

*Hepatitis
Auto-immunes*

*4^{ème} réunion des centres de compétence des
Maladies Inflammatoires des Voies Biliaires*



*Aetiopathogenesis
of autoimmune
hepatitis*

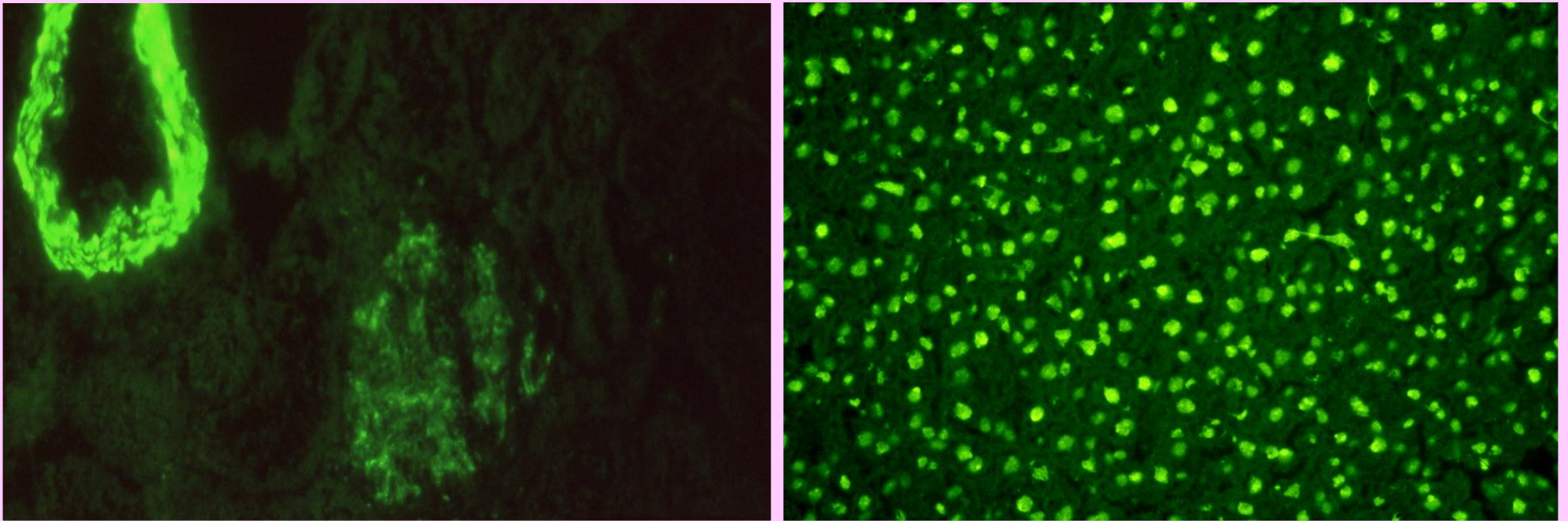
*Diego Vergani
King's College London School of Medicine*

DIAGNOSIS

- ❖ **Progressive inflammatory disorder**
- ❖ **Positive AAB and high IgG**
- ❖ **Exclusion of other pathology
(Wilson, HCV, HBV, NASH)**



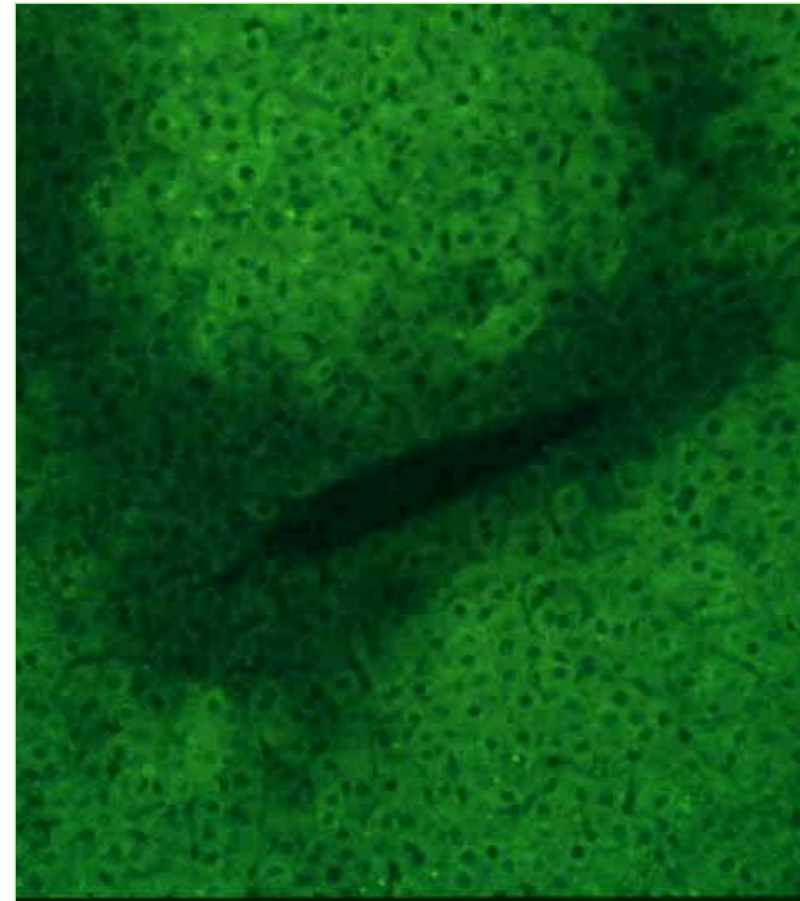
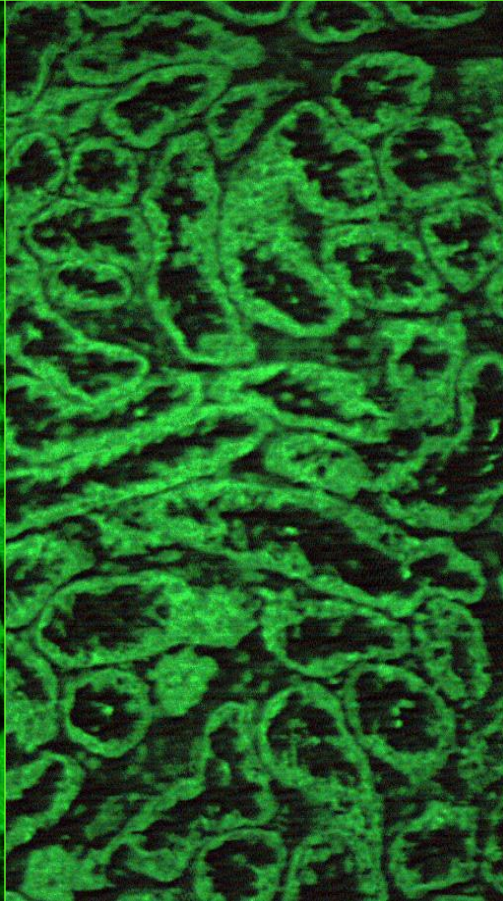
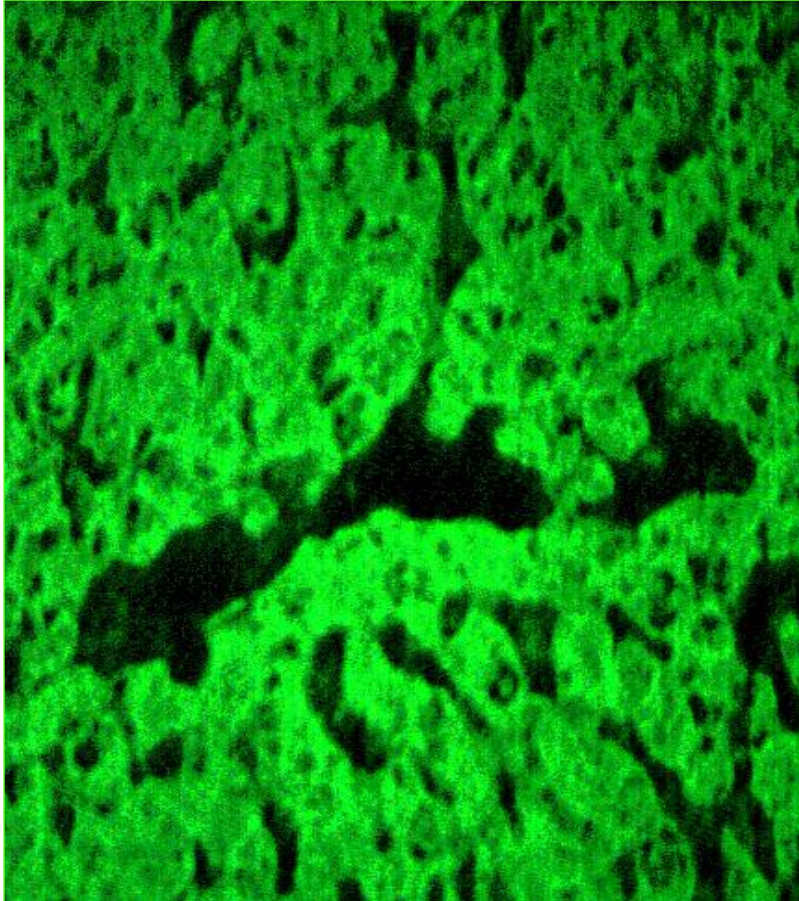
DIAGNOSIS – AIH type 1



- ❖ **Anti-Smooth Muscle (SMA) &**
- ❖ **Anti-Nuclear (ANA) autoantibodies**



DIAGNOSIS – AIH type 2

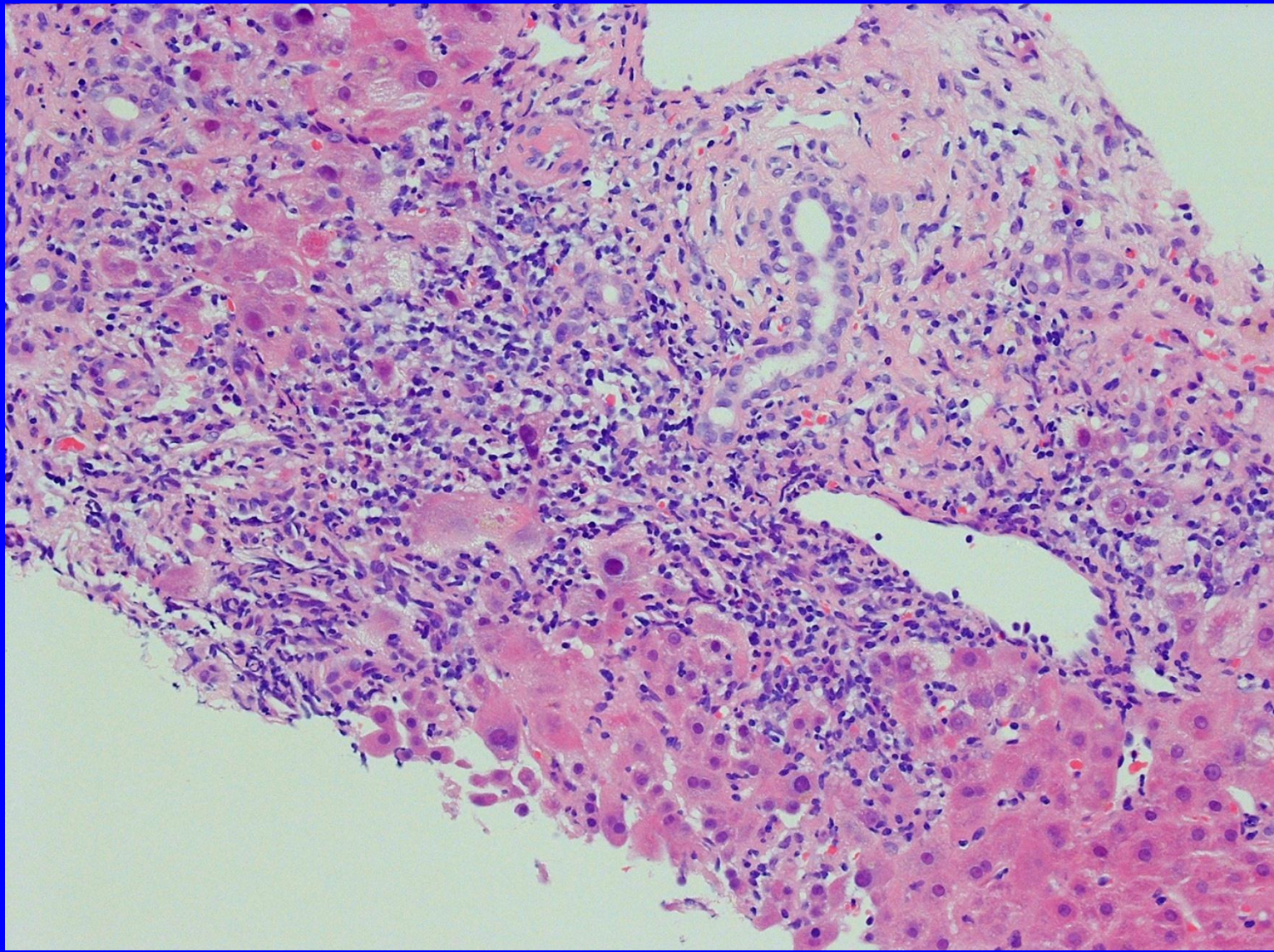


Liver Kidney
Microsomal antibody

Liver Cytosol
Type 1 antibody



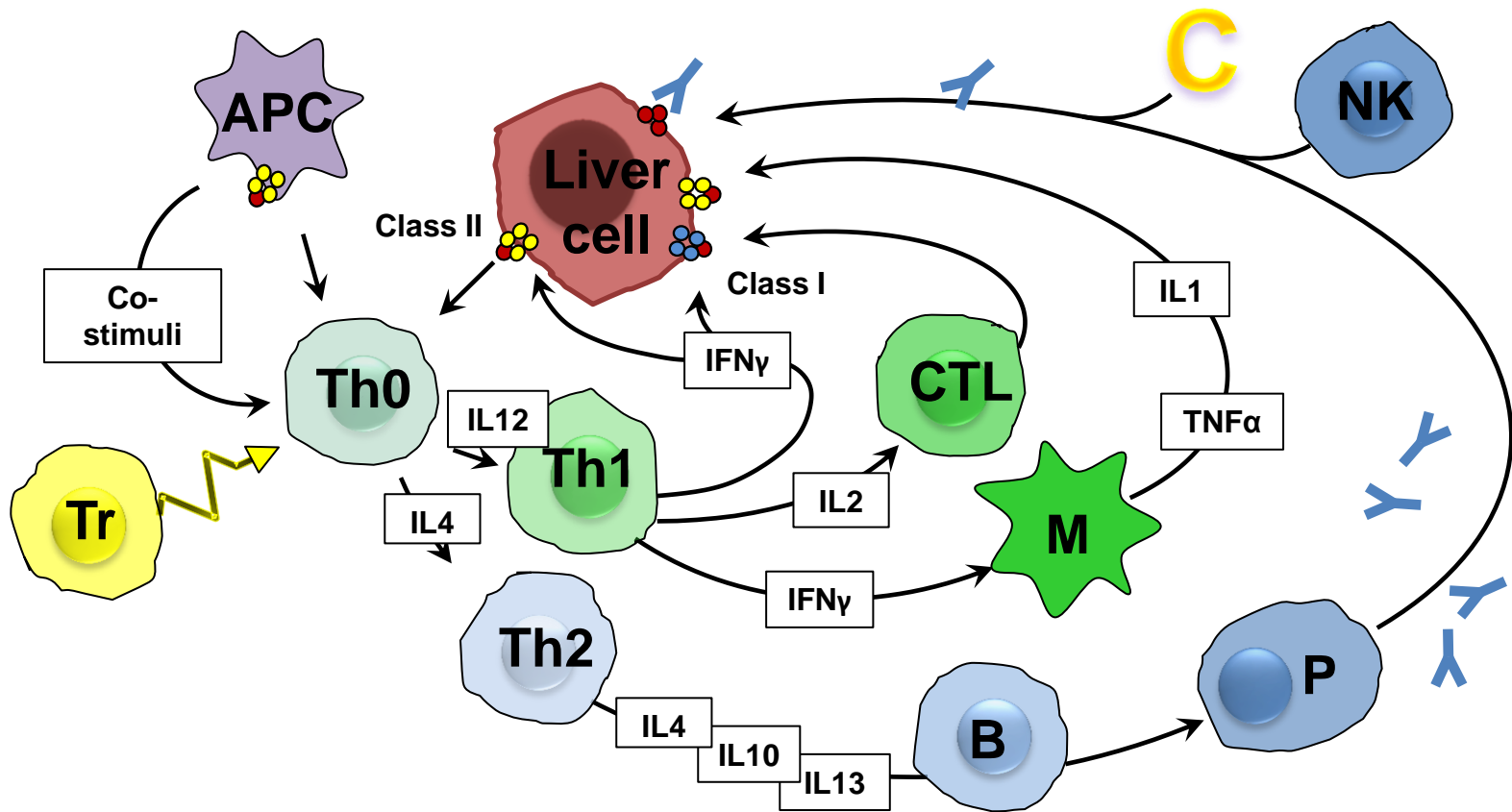
DIAGNOSIS – Histology



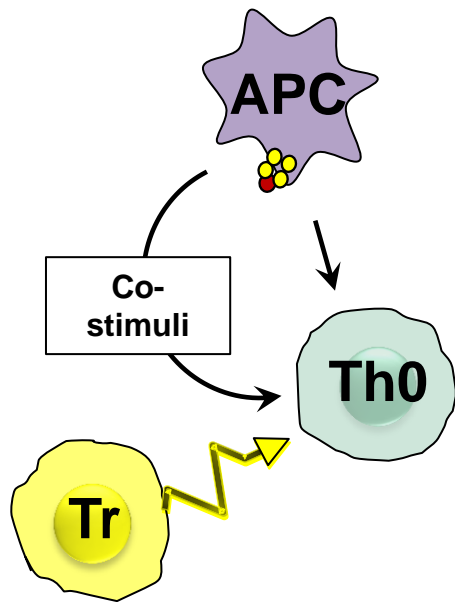
**Interface
hepatitis**

Interface hepatitis

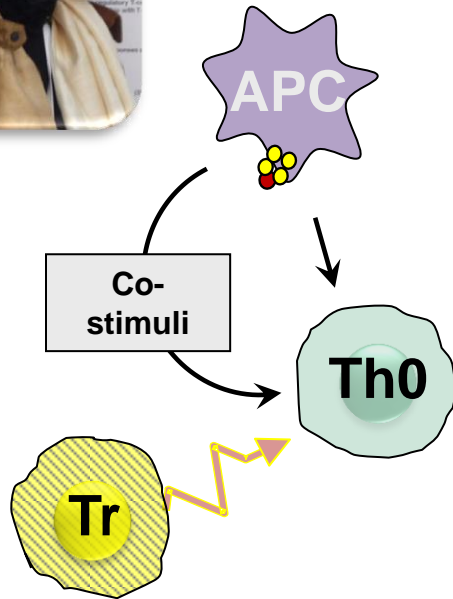
PATHOGENESIS



PATHOGENESIS



PATHOGENESIS: Defective T-regs



Longhi MS et al - Impairment of CD4(+)CD25(+) regulatory T-cells in autoimmune liver disease. *J Hepatol.* 2004;41:31-7

Longhi MS, et al. Effect of CD4+CD25+ regulatory T-cells on CD8 T-cell function in autoimmune liver disease. *J Autoimmunity* 2005;25:63-71

Longhi MS, et al. Functional study of CD4+CD25+ regulatory T-cells in health and autoimmune hepatitis. *J Immunol.* 006;176:4484-91

Longhi MS, et al. Expansion and de novo generation of potentially therapeutic regulatory T cells in patients with autoimmune hepatitis. *Hepatology.* 2008;47:581-91

Longhi MS, et al. Vigorous activation of monocytes in juvenile autoimmune liver disease escapes the control of regulatory T-cells. *Hepatology.* 2009; 50: 30-42

Longhi MS, et al. Auto-antigen-specific regulatory T-cells, a potential tool for immune-tolerance reconstitution in type-2 autoimmune hepatitis. *Hepatology.* 2011; 53: 536-547

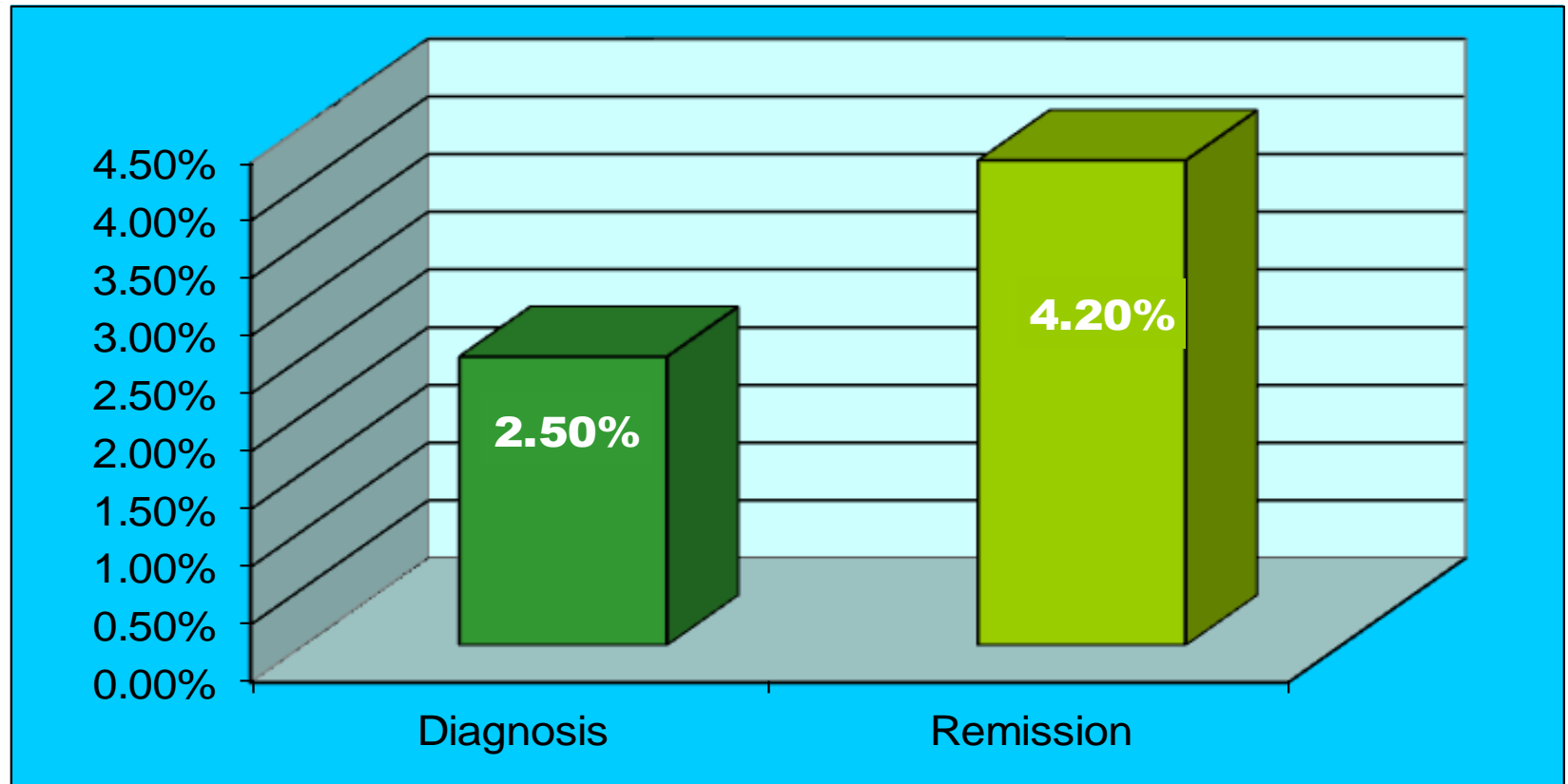
Longhi MS, et al. Inhibition of interleukin-17 promotes differentiation of CD25- cells into stable T regulatory cells in patients with autoimmune hepatitis. *Gastroenterology* 2012;14:1526-1535

Liberal R, et al. The impaired immune regulation of autoimmune hepatitis is linked to a defective Galectin-9/Tim-3 pathway. *Hepatology* 2012;56:677-686

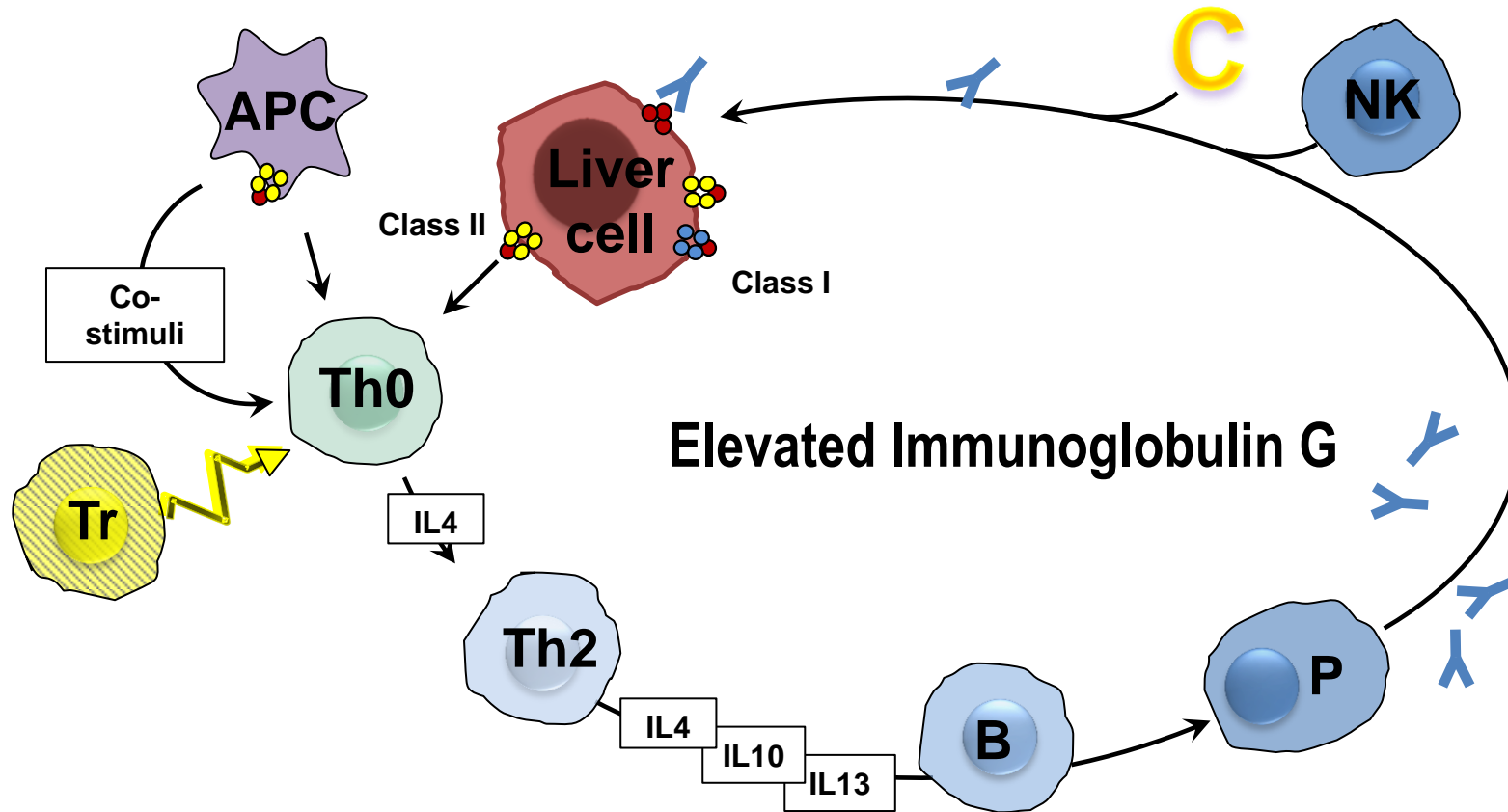


PATHOGENESIS: Defective T-regs

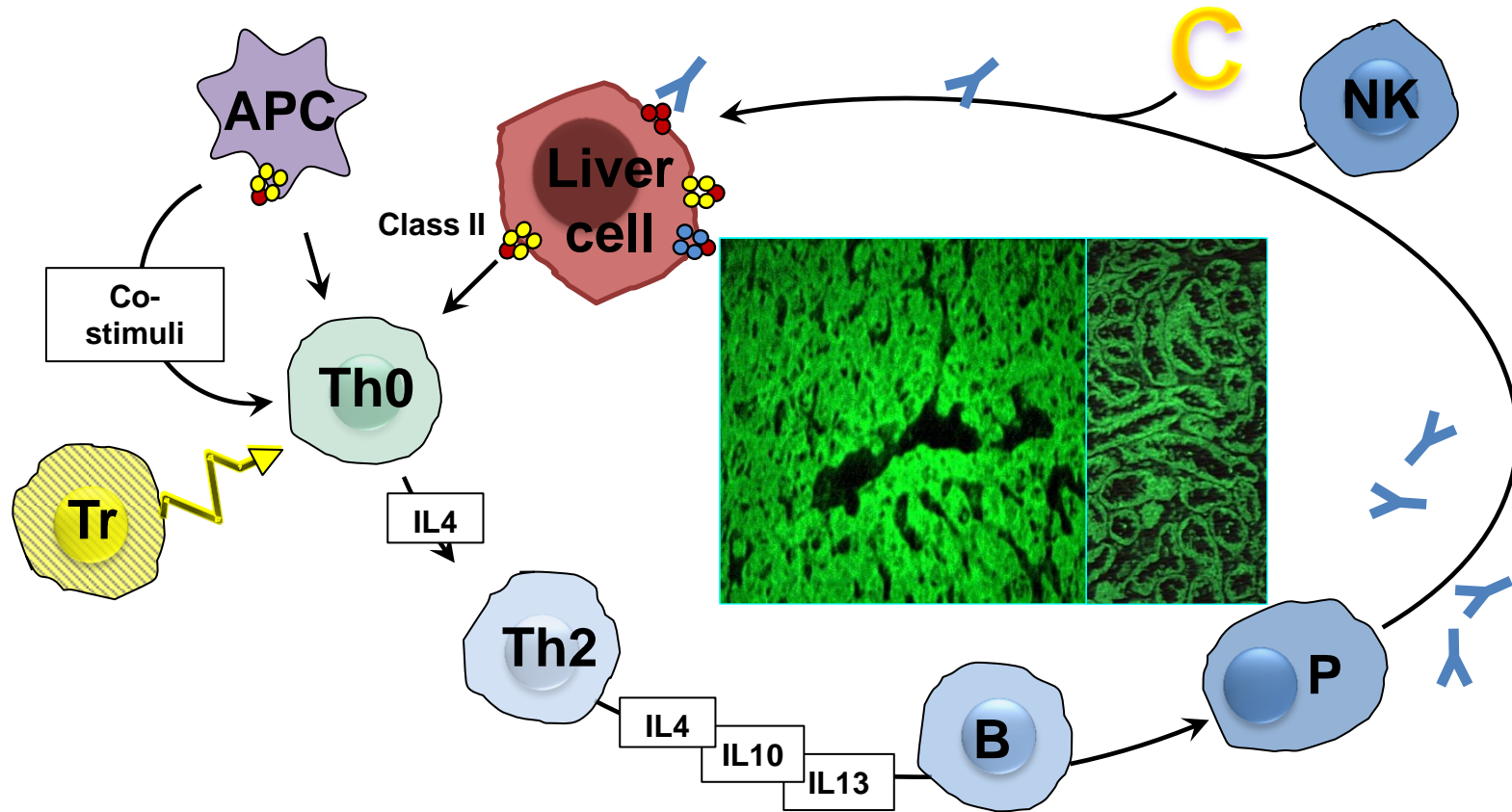
CD4 CD25



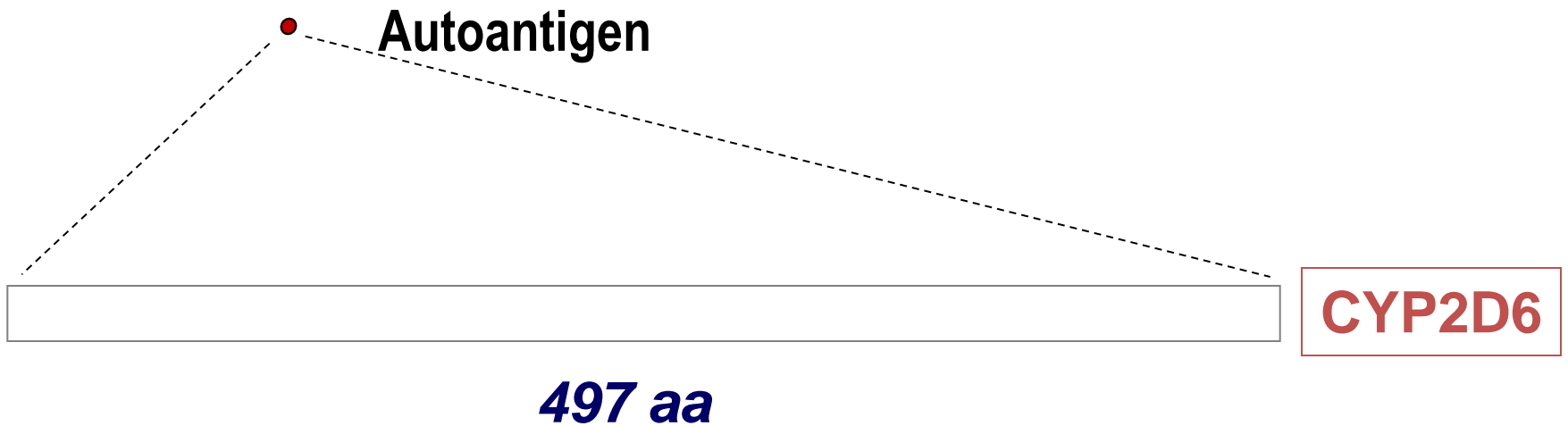
PATHOGENESIS: T_H2



PATHOGENESIS: T_H2

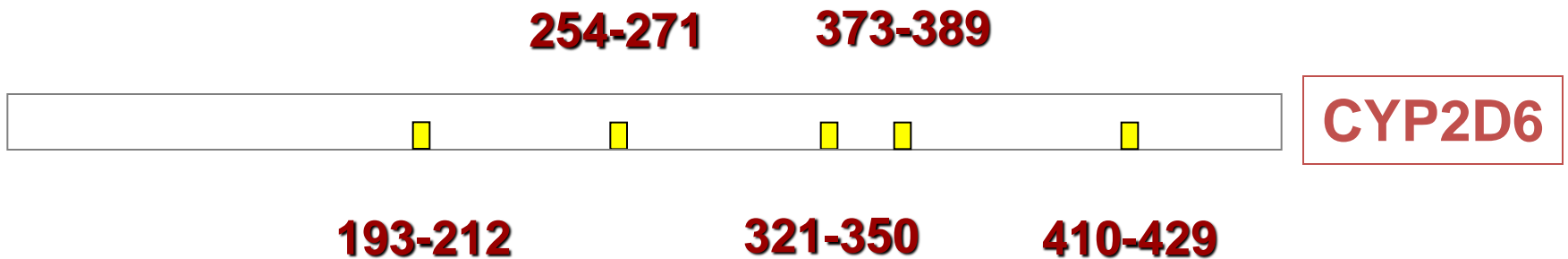


PATHOGENESIS: T_H2



PATHOGENESIS: T_H2

Immunodominant epitopes



Kerkar N, et al. Cytochrome P450D6(193-212): a new Immunodominant... *J Immunol* 2003;170:1841-9

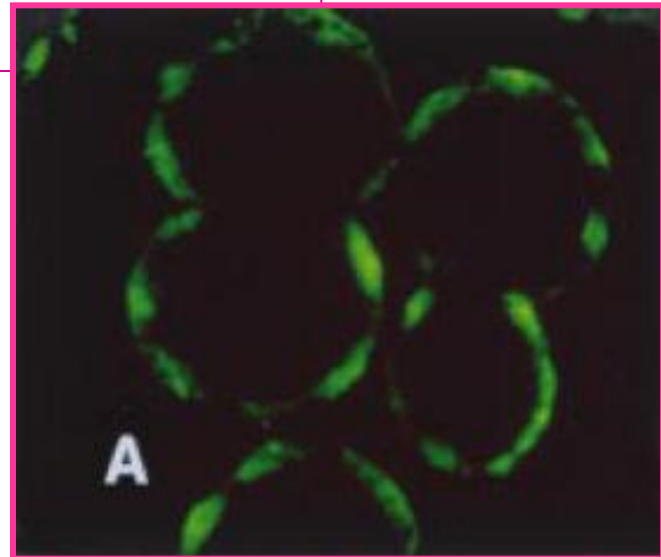


PATHOGENESIS: T_H2

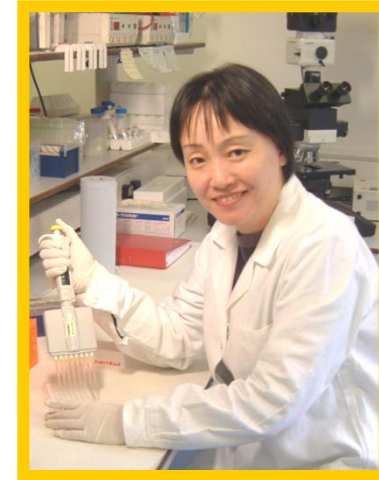
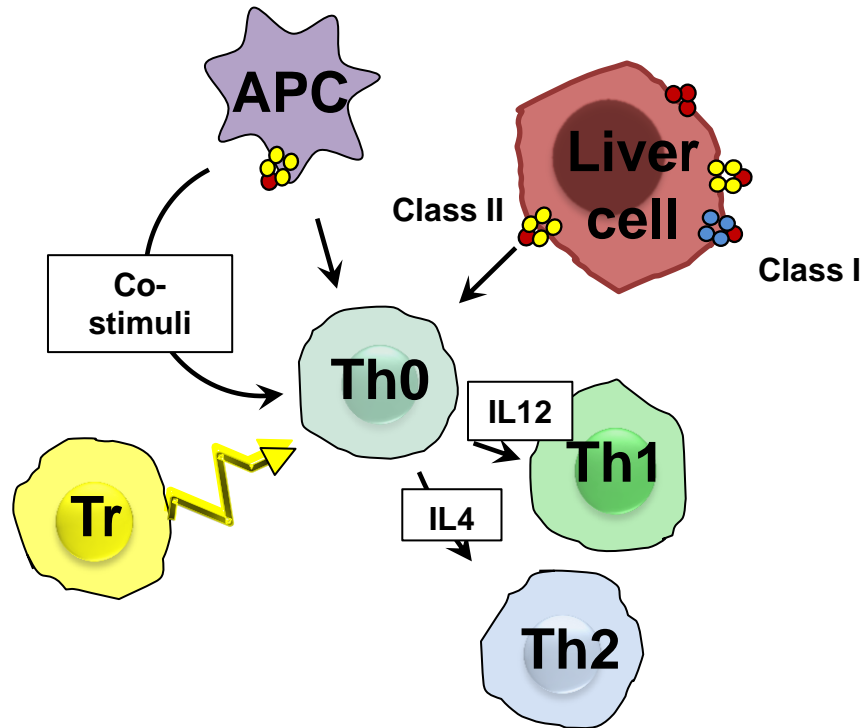
Gut 2000;46;553-561

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

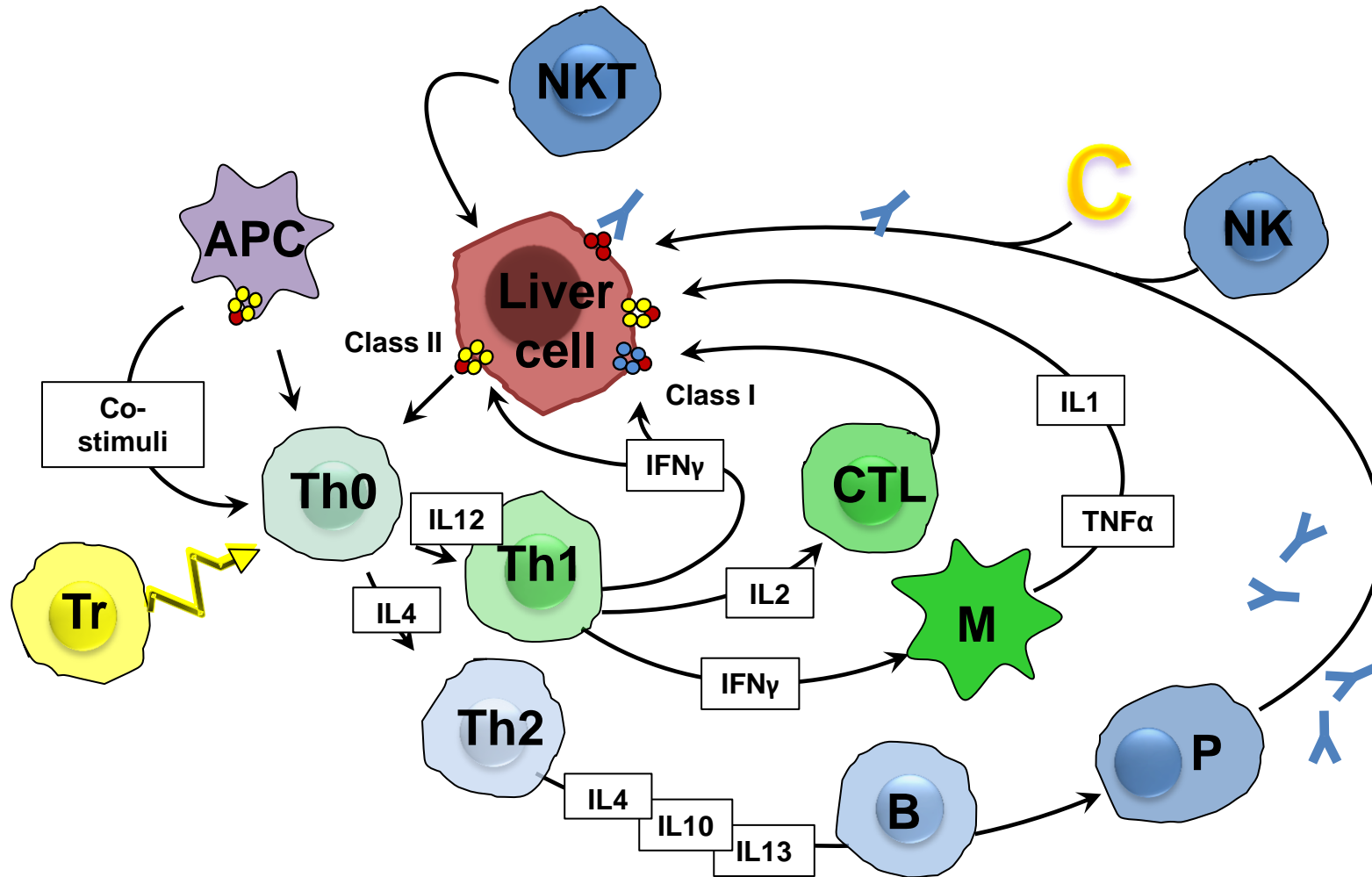
**L Muratori, M Parola, A Ripalti, G Robino, P Muratori, G Bellomo,
R Carini, M Lenzi, M P Landini, E Albano and F B Bianchi**



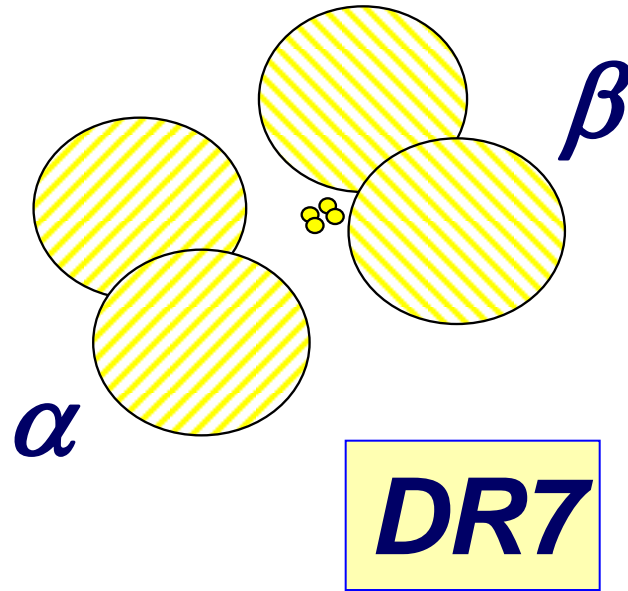
PATHOGENESIS: T_H1



PATHOGENESIS: T_H1



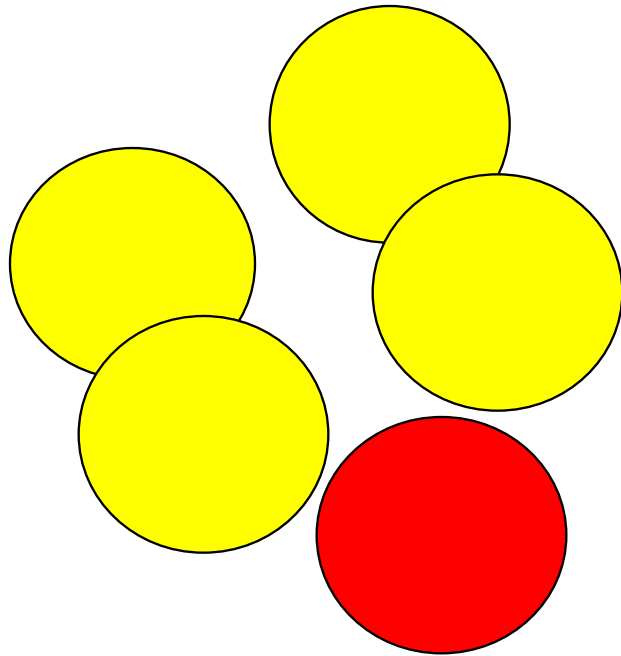
PATHOGENESIS: T_H1



**Predisposing HLA-Class II
allele in AIH-2**



PATHOGENESIS: T_H1



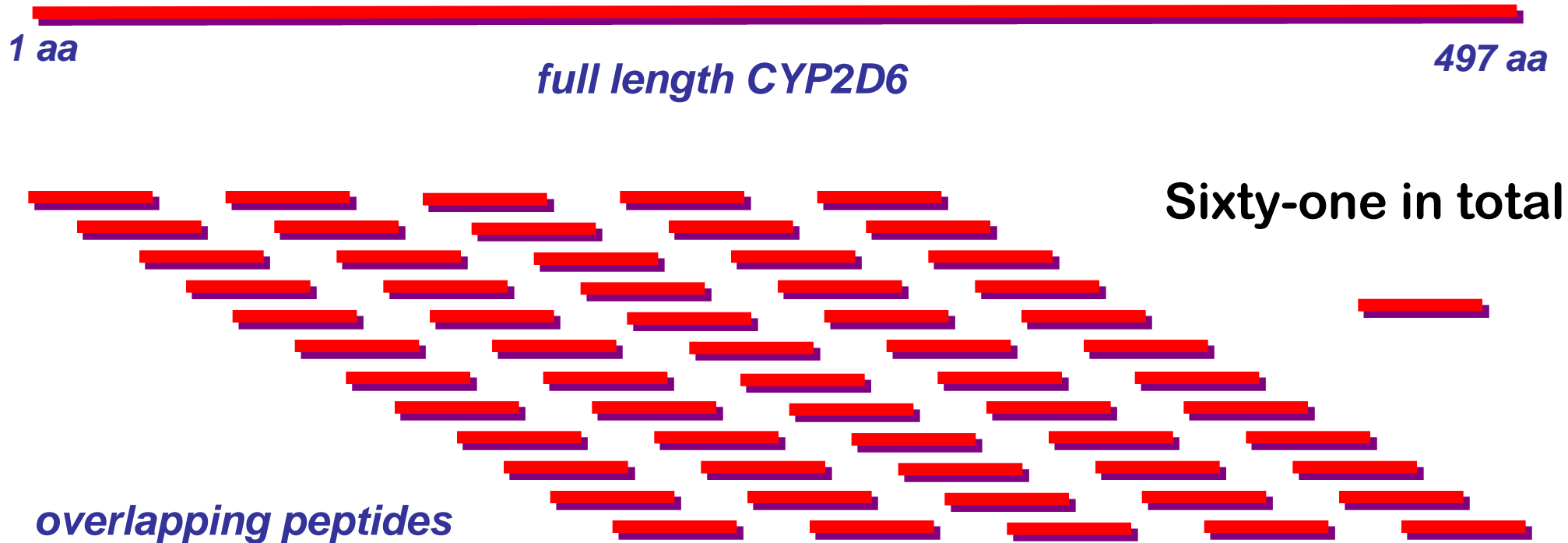
***Prediction of DR7
binding peptides***

***7 predicted high binders
induced proliferation***



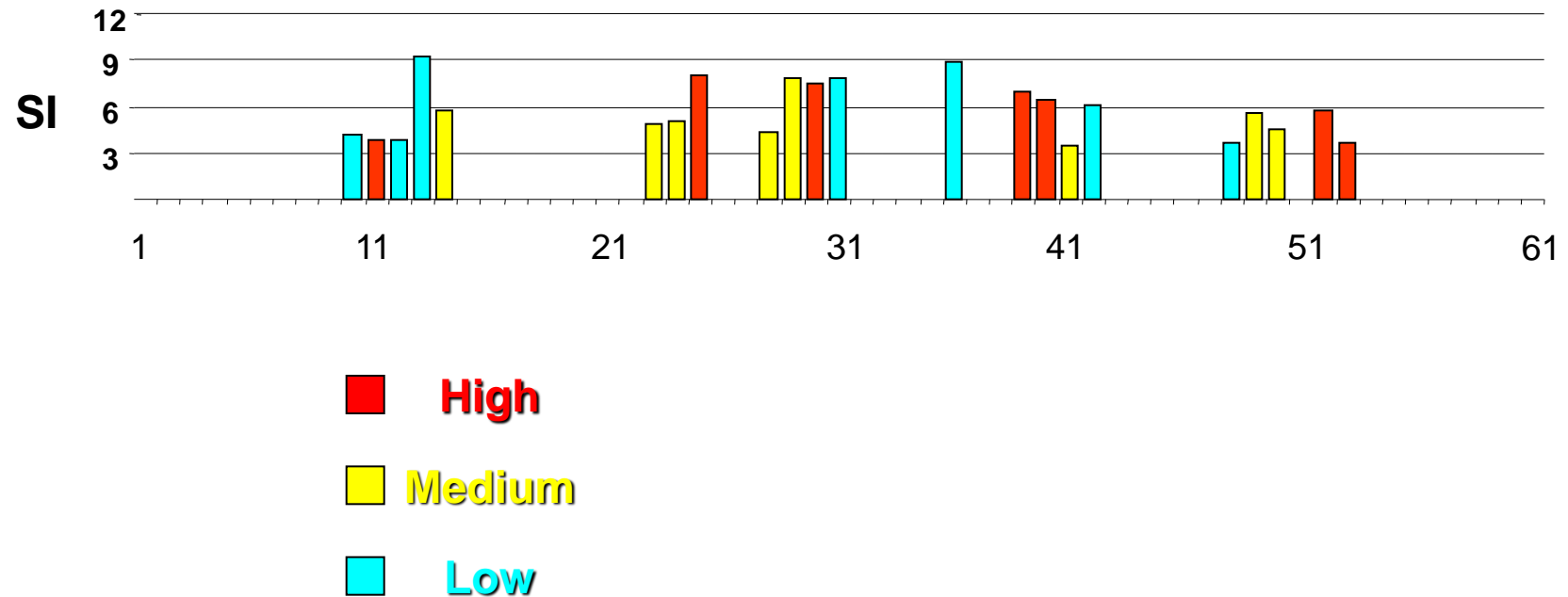
PATHOGENESIS: T_H1

20-mer peptides, overlapping by 12 aa and spanning the entire molecule of CYP2D6 were constructed



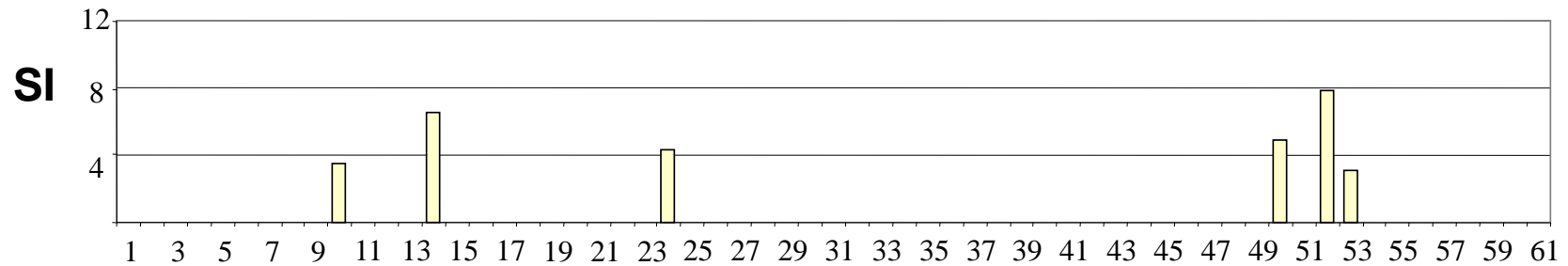
PATHOGENESIS: T_H1

DR7 positive patients

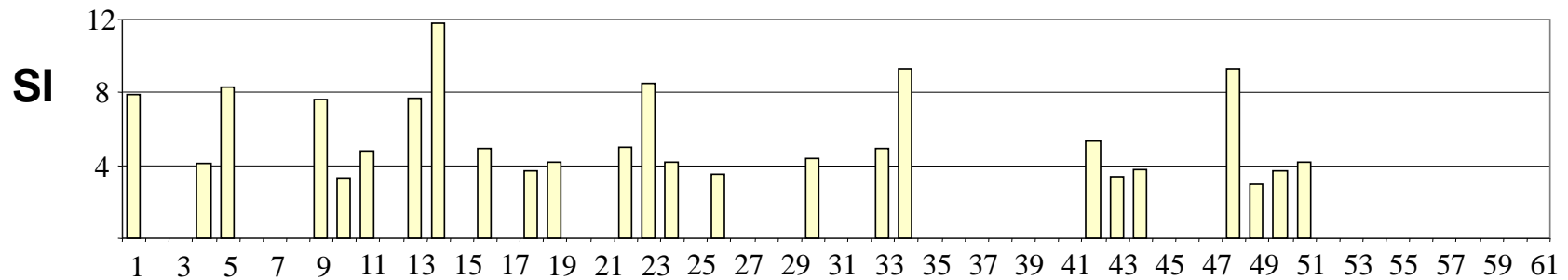


PATHOGENESIS: T_H1

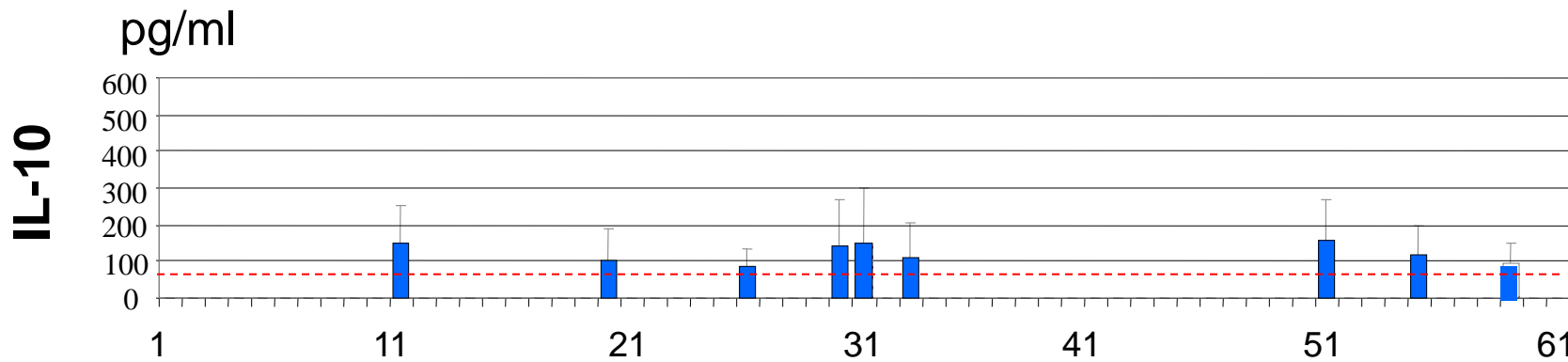
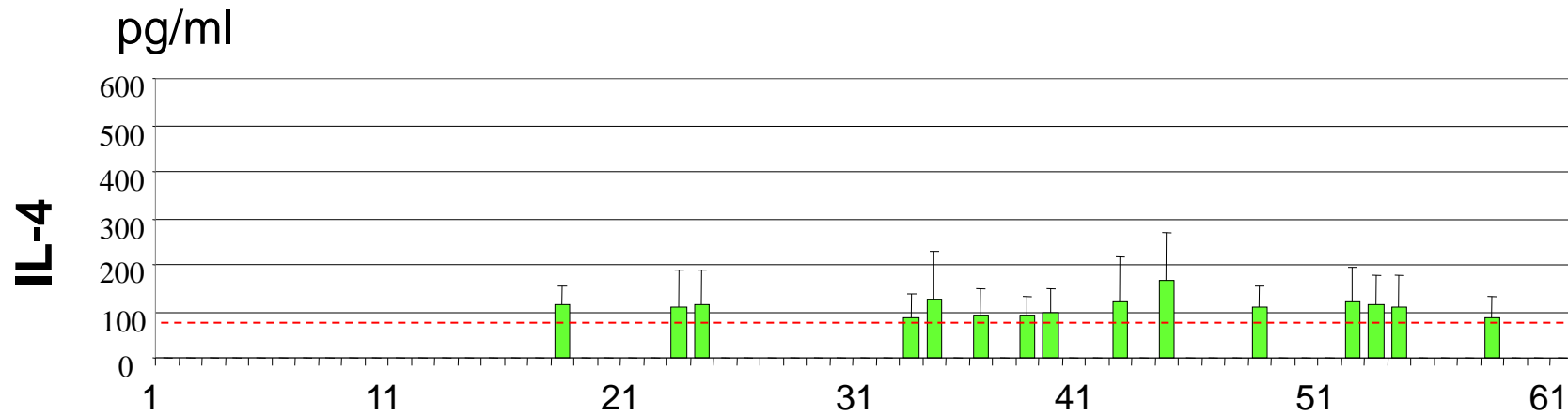
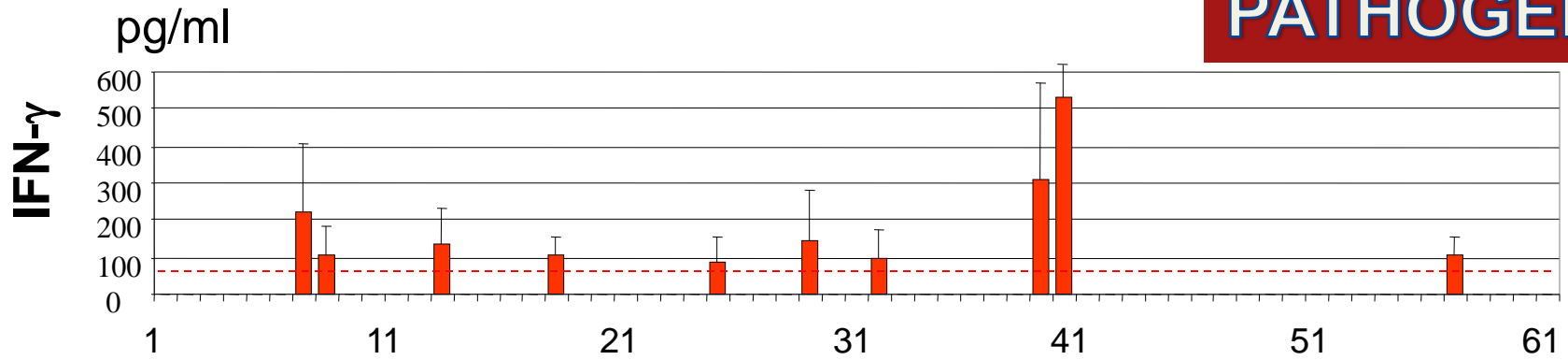
2 months of immunosuppressive treatment



at relapse 6 years after diagnosis



PATHOGENESIS



PATHOGENESIS

Controls

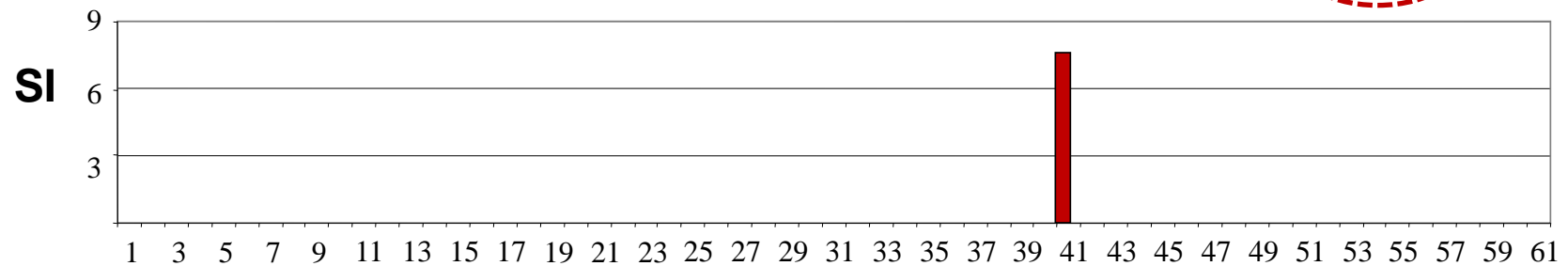
Other autoimmune liver disease 0/46

Non autoimmune liver disease 0/17

Viral liver disease

HBV 0/3

HCV 4/7



Similarity between HCV and CYP2D6

TLAWGLLLMILHPDVQRRVQ

CYP2D6₃₁₃₋₃₃₂

AQGYKVLVLP^{SV}

HCV₁

WPLLLLLL

HCV₇

GLMAL^{TLSP}

HCV₈

LLMCAVHP

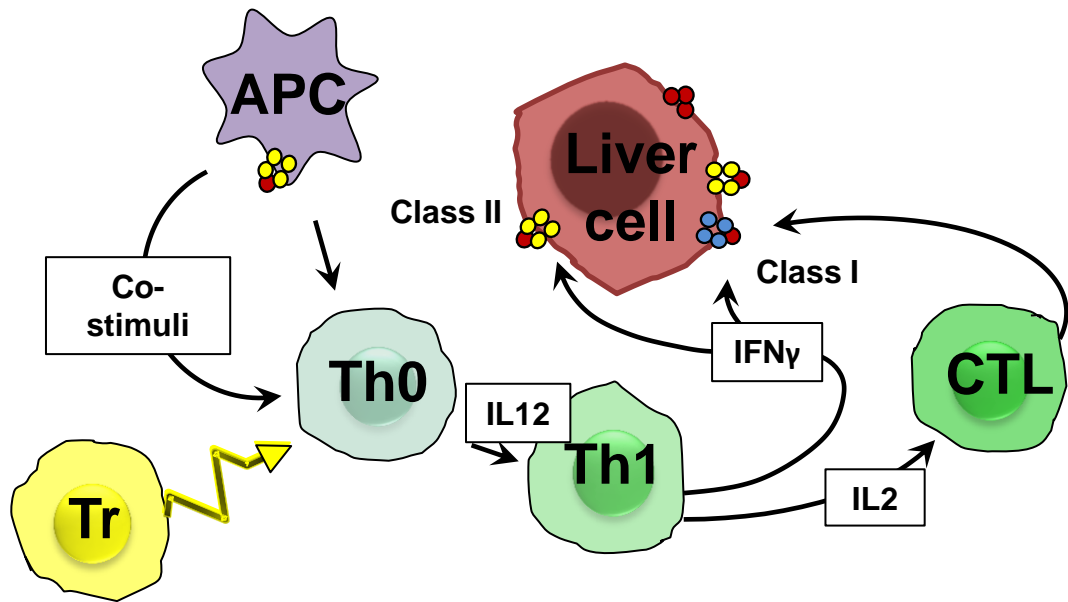
HCV₈

LLAPGKKQNVQ

HCV₄₀₂₋₄₁₂



PATHOGENESIS: CTL

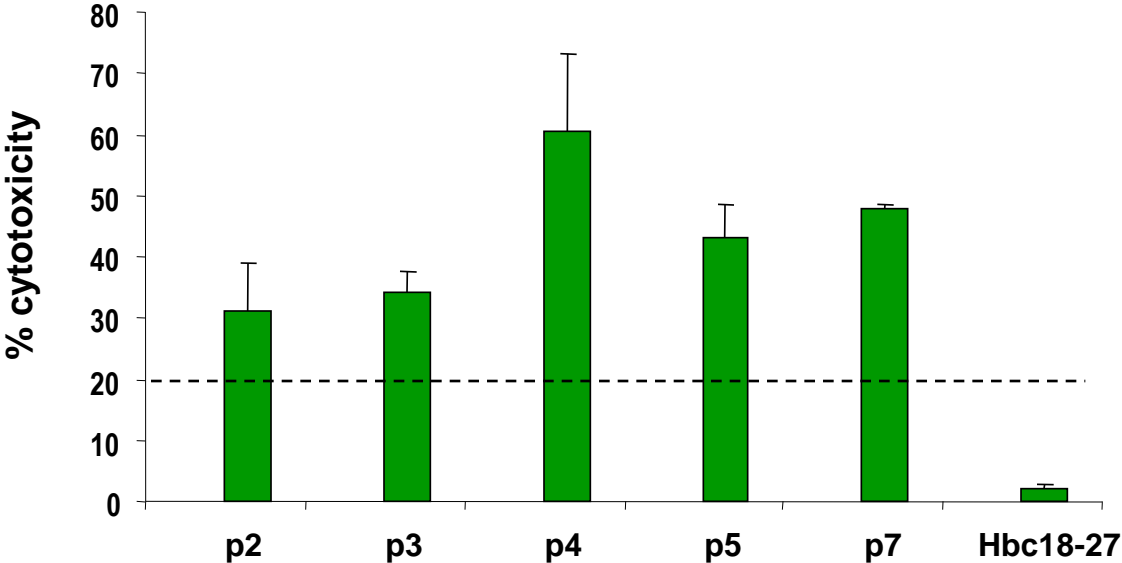


Peptide number	Amino acid position		Binding score
1	176-185	G L L D K A V S N V	28
2	204-213	R L L D L A Q E G L	24
3	2-11	G L E A L V P L A V	22
4	245-254	K A F L T Q L D E L	22
5	393-402	T T L I T N L S S V	22
6	177-186	L L D K A V S N V I	21
7	306-314	G M V T T S T T L	21

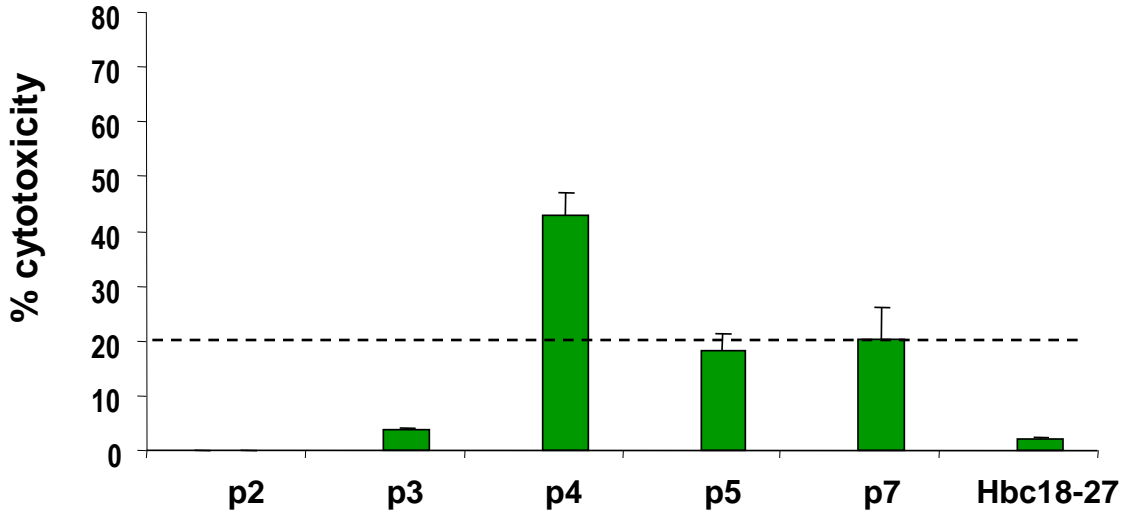


Cytotoxicity of CYP2D6-specific CD8 T cells

Diagnosis

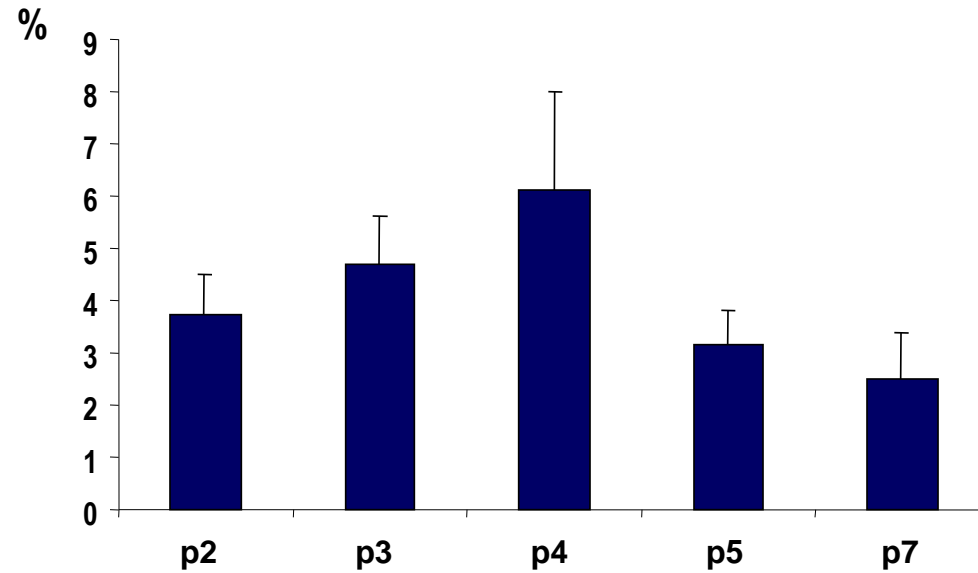


Remission

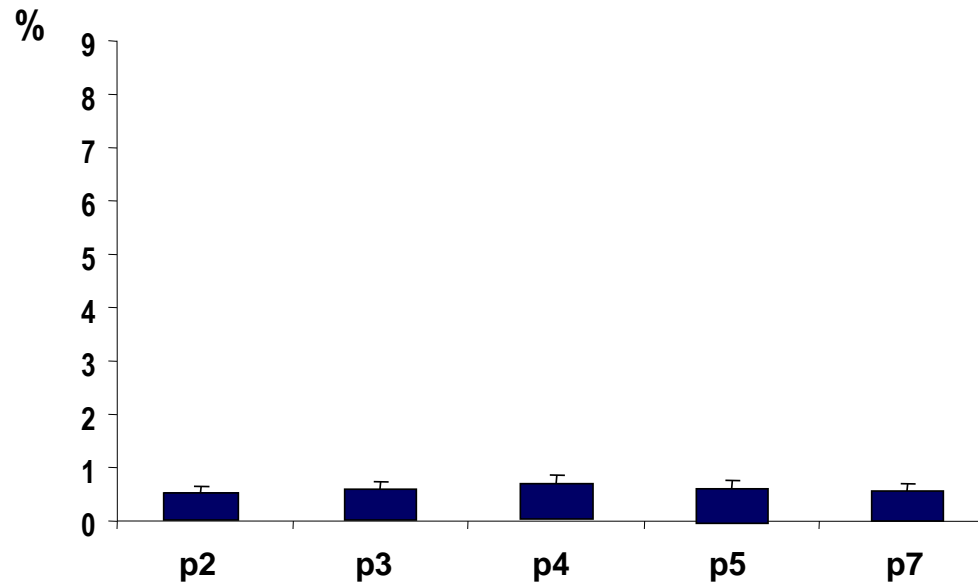


IFN γ producing CYP2D6-specific CD8 T cells

Diagnosis



Remission



PATHOGENESIS

Peptide number	HLA-A*0201 decamers	CYP2D6 sequence	Binding score
	Amino acid position	1 2 3 4 5 6 7 8 9 10	
1	176-185	G L L D K A V S N V	28
2	204-213	R L L D L A Q E G L	24
3	2-11	G L E A L V P L A V	22
4	245-254	K A F L T Q L D E L	22
5	393-402	T T L I T N L S S V	22
6	177-186	L L D K A V S N V I	21
	HLA-A*0201 nonamers		
7	306-314	G M V T T S T T L	21

Cytotoxicity



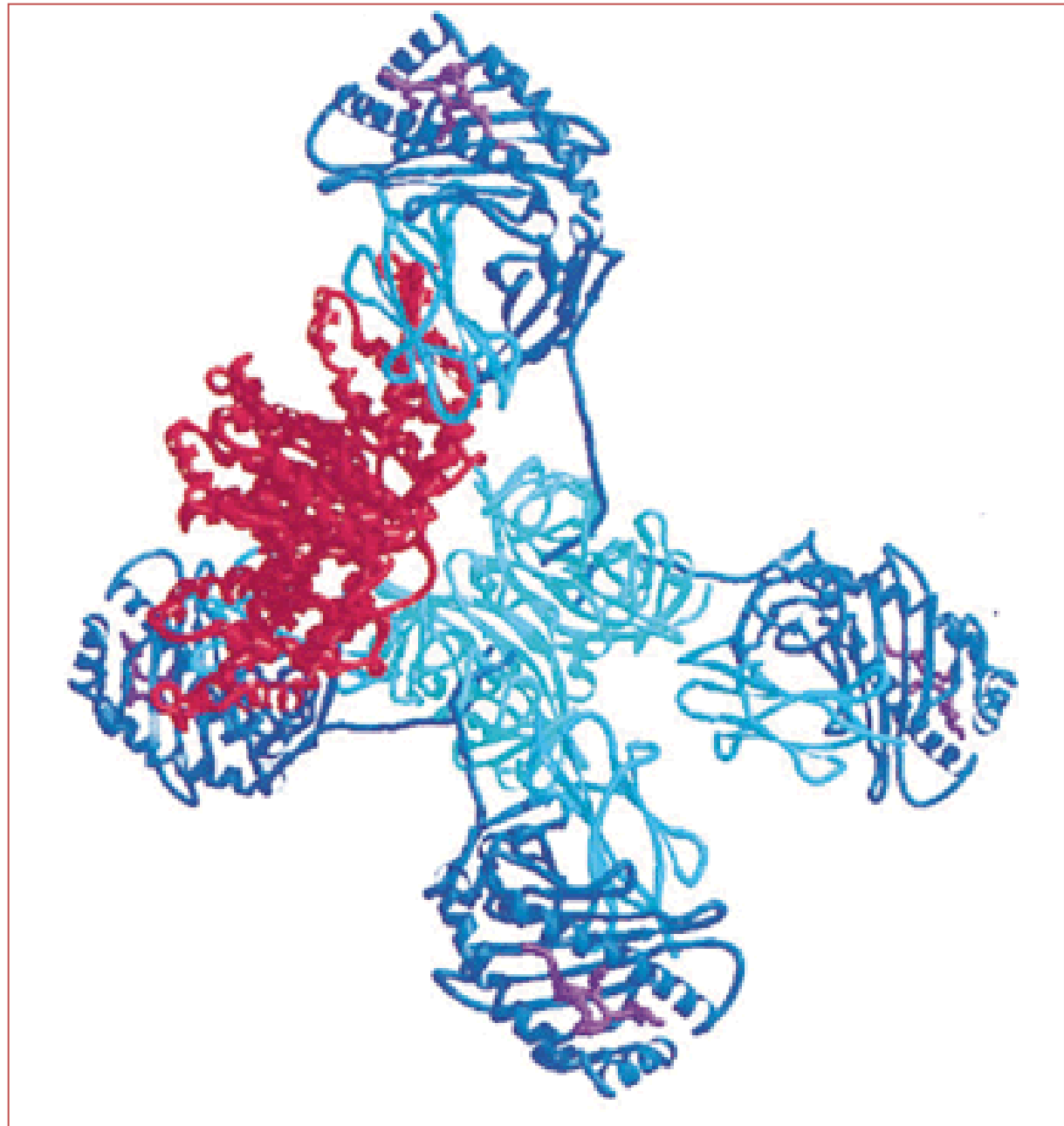
PATHOGENESIS

Peptide number	HLA-A*0201 decamers	CYP2D6 sequence	Binding score
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1	176-185	G L L D K A V S N V	28
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	HLA-A*0201 nonamers		
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Tetramers

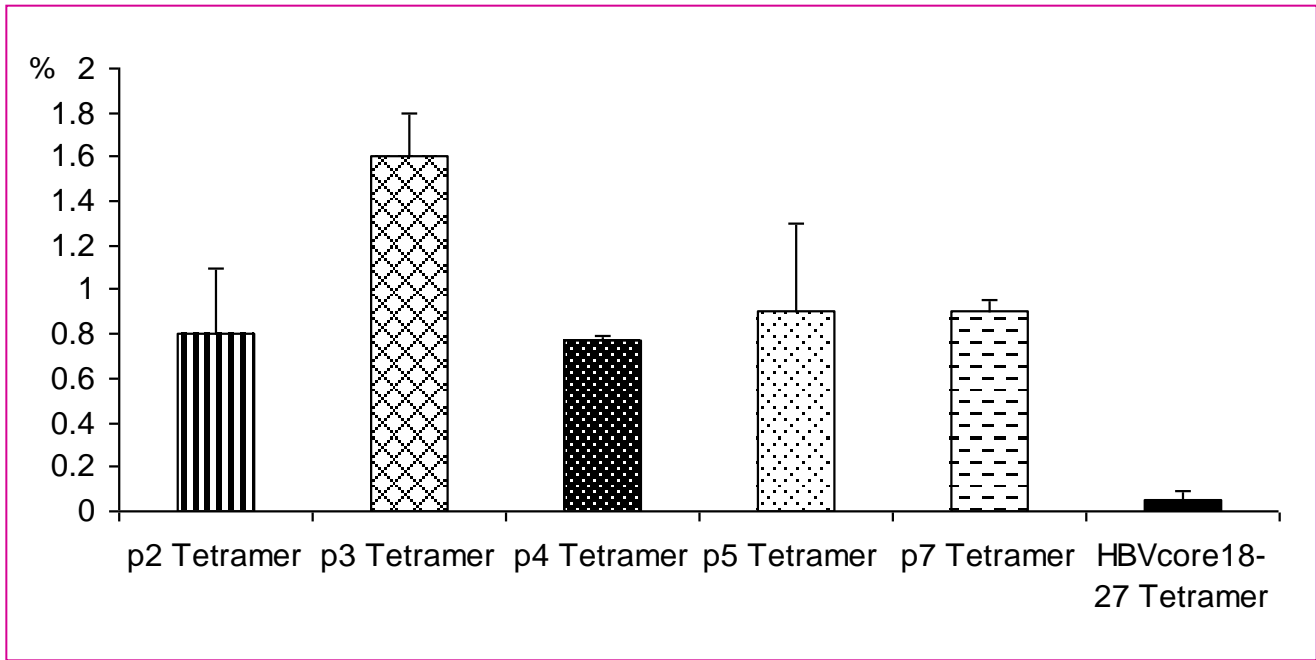


**Tetramer
labelled
with
phycoerythrin**

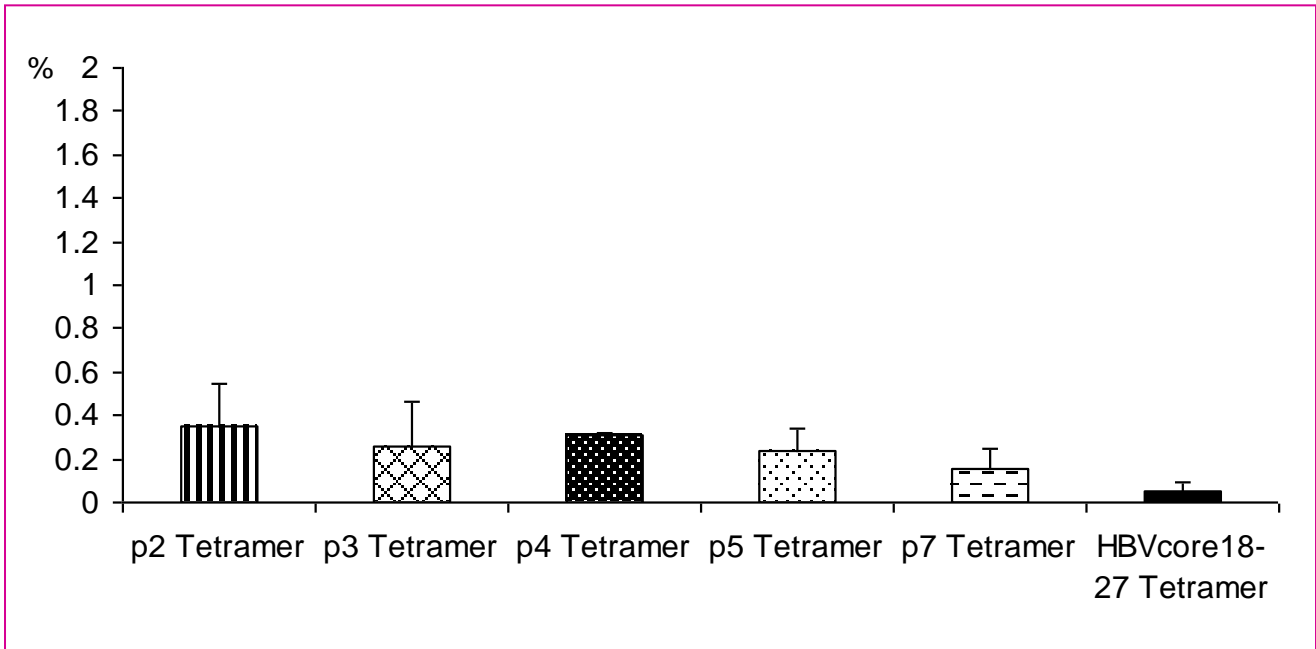


Diagnosis

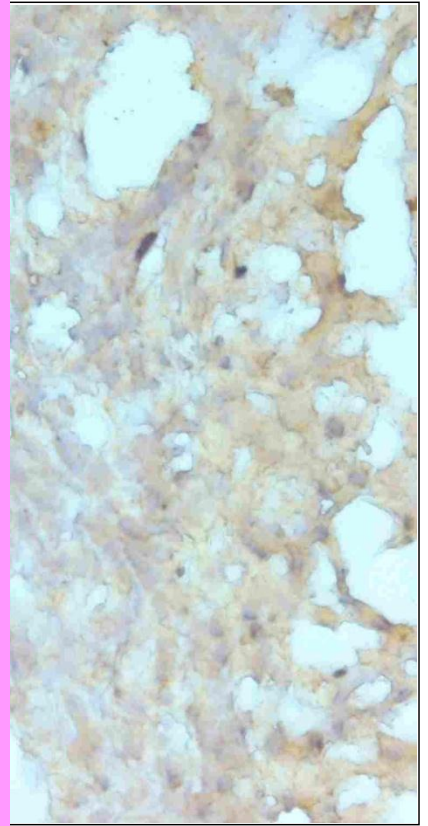
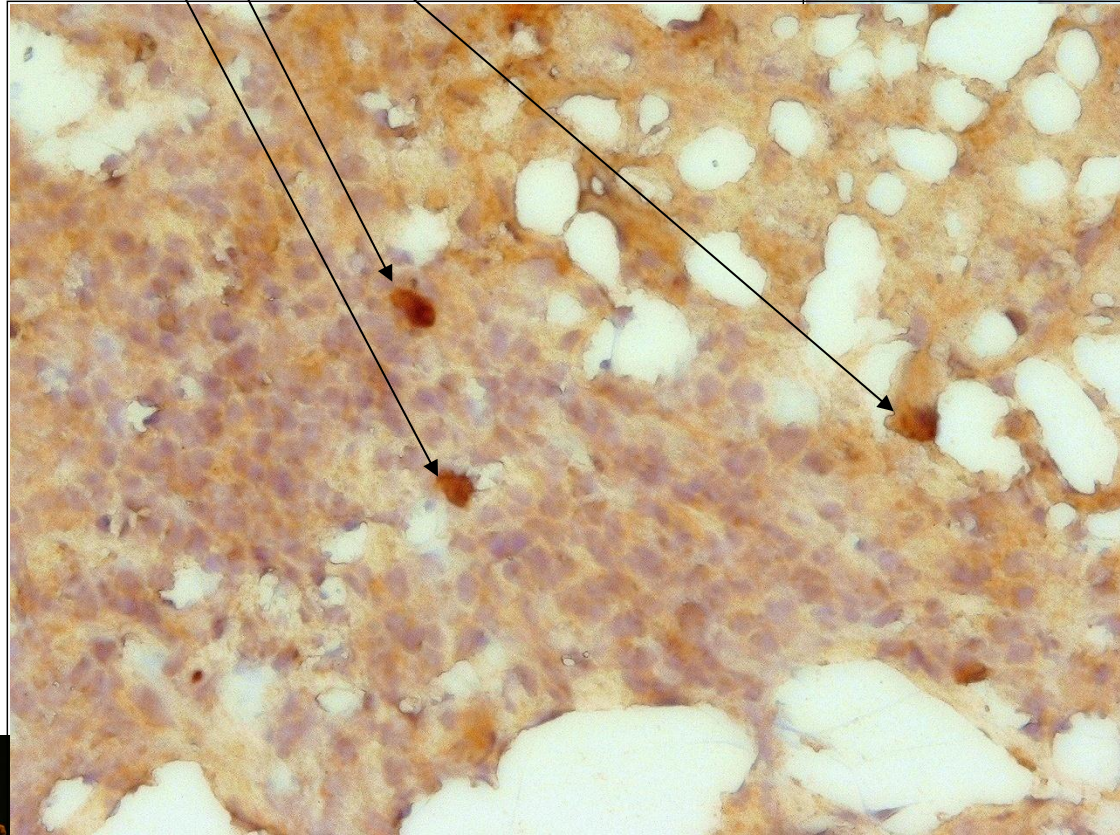
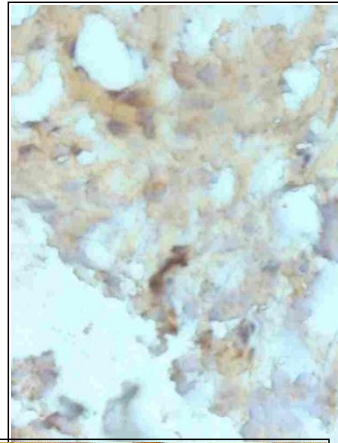
% Tetramer positive CD8 T cells

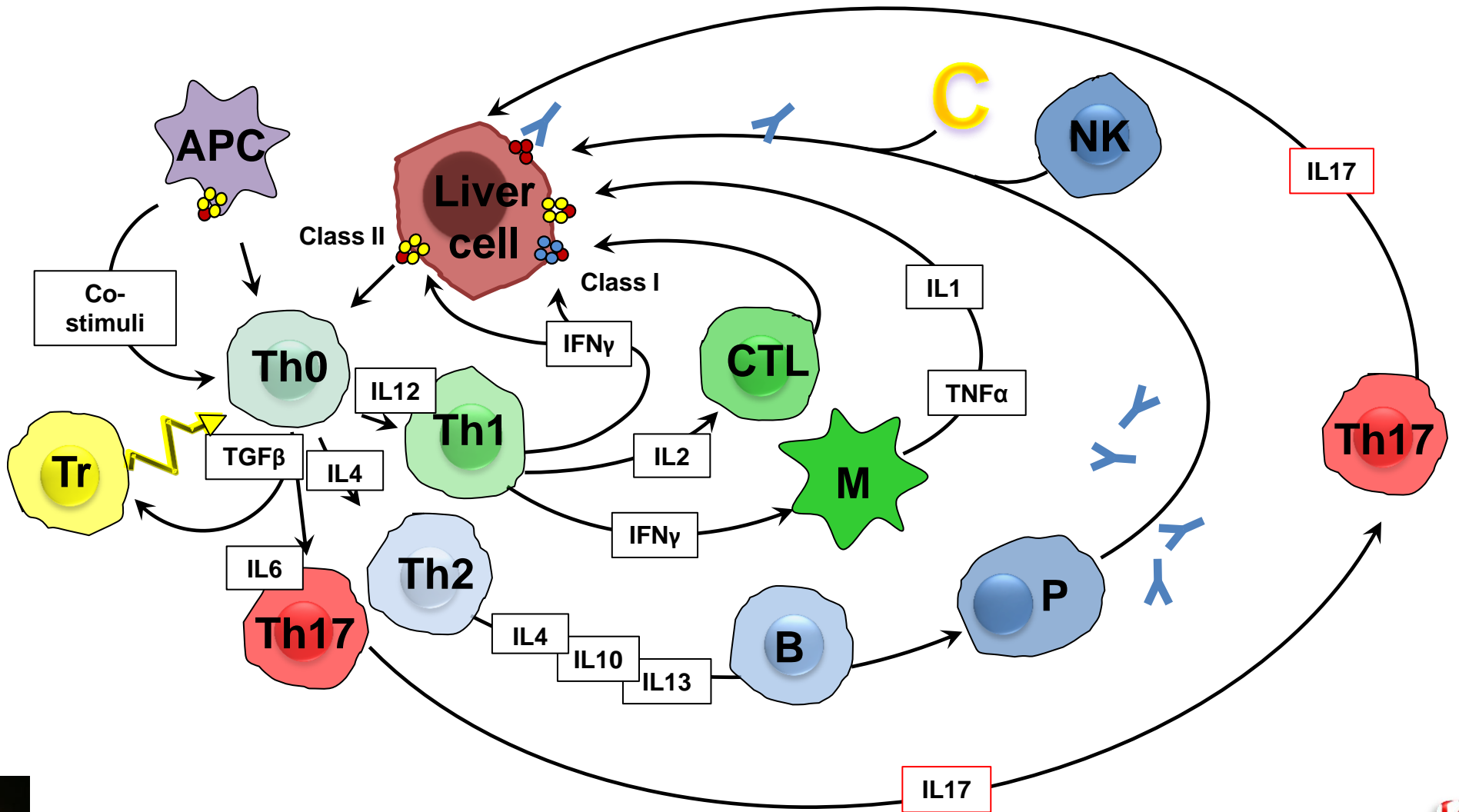


Remission

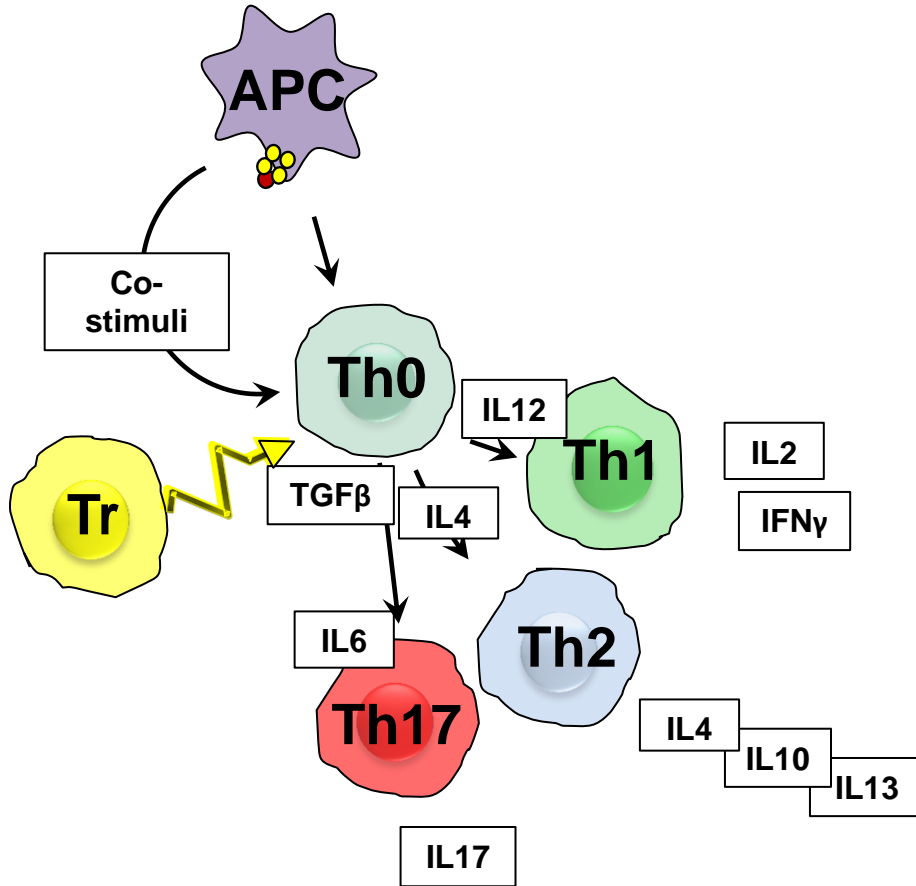


**CYP2D6²⁴⁵⁻²⁵⁴
tetramer positive
CD8 T cells**





Liberal R, et al. The impaired immune regulation of autoimmune hepatitis is linked to a defective Galectin-9/Tim-3 pathway. *Hepatology* 2012;56:677-686



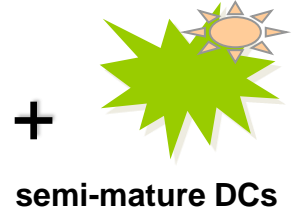
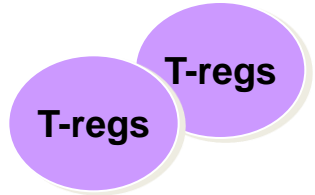
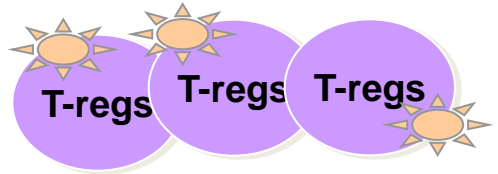
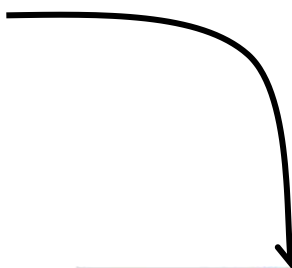
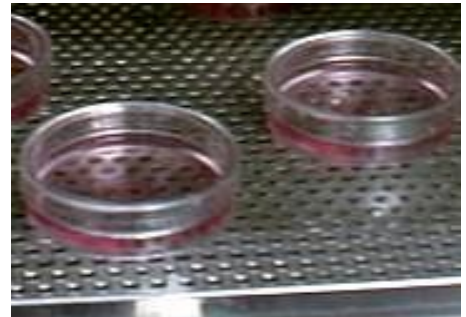
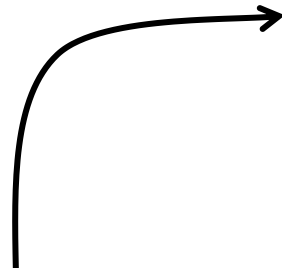
- ❖ **CD4 and CD8 autoepitopes defined**
- ❖ **Correlation with disease activity**
- ❖ **Impairment of regulatory T cells**

What next?

- ❖ **Expand regulatory T cells**
- ❖ **Attempt new modes of treatment**



First-in-human clinical trial



Thank you



*Children's Liver Disease
Foundation*



ROGER DOBSON FUND
YOUNG LIVER RESEARCH

