Drug allergy is no allergy

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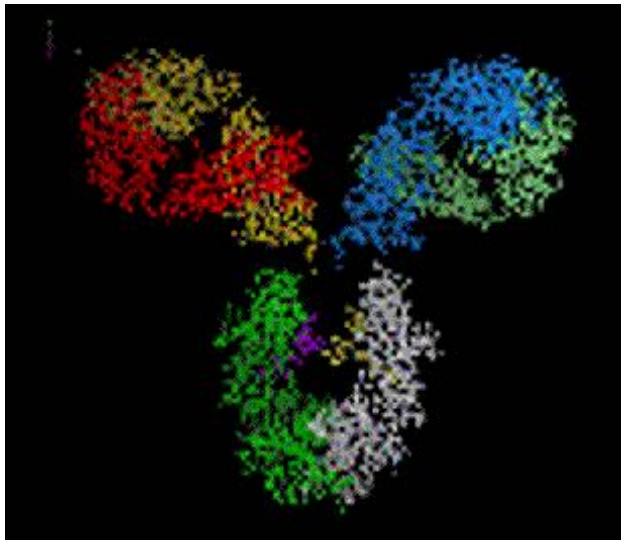
Biologicals > < small drug compounds

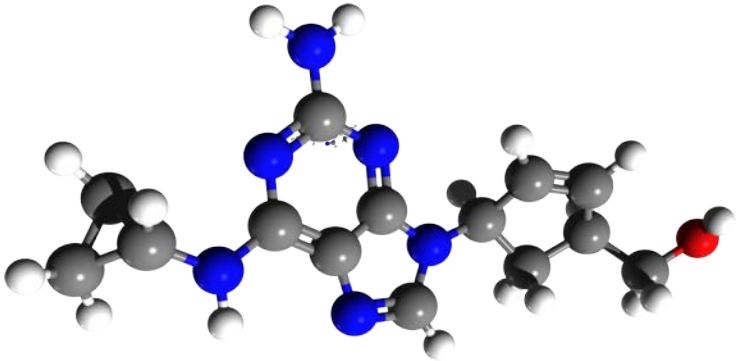
Proteins as drugs:

- large molecule (>20KD)
- digested in GIT (protein)
- i.v., i.m., s.c.



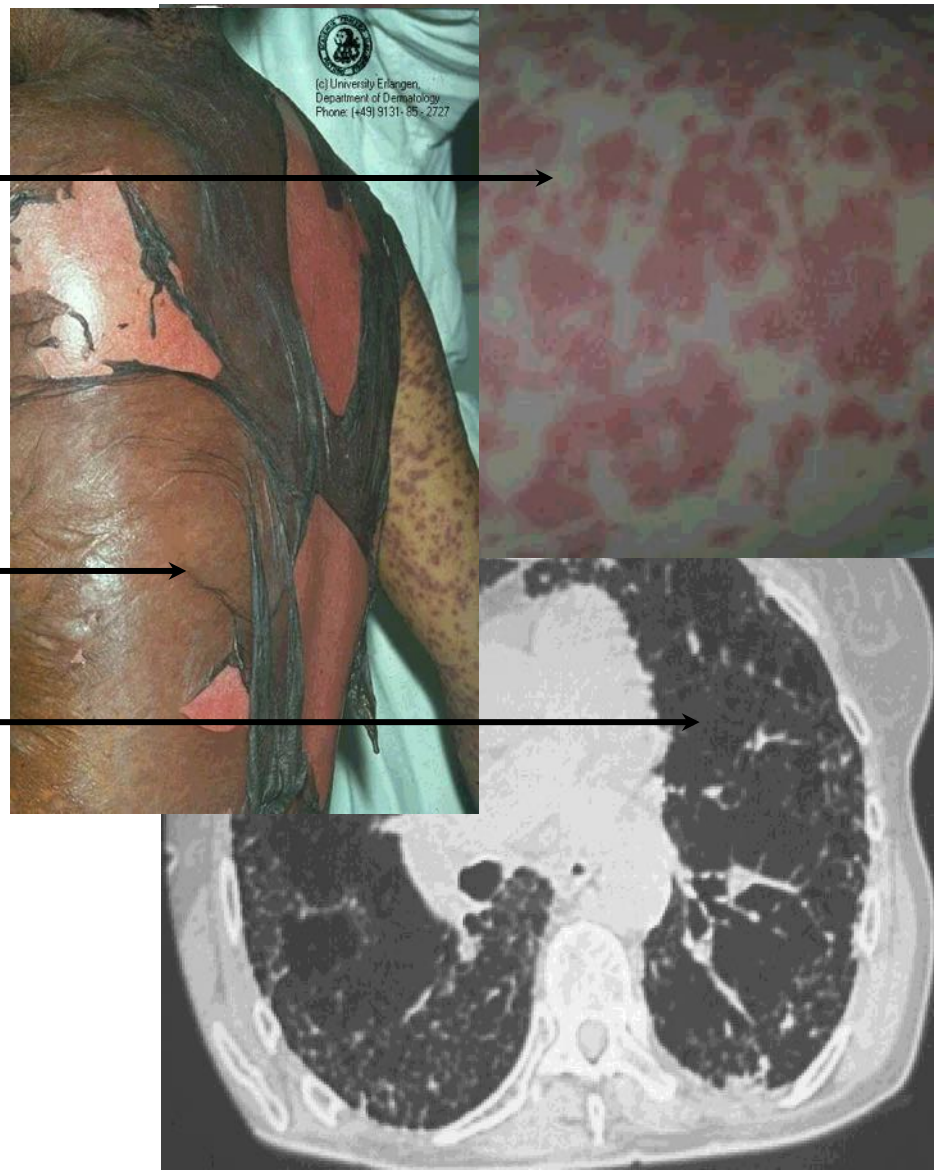
Small compounds:

- small size (<1-2 KD)
- C, O, H, N, S
- oral, i.v., i.m., s.c.



Drug related side effects: **drug allergy**

- Anaphylaxis, Urticaria
- Makulo-papular Exanthem
- bullous Exanthem
- Acute generalized exanthematous Pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS) toxic-epidermal Necrolysis (TEN)
- DRESS, Hepatitis , interstitial Nephritis, Pneumonitis
- Drug induced autoimmunity (SLE, Pemphigus, ...)



HAPTEN CONCEPT:

Based on studies on contact dermatitis it was found in **1930`** that **small molecules alone are not immunogenic** ! An immune reaction to a small compound is linked

– *it`s ability to bind **covalently** to a larger protein*

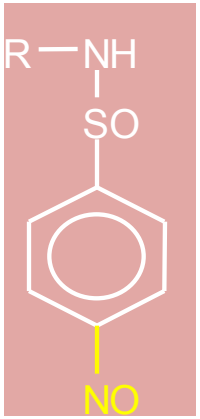
– *the modified protein (= **hapten-carrier complex**) is resistant to intracellular processing. Thus epitopes for T-cells and B-cells are available*

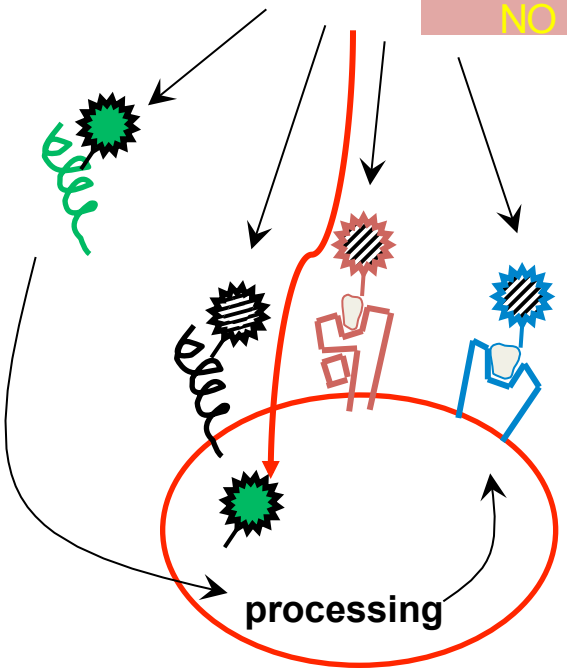
– *the hapten features can also lead to **activation of innate immunity***

Hapten/prohapten specific immunity

Penicillin G

SMX-NO



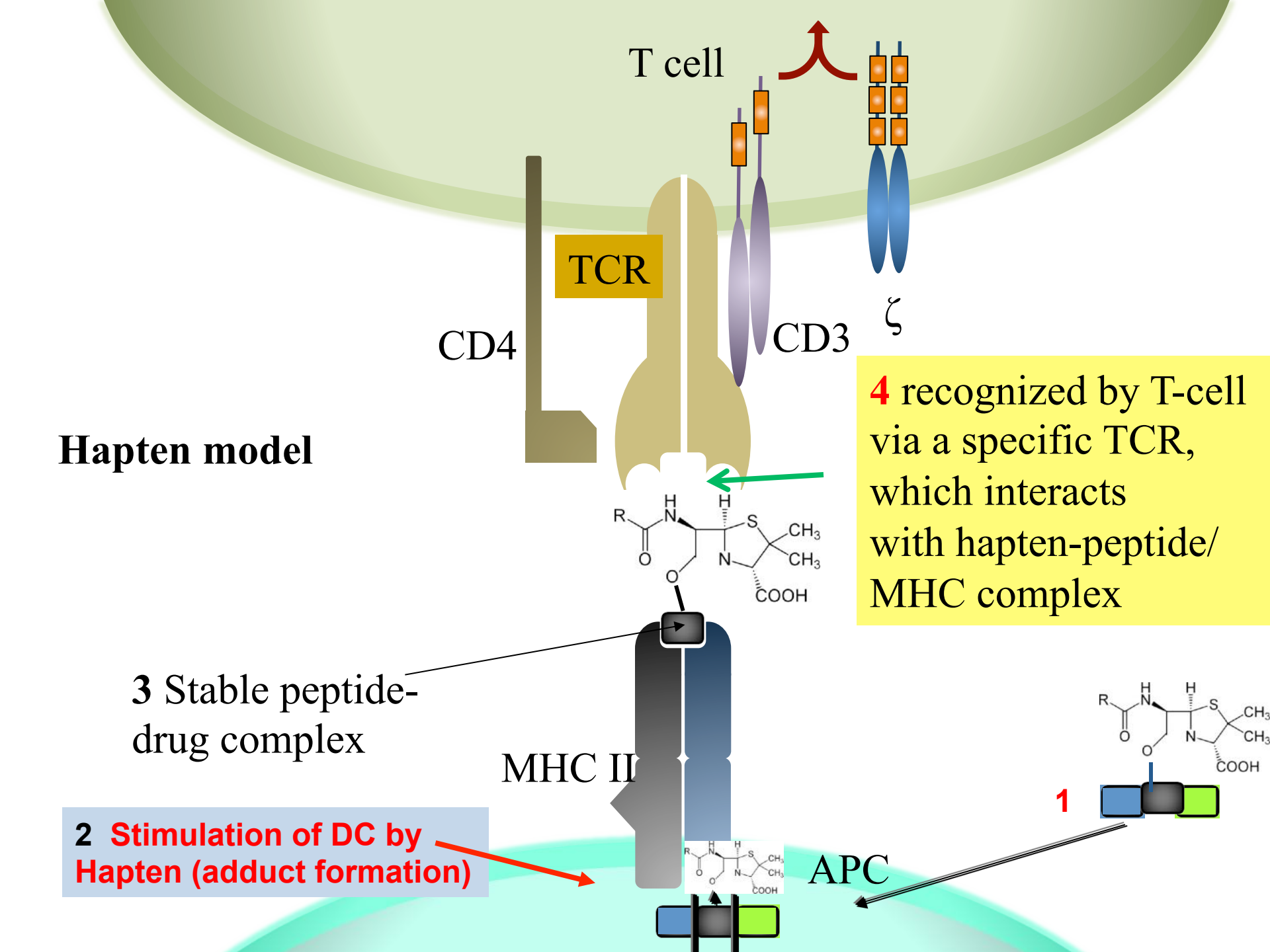


Haptens are chemically reactive compounds able to bind ***covalently*** to proteins.

Adduct formation gives a danger signal to **APC** (CD86 upregulation, IL-1β−secretion)

Adduct formation forms **neoantigenic** determinants able to induce both a **T-cell** and **B-cell** immune response. A hapten stimulates both, T-cells and B-cells !!

INNATE ADAPTIVE


T cell
TCR
CD4
CD3
ζ
Hapten model
4 recognized by T-cell via a specific TCR, which interacts with hapten-peptide/ MHC complex
3 Stable peptide-drug complex
MHC II
1
2 Stimulation of DC by Hapten (adduct formation)
APC

Risk assessment

- Is the drug a hapten ?
- Is it metabolized to be a h
- Is it activating the i e system (dendritic ce
- Is it cli specific antibody or T cell

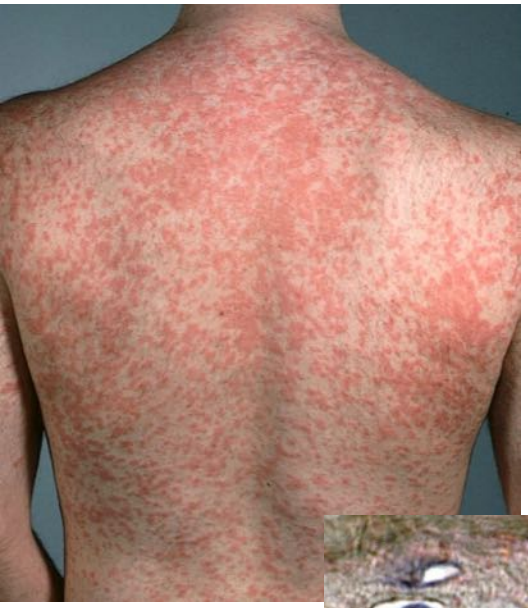
tolerated in animal systems ?

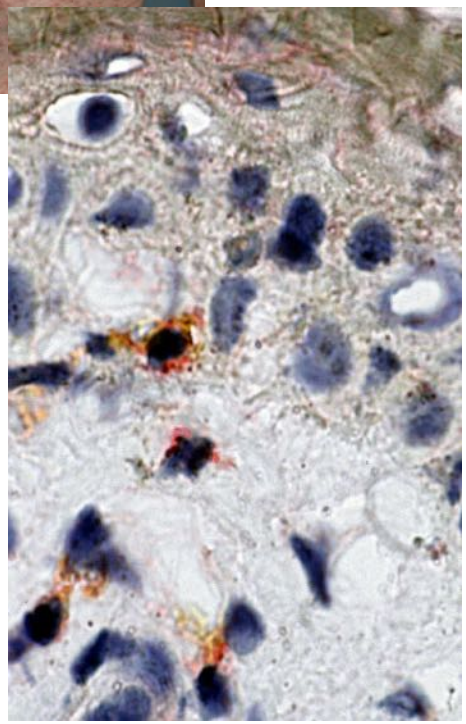
With the exception of assays of DC (monocyte) activation for the potential of contact sensitizers (cosmetic industry), this approach did not prove to be effective in predicting immunotoxicological risk

May be the hapten concept is insufficient?

What is found, if one tests the hapten concept in reality, namely in patients with systemic drug hypersensitivity ?

Ex vivo: *Clinic + Immunohistochemistry*

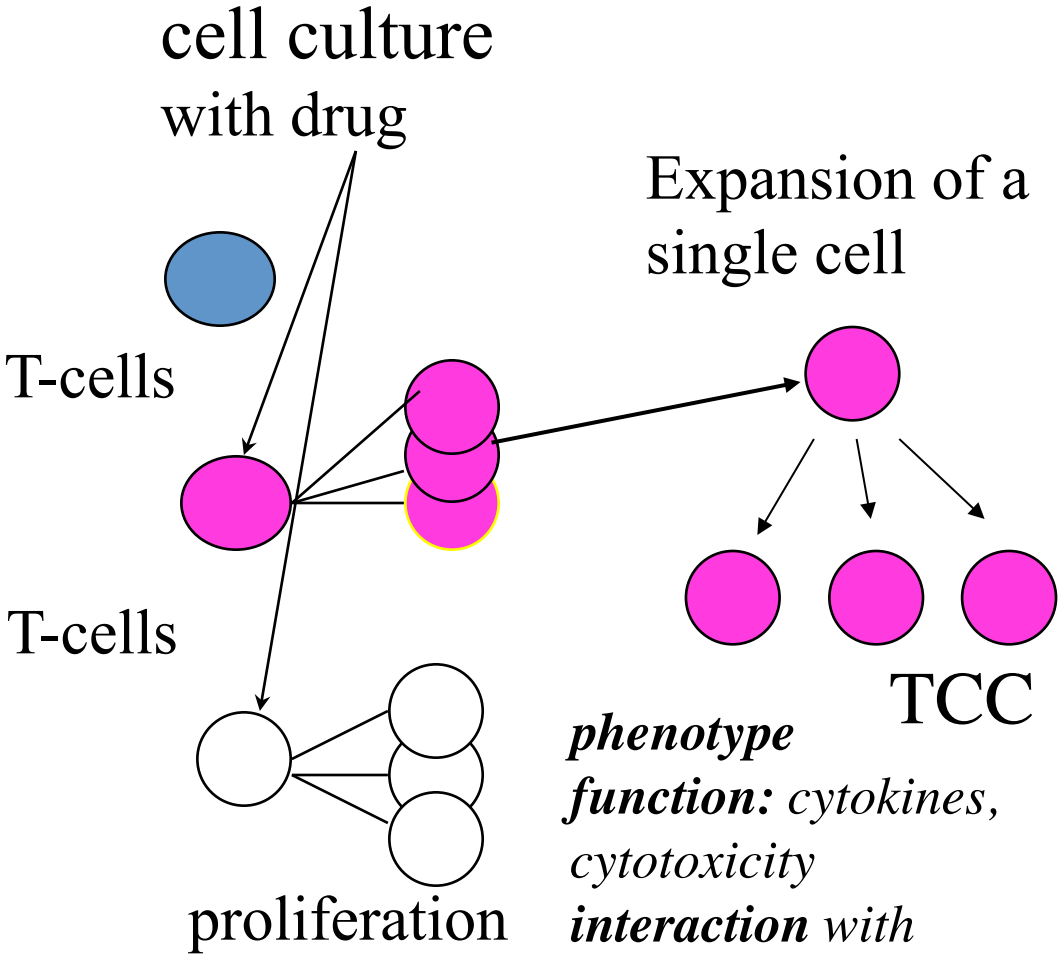




Perforin red

CD4 brown

In vitro: Drug specific T-cell clones (TCC) *from blood and tissue*



phenotype
function: *cytokines, cytotoxicity*
interaction *with APCs (DC), tissue cells,*
drug recognition,
Ca++ influx,
cross-reactivity

Looking at drug hypersensitivity in detail revealed:

1. *Drugs **do not** stimulate like haptens*
2. *Drug hypersensitivity ≠ contact dermatitis*
3. *Various dogmas in DH are **wrong***
4. *Immunotoxicological **risk assessment** fails as it is based on wrong concepts*

Realizing some incompatibilities !

Realizing some incompatibilities !

The T cell stimulation observed in drug hypersensitivity & the rules on an immune response

Innate immunity → danger signals → specific activation of drug specific T cells + costimulation by CD28/CD80 etc. → stimulation and expansion of drug specific T cells → tissue migration → stimulation of drug specific B-cells → activation of various effector cells → clinical manifestations → memory

Realizing some incompatibilities !

The T cell stimulation observed in drug hypersensitivity does not follow the rules on an immune response

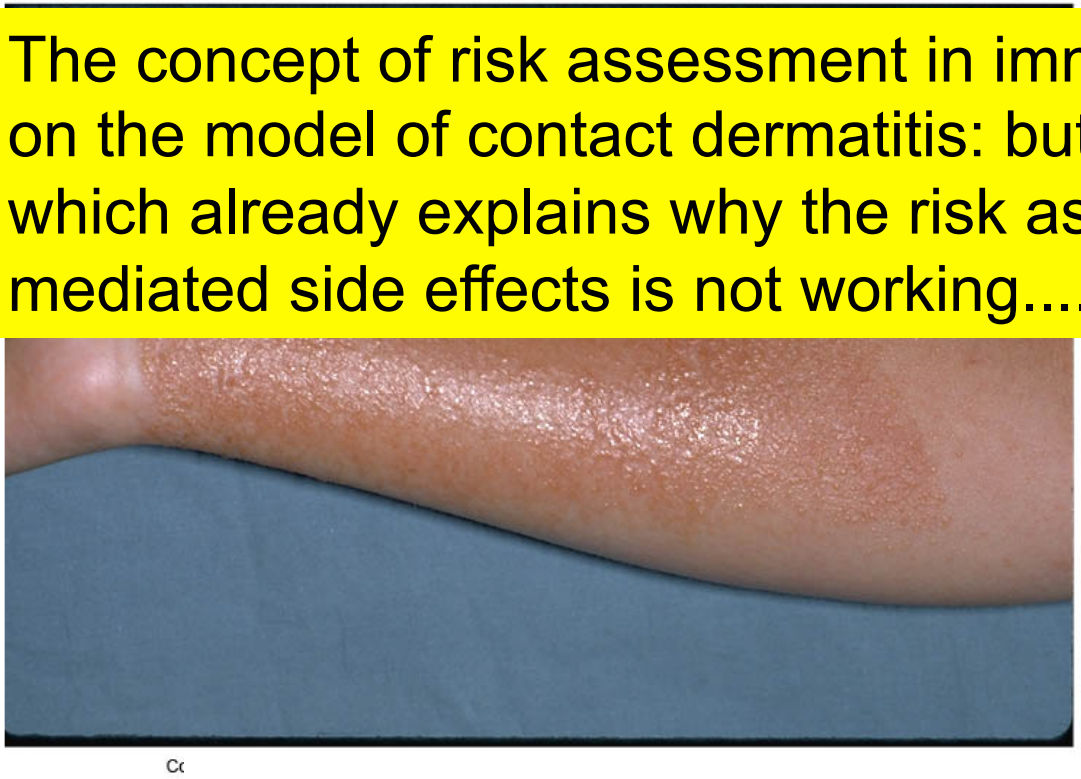
Innate immunity → danger signals → specific activation of drug specific T cells + costimulation by CD28/CD80 etc. → stimulation and expansion of drug specific T cells → tissue migration → stimulation of drug specific B-cells → activation of various effector cells → clinical manifestations → memory

- **it *bypasses* the innate immune system**
- **it *directly* stimulates T-cells**
- **it elicts an *allo- or autospecific* immune response**

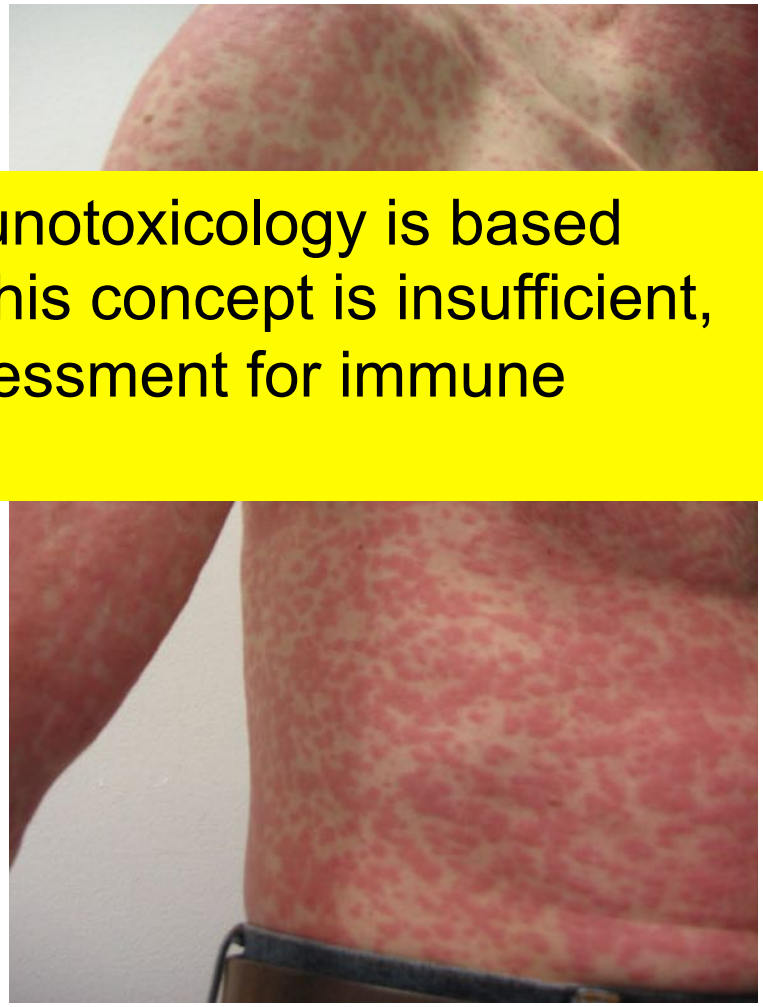
Realizing some incompatibilities

Contact dermatitis ≠ systemic drug hypersensitivity

The concept of risk assessment in immunotoxicology is based on the model of contact dermatitis: but this concept is insufficient, which already explains why the risk assessment for immune mediated side effects is not working.....



Localized, homing to the site where antigen penetrated and caused “danger”



Systemic reaction, no specific homing

Realizing some incompatibilities

Dogma in drug allergy:

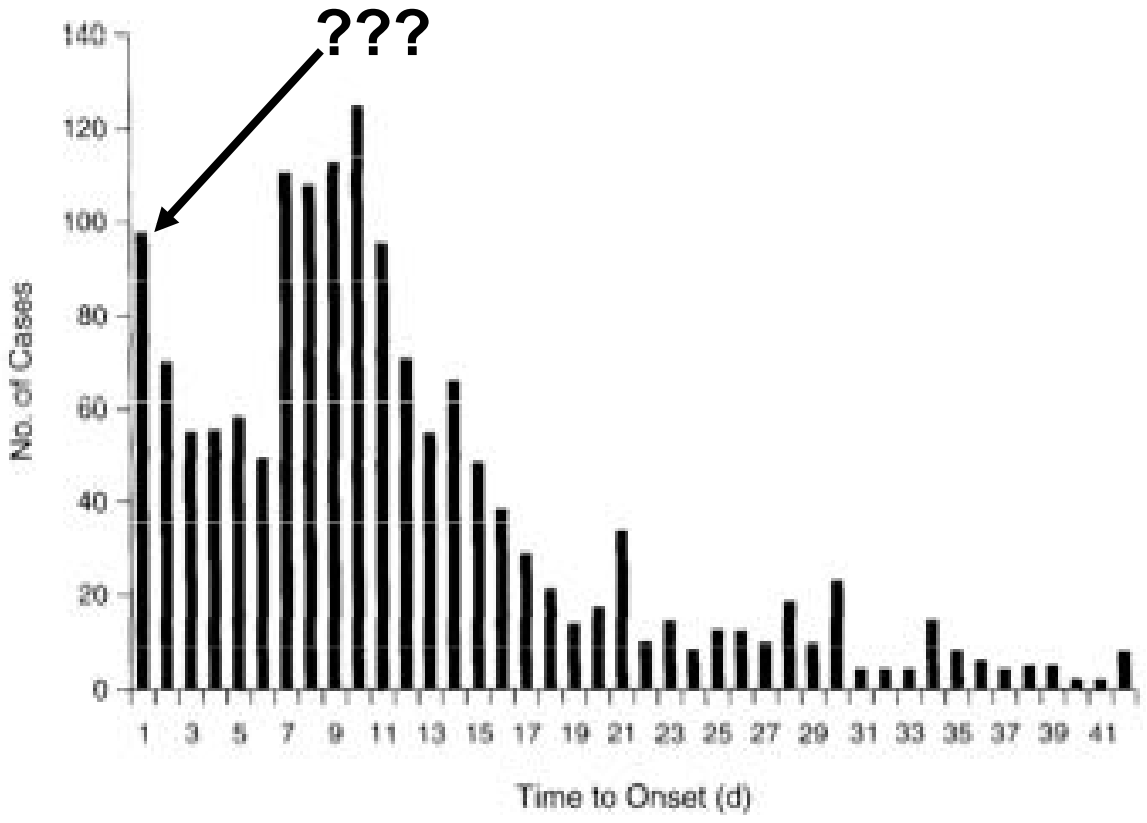
- IgE against a hapten
- DH is not predictable
- Not dose dependent
- Prior exposure necessary

Findings:

- the majority of side effects are T-cell mediated!
- HLA associated DH is predictable ! (abacavir, carbamazepin, allopurinol)
- Clearly dose dependent !
- Obviously not ! IgE-mediated anaphylaxis to NMBA, cephalosporins, RCM at first encounter

Realizing some incompatibilities

Abacavir: onset of symptoms at first encounter on day 1 !!



- no sensitization needed: a rapid reaction occurs, if enough abacavir reactive cells are present

Realizing some incompatibilities

Dogma in drug allergy:	**Findings:**
• IgE against a hapten	• the majority of side effects are T-cell mediated!
• DH is not predictable	• HLA associated DH is predictable ! (abacavir, carbamazepin, allopurinol)
• Not dose dependent	• Clearly dose dependent !
• Prior exposure necessary	• Obviously not ! IgE-mediated anaphylaxis to NMBA, cephalosporins, RCM at first encounter

HLA-alleles and drug hypersensitivity

DRUG	HLA Allele	HLA Carriage Rate	Prevalence of diagnosis	Negative Predictive Value	Positive Predictive Value	NNT to prevent "1"
Abacavir	B*5701	6-8%	8% (includes 3%	100% for	55%	13
Allopurin		Caucasian				250
Carbamazepine	B*1502	10-15% Han Chinese <0.1% Caucasian	<1-6/1000	100% in Han Chinese	3%	1000
Flucloxacillin	B*5701	As for abacavir	8.5/100,000	99.99%	0.12%	13819

Only a particular HLA-allele allows binding of the drug in a way, which results in immune stimulation;

The relevant allele may be common (~ 1 / 20) or rare (< 1 / 2000) in the population (e.g. 15% of Han chinese carry B*1502 but <0,1% of caucasians)

HLA polymorphism in population

ca 14 HLA alleles / individual

> 7400 HLA alleles in human population

some allele the same, some are different

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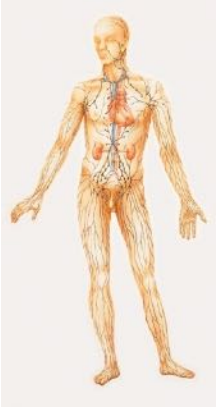

HLA

- **A*02:01, *A* 31:01***
- ***B*10:02; B*57:01***
- **C* 02:01; *C*06:01***
- **DR B1* 01:01; *04:02***
- ***DR* B5* 01:01**
- ***DP* 04:04; 08:01***
- ***DQ* 01:05; 05:01***

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HLA

- **A*02:01, *A* 32:01***
- ***B* 15:02; B*58:01***
- **C* 0201; *C*06:01***
- **DR B1* 01:01*; 04:02***
- ***DR* B5* 01:01**
- ***DP* 03:04; 07:01***
- ***DQ* 02:04; 03:02***

HLA polymorphism in population

ca 14 HLA alleles / individual

ca. 7800 HLA alleles in human population

some alleles are frequent, some are rare

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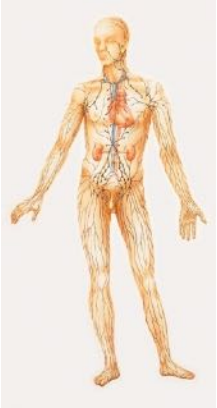

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Risk for Carbamazepine hypersensitivity

Abacavir hypersensitivity

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HLA

- A*02:01, *A* 32:01*
- *B* 15:02; B*58:01*
- C* 0201; *C*06:01*
- DR* B1-01:01*; 04:02*
- *DR** B5-01:01
- *DP* 03:04; 07:01*
- *DQ* 02:04; 03:02*

Risk for Allopurinol hypersensitivity

Risk for Carbamazepine hypersensitivity

Clinical data revealed that most drug allergies are mediated y T cells;

How are T cells stimulated by drugs ?

The p-i concept

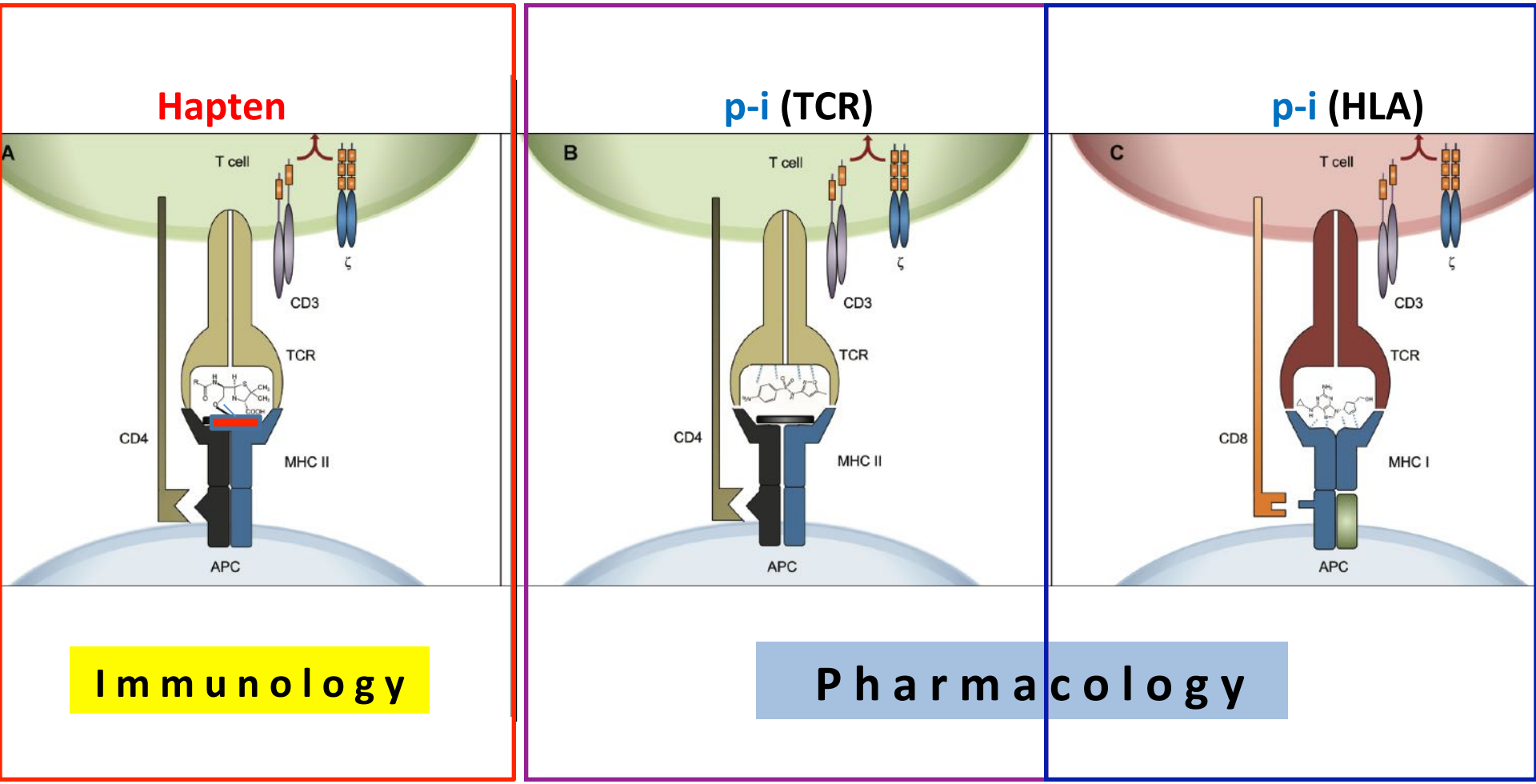
p*harmacological interaction with*

i*mmune receptors*

The p-i concept
Pharmacological Interaction with Immune Receptors

A chemically inert drug, unable to covalently bind to proteins, „happens“ to bind to some of the many (polymorphic) immune receptors (TCR, HLA), as it does to other proteins/receptors. This drug-receptor interaction can under certain circumstances lead to activation and expansion of specific immune cells. The subsequent reaction *imitates* a specific immune response, but has some bizarre clinical and immunological features.

Drugs interact with the immune system via processed hapten-carrier complexes or via direct „pharmacological“ binding (to TCR or HLA)



Pichler W.J. Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. *Curr Opin Allergy Clin Immunol* 2002; 2:301-305

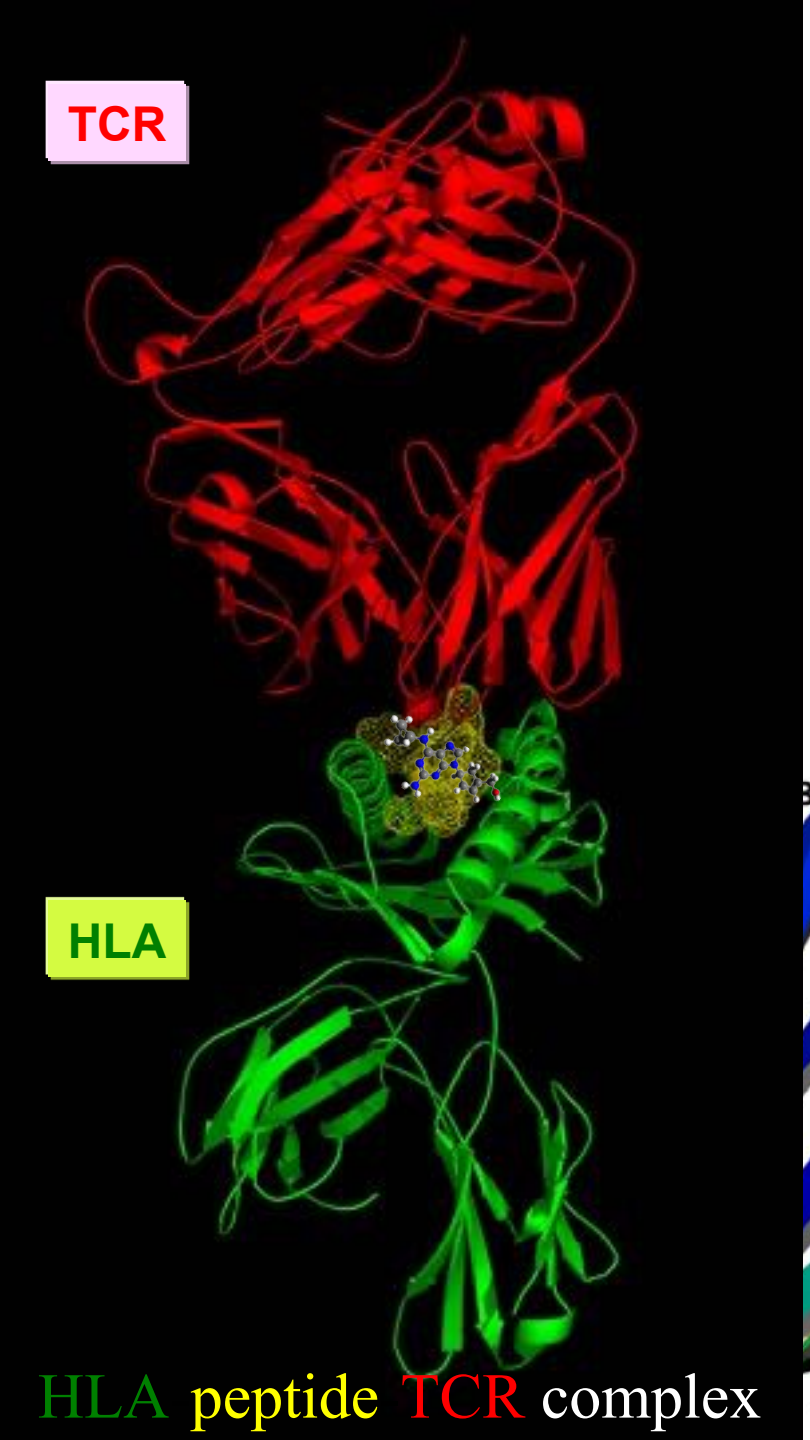
pharmacological interaction with immune receptors

(p-i) concept:

a) the drug binds to the TCR (by non-covalent bonds; not restricted to a HLA-allele)

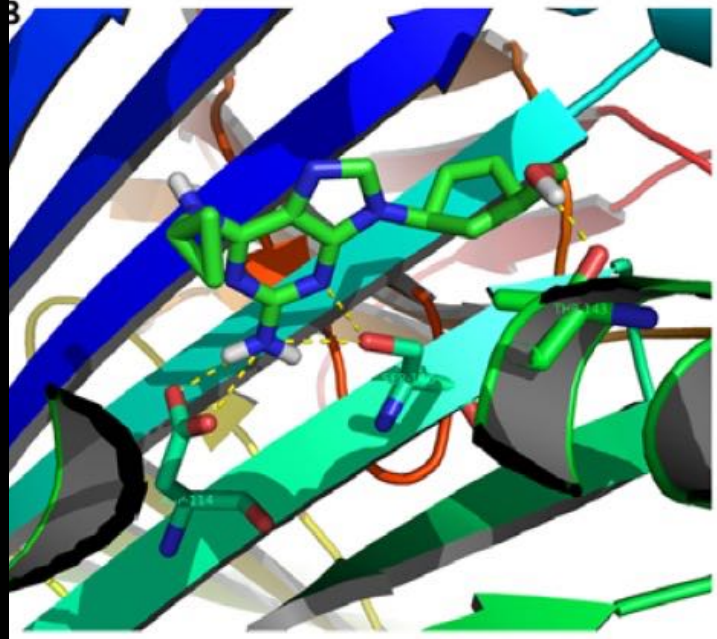
or

b) the drug binds to the HLA molecule, and the HLA-peptide-drug complex is then recognized by the TCR (often HLA-class I restricted, CD8)



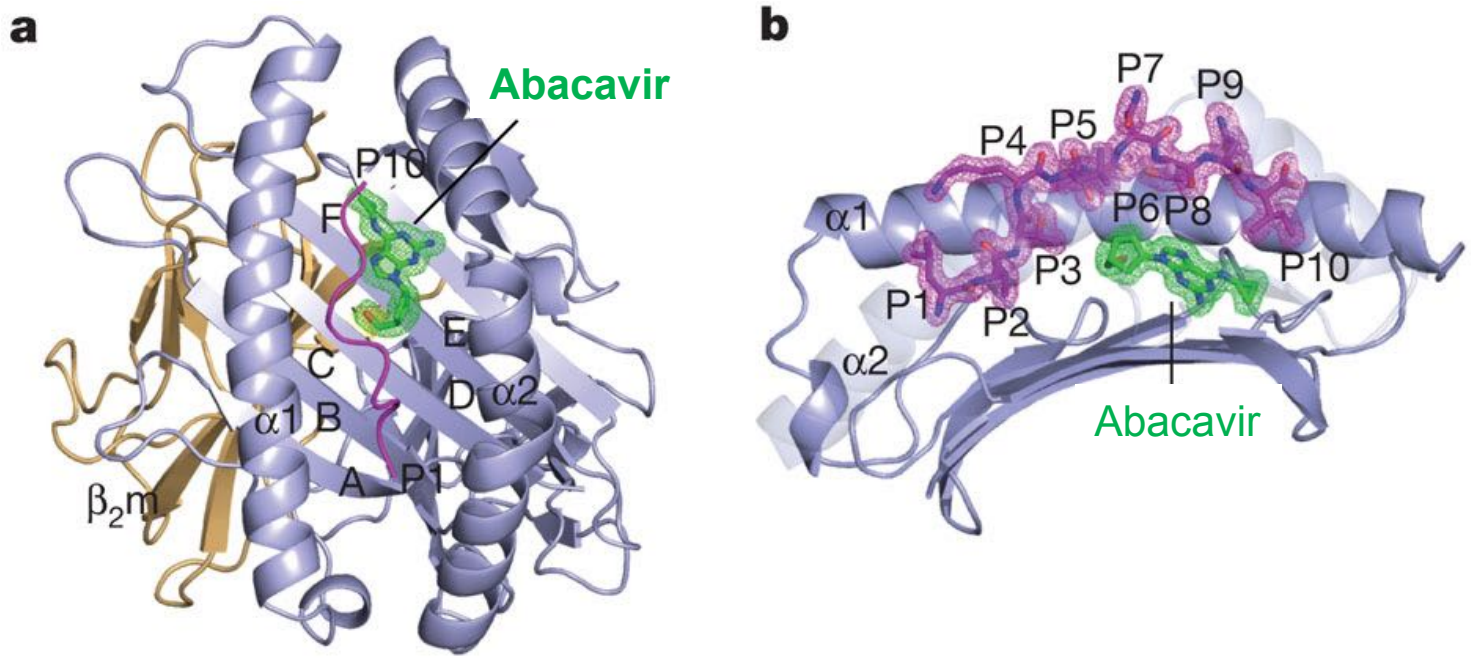
p-i concept: a drug fits into a particular HLA molecule

the drug binds to an allele-typic region in the HLA by van der Waals forces; the HLA-peptide-drug complex is then recognized by the TCR



HLA-B*5701: binding groove for abacavir at position Y116, N114

Altered peptide model

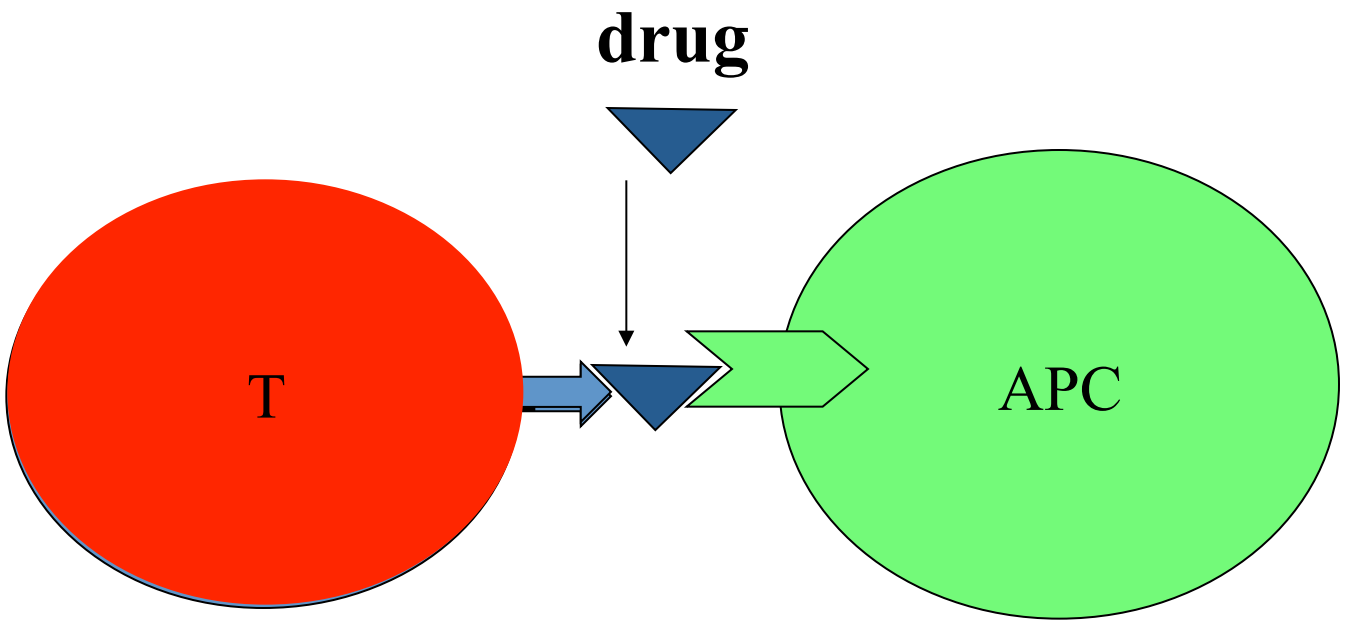


Abacavir (abc) binds to the F-pocket of HLA-B*57:01;

the abc filled F-pocket leads to selection of peptides with valin at position 9 (instead of tryptophan / phenylalanin)

April/May 2012: Illing et al, Nature, Ostrov et al, PNAS, Norcross et al AIDS

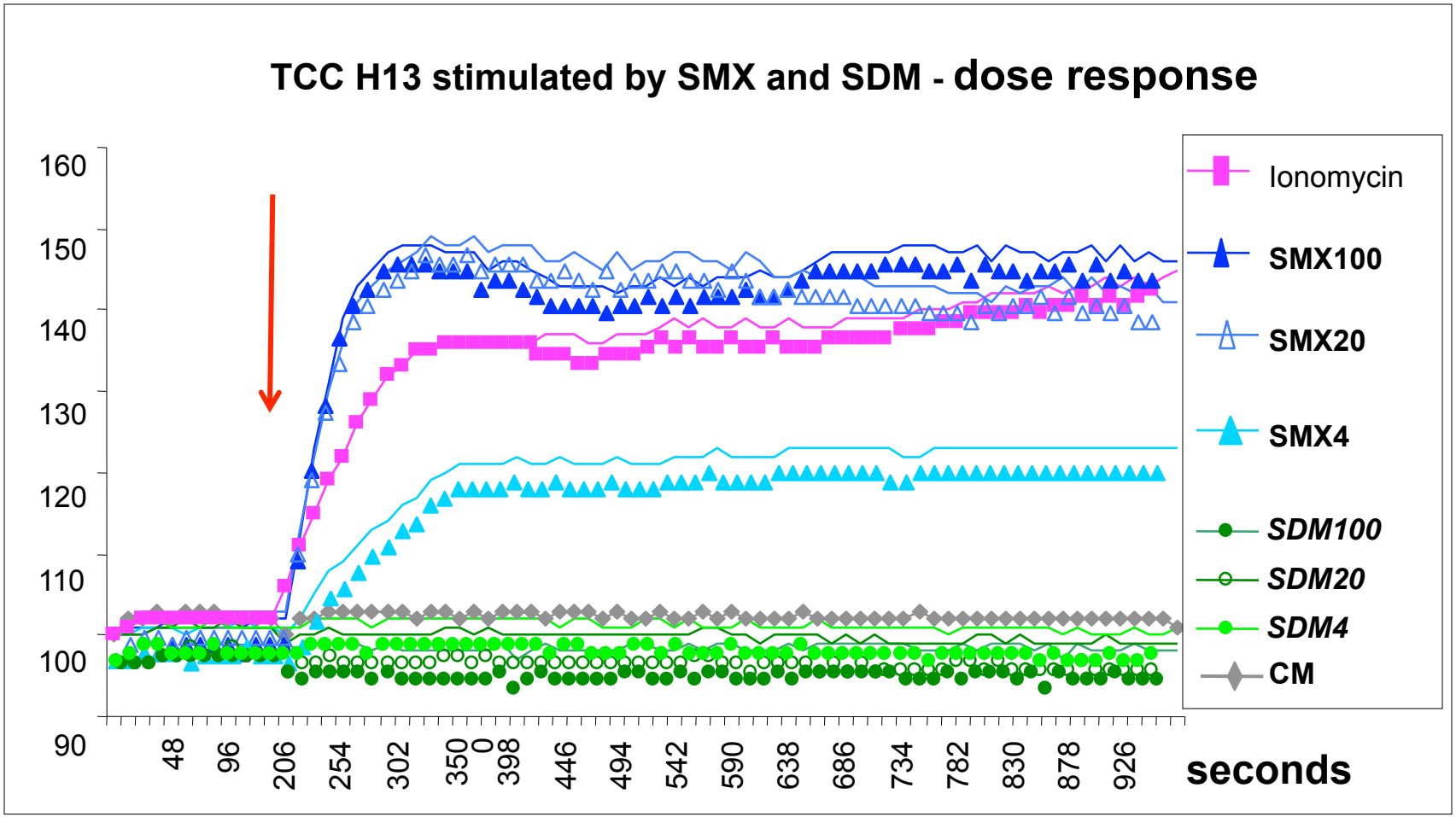
Ca++ influx, a rapid first sign of T cell activation



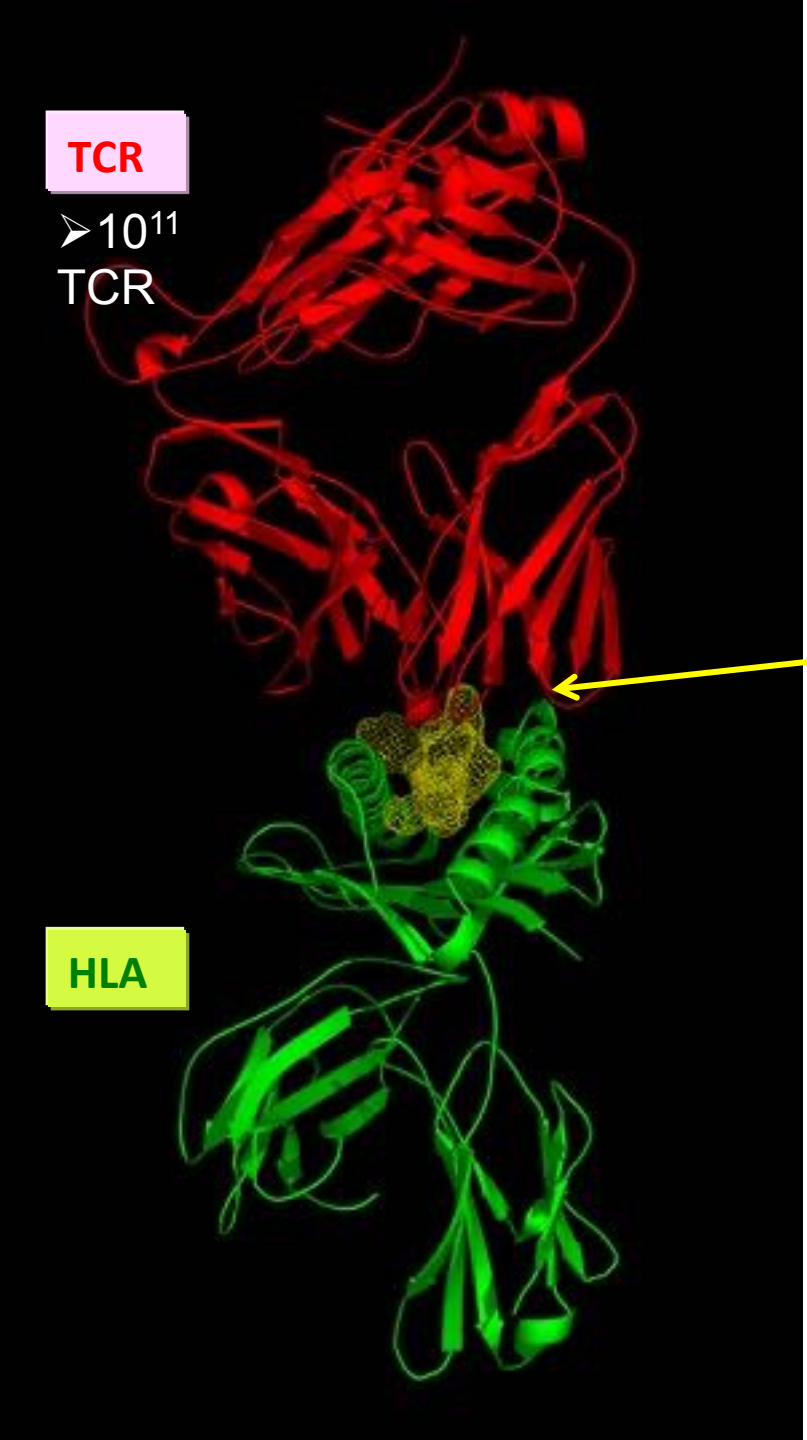
Fura – labelled
drug (abacavir) specific
T-cell (T-cell clone)

APC, presenting
HLA molecuels

SMX-specific CD4+ T cell clone: immediate Ca++ influx to the stimulatory compound



Ca++ influx: SMX (sulfamethoxazole) specific T-cell clone H13 reacts immediately (150sec) and in a dose dependent way to the drug, before uptake, metabolism and presentation can take place



SMX-specific Clone 1.3:

SMX binds to a **unique** site on the CDR3-beta loop of the SMX specific T cell receptor (TCR) 1.3

Conclusion

drug allergy is **not** following the rules of an immune response……

→ **drug hypersensitivity is no allergy !**

Conclusion

→ **drug hypersensitivity is no allergy !**

TAKE HOME

Drug hypersensitivity is a pharmacological "off target" activity of the drug on immune receptors, which elicits an *uncontrolled* immune reaction. The polymorphismus of the immune receptors explains the selective occurence in some individuals only.

MESSAGE

p-i and risk assessement

- Is the drug binding to one of the >7400 HLA alleles ?
  - binding to the HLA-protein (biacore...)
  - binding and **functional** consequence: T cell assays
- Is the drug binding to some of the $>10^{11}$ TCR ?
  - functional assays needed
- Is the drug binding to TCR **&** HLA ?
- Role of peptide ?

Thanks

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