Aetiopathogenesis of autoimmune hepatitis
Positive AAB and high IgG
Progressive inflammatory disorder
Exclusion of other pathology
(Wilson, HCV, HBV, NASH)
DIAGNOSIS – AIH type 1

- Anti-Smooth Muscle (SMA) &
- Anti-Nuclear (ANA) autoantibodies
Liver Kidney Microsomal antibody
Liver Cytosol Type 1 antibody
DIAGNOSIS – Histology

Interface hepatitis
Interface hepatitis

PATHOGENESIS

Liver cell

APC

Th0

Th1

Th2

CTL

Tr

Co-stimuli

IL12

IFNy

IL4

IL2

IFNy

IL12

TNFα

IL1

IL10

IL13

IL4

B

P
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


PATHOGENESIS: Defective T-regs

Diagnosis: 2.50%
Remission: 4.20%

CD4 CD25
PATHOGENESIS: TH2

- Elevated Immunoglobulin G
- Co-stimuli
- Class I
- Class II
- Liver cell
- APC
- Th0
- Th2
- B
- P
- IL4
- IL10
- IL13
- NK
- Tr
PATHOGENESIS: \( Th_2 \)

- Class I Co-stimuli
- Class II Liver cell
- APC
- Th0
- Tr
- Th2
- NK
- B
- P

- IL4
- IL10
- IL13
Immunodominant epitopes

254-271  373-389

193-212  321-350  410-429

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: $T_H^1$
PATHOGENESIS: $T_H^1$

Predisposing HLA-Class II allele in AIH-2

$DR7$
PATHOGENESIS: T H 1

Prediction of DR7 binding peptides

7 predicted high binders induced proliferation
20-mer peptides, overlapping by 12 aa and spanning the entire molecule of CYP2D6 were constructed.

Sixty-one in total
PATHOGENESIS: T$_{H1}$

DR7 positive patients

SI

1  11  21  31  41  51  61

High
Medium
Low
2 months of immunosuppressive treatment

at relapse 6 years after diagnosis
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**

**CYP2D6**

\[313-332\]

**HCV\_1**

**HCV\_7**

**HCV\_8**

**HCV\_402-412**

**A\_QGYKVLLNPSV**

**WPLLILLLL**

**GLMALTLSP**

**LLMCAVHP**

**LLAPCKKQNVQ**
<table>
<thead>
<tr>
<th>Peptide number</th>
<th>Amino acid position</th>
<th>Peptide sequence</th>
<th>Binding score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>176-185</td>
<td>GLLDKAVSNV</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>204-213</td>
<td>RLLDLAQEGL</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>2-11</td>
<td>GLEALVPLAV</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>245-254</td>
<td>KAFLTQLDEL</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>393-402</td>
<td>TTLITNLSSV</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>177-186</td>
<td>LLDKAVSNVI</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>306-314</td>
<td>GMVTTSTTL</td>
<td>21</td>
</tr>
</tbody>
</table>
Cytotoxicity of CYP2D6-specific CD8 T cells

Diagnosis

Remission
IFNγ producing CYP2D6-specific CD8 T cells

Diagnosis

Remission
## Peptide Sequences and Binding Scores

<table>
<thead>
<tr>
<th>Peptide number</th>
<th>HLA-A*0201 decamers</th>
<th>CYP2D6 sequence</th>
<th>Binding score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid position</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>176-185</td>
<td>GLLDKAVSNV</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>204-213</td>
<td>RLLDLAQEGL</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>2-11</td>
<td>GLELVPLAV</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>245-254</td>
<td>KAFLTQLDEL</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>393-402</td>
<td>TTTLTNLSV</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>177-186</td>
<td>LLDKAVSNVI</td>
<td>21</td>
</tr>
<tr>
<td>HLA-A*0201 nonamers</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>306-314</td>
<td>GMTTSTTL</td>
<td>21</td>
</tr>
<tr>
<td>Peptide number</td>
<td>HLA-A*0201 decamers</td>
<td>CYP2D6 sequence</td>
<td>Binding score</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Amino acid position</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>176-185</td>
<td>GLLDKAVSNV</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>204-213</td>
<td>RLDLAQEGL</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>2-11</td>
<td>GLEALVPPLAV</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>245-254</td>
<td>KAFLTQLDEL</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>393-402</td>
<td>TTILTNLSV</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>177-186</td>
<td>LLDKAVSNVI</td>
<td>21</td>
</tr>
<tr>
<td>HLA-A*0201 nonamers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>306-314</td>
<td>GMVTSTTL</td>
<td>21</td>
</tr>
</tbody>
</table>
Tetramer labelled with phycoerythrin
% Tetramer positive CD8 T cells

Diagnosis

Remission
CYP2D6<sup>245-254</sup> tetramer positive CD8 T cells
Impairment of regulatory T cells

CD4 and CD8 autoepitopes defined

Correlation with disease activity

What next?

Expand regulatory T cells

Attempt new modes of treatment
First-in-human clinical trial

T-regs + semi-mature DCs
Thank you