Hepatit B Virüsünün Yaşam Döngüsü ve Tedavi İlişkisi

Levent Doğanay
Gastroenteroloji Kliniği,
SBU Ümraniye EAH

GLAB (Genomik Laboratuvar)
İstanbul Anadolu Kuzey Kamu Hastaneleri Birliği

HBV ENFEKSİYONU

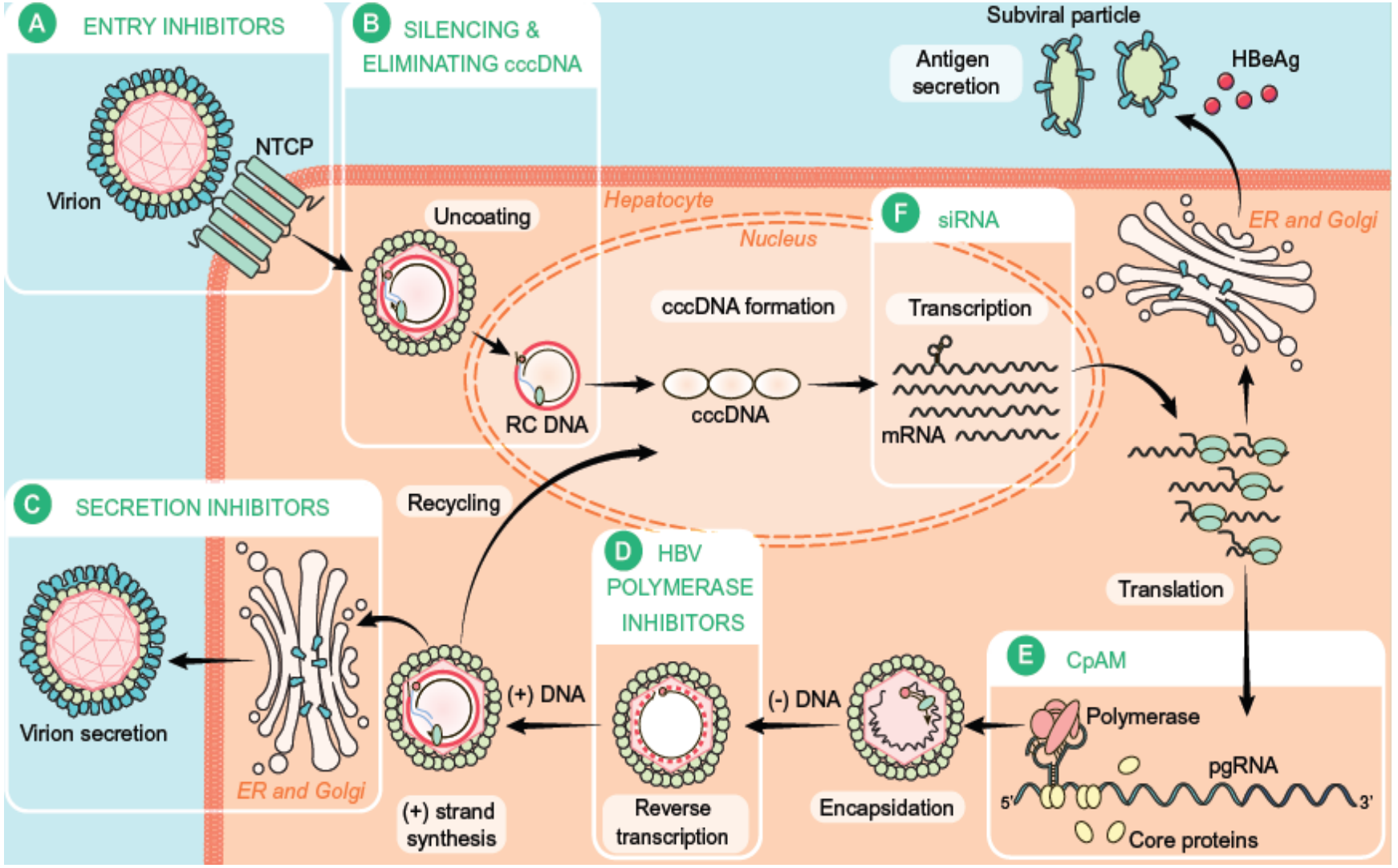
- Tüm dünyada 2 milyar insan virüsle karşılaşmış
- 240 milyon kişi kronik HBV hastası
- Yılda 786.000 kişi HBV ilintili sebeplerden ölmekte (10. sıra)
- Türkiye'de 800.000 kişinin tedavi alması gerektiği öngörülmüştür.
- Tedavi edilmezse önümüzdeki 20 yılda 90.000 siroz, 100.000 HCC vakası görülecektir.
- Türkiye'de KC Tx hastalarının en az %50'si HBV ilintili.

Trepo C, Chan H & Lok A. Hepatitis B virus infection. ***Lancet*** *2014 ; 384:2053-63*

Lozano et al. The Global Burden of Disease Study 2010. ***Lancet*** *2012; 380: 2095–128*

Toy M et al. The cost-effectiveness of treating chronic hepatitis B patients in a median endemic and middle income country, ***Eur J Health Econ****. 2012;13: 663-76*

Prof Y Tokat, Prof. M. Aladağ *kişisel iletişim*



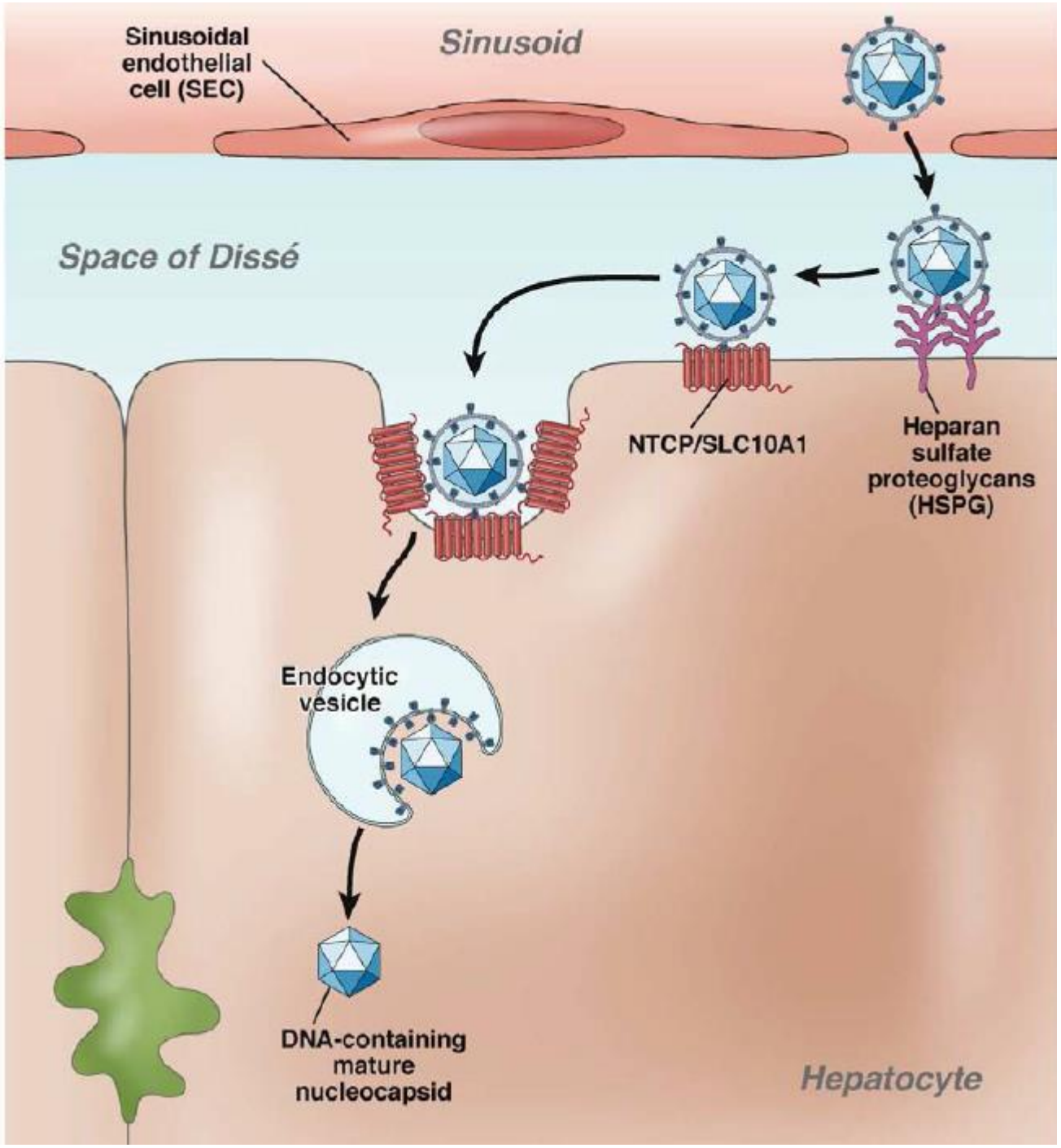
Hepatology Snapshot:

Current therapeutic approaches for HBV infected patients

Upkar S. Gill[1], Patrick T. F. Kennedy[1,*]

[1]Centre for Immunobiology, Blizard Institute, Barts and The London School of Medicine & Dentistry, QMUL, London, UK
[*]Corresponding author: Blizard Institute, Barts and The London School of Medicine & Dentistry, 4 Newark Street, London, E1 2AT. E-mail address: p.kennedy@qmul.ac.uk (P. Kennedy)

EASL | JOURNAL OF HEPATOLOGY


Sinusoidal endothelial cell (SEC)
Sinusoid
Space of Dissé
NTCP/SLC10A1
Heparan sulfate proteoglycans (HSPG)
Endocytic vesicle
DNA-containing mature nucleocapsid
Hepatocyte

Yan *et al*. eLife 2012;1:e00049. DOI: 10.7554/eLife.00049

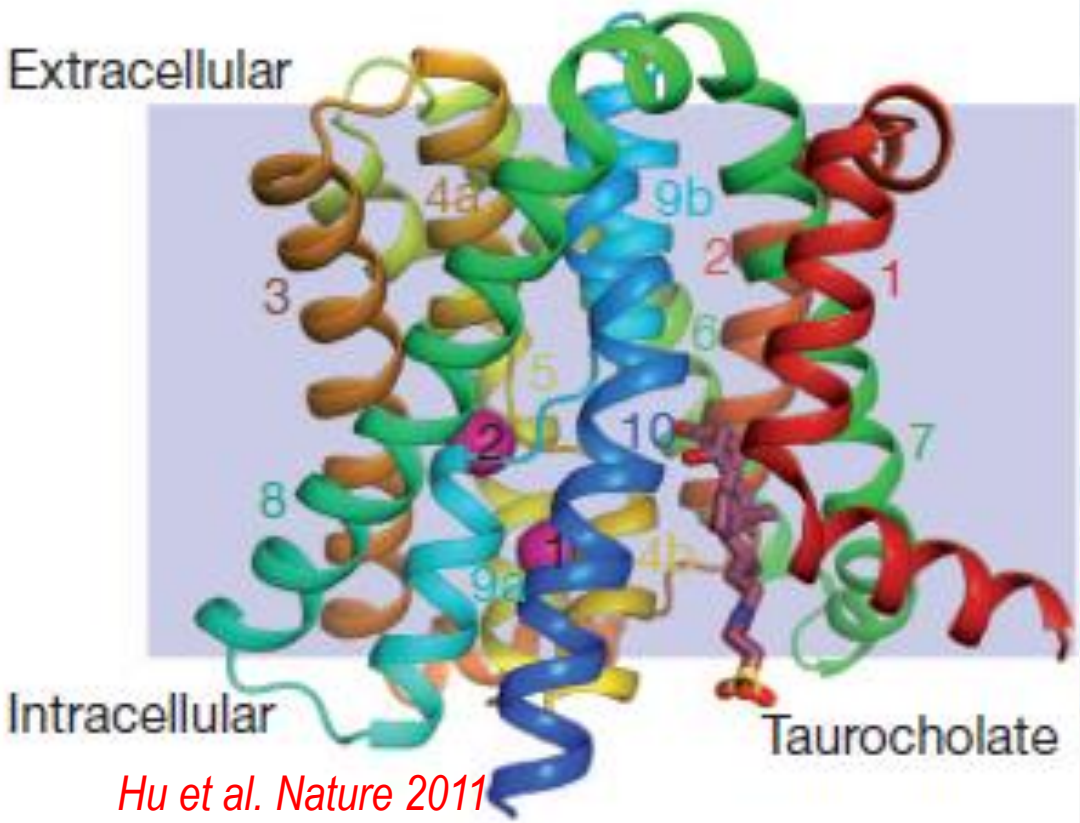
eLIFE
elifesciences.org

RESEARCH ARTICLE

Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus

**Huan Yan[1,2†], G
Zhenchao Gao[1]
Mei Song[2,3], Pa
Xiaofeng Feng**

[1]Graduate prog
[2]National Institu
Chinese Acade
Beijing, China



Hu et al. Nature 2011

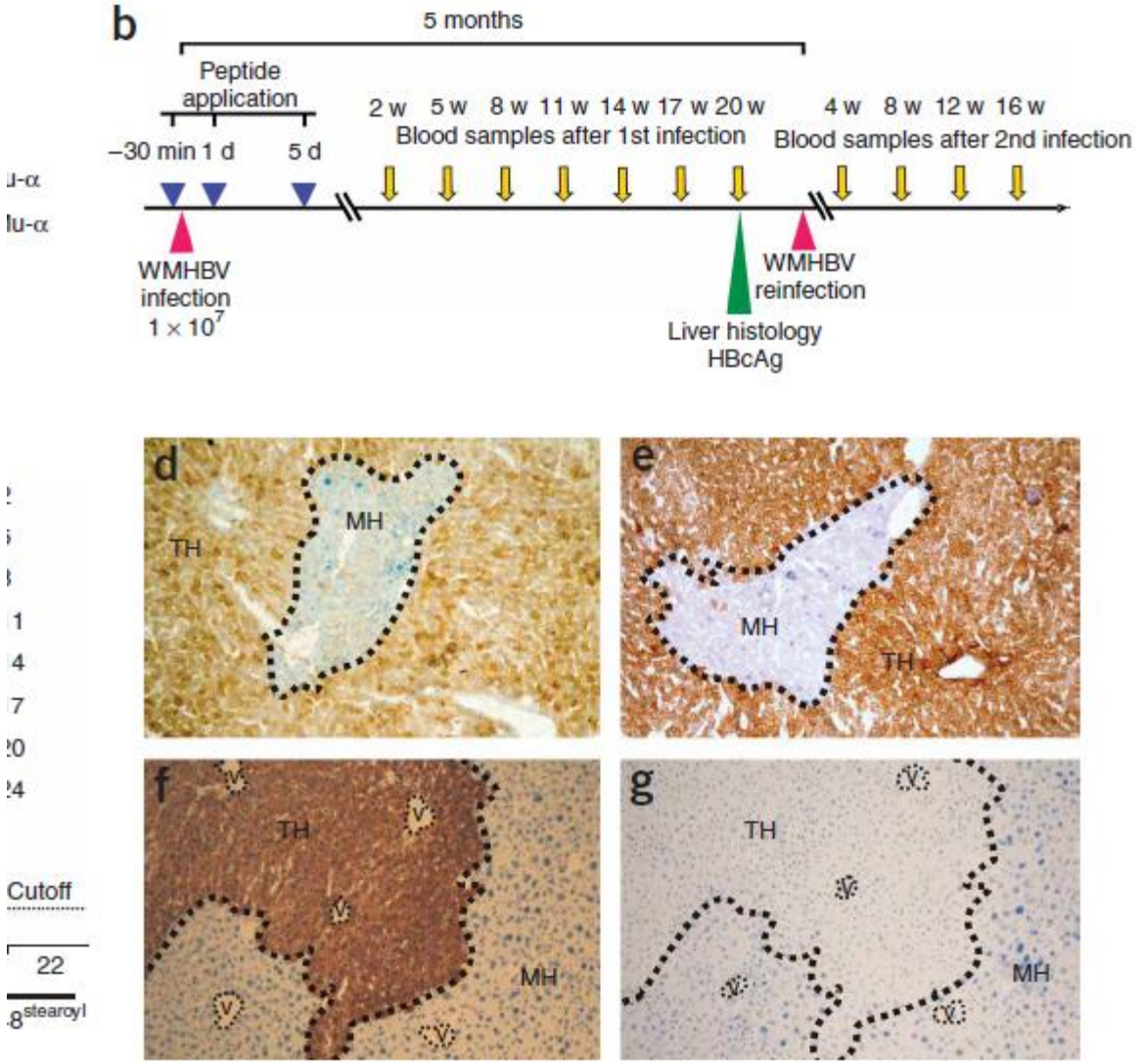
NATURE BIOTECHNOLOGY VOLUME 26 NUMBER 3 MARCH 2008

LETTERS

nature biotechnology

Prevention of hepatitis B virus infection *in vivo* by entry inhibitors derived from the large envelope protein

Joerg Petersen[1,7], Maura Dandri[1,7], Walter Mier[2], Marc Lütgehetmann[1], Tassilo Volz[1], Fritz von Weizsäcker[3,6], Uwe Haberkorn[2], Lutz Fischer[4], Joerg-Matthias Pollok[4], Berit Erbes[5], Stefan Seitz[5] & Stephan Urban[5]


b
5 months
Peptide application
−30 min 1 d
5 d
2 w 5 w 8 w 11 w 14 w 17 w 20 w
Blood samples after 1st infection
4 w 8 w 12 w 16 w
Blood samples after 2nd infection
WMHBV infection
1 × 10^7
WMHBV reinfection
Liver histology
HBcAg
d
TH
MH
e
MH
TH
f
TH
MH
g
TH
MH
Cutoff
22
stearoyl

CrossMark

Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study

Pavel Bogomolov[1,2], Alexander Alexandrov[3], Natalia Voronkova[1,2], Maria Macievich[1,2], Ksenia Kokina[1,2], Maria Petrachenkova[1,2], Thorsten Lehr[4], Florian A. Lempp[5,6], Heiner Wedemeyer[7], Mathias Haag[8,9,10], Matthias Schwab[8,9,10,11,12], Walter E. Haefeli[5,13],

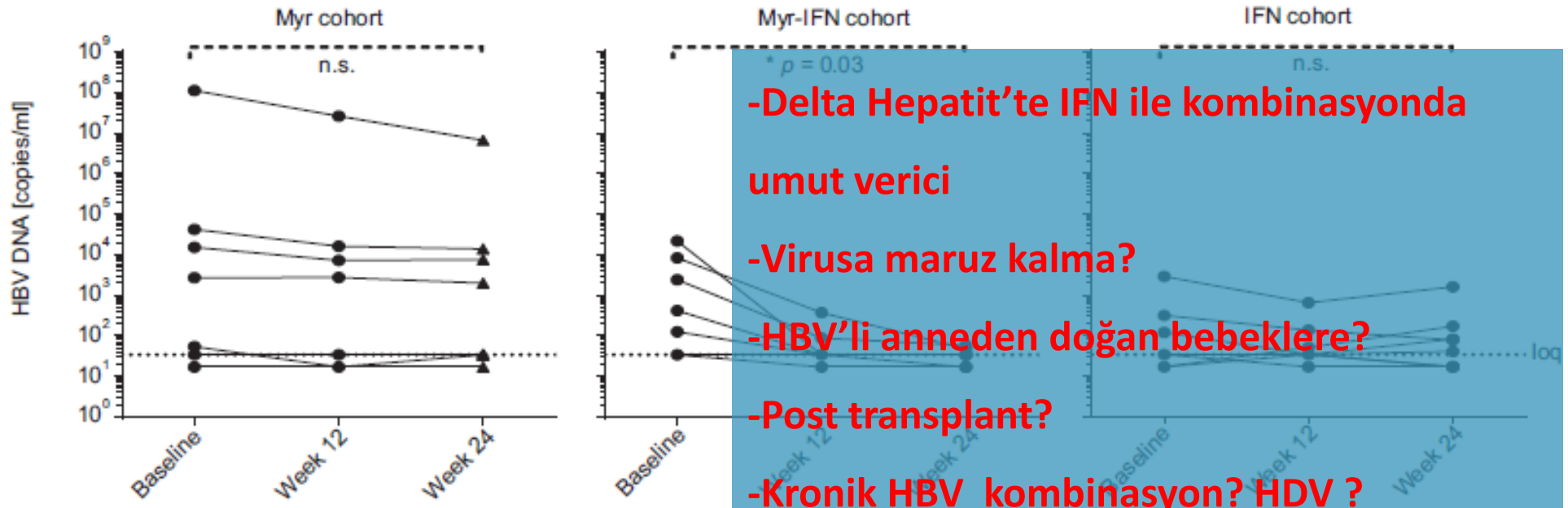


Fig. 4. Virological response to antiviral treatment with myrcludex B and/or pegylated interferon. Expressed as HBV DNA (hepatitis B deoxyribonucleic acid) at baseline and after 12 and 24 weeks of treatment in 8 patients (Myr cohort, IFN cohort) and 7 patients (Myr-IFN cohort).

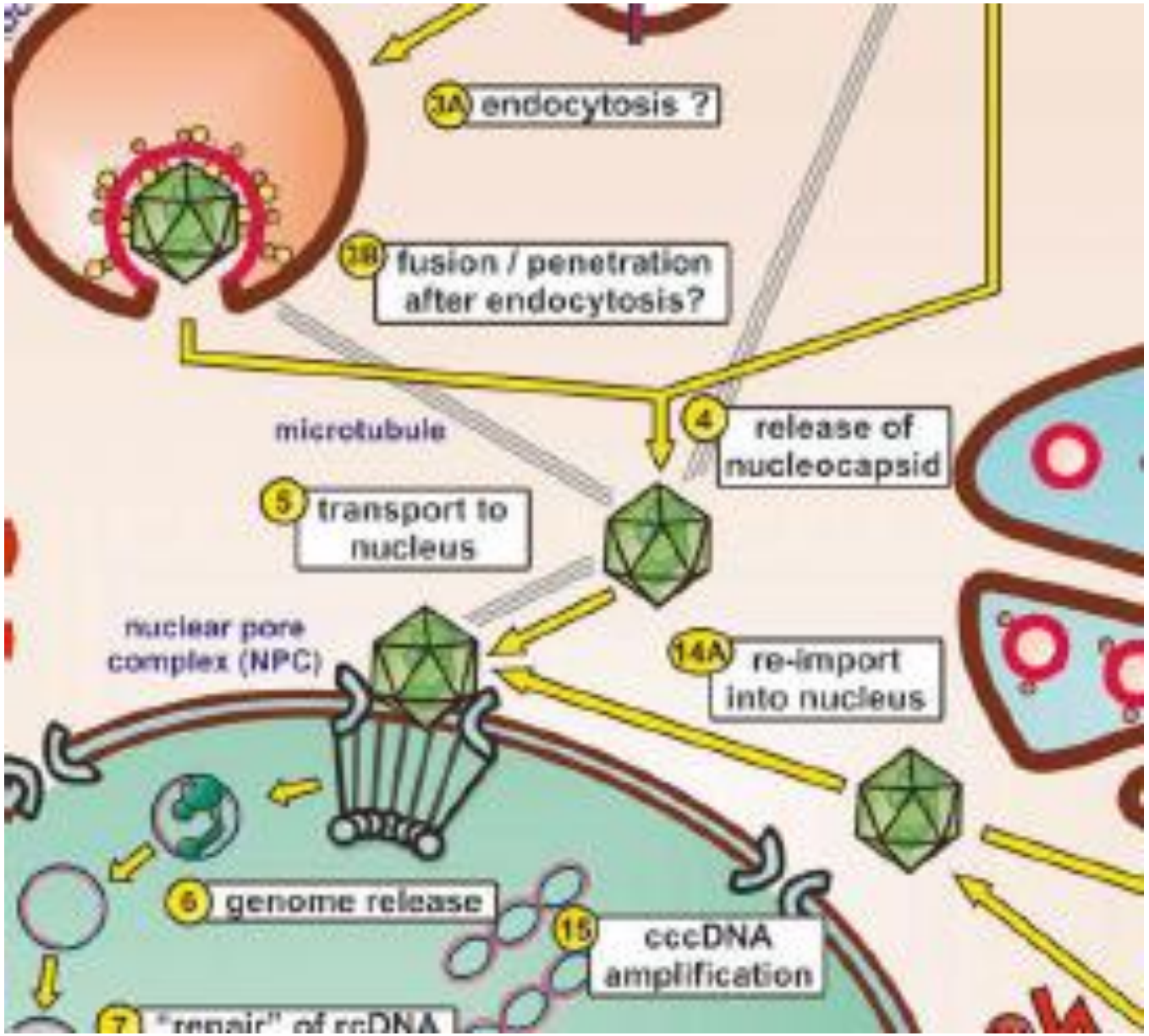
-Delta Hepatit'te IFN ile kombinasyonda umut verici

-Virusa maruz kalma?

-HBV'li anneden doğan bebeklere?

-Post transplant?

-Kronik HBV kombinasyon? HDV ?



Urban S. Et al. Replication cycle of hepatitis B virus. J Hepatology 2010;52:282-4

Inhibition of Hepatitis B Virus Replication by Drug-Induced Depletion of Nucleocapsids

Karl Deres,[1]*† Claus H. Schröder,[7]*† Arnold Paessens,[1]† Siegfried Goldmann,[2] Hans Jörg Hacker,[7] Olaf Weber,[8] Thomas Krämer,[2] Ulrich Niewöhner,[2] Ulrich Pleiss,[3] Jürgen Stoltefuss,[2] Erwin Graef,[1] Diana Koletzki,[1] Ralf N. A. Masantschek,[1] Anja Reimann,[7] Rainer Jaeger,[5] Rainer Groβ,[6] Bernhard Beckermann,[4] Karl-Heinz Schlemmer,[4] Dieter Haebich,[2] Helga Rübsamen-Waigmann[1]†

Chronic hepatitis B virus (HBV) infection is a major cause of liver disease. Only interferon-α and the nucleosidic inhibitors of the viral polymerase, 3TC and adefovir, are approved for therapy. However, these therapies are limited by the side effects of interferon and the substantial resistance of the virus to nucleosidic inhibitors. Potent new antiviral compounds suitable for monotherapy or combination therapy are highly desired. We describe non-nucleosidic inhibitors of HBV nucleocapsid maturation that possess in vitro and in vivo antiviral activity. These inhibitors have potential for future therapeutic regimens to combat chronic HBV infection.

The development of novel combination-based therapies for HBV infections requires antivirals that block the viral life cycle by interference with functions other than those associated with the viral polymerase (*1*–*3*). Here, we present the drug profile and mech-

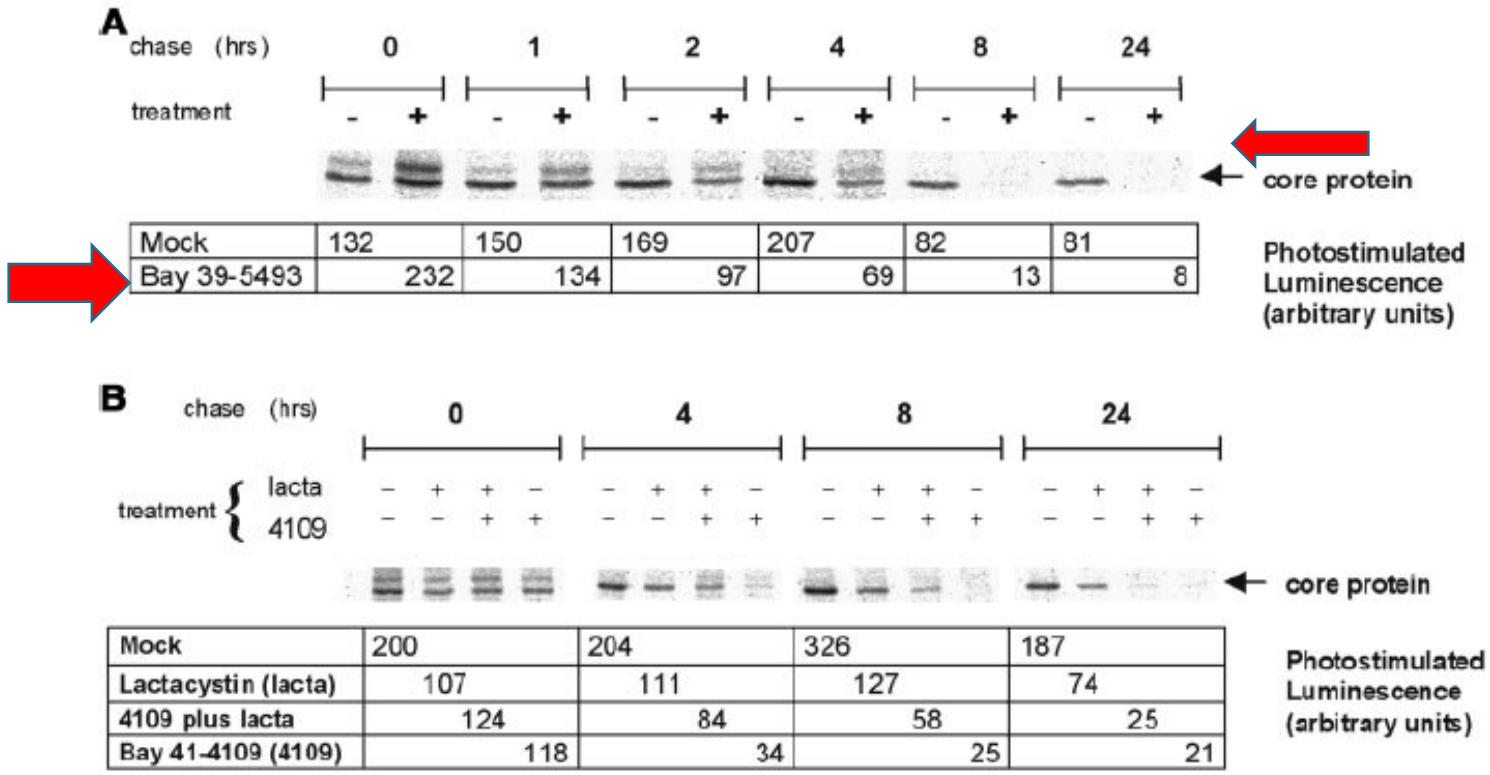
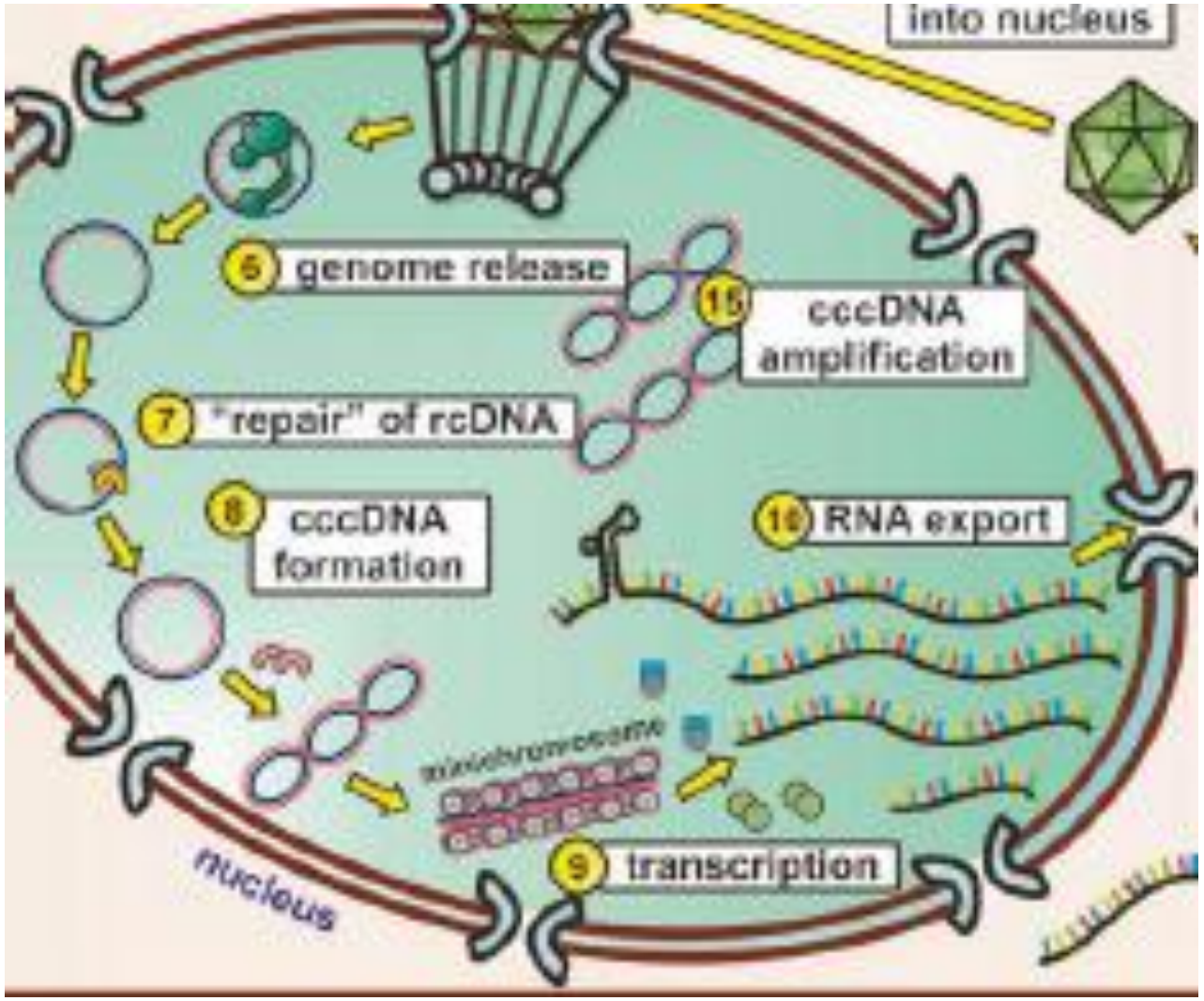


Fig. 4. Bay 41-4109 and Bay 38-7690 induce depletion of newly synthesized core proteins in HepG2.2.15 cells, apparently by way of the proteasome pathway. (**A**) Cells subjected to a pulse-chase procedure after 2 days in the presence or absence of Bay 39-5493 (0.2 μM) were extracted and immunoprecipitated for assay of core protein (*11*). Photostimulated luminescence (*11*) served as a quantitative measure for the amount of recovered labeled core protein. Newly synthesized core protein faded in the presence (+) of Bay 39-5493 (0.2 μM), but not in mock-treated cells (−). (**B**) Cells first treated with or without Bay 41-4109 (4109; 0.2 μM) and/or lactacystin (lacta; 10 μM) for 2 days were subjected to pulse chase (*11*) (top). Lactacystin delayed degradation of newly synthesized core protein by the proteasome pathway (see 4 and 8 hours of chase).

EASL 2017
Faz 2
GLS4JS 1x1 PO
24 HBV hastası
28 günlük tedavi
2.3 log düşüş

Code	HepAD38 EC_{50}, µM	HepAD38 EC_{90}, µM	HepG2 CC_{50}, µM (TI)
02 (B-70)	2.3	5.9	8.4 (3.7)
03 (B-73)	7.6	> 10	3.7 (0.5)
05 (B-79)	1.3	2.9	61 (47)
06 (B-80)	0.4	2.8	5.8 (15)
07 (B-81)	4.3	8.9	4.5 (1.0)
08 (B-83)	7.7	> 10	18 (2.3)
09 (B-89)	1.2	5.2	> 100 (> 83)
10 (B-108)	1.3	7.9	> 100 (> 77)

e	HepAD38 EC_{50}, µM	HepAD38 EC_{90}, µM	HepG2 CC_{50}, µM (TI)
12 (B-120)	0.3	0.9	32 (99)
AZ-13 (B-121)	0.4	1.0	19 (53)
AZ-14 (B-122)	6.9	> 10	47 (6.9)
AZ-16 (B-124)	7.6	> 10	20 (2.7)
AZ-17 (B-125)	8.8	> 10	> 100 (> 11)
AZ-18 (B-142)	5.9	9.2	5.6 (1.0)
AZ-01 (B-61)	*0.49* *0.52*	*1.0* *1.0*	*> 100 (> 200)* *> 100 (> 200)*
3TC (+ control)	*0.06*	*0.2*	*> 100 (> 1000)*



Urban S. Et al. Replication cycle of hepatitis B virus. J Hepatology 2010;52:282-4

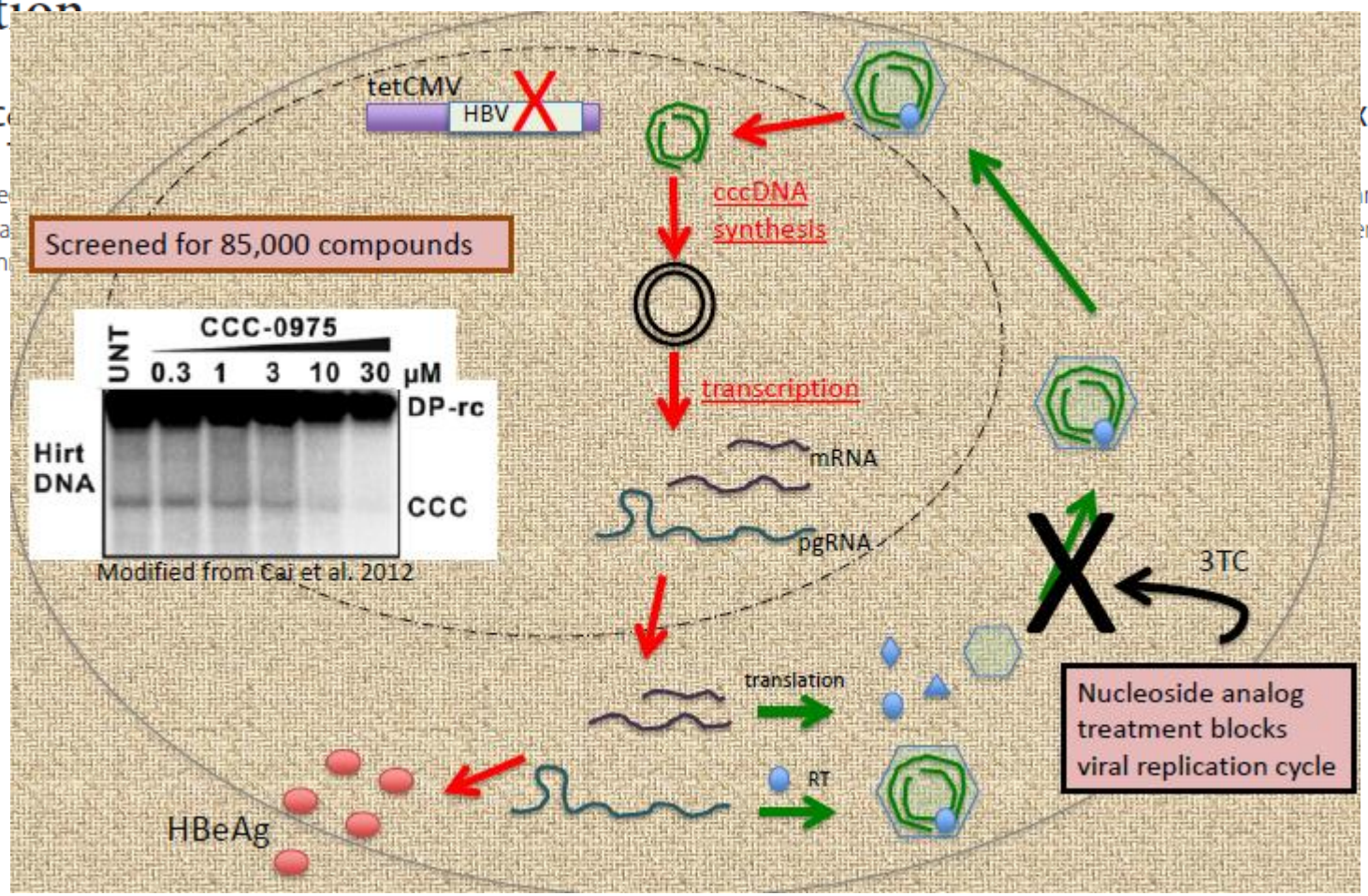
AAC Journals.ASM.org

August 2012 Volume 56 Number 8 Antimicrobial Agents and Chemotherapy p. 4277–4288

Identification of Disubstituted Sulfonamide Compounds as Specific Inhibitors of Hepatitis B Virus Covalently Closed Circular DNA Formation

Dawei Cai,[a] Ce ...u,[b]
Ju-Tao Guo,[a] ...

Institute for Biote... nsylvania, USA[a];
Institute for Hepa... enter,
Philadelphia, Pen...

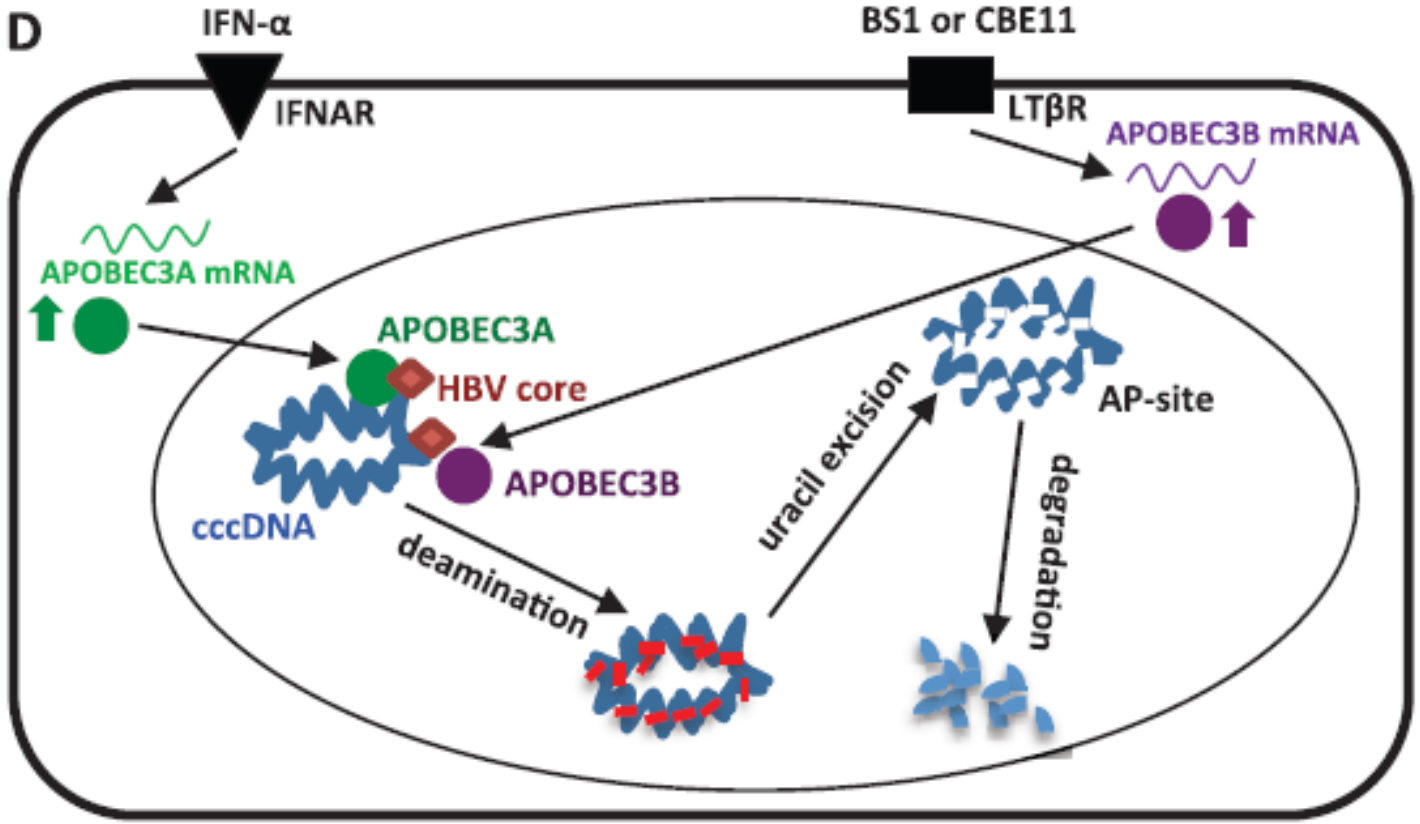


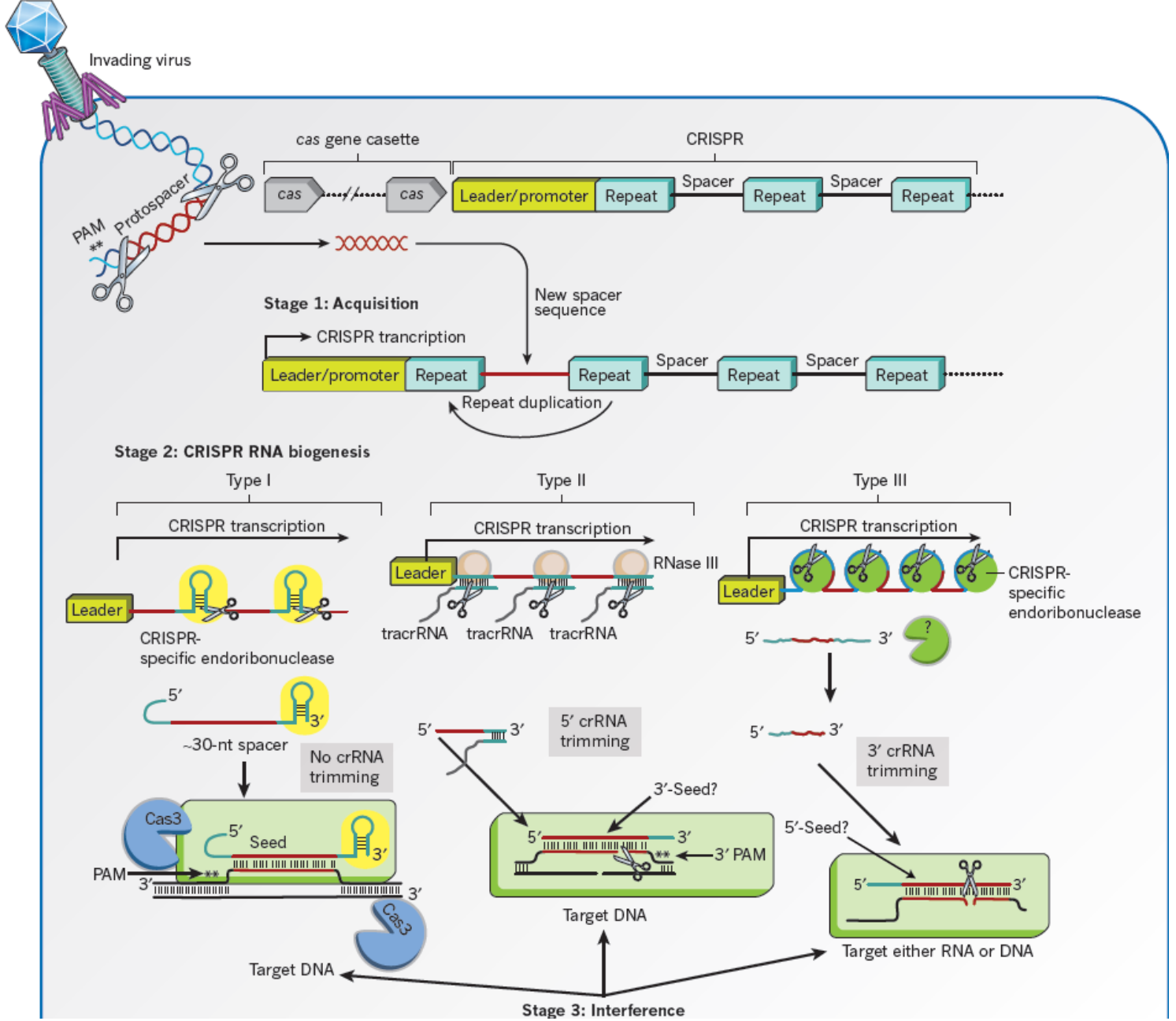
Science
AAAS

Specific and Nonhepatotoxic Degradation of Nuclear Hepatitis B Virus cccDNA

Julie Lucifora *et al.*

Science **343**, 1221 (2014);
DOI: 10.1126/science.1243462





Weidenheft et al.RNA guided gene silencing systems in archea and bacteria.Nature 2012;482:331-38

doi:10.1038/mtna.2014.38

The CRISPI
Intrahepati

of the

Su-Ru Lin[1], Hung-Chih Ya
Chih-Chiang Wang[2], Yueh

rng-Yi Wang[2],
3,4,5

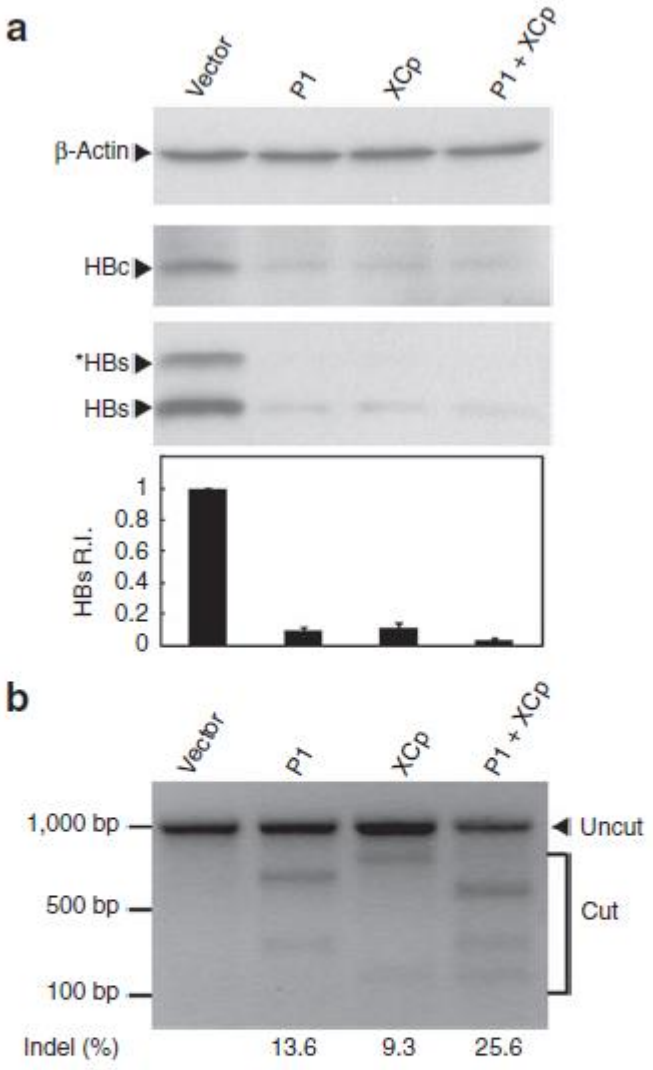
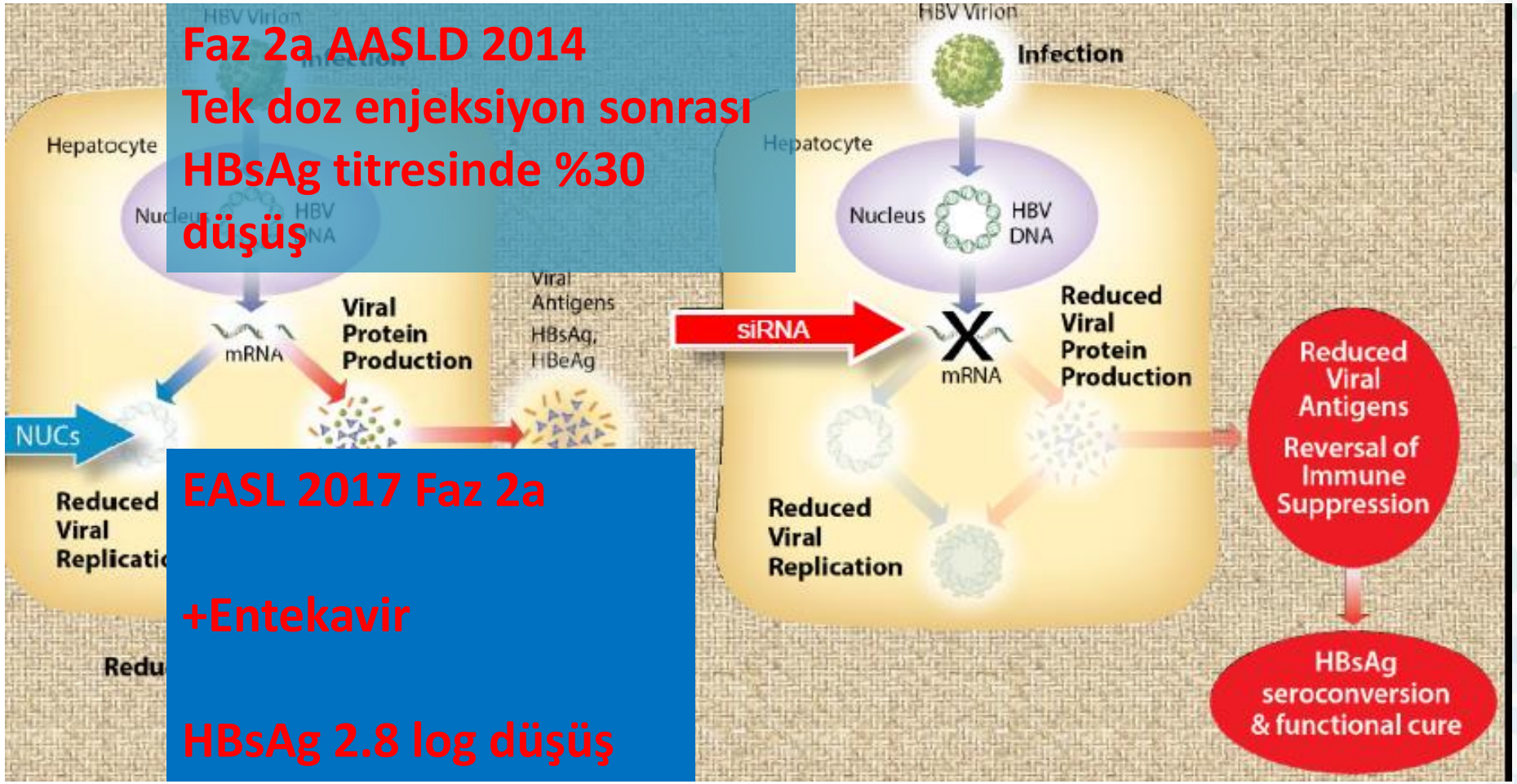


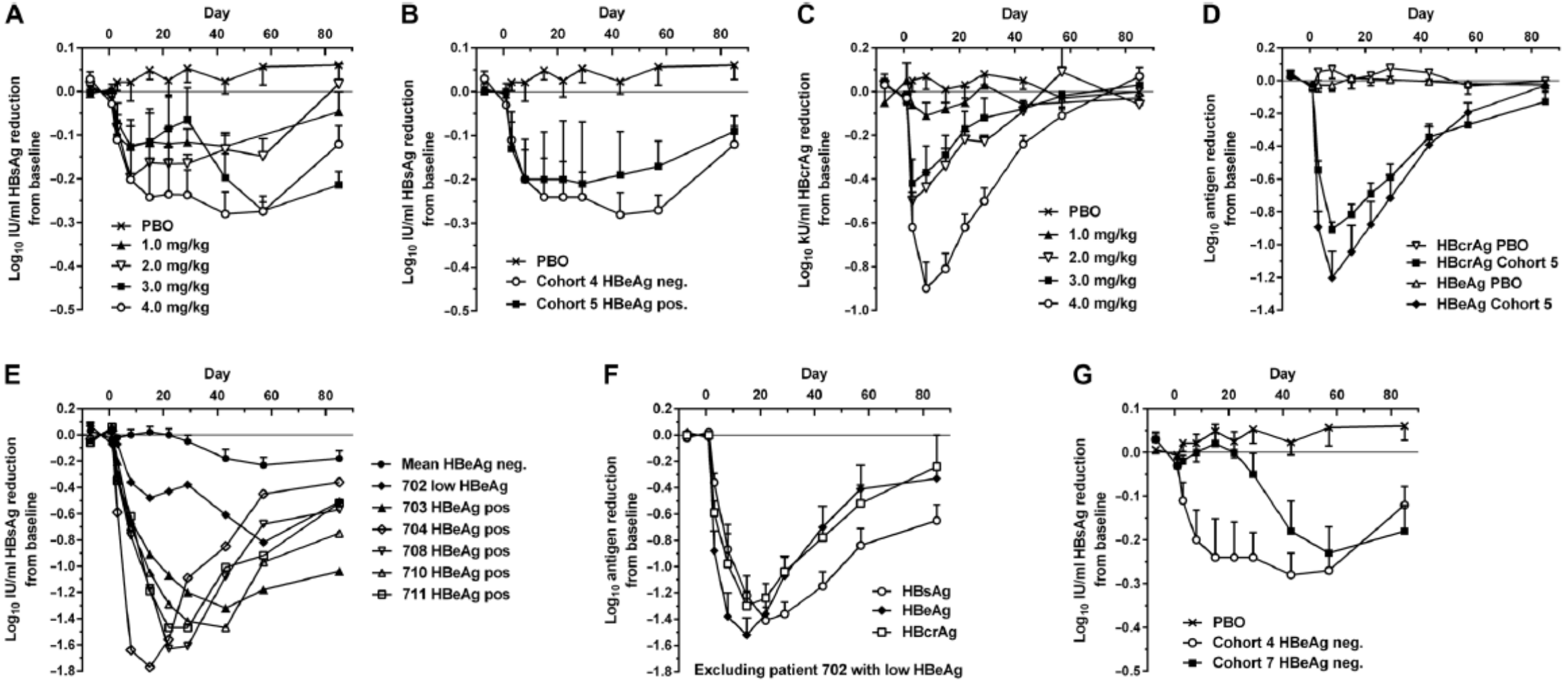
Figure 3 Suppression of the (hepatitis B virus) HBV protein expression via the multiplex HBV-specific gRNA. The HBV-expression vector was cotransfected to Huh7 cells with the gRNA/Cas9 dual expression vectors. The lysate was collected after 48

RNAi -ARC-520


Faz 2a AASLD 2014
Tek doz enjeksiyon sonrası
HBsAg titresinde %30
düşüş
HBV Virion
Infection
Hepatocyte
Nucleus
HBV DNA
mRNA
Viral Protein Production
Viral Antigens
HBsAg, HBeAg
siRNA
NUCs
Reduced Viral Replication
Reduced Viral Protein Production
Reduced Viral Antigens
Reversal of Immune Suppression
HBsAg seroconversion & functional cure
EASL 2017 Faz 2a
+Entekavir
HBsAg 2.8 log düşüş

INFECTIOUS DISEASE

RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated



Characterization of HBV transcripts

	HBeAg-negative 88A010		HBeAg-positive A2A004	
HBV transcripts	Number of transcripts	Percentage	Number of transcripts	Percentage
HBV nonfusion	128	22.7	2466	90.5
HBV-chimpanzee	375*	66.4	35†	1.3
HBV-HBV	57	10.1	218‡	8.0
HBV-other	5	0.9	7	0.3
Total	565	100	2726	100

Antiviral Research 107 (2014) 6–15

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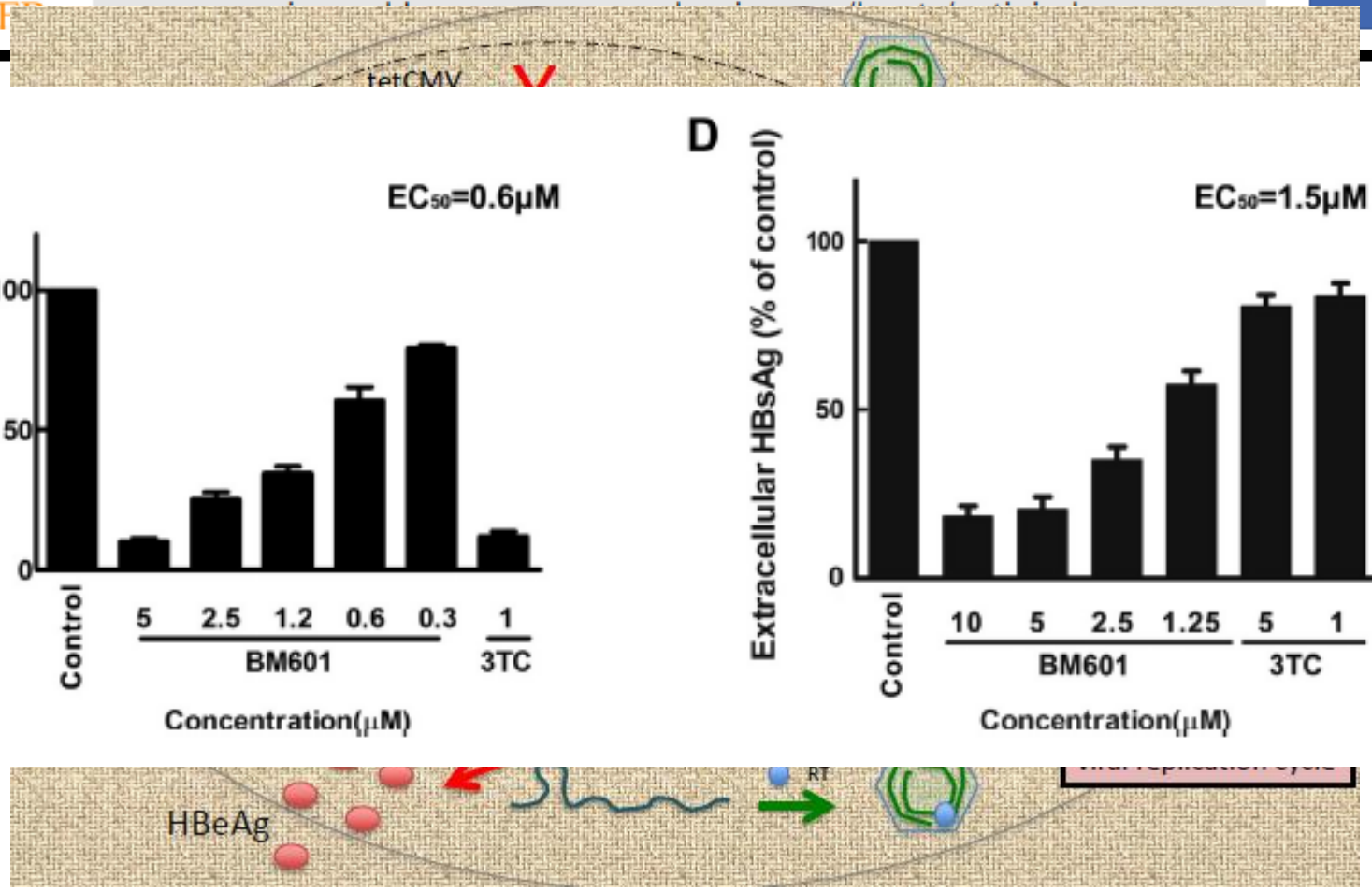
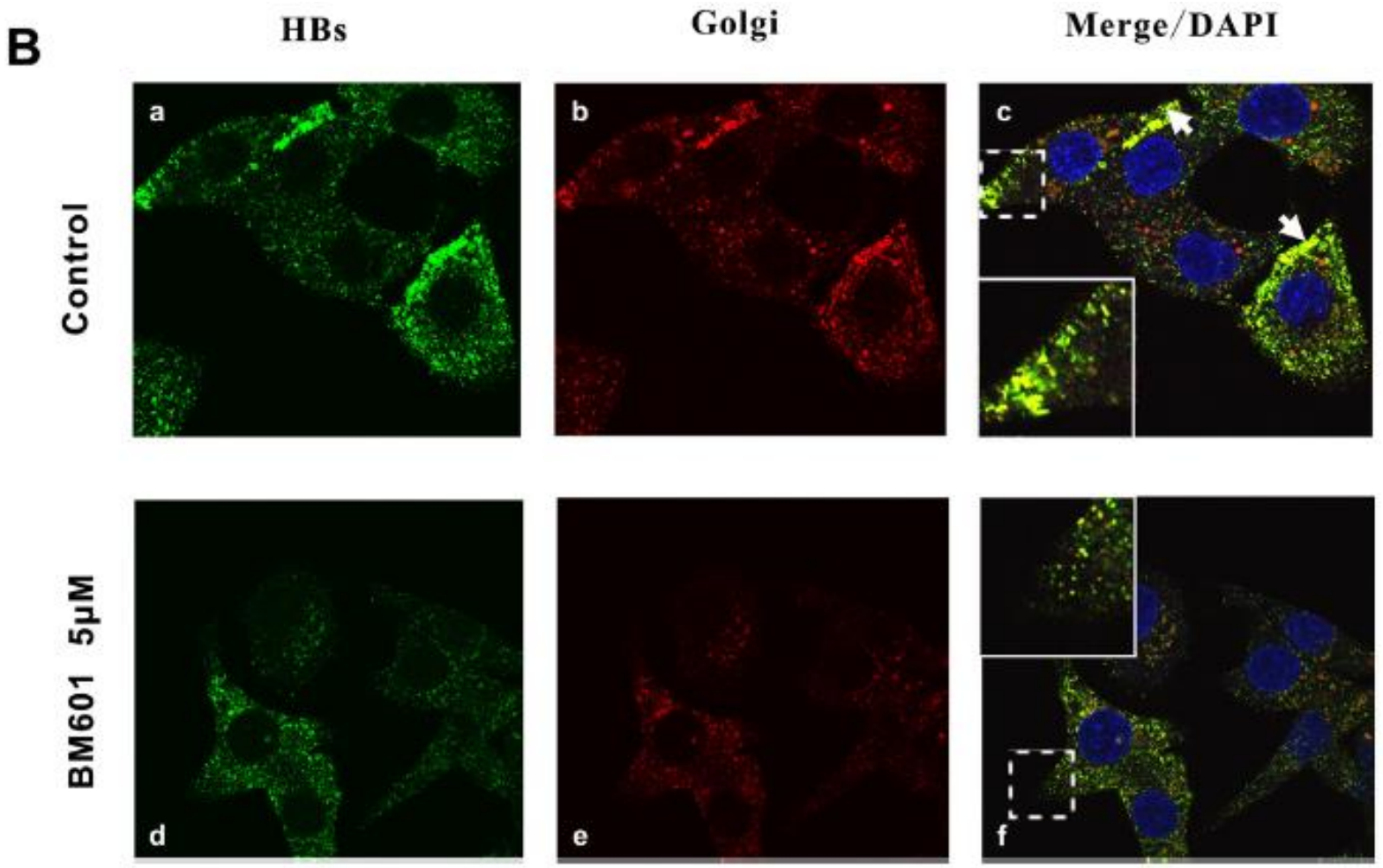
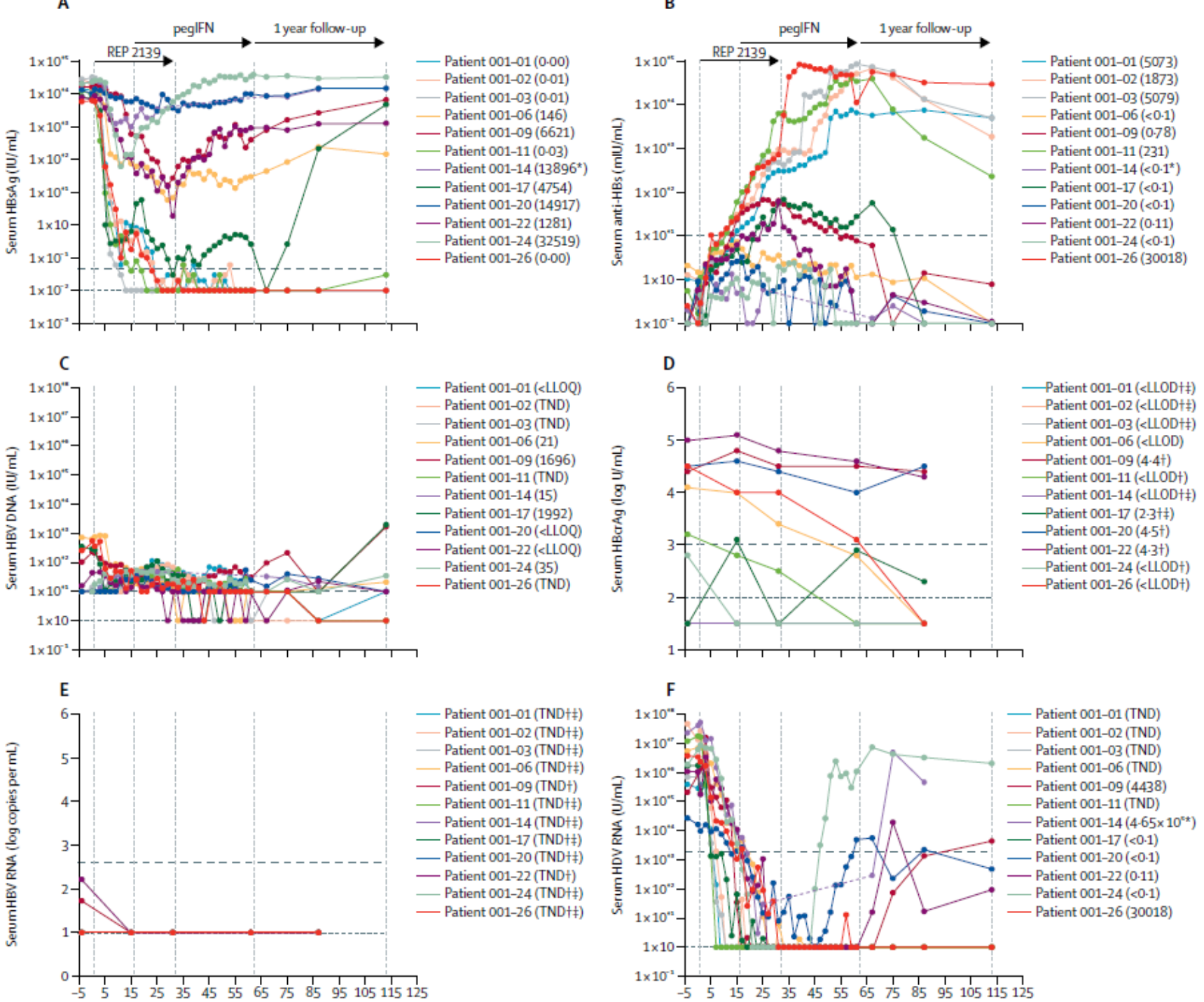



B
HBs
Golgi
Merge/DAPI
Control
BM601 5μM
a
b
c
d
e
f

Safety
alfa-2
virus a
REP 3(

Michel Bazinet,
Emmanuel Gor



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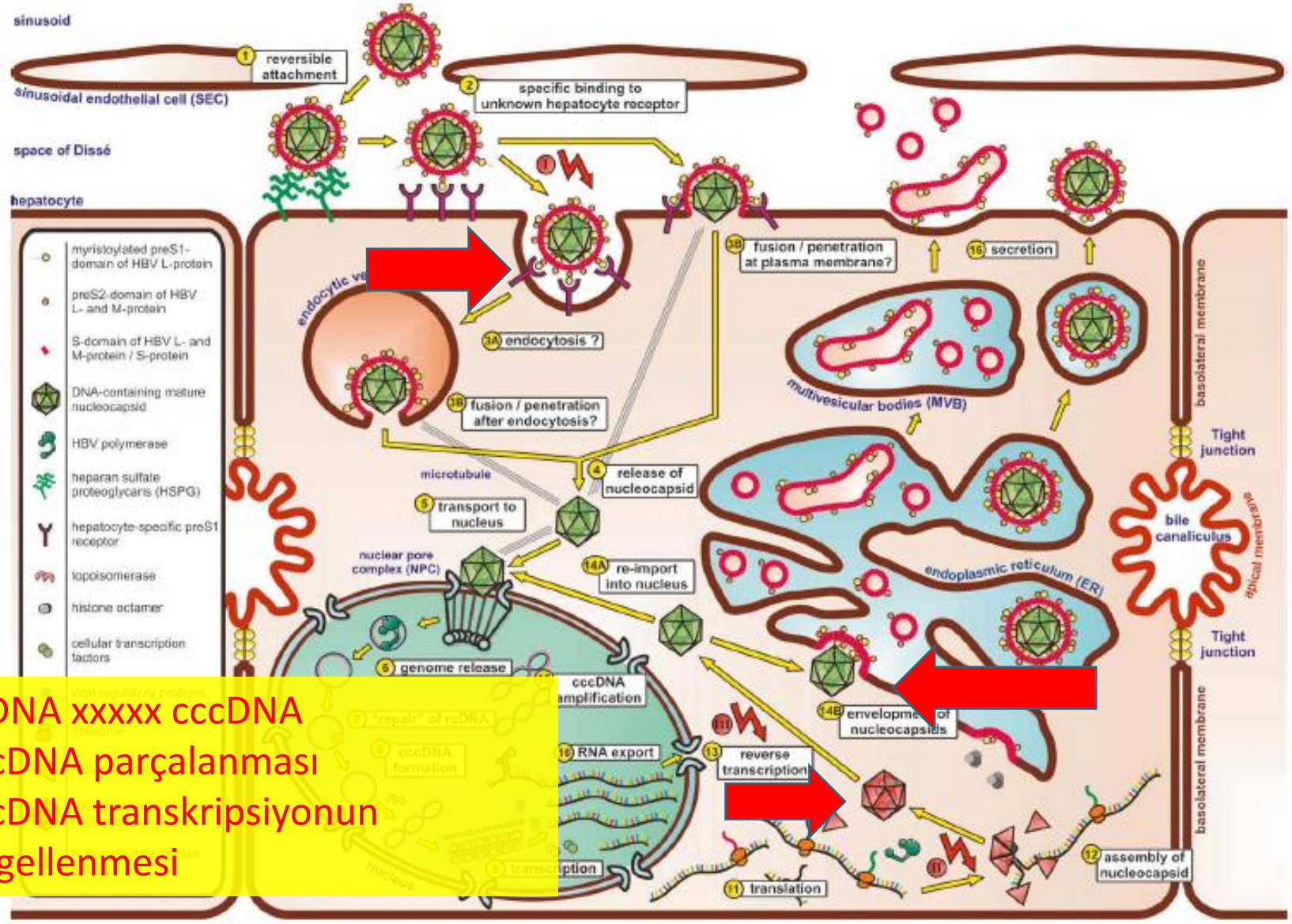
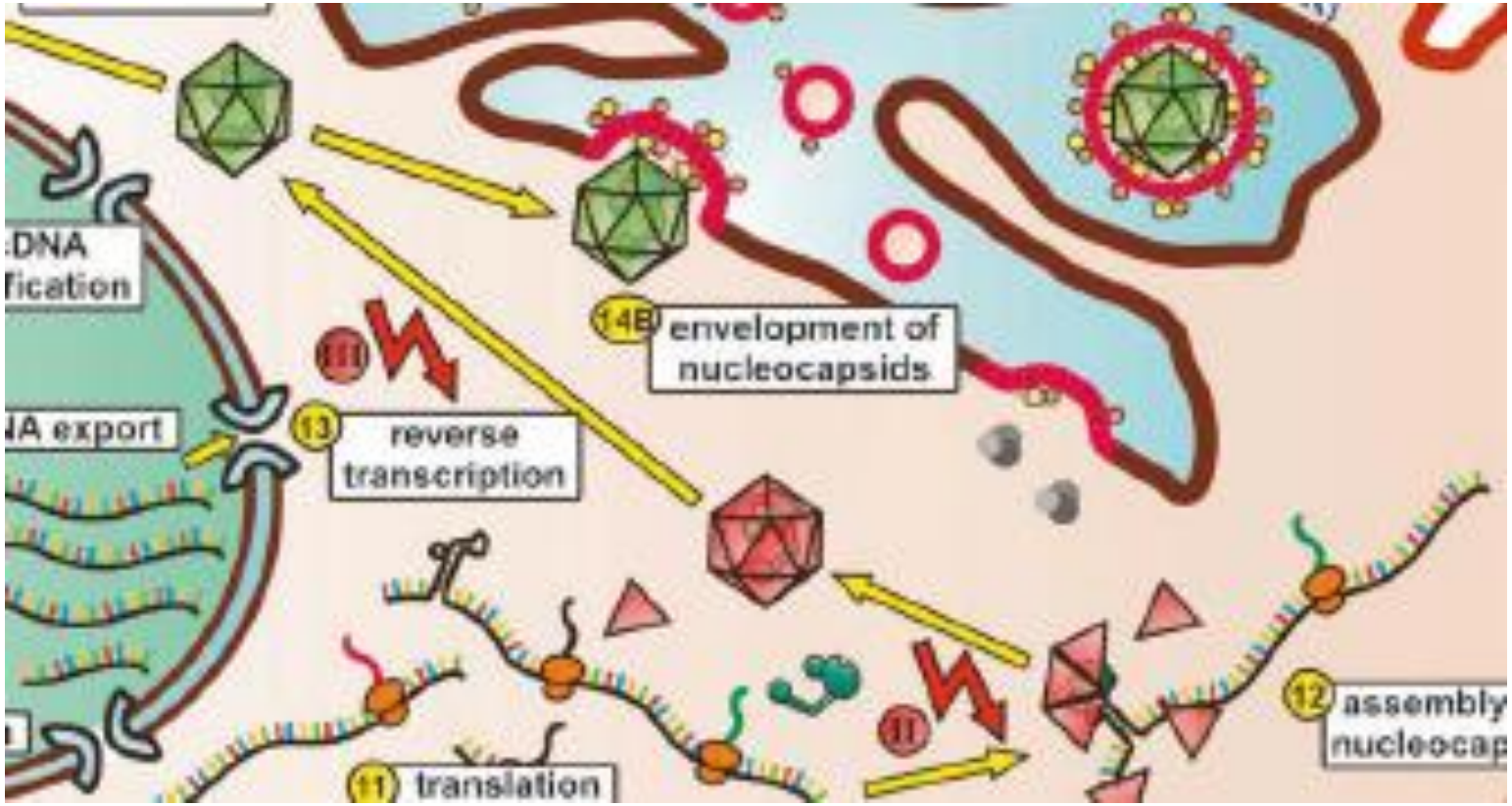


rcDNA xxxxx cccDNA
cccDNA parçalanması
cccDNA transkripsiyonun engellenmesi

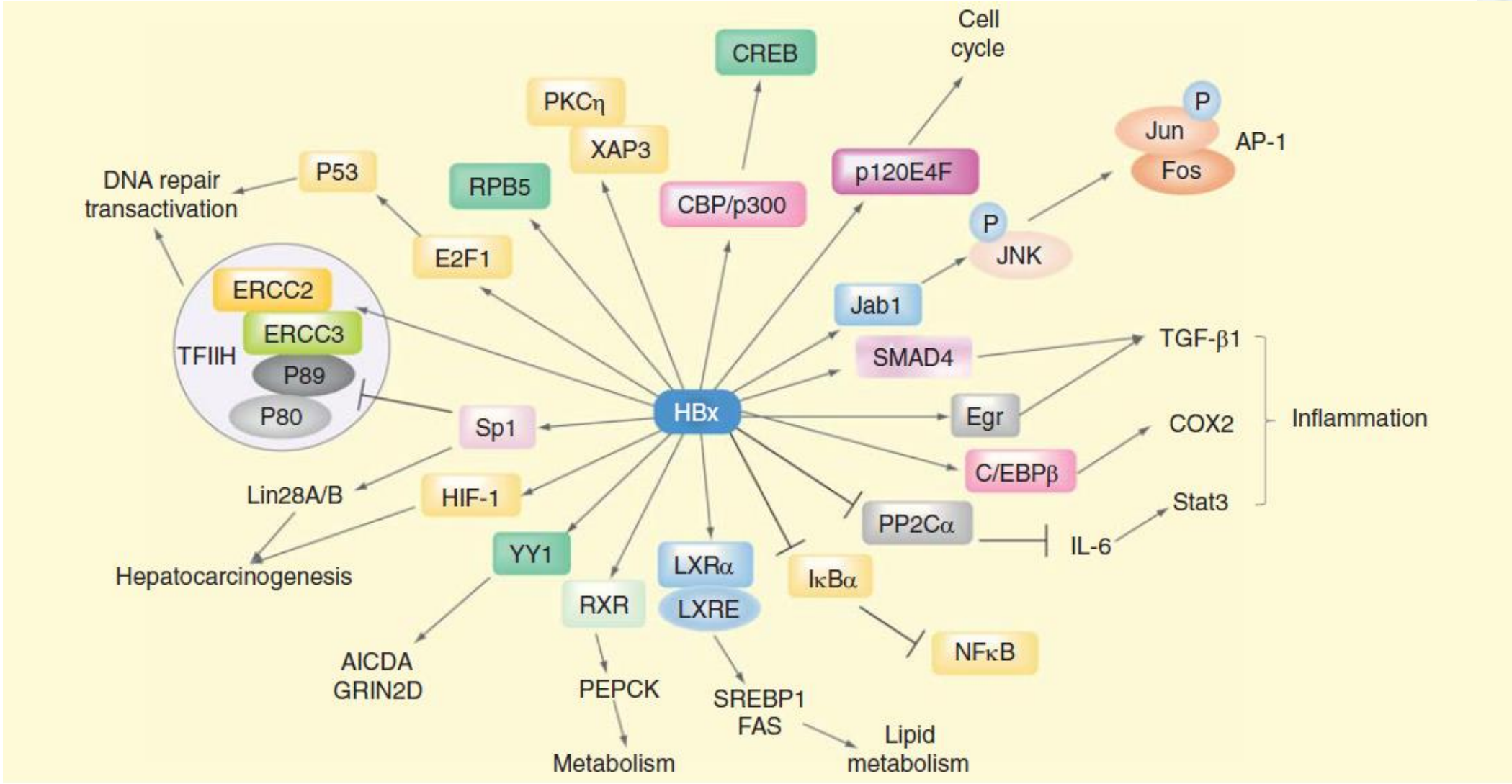
Urban S. Et al. Replication cycle of hepatitis B virus. J Hepatology 2010;52:282-4

Reverse Transcriptase



Urban S. Et al. Replication cycle of hepatitis B virus. J Hepatology 2010;52:282-4

BİZ NE YAPIYORUZ?

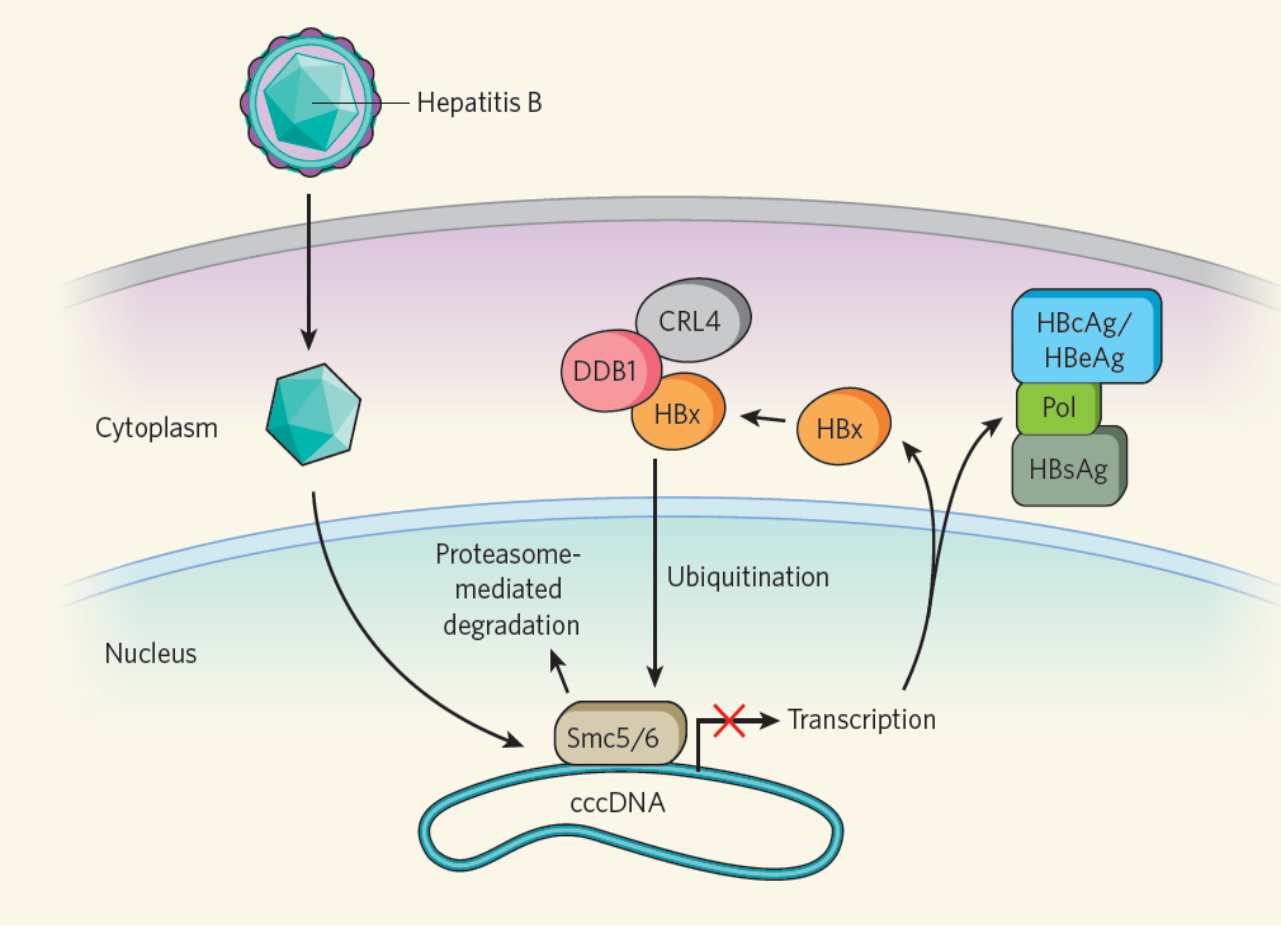


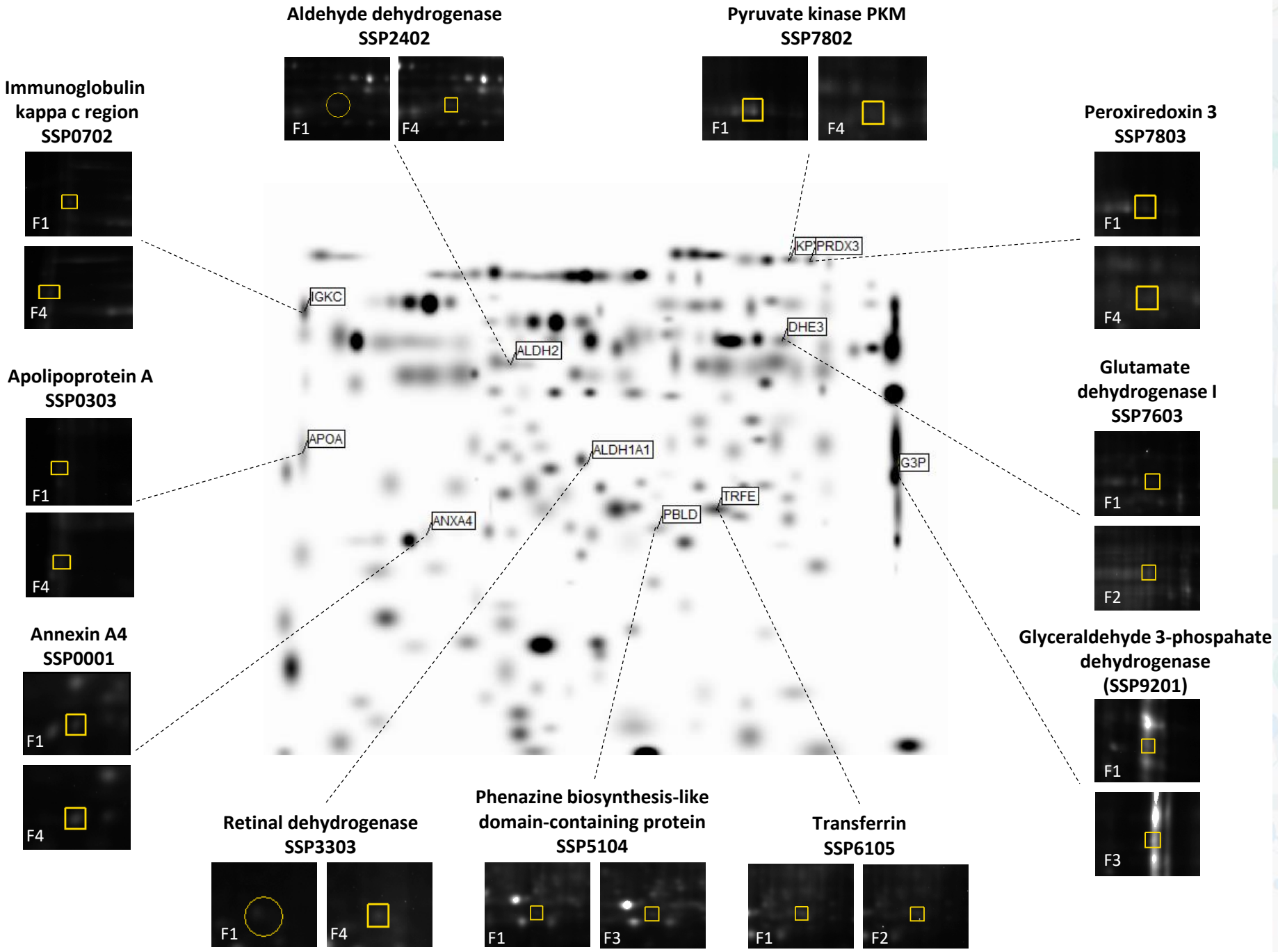
Xie et al. Using proteomics to identify HBx interactome. **Expert Rev. Proteomics** 2014 11(1), 59–74

Hepatitis B virus X protein identifies the Smc5/6 complex as a host restriction factor

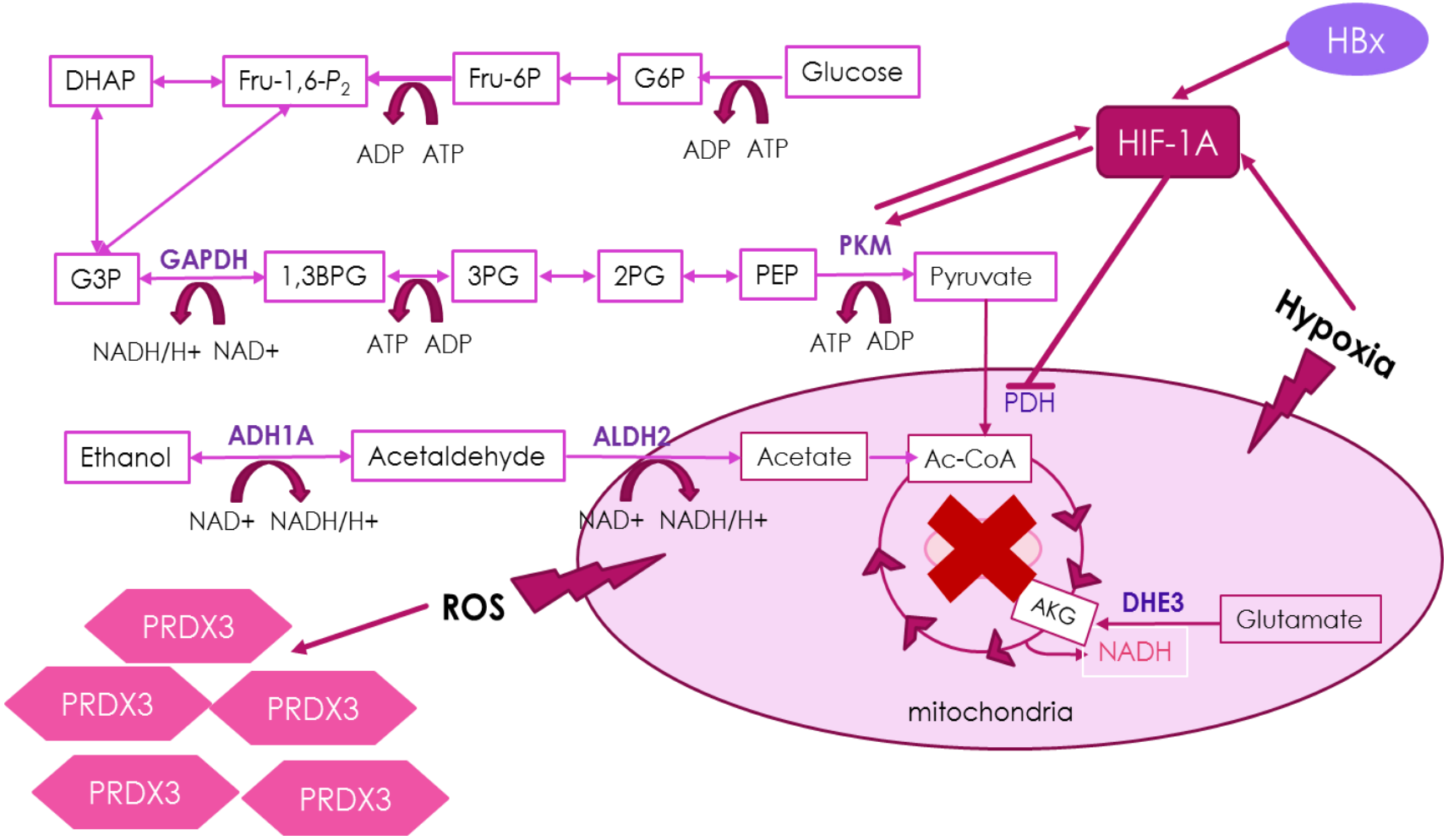
Adrien Decorsière[1]*, Henrik Mueller[1]†*, Pieter C. van Breugel[1]†*, Fabien Abdul[1]*, Laetitia Gerossier[2], Rudolf K. Beran[3], Christine M. Livingston[3], Congrong Niu[3], Simon P. Fletcher[3], Olivier Hantz[2] & Michel Strubin[1]

386 | NATURE | VOL 531 | 17 MARCH 2016




Aldehyde dehydrogenase
SSP2402
F1
F4
Pyruvate kinase PKM
SSP7802
F1
F4
Immunoglobulin
kappa c region
SSP0702
F1
F4
Peroxiredoxin 3
SSP7803
F1
F4
KPYM
PRDX3
IGKC
ALDH2
DHE3
Apolipoprotein A
SSP0303
F1
F4
APOA
ALDH1A1
G3P
Glutamate
dehydrogenase I
SSP7603
F1
F2
TRFE
PBLD
ANXA4
Annexin A4
SSP0001
F1
F4
Glyceraldehyde 3-phospahate
dehydrogenase
(SSP9201)
F1
F3
Retinal dehydrogenase
SSP3303
F1
F4
Phenazine biosynthesis-like
domain-containing protein
SSP5104
F1
F3
Transferrin
SSP6105
F1
F2

HİPOTEZ



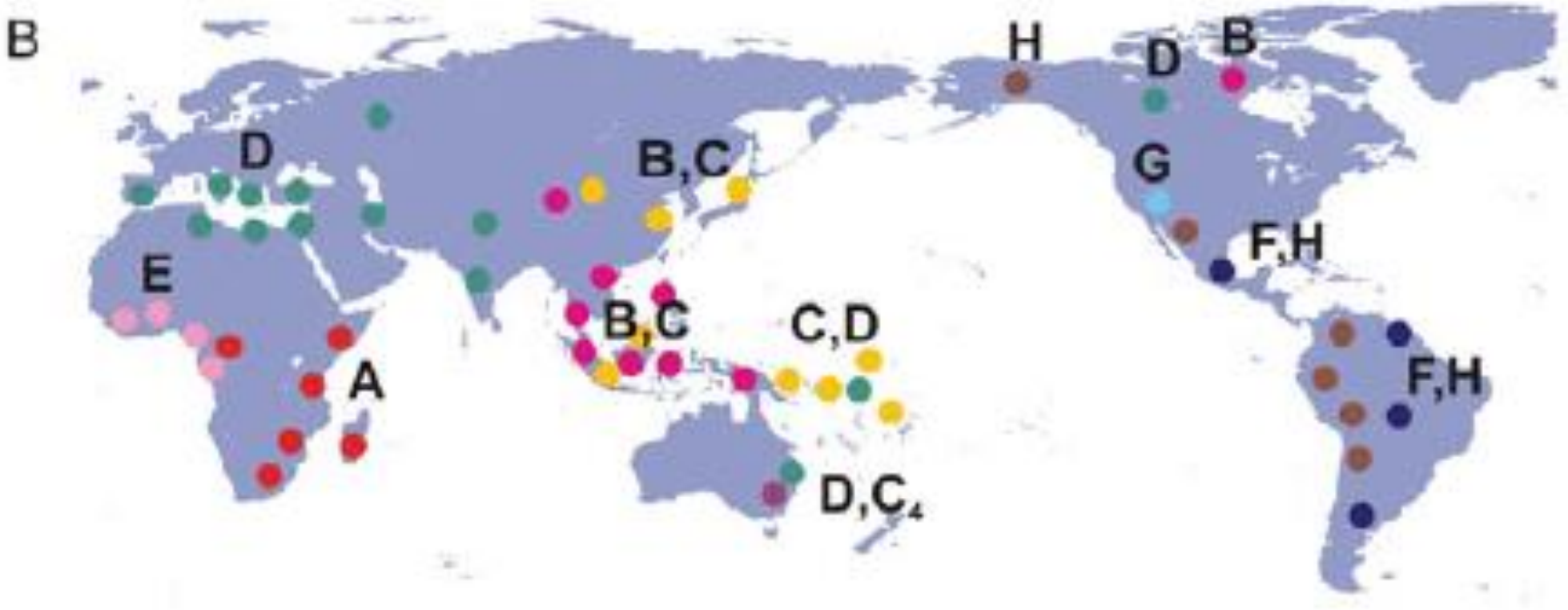
Katrinli S.,……Doganay & Doganay. . Proteomic profiling of HBV infected liver biopsies with different fibrotic stages. Proteome Sci. 2017 Apr 20;15:7

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Dating the Origin and Dispersal of Hepatitis B Virus Infection in Humans and Primates

Dimitrios Paraskevis,[1] Gkikas Magiorkinis,[1,2] Emmanouil Magiorkinis,[1] Simon Y.W. Ho,[3] Robert Belshaw,[2] Jean-Pierre Allain,[4] and Angelos Hatzakis[1]

HEPATOLOGY, Vol. 57, No. 3, 2013


B
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D,C4
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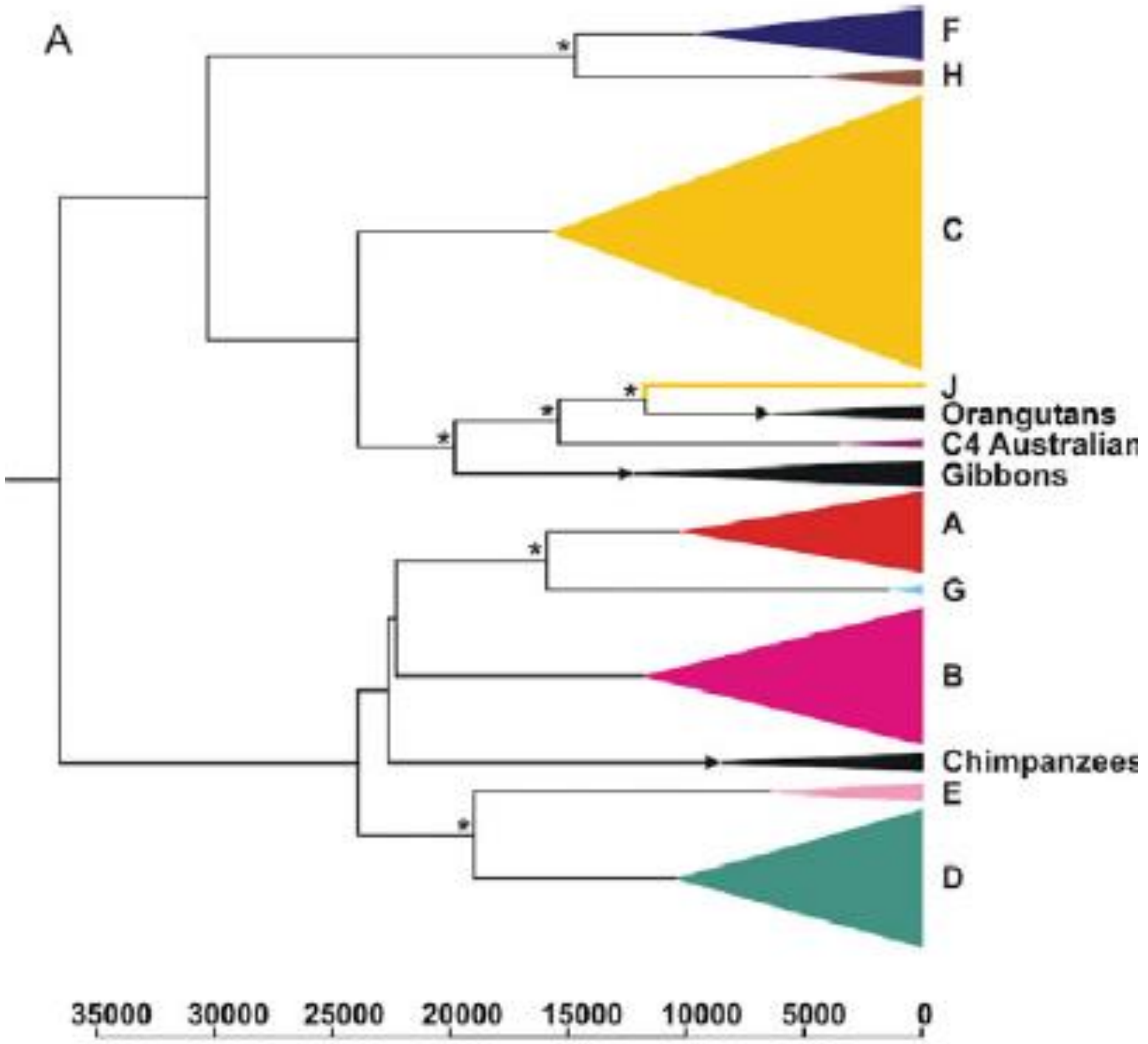
F,H
F,H


A
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H
C
J
Orangutans
C4 Australian
Gibbons
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Chimpanzees
E
D
35000
30000
25000
20000
15000
10000
5000
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GLAB

GENOMIK LABORATUVAR