Tolerance

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Mechanisms of Idiosyncratic Hepatotoxicity

- Immune Idiosyncrasy
  - Shortened delay on rechallenge
  - Eosinophilia and fever
  - Antibodies against drug-modified protein
  - Example: halothane
- Metabolic Idiosyncrasy
  - No decrease in delay on rechallenge
  - No evidence of immune response
  - Example: isoniazid; however, there are no good examples in which differences in metabolism explain the idiosyncratic nature of these reactions.

Tolerance

- When a patient with an idiosyncratic reaction to a drug continues to be treated, the adverse reaction often resolves.
  - Mild rashes often resolve
  - Elevation in transaminases often normalize
- Is this immune tolerance or metabolic tolerance?
- Although a toxic insult usually results in the induction of protective enzymes, the fact the onset of rash or transaminase elevation is almost always delayed suggests to me that the dominant mechanism is immune tolerance.

How Can These Hypotheses Be Tested?

- Clinical characteristics provide important clues, but it is virtually impossible to perform controlled experiments with humans.
- In vitro experiments simply can not reproduce the complexities of idiosyncratic drug reactions.
- Animal models represent an important tool, but idiosyncratic reactions are also idiosyncratic in animals and so valid animal models are rare.

D-penicillamine Induced Autoimmunity in BN Rats

20 mg/day

~3 weeks

~50-80% incidence

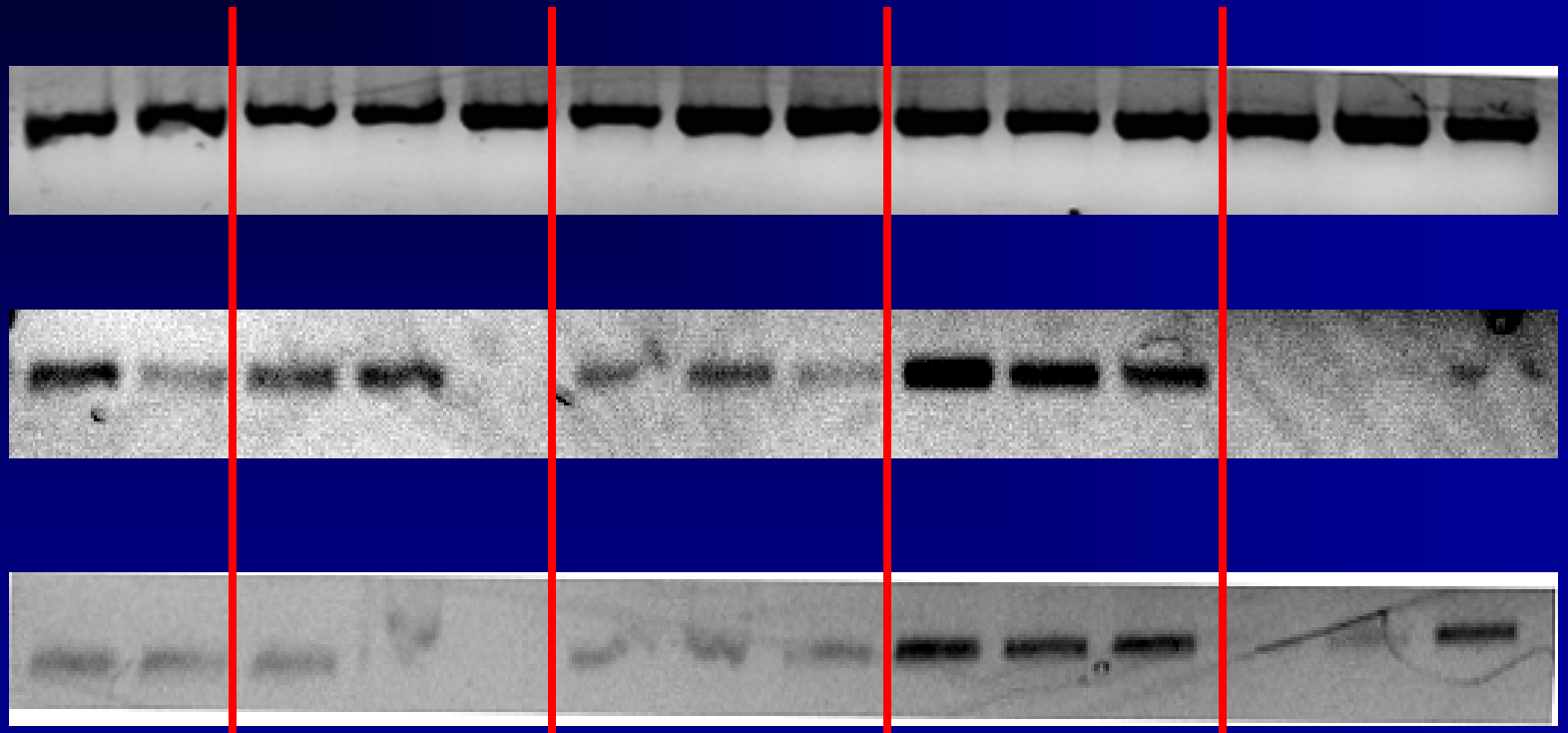
- **Anti-nuclear antibodies**
- **Skin rash**
- **Immune complexes in the kidney**
- **Hepatic necrosis**
- **Swollen, red arthritic limbs**
- **<u>No decrease in delay on rechallenge</u>**

Dose Dependency of Penicillamine-Induced Autoimmunity

- Despite what is often said, all effects, including idiosyncratic drug reactions, are dose dependent.
- The dose required to induce the syndrome is 20 mg/day (incidence 50-80%).
- A dose of 50 mg/day does not increase the incidence.
- A dose of 10 mg/day for 2 weeks induces immune tolerance to the 20 mg/day dose, which can be transferred to a naïve animal with spleen cells.

$CD4^+$ Regulatory Cytokines

Masson & Uetrecht, Chem Res Tox, 17:82, 2004.

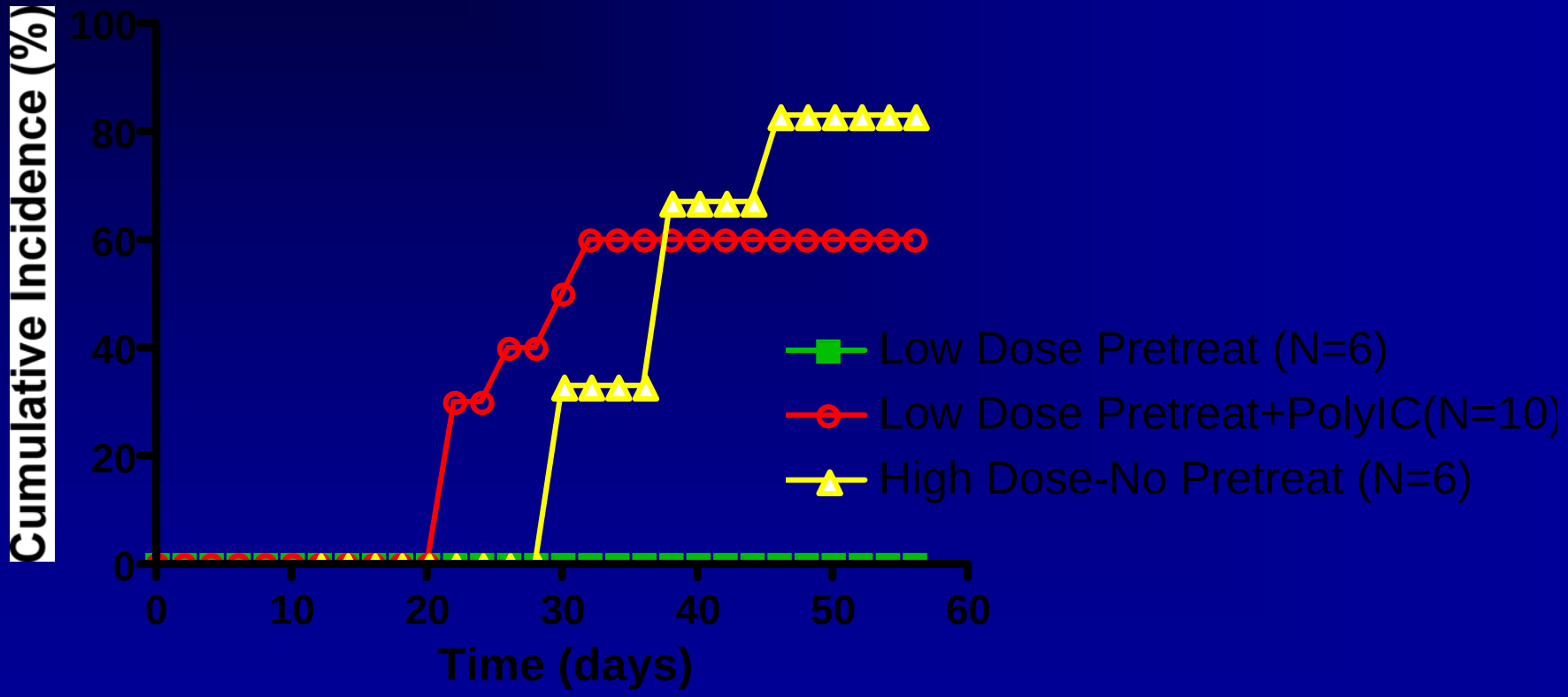


Hypothesis

- The major response of patients who are treated with a drug that can cause idiosyncratic drug reactions may be immune tolerance.
- In the liver, tolerance may be initiated by Kupffer cells and mediated by regulatory T cells.
- Factors that modify tolerance may be the determinants that determine who will have an idiosyncratic reaction.

Poly I:C Reverses Tolerance

Injections given on days 1 & 14



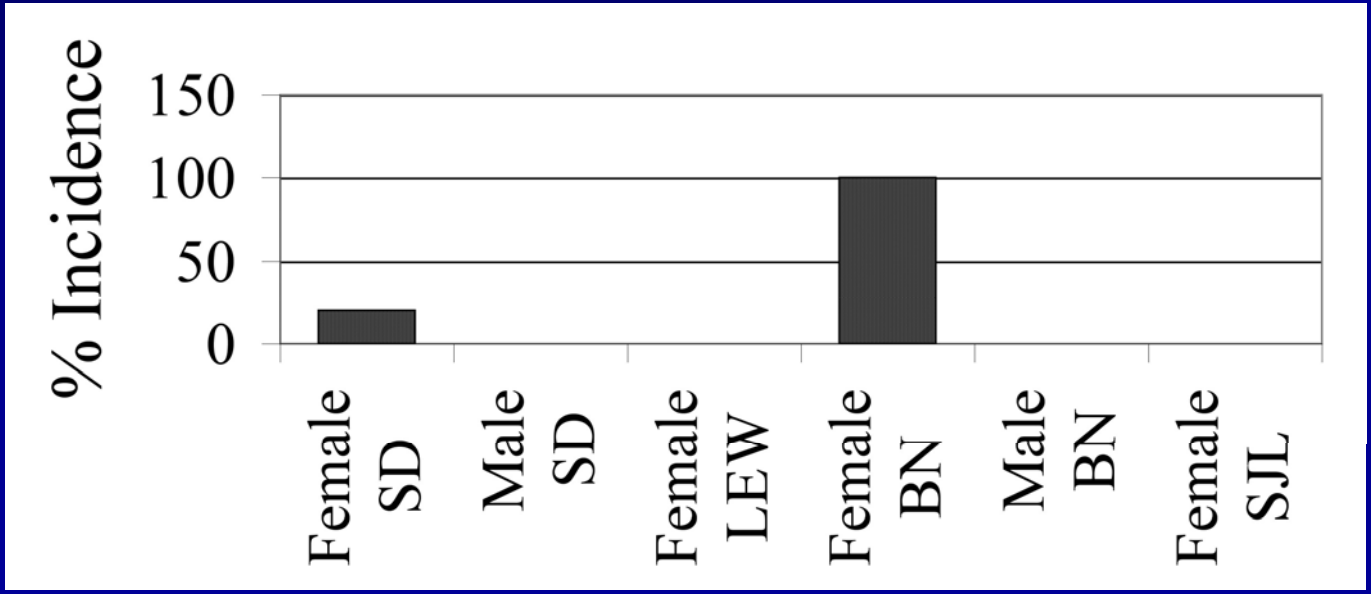
Nevirapine Model of a Drug-Induced Skin Rash

- Nevirapine causes a skin rash in 8-16% of patients and can also cause severe liver toxicity.
- A high CD4 count is a significant risk factor and the incidence is also higher in women.
- Two weeks of low dose treatment decreases the incidence of the rash.
- Nevirapine also causes a skin rash in rats.

Characteristics

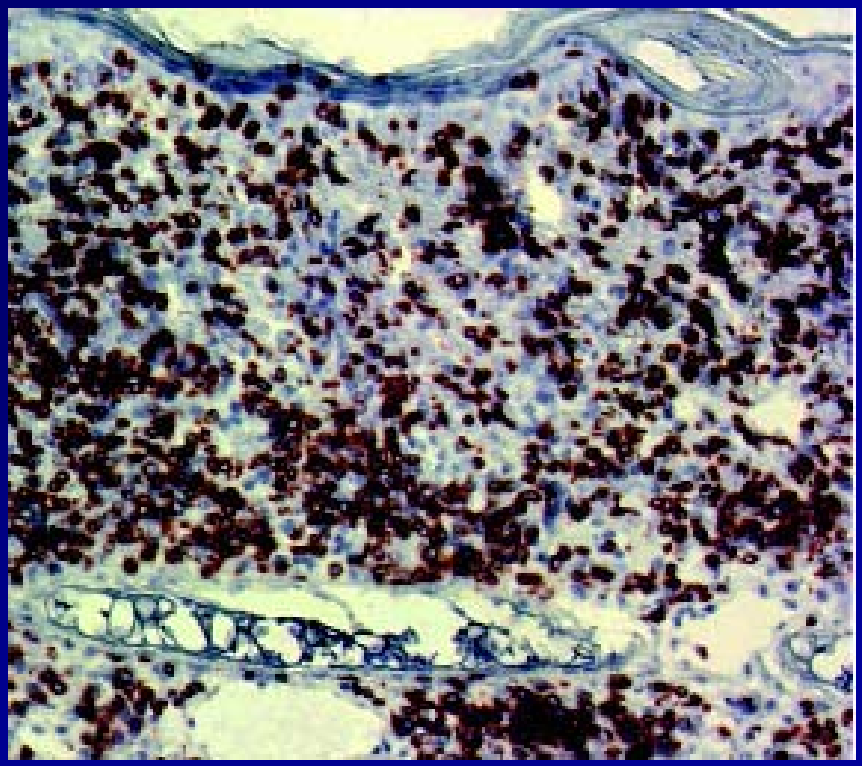
Shenton et al., Chem Res Tox, 16: 1078, 2003

- Incidence is strain and sex dependent.
- Occurs after 2-3 weeks of treatment.
- First sign is red ears and then a rash develops that can cover the body.



Nevirapine-Induced Skin Rash is Immune-Mediated

- Mononuclear cells in skin of rats with rash (CD4 & CD8 T cell, macrophages)
- Syndrome occurs earlier (red ears ~8 h and lesions within days) and is more severe on reexposure
- Sensitivity can be transferred to naïve rat with spleen cells or sometimes CD4 T cells.
- Rash not prevented by depletion of CD8 T cells.



The Characteristics of the Animal Model Are Very Similar to Those in Humans Suggesting the Mechanisms are the Same.

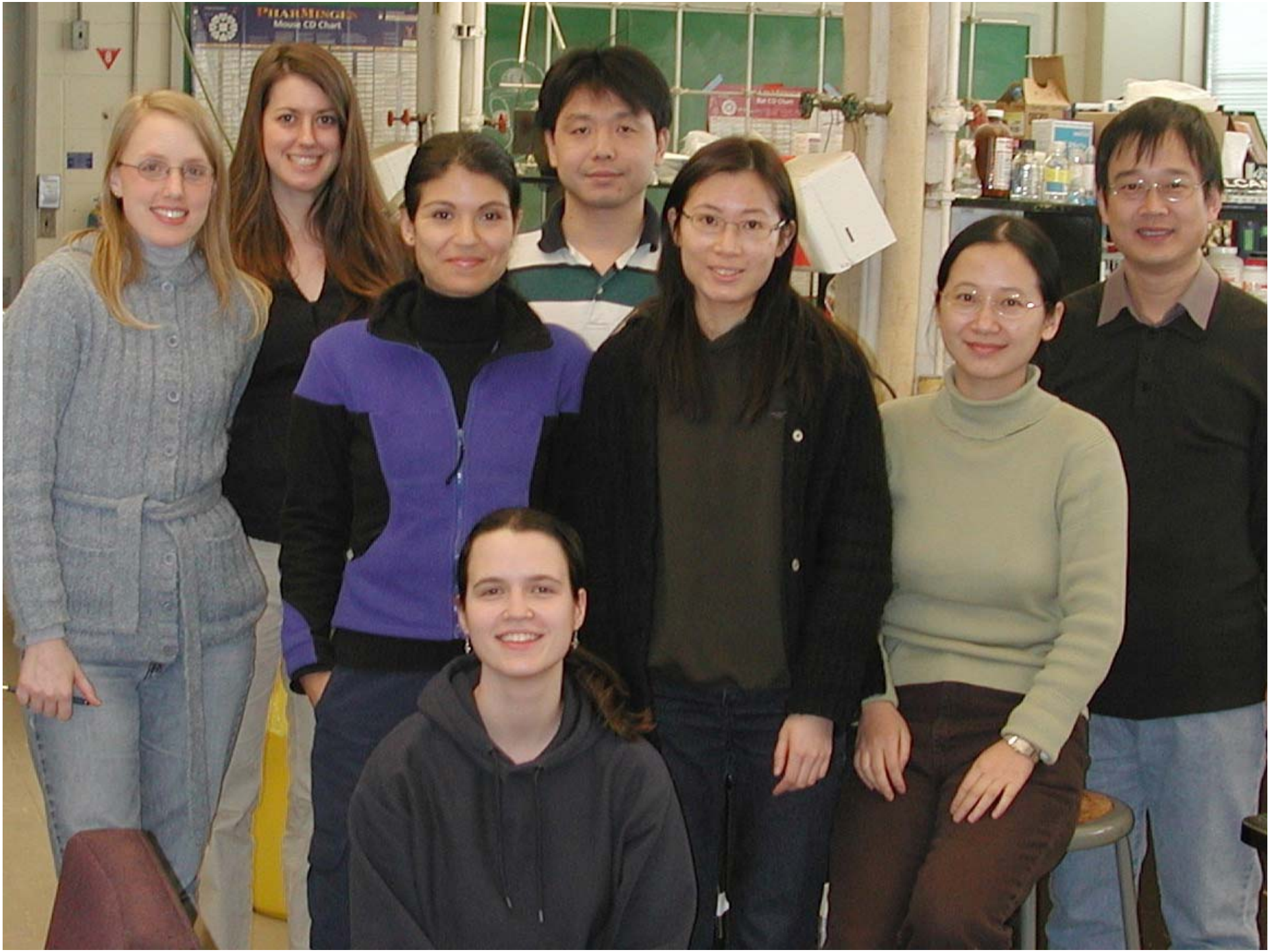
- Idiosyncratic nature, i.e. individual susceptibility and time course are similar.
- Low dose treatment induces tolerance in both rats and humans.
- CD-4 T cells appear to mediate the reaction in both humans and rats.
- However, hepatotoxicity occurs in humans but not in rats.

Low Dose Nevirapine Tolerance

- Although nevirapine-induced skin rash is immune-mediated, the major tolerance induced by low dose treatment is metabolic, i.e. P450 induction.
- The tolerance in not long lasting and is not transferable.
- The tolerance can be broken by inhibitors of drug metabolism.
- The major mechanism of tolerance induced by low dose nevirapine treatment involves induction of drug metabolism leading to low nevirapine blood levels.

Conclusions

- Idiosyncratic liver toxicity is complex and more than one mechanism is likely involved.
- Tolerance is a major characteristic of idiosyncratic drug reactions; in many cases this is immune tolerance, but other mechanisms may be involved.
- A factor that may determine who will sustain an idiosyncratic drug reaction may be one that breaks immune tolerance, but it has not been possible to develop animal models at will by stimulation of the immune system.


PHARMINGEN
Mouse CD Chart