Recap: Day 1

Neil H Shear
University of Toronto
The current standard for diagnosing SJS/TEN is:

1. Measure granulysin levels
2. Determine the HLA genes
3. Clinical features
4. Clinical features and skin biopsy
5. ALDEN
Shear: Syndromes etc

The current standard for diagnosing SJS/TEN is:

1. Measure granulysin levels
2. Determine the HLA genes
3. Clinical features
4. Clinical features and skin biopsy
5. ALDEN
Chung: Pathogenesis etc.

The frequency and severity of drug hypersensitivity is a function of the chemistry of a drug and which of the following:

1. HLAs
2. CYPs
3. Age of the patient
4. Biology of the individual
5. This is not a real equation
The frequency and severity of drug hypersensitivity is a function of the chemistry of a drug and which of the following:

1. HLAs
2. CYPs
3. Age of the patient
4. Biology of the individual
5. This is not a real equation
Pathogenesis of SJS/TEN

Drug Hypersensitivity

Chemistry
- reversible and irreversible protein binding
- metabolism

Immunology
- innate immune system
- adaptive immune system

Pharmacology
- hapten, antigen and immunogen formation

Patient factors
- genetics
- disease

Frequency / Severity of Drug Hypersensitivity = f₁(Chemistry of drug) + f₂(Biology of individual)

The association of HLA B*58:01 with allopurinol-induced SCAR is:

1. Universal across many ancestries
2. Only associated with SJS/TEN
3. Statistically insignificant
4. Associated with renal insufficiency
Chung: HLA association

The association of HLA B*58:01 with allopurinol-induced SCAR is:

1. Universal across many ancestries
2. Only associated with SJS/TEN
3. Statistically insignificant
4. Associated with renal insufficiency
Validate the association between HLA-B*5801 and Allopurinol-SCAR in different populations

<table>
<thead>
<tr>
<th>Study number</th>
<th>1</th>
<th>2 (European study)</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Han Chinese(^{a})</td>
<td>Caucasian(^{b})</td>
<td>Non-European ancestry (two Asians)</td>
<td>Japanese(^{c})</td>
</tr>
<tr>
<td>Case</td>
<td>51/51 (100%)</td>
<td>15/27 (55%)</td>
<td>4/4 (100%)</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>Control</td>
<td>20/135 (15%)</td>
<td>28/1822 (1.5%)</td>
<td>6/493 (1.2%)</td>
<td>7/54 (13%)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>580.3</td>
<td>80</td>
<td>94.7</td>
<td>348.3</td>
</tr>
<tr>
<td>(95% C.I.)</td>
<td>(34.4 - 9780.9)</td>
<td>(34 - 187)</td>
<td>(24.4-367.3)</td>
<td>(19.2 - 6336.9)</td>
</tr>
<tr>
<td>P value</td>
<td>(4.7 \times 10^{-24}) *</td>
<td>(&lt;10^{-6}) *</td>
<td>(1.71 \times 10^{-9})</td>
<td>(1.61 \times 10^{-13})</td>
</tr>
</tbody>
</table>

\(^{a}\) Case: Allopurinol-SCAR; Control: Tolerant control.

\(^{b}\) Case: Allopurinol-SJS/TEN; Control: A mixed European population.

\(^{c}\) Case: Allopurinol-SJS/TEN; Control: Japanese population.

\(^{d}\) Case: Allopurinol-SJS/TEN; Control: Tolerant control.

* Adjusted using Bonferroni’s correction for multiple comparisons to account for observed alleles.
Chung: Carbamazepine

Carbamazepine can induce antigen presenting cells to interact with immune cells directly according to:

1. The hapten hypothesis
2. The p-i concept
3. Altered self–peptide repertoire
4. The theory of everything
Carbamazepine can induce antigen presenting cells to interact with immune cells directly according to:

1. The hapten hypothesis
2. The p-i concept
3. Altered self –peptide repertoire
4. The theory of everything
### How HLA and TCR recognize drugs in drug hypersensitivity?

#### (A) Hapten theory
- Hapten concept: Covalent binding
- Drug activity: Reactive (e.g., penicillin)
- Ag processing: Processing, Non-processing
- MHC restriction: MHC-restricted
- TCR types: Oligoclonal

#### (B) p-i concept
- p-i concept: Non-covalent
- Drug activity: Inert (e.g., carbamazepine)
- Ag processing: Non-processing
- MHC restriction: MHC-restricted, non-restricted
- TCR types: Oligoclonal, polyclonal

#### (C) Altered peptide repertoire model
- altered self-peptide repertoire: Non-covalent
- Drug activity: Inert (e.g., abacavir)
- Ag processing: Processing
- MHC restriction: MHC-restricted
- TCR types: Polyclonal

---

Phillips: Unmet needs

Which of the following was NOT a **challenge** as identified by Prof Phillips?

1. Defining the population.
2. Biological samples.
3. Pharmacogenomic studies.
5. Finding the bathrooms.
Phillips: Unmet needs

Which of the following was NOT a challenge as identified by Prof Phillips?
1. Defining the population.
2. Biological samples.
3. Pharmacogenomic studies
4. Prediction & Prevention
5. Finding the bathrooms
Weaknesses

• Relevant to all but “owned” by none
  • Lack of cohesive patient, provider, or scientific constituency
• Perception as rare and stochastic
• “Fear factor”: Industry constraints/litigation environment
• Burden of disease and cost to healthcare/industry not adequately measured
• Poor provider education
• Few experts and “succession planning”
• Translational hurdles
Opportunities

• Potential for good global return on investment
  • Cost-effectiveness of treatment on a population level
  • Reduced morbidity and mortality, improved drug development pathway and drug safety

• Insights into mechanisms of other hypersensitivity syndromes (roadmap for study)
  • Capacity building for laboratory innovation

• Electronic health record reform; evidence based approaches to mine data from E.H.R.

• Creation of multidisciplinary research teams and new strategic alliances
International Experience (I)

- **Europe**: SCAR – EuroSCAR – RegiSCAR
  - Many successes & High quality validation
  - Good funding (Industry) & Succession...

- **Taiwan**: Drug Relief Fund
  - Able to support major country-wide large population studies

- **iSAEC**: Private-public partnership
  - Also international; important projects

- **Thailand**: National-hospital funding
  - Pharmacogenomic cards
Case Finding...

USA FDA
- Pro/con of multiple data systems
- Future: “DISIN” Network?

Electronic phenotyping
- Possible, rich context, large numbers

Thailand
- Functional national data collection & validation
- Genetic testing
Teri’s Goals

Objectives:

1. Review current state of knowledge of surveillance, pathogenesis, and treatment
2. Examine role of genomics and PGx in etiology, treatment, and eradication of preventable cases
3. Identify gaps, unmet needs, and priorities for future research to eliminate SJS/TEN globally