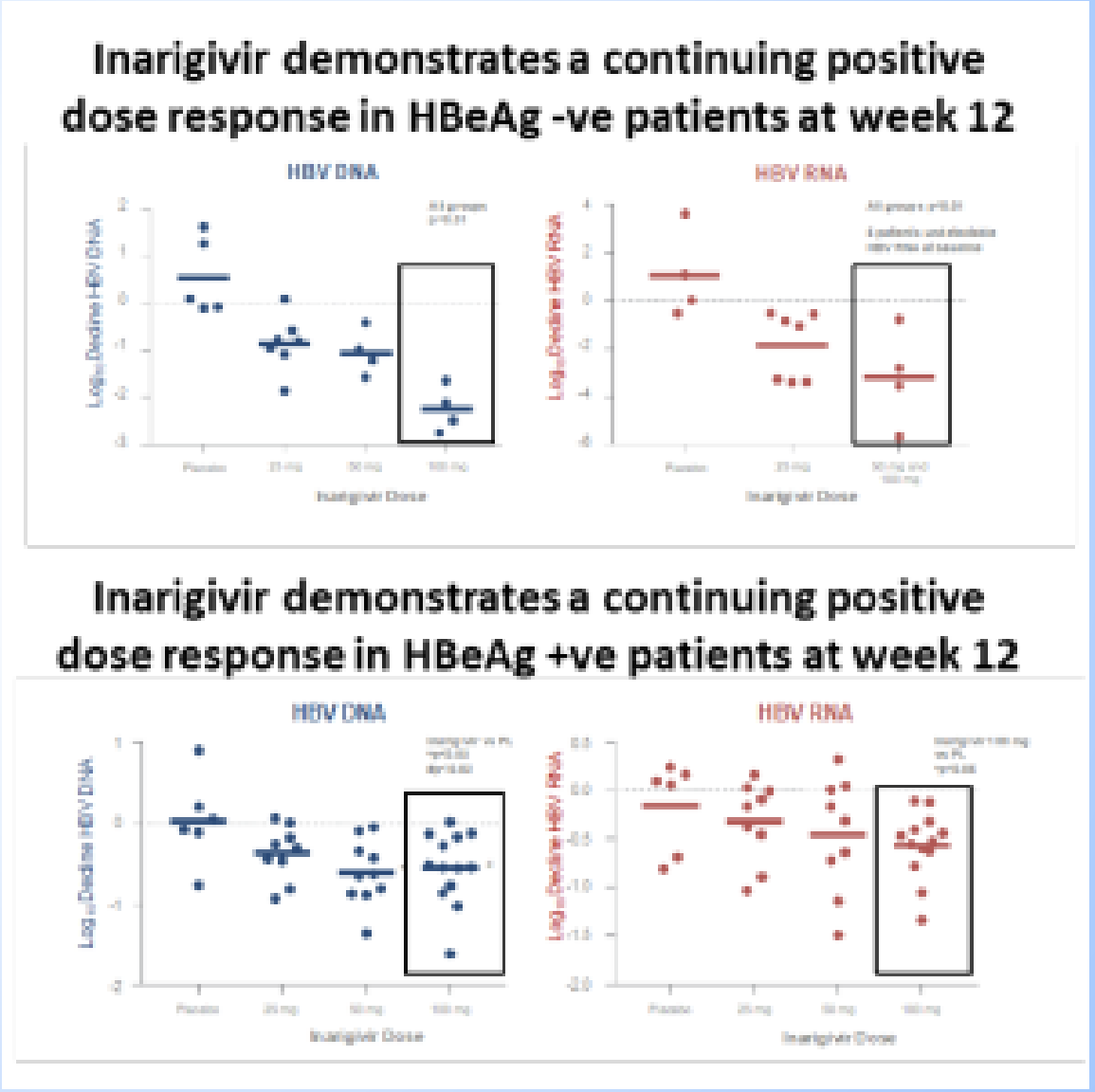
Angus W. Thomson & Percy A. Knolle Nature Reviews Immunology 10, 753-766 (November 2010)

GS-9620 (vesatolimod), TLR 7 agonist, in CHB pts (not on antiviral Rx)

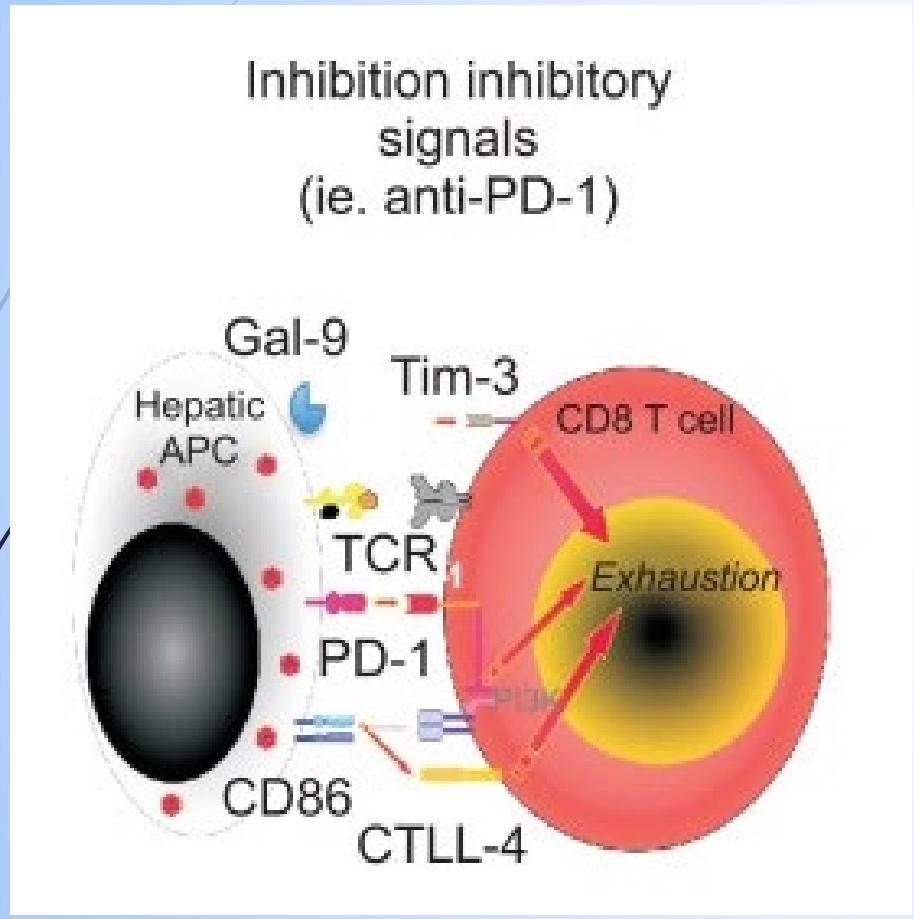


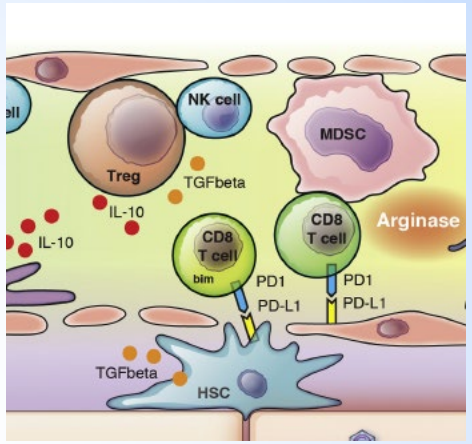
Yuen et al, AASLD, 2018

Springbank's putative RIGI/STING acting small molecule first in class in people



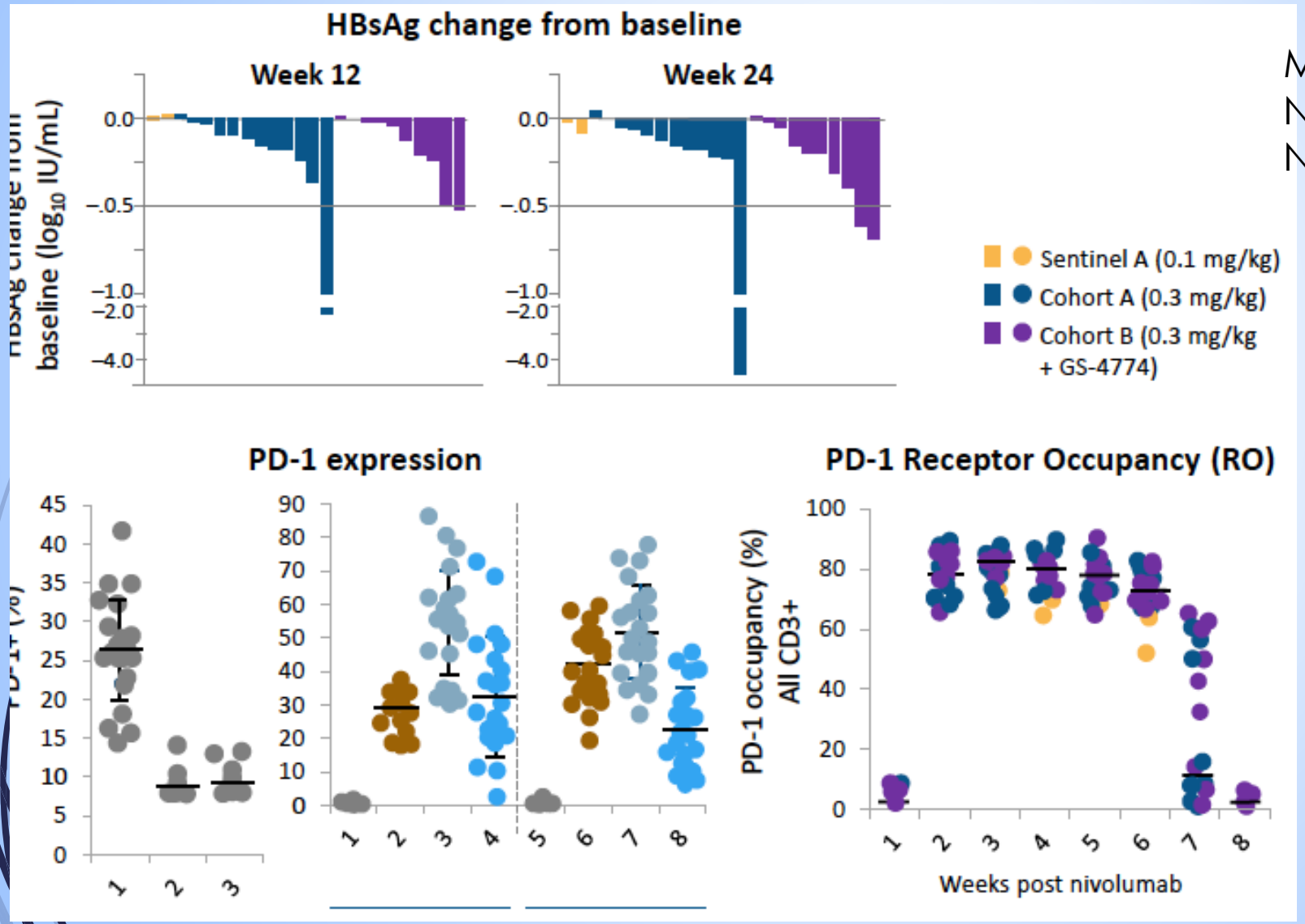
Checkpoint intervention





Bertoletti, A. and Le Bert, N., 2018. Immunotherapy for chronic hepatitis B virus infection. *Gut and liver*, *12*(5), p.497

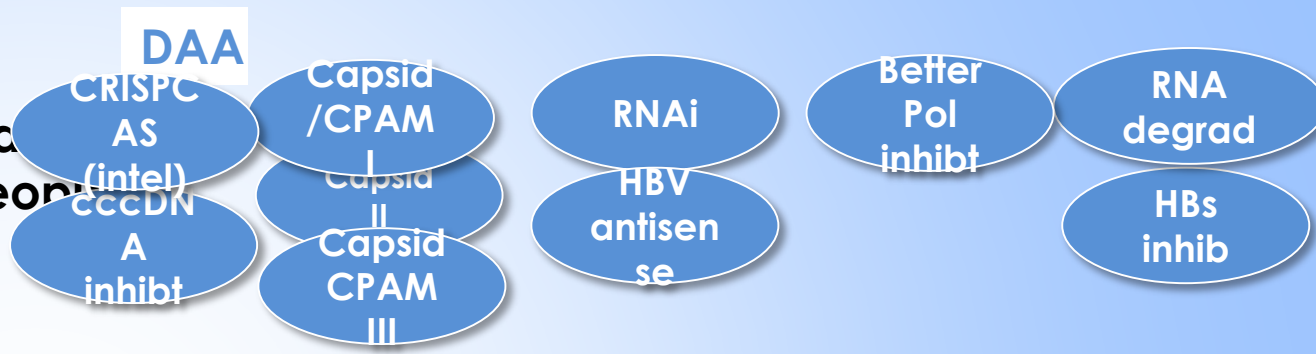
Nivolumab (Anti PDL-1) in HBe neg CHB



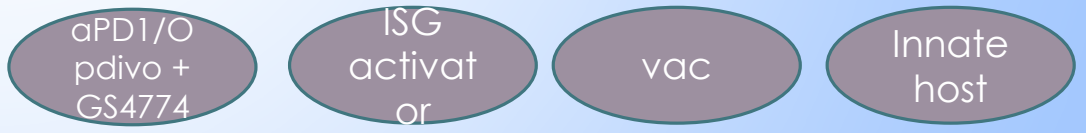
M-2
N=12
N=10 (GS 4774+

Combination for efficacy, not to repress resistance

Repress viremia and antigenemia (2 complimenta
This could be sufficient for a large % of peop



+



Enhance host Immune mediated antiviral response
patient select
after antigen control

Stair way to a cure!!!

Each new drug will be a step up clinical benefit

Acknowledgement

Thanks to the following scientists for providing slides or allowing for presentation of their data:

- Chari Cohen (Hepatitis B Foundation)
- Ju-Tao Guo (Blumberg)
- Tianlun Zhou (Blumberg)
- Jinhong Chang (Blumberg)
- Bruce Givens (Arrowhead)
- Anuj Gaggar (Gilead)
- Chris Moore (Arbutus)
- Mike Sofia (Arbutus)
- Andrew Valient (Replicor)
- Stephan Urban (Heidelburg)
- Phil Pang (Vir)

Thanks to:

The Hepatitis B Foundation, *committed to improving the lives of those affected by hepatitis B*