Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Munir Pirmohamed

* NHS Chair of Pharmacogenetics
  * David Weatherall Chair of Medicine

Department of Molecular and Clinical Pharmacology
Institute of Translational Medicine
University of Liverpool
MRC Centre for Drug Safety Science: Mission

To use the critical mass and knowledge in drug safety science that we have now accrued within the Centre:

- to undertake leading edge science, and train the next generation of drug safety scientists
- to understand the fundamental mechanisms of clinically important, and currently relevant, adverse drug reactions
- to develop strategies to improve the benefit-risk ratio of current and new medicines, for the benefit of patients, industry and regulators.
iSAEC’s Mission

“The iSAEC will identify DNA variants useful in understanding the risk of drug induced serious adverse events.”
**International Consortium on Drug Hypersensitivity (ITCH)**

- 12 international centres
- 50 UK centres
- 1500 patients

**Sponsored by the International Serious Adverse Event Consortium (iSAEC)**
## SJS/TEN Patients

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>SJS/TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLOPURINOL</td>
<td>10</td>
</tr>
<tr>
<td>AMOXICILLIN</td>
<td>16</td>
</tr>
<tr>
<td>AMOXICILLIN/CLAVULANIC ACID</td>
<td>5</td>
</tr>
<tr>
<td>AMPICILLIN</td>
<td>2</td>
</tr>
<tr>
<td>BACAMPICILLIN</td>
<td>1</td>
</tr>
<tr>
<td>CARBAMAZEPINE</td>
<td>33</td>
</tr>
<tr>
<td>LAMOTRIGINE</td>
<td>18</td>
</tr>
<tr>
<td>OTHERS</td>
<td>100</td>
</tr>
<tr>
<td>PHENYTOIN</td>
<td>11</td>
</tr>
<tr>
<td>SULFASALAZINE</td>
<td>6</td>
</tr>
<tr>
<td>TRIMETHOPRIM/SULFAMETHOXAZOLE</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>227</strong></td>
</tr>
</tbody>
</table>

177 Caucasians Cases
All Caucasian SJS/TEN cases

177 cases, 9237 controls

Low frequency HLA-B allele

Protein kinase
ITALIAN SJS/TEN cases:
40 cases, 1203 controls

HLA-B allele
OR 133 (25-709); P=1.02 x 10^{-8}
SJS/TEN: No Other Population Specific Signals

North Europeans: 116 cases, 5315 controls

Spanish population: 21 cases, 2622 controls
### SJS Allopurinol analysis:

9 Caucasian SJS cases

<table>
<thead>
<tr>
<th>SNP</th>
<th>CHR</th>
<th>BP</th>
<th>ODDS</th>
<th>Pvalue</th>
<th>L95</th>
<th>U95</th>
<th>FreqCases</th>
<th>FreqContr</th>
<th>Freq1kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs144129294</td>
<td>6</td>
<td>30406608</td>
<td>568</td>
<td>2.46E-09</td>
<td>70.66</td>
<td>4565</td>
<td>0.1111</td>
<td>0.000379</td>
<td>0.001</td>
</tr>
<tr>
<td>rs150364710</td>
<td>6</td>
<td>30428647</td>
<td>568</td>
<td>2.46E-09</td>
<td>70.66</td>
<td>4565</td>
<td>0.1111</td>
<td>0.000379</td>
<td>0.001</td>
</tr>
<tr>
<td>rs116203030</td>
<td>6</td>
<td>30279907</td>
<td>488.7</td>
<td>3.28E-09</td>
<td>62.86</td>
<td>3800</td>
<td>0.1111</td>
<td>0.000379</td>
<td>0.002</td>
</tr>
<tr>
<td>rs151052569</td>
<td>6</td>
<td>30365915</td>
<td>672</td>
<td>5.86E-09</td>
<td>75.05</td>
<td>6017</td>
<td>0.1111</td>
<td>0.000379</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNP</th>
<th>ODDS</th>
<th>UCI</th>
<th>LCI</th>
<th>Pvalue</th>
<th>FreqCases</th>
<th>FreqContr</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*58:01</td>
<td>45.15</td>
<td>188.2</td>
<td>10.83</td>
<td>1.68E-07</td>
<td>0.2222</td>
<td>0.008567</td>
</tr>
<tr>
<td>HLA-A*74:01</td>
<td>1139</td>
<td>20700</td>
<td>62.63</td>
<td>1.98E-06</td>
<td>0.05556</td>
<td>0.000163</td>
</tr>
<tr>
<td>HLA-A*33:03</td>
<td>68.66</td>
<td>400.5</td>
<td>11.77</td>
<td>2.60E-06</td>
<td>0.1111</td>
<td>0.00244</td>
</tr>
<tr>
<td>HLA-C*03:02</td>
<td>48.3</td>
<td>265.7</td>
<td>8.779</td>
<td>8.31E-06</td>
<td>0.1111</td>
<td>0.002169</td>
</tr>
</tbody>
</table>
TRIMETHOPRIM/SULFAMETHOXAZOLE
17 north European SJS cases 5315 controls
Common Genome wide significant hits on chr13 and chr6
Uncommon genome wide significant hits on chr3
Borderline genome wide significant significant hits on chr22 and chr21
Nevirapine Hypersensitivity in Malawi

- NVP treated Malawian HIV patients included:
  - 182 NVP-tolerant controls
  - 151 Hypersensitive patients
    - 56 Rash
    - 23 DRESS
    - 51 SJS/TEN
    - 21 DILI

- GWAS and proteomic studies

HMGB1 – total and isoforms that stratify according to both mechanism of release (acetylation status) and function (redox status)
Nevirapine-Induced SJS/TEN

51 SJS/TEN and 182 Tolerant controls
Logistic Regression with CD4+ cell count as covariate
Imputed using 1K genomes phase I data
**NVP-Induced SJS/TEN: Replication**

**Replication Cohort**
11 SJS/ TEN and 59 Tolerant controls (Malawian and Ugandan)

**Additional Cases**
27 SJS/ TEN (Mozambique)*

**Initial top hit:** rs5010528 (HLA-C)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Case</th>
<th>Control</th>
<th>MAF</th>
<th>p</th>
<th>OR (95%CI)</th>
<th>Case</th>
<th>Control</th>
<th>OR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>51</td>
<td>182</td>
<td>0.36</td>
<td>1.48x10^-6</td>
<td>4.64 (2.48-8.66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replication</td>
<td>11</td>
<td>59</td>
<td>0.36</td>
<td>0.008</td>
<td>5.63 (1.56-20.35)</td>
<td>11</td>
<td>59</td>
<td>4.81 (2.74-8.44)</td>
<td>4.31x10^-8</td>
</tr>
<tr>
<td>Replication</td>
<td>38</td>
<td>59</td>
<td>0.38</td>
<td>9.6x10^-5</td>
<td>6.40 (2.66-15.43)</td>
<td></td>
<td></td>
<td>5.17 (3.10-8.59)</td>
<td>2.69x10^-10</td>
</tr>
</tbody>
</table>

HLA-C 3D Protein Structure

- Amino Acid 73 is within the a1 subunit (yellow) of the peptide recognition site.
Nevirapine forms protein adducts in patients

**RH(NVP)PYFYAPELLFFAK**

- **y1** Lysine
- **y2** Alanine
- **y3** Phenylalanine
- **y4** Phenylalanine
- **b2** His+NVP
- **y5** Leucine
- **y6** Leucine
- **b4** Tyrosine+NVP
- **y7** Glutamic acid
- **y8** proline

**Mass/Charge, Da**

100 200 300 400 500 600 700 800 900 100
Summary

- iSAEC as private-public partnership has worked well, and has managed to recruit well phenotyped patients
- Genome-wide approaches are now beginning to bear fruit with several hits identified
- Global collaboration is important to further some of these findings
- Genomic studies will identify predisposing loci, but other studies also important to identify diagnostic and prognostic biomarkers

Acknowledgements

1. iSAEC – Paola Nicoletti, Yufeng Shen, Arthur Holden and many others
2. iSAEC collaborators – contributed cases and adjudication (Shear, Friedmann)
3. Malawi team – Carr, Chaponda, Khoo, Laloo and others