# Recap: Day 1

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# Shear: Syndromes etc

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

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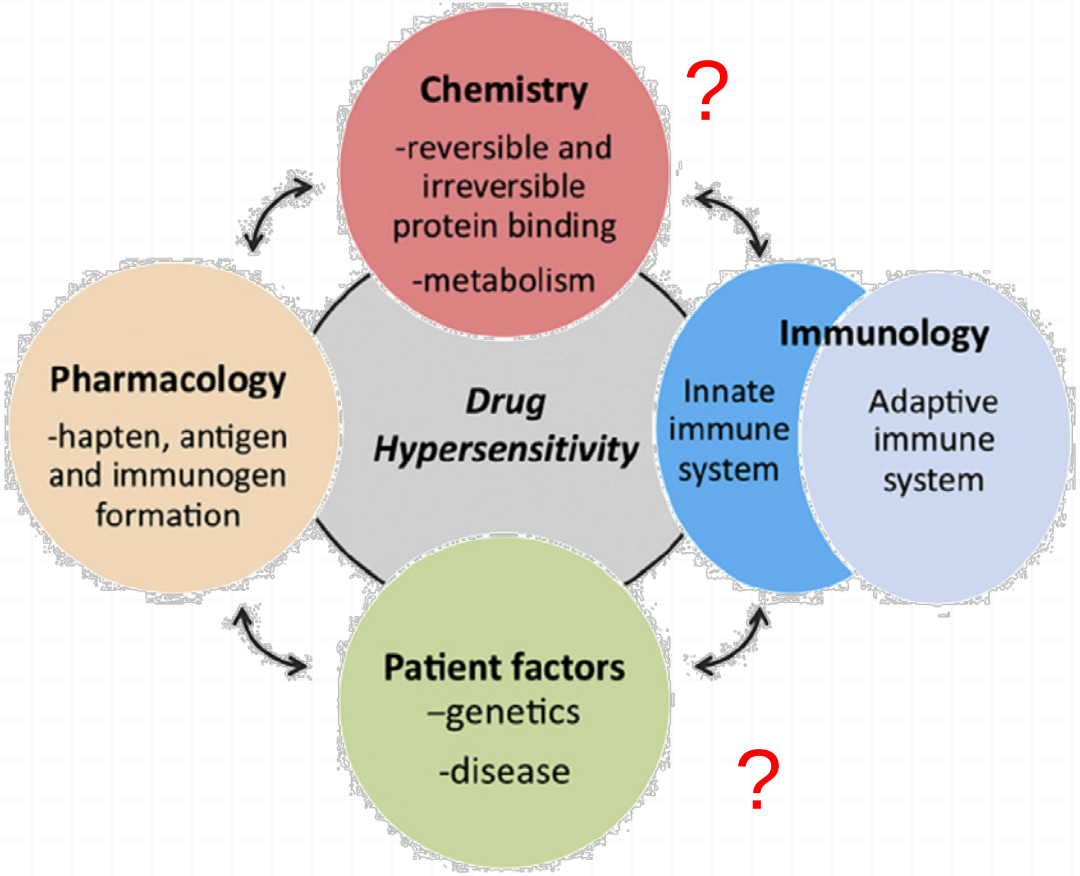
# Pathogenesis of SJS/TEN




$$\text{Frequency / Severity of Drug Hypersensitivity} = f_1\left[\text{Chemistry of drug}\right] + f_2\left[\text{Biology of individual}\right]$$

*Werner J. Pichler,et al. J Allergy Clin Immunol 2011*
*Chung WH et al, J Dermatol Sci, 2012*

# Chung: HLA association

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

1. Universal across many ancestries
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3. Statistically insignificant
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# Validate the association between HLA-B*5801 and Allopurinol-SCAR in different populations

**Table 1. HLA-B*5801 in Allopurinol-induced Severe Cutaneous Adverse reactions (SCAR).**

| Study number | 1 | 2 (European study) | | 3 | 4 |
|---|---|---|---|---|---|
| Study population | Han Chinese[a] | Caucasian[b] | Non-European ancestry (two Asians) | Japanese[c] | Thai[d] |
| Case | 51/51 (100%) | 15/27 (55%) | 4/4 (100%) | 7/13 (54%) | 27/27 (100%) |
| Control | 20/135 (15%) | 28/1822 (1.5%) | | 6/493 (1.2%) | 7/54 (13%) |
| Odds ratio | 580.3 | 80 | | 94.7 | 348.3 |
| (95% C.I.) | (34.4 - 9780.9) | (34 - 187) | | (24.4-367.3) | (19.2 – 6336.9) |
| P value | $4.7\times 10^{-24}$ * | $<10^{-6}$ * | | $1.71\times 10^{-9}$ | $1.61\times 10^{-13}$ |
| Reference | Hung, et al. PNAS, 2005. | Lonjou, et al. Pharmacogenetics and Genomics, 2008. | | Kaniwa, et al. Pharmacogenomics , 2008. Dainichi, et al. Dermatology, 2007. | Wichittra, et al., Pharmacogenetics and Genomics, 2009. |

[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:

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3. Altered self –peptide repetoire
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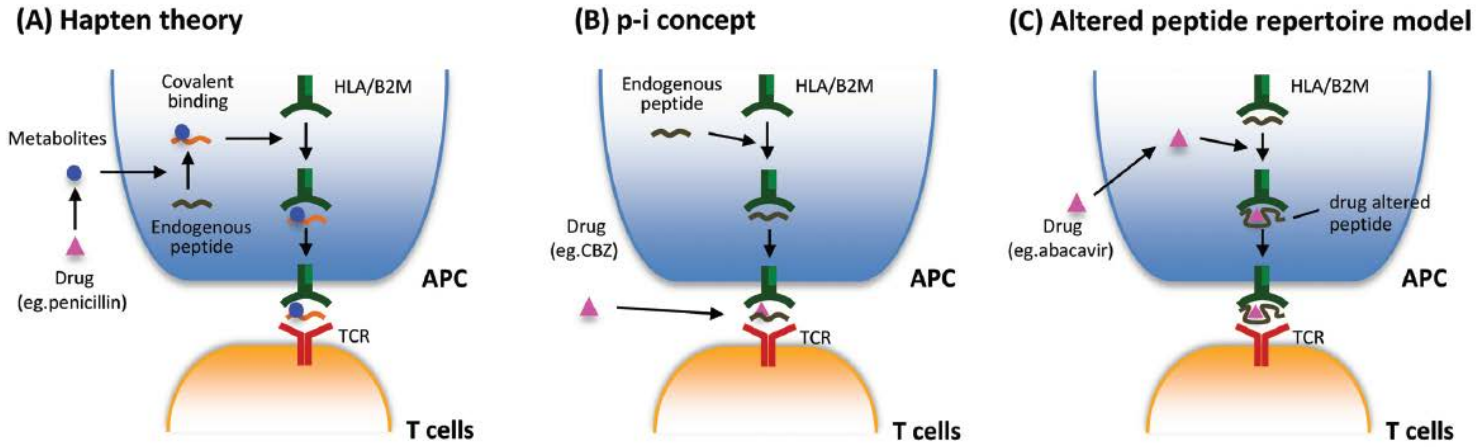
# How HLA and TCR recognize drugs in drug hypersensitivity?




| | Hapten concept | p-i concept | altered self-peptide repertoire |
|---|---|---|---|
| Peptide-drug interaction | Covalent binding | Non-covalent | Non-covalent |
| Drug activity | Reactive (e.g penicillin) | inert (e.g.carbamazepine) | Inert (e.g. abacavir) |
| Ag processing | Processing, Non-processing | Non-processing | Processing |
| MHC restriction | MHC-restricted | MHC-restricted, non-restricted | MHC-restricted |
| TCR types | oligoclonal | Oligoclonal,polyclonal | polyclonal |

*Ren-You Pan et al., Current Immunology Reviews, 2014; Pichler WJ , Allergology International 2006 Jan;55; Illing P et al, Nature 2012*

# 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

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# 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