HLA and Drug Hypersensitivity
MHC-I and drug reactions

• Abacavir hypersensitivity is strongly associated with HLA-B*5701
• Carbamazepine hypersensitivity is strongly associated with B*1502 in Taiwanese and A*3101 in caucasians
• Allopurinol induced Stevens-johnson syndrome is strongly associated with HLA-B58
• Flucloxacillin and hepatic injury-B*5701

What is the mechanism?
## HLA-associated drug reactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>Adverse reaction</th>
<th>HLA association</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC class I associations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td><img src="image" alt="Abacavir Structure" /></td>
<td>AHS</td>
<td>B*57:01</td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
<td>SJS/TEN and HSS</td>
<td>B*58:01</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td><img src="image" alt="Carbamazepine Structure" /></td>
<td>SJS/TEN</td>
<td>B*15:02</td>
</tr>
<tr>
<td>Feprazone</td>
<td><img src="image" alt="Feprazone Structure" /></td>
<td>Fixed drug eruption</td>
<td>B22</td>
</tr>
<tr>
<td>Flucloxacinil</td>
<td><img src="image" alt="Flucloxacinil Structure" /></td>
<td>Hepatitis</td>
<td>B*57:01</td>
</tr>
</tbody>
</table>
Models of T cell reactivity to drugs

Hapten concept
Superantigen interaction
p.i. concept
Altered repertoire
Abacavir hypersensitivity reaction

Hypersensitivity reaction in approximately 5% of treated patients with HIV-1 infection

Clinical symptoms include fever, rash, nausea, diarrhea, lethargy and malaise

Rechallenge recurrence of symptoms within hours more severe and possibly fatal

Strongly associated with HLA-B*57:01-Mallal and colleagues
Abacavir

A pro-drug used to treat HIV

Conversion to the active form carbovir triphosphate

Guanosine analogue

Reverse transcriptase inhibitor – viral DNA chain termination
T cells from abacavir sensitive patients with HIV-1 are expanded in vitro in response to abacavir stimulation.

Day 1
PBMC + abacavir

Day 13

Day 14
Restimulate responding T Cells with and without abacavir loaded APC

Intracellular cytokine staining of T cells

No abacavir

with abacavir
Abacavir hypersensitivity is associated with HLA-B*57:01 but not closely related allotypes HLA-B*57:03 or HLA-B*58:01.

The fine specificity of the abacavir T cell response matches the clinical immunogenetics.
Substitutions on the C/D/E and F-pockets of the cleft affect abacavir recognition

- **HLA-B*57:01**
  - 114 Asp-Asn
  - 116 Ser-Tyr
  - 156 Leu-Arg

- **HLA-B*57:02**
  - 114 Asp-Asn
  - 116 Ser-Tyr

- **HLA-B*57:03**
  - 114 Asp-Asn
  - 116 Ser-Tyr

- **HLA-B*58:01**
  - 45 Met-Thr
  - 46 Ala-Glu
  - 97 Val-Arg
  - 103 Val-Leu

- **HLA-B*57:11**
  - 94 Ile-Thr
  - 95 Ile-Leu
  - 97 Val-Trp

**Untreated**

**Abacavir treated**

**IFN\_γ**

**CD8**
Residue 116 controls fine specificity of abacavir responses

B*5701

B*5703

B*57 (114)

B*57 (116)

2 changes

1 change

1 change

28.4%

10.7%

CD8

IFNγ

+ABC
Abacavir leads to selection of a novel peptide repertoire by B*57:01.
Abacavir structural nomenclature

- **Abacavir**
- **Cyclo propyl moiety**
- **2-amino purine moiety**
- **Cyclopentenyl moiety**
Abacavir co-complexes with self-peptides in the cleft of HLA-B*57:01
Correlation between the structures of the HLA-B*5701:RVAQ-abacavir complex & HLA-B*5701:LTTK-abacavir complex
Abacavir makes extensive contacts across the D, E and F-pockets of B*57:01
The location of the abacavir cyclopropyl group disfavours large residues in the F-pocket.
Binding of abacavir prevents assembly with known B*57:01 self-peptides

LTTKLTNTNI-abacavir-dependent
LSSPVTKSF-normal endogenous
Binding of abacavir is prohibited in B*57:03 and B*58:01

LTTKLTNTNI-abacavir-dependent
LSSPVTKSF-normal endogenous
Binding of abacavir is prohibited in B*57:03 and B*58:01

LTTKLTNTNI-abacavir-dependent
LSSPVTKSF-normal endogenous
Two mechanisms of altered self driven by abacavir
Two mechanisms of altered self driven by abacavir
Two mechanisms of altered self driven by abacavir
How general is the abacavir model of HLA-drug hypersensitivity?
Co-elution of native abacavir with purified HLA-B*57:01 from drug-treated cells
What might be key factors in driving drug hypersensitivity?

• TAP transportation of drugs?
• Sustained concentration of drugs
• Bioavailability
• Stability of HLA-drug-peptide complex
• Reactivity of drugs
• HLA polymorphism
DHS in three unrelated Australian Aborigines with HLA-B*56:02

- phenytoin-induced hypersensitivity syndrome (DIHS) delayed-onset rash 2–6 weeks after initial drug exposure
- haematological abnormalities (eosinophilia and/or atypical lymphocytosis)
- systemic features with prolonged fever and/or lymphadenopathy as well as organ involvement (most frequently hepatitis, but also gastrointestinal, lung and kidney involvement)
- Reactivation of Herpes virus 6
Acknowledgements

Department of Medicine, RMH
Prof Terence J. O’Brien,
Dr Slave Petrovski

St Vincent’ s Hospital,
Sydney
Prof Richard Day
Jacqueline Anderson
Prof Tony Kelleher

Hong Kong
Patrick Kwan

Dept. of Immunology & Microbiology
James McCluskey
Diana Chessman
Mandvi Bharadwaj
Lars Kjer-Nielsen
Tony Purcell
Andrew Brooks
Luda Kostenko
Tess Lethborg
Nicole Mifsud
Nick Williamson
Patricia Illing

Australia Red Cross
Blood Service

Dept. of Biochemistry & Molecular Biology
Jamie Rossjohn
Kate Henderson
WEHI
Bob Anderson
Jason Tye-Din

Dept Clinical Immunology
Royal Perth Hospital
University of West Australia
Simon Mallal
Andrew Lucas
Coral Ann Almeida
David Nolan