

*First International Course on
Translational Hepatology*



*Focus on HCV disease
Florence, March 9-11, 2011*

*Autoreactivity
in HCV infection*

*Diego Vergani
King's College London
School of Medicine*

Autoreactivity in HCV infection

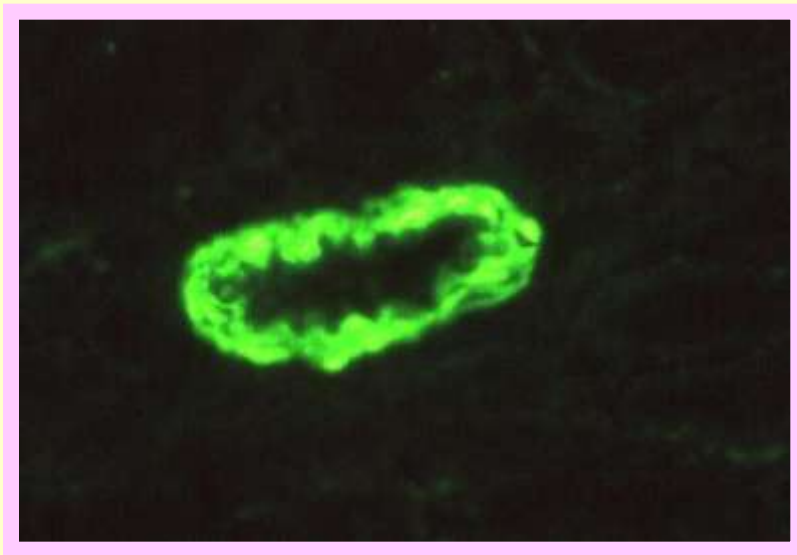
❖ **HCV and serological autoimmunity:
autoantibodies**

❖ **HCV and clinical autoimmunity:
autoimmune disease**

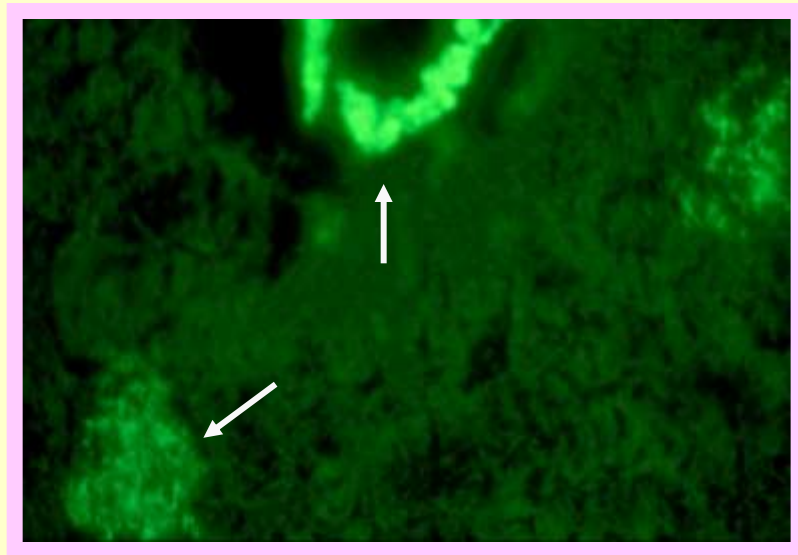
Autoreactivity in HCV infection

Autoantibodies present in chronic Hepatitis C

Anti-Smooth Muscle (SMA) autoantibody



HCV

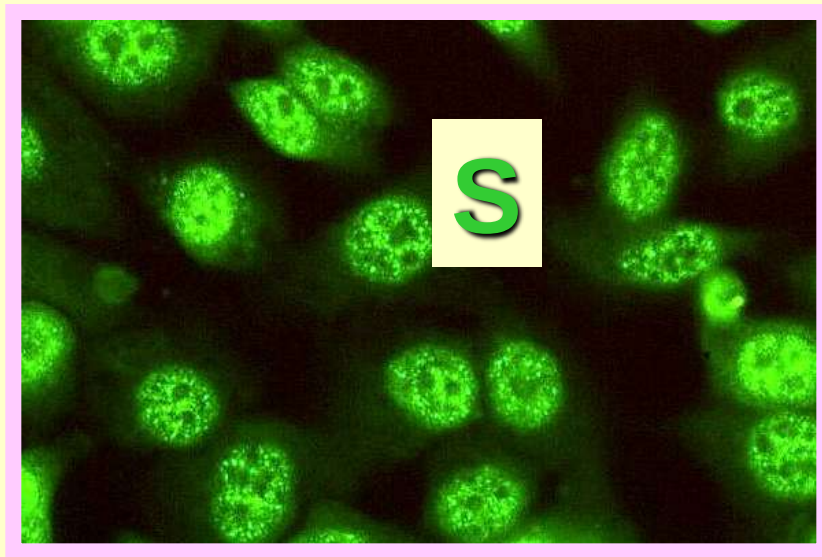


AIH

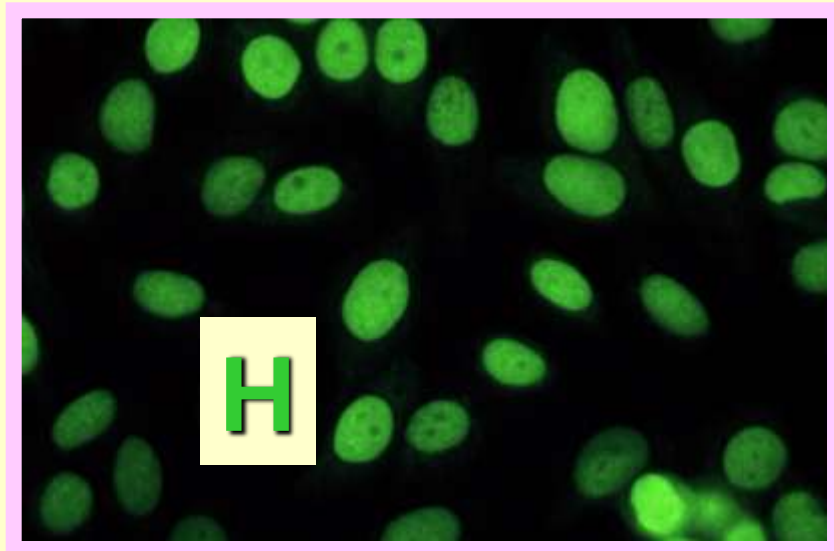
Autoreactivity in HCV infection

Autoantibodies present in chronic Hepatitis C

Anti-nuclear (ANA) autoantibody



HCV



AIH

ANA-SMA in Chronic Hepatitis C and AIH-1

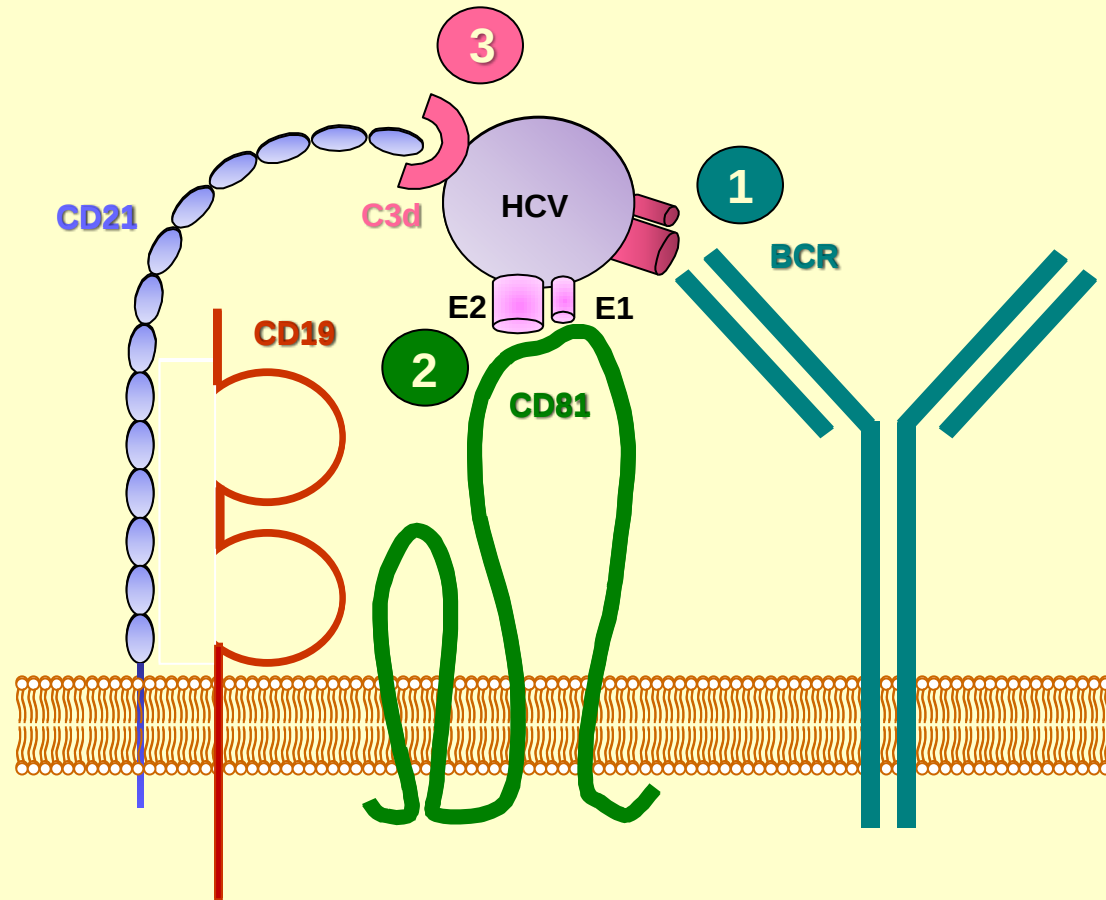
	<i>HCV-CH</i>	<i>AIH-1</i>	<i>p</i>
<i>ANA+ve</i>	<i>26/290 (9%)</i>	<i>28/35 (80%)</i>	
<i>SMA+ve</i>	<i>59/290 (20%)</i>	<i>32/35 (91%)</i>	
<i>ANA-H +ve</i> <i>SMA VGT</i> <i>pattern</i>	<i>0/69 (0%)</i>	<i>16/35 (46%)</i>	<i><10⁻⁶</i>

Autoreactivity in HCV infection

**How do autoantibodies arise
in Hepatitis C?**

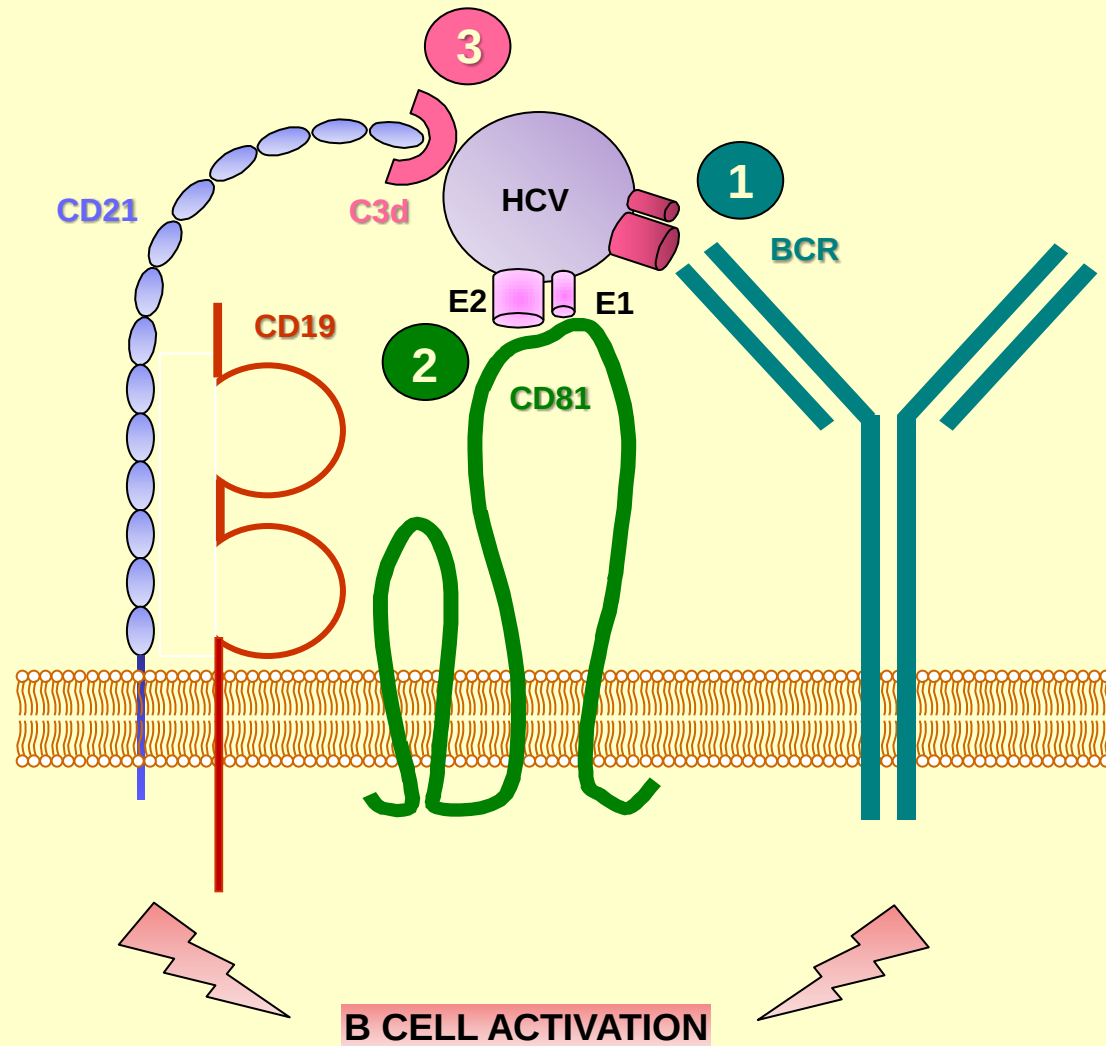
B cell activation

Autoreactivity in HCV infection



B Cell Surface Molecules

Autoreactivity in HCV infection



Autoreactivity in HCV infection

**How do autoantibodies arise
in Hepatitis C?**

B cell activation

Molecular Mimicry

Homologies between HCV and

HCV₇₃₉

Matrin₂₉₄

HCV₁₄₇₉

Histone₁₀

HCV₁₈₅₅

Replication protein₁₃₃

Nuclear

HCV₁₅₂

Vimentin₇₄

HCV₁₀₅₄

Myosin₁₀₃₇

HCV₂₃₄₈

Smoothelin₁₅₄

***Smooth
muscle***

Autoreactivity in HCV infection

SUBJECTS

51 chronic HCV infection

24 chronic HBV infection

36 autoimmune liver disease

12 AIH SMA/ANA+ve

12 AIH LKM+ve

12 ASC SMA/ANA+ve

11 Alagille's syndrome

10 alpha-1- ATD

11 Wilson disease

24 healthy children

Double reactivity to *HCV* & Histone peptides

51 chronic HCV infection	37%
24 chronic HBV infection	0
36 autoimmune liver disease	0
12 AIH SMA/ANA+ve	0
12 AIH LKM+ve	0
12 ASC SMA/ANA+ve	0
11 Alagille's syndrome	0
10 alpha-1- ATD	0
11 Wilson disease	0
24 healthy children	0

Homologies between HCV and

HCV₇₃₉

Matrin₂₉₄

HCV₁₄₇₉

Histone₁₀

HCV₁₈₅₅

Replication protein₁₃₃

Nuclear

HCV₁₅₂

Vimentin₇₄

HCV₁₀₅₄

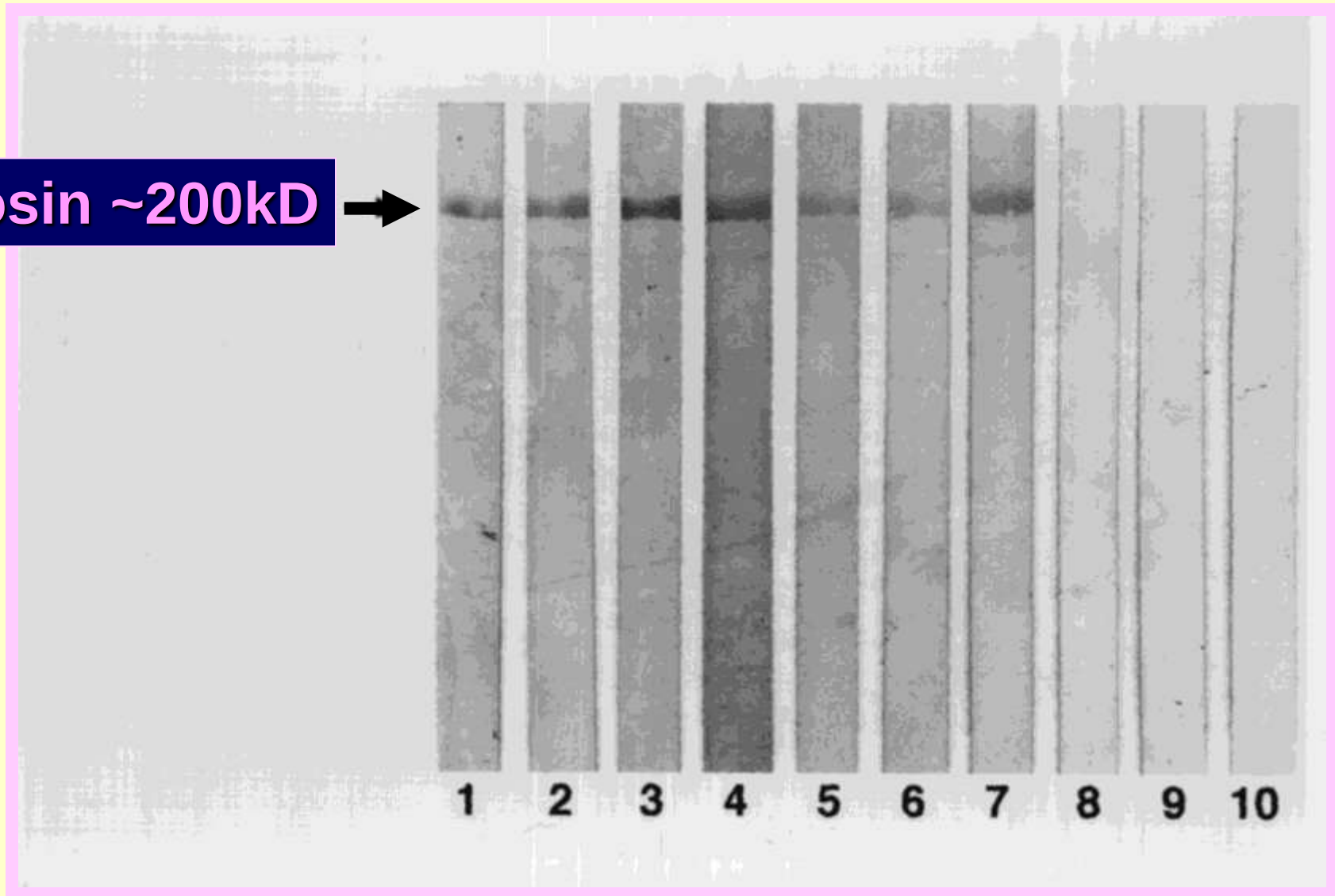
Myosin₁₀₃₇

HCV₂₃₄₈

Smoothelin₁₅₄

***Smooth
muscle***

Myosin ~200kD →



Autoreactivity in HCV infection

Do autoantibodies in chronic hepatitis C matter?

Chronic Hepatitis C

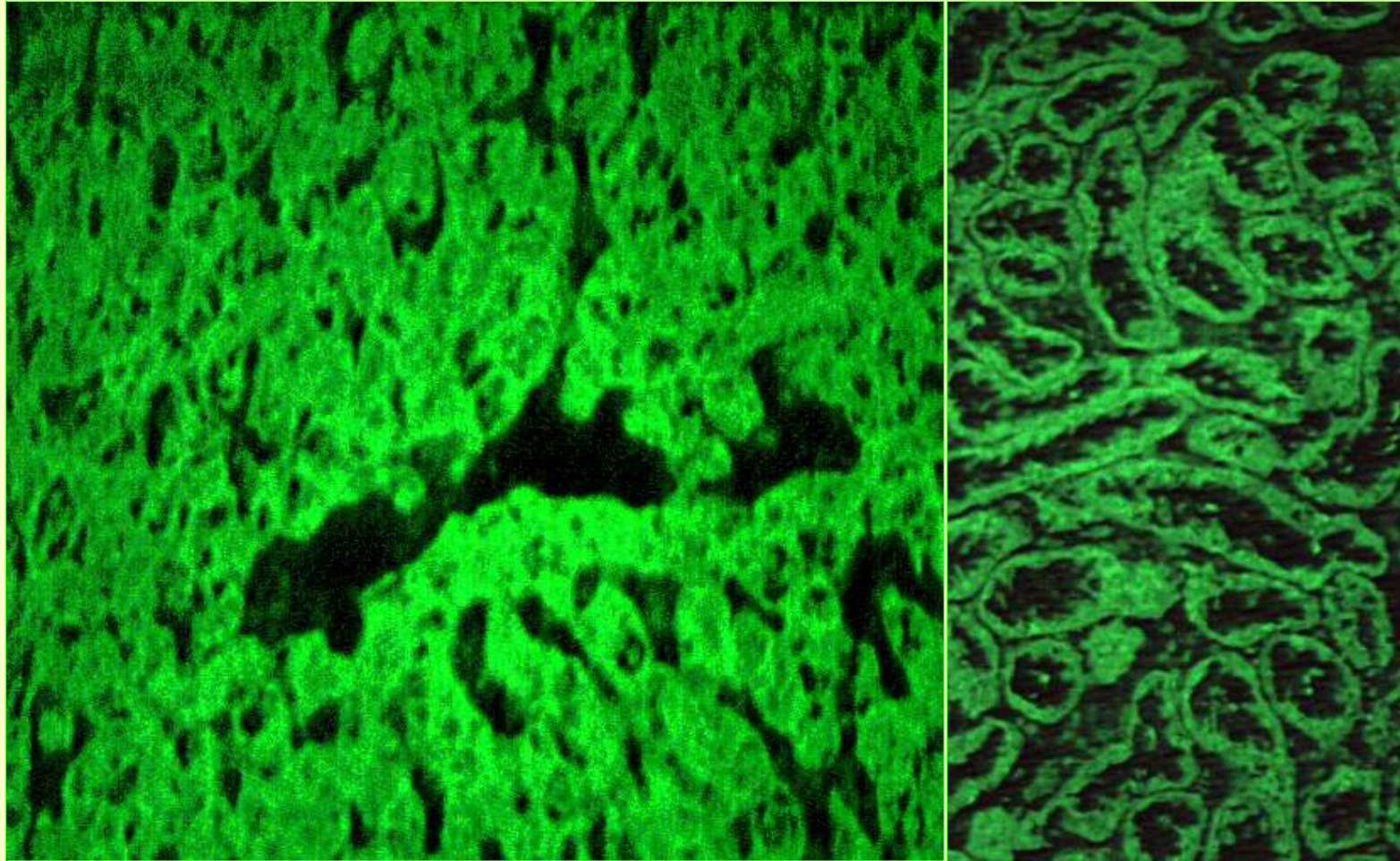
	NOSAs (-)	NOSAs (+)	p
n° cases	203	87	
Sex (M/F)	105/98	32/55	0.027
Age (yrs)*	49±15	47±16	0.309
ALT*	120±97	178 ±150	<0.001
AST*	83±61	112±90	0.002
Alb (g/l)*	39.2 ±5.5	39.6±4.5	0.550
γ-glob (g/l)*	16.3 ±5.8	17.6±4.5	0.063
IgG*	1863 ±622	2039 ±573	0.010
IgA*	289 ±170	253 ±127	0.079
IgM*	237±157	253 ±128	0.403
Scheuer's index (n cases)	109	56	
Port/periport N-I*	1.64 ±0.77	2.05 ±0.93	0.003
Fibrosis*	1.93 ±0.87	2.16 ±0.94	0.120

*mean ± sd

Autoreactivity in HCV infection

Chronic Hepatitis C and Autoimmune Disease

Autoreactivity in HCV infection



CYP2D6

Liver Kidney Microsomal antibody

LKM1 prevalence in chronic hepatitis C

Clifford	1995	2/41	2.4%
Cassani	1997	18/290	6%
Dionysos	1999	3/226	1.3%
Iijima	2001	6/390	1.5%
Stroffolini	2004	11/502	2.2%
Monti	2005	48/2675	1.8%

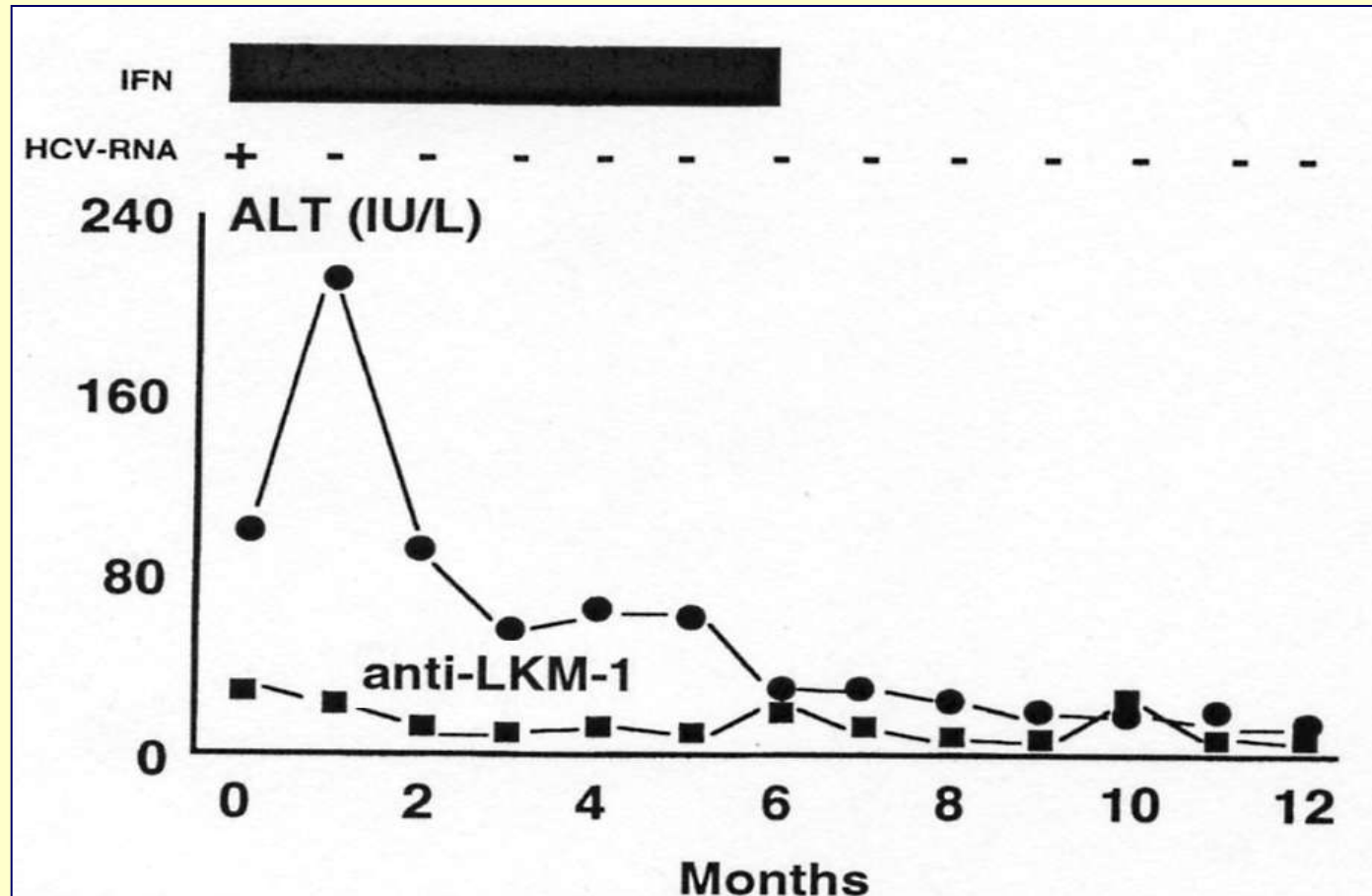
Autoreactivity in HCV infection

Of the 170 million HCV patients

2- 10 million are LKM1 positive

Does it matter?

ALT flare in LKM1/HCV +ve pts on IFN



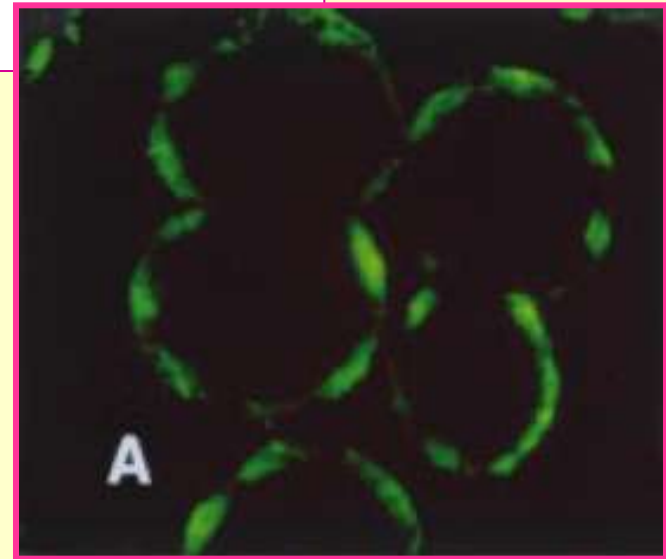
Iijima Y, J Gastroenterol Hepatol 2001

LKM1 directly pathogenic?

Gut 2000;46;553-561

**Liver kidney microsomal antibody type 1 targets CYP2D6
on hepatocyte plasma membrane**

**L Muratori, M Parola, A Ripalti, G Robino, P Muratori, G Bellomo,
R Carini, M Lenzi, M P Landini, E Albano and F B Bianchi**



Suceptibility to Thyroid Disorders in Hepatitis C

Clin Gastroenterol Hepatol 2005;3;595-603

Susceptibility to Thyroid Disorders in Hepatitis C

**L Muratori, DP Bogdanos, P Muratori, M Lenzi, Granito A,
Ma Y, Mieli-Vergani G, Bianchi F B and D Vergani**

Suceptibility to Thyroid Disorders in Hepatitis C

348 consecutive Italian pts with chronic hepatitis C, 196 treated with INF

AITD at baseline

LKM1 +ve > LKM1-ve, $p < 0.005$

AITD on interferon

LKM1 +ve >>> LKM1-ve, $p < 0.0001$

LKM1 +ve/HCV +ve patients have a RR of 11 to develop AIT dysfunction

Target Similarities

V L T E S T L S T A L A

HCV NS5A 2334-2345

		HCV NS5 2334 - 2345	CYP2D6 308 - 319	TPO 803 - 814
HCV+ LKM+ AIT+ INF+	LKM-1	3.2	2.9	4.2
	LKM-2	5.2	4.4	8.9
	LKM-3	3.9	2.9	
	LKM-4	3.2	2.9	3.9
	LKM-5	4.3	3.9	3.8
HCV+ LKM+ AIT+ INF-	LKM-6	2.5	2.3	4.5
	LKM-7	5.1	3.3	3.1

		HCV NS5 2334 - 2345	CYP2D6 308 - 319	TPO 803 - 814
HCV+ AITD+ AIT+ INF+	LKM-1	3.2	2.9	4.2
	LKM-2	5.2	4.4	8.9
	LKM-3	3.9	2.9	
	LKM-4	3.2	2.9	3.9
	LKM-5	4.3	3.9	3.8

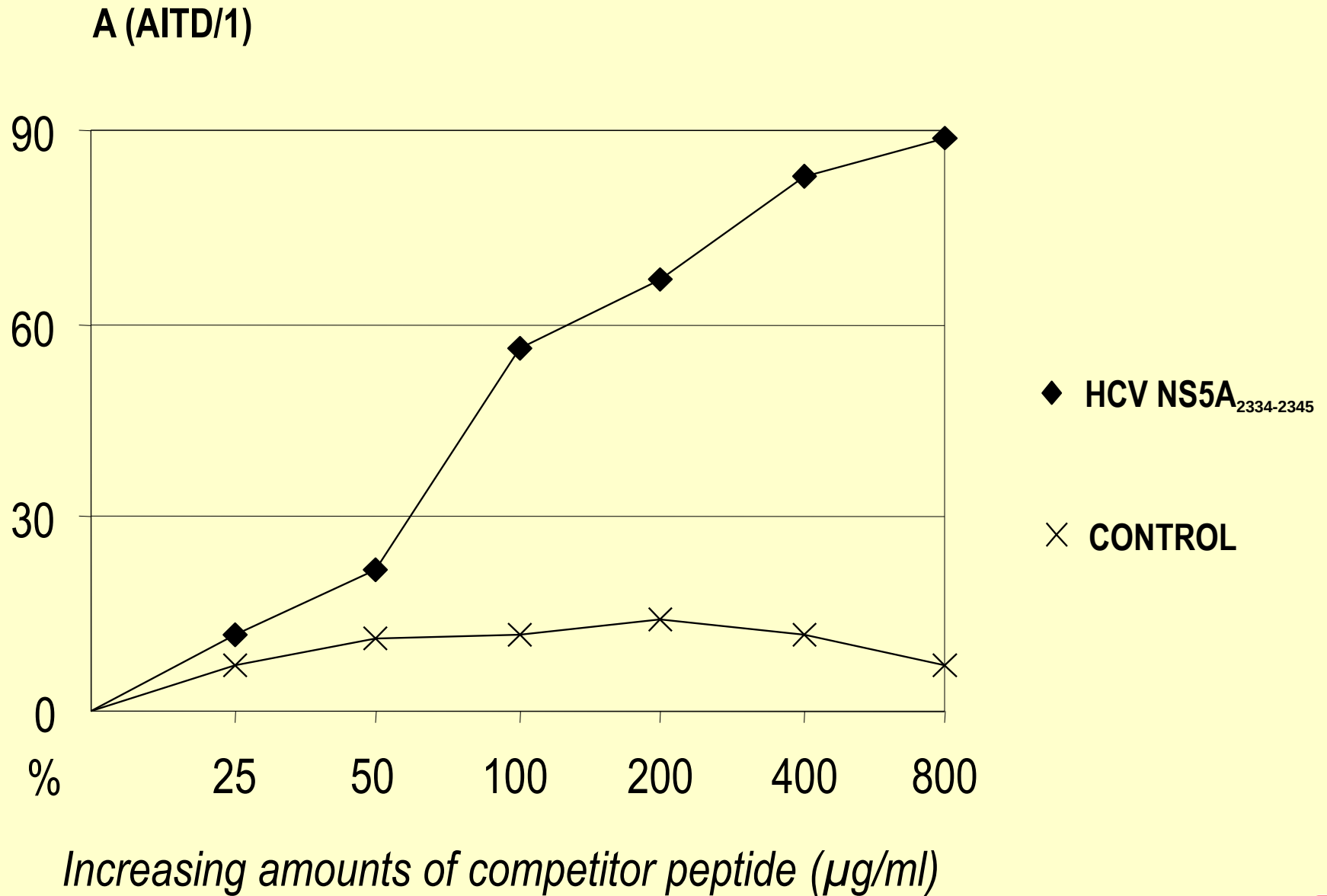
HCV+ AITD+ AIT+ INF-	LKM-6	2.5	2.3	4.5
	LKM-7	5.1	3.3	3.1

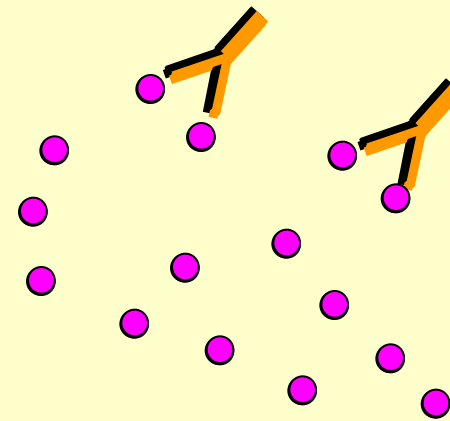
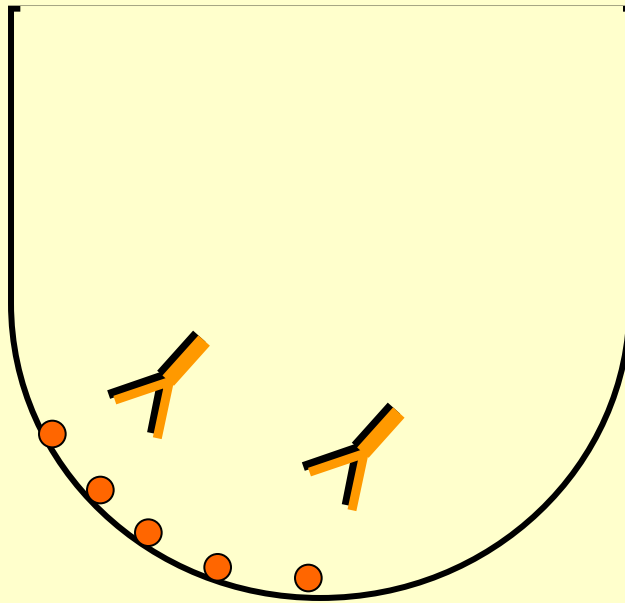
HCV+ AITD+ AIT- INF+	LKM-8			
	LKM-9			
	LKM-10	3	3.8	2
	LKM-11			
	LKM-12			

HCV+ AITD+ AIT- INF-	LKM-13			
	LKM-14	3.4		
	LKM-15			
	LKM-16			
	LKM-17			

		HCV NS5 2334 - 2345	CYP2D6 308 - 319	TPO 803 - 814
HCV- AITD- AIT+ INF-	AITD-1			2.3
	AITD-2			3.4
	AITD-3			
	AITD-4			
	AITD-5			
	AITD-6			8.2
	AITD-7			3.4
	AITD-8	3.2	2.9	5.3
	AITD-9			
	AITD-10			3.9
	AITD-11			
	AITD-12			
	AITD-13	3.1		
	AITD-14			
	AITD-15			3.2
	AITD-16			4.5
	AITD-17			9.1
	AITD-18			4.5
	AITD-19			3.4
	AITD-20			5.7
	AITD-21			4.2
	AITD-22			

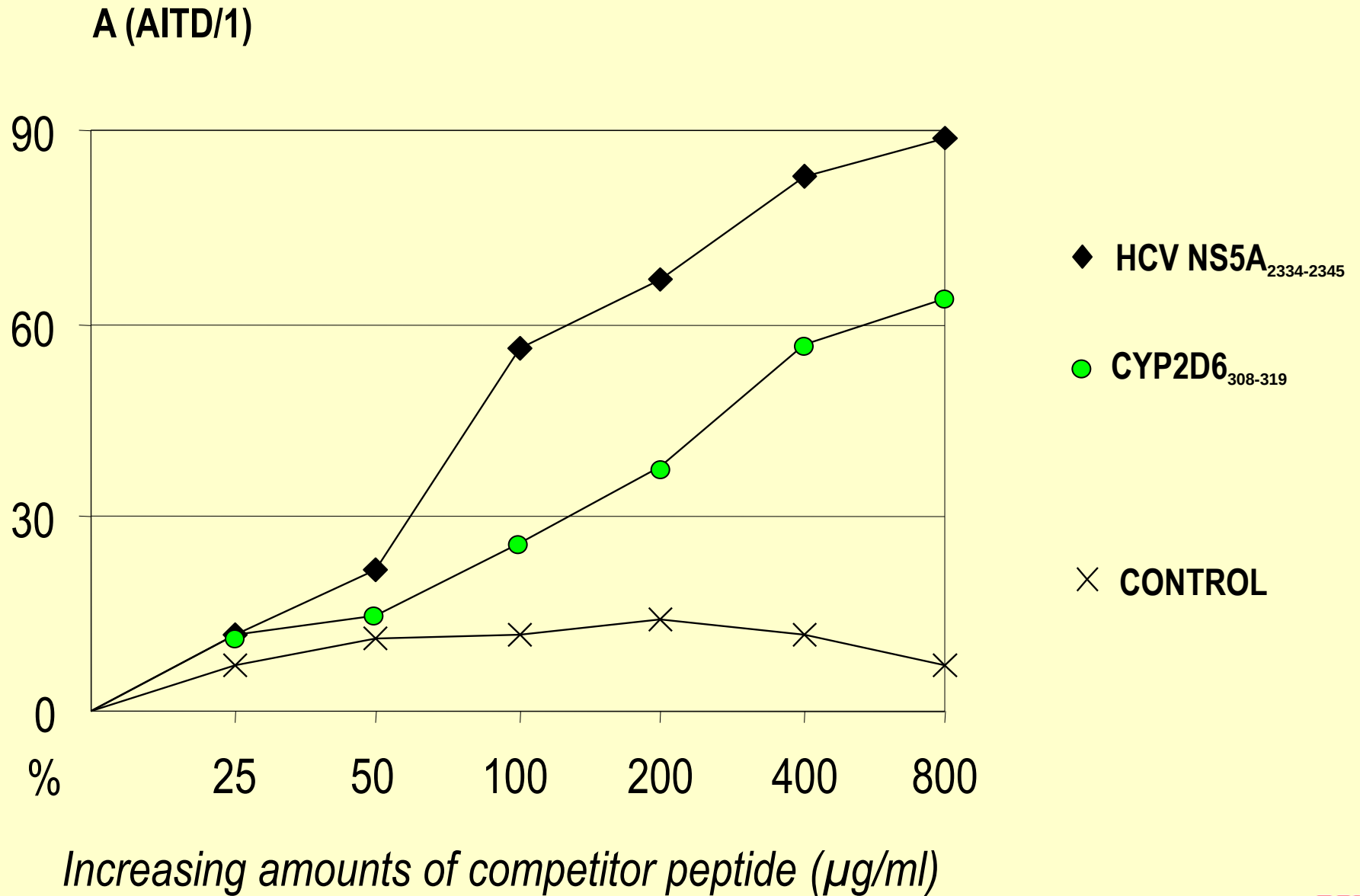
Inhibition of anti- HCV NS5A₂₃₃₄₋₂₃₄₅ reactivity



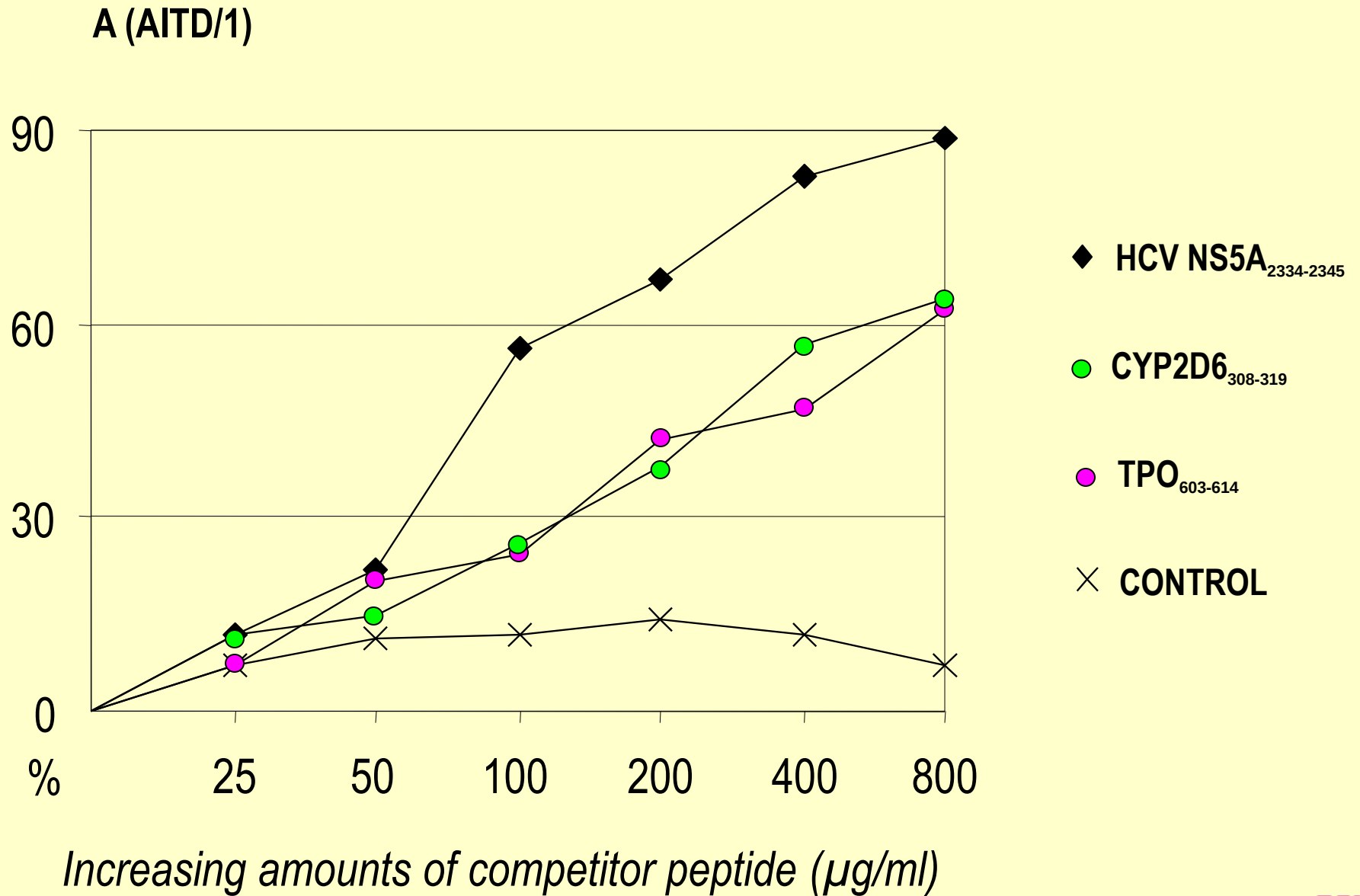


TPO

Inhibition of anti- HCV NS5A₂₃₃₄₋₂₃₄₅ reactivity



Inhibition of anti- HCV NS5A₂₃₃₄₋₂₃₄₅ reactivity



Clinical relevance of AITD1 in hepatitis C

- ❖ **Transaminase flares on IFN**
- ❖ **AITD especially on IFN**

HCV, Molecular Mimicry & Autoimmunity

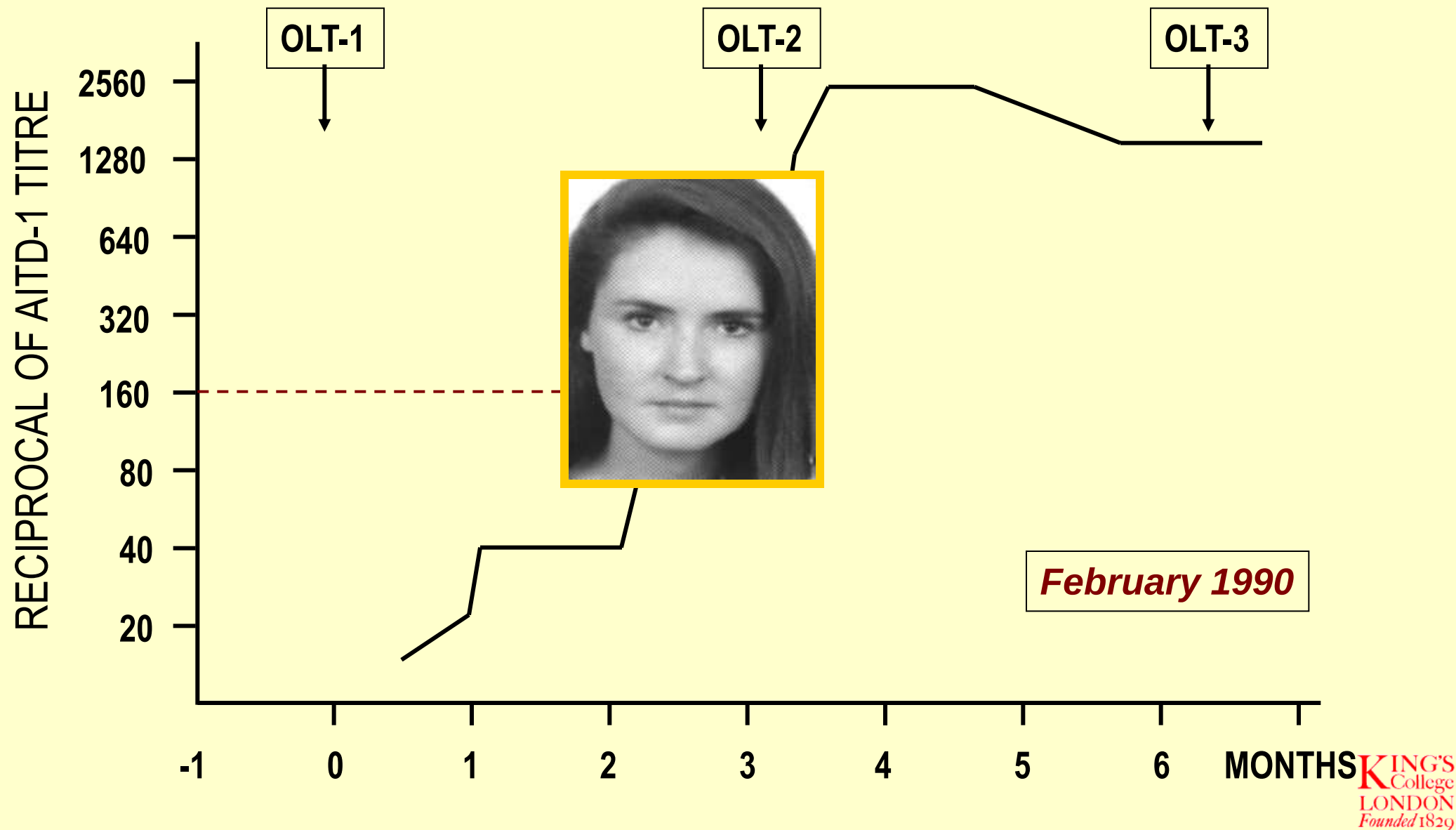
**Does HCV-related
Autoimmunity Progress to
Autoimmune Disease?**

HCV, Molecular Mimicry & Autoimmunity

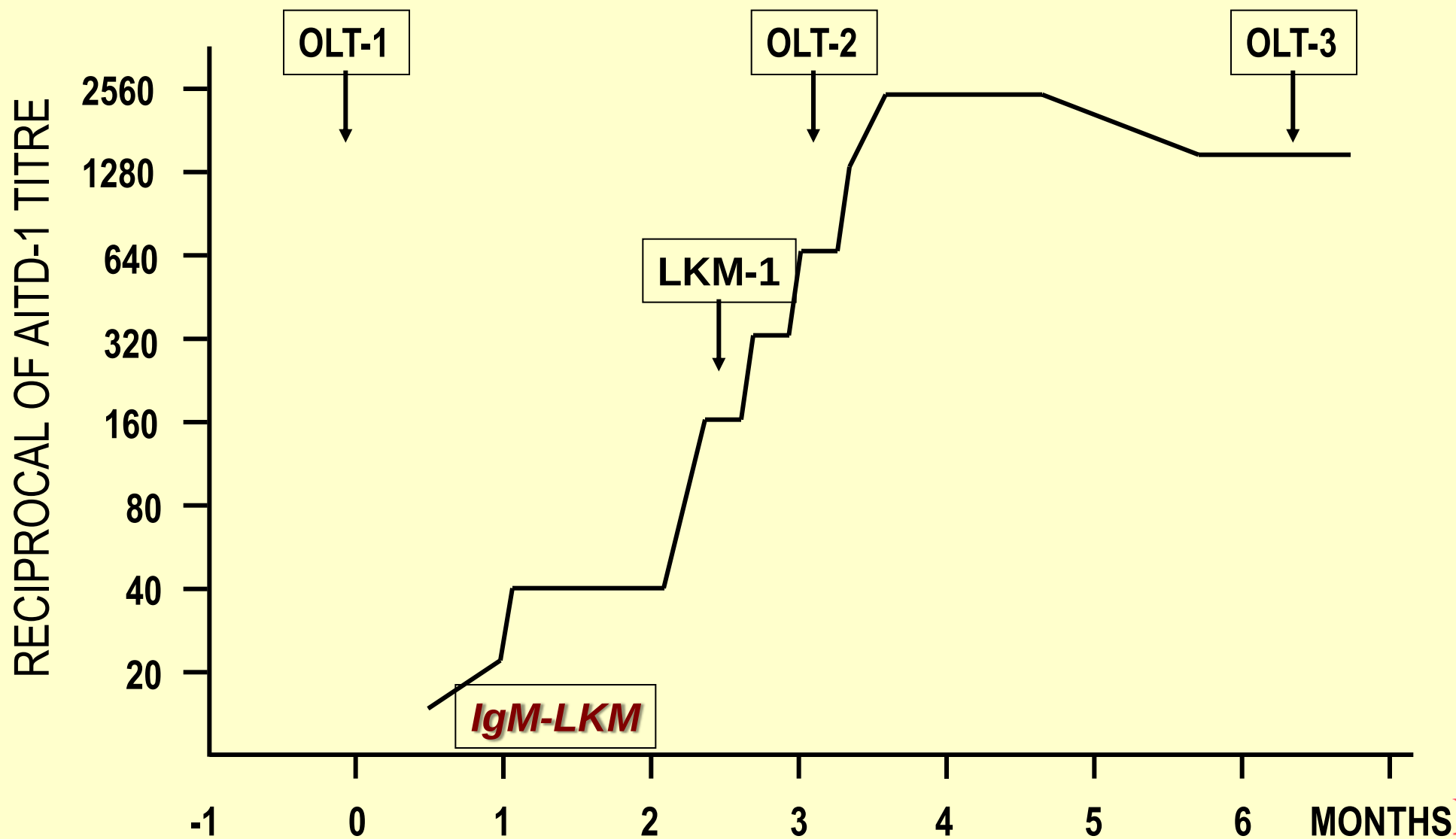
26 July 1998

- ❖ **AST 1512**
- ❖ **Histology = interface hepatitis**
- ❖ **LKM 1/2560**
- ❖ **HCV-RNA negative**
- ❖ **Response to steroids**

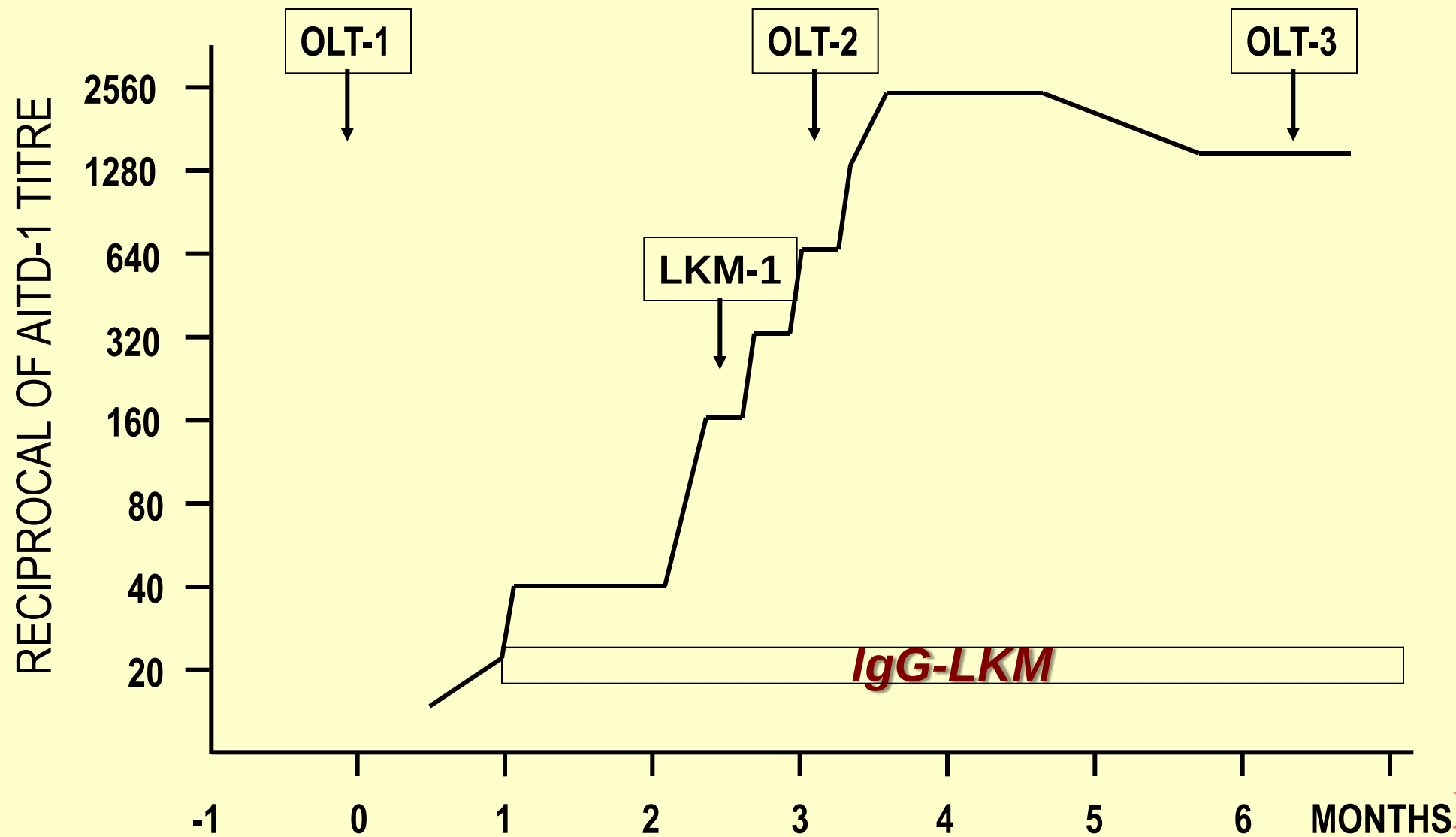
Autoreactivity in HCV infection



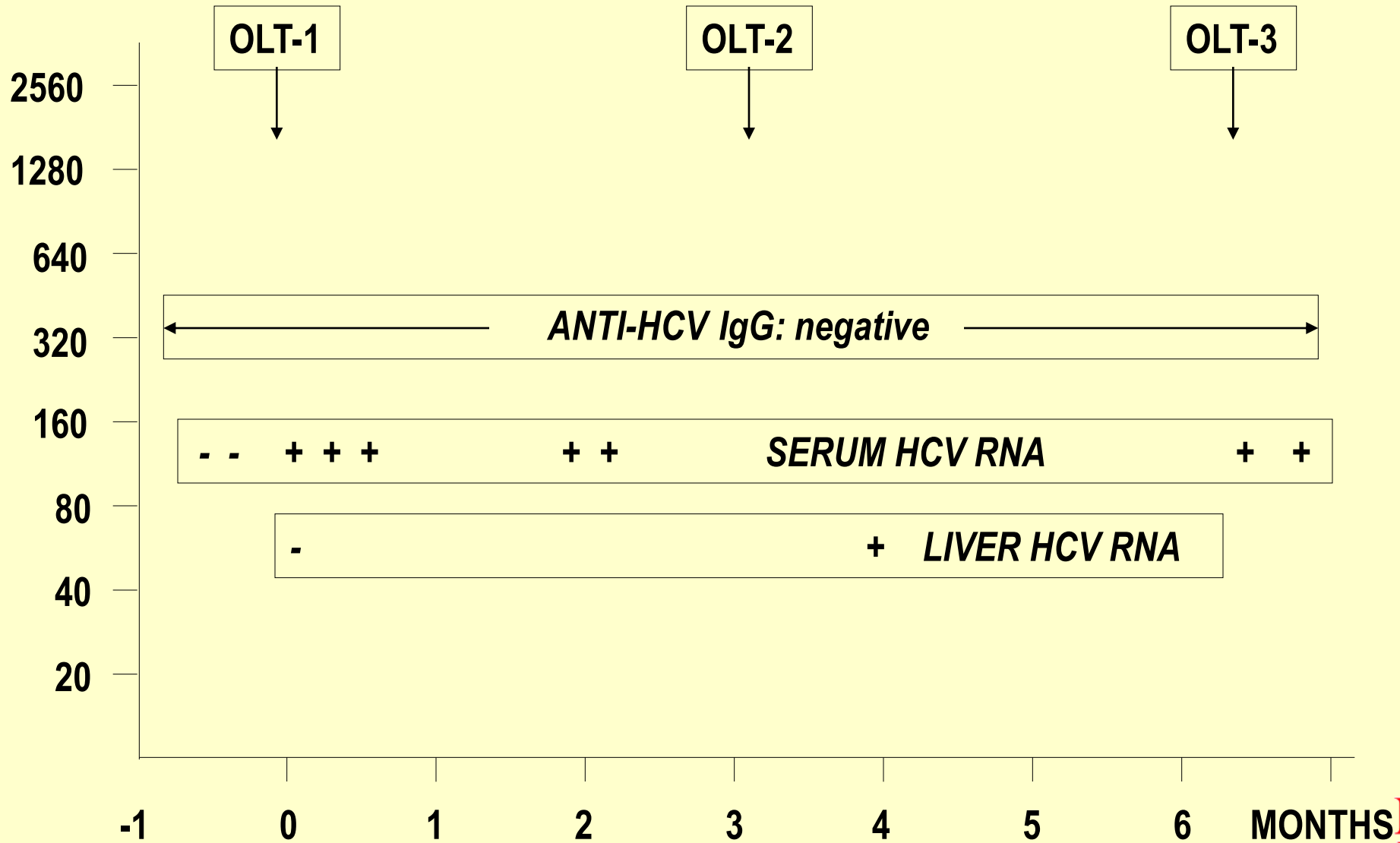
Autoreactivity in HCV infection



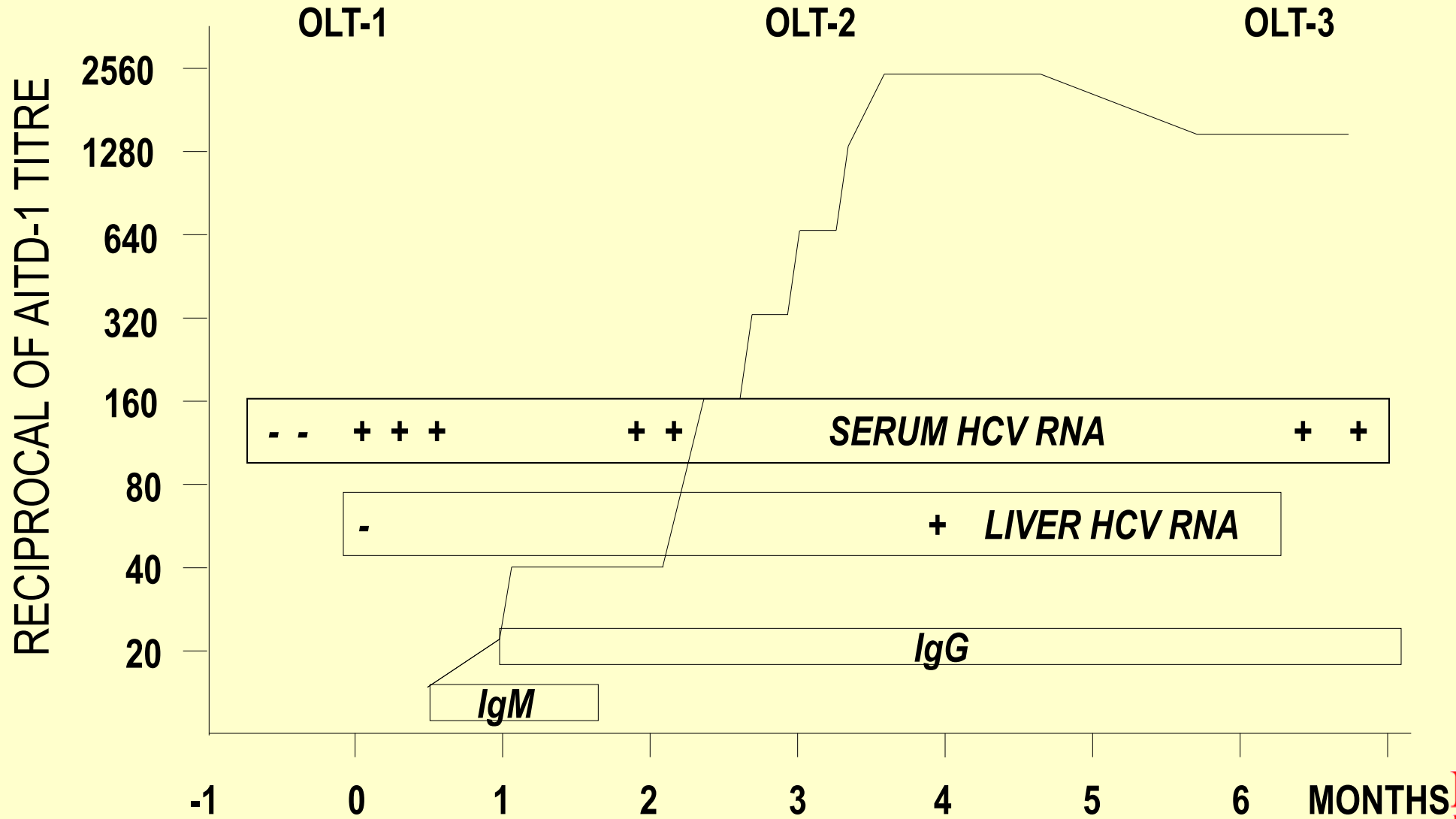
Autoreactivity in HCV infection



Autoreactivity in HCV infection



Autoreactivity in HCV infection



Autoreactivity in HCV infection

CYP2D6

Time

LKM-1

1 ↔ 50

254-71

313-32



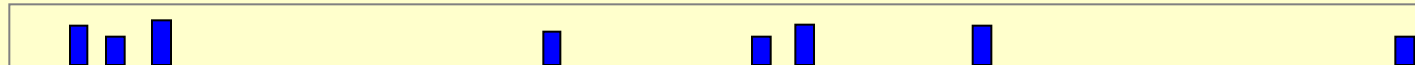
Pre-HCV

neg



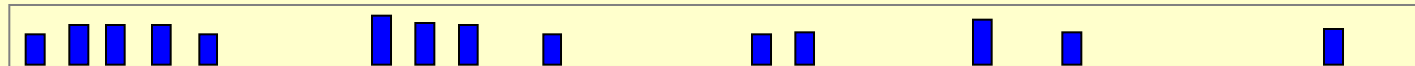
20d

1/20



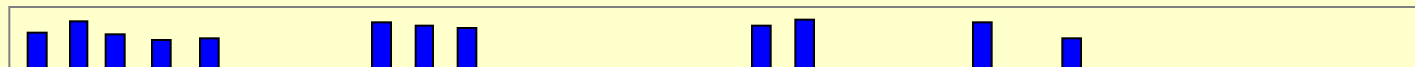
58d

1/160



6mo

1/2560



8yr

1/640

IgM

IgG

Autoreactivity in HCV infection

CYP2D6

Time

LKM-1

254-71

20d

1/20

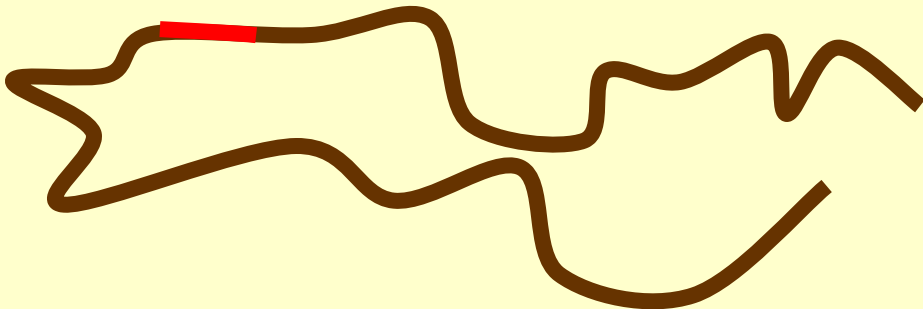
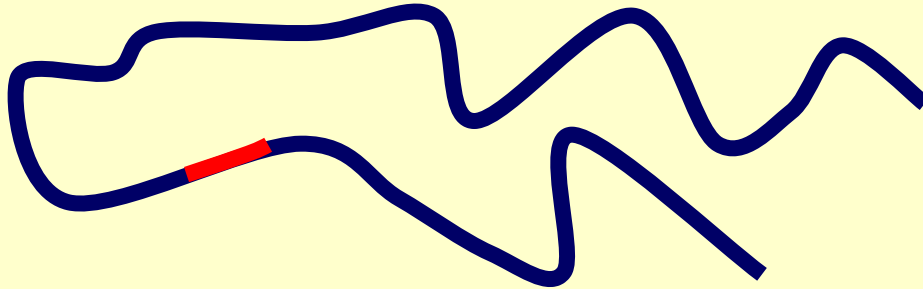
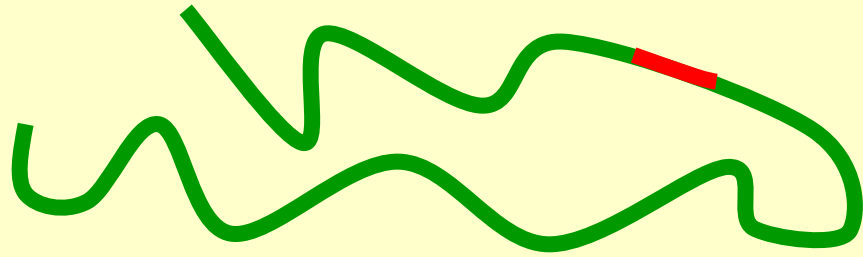
HCV

Autoreactivity in HCV infection

❖ **Focusing of the immune response**

❖ **Due to the original antigenic sin?**

Original and subsequent antigenic sins



Autoreactivity in HCV infection

Similarities between self and viruses

G**HRMAWD**MMMNWSPT

EHRMTWDPAQPPRDL

DRLSPRPPAQPPRR

QLPPPA**A**PAQPPPG**V**

PMIAAAP**PAQPP**SQP

AA**RTAP**A**PAQPP**SPA

E1 HCV

CYP2D6₂₅₇₋₂₇₁

IE 175 HSV-1

EBNA-2 Epstein-Barr

IE63 H. Cytomegalovirus

J1L H. Cytomegalovirus



First International Course of Translational Hepatology, Florence, 2011



Diego Vergani
Allievo Ufficiale Medico
Scuola di Sanità Militare
Costa S.Giorgio - Firenze



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