Pathomechanism of Severe Drug Allergy

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Severe drug allergy

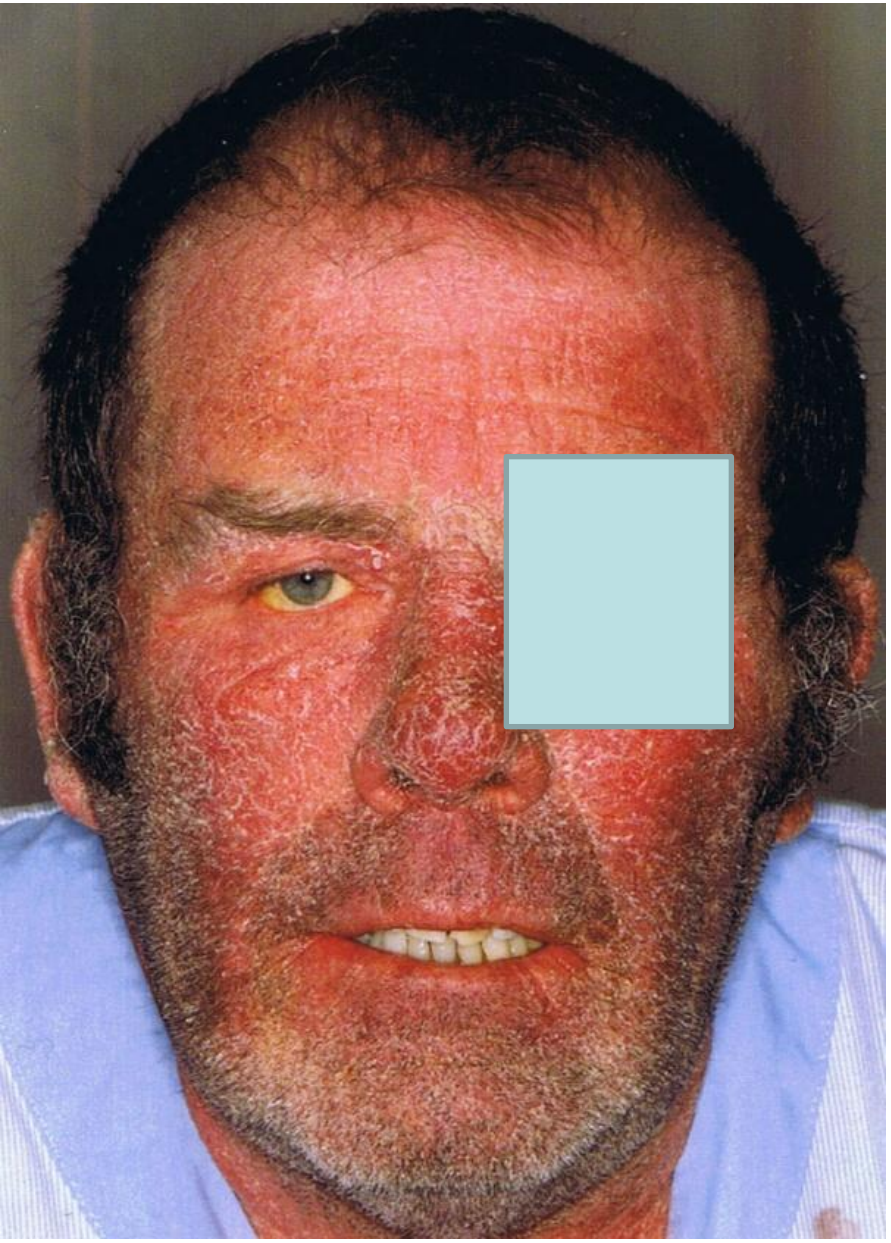
- **Type I, IgE:** **Anaphylaxis**
- **Type II, Ab & FcR** **Blood cell dyscrasia**
- **Type III, immun-complexes, Fc & C`** **Vasculitis**
- **Type IV T cells** **T cell orchestrated inflammations, all organs**

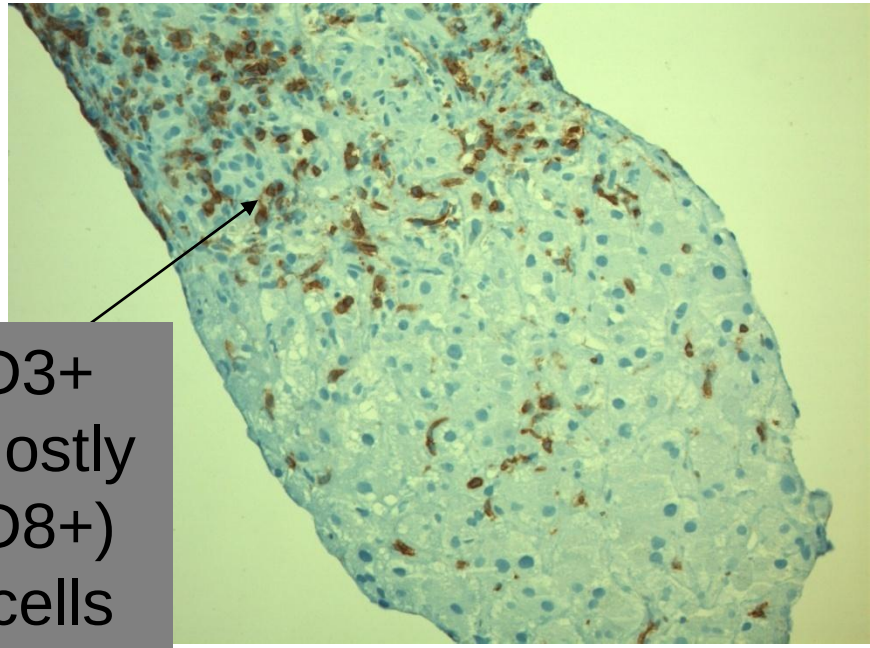
Delayed T-cell mediated drug hypersensitivity

- Maculopapular exanthema
- acute generalized exanthematous pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS), toxic-epidermal necrolysis (TEN)
- interstitial pneumonitis
- interstitial nephritis
- Hepatitis
- DRESS

6 yr old girl, epilesy (Carbamazepin for 3 weeks)

60 yr old man with fatal DRESS (fulminant hepatitis, liver transplantation, death)





CD3+ (mostly CD8+) T-cells

Severe systemic reactions

DRESS

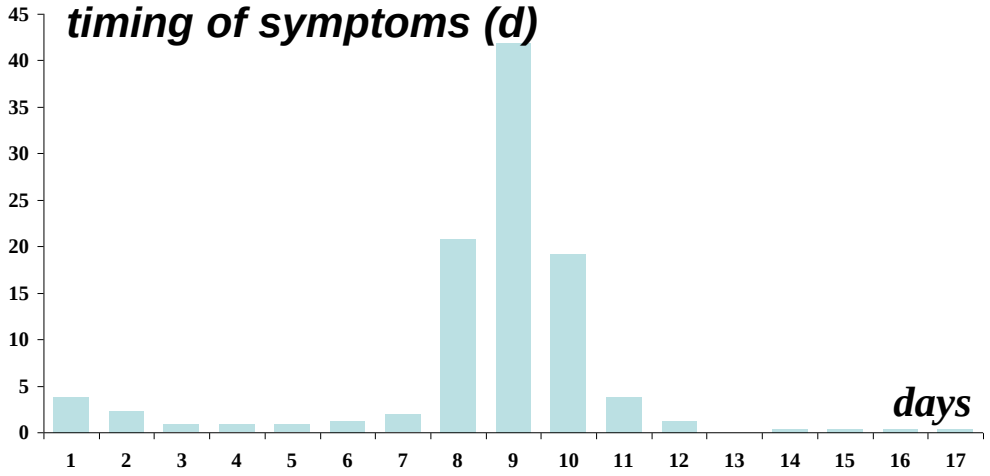
DRESS and haematophagocytic syndrome

Toxic epidermal necrolysis

~ 10% letality

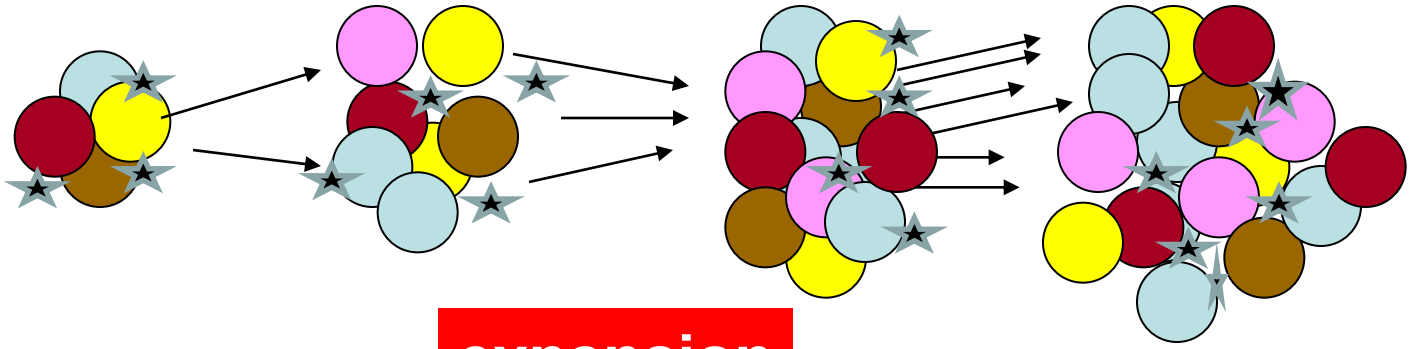
34% letality

Late Reaction



1 2 3 4 5 6 7 8 9 10 **days**

asymptomatic symptoms



expansion

Very few precursor cells

After a certain amount of **T-cells** is reached, symptoms of drug hypersensitivity develop

Late reactions

When does it start?

- **1-3d** (if very, very strong sensitization)
- **8-10d** (in maculopapular reactions)
- **14->56d** (in SJS, DRESS, hepatitis, ...)

Drug hypersensitivity
- patho-physiology -

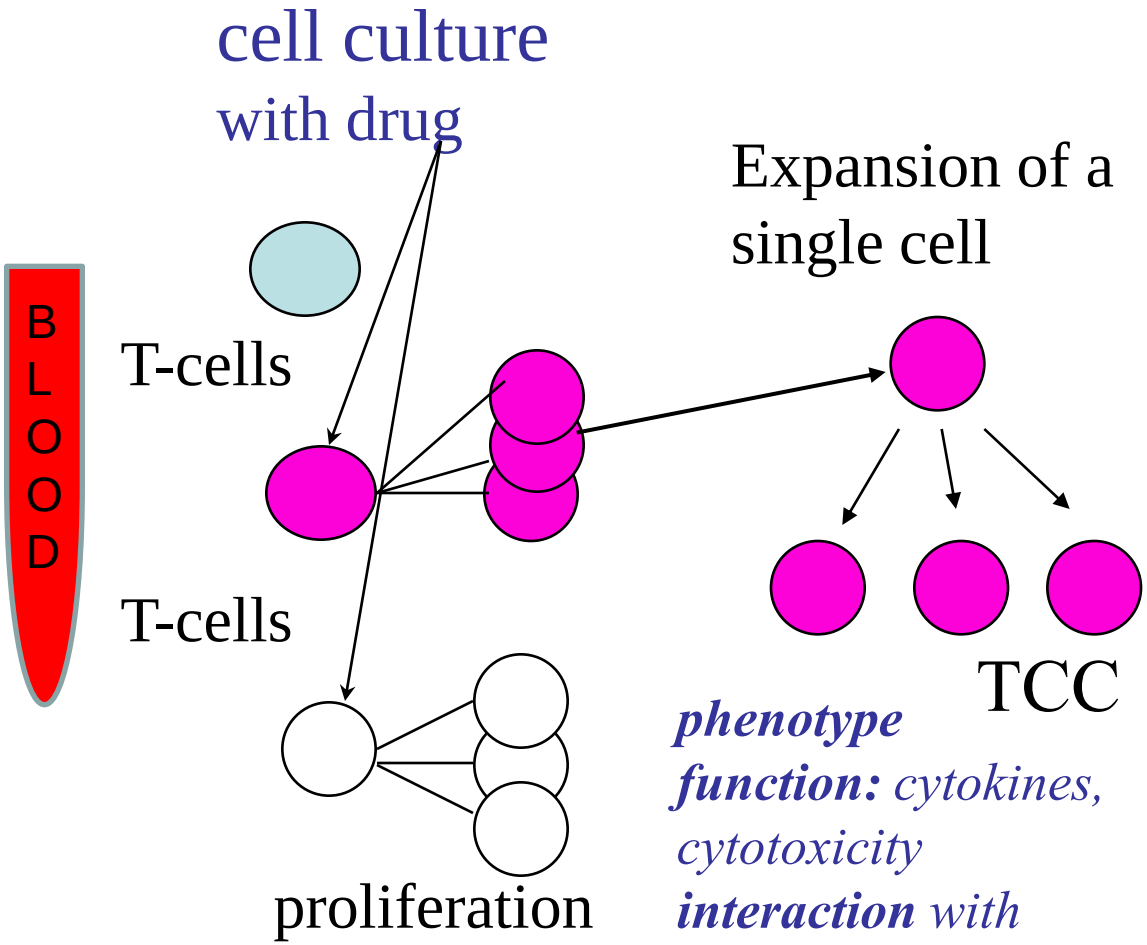
Two questions

- ***How can one explain the heterogeneity of drug allergic diseases ?***

- ***How are T cells stimulated by drugs ?***

(T cells were found to be crucial)

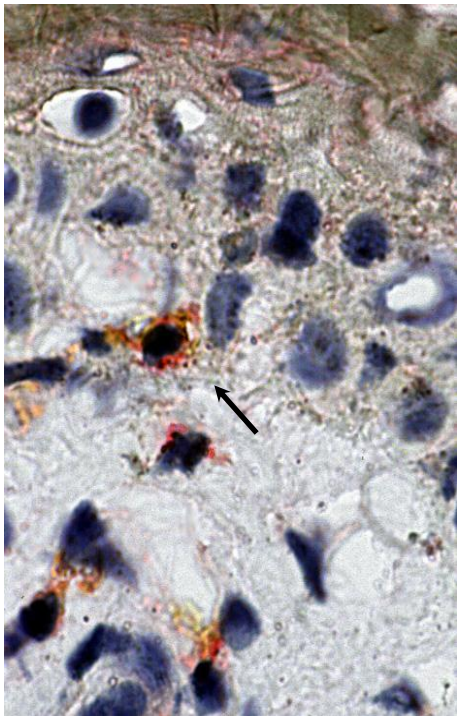
Drug specific T-cell clones (TCC) *from blood and tissue*



phenotype
function: *cytokines, cytotoxicity*
interaction *with APCs, tissue cells*
drug recognition
cross-reactivity
TCR structure

in vitro

Immunohisto-chemistry



Perforin - CD4
red - brown

ex vivo

T-cells react with the drug and exert, dependent on their function, a certain pathology

bullous E.

MPE

AGEP

T-cells react with the drug and exert, dependent on their function, a certain pathology

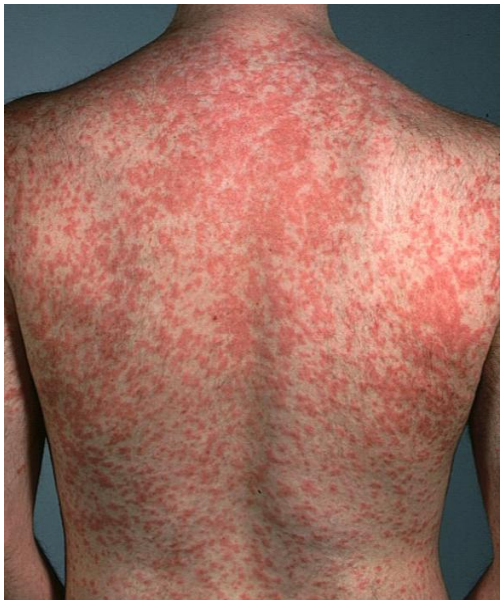
Amoxicillin

bullous E.

cytotoxicity (CD8+)
IFNγ; IL-5

MPE

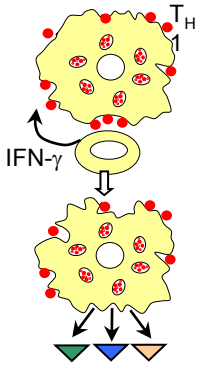
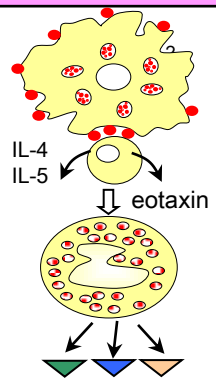
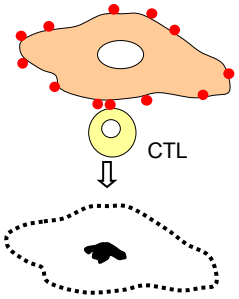
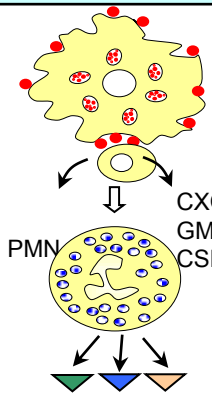
cytotoxicity (CD4+)
IL-5; IFNγ



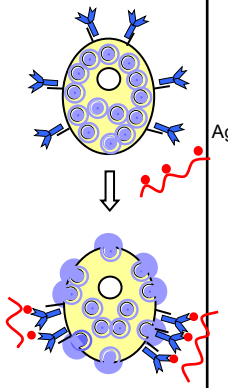
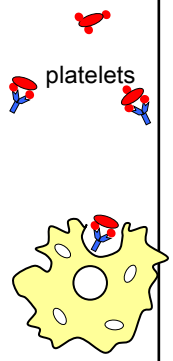
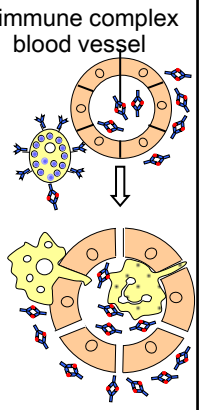
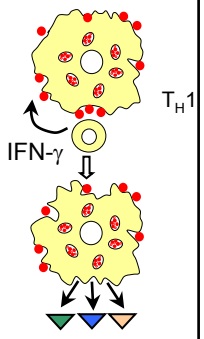
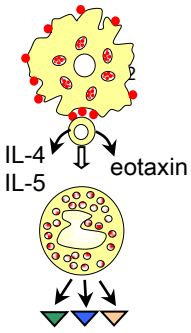
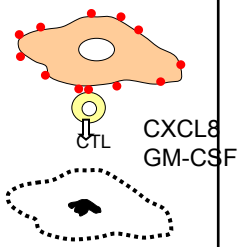
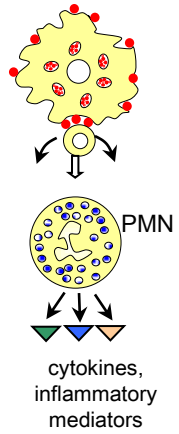
AGEP

cytotoxicity
IL-8; IL-5

Delayed hypersensitivity reactions type IV a, IV b, IV c, IV d

	Type IV a	Type IV b	Type IV c	Type IV d
Immune reactant	IFNγ, TNFα (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ GranzymeB (CTL)	CXCL-8. GM-CSF (T-cells)
Antigen	Processed antigen or direct T cell stimulation	Processed antigen or direct T cell stimulation	Processed antigen or direct T cell stimulation	Processed antigen or direct T cell stimulation
Effector	Macrophage	Eosinophils	T cells	PMN
	 chemokines, cytokines, cytotoxins	 cytokines, inflammatory mediators	 perforin/ granzymeB	 cytokines, Inflammatory mediators
Example of hypersen-sitivity reaction	Tuberculin reaction, Contact dermatitis,	maculo-papular exanthema with eosinophilia, atopic dermatitis chronic asthma, chronic allergic rhinitis	Contact dermatitis Macolopapular and bullous exanthema, AGEP	AGEP; Behçet diseae

Antibody mediated hypersensitivity reactions (I-III) and delayed type hypersensitivity reactions (IV a-d)

	Type I	Type II	Type III	Type IV a	Type IV b	Type IV c	Type IV d
Immune reactant	IgE	IgG	IgG	IIFNγ, TNFα (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ GranzymeB (CTL)	CXCL-8. GM-CSF (T-cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector	Mast-cell activation	FcR^+ cells (phagocytes, NK cells)	FcR^+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Example of hypersen-sitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin) thrombocyto-penia haemolyt.anae mia	Serum sickness, Arthus reaction	Tuberculin reaction , contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema hepatitis	AGEP Behçet disease

How are T cells stimulated by drugs ?

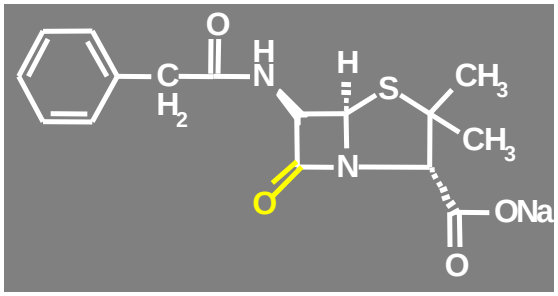
The p-i concept

pharmacological interaction with immune receptors

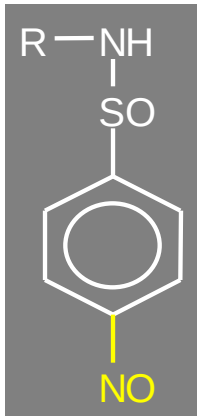
The ***hapten concept***

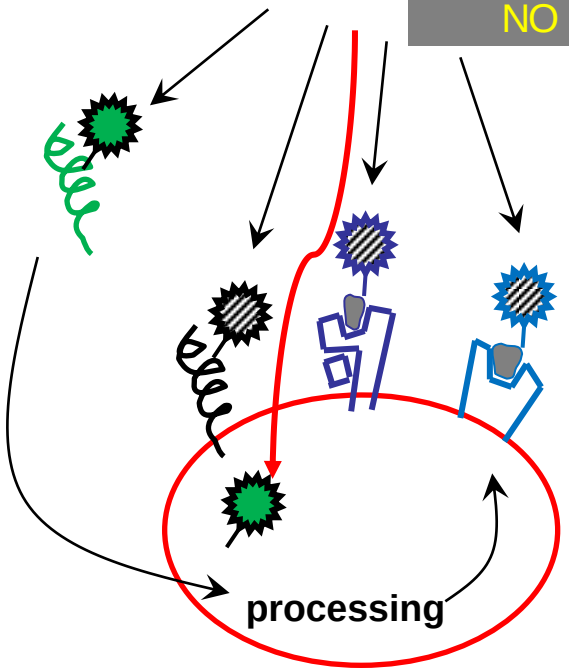
Hapten/prohapten specific immunity

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)

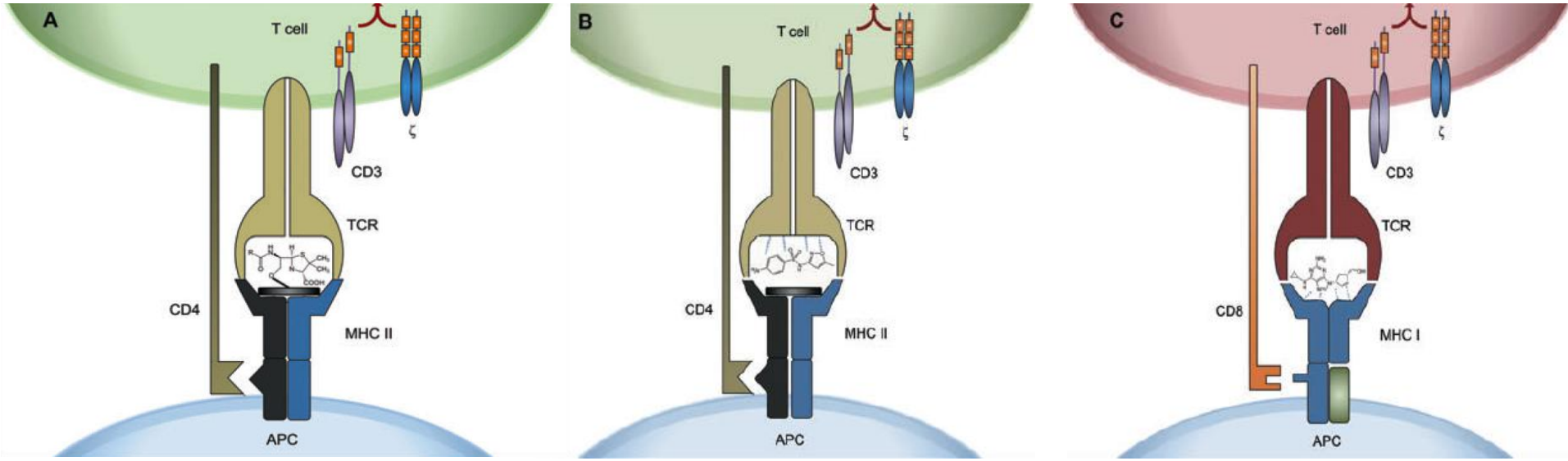
Adduct formation forms neoantigenic determinants able to induce both a **T-cell** and **B-cell** immune response. A hapten stimulates both, T-cells and B-cells !!

The p-i concept
Pharmacological Interaction with Immune Receptors I

A chemically inert drug, unable to covalently bind to proteins, „happens“ to bind (via hydrogen bonds, electrostatic interactions,...) to some of the many immune receptors (as it does to other proteins/receptors). This drug-receptor interaction can occur with TCR ($10x10^{11}$/individual) or to certain HLA molecules (>7400/population).

p-i concept

(pharmacological interaction with immune receptors)



hapten concept

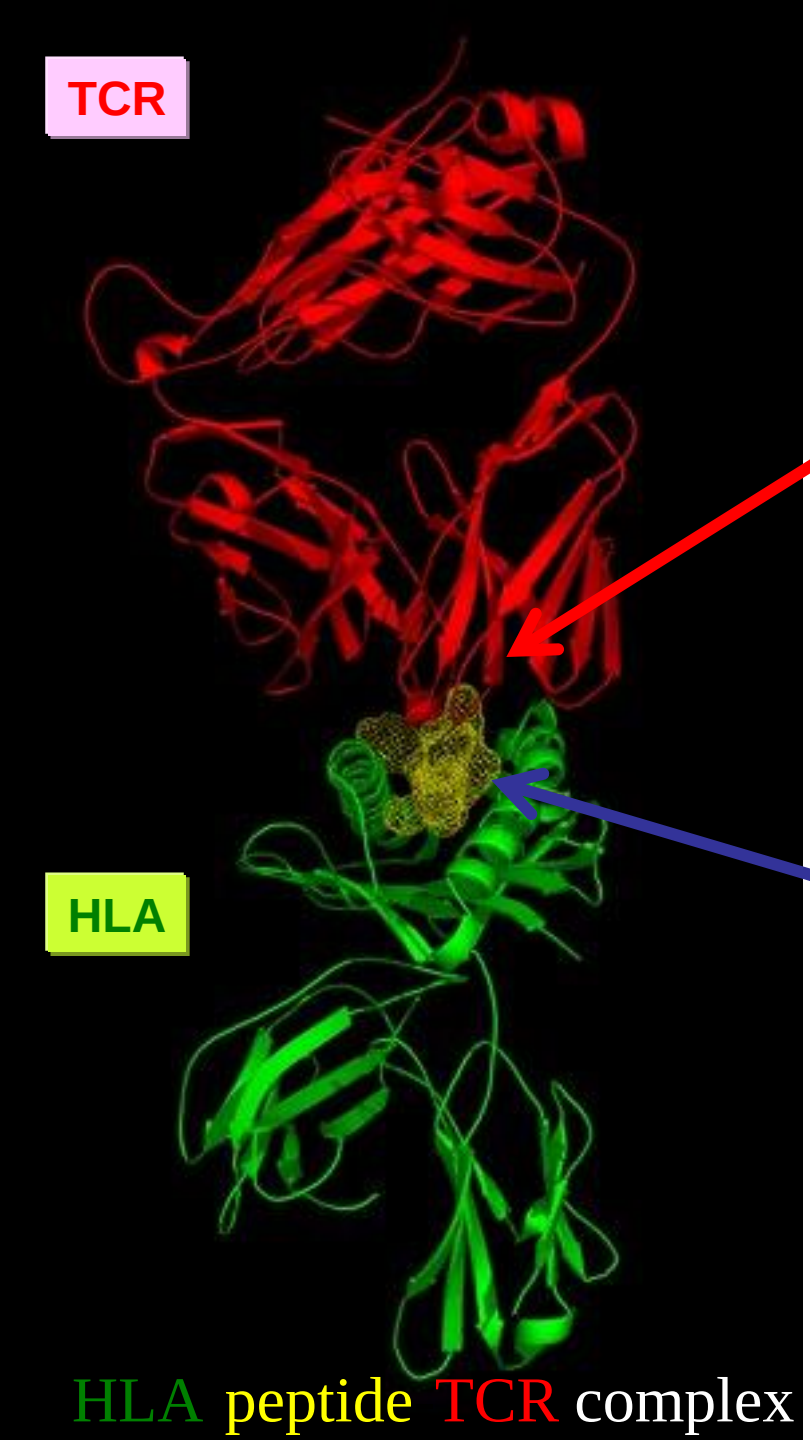
p-i-concept

Antigenic hapten-carrier complexes induces T cell responses

Drugs bind directly…

B) to the TCR

C) to the MHC

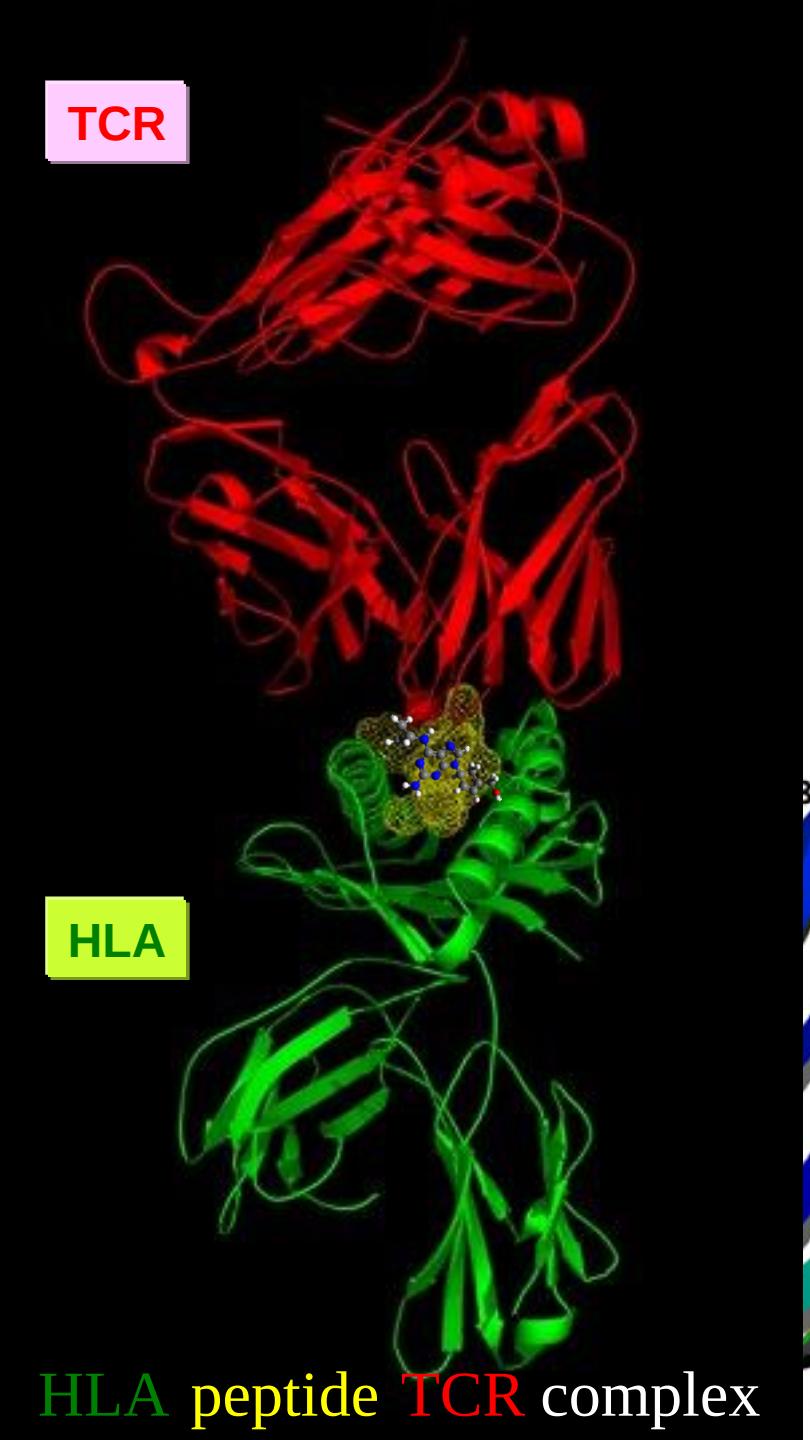


p-i concept:

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

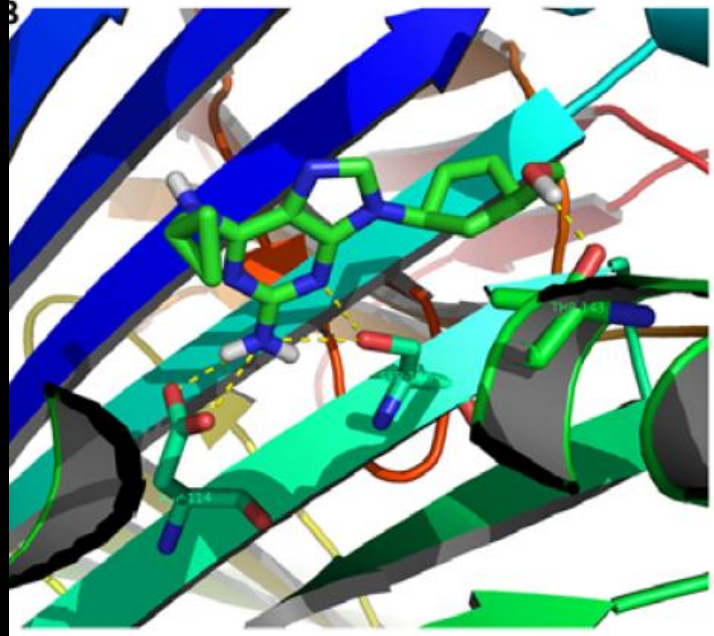
or

b) the drug binds to the HLA molecule, and the HLA-peptide-drug complex is then recognized by the TCR (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;
van der Waals forces;
the HLA-peptide-drug complex is then recognized by the TCR



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

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						13
Allopurino		1-6% Caucasian				50
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 allele / individual

> 7400 HLA alleles in human population

some allele the same, some are different

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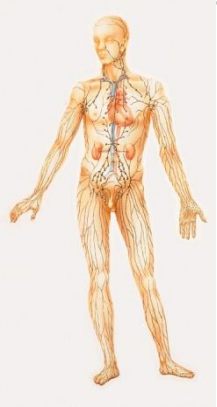

HLA
- A***02:01**, *A* 51:01*
- *B*10:02; B*57:01*
- C* **02:01**; *C*06:01*
- DR* **B1 01:01**; *04:02*
- *DR** **B5 01:01**
- *DP* 04:04; 08:01*
- *DQ* 01:05; 05:01*

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HLA
- A***02:01**, *A* 56:01*
- *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 allele are frequent, some are rare

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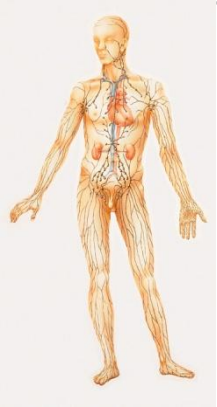

HLA

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→ Risk for Abacavir hypersensitivity

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HLA

- A***02:01**, *A* 56:01*
- *B* **15:02; B*58:01***
- C* **0201**; *C*06:01*
- DR* **B1-01:01**; *04:02*
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- *DP* 03:04; 07:01*
- *DQ* 02:04; 03:02*

→ Risk for Allopurinol Hypersensitivity

→ Risk for Carbamazepine hypersensitivity

The p-i concept
Pharmacological Interaction with Immune Receptors II

The drug interaction with HLA molecules is often involving certain HLA-alleles – which explains the HLA association of some drug hypersensitivity reactions (abacavir, carbamazepine, allopurinol, flucloxacillin,...).

- **The drug binding may alter the HLA-peptide complex or exchange the peptide presented: this stimulates an auto(peptide) or allogeneic immune response.**

or

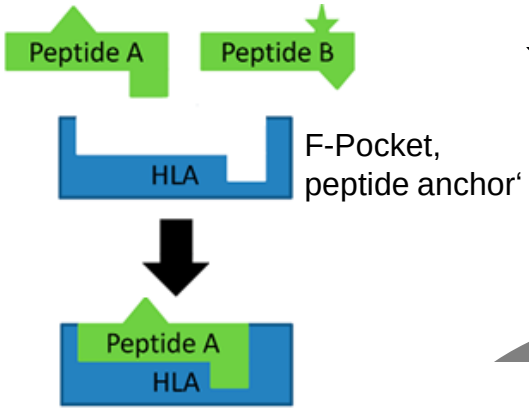
- **The drug binds to the variable region of the TCR. This enhances the interaction of TCR with certain peptide - HLA complexes and elicits reactions similar to superantigen stimulations.**

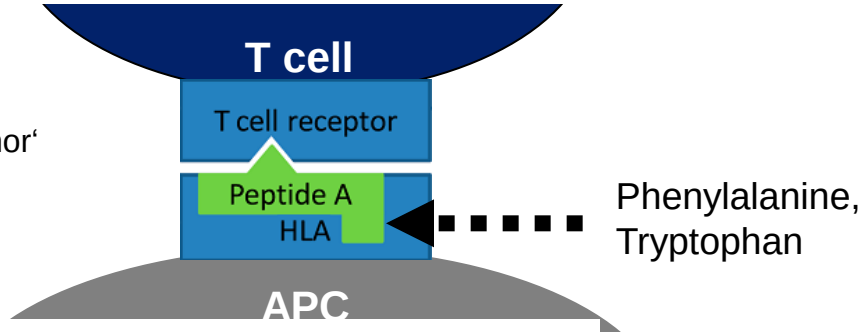
Drug binding to HLA: Altered self peptide repertoire

or

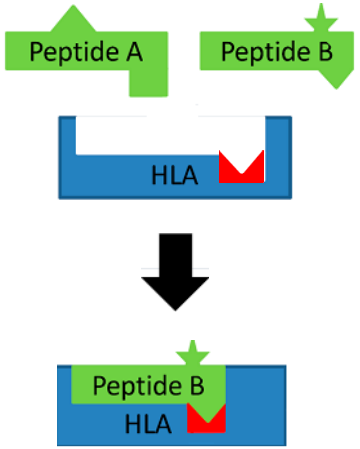
changed HLA-peptide shape

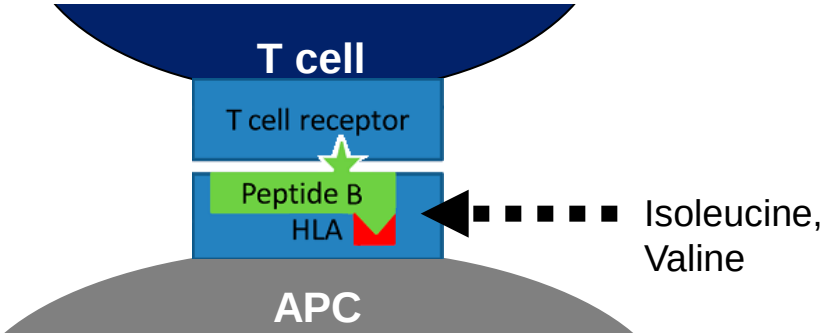
w/o abc





with abc

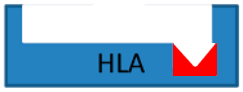


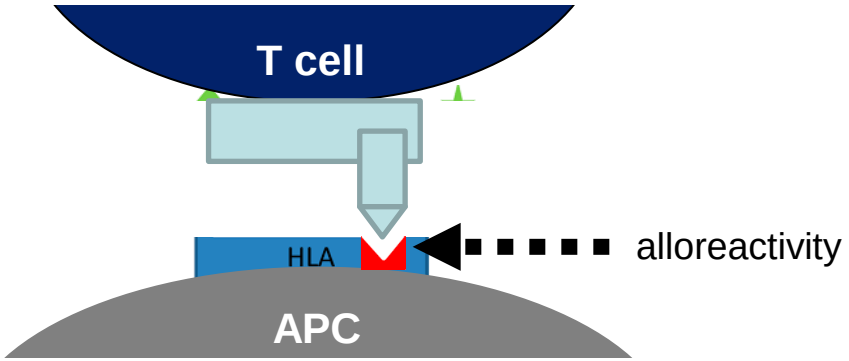


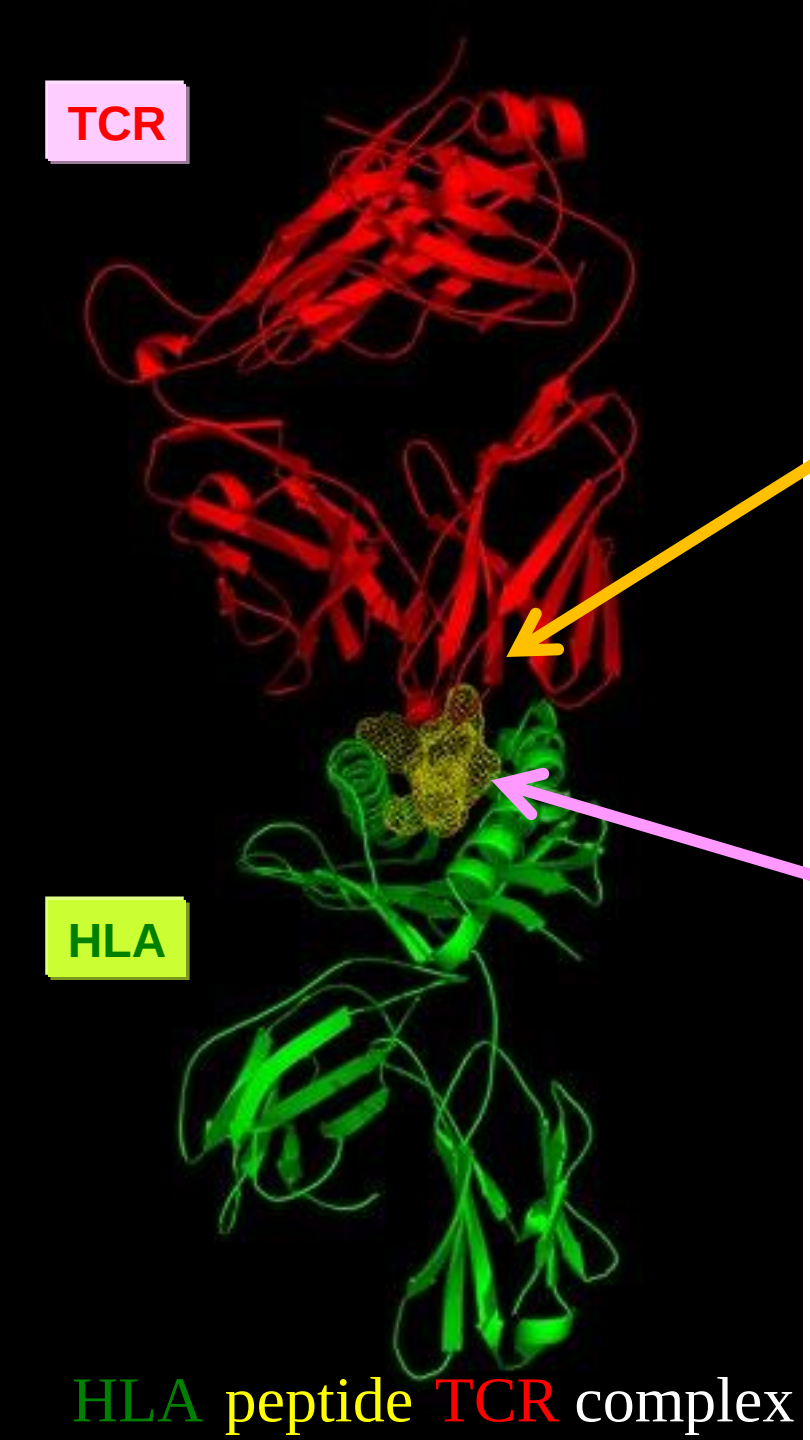
Adapted from Ostrov et al., Proc Natl Acad Sci. 2012 May 29

Drug binding to HLA: Altered self peptide repertoire or changed HLA-peptide shape (alloreactivity)

with abc



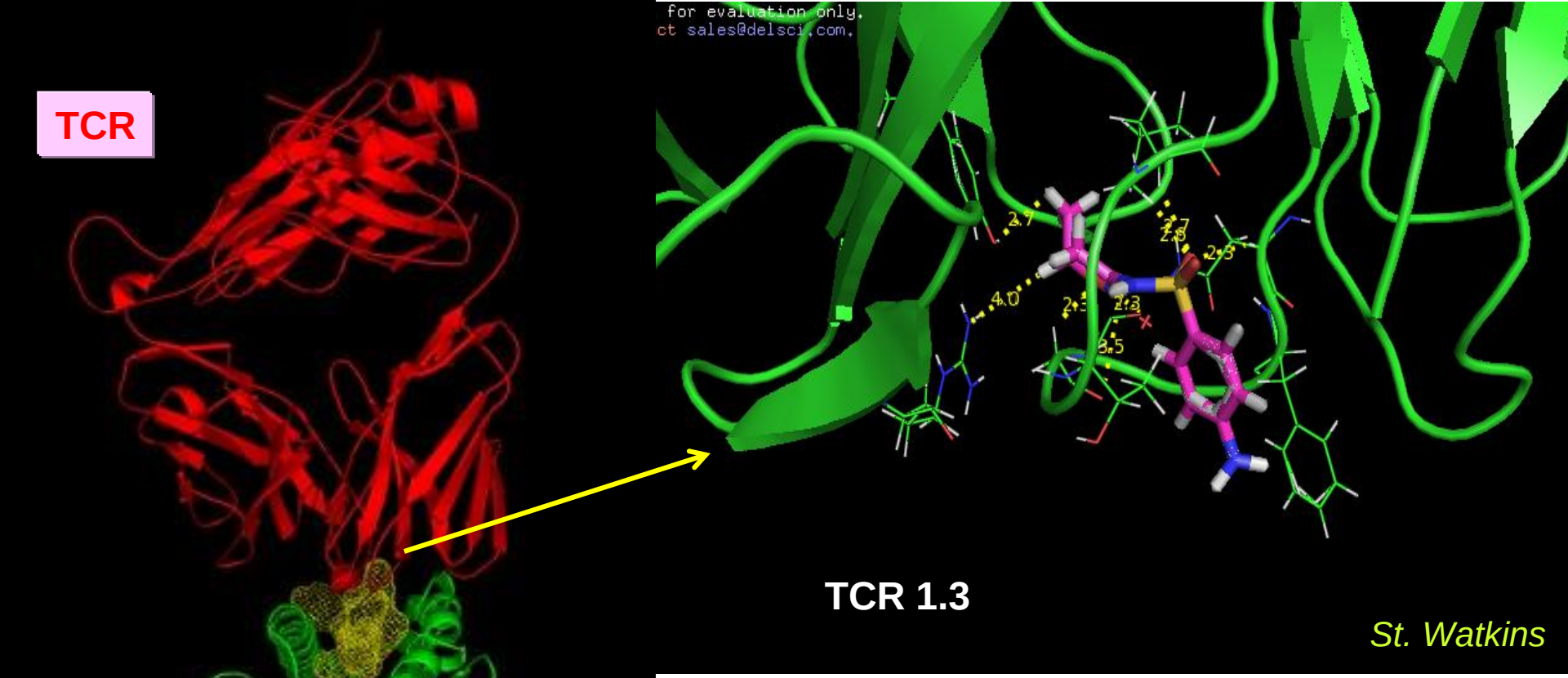




p-i concept:

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

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



SMX-specific Clone 1.3:

SMX binds to the beta loop of CDR3 (TCR)

p-i concept: some clinical mysteries are solved

- *clinical manifestations of DH and skin tests to inert compounds*
- *rapid appearance without prior sensitization*
- *uncontrolled (superantigen like) reactions (SJS/TEN, DRESS)*
- *HLA associations*
- *gvhd like clinical features*
- *drug induced autoimmunity*

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??? (1)

- **Are (delayed) skin tests positive in p-i stimulations ?**

  Yes, sometimes they are only positive in p-i stimulations, as the metabolism required for hapten formations is absent in the skin but the reactive cells are present

- **Are p-i stimulations „sensitizations“ (= complex immune responses) ?**

  not really, but they can cause expansions of T cells reacting with the drug, which later fullfill effector functions

- ***Are drug reactive T cells „specific“ for the drug and do they undergo selection in the thymus?***

  No, the drug reactive cells are not „specific“ for the drug, but are actually specific for a peptide antigen (and selected for peptide reactivity in the thymus); they often show some alloreactivity

??? (2)

- **Are p-i stimulated T-cells persisting (memory)?**

  Yes, the reactive T cells seem to persist for many years.
- **Which stimulations are more frequent, (pro-)hapten or p-i:**

  in contact dermatitis probably hapten, in generalized drug reactions probably p-i.
- ***Are p-i stimulations relevant for severe drug reactions:***

  yes, cytotoxic T cells from blister fluids of SJS/TEN patient were p-i reactive. P-i clones were also seen in DRESS/DiHS, AGEP, MPE, contact dermatitis.
- ***Are p-i reactive T cells cytotoxic, or IFNγ producing or IL-5 producing...***

  yes, the function is as broad as the one of hapten stimulated T cells. It is as variable as the peptide specific T cell immune response.