

FIRST INTERNATIONAL COURSE
ON TRANSLATIONAL HEPATOLOGY
FOCUS ON HCV DISEASE
FLORENCE, MARCH 9-11, 2011



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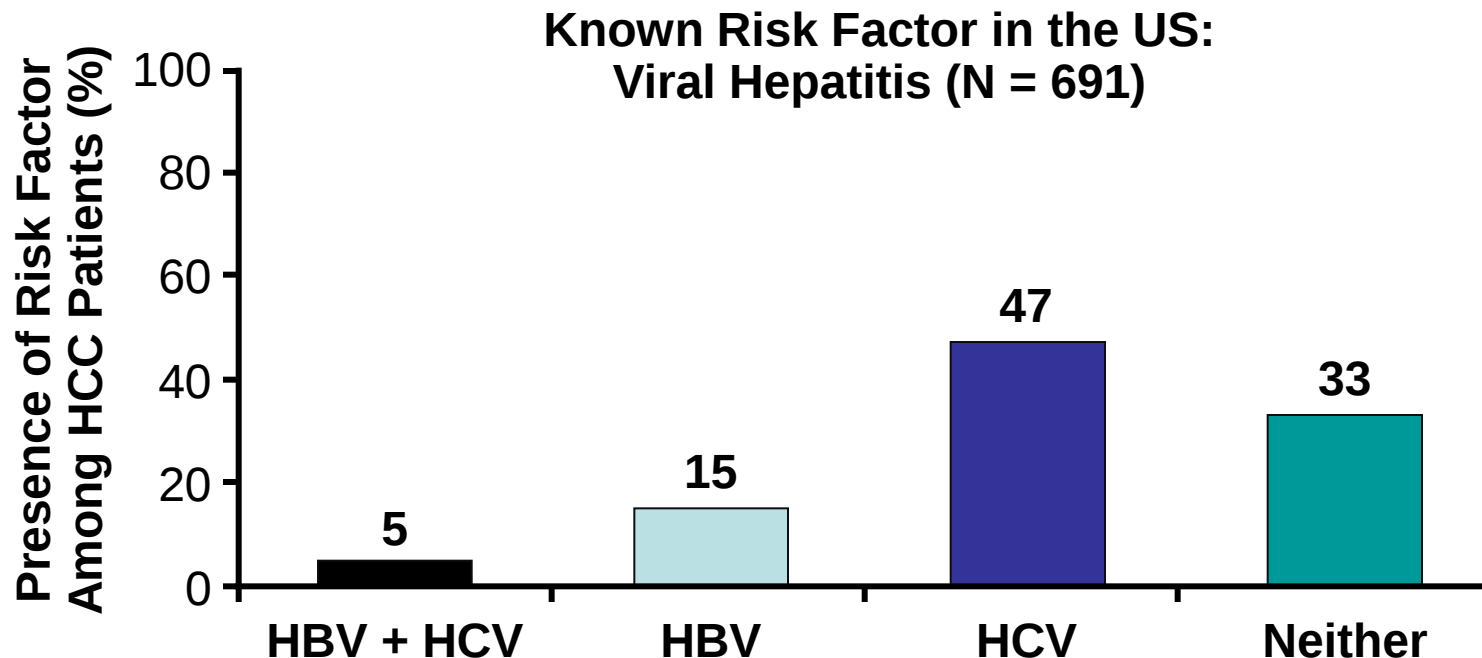
HBV/HCV Co-Infection: Additive Players in Hepatocarcinogenesis?

Giovanni Raimondo

**Clinical and Molecular Hepatology
University Hospital of Messina**

Viral Hepatitis as a Risk Factor for HCC

Worldwide, 75% to 80% of HCC attributable to chronic HBV (50% to 55%) or HCV (25% to 30%)



Di Bisceglie AM, et al. Am J Gastroenterol. 2003;98:2060-2063. El-Serag HB. Gastroenterology. 2004;127:S27-S34. Bosch FX, et al. Gastroenterology. 2004;127:S5-S16.

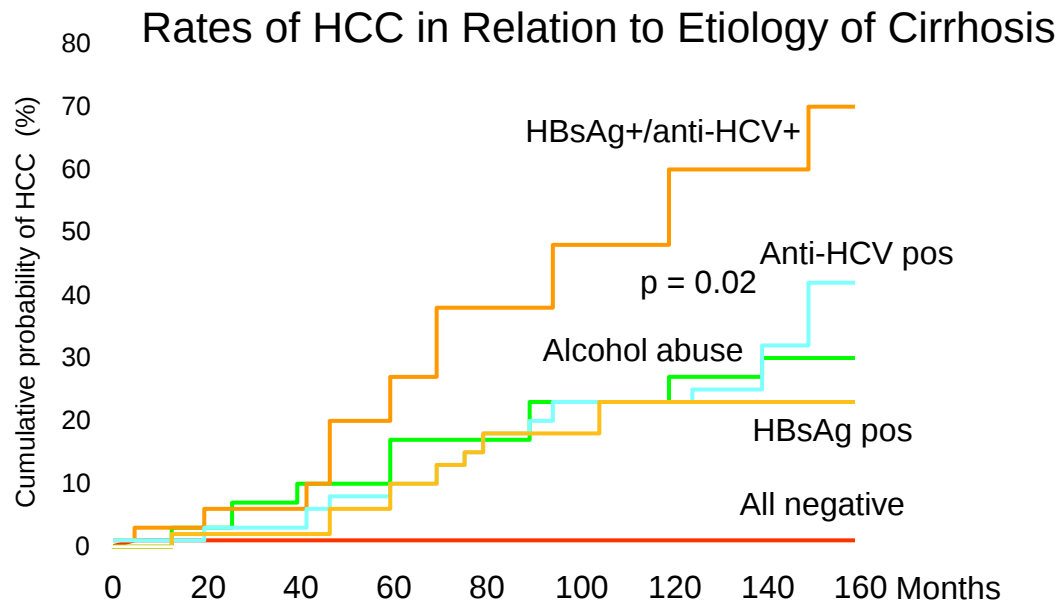
Synergistic Effect of HCV and HBV as Risk for HCC

Case-Control Studies

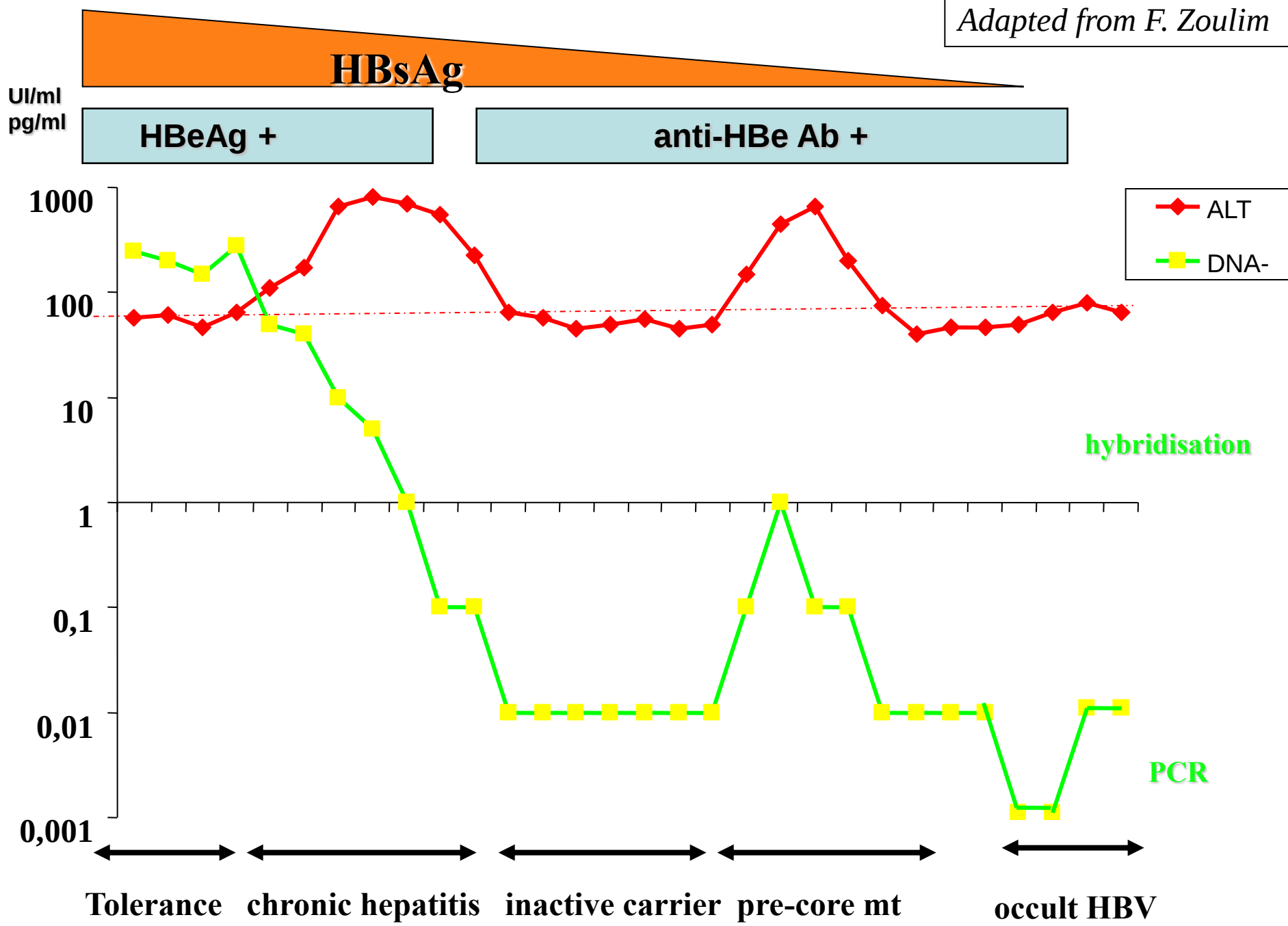
		HBV alone	HCV alone	HBV + HCV
Donato, 1998 (meta-analysis)	OR	22.5	17.3	165

Prospective Studies

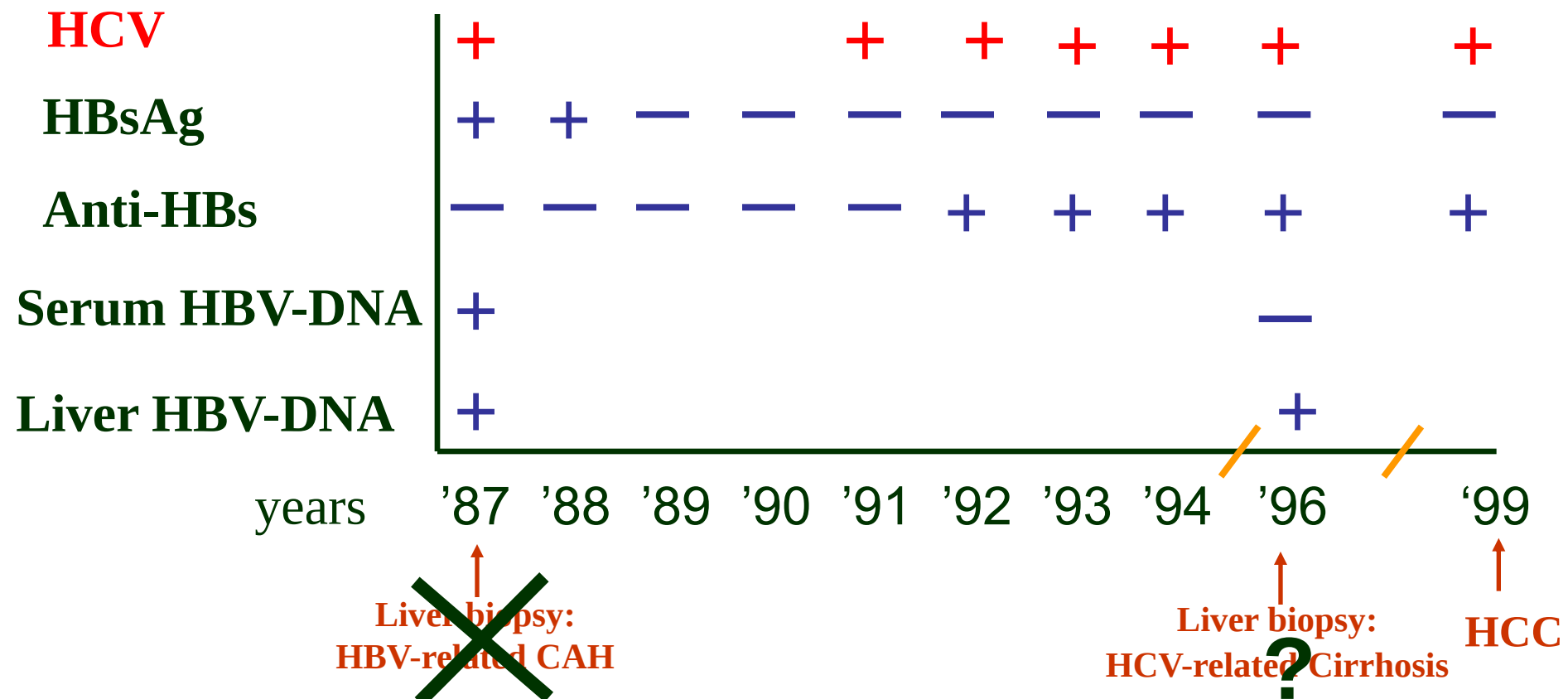
		HBV alone	HCV alone	HBV + HCV
Benvegnù, 1994	RR	n.s.	n.s.	5.1
Tsai, 1997	RR	4.0	3.7	6.4
Chiaramonte, 1999	RR	n.s.	1.2	2.3



Benvegnù, Cancer 1994; 74: 2442-8



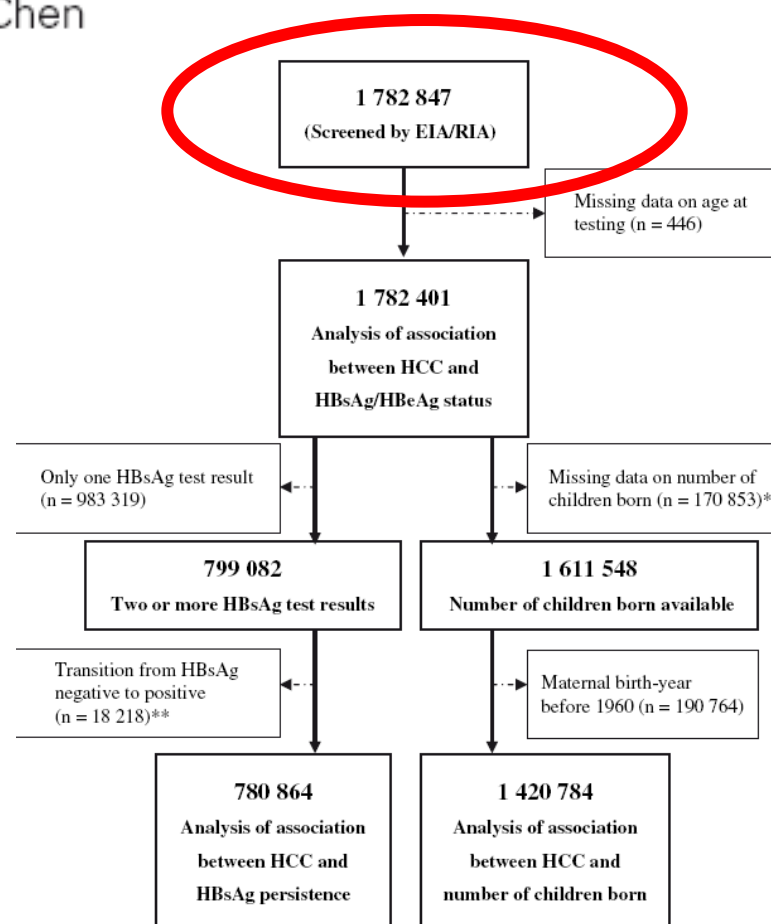
Virological outcome in a patient developing occult HBV infection



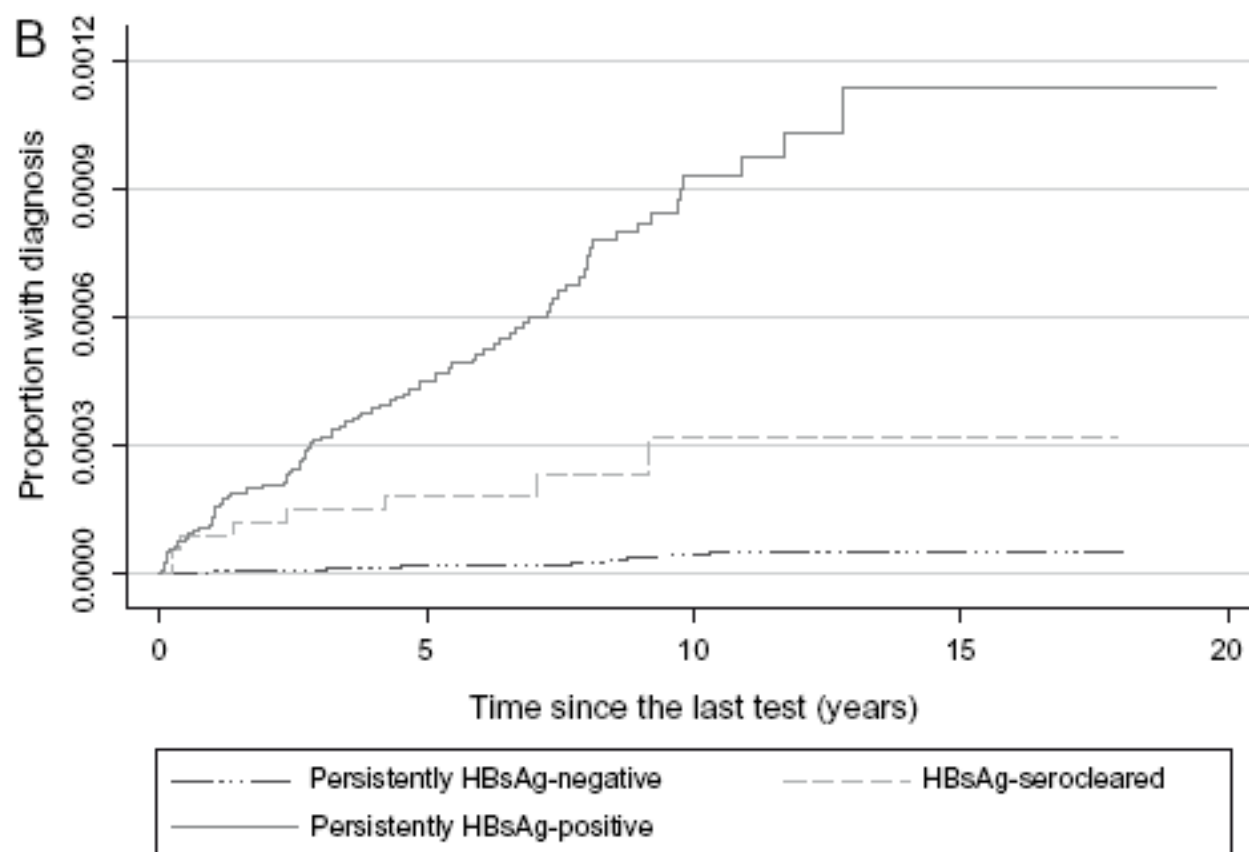
Adapted from Cacciola et al, NEJM 1999

Hepatitis B Virus Infection and Hepatocellular Carcinoma Among Parous Taiwanese Women: Nationwide Cohort Study

Chyng-Wen Fwu, Yin-Chu Chien, Gregory D. Kirk, Kenrad E. Nelson, San-Lin You, Hsu-Sung Kuo, Manning Feinleib, Chien-Jen Chen

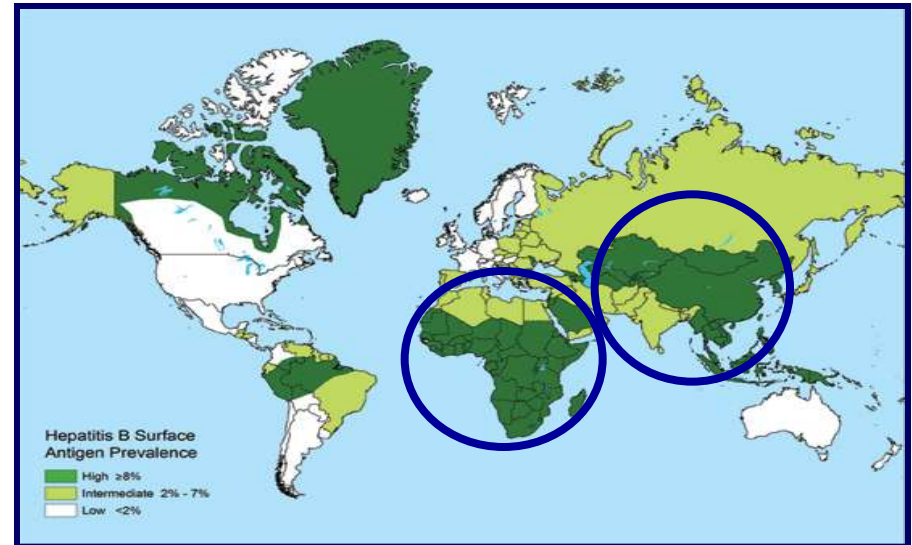
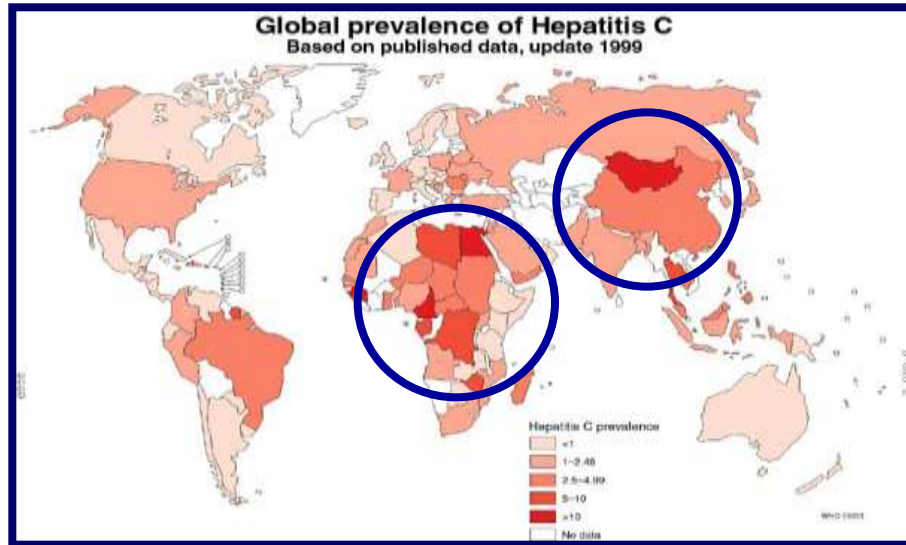


Hepatitis B Virus Infection and Hepatocellular Carcinoma Among Parous Taiwanese Women: Nationwide Cohort Study

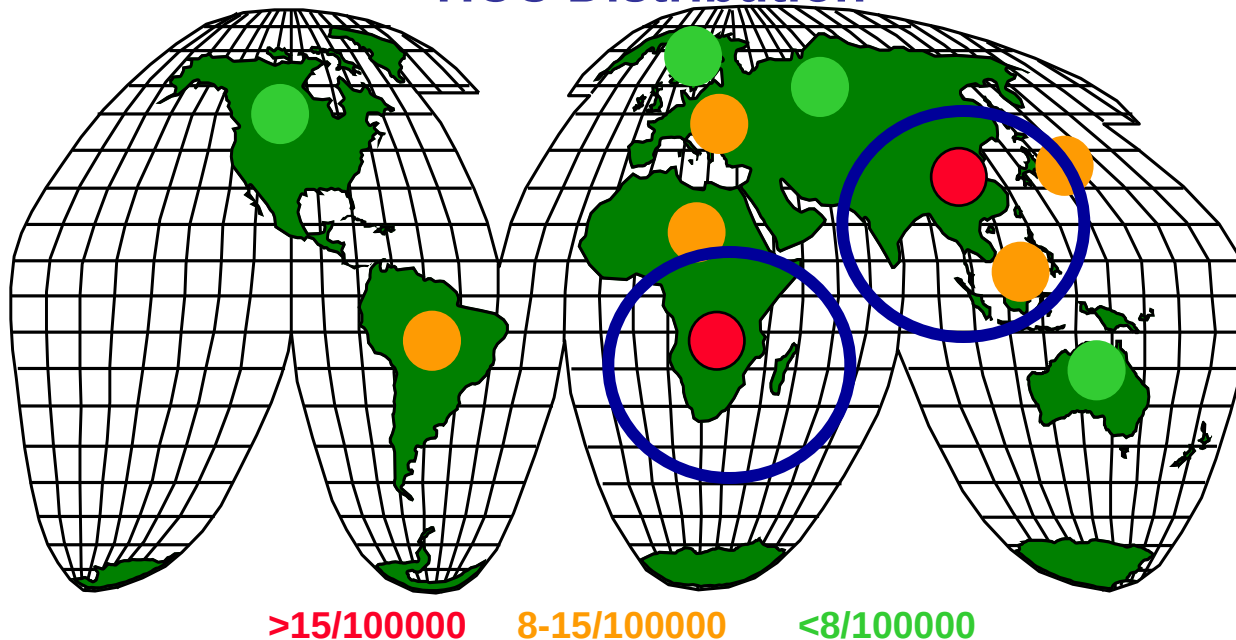


Incidence rates were 0.39, 3.10, and 9.01 per 100 000 person-years, respectively, among persistent noncarriers, HBsAg-serocleared carriers, and persistent HBsAg carriers

Global Distribution of HBV, HCV and HCC

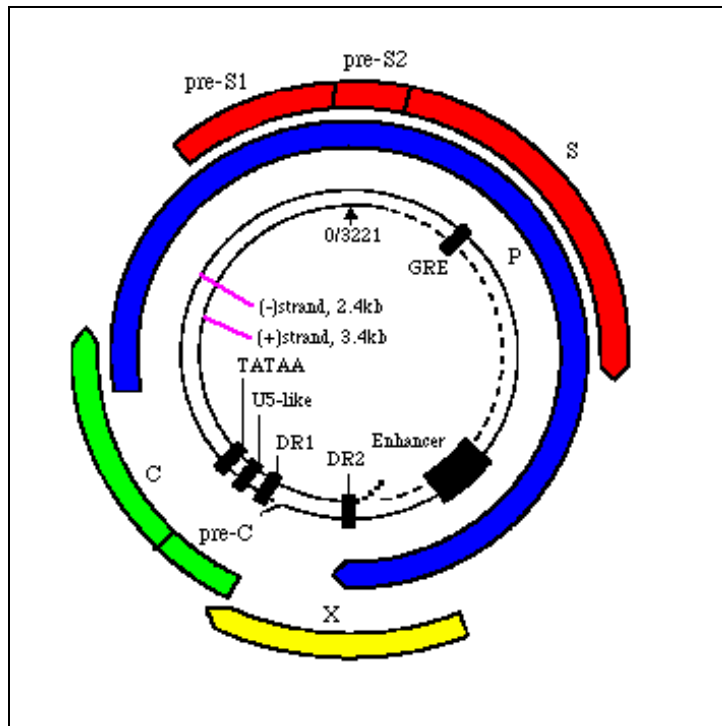


HCC Distribution



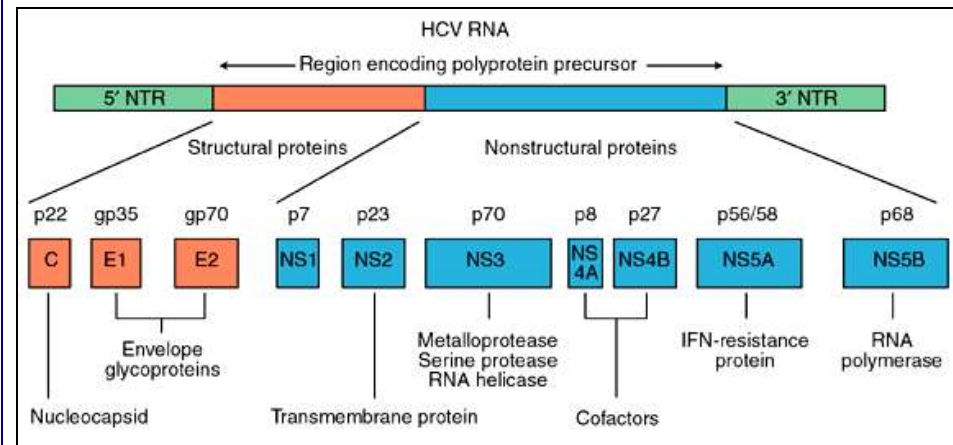
Genome Organisation of HBV and HCV

Hepatitis B Virus



- 3.2 kb pdDNA
- episomal cccDNA, minichromosome
- 3 promoters = Core, S-, and X
- 4 ORF = preC/Core, preS1/preS2/S, polymerase (RT), X-gene

Hepatitis C Virus

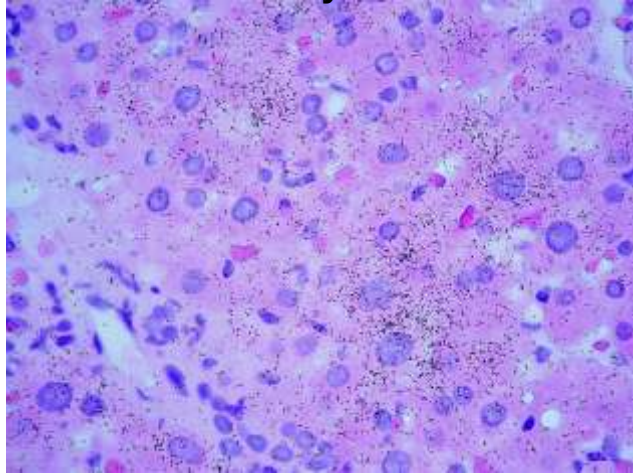


- 9.6 kb ss (+) RNA
- IRES
- 10 proteins

HBV and HCV Infection in Human Liver

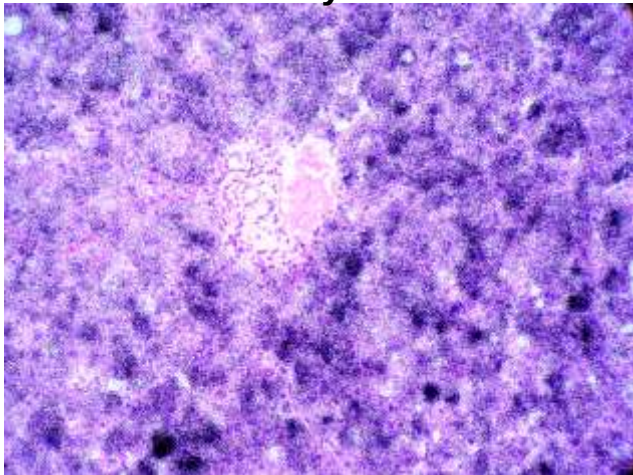
Determination of the Target Cells

HCV *in situ* hybridization



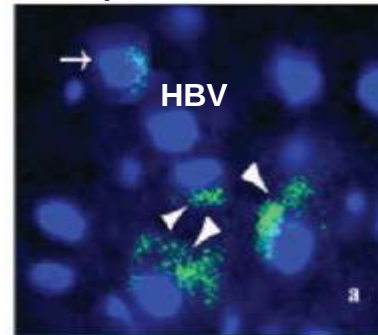
Klingel & Bock 2005

HBV *in situ* hybridization

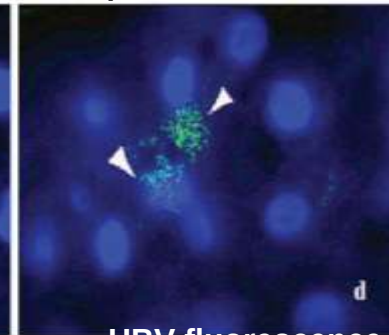


Klingel & Bock 2005

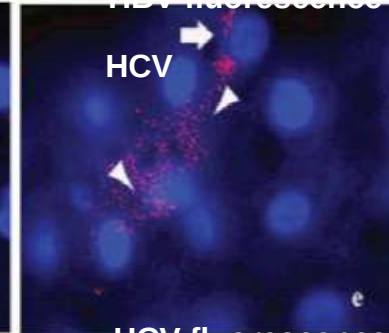
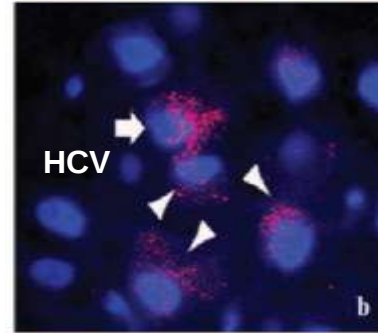
patient A



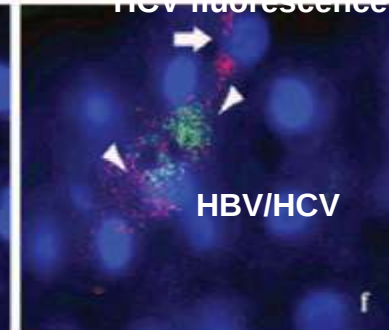
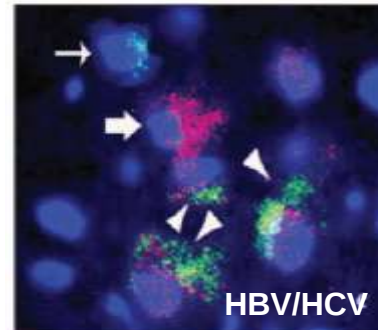
patient B



HBV fluorescence

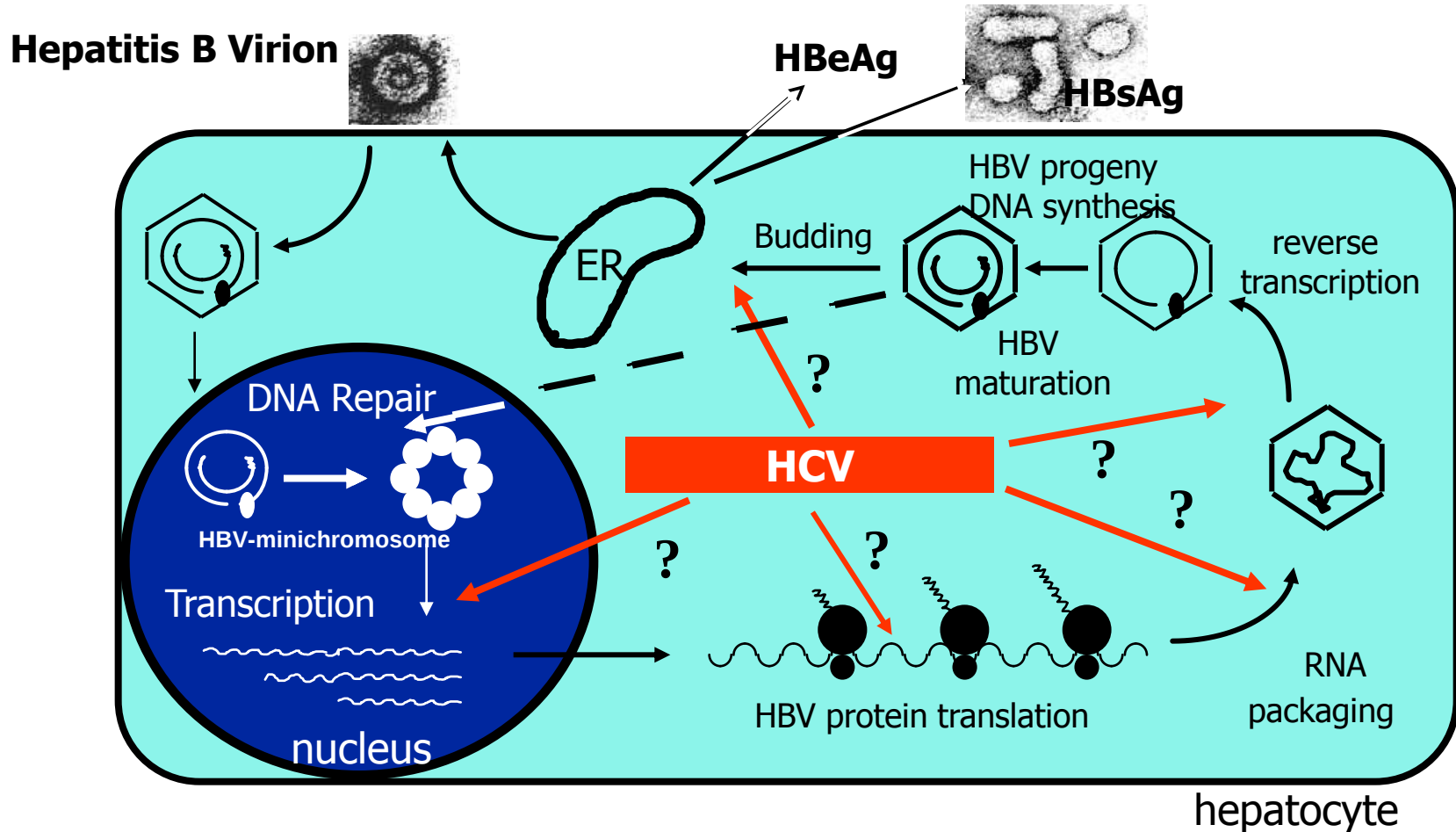


HCV fluorescence

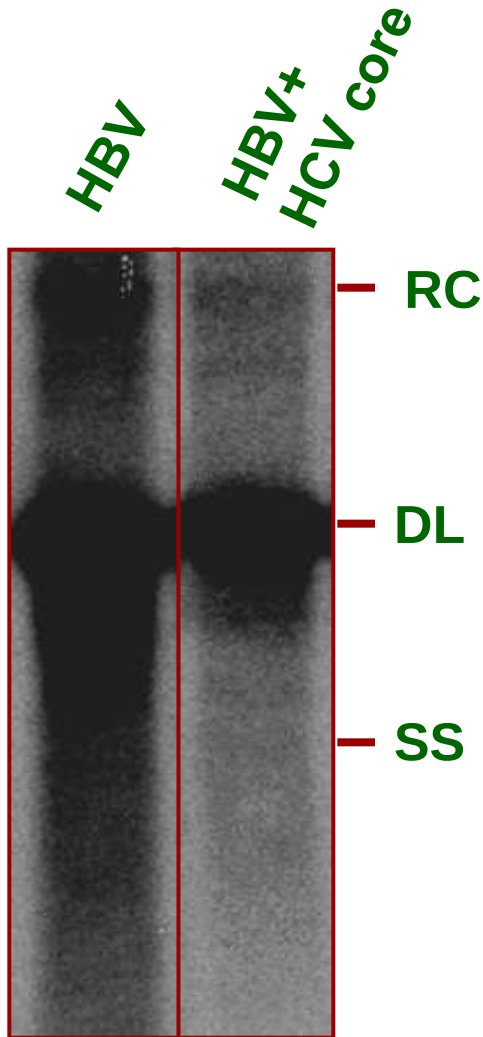


Fluorescent-*in situ* hybridization
Rodriguez-Inigo et al. J Virol 2005

1. Role of molecular viral interference mechanisms
2. Role of virus-host interaction and modulation of cellular signal transduction



In vitro studies suggesting the inhibition of HBV replication by HCV core protein



- *Suppression of HBV hepatitis B virus expression and replication by hepatitis C virus core protein in HuH-7 cells.*

Shih et al, J Virol 1993

- *Modulation of the trans-suppression activity of hepatitis C virus core protein by phosphorylation.*

Shih et al, J Virol 1995

- *Suppression of hepatitis B virus enhancer 1 and 2 by hepatitis C virus core protein.*

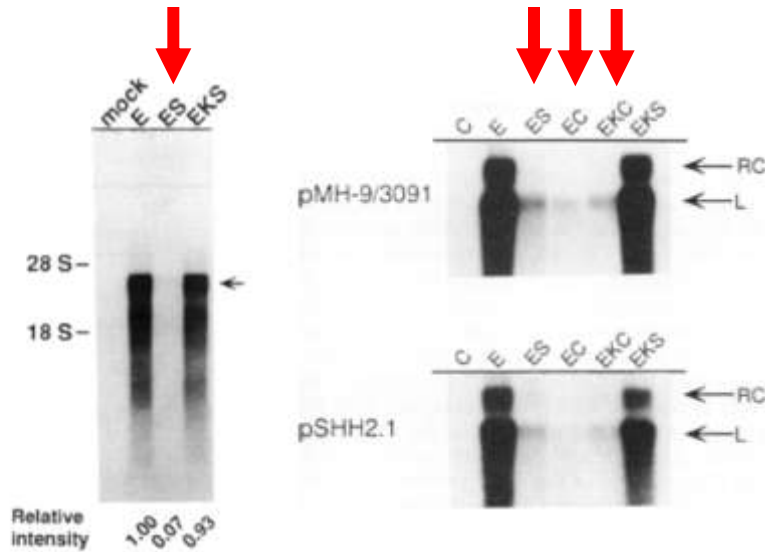
Schuttler et al, J Hepatol 2002

- *Mechanisms for inhibition of hepatitis B gene expression and replication by hepatitis C virus core protein*

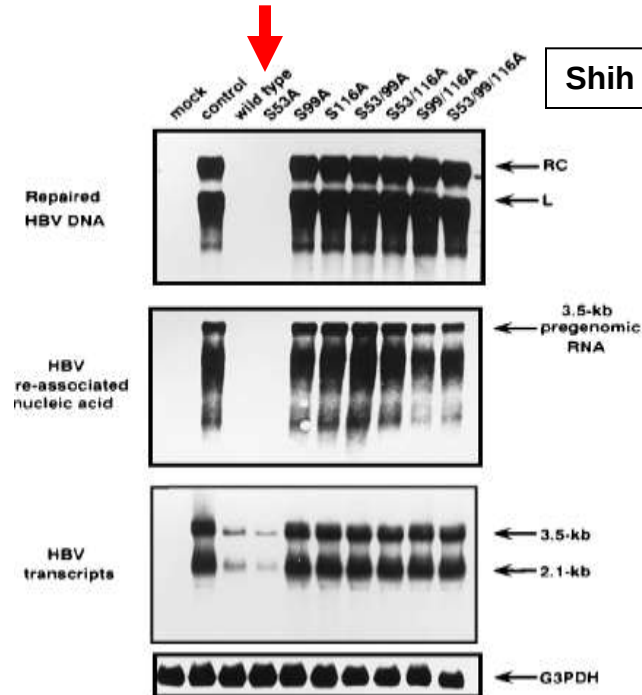
Chen et al, J Biol Chem 2003

HCV-Core Expression Suppresses HBV Enhancer 1 and 2 Activity

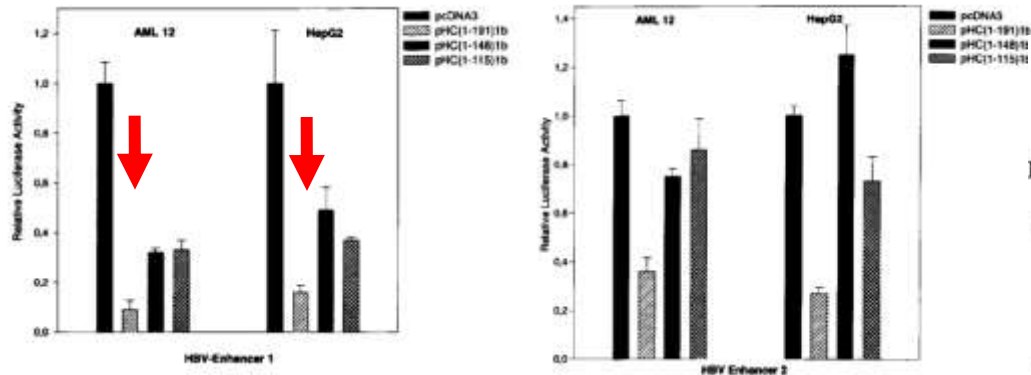
Shih et al JVI 1993



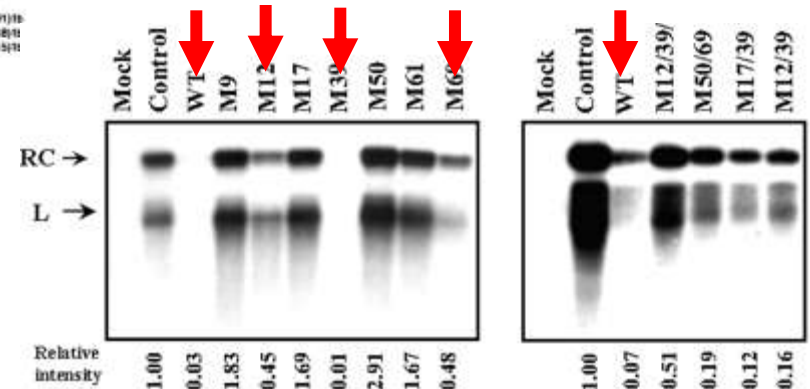
Shih et al JVI 1995



Schüttler et al. J Hep. 2002



Chen et al JBC 2003



Regulation of Hepatitis B Virus Replication by the Phosphatidylinositol 3-Kinase-Akt Signal Transduction Pathway

Haitao Guo, Tianlun Zhang

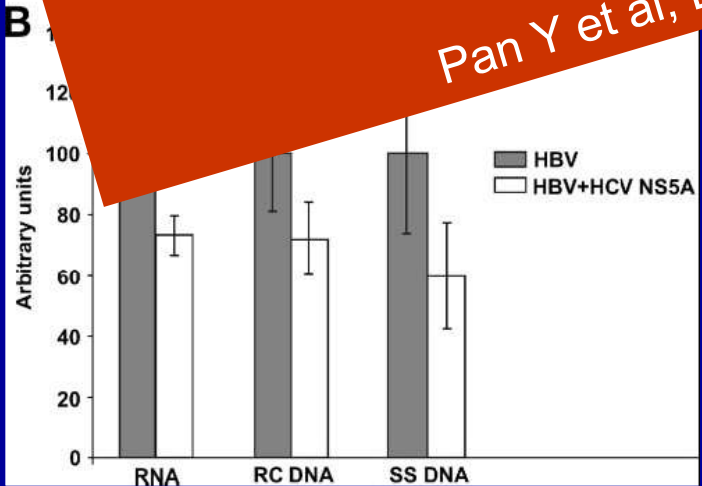
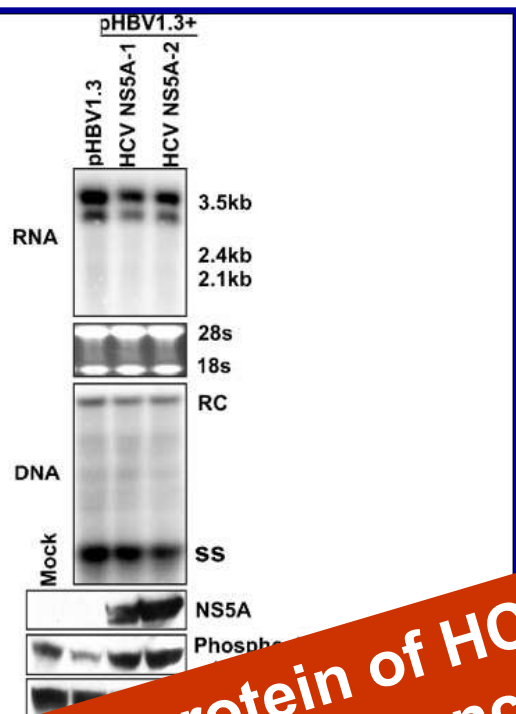
Andrea C. Collier

Ti

**NS5A protein of HCV enhances HBV replication and
resistance to interferon response**

Pan Y et al, Biochem Biophys Res Commun. 2007

**NS5A activates Akt1 and
inhibits HBV replication**



Hepatitis B and C Virus Coinfection: A Novel Model System Reveals the Absence of Direct Viral Interference

Pantxika Bellecave,¹ Jérôme Gouttenoire,¹ Markus Gajer,² Volker Brass,² George Koutsoudakis,³ Hubert E. Blum,² Ralf Bartenschlager,³ Michael Nassal,² and Darius Moradpour¹



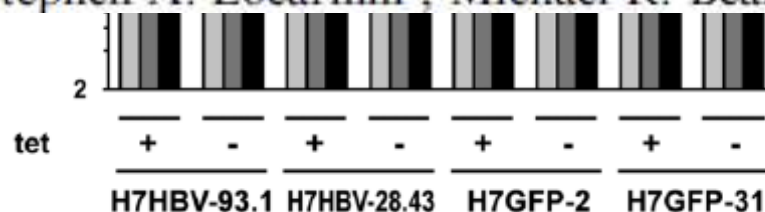
Journal of Hepatology 51 (2009) 446–457

Journal of
Hepatology

www.elsevier.com/locate/jhep

Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells[☆]

Nicholas S. Eyre^{1,2}, Renee J. Phillips^{1,2}, Scott Bowden³, Evelyn Yip^{1,2}, Ben Dewar³, Stephen A. Locarnini³, Michael R. Beard^{1,2,*}

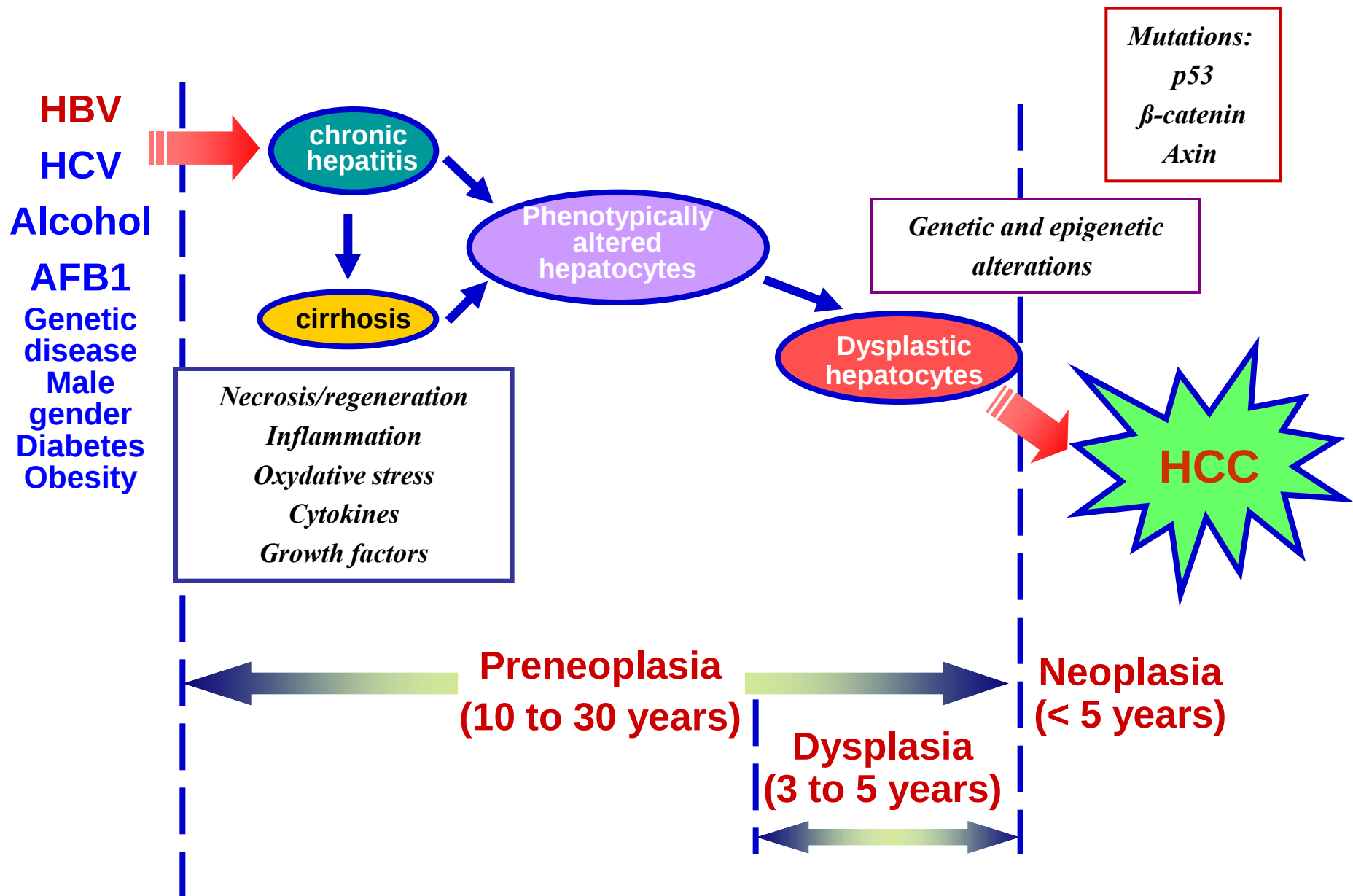


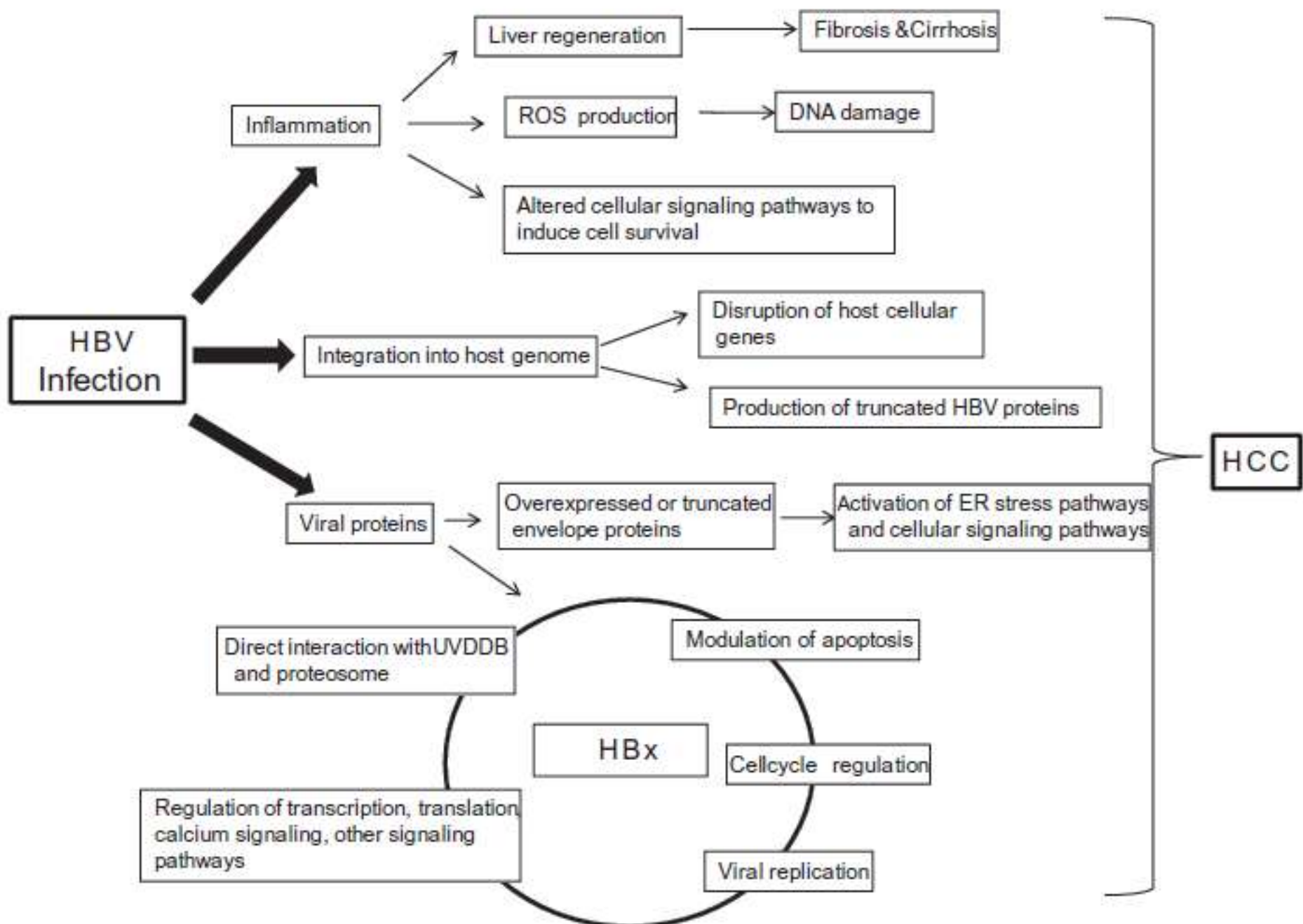
AISF Report : HBV/HCV coinfection

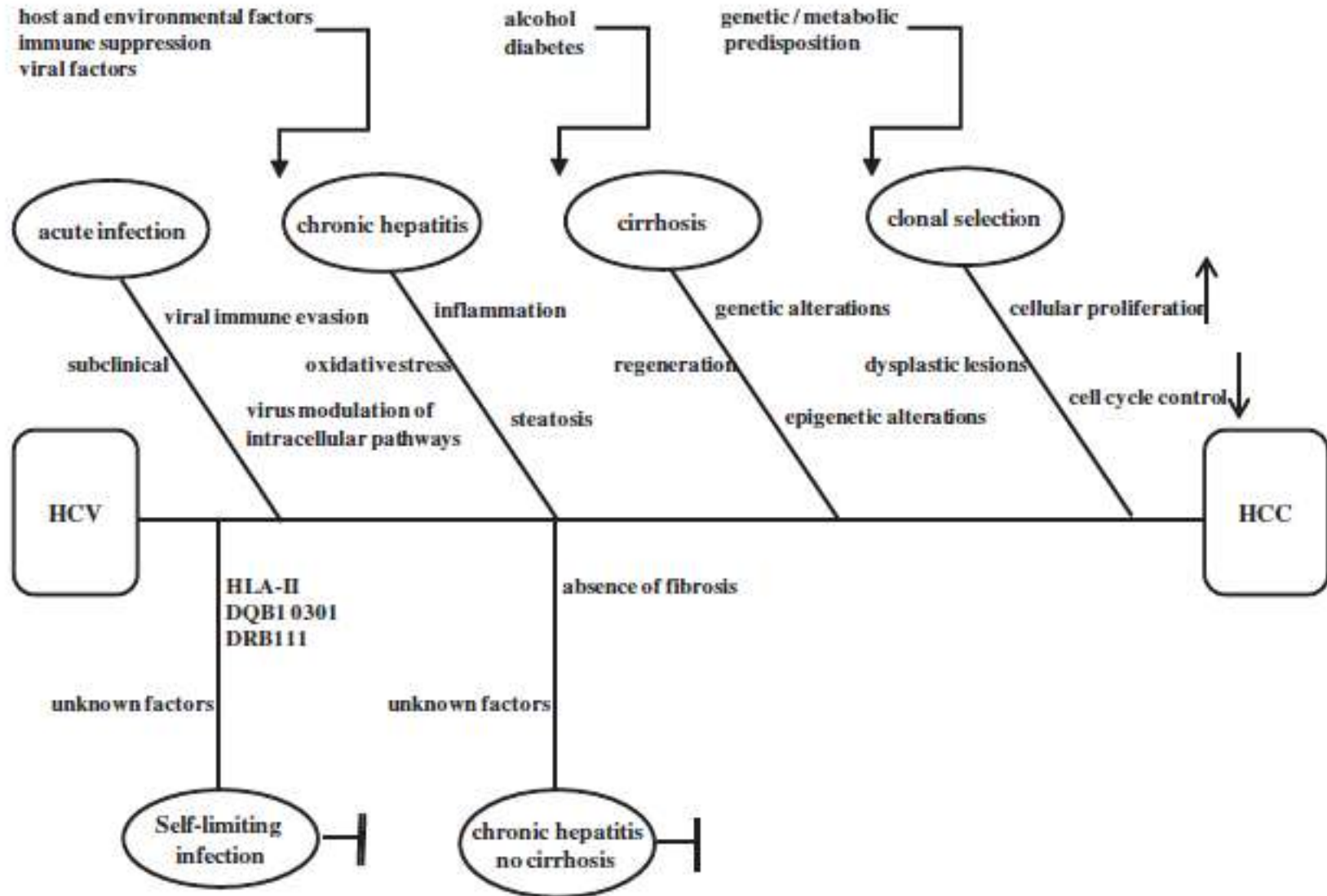
Virological profiles of 103 HBV/HCV coinfected patients

	Basal Time <u>n. of pts</u>	1 yr follow up <u>n. of pts</u>
Active HBV- Active HCV	12	24
Active HBV - Suppr. HCV	14	15
Suppr. HBV - Active HCV	57	49
Suppr. HBV - Suppr. HCV	20	15

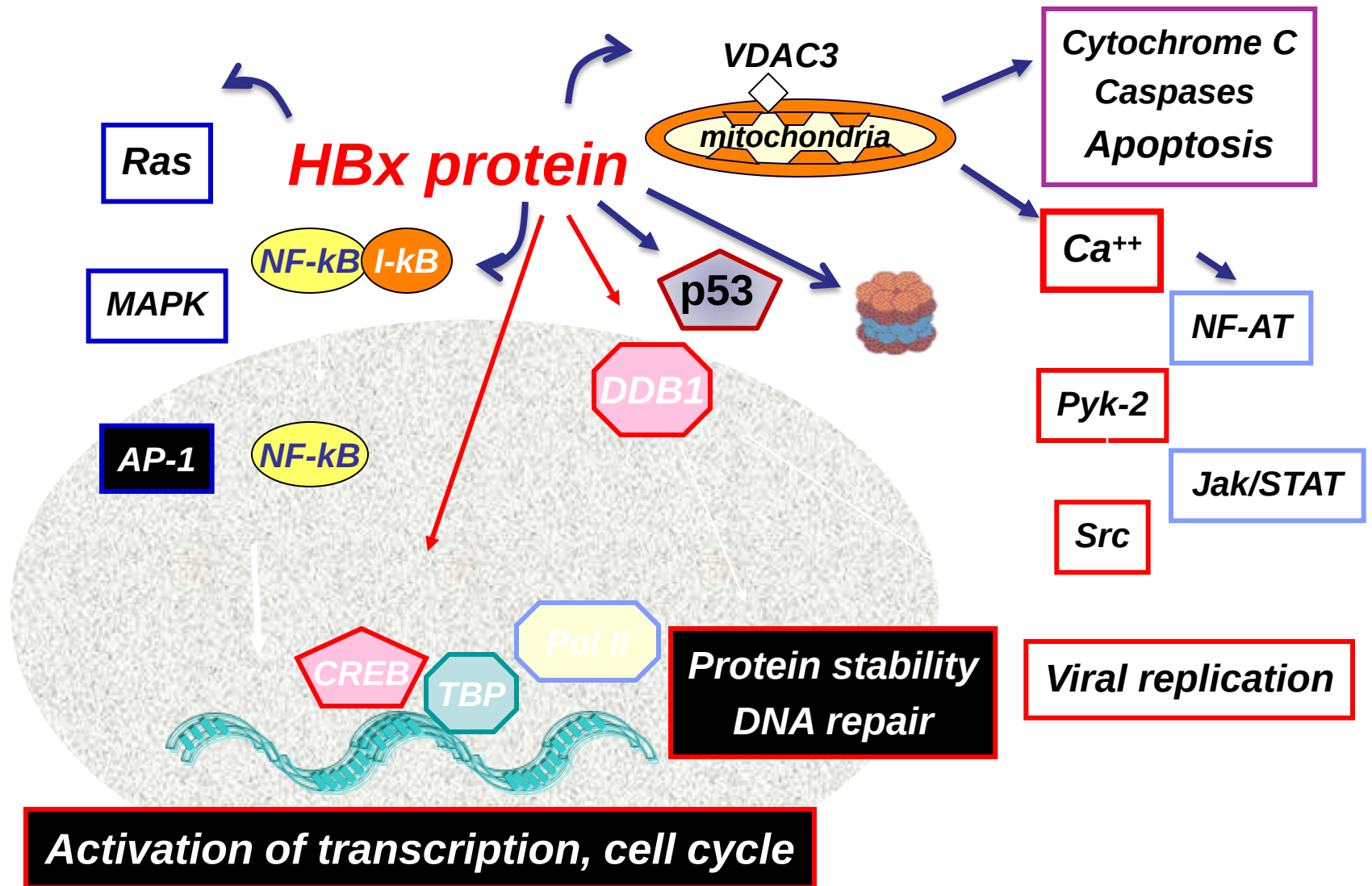
Hepatocarcinogenesis is a multi-step process



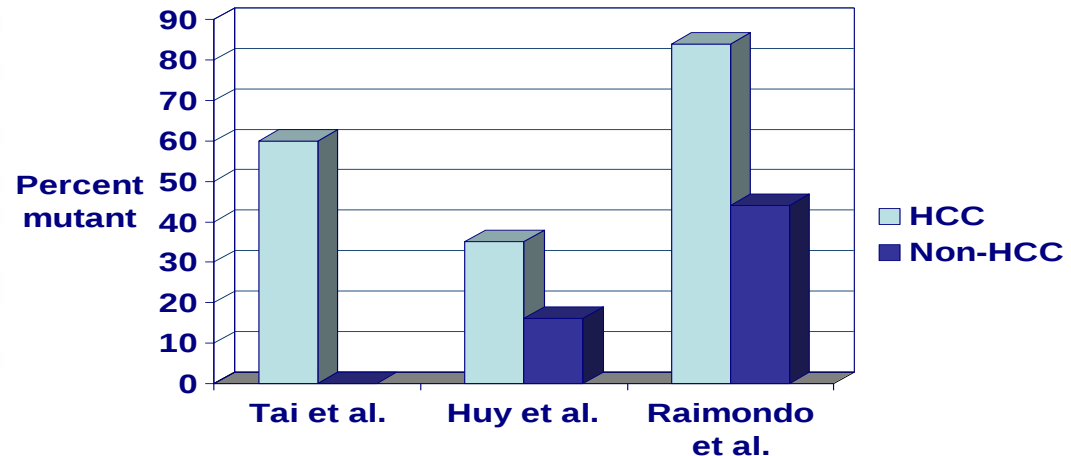
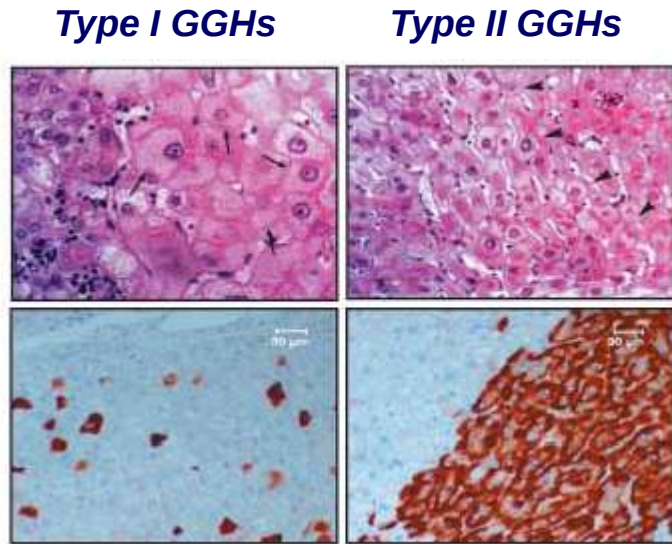
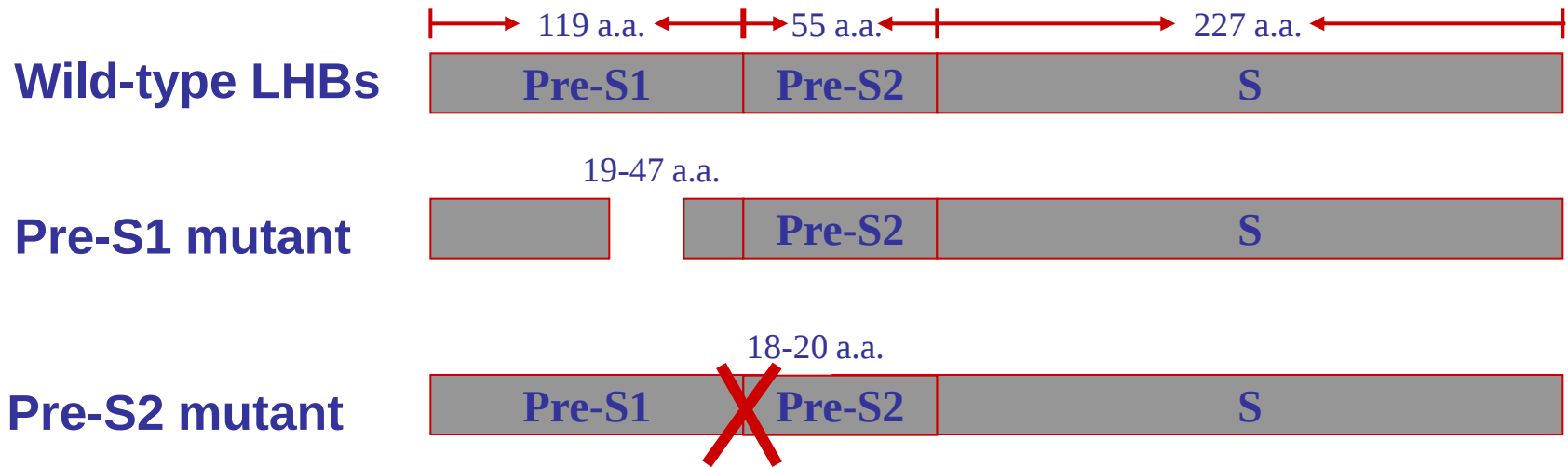




Multiple functions of the regulatory protein HBx



Association of preS2-mutant with HCC

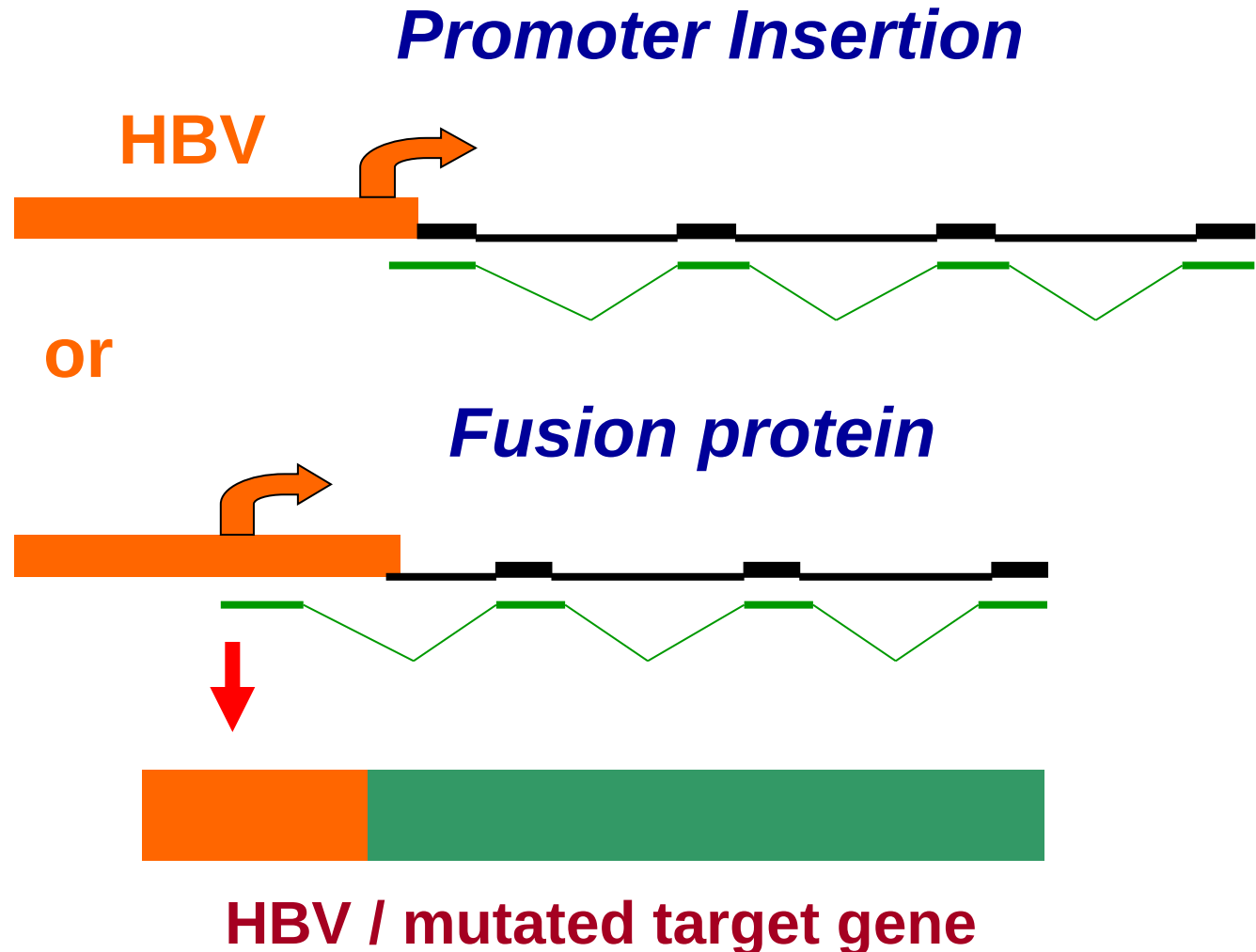


Wang HC et al, Cancer Sci 2006

Mechanisms of HBV-Related Insertional Mutagenesis

Target genes:

- RAR β
- Cyclin A
- Meval. kinase
- sercA1



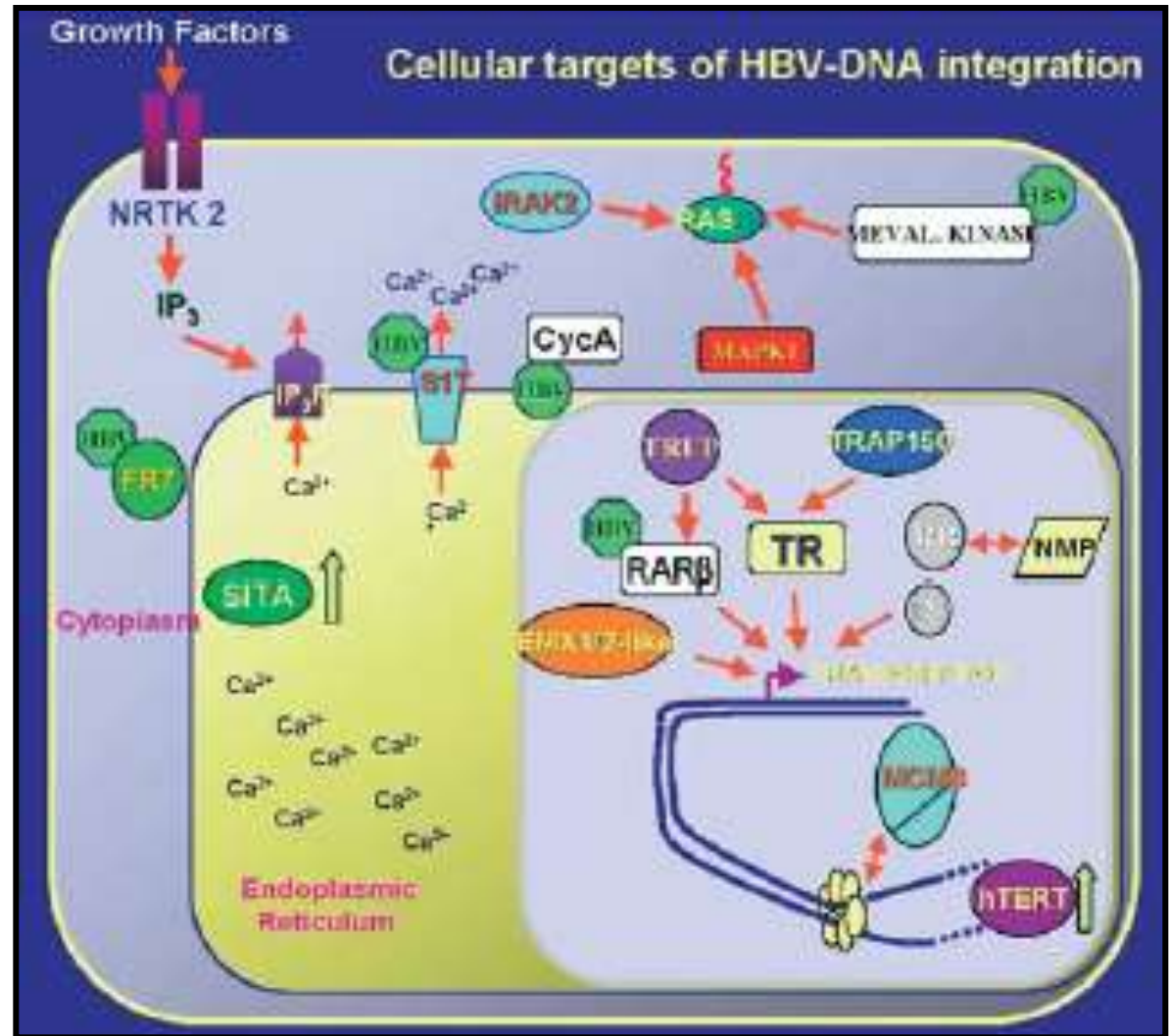
Insertion of HBV Frequently Targets Genes that Regulate Key Cellular Pathways

Unique Target Genes

Meval. Kinase
RAR beta
Cyclin A
MNM8
SERCA1
TRAP150
FR7
EMX2-like
MAPK1
IRAK2
TRUP
NRTK2
Ras-REBP-1
Calmodulin 1

Recurrent Target genes

hTERT
IP3R
MLL2



Brechot, Gastroenterology 2004; Murakami, Gut 2005

Molecular status of occult HBV in tumor and non-tumor tissues of HCC patients

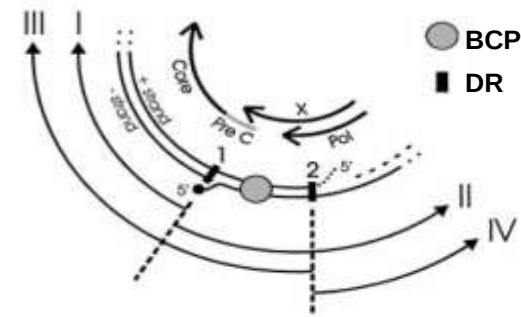
	Samples examined	Positive cases
- Integrated HBV	10	2
- HBV cccDNA	30	20
- HBV RNA	10	10

Pollicino et al, Gastroenterology 2004

ANALYSIS AND CHARACTERIZATION OF HBV DNA INTEGRATION IN PATIENTS WITH OCCULT HBV INFECTION AND HEPATOCELLULAR CARCINOMA

	HBsAg-/OBI + (n.44)	HBsAg-/OBI – (n.10)	HBsAg + (n.10)
HBV INTEGRATION (%)	25 (56.8)	0 (0)	6 (60)

VIRAL INTEGRANTS



Viral-host junctions fully characterized in 11/25 and in 2/6 of OBI positive and HBsAg-positive groups, respectively

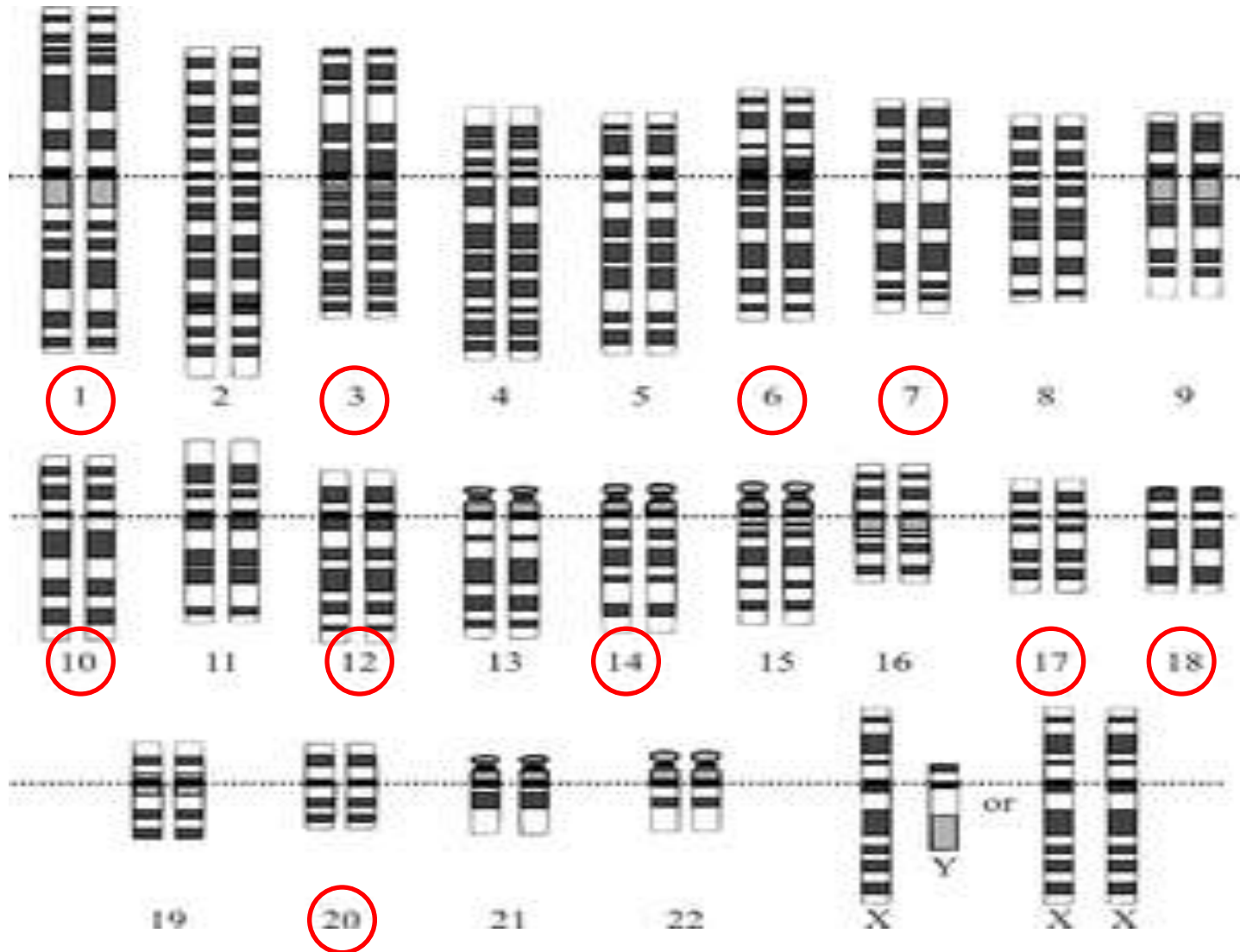
	HBsAg-/OBI + (n.11)	HBsAg + (n.2)*
X gene sequences	6	1
X gene including the X carboxy-terminal portion with enhancer-II and basal-core promoter	1	2
carboxy-terminal end of the S region plus a portion of the Pol gene	2	0
preS1 region including the S1 promoter	1	0
core gene, including the precore and basal-core promoter regions	1	0

*** In one HBsAg+ case a double site of integration has been revealed**

Saitta C et al, AISF & EASL 2011 Annual Meetings

First International Course of Translational Hepatology, Florence, 2011

CHROMOSOMAL LOCALIZATION OF HBV INTEGRANTS



Saitta C et al, AISF & EASL 2011 Annual Meetings

CONCLUSIONS

**Viral integration may play its pro-oncogenic role
in all HBV-infected individuals,
independently of the HBsAg status**

Saitta C et al, AISF & EASL 2011 Annual Meetings

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HBV & HCV Chronic Co-Infection

