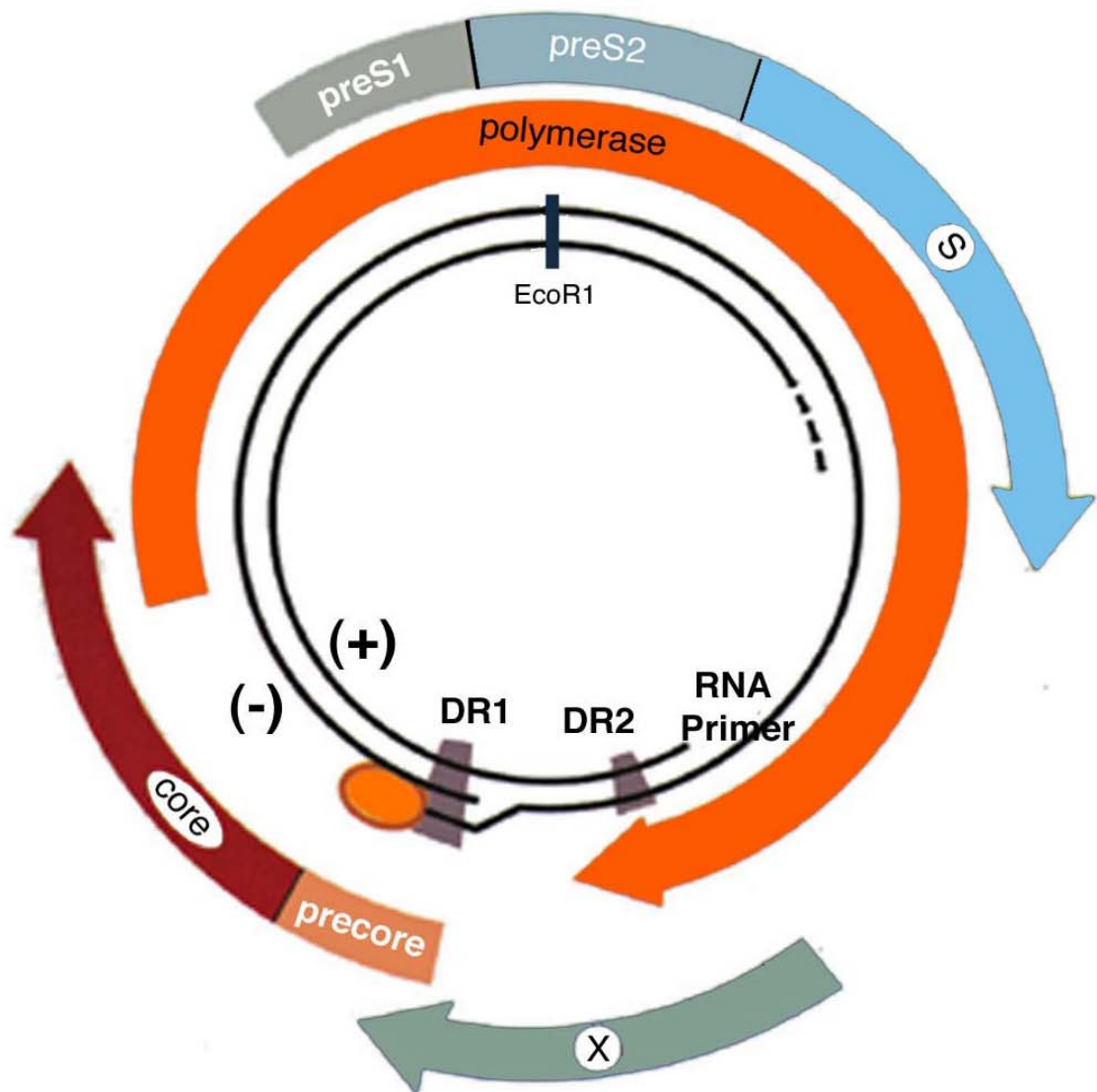
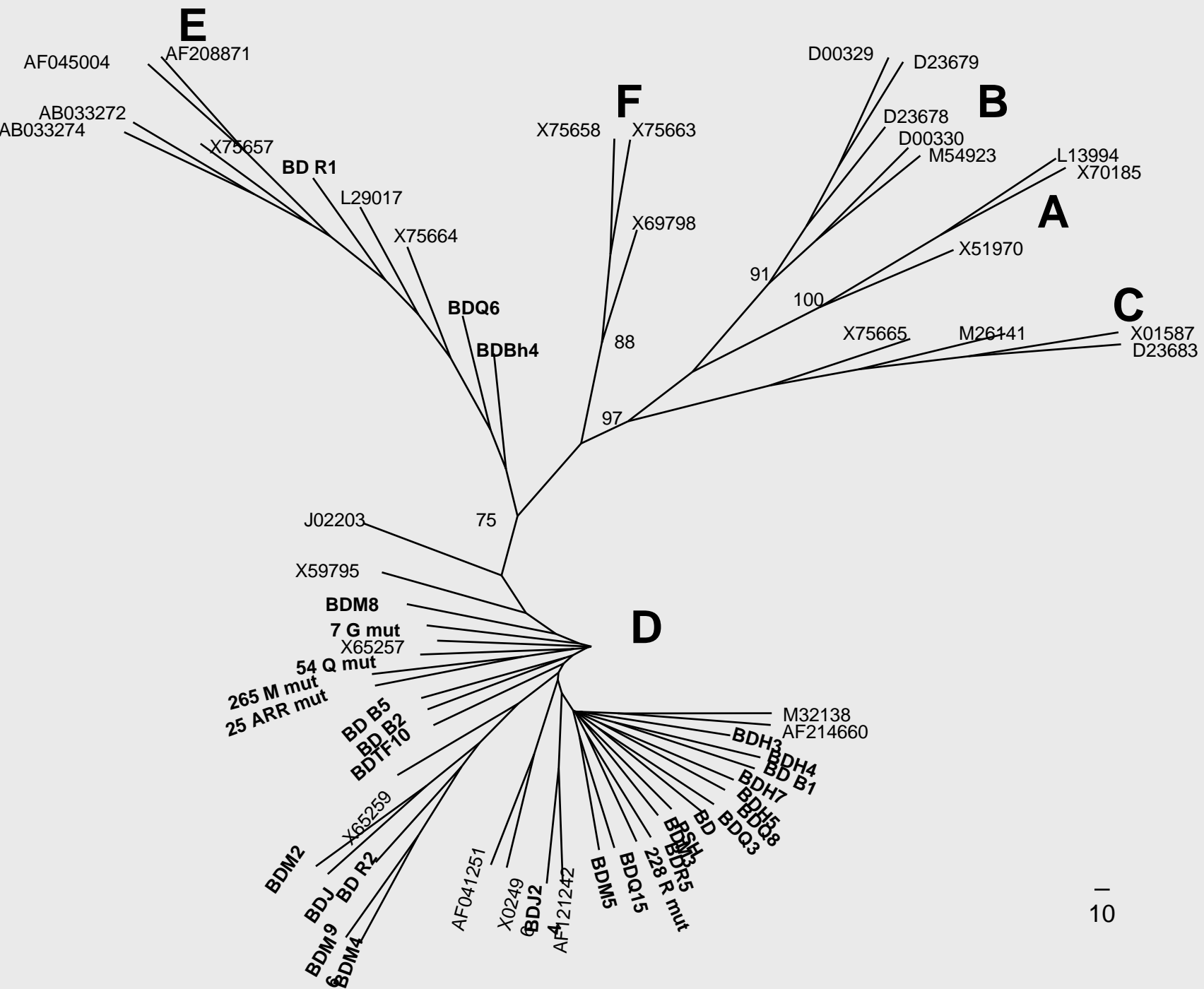
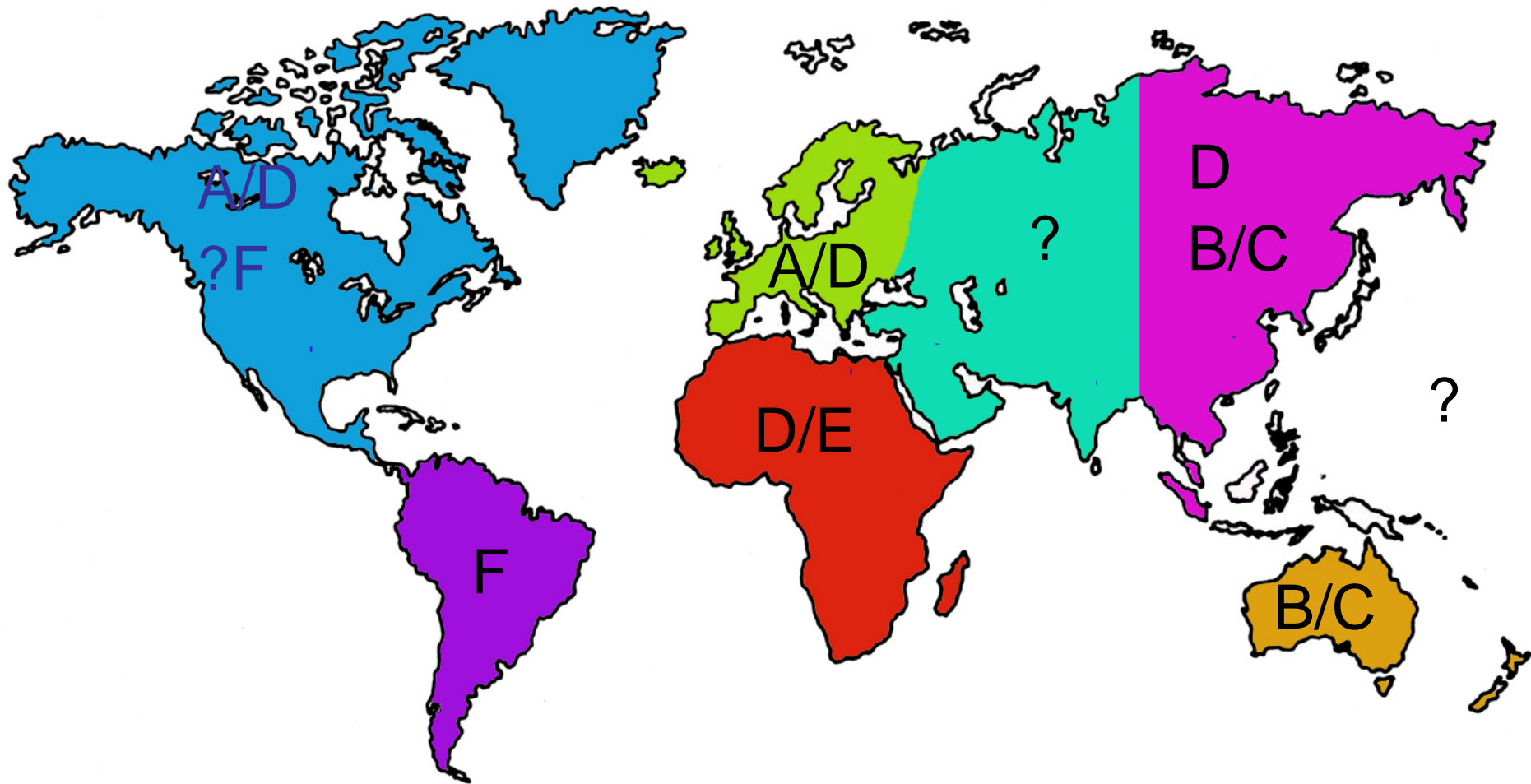


# **HBV Biology – a light(e)ning tour**







B/C

S.E. Asia

C

PNG

C/D

Australia

D

Micronesia

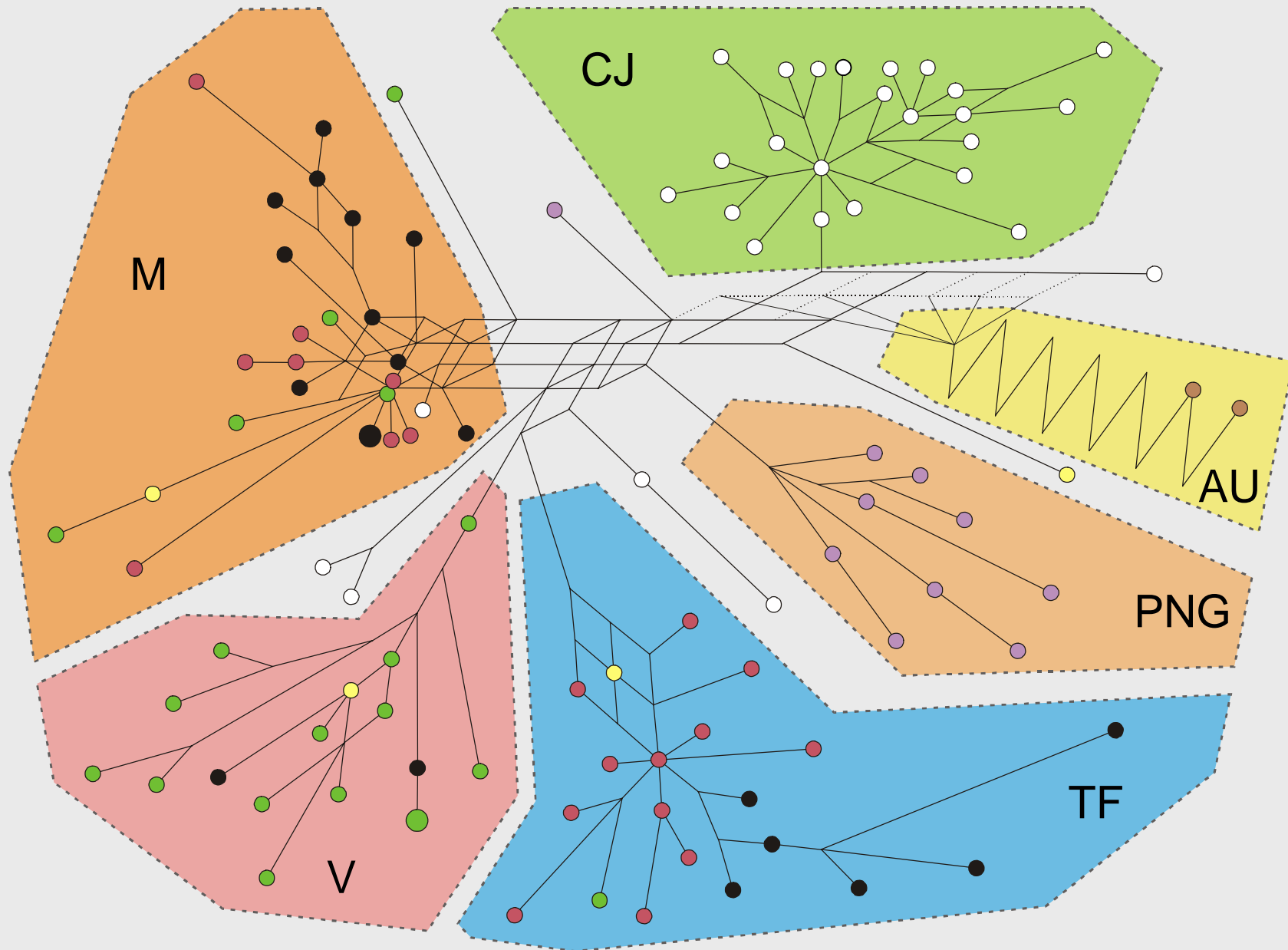
C

Melanesia

C

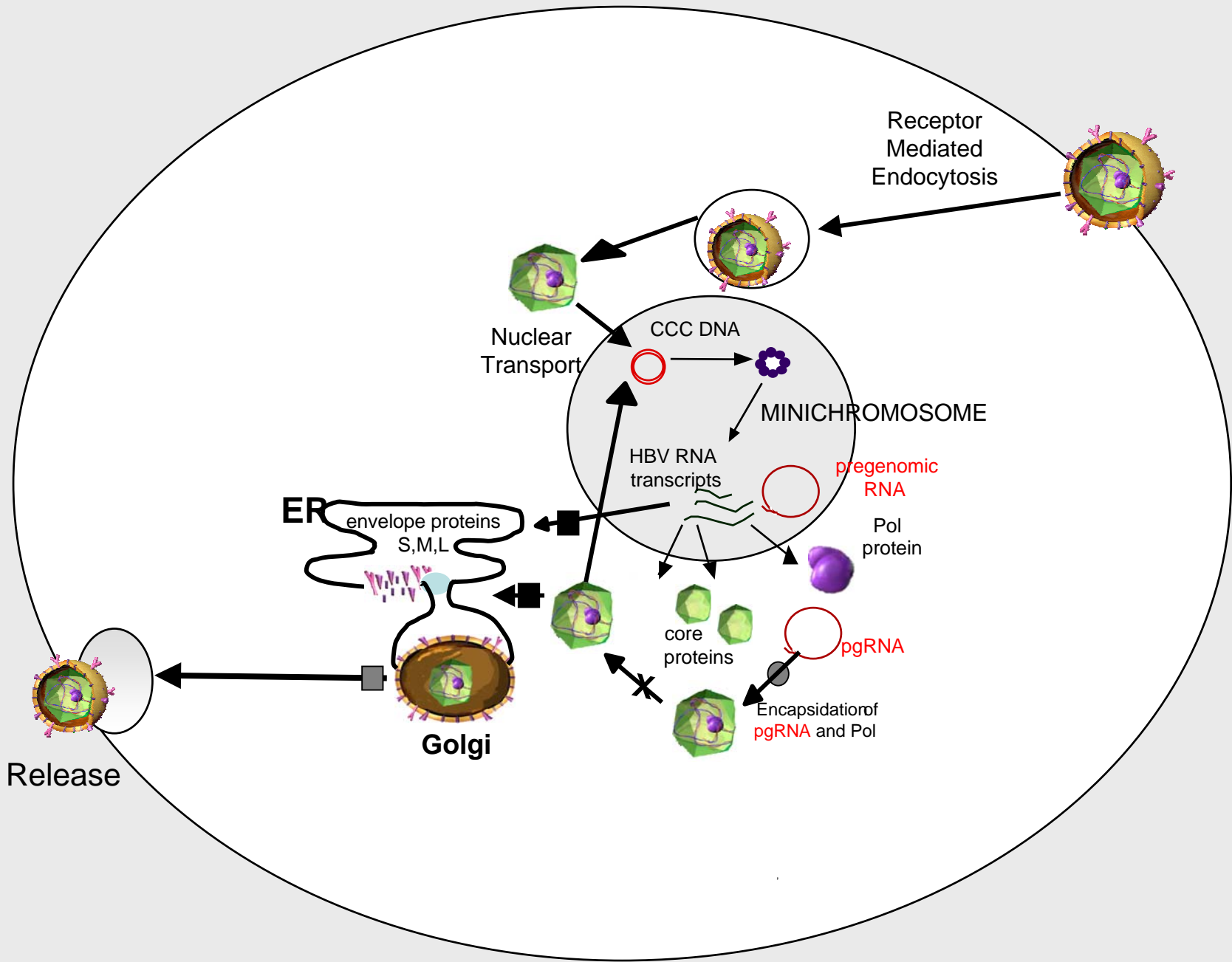
Polynesia

# HBV Genotype C Diversity - Pacific and Eurasia

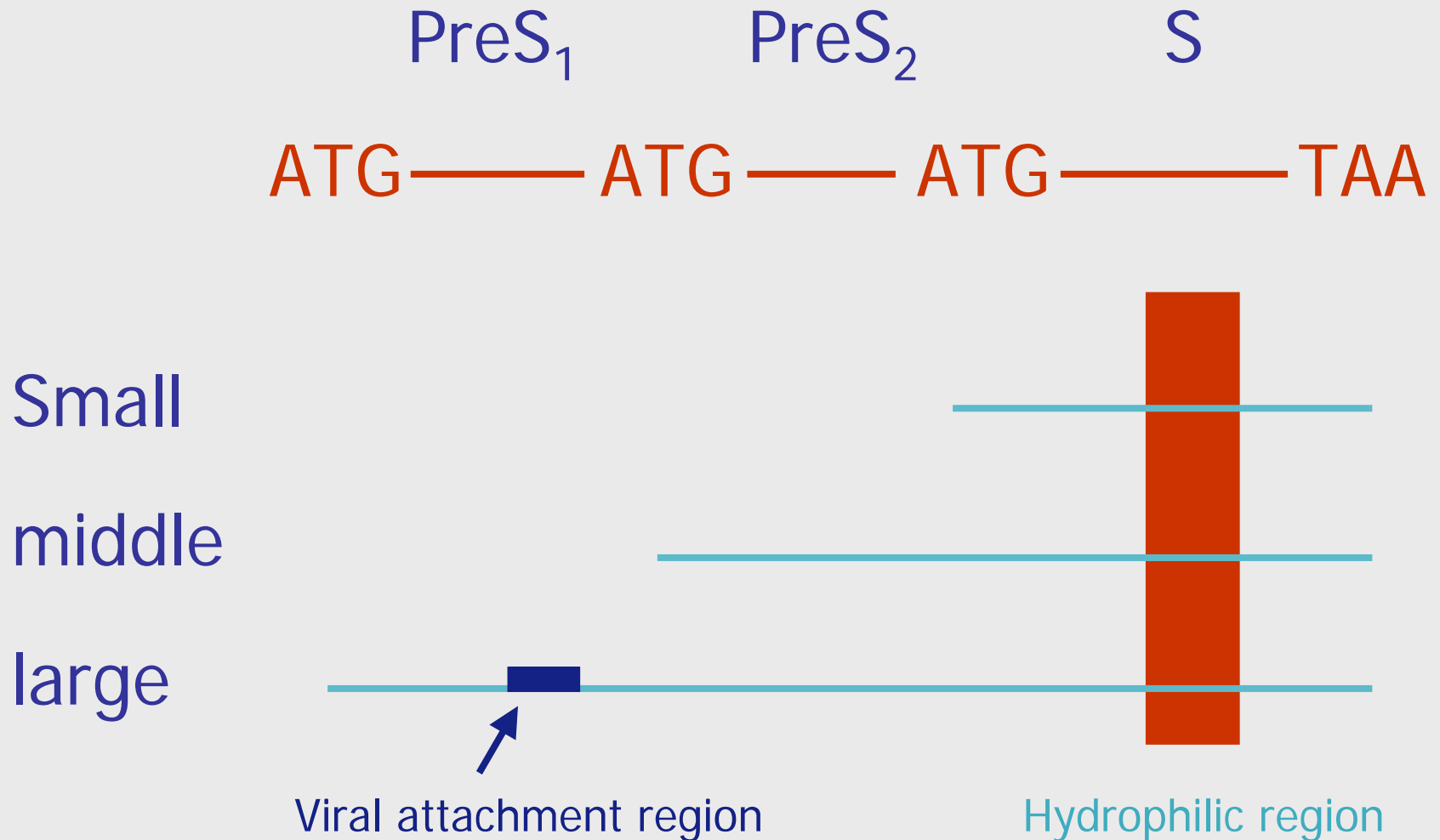


Specific amino acid motifs found in a specific ethnic background.

Ethnicity	Subtype/ Genotype	Amino Acid Variant Position					
		12	27	67	74	83	91
<i>SE-Asian</i>							
<b>China</b>	adr/C	S	I	N	S	E	V
	adw2/B	S	I	N	S	E	V
<b>Korea</b>	adr/C	S	I	N	S	E	V
<b>Japan</b>	adr/C	S	I	N	S	E	V
<b>Vietnam</b>	ayw/1/B	S	I	N	S	E	V
<b>Pacific</b>	adrq-/C	S	I	N	S	E	V
<i>Caucasian</i>							
<b>USA</b>	adw2/A	T	V	T	N	D	T
<b>Italy</b>	adw2/A	T	V	T	N	D	T
	ayw2/D	T	V	T	V	D	T
<b>Scotland</b>	adw2/A	T	V	T	N	D	T
	ayw2/D	T	V	T	V	D	T



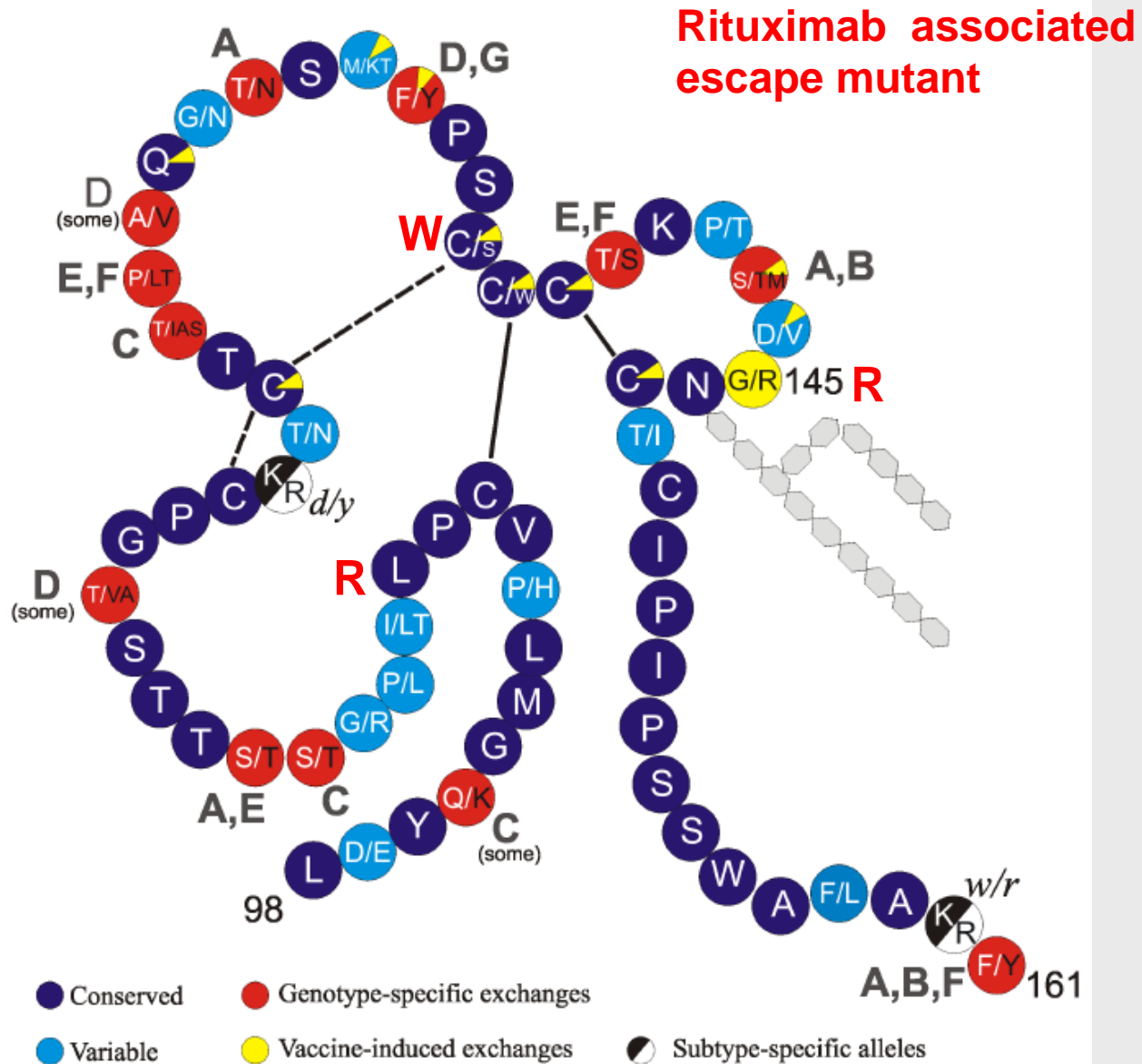
# Protein products of the surface gene



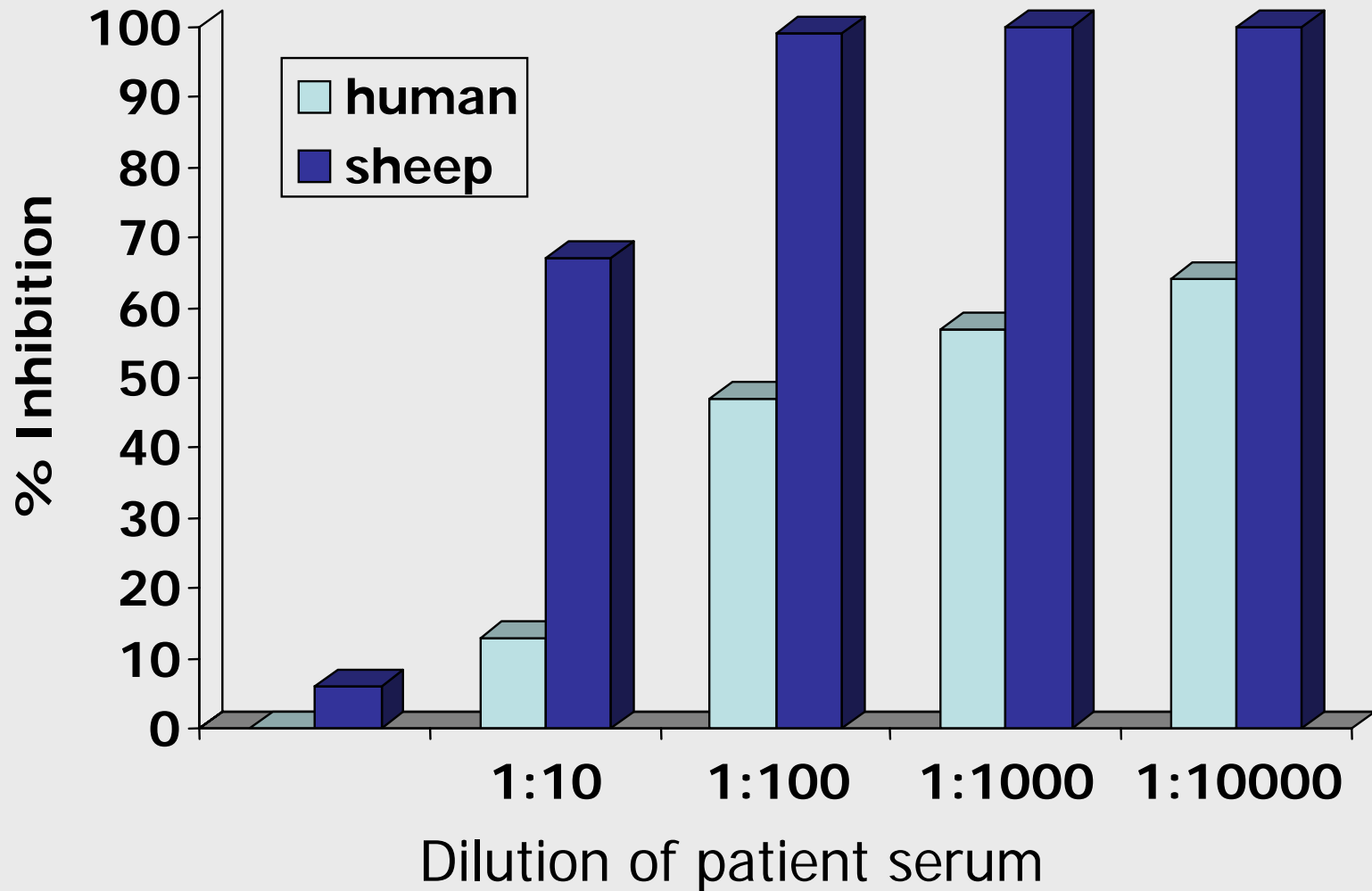
# Reactivation of hepatitis B during immunosuppressive lymphoma therapy

- Italian patient with B cell lymphoma since 1989, several therapies
- 1996 HBsAg neg., anti-HBc neg.  
anti-HBs 612 IU/L; no vaccination
- In 2003 4 cycles of chemotherapy
- July 2003 under chemotherapy
  - HBsAg AxSym **highly pos., not** inhibitable
  - HBsAg VIDAS **neg.**
  - Anti-HBc neg., anti-HBs 93 IU/L
  - No hepatitis
  - **HBV DNA  $1.8 \times 10^8$  copies/mL**
- Lamivudine therapy started
- Escape mutations: L109R, C137W, G145R

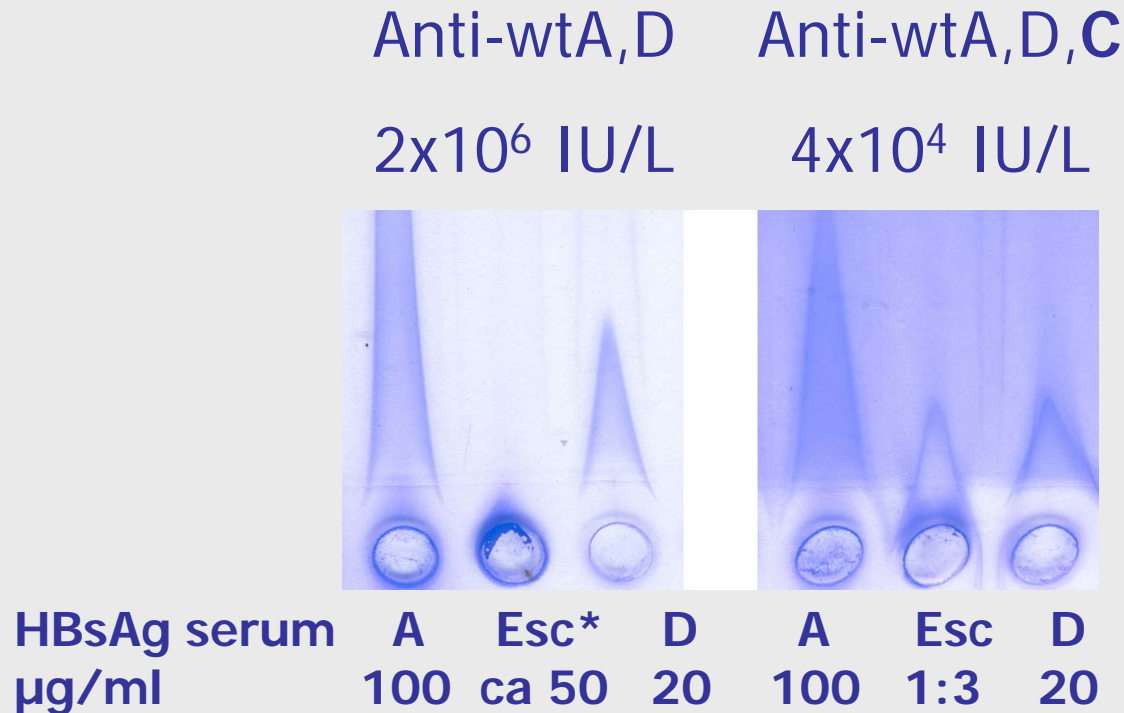
# Genotype- and vaccine-escape induced specific exchanges in the $\alpha$ determinant of SHBs



**Inhibition of HBsAg signals of a patient serum after neutralisation with anti-HBs sera from aHB-vaccinated donor (650 000 IU/L) or from a Sheep immunised with wt HBsAg genotypes A, D, C (40 000 IU)**

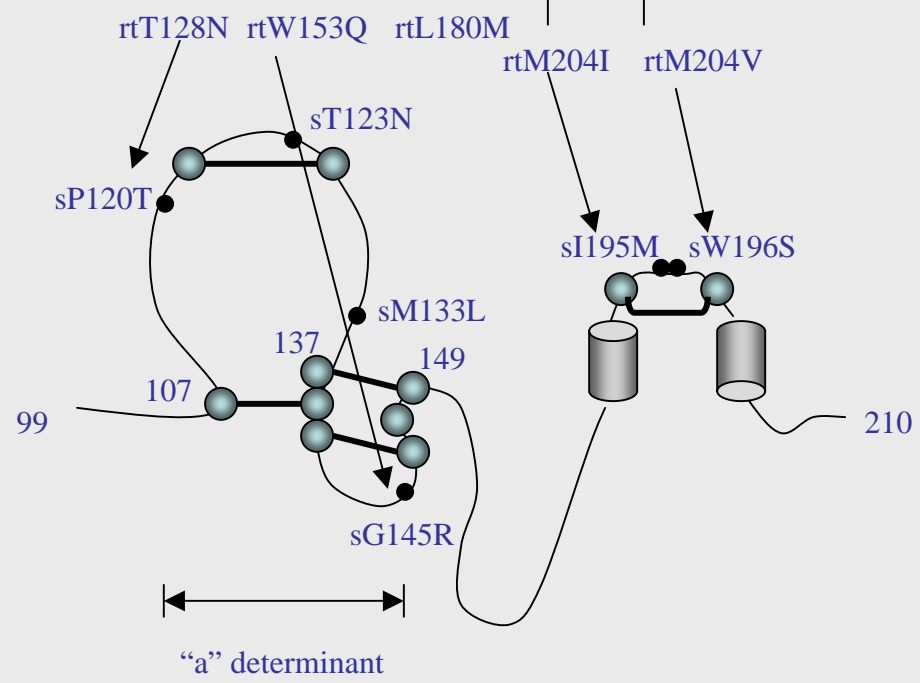
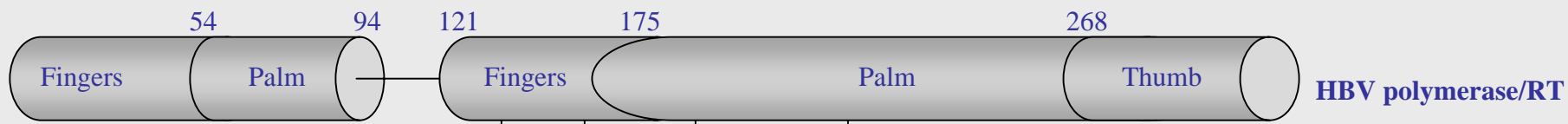


# Laurell Electrophoresis: detection of an HBsAg Escape\* Variant Genotype D with a multivalent anti-HBs sheep antiserum raised with three genotypes



\*Escape mutations: L109R, C137W, G145R

Anti-HBs of the patient neutralised by HBsAg A or D, not C



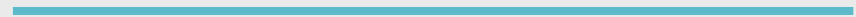
# Protein products of the core gene



Core protein



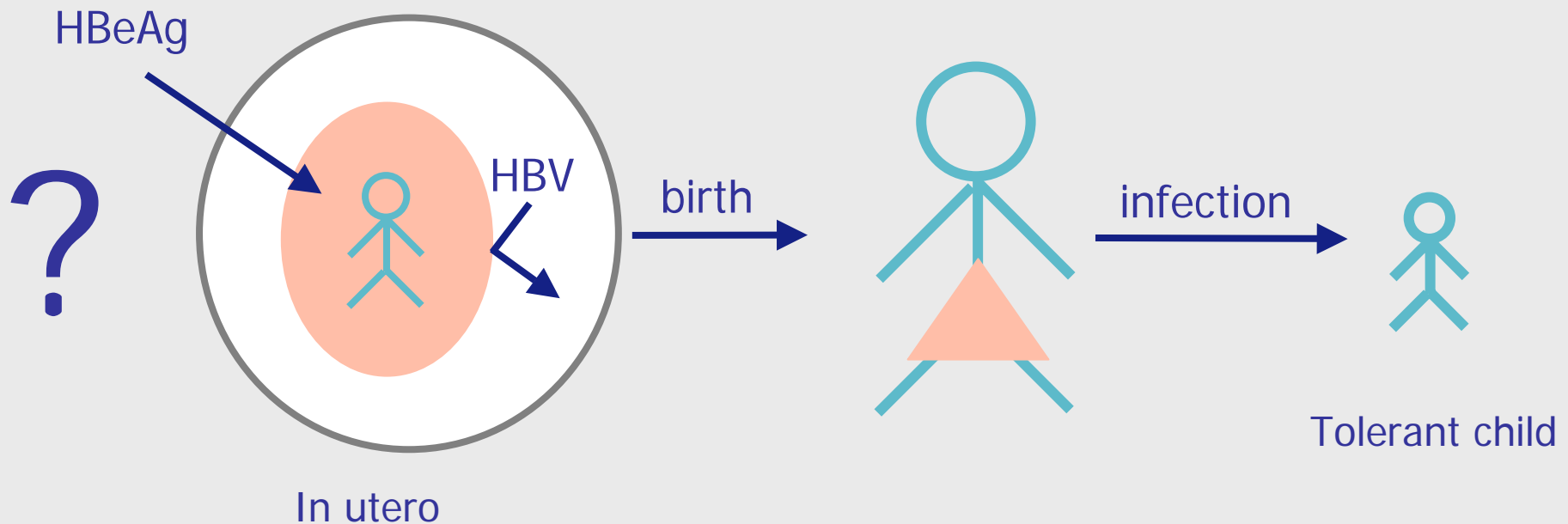
HBeAg



# HBeAg and immunotolerance

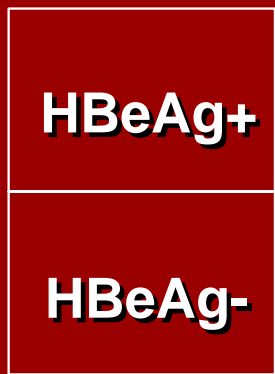
HBeAg is:

- Not part of the virion
- A secreted protein
- Found in all hepadnaviruses
- Associated with high replication



# Pre-core mutants

- Usually found in DNA+ anti-HBe+ patients
- Selected after seroconversion to anti-HBe
- In certain genotypes only
- Do not always correlate with progression
- Associated with fulminant hepatitis (see below)
- Do not directly predict response to interferon
- No effect on nucleoside analogue therapy



?CTL  
?B cell  
?Th



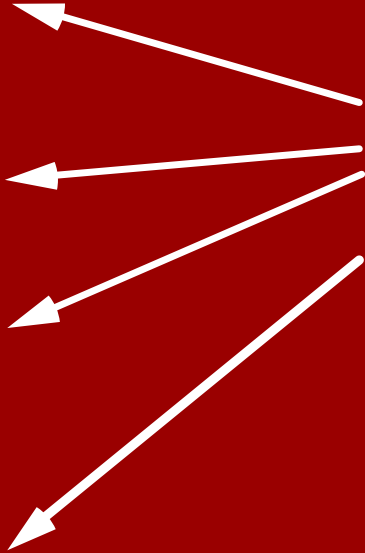
loss of  
immunomodulation



B cell  
Th cell



Ongoing  
Disease

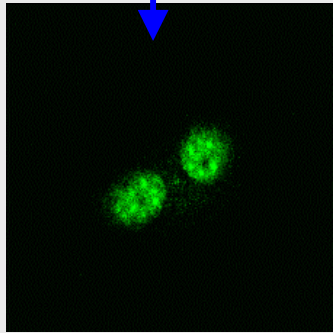


# Does sequence dictate cellular localisation?

HBeAg Positive



No Mutation

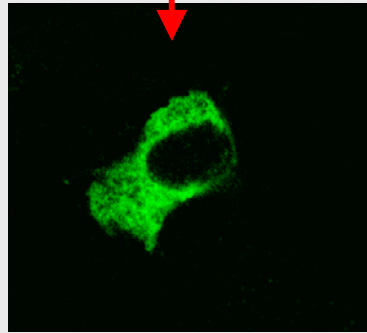


Nuclear

Anti-HBe Positive



B cell Epitope/C-terminus  
Mutations

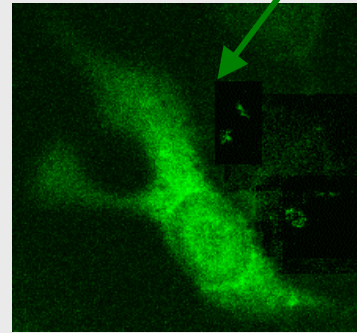


Cytoplasmic

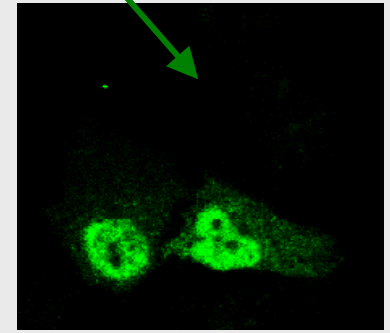
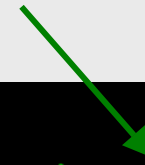
Mutagenesis



B cell/C-terminus mutations  
Reversion to Wild type

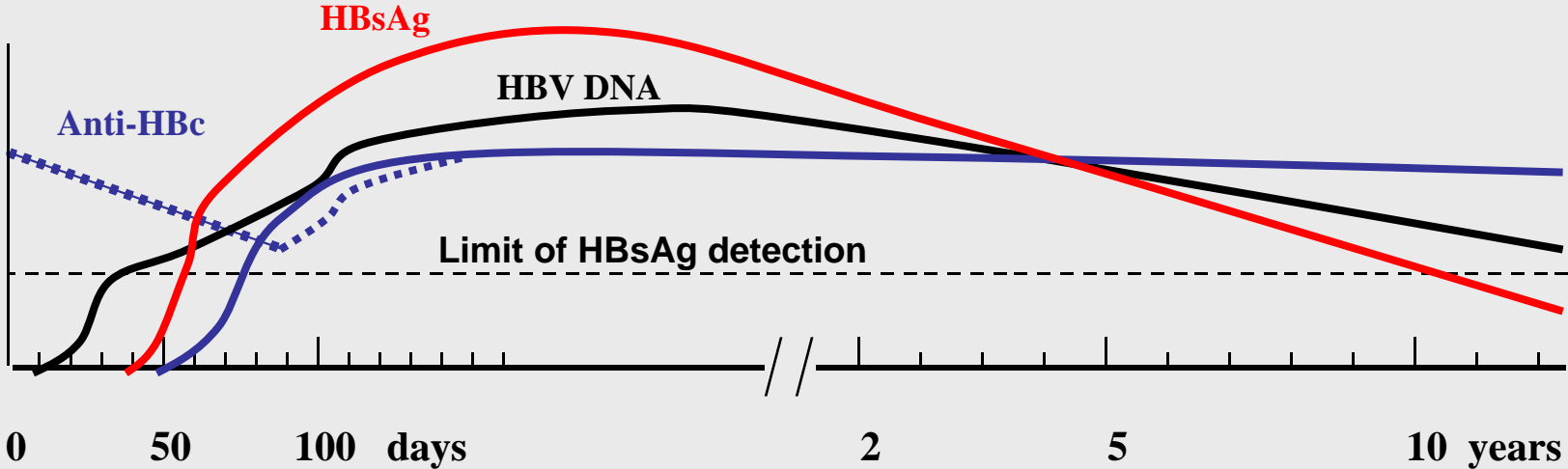
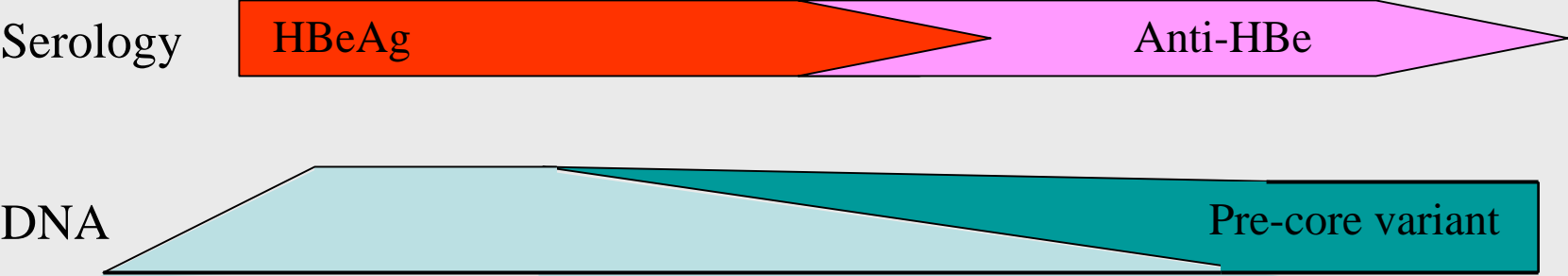


Nuclear &  
Cytoplasmic



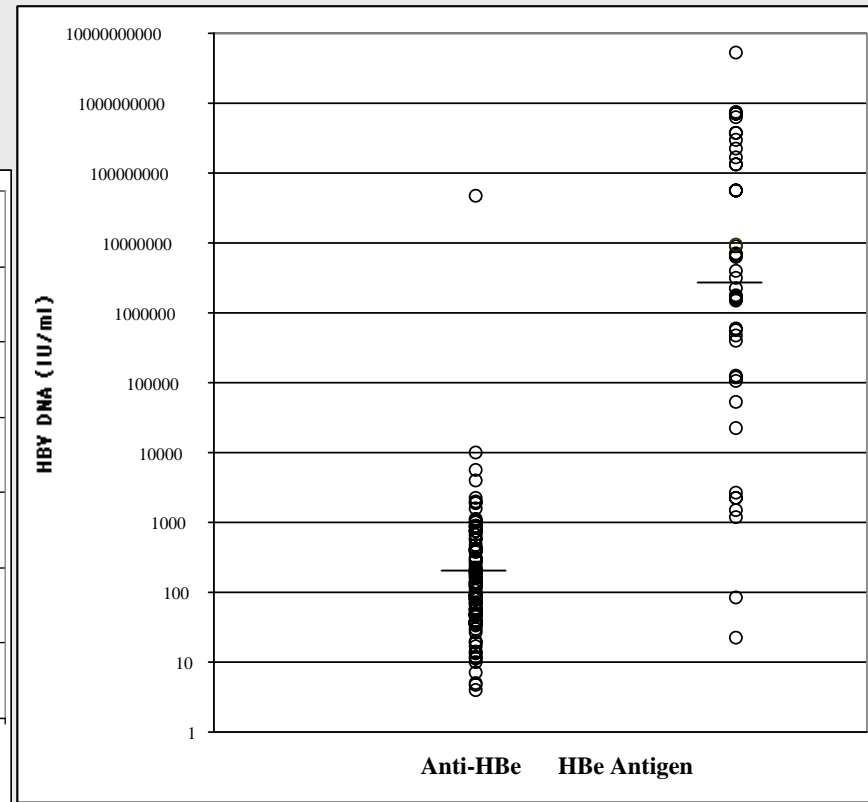
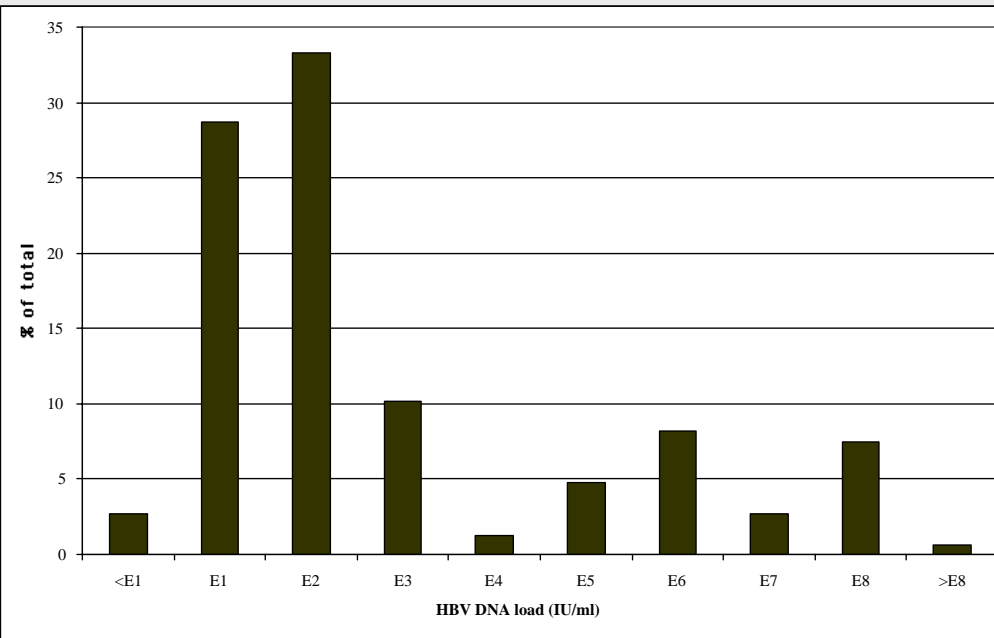
Nuclear

# Natural history of chronic HBV infection



# Distribution of HBV DNA load and relation to HBe Ag/Ab in HBsAg+ Ghanaian blood donors

(Allain et al. Blood 2003)



## Detection of HBV DNA in HBsAg positive samples

Author	Sensitivity IU/ml	DNA in HBsAg + (%)
Jardi	1000	128/193 (66)
Loeb	10	164/195 (84)
Allain	20	156/159 (98)

## Prevalence of anti-HBc only and HBV DNA frequency

<b>Author</b>	<b>Country</b>	<b>No screened</b>	<b>Anti-HBc only (%)</b>	<b>DNA+ (%)</b>
<b>Hennig</b>	<b>Germany</b>	<b>14,251</b>	<b>20 (0.14)</b>	<b>3 (15.0)</b>
<b>Tseliou</b>	<b>Greece</b>	<b>10,629</b>	<b>507 (4.8)</b>	<b>0</b>
<b>Zervou</b>	<b>Greece</b>	<b>6696</b>	<b>105 (1.0)</b>	<b>0</b>
<b>Allain</b>	<b>UK</b>	<b>103,869</b>	<b>69 (0.07)</b>	<b>0</b>
<b>Kleinman</b>	<b>USA</b>		<b>387</b>	<b>4/107 (3.7)</b>
<b>Almeida-Neto</b>	<b>Brazil</b>		<b>112</b>	<b>0</b>
<b>Ren</b>	<b>China</b>		<b>297</b>	<b>1 (0.3)</b>
<b>Sato</b>	<b>Japan</b>	<b>540,161</b>	<b>1103 (0.2)</b>	<b>12 (1.1)</b>
<b>Bernvil</b>	<b>Saudi Arabia</b>	<b>6,035</b>	<b>125 (2.1)</b>	<b>4 (3.2)</b>
<b>Allain</b>	<b>Ghana</b>	<b>242</b>	<b>110 (45.5)</b>	<b>14 (12.7)</b>

# Hidden HBV infection in pre and post-vaccination sera in South Africa

	Pre-vaccination	Post-vaccination	p value
anti-HBs		893/986 (90.6%)*	
anti-HBc	4/203 (1.9%)	9/986 (0.9%)	0.187
HBV DNA	30/459 (6.5%)	4/1213 (0.3%)	<0.00001

\* *Anti HBs reactivity is borderline in 59/986 (6%)*