Pharmacological Interaction of Drugs with Immune Receptors: The p-i Concept

Werner J Pichler¹, Andreas Beeler¹, Monika Keller¹, Marianne Lerch¹, Sinforiano Posadas¹, Daphné Schmid¹, Zoi Spanou¹, Anna Zawodniak¹ and Basil Gerber¹

ABSTRACT
Drug-induced hypersensitivity reactions have been explained by the hapten concept, according to which a small chemical compound is too small to be recognized by the immune system. Only after covalently binding to an endogenous protein the immune system reacts to this so called hapten-carrier complex, as the larger molecule (protein) is modified, and thus immunogenic for B and T cells. Consequently, a B and T cell immune response might develop to the drug with very heterogeneous clinical manifestations.

In recent years, however, evidence has become stronger that not all drugs need to bind covalently to the MHC-peptide complex in order to trigger an immune response. Rather, some drugs may bind directly and reversibly to immune receptors like the major histocompatibility complex (MHC) or the T cell receptor (TCR), thereby stimulating the cells similar to a pharmacological activation of other receptors. This concept has been termed pharmacological interaction with immune receptors the (p-i) concept. While the exact mechanism is still a matter of debate, non-covalent drug presentation clearly leads to the activation of drug-specific T cells as documented for various drugs (lidocaine, sulfamethoxazole (SMX), lamotrigine, carbamazepine, p-phenylendiamine, etc.). In some patients with drug hypersensitivity, such a response may occur within hours even upon the first exposure to the drug. Thus, the reaction to the drug may not be due to a classical, primary response, but rather be mediated by stimulating existing, pre-activated, peptide-specific T cells that are cross specific for the drug. In this way, certain drugs may circumvent the checkpoints for immune activation imposed by the classical antigen processing and presentation mechanisms, which may help to explain the peculiar nature of many drug hypersensitivity reactions.

KEY WORDS
drug hypersensitivity, hapten, p-i concept, prohapten, T cells, T-cell receptor

INTRODUCTION
Modern medicine is based on a thorough understanding of the pathophysiological basis of diseases. Therapeutic interventions often rely on chemicals (xenobiotics) which may enhance or block a certain function of cells or proteins and may thus have a beneficial effect. The confrontation with such xenobiotics is not novel for humans and animals, as plants contain many chemicals. Some plants have even been used for therapeutic purposes for many centuries in the form of phyotherapy. However, the amount and variety of drugs to which we are exposed has surely changed in the last century, where thousands of newly synthesized and pure drugs entered and conquered the market, as some proved to be very efficient for various purposes.

One could argue that the human race is not well prepared to handle this high amount of xenobiotics to which we are exposed in modern life—as such an artificial intervention was not foreseen in evolution. Indeed, adverse side effects to drugs are a common incidence in the clinical practice. Most reactions are caused by the pharmacological or toxicological activities of the drug and are generally predictable (type A). However, non-predictable, idiosyncratic (type B) reactions¹ ² may occur as well, amounting to about 16% of all cases. Most of the type B reactions are con-
Table 1  The p-i-concept: arguments pro and contra

<table>
<thead>
<tr>
<th>PRO</th>
<th>CONTRA</th>
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<tr>
<td><strong>Clinical:</strong></td>
<td>Clearly established for chemically reactive drugs</td>
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<tr>
<td>Appearance at the first encounter with the drug</td>
<td>10-12,16,17</td>
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<tr>
<td>Positive skin tests with drugs gaining immunogenicity by metabolism in the liver</td>
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<tr>
<td>Hypersensitivity reactions to drugs without known metabolism</td>
<td>36,37</td>
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<tr>
<td><strong>Immunological/pharmacological:</strong></td>
<td>Strong associations between several MHC I alleles and drug hypersensitivity</td>
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<tr>
<td>Glutaraldehyde-fixed APC can still present drug</td>
<td>38</td>
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<tr>
<td>Washing removes drug and prevents T cell activation</td>
<td>39</td>
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<tr>
<td>Kinetics of TCR downregulation too fast to allow antigen processing</td>
<td>40</td>
</tr>
<tr>
<td>Kinetics of Ca2+ mobilization too fast to allow antigen processing</td>
<td>41</td>
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<tr>
<td>Inhibition of SMX-NO generation by glutathione increases drug presentation</td>
<td>42</td>
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<tr>
<td>High incidence of unrestricted, drug-reactive clones</td>
<td>43</td>
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<tr>
<td>Elevated frequency of alloreactive drug-reactive clones compared to peptide-specific TCC</td>
<td>44</td>
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<tr>
<td>Exchange or removal of MHCII-associated peptides does not affect drug presentation</td>
<td>45</td>
</tr>
<tr>
<td>Kinetics of ERK phosphorylation too fast to allow antigen processing</td>
<td>46</td>
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Of crucial importance is the way how T cells are stimulated by drugs. During the last years, our group has investigated this problem in detail and we have reached some surprising conclusions. In particular, we proposed a new model, termed pharmacological interaction with immune receptors (p-i) concept. This model could explain some peculiar features of drug allergies and would have a major impact on predictive tests.

**THE HAPTEN AND PROHAPTEN CONCEPT**

An immune reaction starts with the involvement of the innate immune system. The antigen (bacteria, virus, etc.) stimulates the innate immune system via e.g. Toll like receptors (TLR) on dendritic cells, thereby setting an initial alarm signal. The activated dendritic cells function as antigen-presenting cells (APC) as they take up and process complex and larger antigens, which subsequently are presented as peptides to T cells in a suitable environment, mainly the lymph nodes. The ensuing immune response is variable and efficient, as different antigens like soluble or cell bound viral antigens elicit a distinct immune response, capable to eliminate the infectious agent.

Small low-molecular weight compounds (MW < 1000D) are thought to be too small to elicit such an immune response per se. Nevertheless, small compounds such as drugs or metal ions have been found to be able to trigger an immune response.1-3 The hapten (and pro-hapten) model has been developed and is currently the accepted explanation for these observations: Chemically reactive, small compounds (=haptens) bind to proteins or peptides and modify them.10-12 Thus, these haptens have two features essential for triggering an immune response:

a) they may stimulate the innate immune system by covalently binding to cellular proteins, thereby transmitting a danger signal, which results in stimulation of cells of the innate immune system.13,14 Or, as shown for imiquimod, they may happen to bind to TLR7 & 8 directly and thus stimulate dendritic cells.15

b) they may stimulate the specific immune system: By forming hapten-carrier complexes they form neo-antigens. The hapten-protein complexes are proc-
The p-i Concept

![Diagram of T cell interaction]

**Fig. 1** A comparison of different small antigens stimulating T-cells via the hapten, a hapten-like and the p-i mechanism. Penicillin, nickel ions (black ball), and SMX serve as the respective examples. Strong, covalent bonds between the antigens and the MHC and the TCR are indicated by solid lines, while weaker, noncovalent interactions are depicted as dashed lines. For haptens, the majority of the antigen-binding energy stems from the interaction with the MHC-peptide complex via few but strong covalent bonds (hapten; note that certain haptens may be strongly associated not only with the MHC but the TCR as well). Ni may interact either like a non-covalent hapten, or as depicted here, forming equally strong, non-covalent interactions with both MHC and TCR (nickel), while at least some drugs would derive the majority of their binding energy from weak, non-covalent interactions with the TCR (p-i-concept). These different modes of interaction represent a continuum of possibilities, with the (pro)hapten mode on one extreme of the spectrum, the p-i-concept mode representing the other extreme, and the Ni mode as an intermediate possibility.

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Cloned drug-specific T cells can be generated from patients with drug allergy. Some drugs appear to be able to stimulate an apparently specific immune response to a drug at the first encounter, before an immune response has had time to evolve. Other reactions seem to occur in less than three days. These time intervals seem too short to mount a specific immune response.

Some drugs causing delayed hypersensitivity reactions are not known to be metabolized to a chemically reactive compound: e.g. contrast media can cause delayed, clearly T-cell mediated hypersensitivity reactions in 1–2% of patients exposed to it, often at the first encounter, but no metabolism occurs and no protein binding has been detected. Thus, the hapten concept cannot explain allergic side effects to these drugs.

Many chemically inert drugs, unable to form hapten-carrier complexes in the skin, are nevertheless able to cause positive skin tests with lymphocyte infiltration. It is difficult to imagine that a drug locally applied in an epicutaneous patch tests is transported to the liver, metabolized there and returned to the skin to cause a local reaction there.
paved the way to a better analysis of drug—T cell stimulations: Several observations argue against processing or covalent binding.

1) Only some T cells of a patient with drug hypersensitivity react with the drug. Using TCC, many different, chemically inert drugs were found to be able to stimulate T cells via the TCR in an MHC-dependent way, in particular lamotrigine, carbamazepine, sulfamethoxazole (SMX), mepivacaine, and lidocaine, ciproxin or moxifloxacin, and radio contrast media (RCM).

2) Specific TCC reacted even if the APC were fixed by glutaraldehyde, excluding that either processing or intracellular metabolism is involved.

3) Unlike typical haptons, certain drugs do not require covalent binding. Upon pulsing of APC (incubation of APC with the drug for 1h followed by two washing steps, which remove the drug), no T cell stimulation was observed for lidocaine, lamotrigine, carbamazepine, ciproxin and SMX. SMX has been characterized particularly well, as its reactive metabolite SMX-nitroso (SMX-NO), acting as a typical hapten, was available for comparison. In contrast, the hapten SMX-NO, capable of covalently modifying the MHC-peptide complex, was still able to stimulate hapten-reactive T cells.

4) For a number of drugs, the kinetics of T cell activation are simply much too fast for any involvement of antigen processing. In the presence of APC, lidocaine and SMX activate T cells quasi immediately as revealed by a rapid and sustained intracellular Ca²⁺ increase. It is impossible to reconcile this timing with an intermediate metabolism and processing step, which needs 60 min or longer to occur. Also, the kinetics of TCR down-regulation on drug reactive TCC after encountering the inert drug are similar to the recognition of pre-processed, immunogenic pep-
acted with SMX-NO. The use of inhibitors of me-
nority of TCC derived from SMX-allergic patients re-
covalently modified by SMX-NO. The antioxidant glutathione is known to protect cells from reactive metabolites like SMX-NO by conjuga-
tion and subsequent dissociation to SMX-NHOH and/or SMX.33 In contrast to this concept, only a mi-
nority of TCC derived from SMX-allergic patients re-
acted with SMX-NO.34 The use of inhibitors of me-
tabolism further supported the role of SMX and not of SMX-NO: Addition of glutathione to peripheral blood mononuclear cells enhanced rather than reduced the proliferation to SMX-metabolites,35 presumably by transforming SMX-NO back to the “original” antigen, SMX. The response of SMX-NO-specific TCC was abrogated when glutathione was present during the co-
valent modification of antigen presenting cells (APC). Collectively, these experiments support the concept that T cells in allergic individuals recognize the non-
covalently bound parent drug SMX rather than APC covalently modified by SMX-NO.34,35

6) Last but not least, drug specific TCC show some peculiar features, reminiscent of superantigen stimulations, but not seen with classical peptide antigens: Many drug-specific TCC were found to be MHC-
unrestricted,36 and the frequency of alloreactive TCC is much higher among drug-
than peptide-specific TCC from the same donor.37 The MHC-bound peptide seems to be irrelevant for SMX-specific T cell activation.38 Lastly, drugs simultaneously elicit a CD4 and CD8 T cell response to the same compound.

T-CELL RECEPTOR TRANSFECTED HYBRI-
DOMA CELLS:
To further study these unusual characteristics of drug-T-cell interactions we recently developed drug-
specific TCR transfectants, which incontrovertibly demonstrated that T-cell activation by drugs is TCR-depen
dent39: Two SMX-specific human TCR were intro-
duced into the mouse T cell hybridoma cell line 54 ζ17 (O. Acuto, Paris, France) according to the

Table 3 Drugs documented to stimulate T-cells via non-covalent binding and corresponding clinical symptoms

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Symptoms</th>
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<tr>
<td>Sulfamethoxazole (SMX)</td>
<td>Maculopapular exanthema25</td>
</tr>
<tr>
<td></td>
<td>Toxic epidermal necrolysis96</td>
</tr>
<tr>
<td>Lidocaine/Mepivacaine</td>
<td>Contact dermatitis &amp; erythema exsudativum multiforme24</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Acute generalized exanthematous pustulosis67</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Drug rash with eosinophilia and systemic symptoms6</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Drug rash with eosinophilia and systemic symptoms7</td>
</tr>
<tr>
<td>Ciproxin</td>
<td>Maculopapular exanthema31</td>
</tr>
<tr>
<td>P-phenylenediamine</td>
<td>Contact dermatitis28</td>
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tides (occurring within the first 30 min), and clearly differ from the recognition of proteins, which requires several hours.26

5) Hypersensitivity to the drug SMX was thought to be a consequence of bioactivation to the hydrox-
ylamine metabolite (SMX-NHOH) and further oxidation to the ultimate, reactive metabolite SMX-NO. While the MHC-peptide complex would not contrib-
tute (much) to the binding energy, it would still be necessary a) for full T cell activation and b) to direct ERK phosphorylation at a target cell. This model has been elucidated for TCR activation in the presence of antigen presenting cells (APC), resulting in IL-2 secretion. These TCR-transfected hybridoma cells behaved like drug-specific TCC, as the drug could be washed away (contrary to hapten co-
valently bound to carrier molecules), the presence of APC (MHC) was required for IL-2 production, and fixed APC were still able to present the drug. Similarly, the kinetics of TCR activation were too fast to involve antigen processing, as antigen-dependent ERK phosphorylation was detected within one minute of SMX exposure.

Since the hapten concept does not suffice any more to account for all the above observations we have re-
cently proposed a third model, which is meant to sup-
plement the hapten/pro-hapten concept.41 TCR activa-
tion would be metabolism- and processing-independent and in fact mimic drug inter-
actions with other, non-immunological receptors. While the MHC-peptide complex would not contrib-
ute (much) to the binding energy, it would still be necessary a) for full T cell activation and b) to direct the cytotoxic immune response at a target cell. This model has been elucidated for TCR, but it is possible that also BCR on B-cells are activated via a similar mechanism.

Why do we think the TCR to be the more likely candidate for drug binding than the MHC, which is the “traditional” antigen-binding receptor? Such a mechanism seems feasible and at least one precedent has already been reported: Divalent Nickel ions (Ni) do not bind to proteins covalently but rather by forming reversible coordination complexes.42 Weltzien and coworkers identified and characterized a HLA-
DR-promiscuous, Ni-specific TCR where Ni interacts
simultaneously with the MHC and TCR by making contacts with a conserved His81 in the HLA-DR α-chain as well as Tyr29 and Tyr94 in CDR1α of the TCR. Thus, Ni forms a bridge between both receptors—much like a superantigen even though requiring idiotypic residues in the TCR.16 Ni has six coordination sites, of which only three are known for this complex at present. Nevertheless, a substantial part of its binding energy will be derived by the (at least) two contacts with the TCR of this complex. In fact, Ni binding may represent a “compromise” between how a typical hapten and a small antigen incapable of covalent binding may interact with the MHC and the TCR (see Figure 1 and legends for a detailed explanation).

It has been known for many years that drugs can activate receptors that have peptides or proteins as endogenous receptors, the classical example being the opiate alkaloids. For these as well as many other serpentine receptors, a myriad of compounds are known to bind to these receptors and evoke many pharmacologically different responses. More recently, non-peptide agonists have also been found for tyrosine kinases as well as growth factor and cytokine receptors.43 αβ TCR are peptide receptors. However, apart from a hydrophobic cleft between the CDR3α and CDR3β regions, the TCR does not feature a “suitable” binding pocket or groove for small molecular weight compounds such as other peptide receptors. Still, one should certainly not exclude categorically that some drugs may bind to a particular TCR, especially given the huge TCR repertoire and the high level of cross-reactivity just from a probabilistic point of view alone.44 It is also worthwhile remembering that the overwhelming majority of low molecular weight, “drug-like” compounds known to bind to differing receptor classes act as antagonists. In analogy to these findings, it seems not unlikely that at least some drugs may not only activate but also block their (drug-specific) TCR.

THE P-I CONCEPT: BYPASSING THE INNATE IMMUNE SYSTEM BY VIRTUE OF CROSSREACTIVITY WITH PEPTIDE ANTIGENS

The p-i concept has major implications for our interpretation of drug induced immune mediated side effects: It actually puts some drug induced hypersensitivity reactions outside the realms of a normal immune response (Fig. 2).45 This reasoning could explain some peculiar clinical findings, namely that drug-induced, T cell-mediated skin reactions can occur already within a few hours after administration and/or without previous exposure to the drug, as e.g. documented for RCM.29,30 The kinetics of such a reaction are much too fast to be explained by the induction of a classical, primary response, which is mounted in the course of several days only. More-over, how do RCM or other inert drugs stimulate the innate immune system, a step normally required to induce an immune response? Such features have been described for certain haptens causing contact dermatitis, but are not described for inert drugs.13,14

To explain these phenomena we proposed that such drugs are bypassing the innate immune system as they stimulate memory T cells (with a peptide specificity).46,47 Such memory T cells have a lower threshold of reactivity compared to naïve T cells, which might be decreased even further if a generalized immune reaction with its abundance of cytokines is occurring. A secondary, memory response by the immune system is generally much faster and can lead to an immune reaction within the time frame observed for some adverse drug reactions. Moreover, these features would explain the higher incidence of drug hypersensitivity reactions during such infections or autoimmune diseases. It implies that drug hypersensitivity reactions are actually due to cross-reactivity of peptide specific memory T cells, which “just happen” to react with some drugs as well. In line with this notion is the observation that the vast majority of drug-specific TCC have been found to bear αβ TCR, which usually recognize peptides, and that a general stimulation of T cells as in HIV or EBV, CMV infection48 or certain exacerbations of autoimmune diseases49 is an important risk factor for drug hypersensitivity. On the other hand, recent data suggest that a drug-induced T cell activation leads to a reaction of dormant herpes viruses, and that the subsequent symptoms are largely related to reactivated herpes virus infections.50,51 The normal incidence of SMX allergy in normals is ca. 2–4%, but during HIV infection it might go up to ca. 50%, while amoxicillin hypersensitivity increases from 4–5% in normals to > 90% during an acute EBV infection (infectious mononucleosis). Such immune reactions go along with the expansion of a polyclonal CD8+ T cell response, and such T-cells are also found in the circulation of patients with maculopapular and bullous exanthema.52 Even more, it seems likely that drug-specific cells exist even in individuals that are not hypersensitive: in an in vitro study, several blood donors who had never been exposed to SMX nevertheless harbored SMX- and SMX-NO-specific cells in their T cell repertoire.53

Preclinical testing for drug hypersensitivity is of notoriously bad reliability54: One explanation might be that the attempts to perform preclinical tests rely on the hapten-prohapten concept only, but ignore the p-i concept. As shown in Figure 2, the p-i and hapten concepts have quite distinct features and would require different approaches. Tests relying on chemical reactivity and aimed to detect hapten formation and the induction of a classical immune response would necessarily miss drugs that elicit hypersensitivity reactions via non-covalent binding to the TCR. Of note and as shown in Table 3, this may be the case for a
ARGUMENTS AGAINST THE P-I CONCEPT:

The p-i concept was not conceived to oppose the hapten or pro-hapten concept, but to complement it. Certain drugs like penicillins clearly do cause hypersensitivity reactions due to hapten-carrier formation. Others, like quinolones and sulfanilamides, may cause hypersensitivity by the hapten and p-i mechanisms simultaneously.4,31,34 Thus, if the hapten concept is well proven for a certain drug like p-phenylendiamine or sulfamethoxazole, it cannot be ruled out that the p-i concept may not also play some role.

The p-i concept is contradicting many rules well established in immunology, which makes it at first sight a hypothesis “hard to digest”. However, the findings in drug allergy do also contradict many established rules,45 and exactly the fact that the p-i concept is not postulating a primary immune response to a drug may explain many of these puzzling findings. Drug hypersensitivity generated according to the p-i concept does not require the involvement of the innate immune system to trigger immunity, as this form of drug hypersensitivity is not due to a newly generated immune response to the drug but is the consequence of cross-reactivity. Animal experiments aimed to prove or disprove the p-i concept by immunizing animals with the inert drug will necessarily fail—as inert drugs do not stimulate an immune response under normal conditions.55,56 In fact, it might be impossible to prove the p-i concept by the usual immunological tests; rather, it will be corroborated by a pharmacological characterization of the TCR-drug interactions.

The strongest argument against the p-i concept and our idea that drugs primarily activate the TCR comes from new immunogenetic data. Already early on, the idiosyncratic nature of hypersensitivity reactions has prompted an intensive search for genetic factors explaining their occurrence in a small subset of treated persons (reviewed in ).57 In accordance with the (pro) hapten concept, the major emphasis was put on pharmacogenetic factors such as an altered metabolism, as the generation of a more reactive intermediate able to modify autologous proteins would have been the most stringent explanation for the occurrence of immunological side effects. However, associations of hypersensitivities with particular pharmacological genotypes remained often tenuous and even controversial,38 such as the slow acetylator phenotype reported to enhance the occurrence of side effects to SMX, and the moderate association of certain TNF-α promoter polymorphisms with carbamazepine hypersensitivity.50

More recent studies focusing on immunological rather than metabolic factors have now revealed surprisingly clear associations of certain drug hypersensitivity reactions with HLA-class I alleles. In approximately 5% of treated patients, abacavir causes a severe hypersensitivity reaction affecting multiple organs. The majority of these patients carried the HLA-B*5701 allele. This association was strongest in Caucasians, and the particular allele was present in 94.4% of patients but only 1.7% of controls.62 Possibly even more striking is the association of carbamazepine treatment with the appearance of Stevens-Johnson syndrome in Han-Chinese carrying the HLA-B 1502 allele, which is stronger than any other described so far for any HLA marker with a disease. In another case-control association study, the same authors identified HLA-B*5801 as an important genetic risk factor for severe allopurinol-induced cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.64

It is clear that such strong associations with HLA-alleles support an important role for HLA molecules in drug hypersensitivity, and they certainly seem to favor the hapten concept at least for these drugs. However, albeit the association with HLA-alleles is very strong, there are some open questions: Many patients with HLA-B*5801 are exposed to allopurinol yet they do not develop hypersensitivity.64 Caucasians do not show the association of HLA-B*5701 and carbamazepine hypersensitivity, but most TCC to carbamazepine generated from Caucasians reacted with the parent compound—and it is therefore possible that the particular Chinese population reacted to a hapten of carbamazepine. Also and as reported by the authors of these studies, other factors located in this region of chromosome 6 may be important as well (e.g. hsp 70 and other genes). Last but not least, not the HLA complex but the TCR as its counterpart might be crucial for the reaction, as the positive and negative selection of T cells in the thymus is co-determined by the autologous HLA-molecules and peptides that can be presented at all, thus influencing the TCR repertoire of the individual patient.

CONCLUSIONS

A series of clinical and laboratory investigations contradict the hapten model and suggest that the hapten model as the sole molecular explanation for drug-induced hypersensitivity may not be sufficient. Other possibilities should be considered and we recently proposed the p-i concept, which supplements the hapten-concept. In this concept certain drugs are considered to be able to activate T cells in a direct way by drug binding to T-cell receptors and subsequent cell activation. This mechanism would explain many of the peculiar findings in drug hypersensitivity, and would open new possibilities for immunopharmacology, as this drug binding may be stimulatory or inhibitory.

REFERENCES

1. Park BK, Pirmohamed M, Kitteringham NR. Role of drug
37. von Greyerz S, Bultemann G, Schynder K et al. Degener-
acy and additional alloreactivity of drug-specific human al-
38. Burkhart C, Britschgi M, Strasser I et al. Non-covalent
presentation of sulfamethoxazole to human CD4+ T cells is
independent of distinct human leucocyte antigen-bound
39. Depta JP, Altmann F, Gamberdinger K, Burkhart C,
Weltzien HU, Pichler WJ. Drug interaction with T-cell re-
ceptors: T-cell receptor density determines degree of
cross-reactivity. J. Allergy Clin. Immunol. 2004; 113:319-
527.
40. Vollmer J, Weltzien HU, Dormoy A, Pistoof F, Moulon C.
Functional expression and analysis of a human HLA-DQ
restricted, nickel-reactive T cell receptor in mouse hybri-
doma cells. Journal of Investigative Dermatology 1999;
113:175-181.
41. Pichler WJ. Pharmacological interaction of drugs with
42. Thierse HJ, Gamberdinger K, Junkses C, Guerreiro N,
Weltzien HU. T cell receptor (TCR) interaction with hap-
tens: metal ions as non-classical haptons. Toxicology 2005;
44. Mason D. A very high level of crossreactivity is an es-
19:395-404.
45. Pichler WJ. Lessons from drug allergy: against dogmata.
46. Pichler WJ. Direct T-cell stimulations by drugs—bypass-
ing the innate immune system. Toxicology 2005; 209:95-
100.
47. Gerber BO, Pichler WJ. Cellular mechanisms of T cell
49. Pichler WJ. Predictive drug allergy testing: an alternative
50. Hashimoto K, Yasukawa M, Tohyama M. Human herpes
Drug-induced hypersensitivity syndrome due to me-
xelline associated with human herpes virus 6 and cy-
tomegalovirus reactivation. J. Dermatol. 2005; 32:278-
281.
52. Harý Y, Frutig-Schnyder K, Hurni M et al. T cell
involvement in cutaneous drug eruptions. Clin. Exp. Allergy
2001; 31:1398-1408.
53. Engler OB, Strasser I, Naisbitt DJ, Cerny A, Pichler WJ. A
chemically inert drug can stimulate T cells in vivo by
their T cell receptor in non-sensitised individuals. Toxicol-
ogy 2004; 197:47-56.
54. Bala S, Weaver J, Hastings KL. Clinical relevance of pre-
clinical testing for allergic side effects. Toxicology 2005;
55. Naisbitt DJ, Gordon SF, Pirmohamed M et al. Antigenic-
ity and immunogenicity of sulfamethoxazole: demon-
stration of metabolism-dependent haptenation and T-cell
56. Naisbitt DJ, Farrell J, Gordon SF et al. Covalent binding
of the nitroso metabolite of sulfamethoxazole leads to tox-
city and major histocompatibility complex-restricted anti-
57. Pirmohamed M, Park BK. Genetic susceptibility to ad-
305.
58. Pirmohamed M, Park BK. Cytochrome P 450 enzyme
polymorphisms and adverse drug reactions. Toxicology
2003; 192:23-32.
59. Alfivric A, Staford AC, Vilar FJ, Wilkins EG, Park BK,
Pirmohamed M. Slow acetylator phenotype and genotype
in HIV-positive patients with sulphonamethoxazole hyper-
60. Pirmohamed M, Lin K, Chadwick D, Park BK. TNF-alpha
promoter region gene polymorphisms in carbamazine-
61. Mallal S, Nolan D, Witt C et al. Association between pre-
ence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hyper-
sensitivity to HIV-1 reverse-transcriptase inhibitor abac-
62. Martin AM, Nolan D, Gaudieri S et al. Predisposition to
abacavir hypersensitivity conferred by HLA-B*5701 and a
A. 2004; 101:4180-4185.
63. Chung WH, Hung SI, Hong HS et al. Medical genetics: a
marker for Stevens-Johnson syndrome. Nature 2004; 428:
486.
64. Hung SI, Chung WH, Liou LB et al. HLA-B*5801 allele as
a genetic marker for severe cutaneous adverse reactions
102:4134-4139.
65. Stockl J, Magdic O, Fischer G, Maurer D, Knapp W.
Monomorphic molecules function as additional recogni-
tion structures on haptenated target cells for HLA-A1-
restricted, hapten-specific CTL. J. Immunol. 2001; 167:
2724-2733.
cytotoxic T-cells in the skin lesions of a patient with toxic
epidermal necrolysis. J. Invest. Dermatol. 2002; 118:
728-733.
67. Britschgi M, Steiner UC, Schmid S et al. T-cell
involvement in drug-induced acute generalized exanthematous