

Severe Delayed Drug Reactions



Role of Genetics and Viral Infections

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KEYWORDS

- Human leukocyte antigen • T-cell receptor • Adverse drug reaction
- Pharmacogenomics • Human herpes virus
- Drug reaction with eosinophilia and systemic symptoms • Steven Johnson syndrome
- Toxic epidermal necrolysis

KEY POINTS

- Severe delayed drug reactions are typically off-target reactions that are immunologically mediated and associated with long-lasting immunologic memory.
- There are many strong associations between these immunologically mediated adverse drug reactions (IM-ADR) and the major histocompatibility complex.
- Despite this, the minority of these have been implemented into clinical practice as cost-effective pretreatment screening tests.
- A heterologous immune model of delayed drug hypersensitivity may explain why, for most drugs, less than 5% of those carrying an HLA risk allele will develop an IM-ADR.
- It is proposed that pathogen-specific T-cell responses generate either migratory or resident memory T-cells which cross-react with drug-modified self-peptide epitopes when the risk drug is introduced later in life.

INTRODUCTION

Adverse drug reactions (ADRs) account for a significant source of patient morbidity and mortality and represent a major burden to the health care and drug development systems. It is estimated that up to 50% of such reactions are preventable.^{1–8} Although

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many ADRs can be predicted based on the on-target pharmacologic activity of the drug (Fig. 1),^{1–3,6,8–10} ADRs arising from drug interactions with off-target receptors are now more commonly recognized. Off-target ADRs include the immune-mediated ADRs (IM-ADRs) as well as pharmacologic drug effects such as those associated with non-IgE-mediated mast cell activation (see Fig. 1).¹¹ In this review, we discuss what is known about the immunogenetics and pathogenesis of IM-ADRs and the hypothesized role of preexisting pathogen exposure as a predisposing factor for the development of an IM-ADR.

CLINICAL PHENOTYPES OF IMMUNE-MEDIATED ADVERSE DRUG REACTIONS

IM-ADRs encompass a number of phenotypically distinct clinical diagnoses that include both B-cell (antibody-mediated, Gell Coombs types I–III) and purely T-cell-mediated reactions (Gell-Coombs type IV). T-cell-mediated IM-ADRs have been classified into delayed exanthema without systemic symptoms (ie, maculopapular eruption), contact dermatitis, drug-induced hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, fixed drug eruption, single organ involvement pathologies such as drug-induced liver injury, and the abacavir hypersensitivity syndrome.^{12,13}

Drug Reaction with Eosinophilia and Systemic Symptoms

The clinical presentation of DRESS is characterized by a generalized rash of varying severity without skin separation, fever, internal organ involvement (usually hepatitis), and hematologic abnormalities (often atypical lymphocytes and/or eosinophilia). Clinical features of this syndrome are variable, but may also include diffuse lymphadenopathy, pneumonitis, encephalitis, myocarditis, and nephritis. Onset of symptoms typically occurs 2 to 8 weeks after initiation of the inciting drug and the patient may have a protracted clinical course. Prolonged or recurrent symptoms, sometimes weeks after cessation of the offending drug and often related to discontinuation of systemic corticosteroids, is frequently observed and late onset autoimmune diseases including thyroiditis, systemic lupus, and type I diabetes are well-described long-term sequelae that can occur at least up to 4 years after the resolution of acute disease.^{14–22}

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN are the most severe cutaneous hypersensitivity syndromes and are thought to represent a spectrum of disease defined by the percentage of total body surface area (TBSA) involvement. Characteristic features include epidermal necrosis leading to the formation of fluid-filled blisters and epidermal sloughing, fever, mucosal and eye involvement, internal organ involvement, and secondary complications such as sepsis. Generally, SJS is diagnosed in cases where less than 10% of TBSA has blistering and epidermal detachment, whereas TEN is diagnosed in instances where more than 30% of the TBSA is affected. SJS/TEN describes the overlap in this spectrum in which 10% to 30% of TBSA is affected. However, patients with severe epidermal detachment and skin necrosis are classified as TEN regardless of the percentage of TBSA involved. These syndromes are often associated with significant mortality as well as short- and long-term morbidity, including respiratory, gastrointestinal, and genitourinary complications, as well as permanent corneal scarring and vision loss.^{7,12} The mortality associated with TEN is higher with aging and comorbidities and may reach 30% to 50%.^{12,13,23,24}

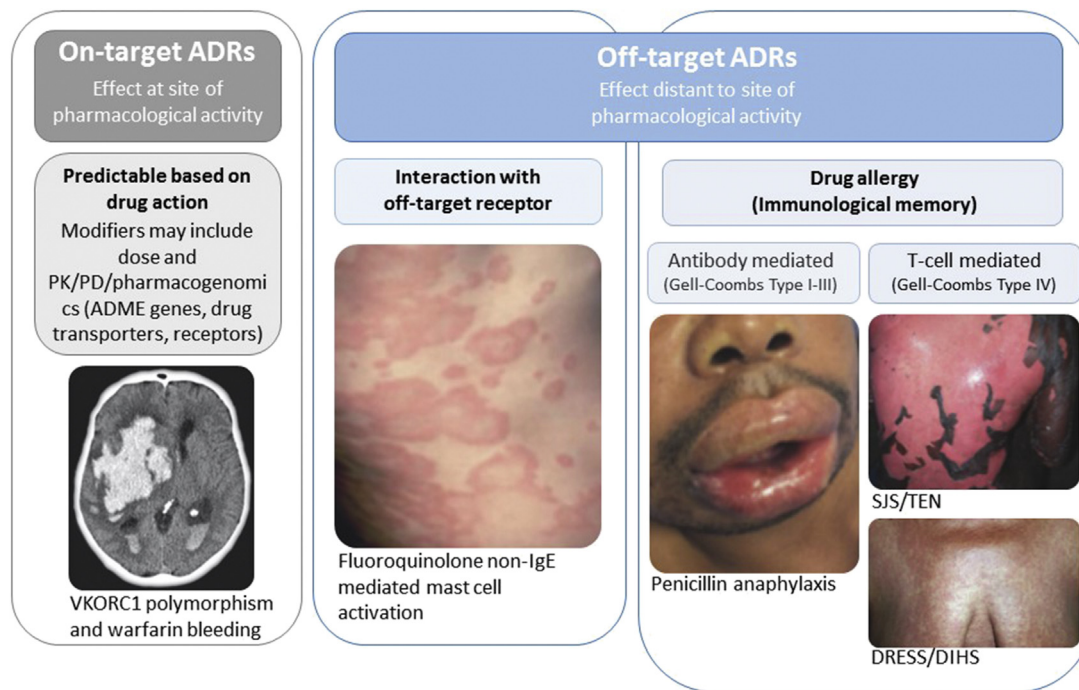


Fig. 1. Classification of adverse drug reactions (ADRs). ADRs may result from either on-target or off-target interactions between the drug and cellular proteins. On-target ADRs account for 80% or more of ADRs and are generally predictable based on the drug pharmacology. Variation in the cellular processes that modulate drug absorption, distribution, metabolism, and excretion (ADME), drug transporters, target receptor expression, and drug dosing or administration errors contribute to ADRs that are primarily mediated by pharmacologic mechanisms. Off-target adverse effects account for a smaller proportion of total ADRs ($\leq 20\%$) and include both immune-mediated and non-immune-mediated syndromes. The non-IgE mediated mast cell activation syndrome, which phenotypically resembles anaphylaxis, has recently been shown in a murine model to result from off-target binding of drug to G-protein-coupled receptors without involvement of the adaptive immune system.¹¹ The IM-ADRs include both B-cell-mediated and T-cell-mediated reactions (types I–IV reactions according to the Gell-Coombs schema) and are associated with immunologic memory. DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; SJS/TENS, Stevens–Johns syndrome/toxic epidermal necrolysis; PD, pharmacodynamic; PK, pharmacokinetic. (Adapted from Peter JG, Lehloeny R, Dlamini S, et al. Severe Delayed Cutaneous and Systemic Reactions to Drugs: A Global Perspective on the Science and Art of Current Practice. *J Allergy Clin Immunol Pract* 2017;5(3):549; with permission.)

The Abacavir Hypersensitivity Syndrome

Abacavir is a guanosine analogue that is used for the treatment of infection with human immunodeficiency virus type 1 (HIV-1). In the premarketing phase of drug development, a hypersensitivity syndrome characterized by fever, malaise, gastrointestinal, respiratory symptoms, and/or generalized rash was reported in approximately 5% to 8% of patients within the first 6 weeks after initiation of abacavir. The immunologic basis for the abacavir hypersensitivity syndrome has been well-described and is discussed in subsequent sections of this review.

Emerging Immune-mediated Adverse Drug Reactions: Immune Checkpoint Inhibitors

Novel monoclonal antibodies that target surface proteins that suppress T-cell cytotoxic function have shown significant efficacy as cancer therapeutics. The immune checkpoint inhibitors ipilimumab (targeting anti-cytotoxic T-lymphocyte antigen 4 [CTLA-4]) and nivolumab or pembrolizumab (targeting the anti-programmed death receptor-1 [PD-1]), used alone or in combination, and are now first line therapies for the treatment of metastatic melanoma. The checkpoint inhibitors and are also licensed for treatment of selected types of skin cancer, head and neck cancer, lung cancer, bladder cancer, lymphoma, and kidney cancer (available at: <https://medi-paper.com/approved-immunotherapies/>). Immune checkpoint inhibitors have been associated with an increasing range of organ specific IM-ADRs, also called immune-related adverse events (irAEs), including rash (rarely, SJS/TEN), gastrointestinal syndromes, hepatitis, endocrine syndromes (thyroiditis, pancreatitis, hypophysitis), hematologic syndromes (red cell aplasia), neurologic (Guillain–Barre syndrome, aseptic meningitis), myocarditis, and rheumatologic syndromes (systemic lupus erythematosus, polyarthritis). Onset of irAEs most commonly occur 3 to 6 months after initiation of immune checkpoint inhibitor therapy and usually manifest as mild syndromes that are not treatment limiting and often steroid responsive. However, an increasing number of severe reactions with high morbidity and mortality have been recently described, particularly with the use of combination CTLA-4 and PD-1 blockade.^{25–27} Recent studies showing superior tumor response to checkpoint inhibitor therapy in patients who develop irAEs support the hypothesis that these irAEs are mediated by a cross-reactive memory T-cell response between the tumor and a self or pathogen epitope.²⁶ Further, a report of 2 cases of fatal myocarditis after combination PD-1 and CTLA-4 inhibitor therapy for the treatment of metastatic melanoma demonstrated that an identical dominant T-cell clonotype and overall repertoire was present in posttherapy tumor tissue and myocardium.²⁸ The relative risk of T-cell-mediated ADRs in the presence of immune checkpoint inhibitor is unknown and is a focus of ongoing research.

Clinical Mimics of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Bullous erythema multiforme is a severe acute bullous disorder characterized by raised typical or atypical target lesions affecting less than 10% of the TBSA.²⁹ Unlike SJS, erythema multiforme is most commonly associated with infectious diseases including herpes simplex virus (HSV)^{30–35} and *Mycoplasma pneumoniae*.^{36,37} Although SJS/TEN is most often associated with drug exposure, there are many reported cases of SJS/TEN for which there is no causative drug implicated. In such cases, a coincident viral infection similar to those seen with erythema multiforme may explain the observed clinical features. In 1922, M. Stevens and F. C. Johnson described the first 2 cases of SJS, neither of which were associated with antecedent medication exposure. One of these cases had a concurrent pneumonia, a presentation that is

consistent with what is now known as *M pneumoniae*-induced rash and mucositis.^{38,39} Studies have reported that 14% to 63% of children with clinical SJS/TEN have detectable *M pneumoniae* serum antibodies^{40,41} and *M pneumoniae* is recognized as a major trigger for recurrent SJS episodes, particularly in children and adolescents.^{40,42} SJS/TEN with eye involvement is more common in children with concurrent *M pneumoniae* (26.7%) or HSV (15.6%) infections.³¹

There are reports of atypical hand, foot, and mouth disease caused by coxsackievirus A6 that share features of drug-induced eruptions. Patients exhibit widespread blistering mucocutaneous reactions with inflammatory infiltration of cytotoxic T cells and granulysin producing natural killer cells.⁴³ Intact coxsackievirus A6 virus particles have been detected in the blister fluids and skin lesions of these patients.⁴⁴

GENETIC ASSOCIATIONS OF IMMUNE-MEDIATED ADVERSE DRUG REACTIONS

Human Leukocyte Antigen

Many strong associations have been described between human leukocyte antigen (HLA) alleles and drug-specific IM-ADRs such as DRESS/drug-induced hypersensitivity syndrome, SJS/TEN, and drug-induced liver injury. The T-cell receptors (TCRs) on the surface of a T cell recognize peptides that are bound and displayed by surface HLA molecules expressed on various cells of the immune system. Class I major histocompatibility complex (MHC) molecules (HLA-A, -B, and -C) are expressed on all nucleated cells and are responsible for activating CD8⁺ cytotoxic T lymphocytes, whereas class II MHC molecules (HLA-DP, HLA-DQ, and HLA-DR) are expressed only on professional antigen presenting cells (B cells, macrophages, and dendritic cells) and activate CD4⁺ helper T lymphocytes. In an era when HLA typing was performed by serology, weak 2-digit associations were described for allopurinol (B58) and sulfa antimicrobial hypersensitivity.^{45–47} The strong association between HLA-B*57:01 and the abacavir hypersensitivity syndrome was identified in 2002 and marked the advent of a new era of discovery made possible by high-resolution HLA typing in patients with specifically phenotyped drug hypersensitivity syndromes.^{48,49} This discovery was followed by the reported associations between carbamazepine SJS/TEN and HLA-B*15:02 and allopurinol DRESS/SJS/TEN and HLA-B*58:01^{48,50–52} (Table 1). Investigations of these 3 well-characterized drug related syndromes have since suggested new models for the immunopathogenesis of T-cell-mediated IM-ADRs.

The crystal structure(s) of abacavir noncovalently bound to the floor of the peptide binding groove of HLA-B*57:01 demonstrated how the drug is able to affect the peptide binding properties of the HLA molecule.^{53,54} It is as yet unclear whether the same mechanism will generalize to other HLA-associated IM-ADRs. Abacavir hypersensitivity syndrome only occurs in individuals with HLA-B*57:01, and 55% of those with HLA-B*57:01 exposed to the drug will develop hypersensitivity. This 100% negative predictive value combined with this unusually high positive predictive value (PPV) facilitated successful implementation of allele screening before the initiation of abacavir therapy.⁵⁵ Other HLA-associated IM-ADRs have much lower PPVs (<3%) for the development of hypersensitivity. Although HLA risk alleles are necessary but not sufficient for IM-ADRs, identifying other genetic or ecological factors that account for the “PPV gap” will be necessary to enhance current mechanistic models of the pathogenesis of these syndromes.

Carbamazepine is an aromatic amine anticonvulsant known to cause a spectrum of IM-ADRs, including maculopapular exanthema, DRESS, and SJS/TEN. The original association between HLA-B*15:02 and the development of SJS/TEN was reported

Table 1
Pharmacogenomics of off-target reactions associated with immunologic memory

Drug	DHR	Alleles ^c	PPV	NPV	NNT	Populations	LOE ^a
Abacavir	HSS, DIHS	B*57:01 ^{48,49,55,136}	55%	100%	13	European, African	1a
Carbamazepine	SJS, TEN	B*15:02 ^{50,52,57,62,137–141}	3%	100% in Han Chinese	1000	Han Chinese, Thai, Malaysian, Indian	1a
		B*15:11 ^{60,142}				Korean, Japanese	3
		B*15:18, B*59:01 and C*07:04 ¹⁴³				Japanese	3
		A*31:01 ^{65–67,142}				Japanese, northern European, Korean	2b
	HSS, DIHS, DRESS	A*11:01 ⁶⁸				Spanish	
		8.1 AH (HLA A*01:01, Cw*07:01, B*08:01, DRB1*03:01, DQA1*05:01, DQB1*02:01) ¹⁴⁴				Caucasians	3
		A*31:01 ¹⁴⁵	0.89%	99.98%	3334	Europeans	1a
		A*31:01 ¹⁴⁵	0.59%	99.97%	5000	Chinese	1a
		A*31:01 ^{65–68,142}				Northern Europeans, Japanese, and Korean, Spanish	1a
		A*11 and B*51 (weak) ⁶⁶				Japanese	3
	MPE	A*31:01 ⁵²	34.9%	96.7%	91		1a
Allopurinol	SJS, TEN, DIHS, DRESS	B*58:01 (or B*58 haplotype) ^{45,51,71,146–150}	3%	100% in Han Chinese	250	Han Chinese, Thai, European, Italian, Korean	1a
Oxcarbazepine	SJS, TEN	B*15:02 and B*15:18 ^{63,64,151,152}				Han Chinese, Taiwanese	2b
Lamotrigine	SJS, TEN	B*15:02 (positive) ⁶³				Han Chinese	3
		B*38:01 ⁶⁸				Spanish	
		B*15:02 (no association) ^{153,154}				Han Chinese	3
	DRESS	A*24:02 ⁶⁸				Spanish	3
	SCAR	A*31:01 ¹⁵⁵				Korean	3

Phenytoin	SJS, TEN	B*15:02 (weak), Cw*08:01 and DRB1*16:02 ^{62,63,78,138}				Han Chinese	3
						Thailand	3
	DRESS, MPE	B*13:01, B*56:02/04, CYP2C19*3 ^{79,80}				Spanish	3
		CYP2C9*3 ⁷⁸				Han Chinese	3
		A*02:01/Cw15:02 ⁶⁸					3
		B*13:01(weak), B*5101 (weak) ⁷⁸					3
		CYP2C9*3 ⁷⁸					1a
Phenobarbital	SCAR, MP rash	A*01:01 and B*13:01, CYP2C19*2 ^{156,157}				Thailand	3
		B*15:02 and –B*15:11 ¹⁵⁸				Chinese	3
Nevirapine	SJS, TEN HSS, DIHS, DRESS	C*04:01 ⁸⁸	18%	96%		Malawian	3
		DRB1*01:01 and DRB1*01:01 (hepatitis and low CD4+) ^{85,86}				Australian, European and South African	1b
		DRB1*01:02					1b
		Cw*8 or Cw*8-B*14 haplotype ^{84,159}				Italian and Japanese	2b
		Cw*4 ^{85,160}				Blacks, Asians, Whites	1b
	Delayed rash	B*35 ¹⁰⁴	16%	97%		Han Chinese	1b
		B*35:01 ⁸³				Asian	1b
		B*35:05 ⁸⁷					1b
		DRB1*01 ¹⁶¹				French	2b
		Cw*04 ^{85,162}				African, Asian, European, and Thai	3
		B*35:05, rs1576*G CCHCR1 status ^{87,163}				Thai	2b

(continued on next page)

Table 1
(continued)

Drug	DHR	Alleles ^c	PPV	NPV	NNT	Populations	LOE ^a
Dapsone	HSS	B*13:01 ¹⁶⁴ B*13:01 ¹³²	7.8%	99.8%	84	Chinese	1b 1b
Co-trimoxazole	SJS, TEN	B*15:02, C*06:02, and C*08:01 ¹⁶⁵				Thailand	3
Piperacillin, tazobactam	DRESS	B*62 ¹⁶⁶				UK	3
Strontium ranelate	SJS, TEN	A*33:03, B*58:01 ¹⁶⁷				Han Chinese	3
Efavirenz	Delayed rash	DRB1*01 ¹⁶¹				French	3
Sulfamethoxazole	SJS, TEN	B*38 ¹⁴⁸				European	
Amoxicillin-clavulanate	DILI	DRB1*15:01				European	1b
		A*02:01					1b
		DRB1*07 and HLA-A1 (protective)					3
		DQB1*06:02					1b
		And rs3135388, a tag SNP of DRB1*15:01-DQB1*06:02 ¹⁶⁸⁻¹⁷⁰					1b
Lumiracoxib	DILI	DRB1*15:01-DQB1*06:02- DRB5*01:01-DQA1*01:02 haplotype ¹⁷¹				International, multicenter	3
Ximelagatran	DILI	DRB1*07 and DQA1*02 ¹⁷²				Swedish	2b
Diclofenac	DILI	B11, C-24T, UGT2B7*2, IL-4 C-590-A ¹⁷³⁻¹⁷⁵				European	3
Flucloxacilin	DILI	B*57:01 DRB1*01:07-DQB1*01:03 ^{174,176}	0.12%	99.99%	13,819	European	1b

Lapatinib	DILI	DRB1*07:01-DQA2*02:01-DQB1*02:02/02:02 ¹⁷⁷	International, multicenter			1b	
Minocycline	DILI	B*35:02 ¹⁷⁸	Caucasian			3	
Asparaginase	Anaphylaxis	DRB1*07:01 ¹³¹	European			2b	
Penicillin ^b	IgE- mediated allergy	IL-4Ralpha Q576R ¹⁷⁹	Chinese			3	
		STAT6 in 2SNP3 ¹⁸⁰	Spanish			3	
		DRA rs7192 and rs8084, ZNF300 rs4958427 ¹⁸¹					
	Urticaria	IL-4Ralpha I75V ¹⁷⁹	Chinese			3	
Methimazole, carbimazole	Agranulocytosis	B*38:02 ^{182,183}	7%	99.9%	211	Southeast Asian	1b
Antithyroid drugs		B*27:05 ¹⁸⁴ (3 SNPs)	30%	>99%	238	European	1b
Statin	Myopathy	DRB1*04:06 ¹⁸⁵	Japanese			3	
Raltegravir	DRESS	B*53-C*04 haplotype ¹⁸⁶	African			4	

Abbreviations: DHR, Drug hypersensitivity reaction; DIHS, drug-induced hypersensitivity syndrome; DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic symptoms; HSS, hypersensitivity syndrome; LOE, levels of evidence; MP rash, maculopapular rash; MPE, maculopapular eruption; NNT, number needed to treat; NPV, negative predictive value; PPV, positive predictive value; SCAR, severe cutaneous adverse reactions; SJS, Stevens–Johnson syndrome; SNP, single nucleotide polymorphism; TEN, toxic epidermal necrolysis.

^a Levels of evidence (PharmGKB [102]): Level 1a, Annotation for a variant-drug combination in a Clinical Pharmacogenetics Implementation Consortium (CPIC) or medical society-endorsed pharmacogenomics guideline, or implemented at a Pharmacogenomics Research Network (PGRN) site, or in another major health system; Level 1b, Annotation for a variant-drug combination in which the preponderance of evidence shows an association. This association must be replicated in more than one cohort with significant *P*-values and preferably with a strong effect size; Level 2a, Annotation for a variant-drug combination that qualifies for level 2b, in which the variant is within a Very Important Pharmacogene (VIP) as defined by PharmGKB where their functional significance is more likely known; Level 2b, Annotation for a variant–drug combination with moderate evidence of an association. This association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small; Level 3, Annotation for a variant–drug combination based on a single significant (not yet replicated) study or annotation for a variant–drug combination evaluated in multiple studies but lacking clear evidence of an association; Level 4, Annotation based on a case report, nonsignificant study, *in vitro*, molecular or functional assay evidence only.

^b Associated with immunologic memory but responses are not maintained over time (loss of skin test reactivity).

^c HLA alleles.

in the Han Chinese, and other South-East Asian populations where the frequency of HLA-B*15:02 carriage is relatively high.^{52,56–58} This association is specific to the carbamazepine–SJS/TEN phenotype and HLA-B*15:02 has not been reported with DRESS or maculopapular eruption.⁵⁹ However, HLA molecules of the same B75 serotype (HLA-B*15:08, -B*15:11, and -B*15:21) with similar peptide binding properties have also been implicated in carbamazepine-induced SJS/TEN.^{56,60,61} In addition, IM-ADR secondary to other aromatic amine anticonvulsants, including oxcarbazepine, phenytoin, and lamotrigine, are also associated with HLA-B*15:02, suggesting a potential shared interaction between the HLA allele and the drugs.^{62–64} Overall, the carbamazepine example highlights that structural interactions between the drug and specific HLA alleles as well as risk allele carriage frequency in different populations are likely to affect the likelihood of identifying genetic associations. For many of the HLA alleles that are associated with IM-ADRs, the risk allele is present on a conserved haplotype that has been maintained at high frequency in particular populations, whereas haplotypes with nonrisk HLA alleles dominate in other ethnic groups.

In South-East Asian populations, carbamazepine–SJS/TEN is most often associated with HLA-B*15:02 and less commonly associated with other HLA-B75 serotype alleles. In European and Japanese populations, however, where HLA-B*15:02 and other B75 serotype HLA carriage is less than 1%, carbamazepine–DRESS, maculopapular exanthema, and SJS/TEN have been associated with the carriage of HLA-A*31:01.^{65–67} Similarly, in South and Southeast Asians, the risk for HLA-B*15:02-associated IM-ADRs secondary to other aromatic amine anticonvulsants such as phenytoin and lamotrigine is lower than for carbamazepine and oxcarbazepine and HLA associations are unique in Europeans (see [Table 1](#)).⁶⁸

Drug Metabolism and Transport

In contrast with the HLA allele-specific phenotype associations observed for carbamazepine IM-ADRs, HLA-B*58:01 is a genetic marker for both SJS/TEN and DRESS induced by allopurinol, a xanthine oxidase inhibitor used in the treatment of hyperuricemia and gout.⁵¹ First described in the Han Chinese, the association of HLA-B*58:01 with severe cutaneous adverse reactions (SCAR) is also reported in Japanese and European populations.^{51,69–72} Oxypurinol is the main metabolite of allopurinol produced via aldehyde oxidoreductase and is cleared almost entirely by urinary excretion. In keeping with this, renal impairment, increased plasma levels, and delayed clearance of oxypurinol correlate with an increased risk and mortality from allopurinol SCAR.⁷³ Several studies have examined genetic variability in genes of allopurinol metabolism and clearance relative to allopurinol response and prescribed dose. For example, the single nucleotide polymorphism Hist1270Arg in aldehyde oxidase is significantly associated with therapeutic allopurinol dose and other studies have shown enhanced conversion of some substrates by aldehyde oxidase with this single nucleotide polymorphism and other genetic variants.^{74,75} In addition, adenosine triphosphate-binding cassette subfamily G member 2 (ABCG2) is as an allopurinol transporter⁷⁶ and an ABCG2 missense allele (rs2231142) is associated with a reduced response to allopurinol.⁷⁷ As yet, these and similar candidate genes in allopurinol metabolism and clearance have not been examined specifically in relation to the development allopurinol induced IM-ADRs and are good candidates for further study.

The cytochrome P450 (CYP) group of enzymes metabolize thousands of endogenous and exogenous chemicals and are the major enzymes in drug metabolism. A combination of metabolic and immunologic factors is associated with predisposition for some drugs associated with IM-ADRs, such as phenytoin-associated SCARs,

including maculopapular exanthema, DRESS, and SJS/TEN. A recent genome-wide association study across mixed ethnic populations, including individuals from Taiwan, Japan, and Malaysia, identified a missense variant of the CYP2C9 gene, whose protein product is responsible for metabolizing phenytoin in the liver. The variant identified as CYP2C9*3 was strongly associated with development of SCARs and reduced phenytoin clearance.^{78,79} However, delayed clearance was also observed in individuals without this variant allele, suggesting other contributing factors such as hepatic or renal insufficiency or a drug–drug interaction. This study, which mainly consisted of Southeast Asians (Taiwanese and Malaysians) and a smaller population of Japanese participants, also demonstrated weaker genetic associations with HLA-B alleles, including HLA-B*13:01, HLA-B*15:02, and HLA-B*51:01, respectively.^{79–82} Therefore, a combination of both pharmacologic and immunologic mechanisms contributes to the development of phenytoin-related SCAR.

The nonnucleoside reverse transcriptase inhibitor nevirapine, used to treat HIV-1 infection, is associated with both cutaneous and hepatitis hypersensitivity variants that have class I and II MHC associations. Nevirapine is associated with a spectrum of cutaneous adverse reactions ranging from mild rash to the severe SJS/TEN and DRESS.⁸³ HLA alleles associated with specific nevirapine phenotypes include HLA-B*35 and HLA-C*04 with cutaneous reactions, HLA-DRB1*01 with hepatic symptoms, and the HLA-B*14-C*08 haplotype with eosinophilia.^{83–88} In addition, CYP2B6 516G > T and 983T > C are associated with reduced clearance of the drug and cutaneous adverse reactions, with the strongest effect in African populations, where this variant is present in 20% of the population.^{85,89,90}

IMMUNE MECHANISMS OF IMMUNE-MEDIATED ADVERSE DRUG REACTIONS

As described, many type IV IM-ADRs are strongly associated with allelic variation in the class I and class II HLA genes, which encode the restricting elements for CD8⁺ and CD4⁺ T cells, respectively (see [Table 1](#)). Currently, 3 models have been proposed to describe how a drug might interact with immune proteins to elicit a T-cell response. These include the hapten/prohapten model, the pharmacologic interaction model, and the altered peptide repertoire model ([Fig. 2](#)).

In the hapten/prohapten model, the drug or drug metabolite covalently binds to an endogenous (self) protein that then undergoes intracellular processing to generate a pool of chemically modified peptides referred to as neoepitopes. When presented in the context of HLA proteins, these modified peptides will be recognized as “foreign” by T cells and elicit an immune response.^{91,92} The pharmacologic interaction model postulates that the offending drug interacts in a noncovalent manner with either the TCR or HLA protein in a peptide-independent manner to directly activate T cells. This model has been hypothesized to explain in vitro T-cell reactivity that is labile (ie, reactivity is abrogated by washing drug from the surface of antigen-presenting cells) and/or is observed within seconds of drug exposure, a time course too short to require intracellular antigen processing.^{93,94} The altered peptide repertoire model was defined through structural and peptide elution studies demonstrating the interactions of the antiretroviral drug abacavir and the HLA-B*57:01 protein. These studies demonstrated that abacavir binds to the HLA-B*57:01 peptide binding groove, thereby changing the chemistry of the binding cleft and resulting in presentation of a pool of peptides that are not normally bound to HLA-B*57:01 in the absence of drug. It is proposed that peptides presented in this context are recognized as “foreign” by the immune system and therefore elicit a T-cell response.^{53,54}

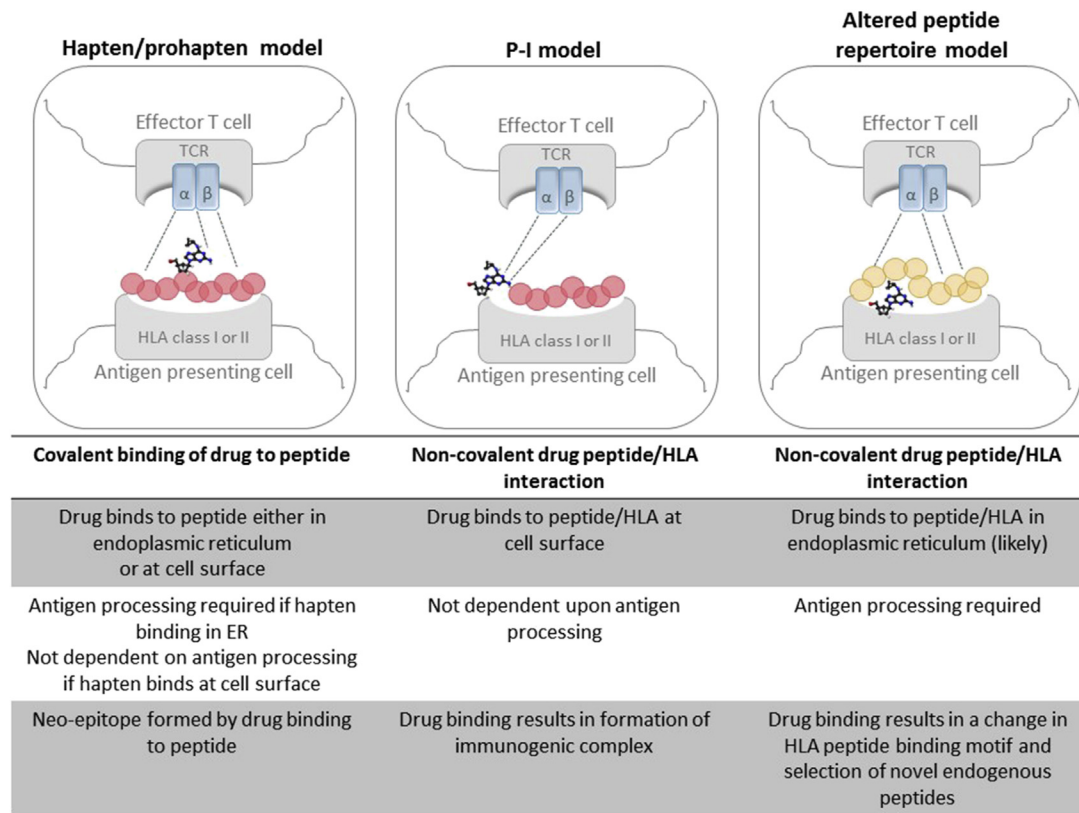


Fig. 2. Models of T-cell activation by small molecules. Three models have been proposed to explain T-cell stimulation by small molecule pharmaceuticals. The hapten/prohapten model postulates that the drug binds covalently to peptide (either in the intracellular environment before peptide processing and presentation or at the cell surface) to generate a neoantigen that stimulates a T-cell response. The P-I model proposes that a small molecule may bind to HLA in a noncovalent manner to directly stimulate T cells. The altered peptide model postulates that a small molecule can bind noncovalently to the major histocompatibility complex binding cleft to alter the specificity of peptide binding. This results in the presentation of novel peptide ligands to elicit an immune response. ER, endoplasmic reticulum; TCR, T-cell receptor. (Adapted from White KD, Chung WH, Hung SI, et al. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: The role of host, pathogens, and drug response. J Allergy Clin Immunol 2015;136(2):223; [quiz: 235]; with permission.)

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

The strong association between carriage of specific class I HLA alleles and risk of drug-induced SJS/TEN has been well-established (see [Table 1](#)) and is consistent with evidence suggesting that cytotoxic CD8⁺ T cells, natural killer cells, and CD3⁺CD56⁺ natural killer T cells mediate epidermal cell death in SJS/TEN through the production of soluble cytotoxic factors, such as granulysin.^{95–98} Granulysin is a cytolytic peptide that is present in high concentrations in blister fluid and serum levels of granulysin have been shown to correlate with the severity of acute SJS/TEN and predict mortality.^{73,99}

Mutagenesis studies suggest that carbamazepine likely binds to B pocket of the HLA-B*15:02 peptide binding groove and that the B pocket residues Arg62, Asn63, Ile95, and Leu156 contribute to drug–HLA interactions. Experiments using next generation TCR sequencing of circulating and blister fluid–derived T cells from patients with HLA-B*15:02–associated carbamazepine SJS/TEN have identified a shared CD8⁺ T-cell clonotype bearing a common CDR3 sequence that is not found in the peripheral blood of drug tolerant controls or in blister fluid from patients with SJS/TEN secondary to another drug.^{100,101} This finding suggests that the pathogenesis of HLA-B*15:02 associated carbamazepine-SJS/TEN depends on the concomitant involvement of both a specific HLA allotype and a specific TCR clonotype.

As mentioned, the pathogenesis of HLA-B*58:01–associated allopurinol IM-ADRs is mediated by oxypurinol, the active metabolite of allopurinol. Mutagenesis and in silico modeling studies suggest that oxypurinol binds the HLA-B*58:01 peptide binding groove and this interaction depends on contact with the Arg97 residue of HLA-B*58:01.¹⁰² Cell culture experiments have shown that T cells isolated from patients with allopurinol-associated IM-ADRs expand and acquire effector functions after stimulation with allopurinol or oxypurinol but that high concentrations of oxypurinol (up to 100 µg/mL, 10 times that expected with a therapeutic dose) is the primary driver of T-cell reactivity.^{73,103} As seen for HLA-B*15:02–associated carbamazepine SJS/TEN, CD8⁺ T cells are known mediators of pathogenesis in allopurinol SJS/TEN. However, 1 study using bulk next-generation TCR sequencing examined the CD8⁺ T-cell repertoire among blister fluid and peripheral blood cells from multiple patients with allopurinol-associated SJS/TEN demonstrated some degree of clonotypic restriction for some, but not all, patients with no evidence of a shared clonotype as seen for carbamazepine-associated SJS/TEN.¹⁰³ The role of these clonotypes in the pathogenesis is under investigation.

Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS is characterized by the expansion of circulating and dermal-infiltrating effector T cells and CD4⁺FoxP3⁺ regulatory T cells.^{104,105} Skin homing CD4⁺FoxP3⁺ T cells are hypothesized to limit the severity of acute disease by suppressing effector T-cell responses.¹⁰⁶ Reactivation of human herpesviruses (HHV), including HHV-6, Epstein–Barr virus, HHV-7, and cytomegalovirus is often observed during acute and recovery phase DRESS ([Table 2](#)). HHV-6 and Epstein–Barr virus reactivation is observed as early as 2 to 3 weeks after onset of rash and antiviral CD8⁺ effector T cells are concurrently expanded during acute disease. How viral reactivation and antiviral T-cell responses contribute to pathology in DRESS is currently under investigation. It is not clear whether viral replication contributes to the events inciting DRESS or is instead the result of general immune dysfunction, such as breakdown of regulatory T cells suppressor function or the upregulation of the HHV-6 receptor, CD134, on CD4⁺ T cells.^{105–108} Nevertheless, viral replication and virus-specific T-cell responses

Table 2 Viral reactivation reported during DRESS/DIHS		
Drug	Virus	Reference
Allopurinol	HSV-2, HHV-6, HHV-7, CMV, EBV	108,114,187–190
Amoxicillin	HHV-6	191
Aspirin	HHV-6	192
Carbamazepine	HHV-6, HHV-7, CMV, EBV, Parvoviridae	82,108,109,187,193–200
Cold and flu tablets ^{a,b}	HHV-6	201,202
Ibuprofen	HHV-6	194
Isoniazid, rifampin, ethambutol, and pyrazinamide	HHV-7	203
Lamotrigine and valproic acid	HHV-6	204
Mexiletine	HHV-6, EBV, CMV	109,187
Minocycline	HHV-6	114
Phneobarbital, phenobarbital- zonisamide	HHV-6, HHV-7, CMV, EBV	109,187,188,205
Strontium ranelate	HHV-7	206
Sulfasalazine-salazosulfapyridine	HHV-6	187,194,207,208
Sulfamethoxazole	HHV-6, HHV-7, EBV	108
Trimethoprim-sulfamethoxazole	HHV-6	209,210
Vancomycin-teicoplanin	HHV-6	211
Zonisamide	HHV-6, HHV-7, CMV	187,188
Drug not specified for each case	HHV-6, HHV-7, EBV, CMV	212–215

Abbreviations: CMV, cytomegalovirus; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein–Barr virus; HHV, human herpes virus; HSV, herpes simplex virus.

^a Acetaminophen, clemastine fumarate, dihydrocodeine phosphate, noscapine, dl-methyl ephedrine hydrochloride, potassium guaiacolsulfonate, anhydrous caffeine, benfotiamine and lysozyme hydrochloride.

^b Acetaminophen, isopropylantipyrine, and/or allylisopropyl-acetylurea.

likely contribute to the clinical features of DRESS including prolonged and relapsing disease and multiorgan involvement. Although there are more complex individual host factors involved, autoimmune diseases including thyroiditis, graft-versus-host disease–like lesions, autoimmune polyglandular syndrome, systemic lupus, fulminant type I diabetes, and hemophagocytic syndrome after resolution of acute DRESS are hypothesized to occur in the setting of viral reactivation.^{17,109,110} These autoimmune diseases may occur as either subclinical or clinical later complications of DRESS. The most common long-term complication of DRESS is autoimmune thyroid disease.^{111–114} Recent studies have shown an association between autoimmune thyroid disease and HHV-6 infection and in vitro HHV-6 virus modulation of micro-RNA expression in thyrocytes and T-cell lines.^{115–118}

The Heterologous Immunity Hypothesis as a Model for the Pathogenesis and Risk of Immune-Mediated Adverse Drug Reactions

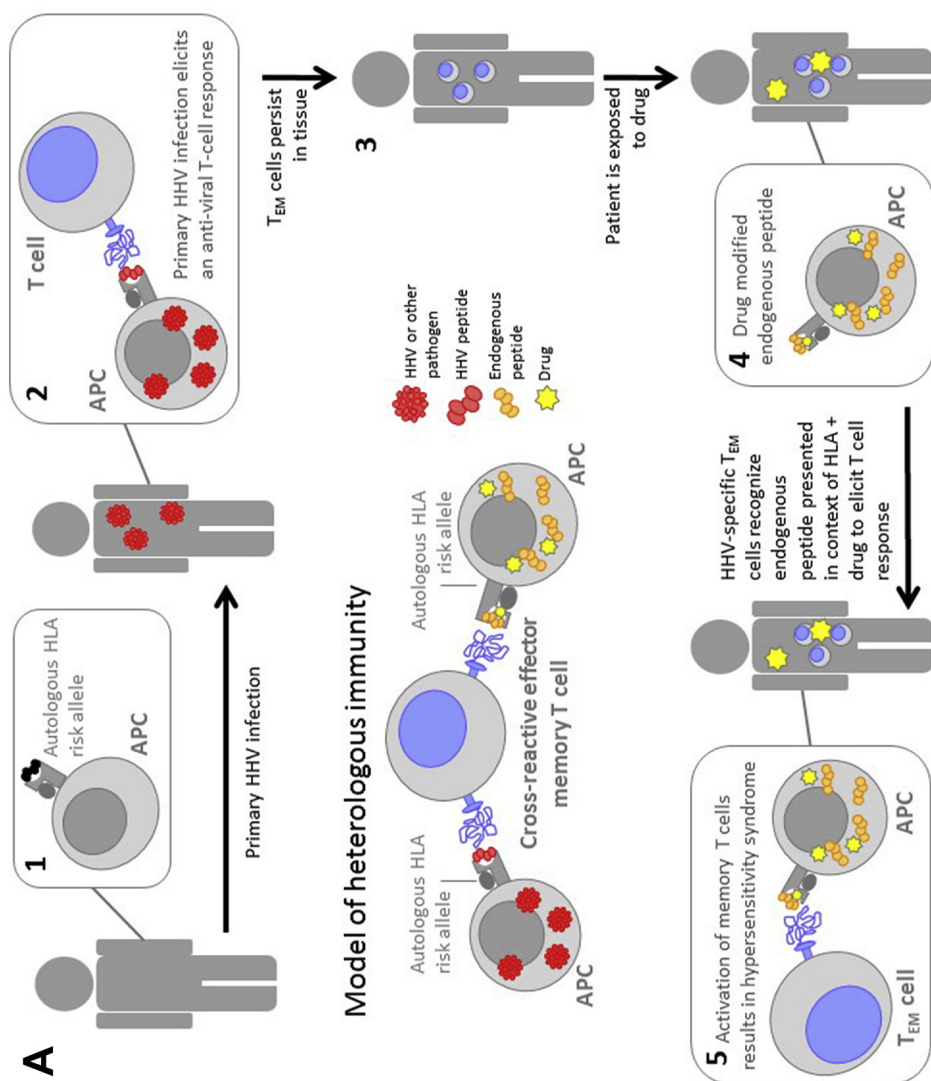
The adaptive immune system has evolved to contend with antigenic diversity through the generation of polyspecific TCRs that are capable of recognizing multiple epitopes

thereby enhancing our ability to defend against the wide microbial universe. This concept is termed heterologous immunity, and there exist numerous examples of clinical and experimental observations to support this paradigm.^{119,120} In the setting of organ transplantation, virus-specific memory T cells that are cross-reactive with allogeneic HLA have been implicated in allograft rejection. Recently, it has been recognized that these virus-specific memory T cells may be cross-reactive, sometimes mediated by a public TCR shared by unrelated individuals.¹²¹

Several observations regarding the clinical presentation and epidemiology of severe delayed IM-ADRs suggest that factors in addition to carriage of specific HLA alleles confer risk for the development of these reactions.

- *The “PPV gap.”* As noted, delayed IM-ADRs are characterized by a high negative predictive value for HLA association (approaching 100% in many cases) but a low PPV and, thus, only a minority of patients carrying an HLA risk allele will develop a hypersensitivity reaction (see [Table 1](#)). What are the genetic or ecologic factors that differ among those individuals who develop hypersensitivity and those who carry the risk HLA allele but tolerate the drug?
- *Diverse clinical phenotypes.* Delayed IM-ADRs are characterized by variable clinical phenotypes and specific phenotypes have been associated with carriage of different HLA alleles. What explains the phenotypic variation seen among these HLA-restricted IM-ADRs?
- *Latency period for clinical disease.* The time from first drug administration to the onset of clinical disease is widely variable across the delayed IM-ADR syndromes. For example, immunologically mediated abacavir hypersensitivity, defined as patch test–positive, HLA-B*57:01–positive abacavir reactivity, occurs in a narrow time window of less than 2 days to 3 weeks from first exposure to drug. SJS/TEN has a shorter latency period than DRESS and typically occurs 4 to 28 days after first drug exposure. Factors contributing to the variable timing of these syndromes are currently unclear.
- *Immunologic memory.* In some cases, immunologically mediated drug-specific recall reactions have been demonstrated several years after drug exposure and withdrawal. For example, abacavir- and carbamazepine-specific *in vivo* (skin patch test) and *ex vivo* (ELISpot) responses may remain positive many years after clinical IM-ADR in the absence of subsequent reexposure to a drug. Factors that lead to the maintenance of these long-lasting memory T-cell responses in some but not all T-cell-mediated ADRs are not known.

In the context of IM-ADRs, the requirement for preexisting virus-specific memory T cells that recognize drug-modified antigen could explain many clinical and immunologic features of IM-ADRs as well as the low PPV for HLA allele carriage as a sole predictor of IM-ADR risk^{122,123} ([Fig. 3A](#)). Of the pathogens that might prime such cross-reactive T cells, the HHV stand out as likely candidates. HHV are ubiquitous pathogens that establish lifelong infection and cellular latency and include HSV-1 and HSV-2, varicella zoster virus, Epstein–Barr virus, and cytomegalovirus. HHV are known to prime heterologous immune responses and act as likely sources of persistent antigen for the generation of long-lasting cross-reactive memory T cells. The heterologous immunity hypothesis for IM-ADR predicts that polyspecific T cells that are primed and maintained by HHV antigen cross-react with drug-modified peptide epitopes to elicit memory T-cell responses that result in the clinical IM-ADR syndromes (see [Fig. 3A, B](#)). This is one model by which the risk of IM-ADR might be predicted based on both genetics (HLA genotype) and ecologic factors such as past pathogen exposure that shape the repertoire of the memory T-cell pool. Future work to precisely



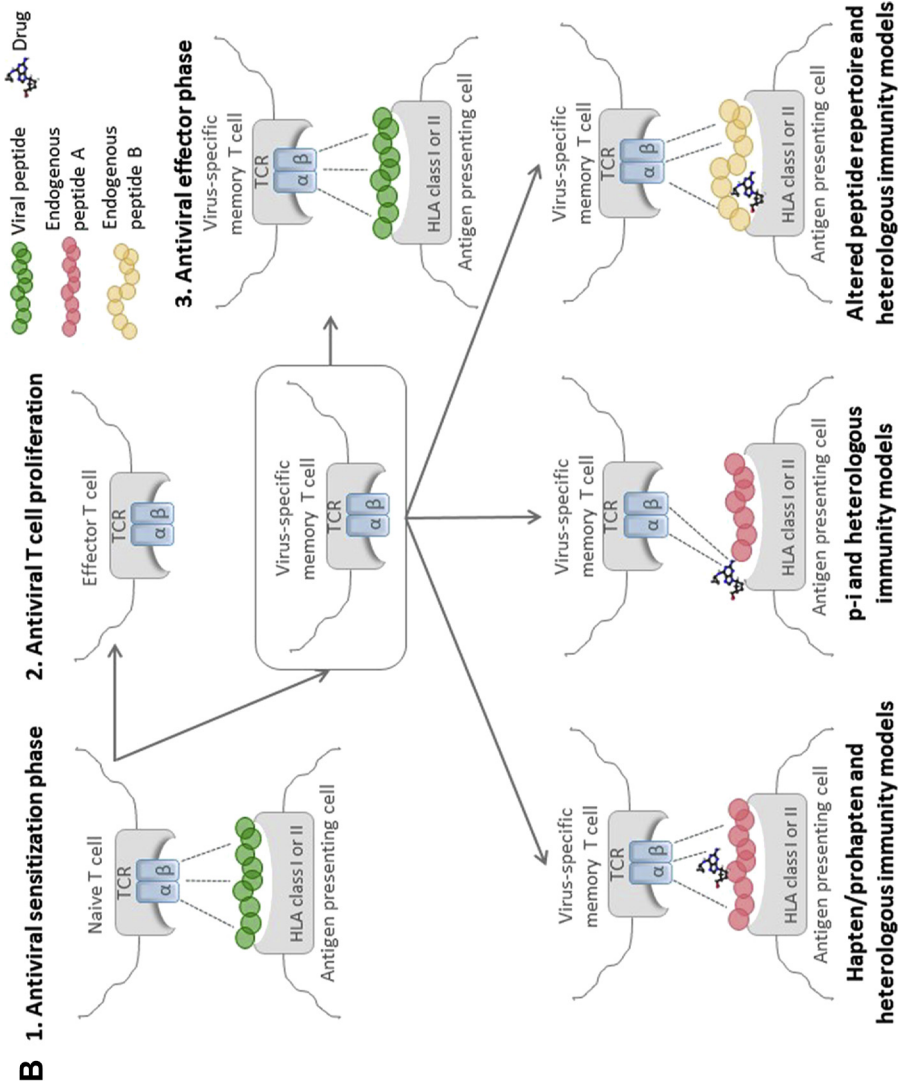


Fig. 3. (continued).

identify the T-cell subsets that participate in clinical IM-ADR is needed to define the pathogenesis of these ADRs.

OPPORTUNITIES FOR TRANSLATION INTO THE CLINICAL SETTING

The development of pharmacogenetic and immunologic assays to identify patients at risk for an IM-ADR before drug administration is a translational research priority given the substantial morbidity, mortality, and cost associated with these reactions. A few key examples demonstrate how basic science discoveries in this field have been translated into clinical practice to improve drug safety. After the PREDICT-1 and SHAPE trials in 2008, HLA-B*57:01 screening before abacavir prescription became part of international HIV treatment guidelines and has been incorporated into routine HIV clinical practice across the developed world.^{124–128} In 2007, the US Food and Drug Administration recommended HLA-B*15:02 screening in persons of Southeast Asian ancestry, where carriage of this allele is prevalent, before carbamazepine prescription and avoidance of carbamazepine therapy in all HLA-B*15:02 carriers, regardless of ethnicity, unless the benefits of treatment clearly outweigh the risk of ADR.^{129,130} In Taiwan, HLA-B*15:02 screening and restriction of off-label use of carbamazepine have resulted in dramatic decreases in the incidence of carbamazepine-associated IM-ADRs since these measures were implemented in 2010. Similar programs have been successfully implemented and shown to be cost effective in other parts of Southeast Asia. Screening for HLA-B*58:01 before the initiation of allopurinol has been recommended by the American College of Rheumatology for those with advanced renal failure and/or from high-risk populations such as persons of Southeast Asian ancestry.¹³¹ Similar conclusions are observed for HLA-B*13:01 screening before the use of dapsone among high-risk populations and where the mortality from dapsone hypersensitivity syndrome has been shown to be significant.¹³² For HLA screening to be safe and cost effective, it must be quality assured and used in the way intended to show “real world cost-effectiveness.”¹³³ A Hong



Fig. 3. Generation of heterologous immune responses that may contribute to the pathogenesis of severe delayed adverse drug reaction (ADRs). (A) According to the heterologous immunity model, the pathogenesis of a T-cell-mediated ADR, considered over the course of an affected individual's lifetime, can be summarized as follows. (1) A prerequisite feature of each T-cell-mediated ADR is carriage of the HLA risk allele; this is necessary but not sufficient for the reaction. (2) Infection by human herpes virus (HHV; or other pathogen) elicits a polyclonal T-cell response that contains viral infection. HHV establishes latency in the host. (3) Virus-specific memory T cells persist in the host. (4) At a subsequent time point, the subject is exposed to the offending drug. Drug endogenous peptide HLA epitopes are formed as described by 1 of 3 models outlined in Figs. 2 and 3B. (5) Virus-specific memory T cells are cross-reactive with drug endogenous peptide-HLA epitopes and acquire cytotoxic function directed against cells displaying drug-modified epitopes. This results in clinical immune-mediated (IM)-ADR. (B) Integration of the models of T-cell activation by small molecules and heterologous immunity. In the heterologous immunity model, memory T cells are generated after pathogen exposure and reside at specific anatomic sites. These memory T cells may cross-react with (1) haptenated endogenous peptides presented in the context of the HLA risk allele, (2) drugs that bind the T-cell receptor (TCR) and/or major histocompatibility complex (MHC) in a noncovalent manner under the P-I model, or (3) an altered repertoire of endogenous peptides after drug binding to the MHC. APC, antigen-presenting cell. (*Adapted from* White KD, Chung WH, Hung SI, et al. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: the role of host, pathogens, and drug response. *J Allergy Clin Immunol* 2015;136(2):226; [quiz: 235]; with permission.)

Kong trial showed that in the initial phase of mandatory HLA-B*15:02 screening the use of carbamazepine was displaced with use of phenytoin in HLA-B*15:02-negative individuals and the incidence of SJS/TEN overall remained unchanged.^{134,135}

SUMMARY AND FUTURE DIRECTIONS

Key attributes that have contributed to the translation of some HLA–drug–IM-ADR associations into routine clinical screening include the 100% negative predictive value for lack of IM-ADR in the absence of HLA allele carriage in the target population, the prevalence of the IM-ADR, the low number needed to test to prevent one case, and the paucity of safe, efficacious, and effective therapeutic alternatives. For IM-ADR with known HLA associations that do not meet these criteria, such as seen with the antibiotic flucloxacillin, HLA genotyping is neither cost effective nor feasible. In the case of flucloxacillin, approximately 14,000 patients would need to be screened to prevent 1 case of flucloxacillin-associated drug induced liver injury, and this feature makes flucloxacillin a poor target for preprescription screening at present. All delayed IM-ADRs with a known HLA association aside from HLA-B*57:01–restricted abacavir hypersensitivity (PPV 55%) defined to date are associated with a low PPV (<1%–5%) for risk as determined by HLA genotype alone. As a result, screening strategies that focus solely on HLA genotyping will inevitably lead to the denial of therapy to a large number of carriers of HLA risk alleles who would ultimately tolerate the drug in question without complication. Elucidation of factors in addition to or outside of the MHC that predict risk for development of an IM-ADR will provide further insights into the immunopathogenesis of IM-ADRs and to capabilities for both preclinical (drug development and design) and clinical prevention of these reactions.

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