Understanding Immune-Mediated Drug Toxicities: A Roadmap for Translation and Discovery

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ASCPT March 14, 2019: Applications of Immunopharmacogenomics
Disclosures

- Patent: Equity in IIID that has a patent for HLA-B*57:01 testing for abacavir hypersensitivity
- Provisional patent: testing for vancomycin hypersensitivity
Key Messages

- HLA associations with severe T-cell mediated adverse drug reactions
- Translational road map successes
- HLA associations have helped define mechanisms
- "Negative predictive gap"
  - Associations with many drugs/populations still to be defined
- "Positive predictive gap"
  - Why do only a small fraction of those carrying a risk allele develop disease
- HLA testing and its utility beyond screening
- What to look forward to
Classification of Adverse Drug Reactions

Case

- 48 year old woman otherwise healthy
- Donated blood and weeks later develops high fever and found to be bacteremic with E. coli and MRSA RUL infiltrate.
- Started vancomycin + levofloxacin
- 2 weeks later generalized rash, facial edema and fever
- Eosinophilia peak 1.7 and LFTs ALT 4 x ULN
- On high dose prednisone weaned over 5 months
Questions?

- What is the likely diagnosis?
- Is this drug related?
- Is there a most likely implicated drug and how you determine this?
- Can this be prevented or preempted?
- Would knowledge of genetic background help in the diagnosis?
Key Messages

- **HLA associations with severe T-cell mediated adverse drug reaction**
- Translational road map successes and implementation challenges
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VARIATION IN HLA AND DISEASE ASSOCIATIONS

* Top Hit

1970s-2000s

- Autoimmune
- Cancer
- Infectious Diseases
- Neurology
- Drug Hypersensitivity

2002-present

- Malaria
- Leprosy*
- Narcolepsy*
- Celiac Disease*
- Primary biliary cirrhosis*
- Follicular Lymphoma*
- HBV Clearance*
- Abacavir Hypersensitivity
- Carbamazepine SJS/TEN
- Allopurinol DRESS/SJS/TEN
- Fluvoxacin DILI
- Nevirapine DRESS
- Dapsone Hypersensitivity
- Amoxicillin-clavulanate DILI
- Nevirapine Rash+hepatitis
- Azathioprine pancreatitis
- Amoxicillin-clavulanate DILI
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- Malaria/Cerebral Malaria
- HIV Control*
- Multiple Sclerosis*
- Parkinsons
- Ankylosing Spondylitis*
- Vitiligo*
- Psoriasis*
- Schizophrenia*
- Nasopharyngeal carcinoma*

- Carabamazepine MPE/DRESS/SJS/TEN
- Ticlopidine DILI
- Terbinafine DILI
- Vancomycin DRESS

1970s-2000s

- 1970s-2000s

2002-present
Key Messages

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• **Translational road map successes**
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  • "Negative predictive gap"
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• Beyond – potential utility of HLA as adjunctive diagnostic test
• What to look forward to
HIV Drug Abacavir - HLA Translation “Death” of Hypersensitivity Syndrome

- 5-8% of patients developing fever, malaise and later rash average 8 days into treatment
- Symptoms disappear rapidly on stopping drug
- Hypotension, shock, death could occur rapidly on rechallenge
- Seen less commonly in those of non-European origin
- Warning card issued and used as clinical safety strategy until HLA-B*57:01 guideline based widespread screening
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**December 2012**

**Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire**


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**LETTER**

**Immune self-reactivity triggered by drug-modified HLA-peptide repertoire**

Patricia T. Illing, Julian P. Vivian, Nadine L. Dudicic, Lyudmila Kostenko, Zhanjun Chen, Manohri Bhardwaj, John J. Mikolajczyk, Lars Kjer-Nielsen, Stephanie Gaus, Nicholas A. Williamson, Scott R. Burrows, Anthony W. Purcell, Jarrod Rossjohn, and James McCluskey

Abacavir alters repertoire of self-peptides presented to CD8+ T cells
In all HLA-B*57:01+
in the absence of CD4+ T-cell depletion dendritic cells remain in an immature state and there is tolerance to the altered peptide repertoire
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25.7 Million Africans Living with HIV

About 5000 new HIV infections (adults and children) a day | 2017

- About 66% are in sub-Saharan Africa
- About 500 are among children under 15 years of age
- About 4400 are among adults aged 15 years and older, of whom:
  - almost 43% are among women
  - about 33% are among young people (15–24)
  - about 19% are among young women (15–24)
Severe Immune Mediated ADRs are the Limiting Toxicity of Nevirapine

Nevirapine Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis in South Africa
HLA-C*04:01 is a Risk Allele for Nevirapine SJS/TEN
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## HLA: Global Implications for Translation

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA Allele</th>
<th>Population</th>
<th>OR</th>
<th>PPV</th>
<th>NPV</th>
<th>Number to test to prevent 1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>B*57:01</td>
<td>European &amp;&lt;1% Africa/Asia</td>
<td>960</td>
<td>55%</td>
<td>100%</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>81</td>
<td>0.14%</td>
<td></td>
<td>14000</td>
</tr>
<tr>
<td>Abacavir SJS/TEN</td>
<td>B*15:02</td>
<td>Southeast Asian &amp;&lt;1% European &amp;&lt;1% African</td>
<td>&gt;1000</td>
<td>3%</td>
<td>variable</td>
<td>1000</td>
</tr>
<tr>
<td>Dapsone</td>
<td>B*13:01</td>
<td>East Asians &amp;0% Europeans &amp;0% African</td>
<td>20</td>
<td>7.8%</td>
<td>variable</td>
<td>84</td>
</tr>
</tbody>
</table>

*in populations of high prevalence
Not all patients with an HLA risk allele develop disease “Positive Predictive Gap”

Abacavir Hypersensitivity Syndrome

55% of HLA-B*57:01

Allopurinol DRESS or SJS/TEN*

3% of those carrying HLA-B*58:01

*Drug reaction with eosinophilia and systemic symptoms
Stevens-Johnson syndrome/toxic epidermal necrolysis
Drug Interacts with HLA Protein on Antigen Presenting Cell which Activates T cells

keratinocyte

peptide

carbamazepine

TCR

CD8+ T-cell

APC

HLA-B*15:02

peptide

oxypurinol

TCR

CD8+ T-cell

APC

HLA-B*58:01

peptide

TCR

CD8+ T-cell
Role of Antigen Processing in HLA-C*04:01 Carriers

- Altered trimming activity
- HLA-B*27+ spondyloarthropathies

86% of C*04:01 SJS/TEN versus 6.1% of C*04:01+ NVP tolerant

P<0.001
Nevirapine HLA-C*04:01 Implementation Considerations

1000 patients starting on nevirapine

100 would carry C*04:01+rs27044C

5 would develop nevirapine SJS/TEN

Therefore 100 needed to screen to prevent one case of NVP SJS/TEN
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## Drug Rash with Eosinophilia and Systemic Symptoms

<table>
<thead>
<tr>
<th>ACUTE</th>
<th>Weeks to years</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fever</td>
<td></td>
</tr>
<tr>
<td>• Facial edema</td>
<td></td>
</tr>
<tr>
<td>• Extensive rash (&gt;50% BSA)</td>
<td></td>
</tr>
<tr>
<td>• Organ (liver, kidney)</td>
<td></td>
</tr>
<tr>
<td>• Hematology (eosinophilia, atypical lymphocytosis)</td>
<td></td>
</tr>
<tr>
<td>• Lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>• Supportive pathology</td>
<td></td>
</tr>
<tr>
<td>• EBV/CMV/HHV-6 reactivation</td>
<td></td>
</tr>
<tr>
<td>• Relapse</td>
<td></td>
</tr>
<tr>
<td>• Autoimmune thyroiditis</td>
<td></td>
</tr>
<tr>
<td>• Other autoimmune manifestations (lupus, diabetes)</td>
<td></td>
</tr>
</tbody>
</table>

10% Mortality secondary to organ failure or complications of immunosuppression
Drug Reaction with Eosinophilia and Systemic Symptoms

• What is the most likely drug?

Drug timeline

Levofloxacin--------------------------
Facial Edema
Fever Rash Transaminitis

Vancomycin--------------------------
Day 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
• Can this reaction be prevented or preempted?
• Could knowledge of genetics help in causality assessment in DRESS occurring on multiple antibiotics
8 cases out of 174 both met criteria (RegiSCAR ≥ 4 for DRESS and had DNA or typing available)

-6/8 carried the same HLA class I allele; this same allele present in <7% of population
Vancomycin DRESS: Prospective Study

• Three centers (VUMC, Institute for Immunology & Infectious Diseases (Perth Hospitals) and Austin Hospital (Melbourne)
• Adults developed DRESS 2009-2018
• RegiSCAR criteria probable >4 and Naranjo >5
• PBMCs, DNA and skin collected
• HLA ABC DR DQ DP typing on all cases
• \( \gamma \)-interferon ELISpot done on all cases acutely, follow-up, multiple time points when possible to all possible implicated drugs
8 cases met RegiSCAR/Naranjo Criteria

15 cases had been enrolled in prospective study meeting RegiSCAR/Naranjo criteria where one of implicated drug was vancomycin

91% on multiple antibiotics at the time of DRESS

14/15 had ELISpot done and 12/14 were positive for vancomycin

23 cases matched age, race and sex 2:1 with vancomycin tolerant controls from BioVu (with available imputed HLA typing) defined as ≥5 weeks of vancomycin with therapeutic trough levels
HLA-A*32:01 is Strongly Associated With Vancomycin DRESS

P= 1 x 10^{-8} conditional logistic analysis; Bonferroni control for multiple comparison

92% (11/12) of the Vancomycin ELISpot Positive Cases Carried the Risk Allele

*approximately 20% of patients carrying HLA-A*32:01 developed DRESS by 4 weeks

HLA-A*32:01 and Vancomycin DRESS Implications for Translation

- **SCREEN** – for emergent use not practical but DRESS latency >2 weeks

- **PREEMPT** – intervene early if patient at risk

- **DIAGNOSIS** – adds to causality (with clinical and functional assessments)
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HLA-B*58:01 + allopurinol SJS/TEN
Blister Fluid Clusters

- Inactivated T cells
- Dominant pathogenic clonotype
- CXCL13+ clonotype
- Monocytes, Langerhans cells, APCs
Granulysin as Biomarker for Earlier Diagnosis of SJS/TEN

Positive rapid granulysin test in child with vancomycin SJS/TEN

Lin et al Frontiers Pediatrics 2018:6

A New Era of Precision Drug Hypersensitivity

• The right drug to the right patient at the right time without drug safety concerns
• Not just prediction and prevention but early diagnosis and diagnosis
• Phenotypes, clinical diagnoses, mechanisms, risk stratification and treatment will increasingly be driven by what we find at a cellular and molecular level.
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