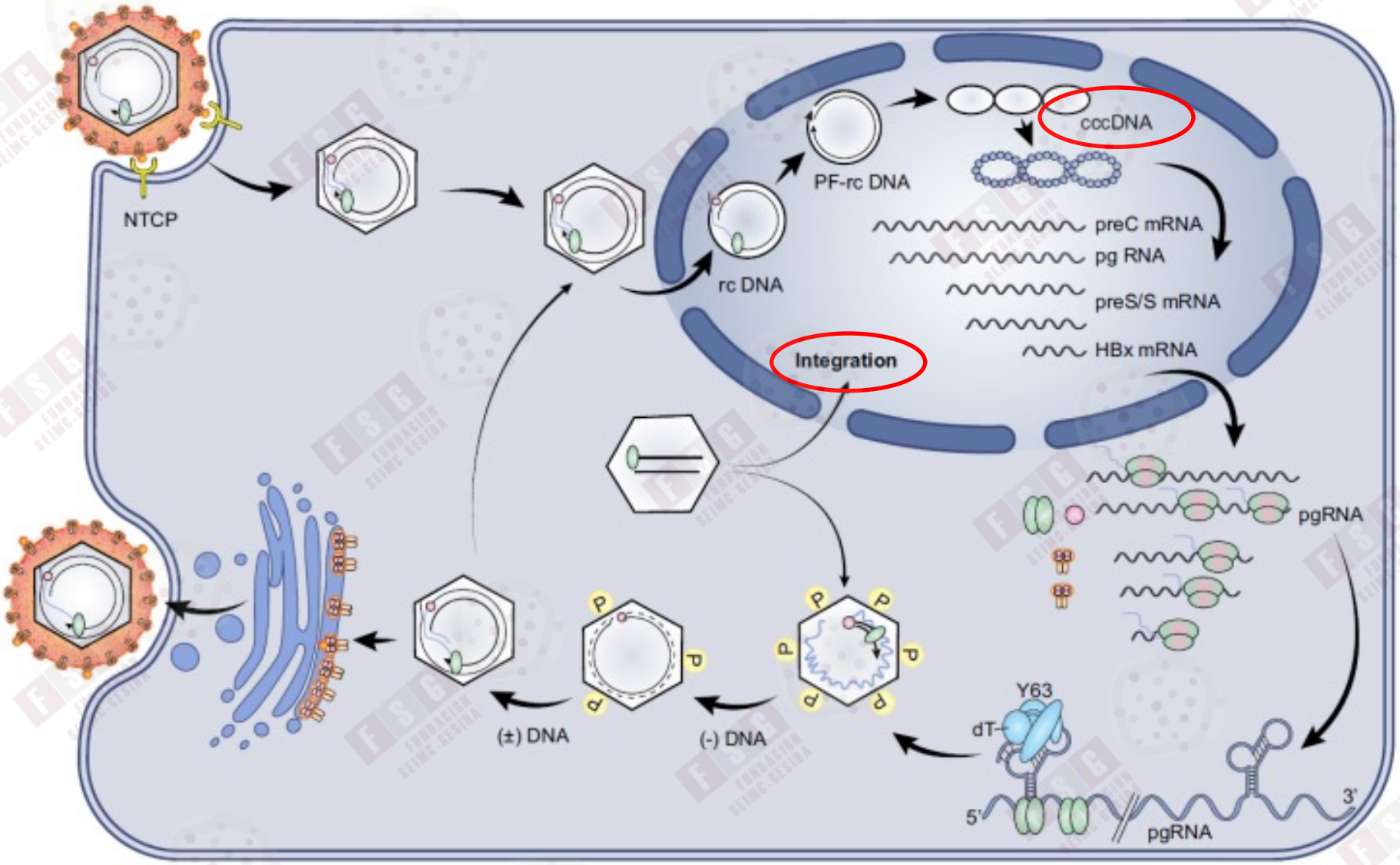
JORNADAS DOCENTES_04

Perspectivas de tratamiento futuro de la hepatitis B, ¿es posible la erradicación?

Juan R. Larrubia
Hospital Universitario de Guadalajara
Universidad de Alcalá

Una actividad de:

Con la colaboración de:



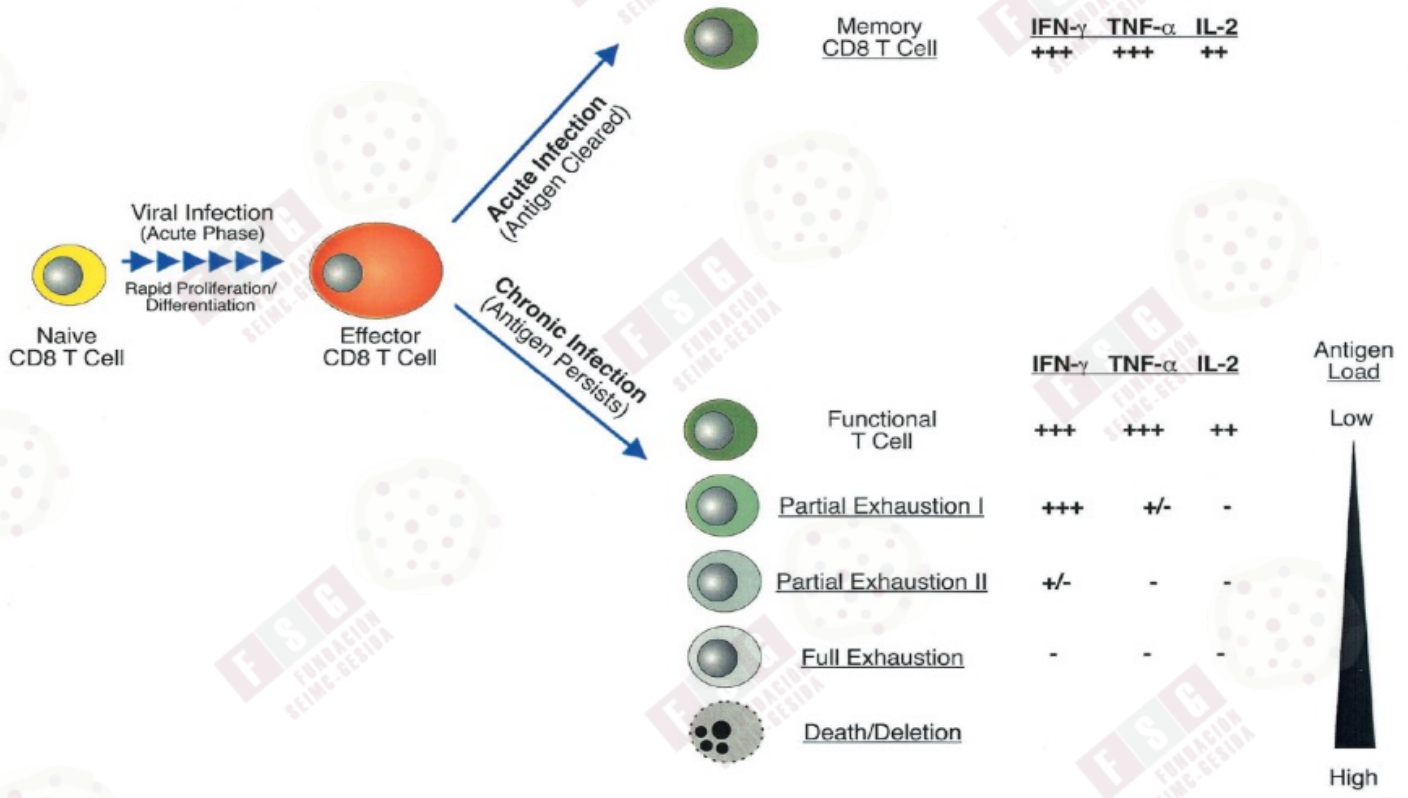
Tong S. J Hepatol. 2016; 64(S1):S4-S16.

Concepto de curación

- Curación completa: HBsAg (-), HBV DNA (-), cccDNA (-), HBV integrado (-)
- Curación funcional: HBsAg (-), HBsAb (+/-), HBV DNA (-) tras tto finito
- Curación parcial: HBsAg (+), HBV DNA (-) tras tto finito/infinito

Lok, A. Hepatol. 2017

Modelo jerárquico de agotamiento de las células T durante una infección crónica viral



Wherry EJ, J Virol 2003; 77: 4911-27

Pérdida de HBsAg con los tratamientos actuales

HBeAg positivo

	PegIFN		Nucleoside analogues			Nucleotide analogues		
	PegIFNα2a	PegIFNα2b	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	180 µg	100 µg	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
Anti-HBe-seroconversion	32%	29%	16–18%	22%	21%	12–18%	21%	10%
HBV DNA <60–80 IU/ml	14%	7%	36–44%	60%	67%	13–21%	76%	64%
ALT normalisation#	41%	32%	41–72%	77%	68%	48–54%	68%	72%
HBsAg loss	3%	7%	0–1%	0.5%	2%	0%	3%	1%

HBeAg negativo

	PegIFN	Nucleoside analogues			Nucleotide analogues		
	PegIFNα2a	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	180 µg	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
HBV DNA <60–80 IU/ml	19%	72–73%	88%	90%	51–63%	93%	94%
ALT normalisation#	59%	71–79%	74%	78%	72–77%	76%	83%
HBsAg loss	4%	0%	0%	0%	0%	0%	0%

J Hepatol 2017; 67: 370–398

Nuevas estrategias para alcanzar la cura funcional

- Contra VHB: Agentes anti-virales directos (AAD)

- Potenciar la respuesta inmune:
  - Mejorar la respuesta innata
  - Mejorar la respuesta adaptativa

AAD contra el VHB en fase de desarrollo

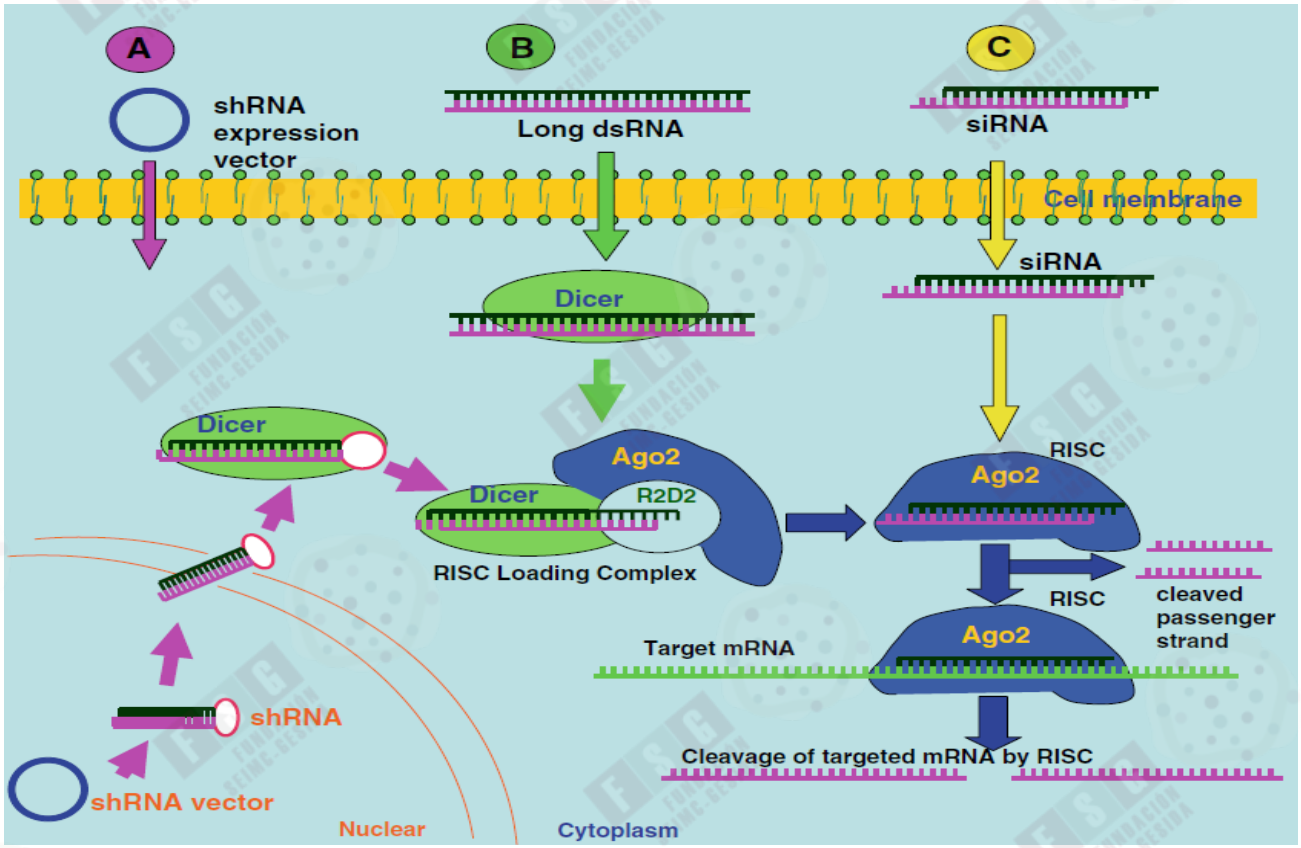
Entry inhibitors	
Myrcludex B	Phase I
RNA interference	
ALN-HBV	Phase I–II
ARC-520	Phase II
ARB-1467	Phase II
Lunar-HBV	Preclinical
BB-HB-331	Preclinical
Ionis HBVRx (GSK3228836)	Phase I
IONIS-HBVLRx (GSK33389404)	Phase I
Capsid assembly modulators/core inhibitors	
GLS-4 (morphothiadine mesilate)	Phase II
NVR 3-778	Phase Ia
BAY41-4109	Phase I
JNJ56136379	Phase I
Core protein allosteric modifier	Phase I

Nucleoside/nucleotide analogues	
AGX-1009 (prodrug of tenofovir)	Phase III
LB80380 (besifovir)	Phase III
CMX-157 (prodrug of tenofovir)	Phase IIa
Surface antigen/release inhibitors	
REP 2139 and REP 2165	Phase II
RO7020322 (RG7834)	Phase I
GC 1102	Phase II

Areends, JE. Infect Dis Ther (2017) 6:461–476

RNA de interferencia

Diferentes estrategias de silenciación de un mRNA

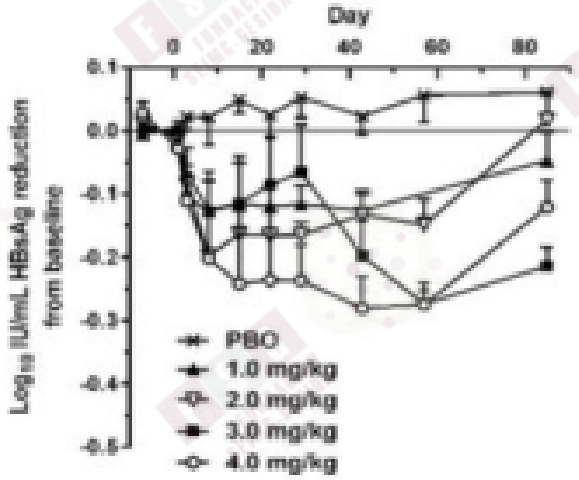


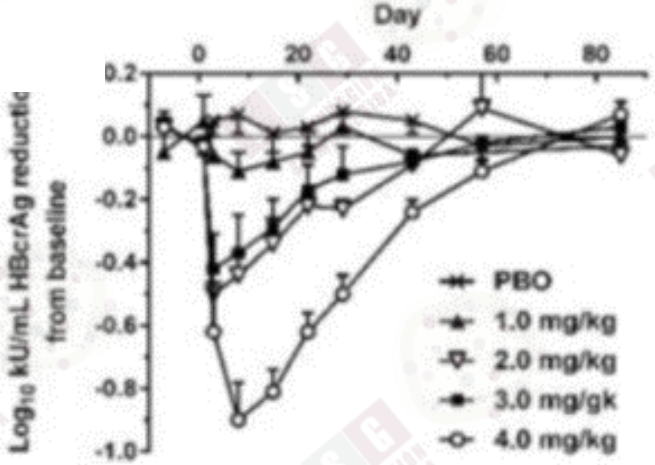
- RISC: RNA induced silencing complex
- Ago2: Splicing protein Argonaute2
- siRNA: Small Interference RNA

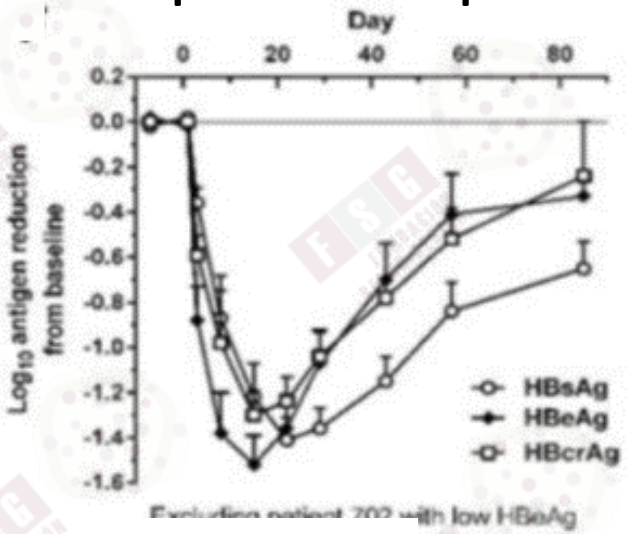
Chen Y et al. Pharm Res 2008; 25: 72-86

Estudio piloto en humanos con ARC-520 (siHBV-74/siHBV-77) (Una dosis iv de 1 a 4 mgs + NUC)

- Péptido similar a melittin conjugado con N-acetilglucosamina (NAG-MLP) unido a un siRNA conjugado con colesterol con tropismo hepático







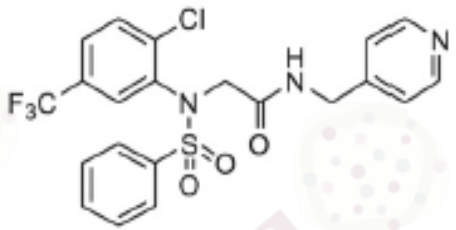
ClinicalTrials.gov Identifier: NCT02065336

Suspendido por investigación sobre EA relacionado con vehículo

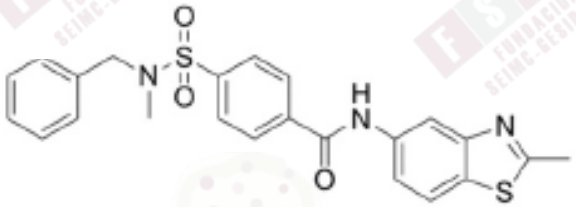
Wooddell C et al. Sci Transl Med 2017; 9 (409)

AAD contra el cccDNA

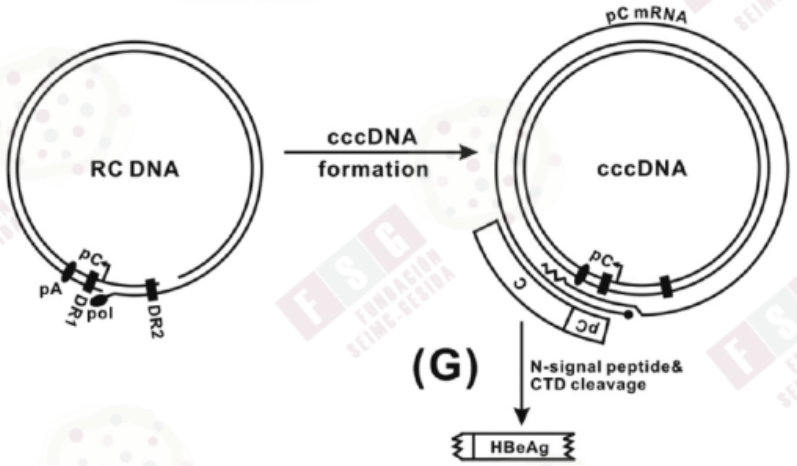
Bloqueo de la formación del cccDNA



CCC-0975

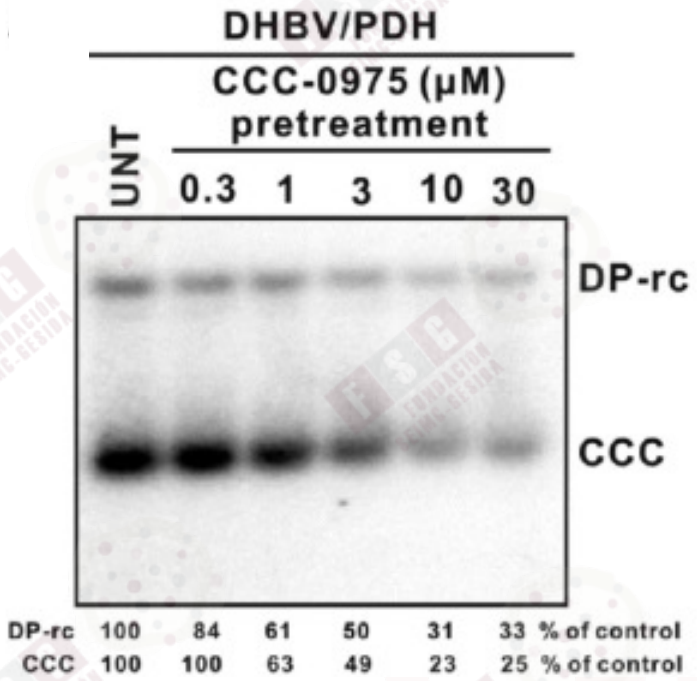


CCC-0346



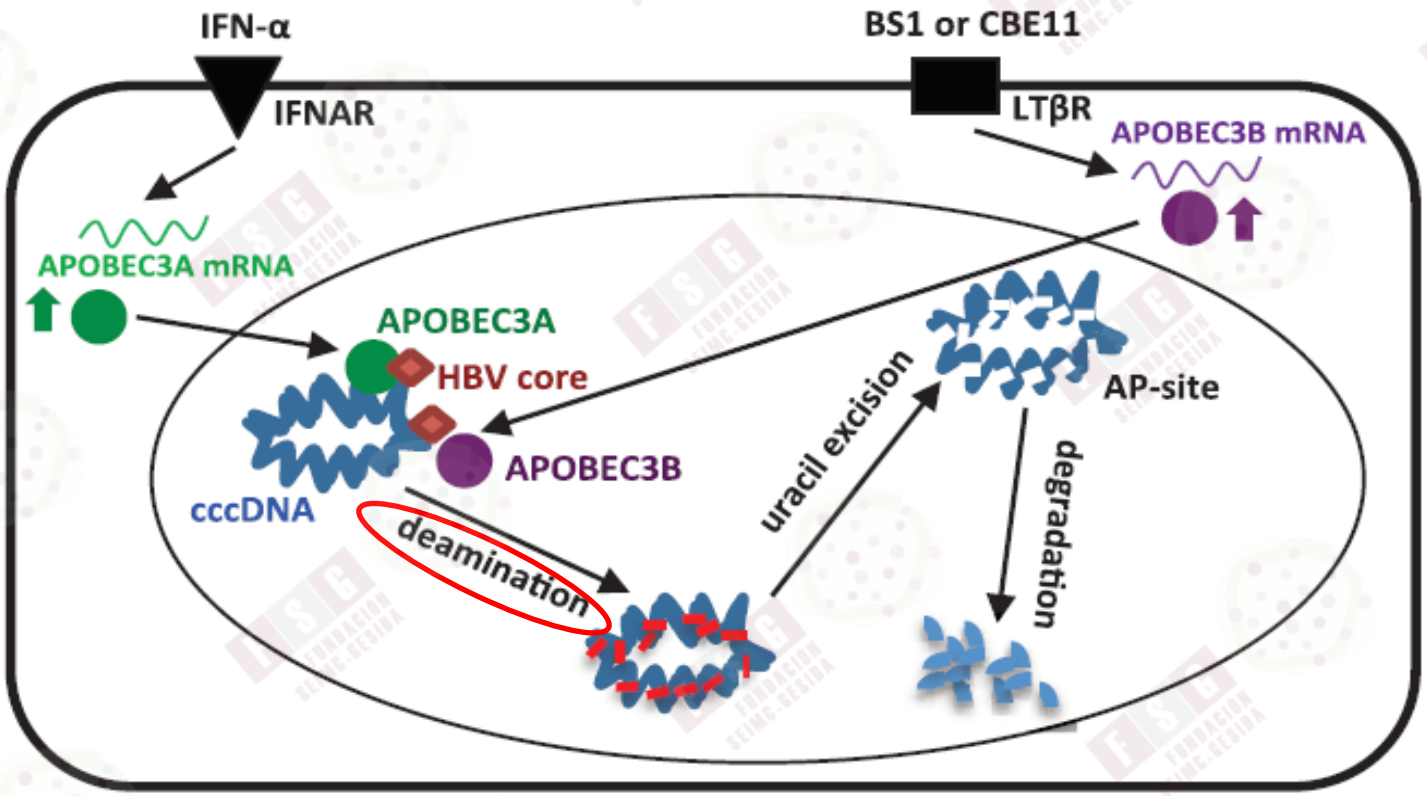
- Sulfonamidas disubstituidas (DS
- Bloquean el paso de rcDNA a cccDNA

Primary duck hepatocytes



Cai D et al. Antimicrob Agents Chemother. 2012;56(8):4277–88.

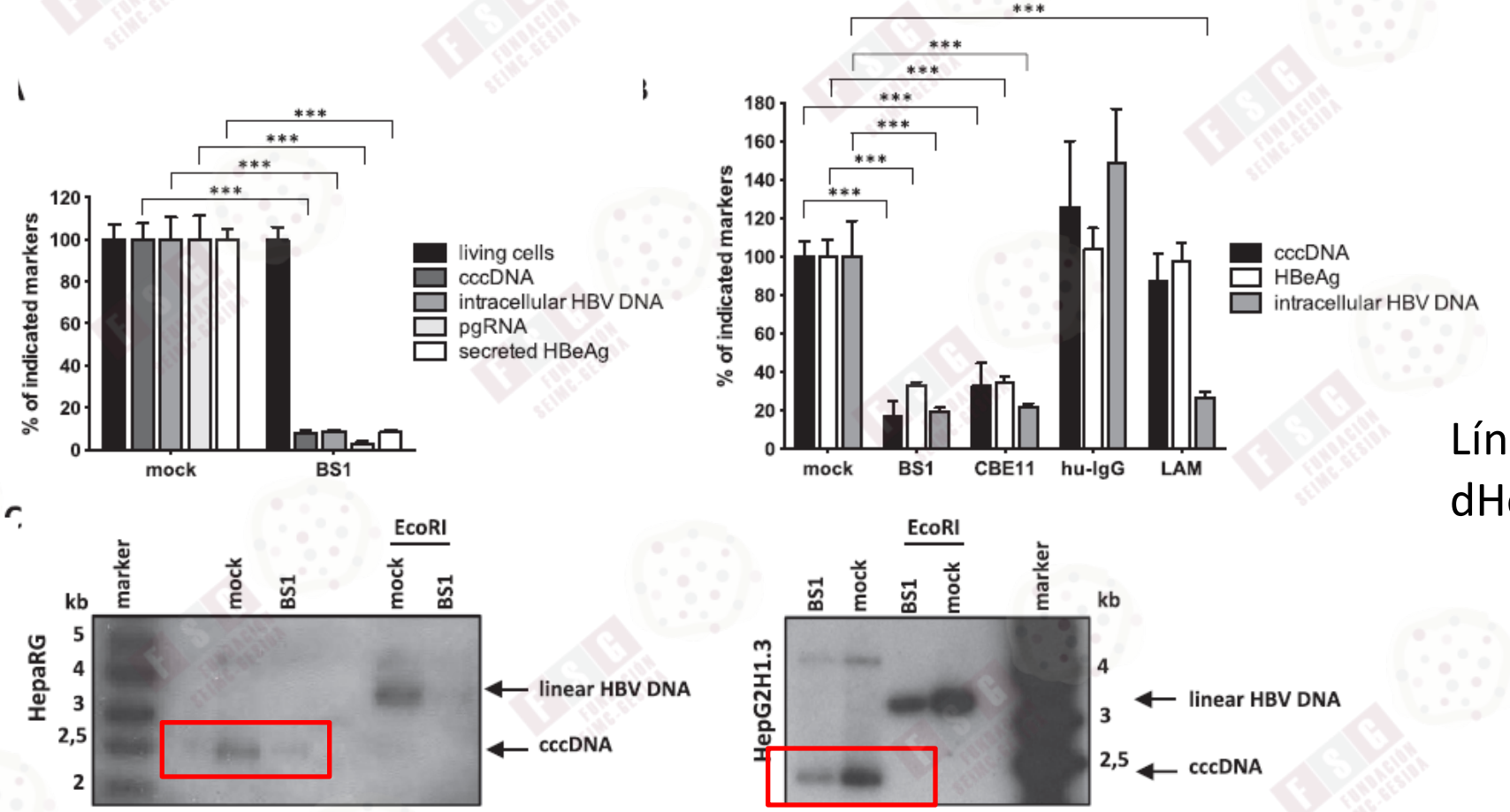
Degradación del cccDNA por medio de la activación del receptor de la linfotoxina B



- APOBEC3A/3B: Apolipoprotein B mRNA editng enzyme catalytic polypeptide 3A/3B

Lucifora J, Science. 2014;343(6176):1221–8

Degradación del cccDNA por medio de la activación del receptor de la linfotoxina B



Líneas celulares:
dHepaRG y HepG2-H1.3

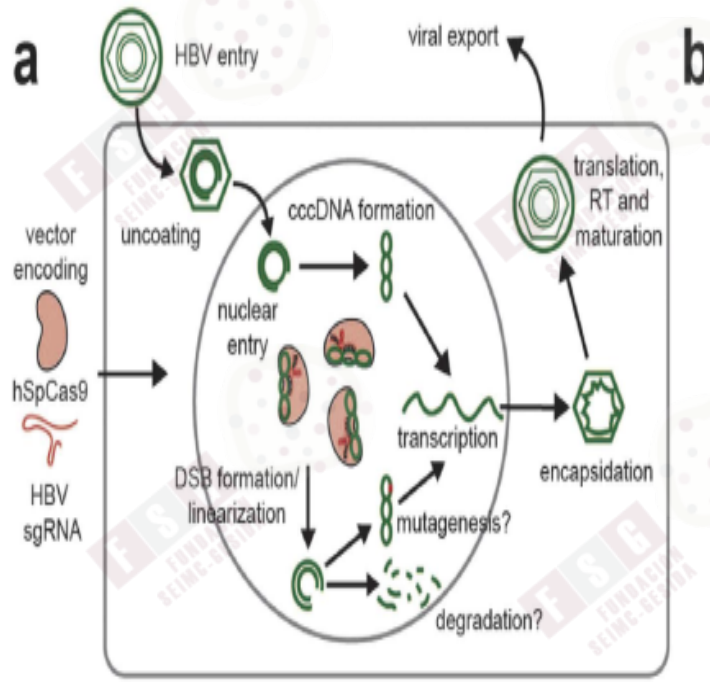
Lucifora J, Science. 2014;343(6176):1221–8

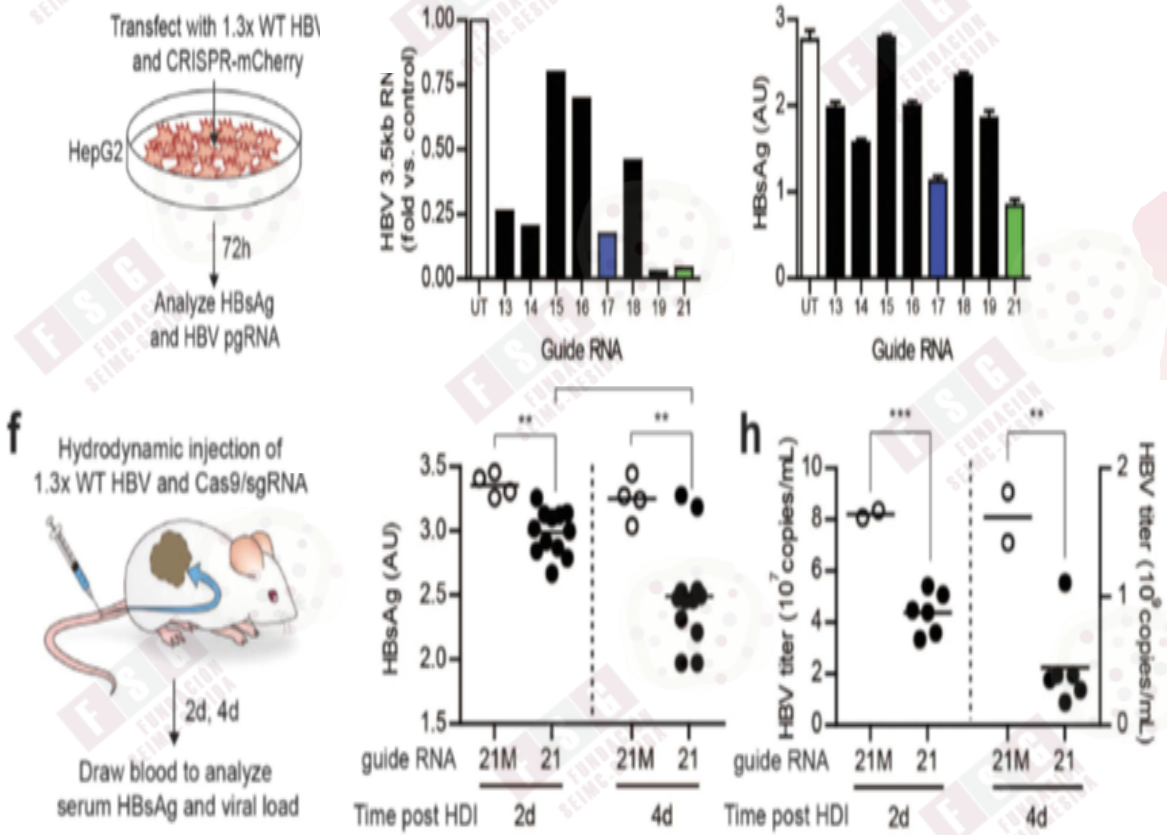
Endonucleasas específicas contra el DNA VHB

Inducen mutaciones/delecciones que inactivan genes de VHB:

- Zinc finger nucleases (ZFNs).
- Transcription activator-like effector nucleases (TALENs).
- CRISPR (clustered, regularly interspaced, short palindromic repeat)/ Cas9 genome editing tool.

CRISPR (Clustered regularly interspaced short palindromic repeats)/Cas9 para eliminar cccDNA





Ramanan V, Sci Rep 2015; 10833

Agentes anti-virales directos contra la formación de la cápside

Inhibidores de la formación de la cápside

- Heteroaryldihydropyrimidines (HAPs)
  - Defectos de ensamblaje
  - Formación de cápsides defectivas
- Phenylpropenamides
  - Empaquetamiento y formación
- Sulphamoyl-benzamide
  - Inhibe encapsidación pgRNA

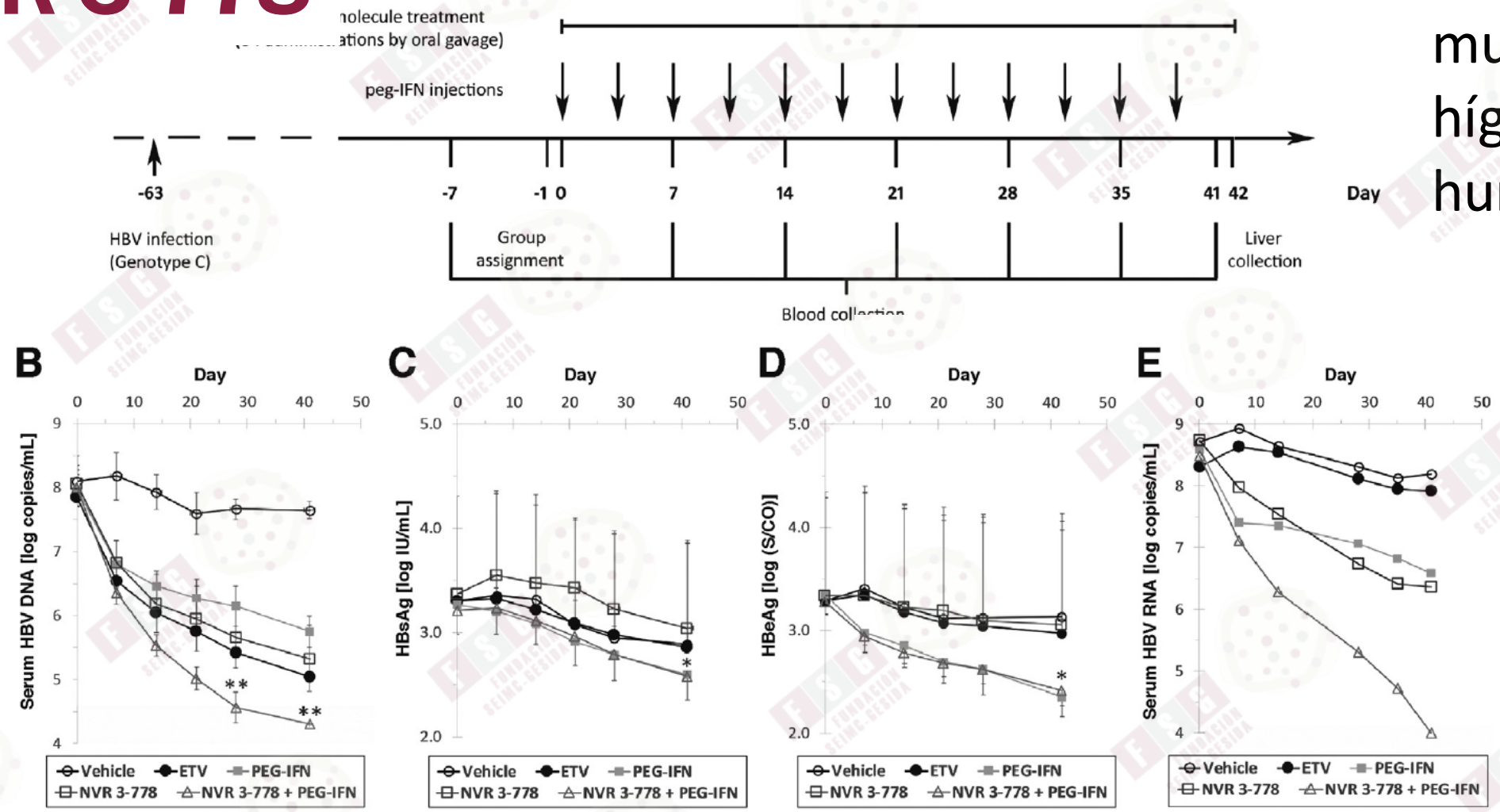
Table 2 Capsid inhibitors and core protein allosteric modifiers currently undergoing trials

Drug/compound	Clinical study
Morphothiadin (GLS4)	Phase II
AL-3778 (formerly NVR 3-778)	Phase II
RO6864018	Phase II
AIC 649	Phase I
JNJ56136379	Phase I
HBV CpAM	Preclinical
AB-423	Preclinical

CpAM core protein allosteric modifier, *HBV* hepatitis B virus

NVR 3-778

Modelo murino con hígado humanizado

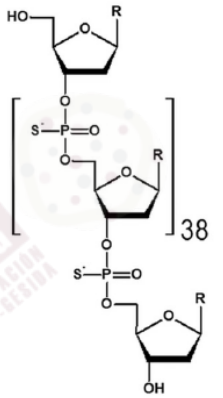


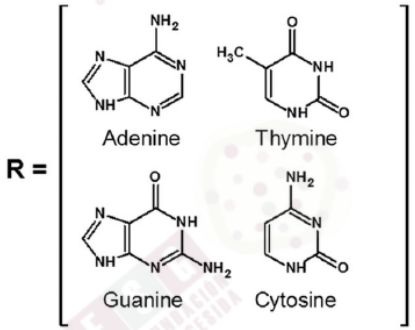
Klump,K. Gastroenterology. 2018 Feb;154(3):652-662.e8.

Agentes anti-virales directos contra el HBsAg:
Secreción HBsAg
Entrada VHB en hepatocito

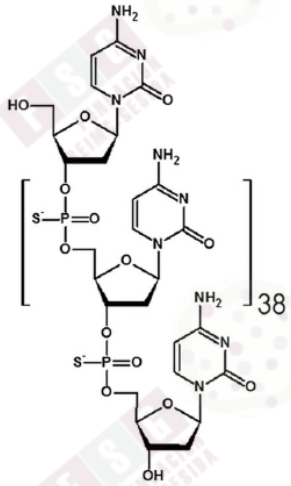
Inhibidores de la secreción de HBsAg

Polímeros de ácidos nucleicos

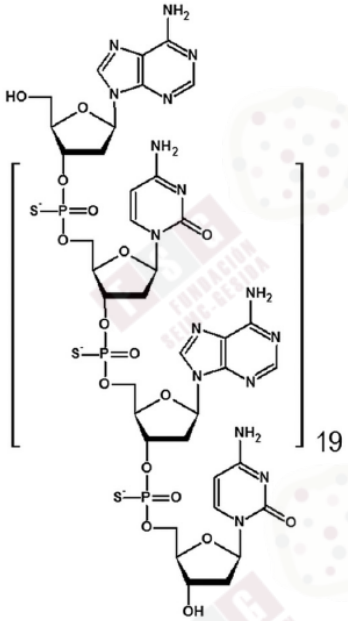




REP 2006

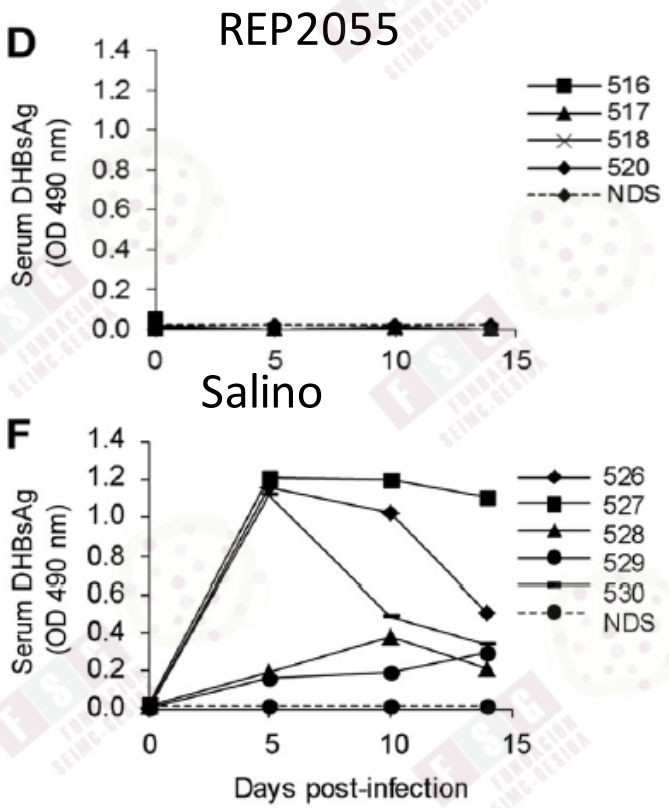


REP 2031



REP 2055

Hepatocitos de pato infectados con DHBV

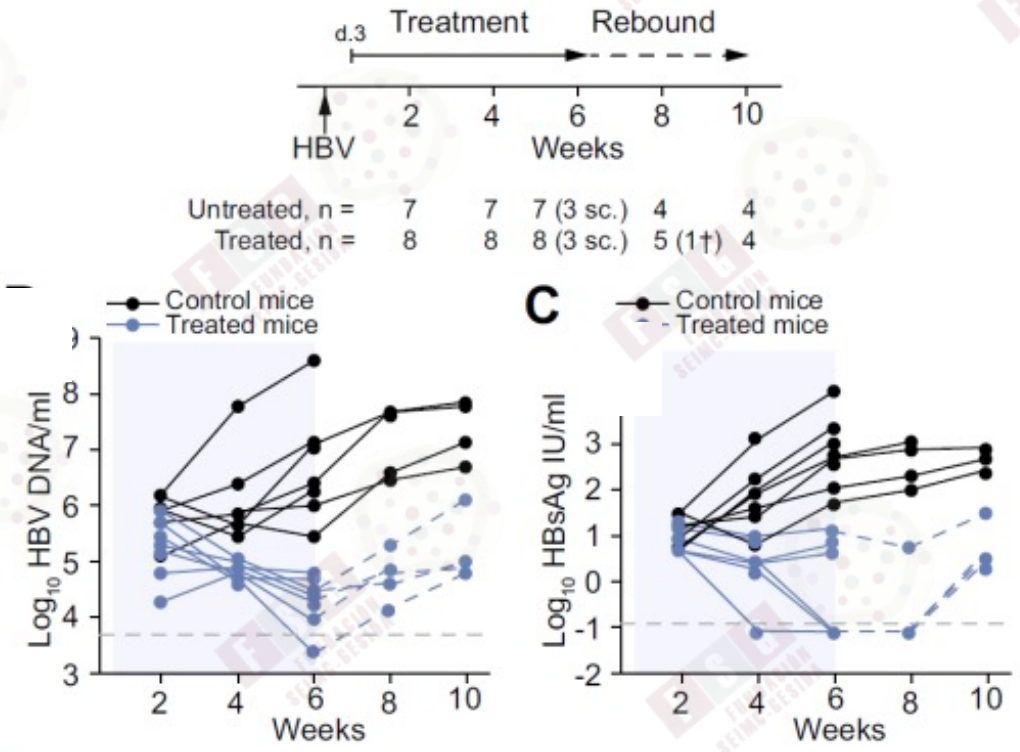


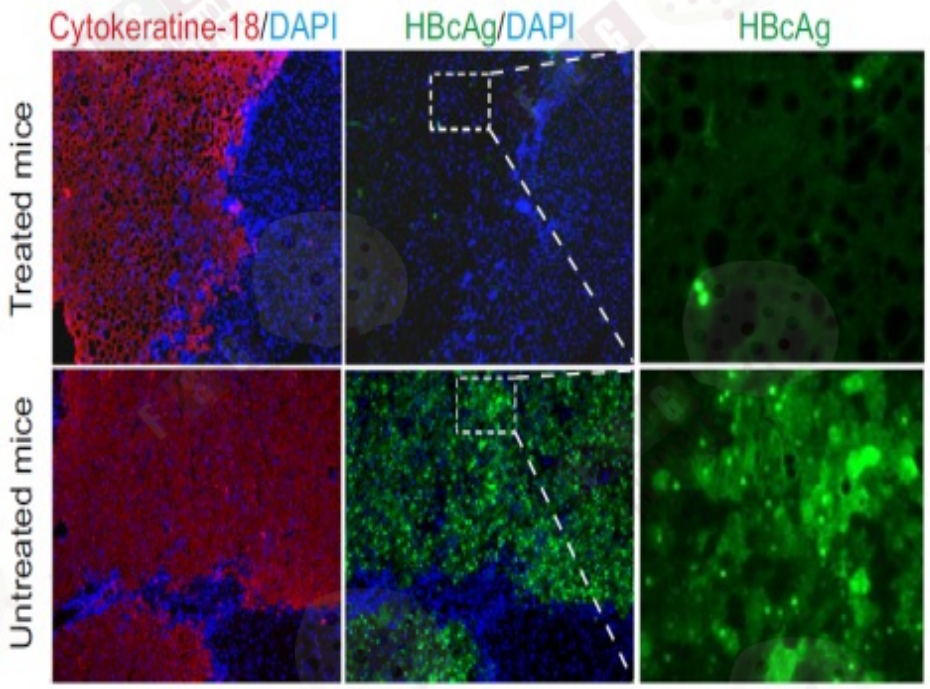
Noorden F. Antimicrob Agents Chemother. 2013;57(11):5299–306

Inhibidores de la entrada VHB

- Anticuerpos neutralizantes contra el dominio S o pre-S1
- Inhibidores de anclaje: proteoglicanos heparan sulfatos
- Substratos de NTCP: ezitimibe, taurocolato
- Inhibidores irreversibles de NTCP: Myrcludex, ciclosporina

Myrcludex

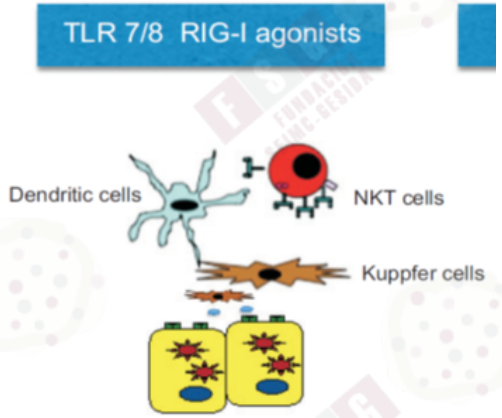




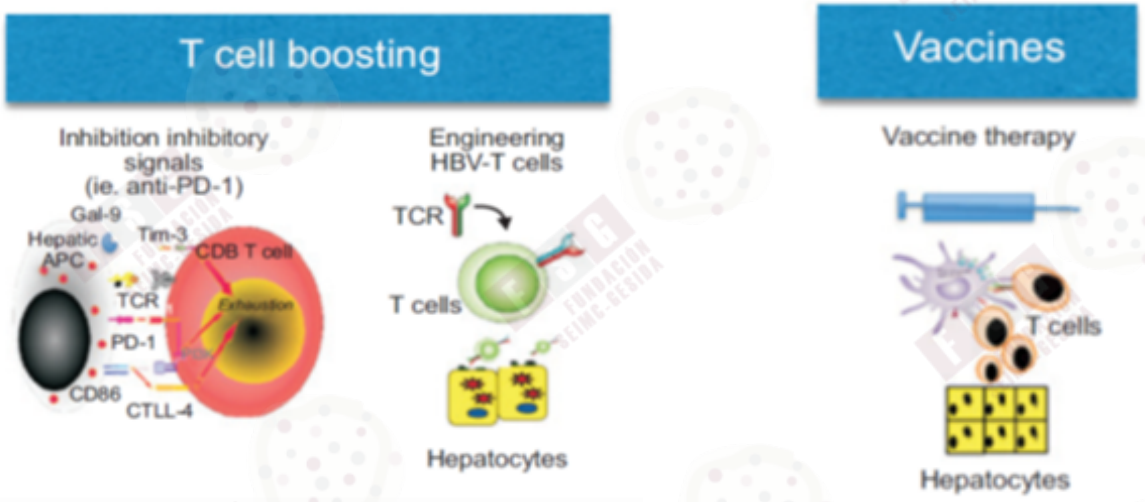
Volz T, J Hepatol 2013; 58:,861-867

Potenciación de la respuesta inmune innata y adaptativa

Activación de la respuesta inmune innata intrahepática



Restauración de la respuesta inmune específica contra el VHB



Bertoletti, A. Gut & Liver 2018

Tratamientos para mejorar la respuesta inmune innata y adaptativa

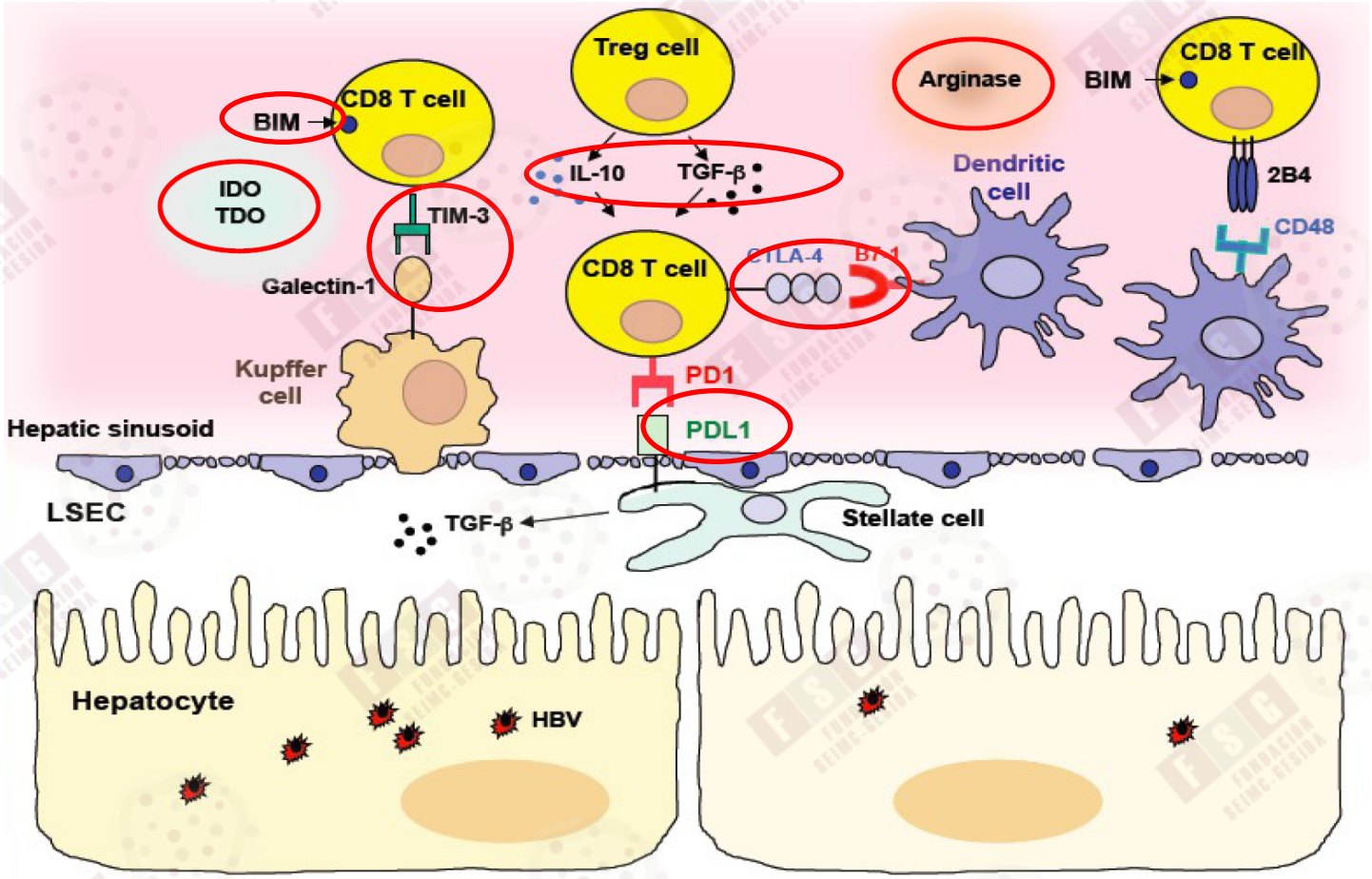
Table 1. Therapeutic Strategies Aimed at Increasing Innate and Adaptive Immunity

Compound	Mode of action	Stage of development
TLR-7 agonist	Preferential activation of intrahepatic dendritic cells triggers production of type I and II interferons and activation of intrahepatic NK and MAIT cells	GS9620 tested *in vitro*, animal models (chimpanzees and woodchucks; dose, 1 mg/kg) and CHB patients (lower dose, 4 mg total)
TLR-8 agonist	Preferential activation of intrahepatic dendritic cells and other myeloid cells. Production of IL-12/IL-18 activation of NK and MAIT cells	*In vitro* and animal models (woodchucks)
RIG-I agonist	Activation of intrahepatic innate immunity	*In vitro* trial in human started
TCR-like antibodies	Direct recognition of HBV infected hepatocytes/not blocked by secreted HBeAg/HBsAg	*In vitro* only
Anti-HBV antibodies	Prevent HBV infection of hepatocytes. Possible recognition of HBV infected cells, lysis through ADCC	*In vitro* and animal models (mouse models)
Check point inhibitors (anti-PD-1)	Restoration of function of exhausted HBV-specific T cells	*In vitro*, *in vivo* and in patients (trial in anti-HBe CHB patients and in patients with HCC in HBV infection)
Therapeutic vaccines (different preparations with arrays of HBV proteins produced by different vectors and adjuvants)	Induction of new HBV-specific T and B cell immunity with curative ability	Several preparations have been tested in animal models and humans
TCR/CAR redirected T cells	Engineering new HBV-T cells with classical TCR or with CAR	Tested in HBV transgenic mice and in patients with relapses of HBV-related HCC

Bertoletti, A. Gut & Liver 2018

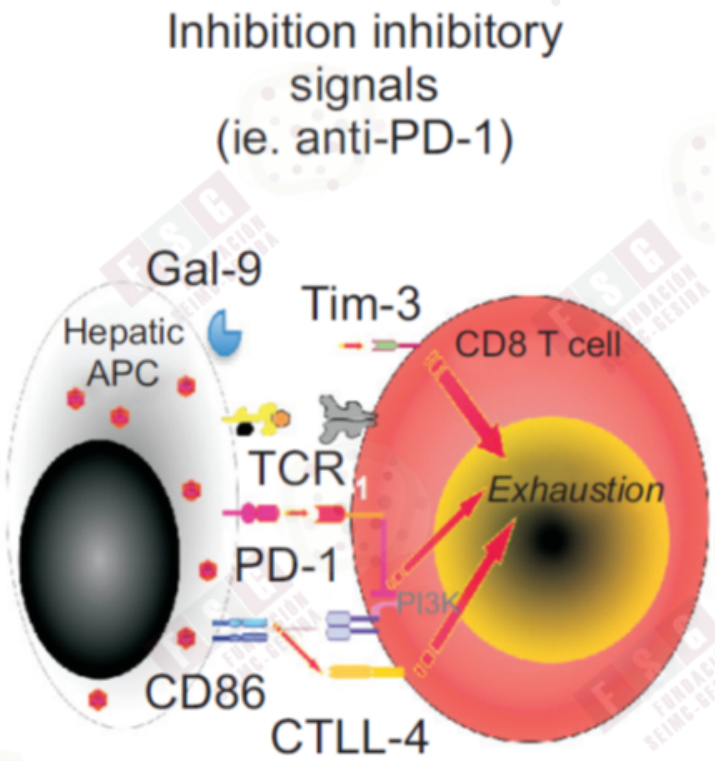
Estrategias para incrementar la respuesta inmune adaptativa

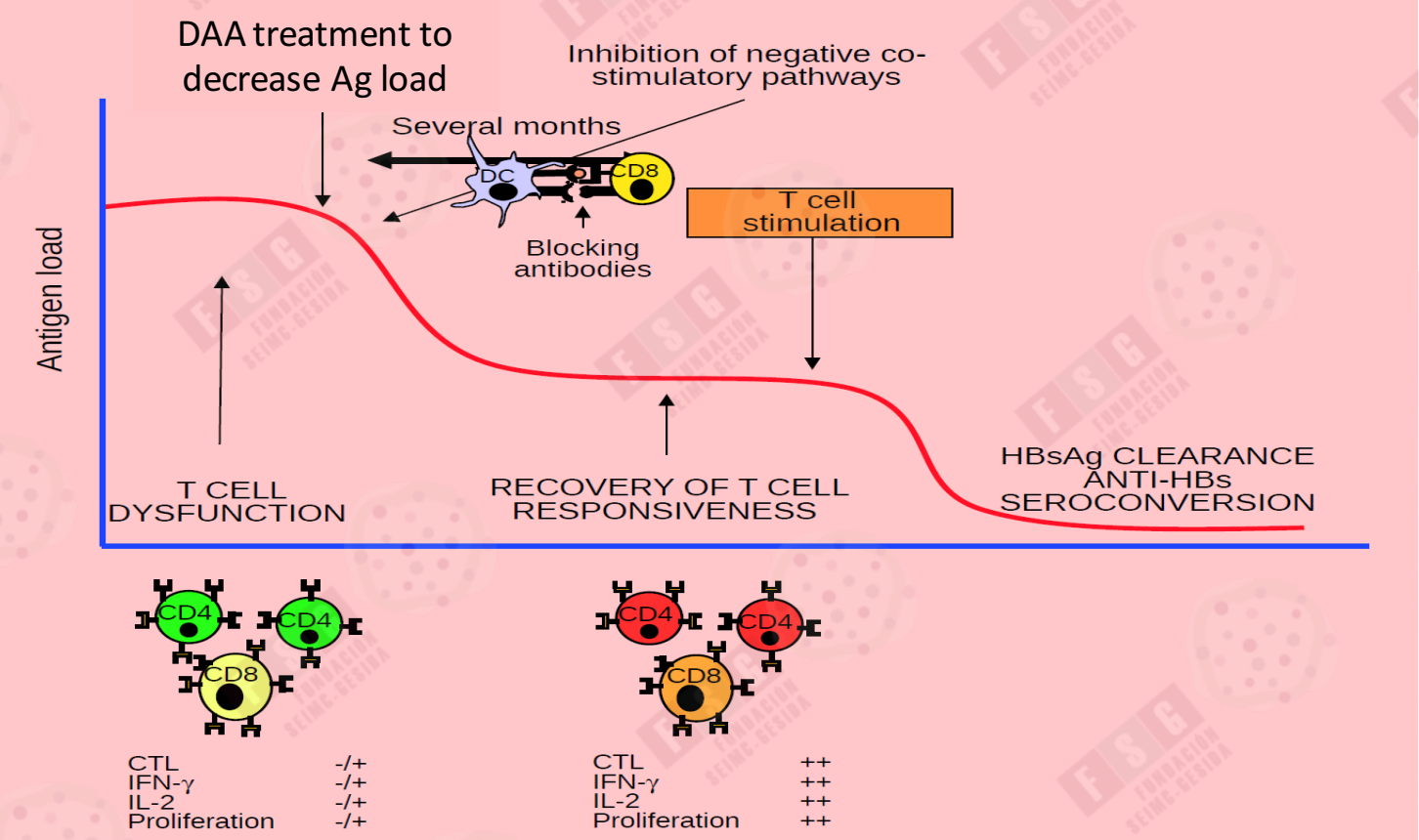
Disfunción del sistema inmune adaptativo durante la infección crónica por VHB



Protzer, Nature Reviews Immunol 2012

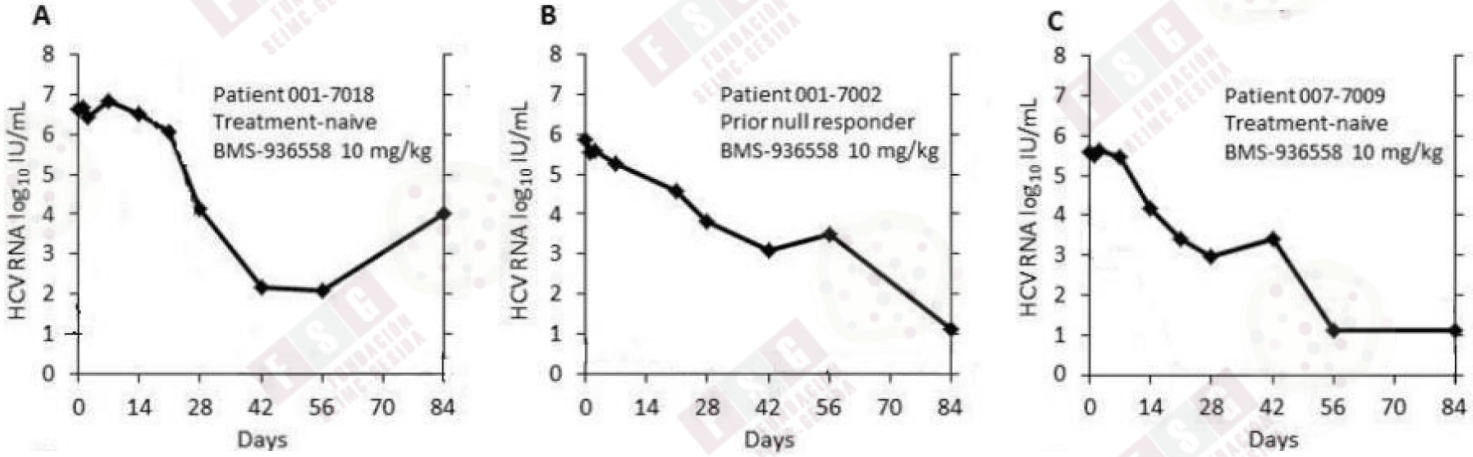
Bloqueo de vías co-estimuladoras negativas en células T





Ferrari, Gastroenterology 2008

Prueba de concepto: anti-PD-1 en hepatitis C

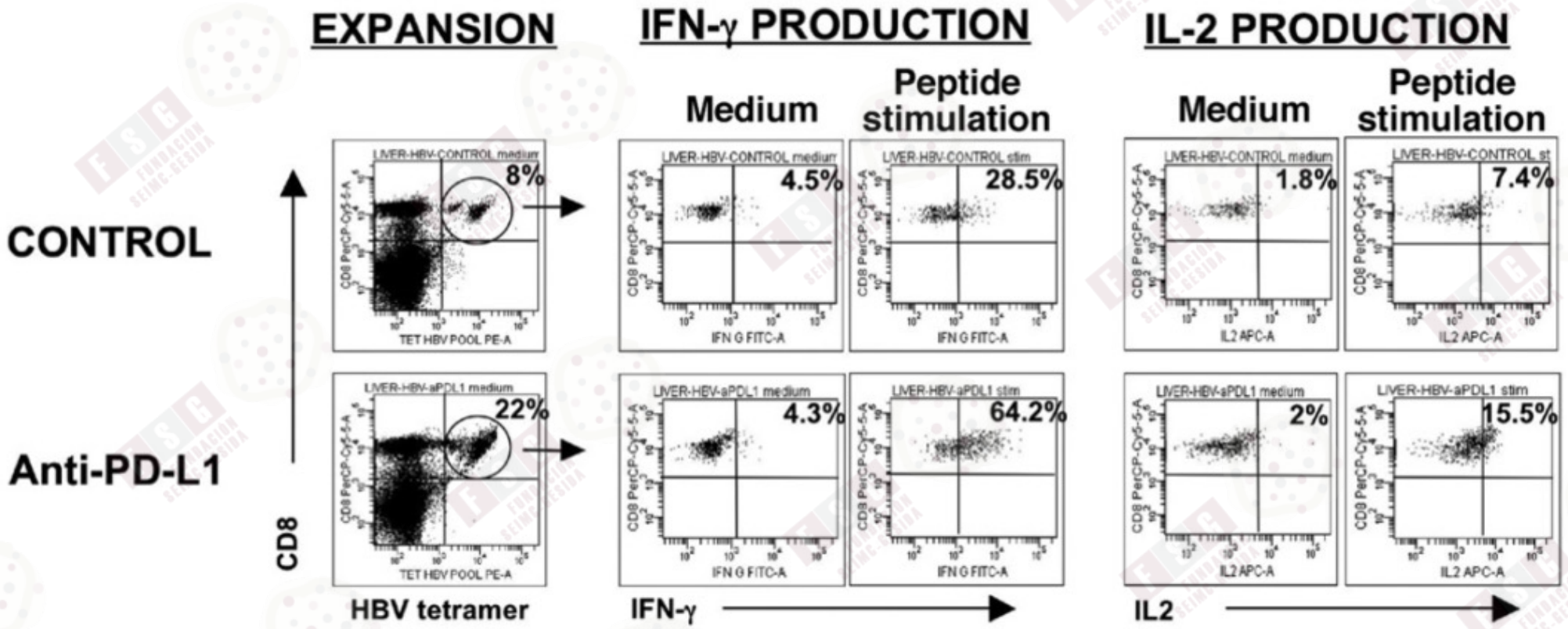


- Estudio ciego, controlado con placebo
- 0.03-10 mg/kg
- Tres casos con descenso de más de 3 log en RNA VHC
- Un caso continua negativo tras un año de seguimiento

Gardiner, Plos ONE 2013

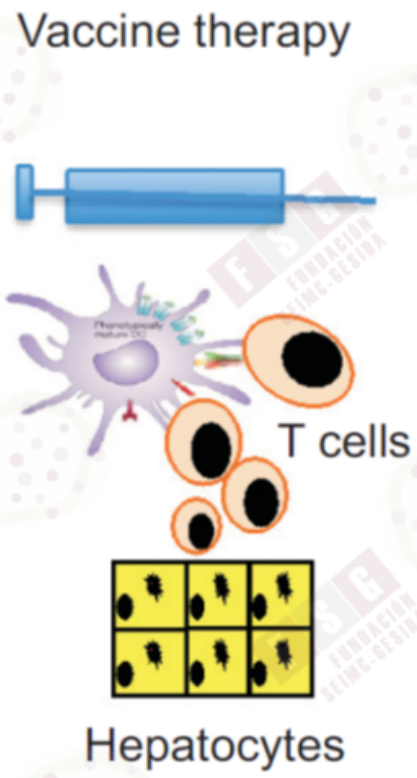
El bloqueo de la vía PD-1/PD-L1 restaura la capacidad efectora de las células citotóxicas intrahepáticas específicas contra el VHB

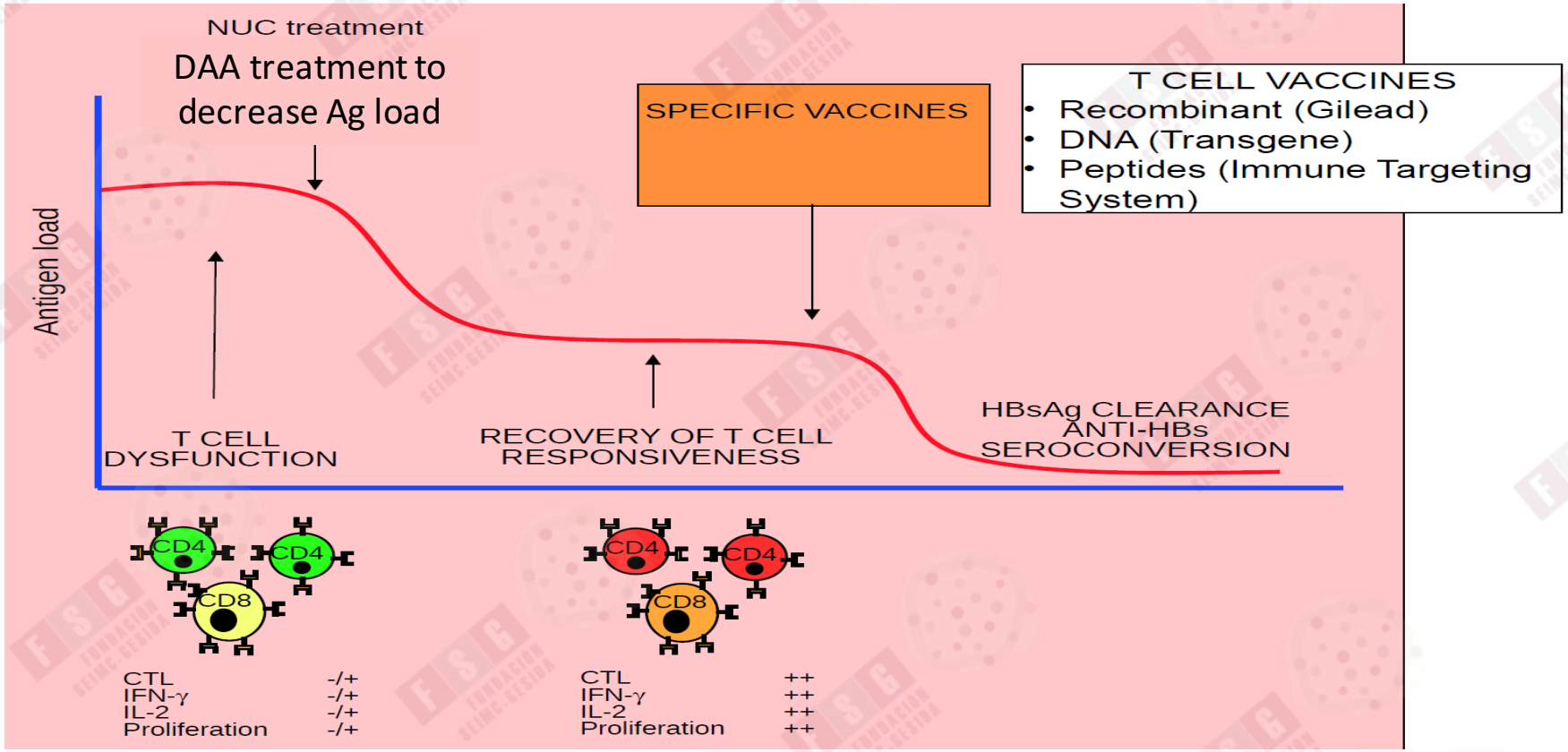
Células T intrahepáticas



Fisicaro, Gastroenterology 2010

Combinación de tratamiento estándar con vacuna terapéutica

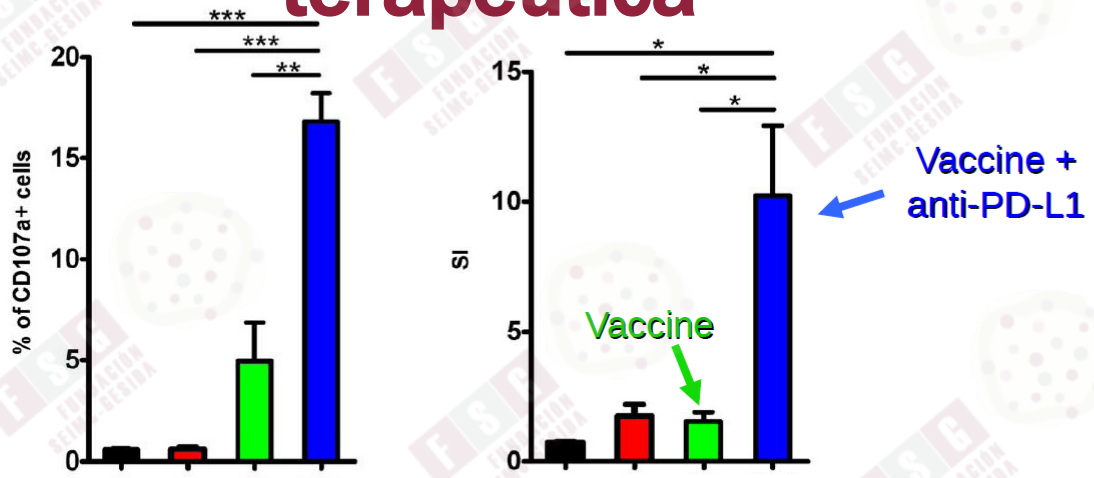




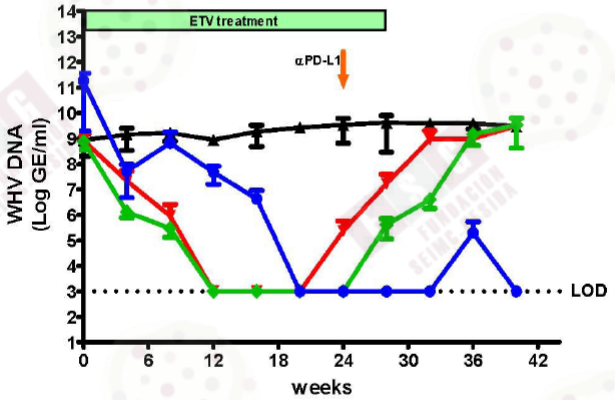
Ferrari, Gastroenterology 2008

Efecto sinérgico: bloqueo del check-point PD-1 y vacuna terapéutica

T cell immunity



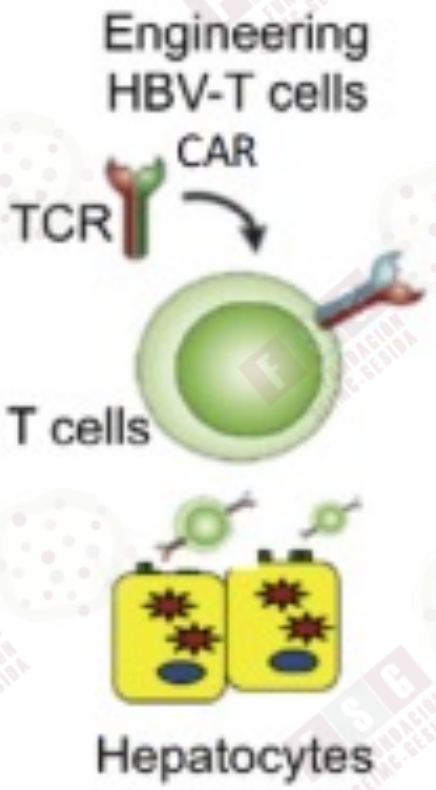
WHA replication

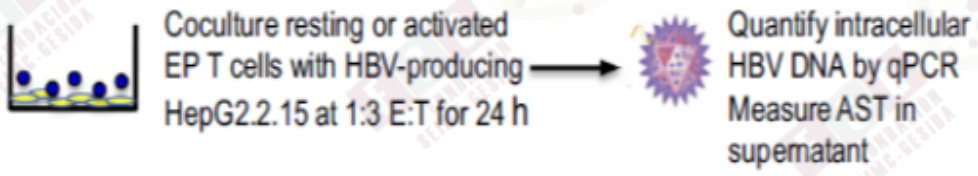


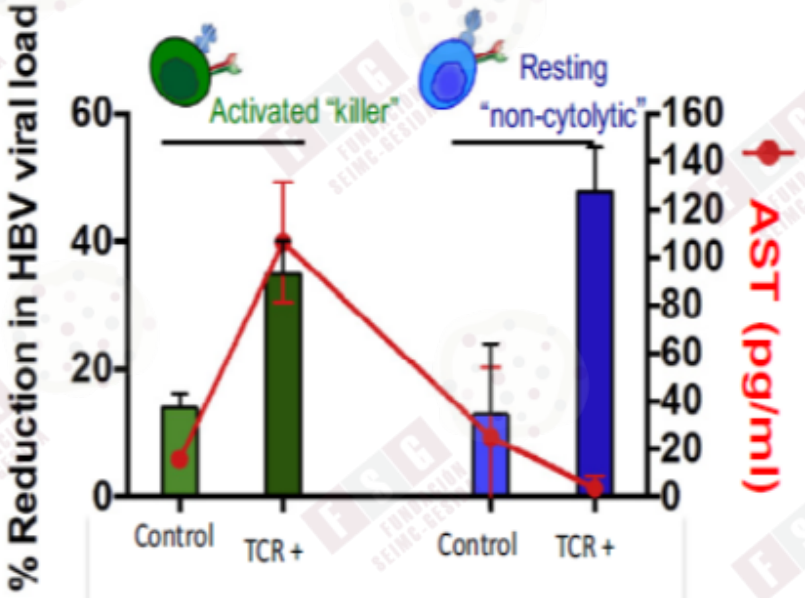
- Control
- Entecavir
- Entecavir + DNA vaccination
- Entecavir + DNA vaccination + anti-PDL1

Liu J, Plos Pathogens 2014

Redireccionamiento de células T



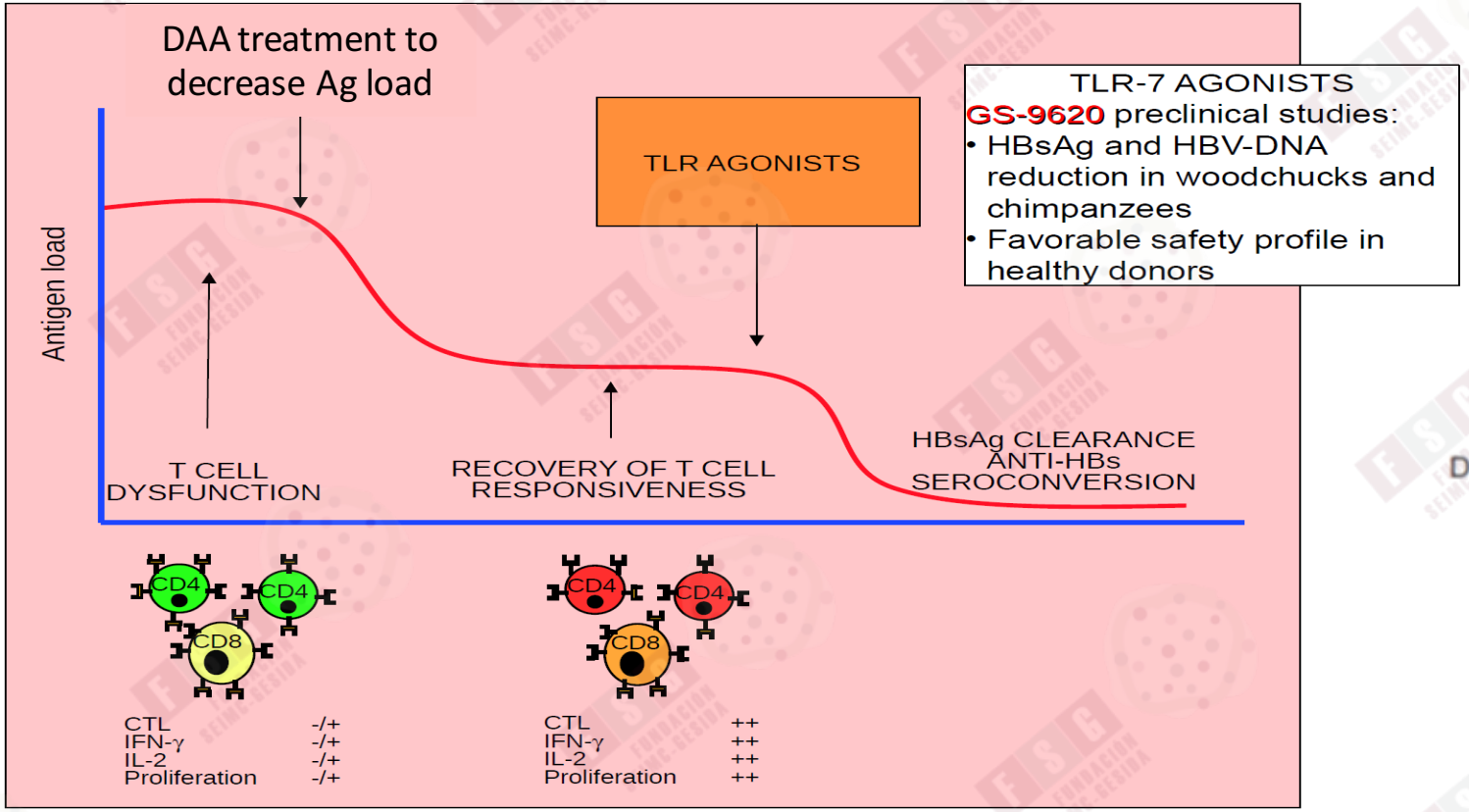


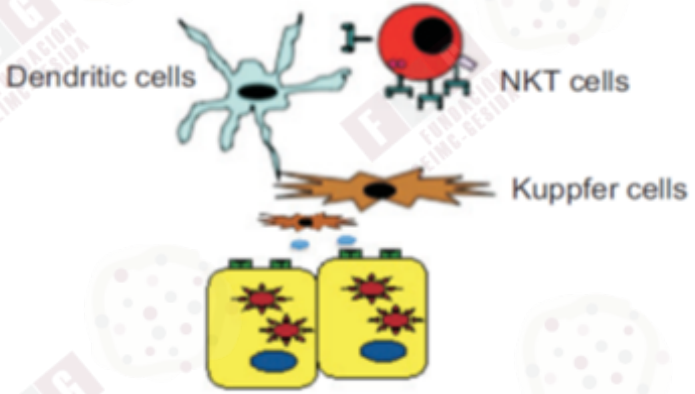


Bertoletti A. Cytotherapy 2017

Estrategias para incrementar la respuesta inmune innata

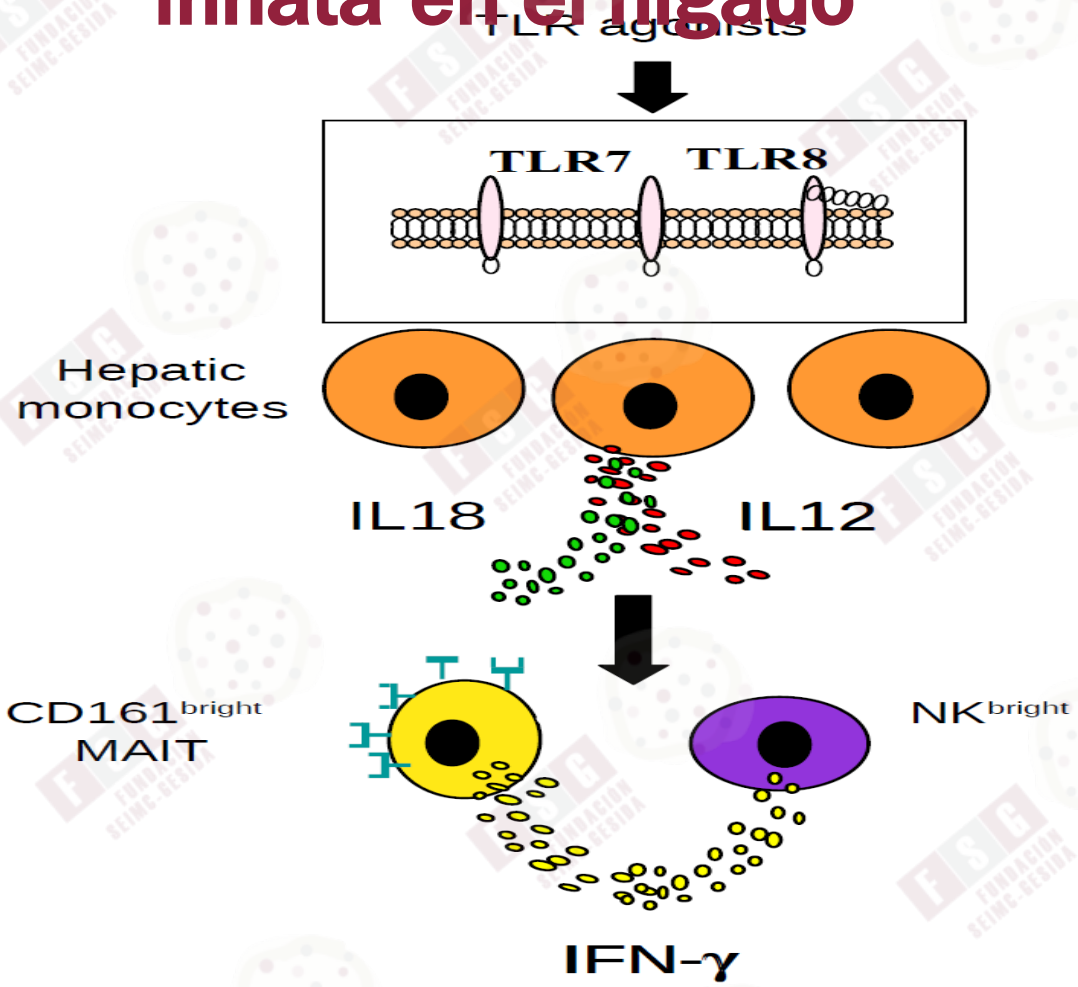
Potenciación de la respuesta inmune innata





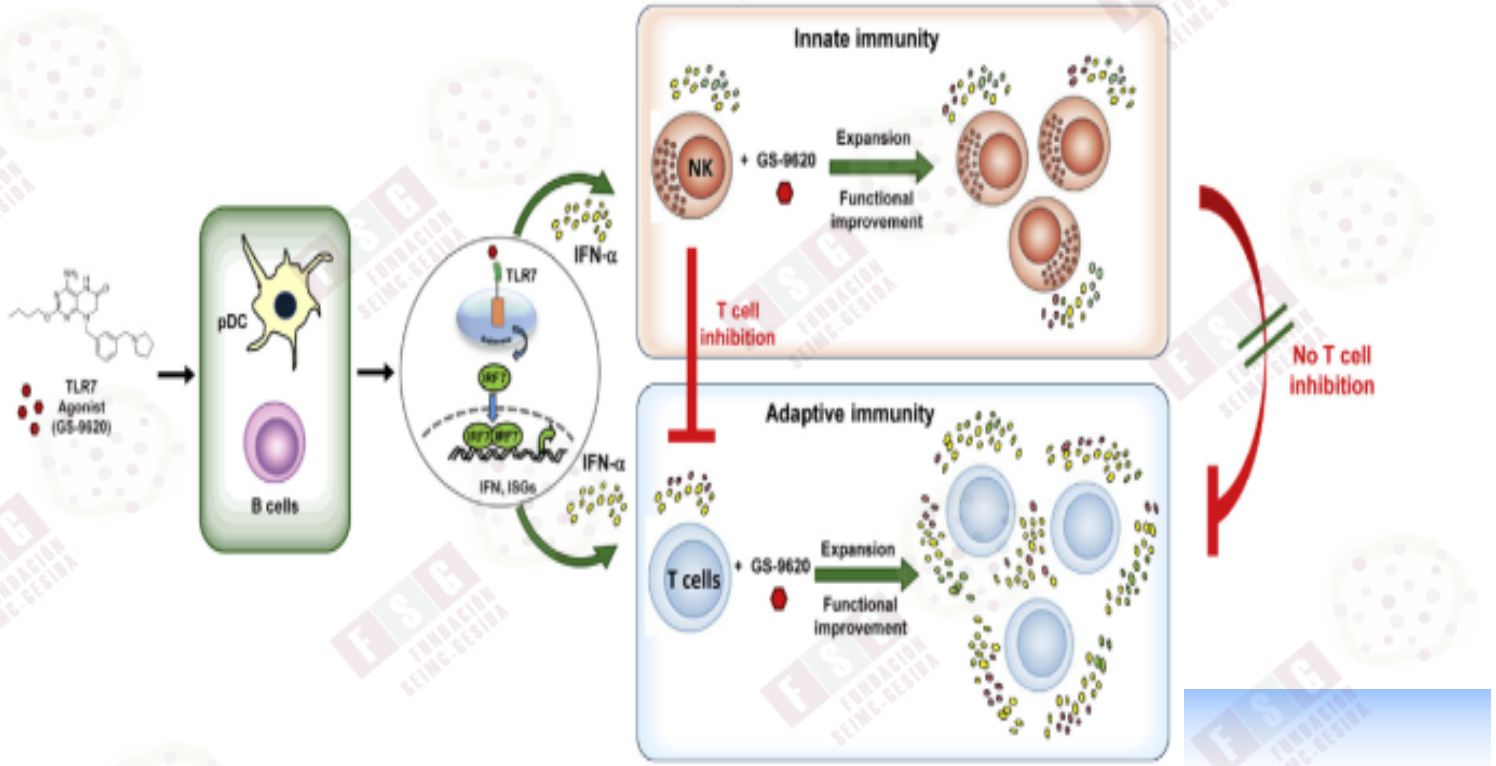
Ferrari, Gastroenterology 2008

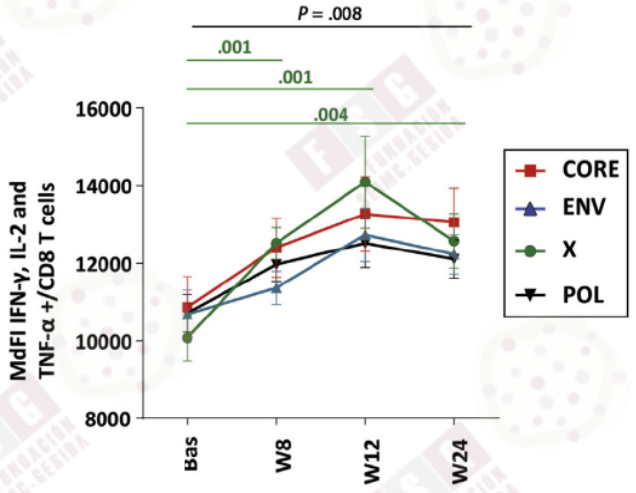
Los agonistas de los TLR inducen la activación de la respuesta innata en el hígado

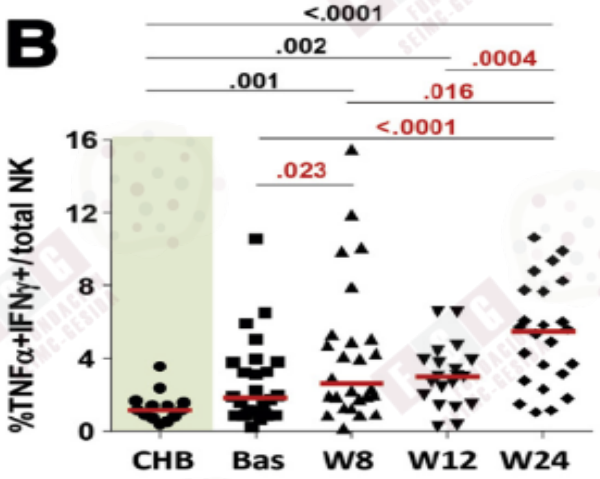


Jo, J. Plos Pathogens 2014

El tratamiento combinado con NUC más el agonista del TLR7 GS-9620 mejora la respuesta celular citotóxica y NK

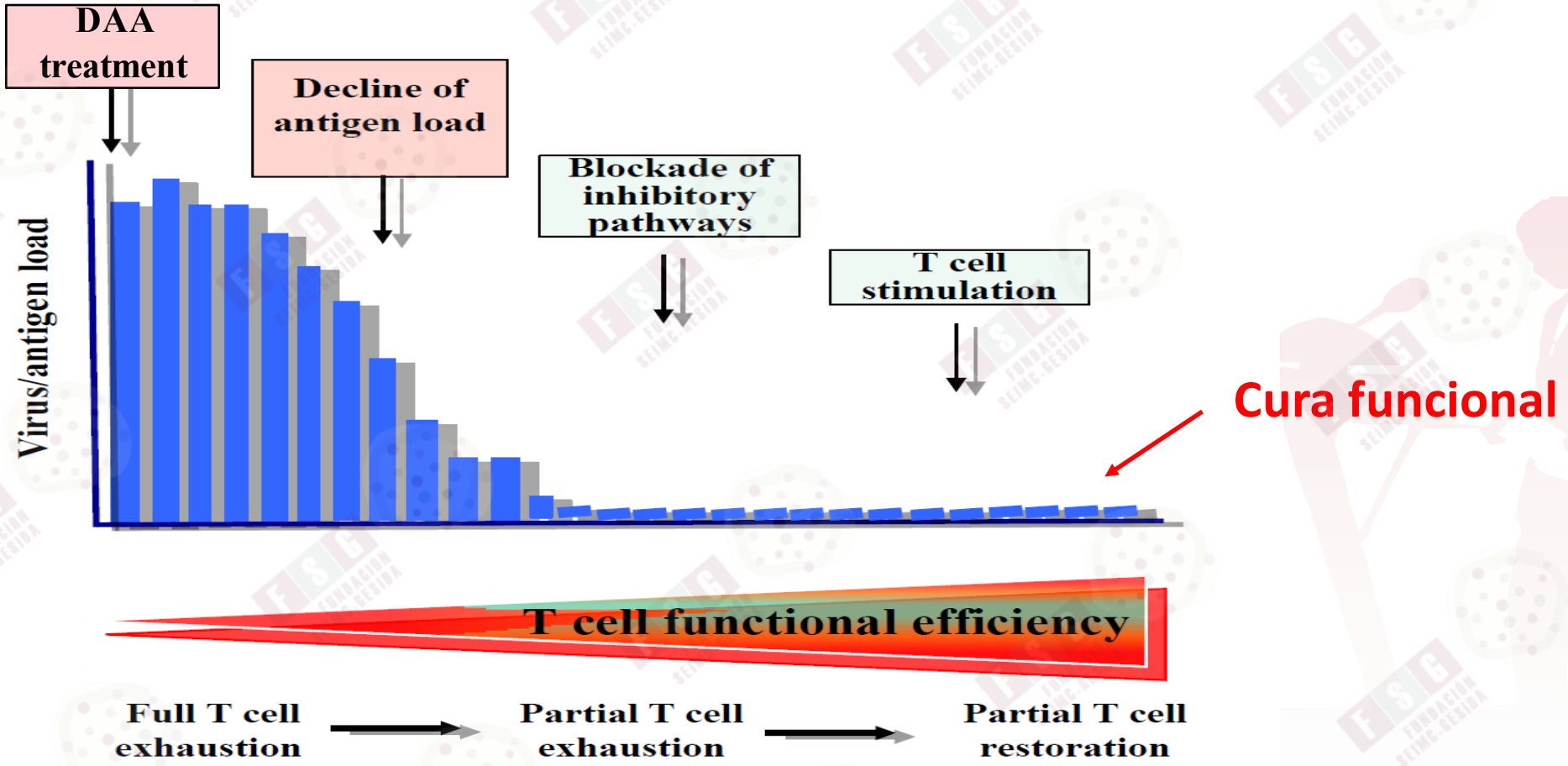




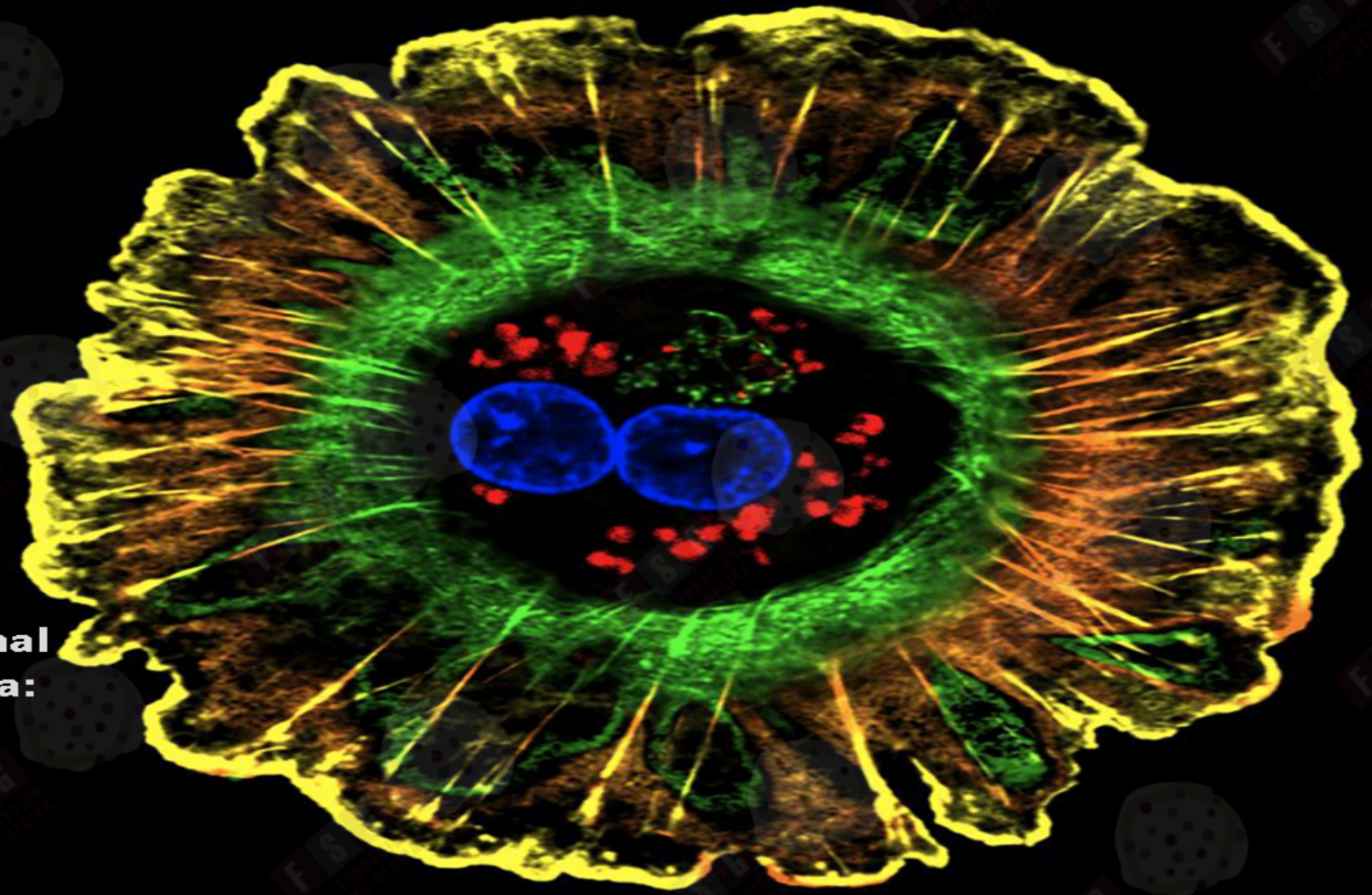


Boni, C. Gastroenterology 2018

Conclusiones



¡Gracias por la atención!



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Hepatocito. Donna Beer. Univ Pittsburgh. NIH's Life

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