Clinical reviews in allergy and immunology

Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

Evolving models of the immunopathogenesis of T cell–mediated drug allergy: The role of host, pathogens, and drug response

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: K. D. White has received research support from the National Institutes of Health (NIH). S. Mallal has received research support from NHMRC Australia and the NIH, receives royalties from UpToDate, and has a patent for HLA-B*57:01 testing for abacavir HSR. E. J. Phillips has received research support from NHMRC Australia and the NIH, receives royalties from UpToDate, has received honoraria from Merck and ViV, and has a patent for HLA-B*57:01 testing for abacavir HSR. The rest of the other authors declare they have no relevant conflicts of interest.

Activity Objectives:

1. To understand the role of host genetics, microbes, and drugs in the development of immune-mediated (IM) adverse drug reactions (ADRs).
2. To understand the existing models and proposed heterologous immunity model in the pathogenesis of IM-ADRs.
3. To understand the importance of genetic screening before drug administration in selected high-risk populations to prevent ADRs.

Recognition of Commercial Support: This CME activity has not received external commercial support.

List of CME Exam Authors: Karen Tuano, MD, Qurat Kamili, MD, Shuya Wu, MD, PhD, Sana Hasan, MD, Atoosa Kourosh, MD, MPH, Kwei Akuete, MD, MPH, Evan Li, MD, Rachel Jones, Larraine Lyter-Reed, NP, Teddi Thornhill, MD, Mehtap Abul, MD, Lenora Noroski, MD, MPH, and William T. Shearer, MD, PhD.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The exam authors disclosed no relevant financial relationships.

Immune-mediated (IM) adverse drug reactions (ADRs) are an underrecognized source of preventable morbidity, mortality, and cost. Increasingly, genetic variation in the HLA loci is associated with risk of severe reactions, highlighting the importance of T-cell immune responses in the mechanisms of both B cell–mediated and primary T cell–mediated IM-ADRs. In this review we summarize the role of host genetics, microbes, and drugs in IM-ADR development; expand on the existing models of IM-ADR pathogenesis to address multiple unexplained observations; discuss the implications of this work in clinical practice today; and describe future applications for preclinical drug toxicity screening, drug design, and development. (J Allergy Clin Immunol 2015;136:219-34.)

Key words: *Abacavir, adverse drug reaction, allopurinol, altered peptide, carbamazepine, drug reaction with eosinophilia and systemic symptoms, hapten, heterologous immunity, human herpesvirus, human leukocyte antigen, major histocompatibility complex, p-i, pharmacogenetics, pharmacogenomics, Stevens-Johnson syndrome, T-cell receptor, toxic epidermal necrolysis*

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Work reported in this article was supported in part by National Institutes of Health grant P50GM115305.

Received for publication March 11, 2015; revised May 11, 2015; accepted for publication May 12, 2015.

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0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2015.05.050

Abbreviations used

ADR: Adverse drug reaction
APC: Antigen-presenting cell
CDR: Complementarity-determining region
CMV: Cytomegalovirus
DRESS: Drug reaction with eosinophilia and systemic symptoms
FDA: US Food and Drug Administration
HHV: Human herpesvirus
HSV: Herpes simplex virus
IM: Immune mediated
OR: Odds ratio
p-i: Pharmacologic interaction
PREDICT-1: Prospective Randomized Evaluation of DNA Screening in a Clinical Trial
SHAPE: Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation Study Team
SJS: Stevens-Johnson syndrome
TCR: T-cell receptor
T_{EM}: Effector memory T
TEN: Toxic epidermal necrolysis
VZV: Varicella zoster virus

Adverse drug reactions (ADRs) are sources of major burden to patients and the health care system, and 50% of such reactions are preventable.[1-8] The majority of ADRs are predictable based on the on-target pharmacologic activity of the drug (Fig 1).[2,4-7,9,10] Up to 20% of all ADRs are not readily anticipated based on pharmacologic principles alone and, until recently, were considered "idiopathic" and "unpredictable." We now know that these reactions stem from specific off-target drug activity and include the immune-mediated (IM) ADRs, as well as off-target pharmacologic drug effects, such as those seen in patients with non–IgE-mediated mast cell activation syndrome (Fig 1).[11] IM-ADRs encompass a number of phenotypically distinct clinical diagnoses that comprise both B cell–mediated (antibody-mediated, Gell-Coombs types I-III) and purely T cell–mediated (Gell-Coombs type IV) reactions. The clinically relevant T cell–mediated drug reactions have been classified into delayed exanthema without systemic symptoms (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, and single organ involvement pathologies, such as drug-induced liver injury and pancreatitis. Allelic variation in the genes that encode the MHC family of proteins is often associated with risk of T cell–mediated drug hypersensitivity reactions in certain populations (Table I).[12-69]

This review focuses on the purely T cell–mediated drug hypersensitivity reactions, although the same principles and models likely apply to B cell–mediated reactions as well.[12,70,71] Here we provide an overview of the data supporting current models of T cell–mediated drug hypersensitivity reactions, propose a new model of drug hypersensitivity that expands on the existing models to include the role of microbial pathogen exposure in the generation of drug-specific T-cell responses, and discuss the implications for clinical practice and drug safety, design, and development.

OVERVIEW OF THE T-CELL IMMUNE RESPONSE, THE αβ T-CELL RECEPTOR, AND MHC

During maturation in the thymus, developing T cells undergo the sequential processes of positive and negative selection to generate a functional repertoire composed of a subject-specific, HLA-restricted subset of the total possible repertoire encoded by the T-cell receptor (TCR) genes. Engagement of the TCR by the appropriate peptide-MHC ligand results in T-cell clonal proliferation and differentiation into effector and memory phenotypes (Fig 2, *A*). A subset of the memory population, termed effector memory T (T_{EM}) cells, is characterized by the expression of the cellular marker CD45RO and lack of expression of the lymph node homing receptor CCR7.[72] This allows these cells to maintain surveillance in the tissue site of the initial antigen encounter, which is often the site of pathogen re-exposure. Because these cells require fewer costimulatory signals for activation and retain the ability to secrete proinflammatory cytokines (TNF-α, IL-2, and IFN-γ) and cytotoxic peptides, they are equipped and poised at strategic anatomic sites to initiate a swift immune response at reencounter with pathogen-specific antigens.[72-79] Contact with peptide-MHC is mediated by the αβ TCR, which is composed of 2 polypeptide chains that each contain a variable region (V_α and V_β). The distal residues of these variable sequences comprise 6 complementarity-determining regions (CDRs) that engage peptide-MHC on the surface of the target cell. The CDR1 and CDR2 loops mediate contact with the MHC binding groove α-helices, whereas the CDR3 loops mediate the majority of peptide contacts and thus display the greatest degree of sequence variability in the TCR gene.[80] The majority of MHC sequence diversity is found among amino acids in the binding groove that mediate peptide binding to the MHC. This polymorphism is presumably the legacy of selection pressure to confer immunity against a myriad of infectious pathogens.[81,82] Subjects who are heterozygous at the HLA loci will express a more diverse array of MHC proteins, thereby increasing the diversity of peptides presented to T cells. Theoretically, this will increase the probability that a pathogen will be recognized and elicit an immune response.[83-87]

IMMUNOPATHOGENESIS OF DRUG HYPERSENSITIVITY: ESTABLISHED MODELS

The role of T cell–mediated immune responses in the pathogenesis of many IM-ADRs has been firmly established. However, the specific molecular mechanisms that underpin these reactions have been elucidated in only a handful of cases. This is in contrast to the numerous reported associations among HLA alleles and drug-specific hypersensitivity reactions (reviewed in White et al[88] and Pavlos et al[12]). Three nonmutually exclusive models that describe how a small-molecule pharmaceutical might elicit T-cell reactivity have been developed, namely the hapten/prohapten model, the pharmacologic interaction (p-i) model, and the altered peptide repertoire model (Fig 2, *B*).

In the hapten/prohapten model the offending drug or a reactive metabolite of the drug binds covalently to an endogenous protein that then undergoes intracellular processing to generate a pool of chemically modified peptides. When presented in the context of MHC, these modified peptides will be recognized as "foreign" by T cells and elicit an immune response that might also include a B cell–mediated antibody response.[89-92] Examples of IM-ADRs that are associated with hapten modification of endogenous proteins include the binding of penicillin derivatives to serum

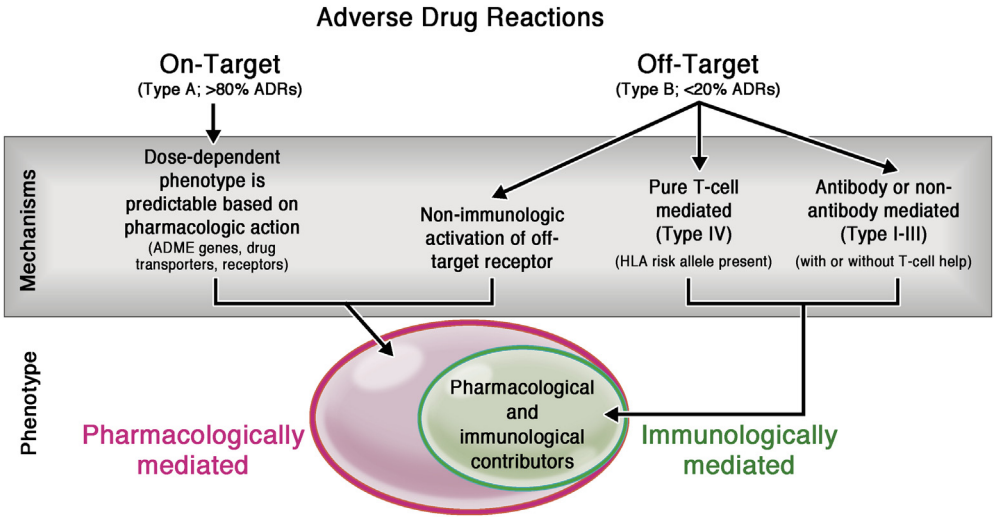

FIG 1. Overview of ADRs. ADRs can result from either on-target or off-target interactions between the drug and cellular components. Variation in the cellular processes that modulate drug absorption, distribution, metabolism, and excretion *(ADME)*; drug transporters; and target receptor expression contribute to ADRs that are primarily mediated by pharmacologic mechanisms *(pink oval)*. Off-target adverse effects can occur through both non-IM and IM mechanisms *(green oval)*. IM-ADRs include both antibody- and non–antibody-mediated (type I-III) and T cell–mediated (type IV) reactions.

albumin and protein modification by the nitroso sulfamethoxazole metabolite of sulfamethoxazole.[92,93]

Under the p-i model, the offending drug is postulated to bind noncovalently to either the TCR or MHC protein in a peptide-independent manner to directly activate T cells.[94] Experiments demonstrating that some drugs are able to trigger T-cell responses in the absence of intracellular peptide processing, such as after fixation of antigen-presenting cells (APCs), support this hypothesis.[95-98] This model has also been hypothesized to explain the *in vitro* T-cell reactivity that has been observed within seconds of drug exposure, a time course that is inconsistent with intracellular antigen processing or for IM-ADRs that are observed after the first encounter with a drug.[90,94]

When IM-ADRs adhere to the altered peptide repertoire model, the offending drug occupies a position in the peptide-binding groove of the MHC protein, thereby changing the chemistry of the binding cleft and the peptide specificity of MHC binding. It is proposed that peptides presented in this context are recognized as "foreign" by the immune system and therefore elicit a T-cell response.[99-101] Examples of well-described T cell–mediated drug hypersensitivity reactions are discussed below.

Drug-specific models: Abacavir

Data to support the altered peptide repertoire model of IM-ADRs have stemmed from careful characterization of the hypersensitivity reaction associated with the antiretroviral drug abacavir.[101-103] Abacavir is a guanosine analog that inhibits the HIV-1 reverse transcriptase enzyme and is used as part of combination therapy for the treatment of HIV-1 infection. In early studies hypersensitivity-type reactions were reported in approximately 5% to 8% of patients within the first 6 weeks after initiation of abacavir. These reactions were named the abacavir hypersensitivity syndrome and were characterized by fever, malaise, and gastrointestinal symptoms, respiratory symptoms, or both.[104,105] In 2002, a strong association between carriage of the HLA class I allele HLA-B*57:01 and abacavir hypersensitivity syndrome was reported.[13,14] Key clinical studies that confirmed the immunologic basis of this syndrome included the use of epicutaneous patch testing to demonstrate responses to abacavir in HLA-B*57:01–positive patients with a history of abacavir hypersensitivity syndrome.[15,16,106-108] These observations were followed by the Prospective Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT-1) and Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation Study Team (SHAPE) trials, which showed that screening for and exclusion of HLA-B*57:01 carriers from abacavir drug exposure could eliminate the incidence of abacavir hypersensitivity syndrome with a 100% negative predictive value and a 55% positive predictive value.[15,16] The PREDICT-1 study also showed that clinical onset of patch test–confirmed abacavir hypersensitivity cases occurred in as little as 1.5 days and up to 3 weeks after initiation of therapy (median, 8 days).[109] *Ex vivo* studies have shown that $CD8^+$ T cells derived from abacavir-hypersensitive patients are activated after exposure to abacavir-stimulated HLA-B*57:01–expressing APCs.[110,111] Additionally, T cells isolated from abacavir-naive, HLA-B*57:01–positive subjects have been shown to proliferate and become activated in response to abacavir exposure in 14-day cell culture systems.[112,113] Studies indicate that these reactive $CD8^+$ T cells have been shown to originate from both memory and naive T-cell populations and do not require costimulatory signals or $CD4^+$ T-cell help.[109,113] Additionally, Adam et al[113] demonstrated that a subset of abacavir-reactive T-cell clones derived from HLA-B*57:01–positive, abacavir-naive subjects cross-react with endogenous peptide presented in the context of HLA-B*58:01.[113] These data provide evidence that an abacavir-induced neoepitope can stimulate cross-reactive T cells *in vitro*. However, it remains unclear how these findings might account for the pathogenesis of abacavir hypersensitivity syndrome *in vivo*. Patch test confirmed abacavir hypersensitivity syndrome has only been associated with HLA-B*57:01 carriage and not with carriage of closely related B17 serotype alleles such as

TABLE I. HLA-associated drug hypersensitivity reactions

Drug	IM-ADR	Associated HLA alleles	PPV	NPV	NNT	Populations
Abacavir	Hypersensitivity syndrome	B*57:01[13-16]	55%	100%	13	European, African
Carbamazepine	SJS/TEN	B*15:02[17-22,28,31,37-39]	3%	100% in Han Chinese	1,000	Han Chinese, Thai, Malaysian, Indian
		B*15:11[23,24]				Korean, Japanese
		B*15:18, B*59:01, and C*07:04[40]				Japanese
		A*31:01[23,25-27]				Japanese, Northern European, Korean
	DRESS	8.1 AH (HLA A*01:01, Cw*07:01, B*08:01, DRB1*03:01, DQA1*05:01, DQB1*02:01)[41]				White
		A*31:01[29]	0.89%	99.98%	3,334	European
		A*31:01[29]	0.59%	99.97%	5,000	Chinese
		A*31:01[23,25-27]				Northern European, Japanese, and Korean
		A*11 and B*51 (weak)[26]				Japanese
	MPE	A*31:01[28]	34.9%	96.7%	91	
Allopurinol	SJS/TEN, DRESS	B*58:01 (or B*58 haplotype)[34-36,42-45]	3%	100% in Han Chinese	250	Han Chinese, Thai, European, Italian, Korean
Oxcarbazepine	SJS/TEN	B*15:02 and B*15:18[32,46]				Han Chinese, Taiwanese
Lamotrigine	SJS/TEN	B*15:02 (positive)[32]				Han Chinese
		B*15:02 (no association)[47,48]				Han Chinese
Phenytoin	SJS/TEN	B*15:02 (weak), Cw*08:01 and DRB1*16:02[20,30-32] CYP2C9*3[30]				Han Chinese
	DRESS/MPE	B*13:01 (weak), B*5101 (weak)[30] CYP2C9*3[30]				Han Chinese
Nevirapine	SJS/TEN	C*04:01[49]				Malawian
	DRESS	DRB1*01:01 and DRB1*01:02 (hepatitis and low $CD4^{+}$)[33,50]	18%	96%		Australian, European, and South African
		Cw*8 or Cw*8-B*14 haplotyp[106,107]				Italian and Japanese
		Cw*4[33,53]				Black, Asian, White, and Han Chinese
	Delayed rash	B*35,[33] B*35:01,[54] B*35:05[55]	16%	97%		Asian
		DRB1*01[56]				French
		Cw*04[33,57]				African, Asian, European, and Thai
		B*35:05, rs1576*G CCHCR1 status[55,58]				Thai
Dapsone	HSS	B*13:01[59]	7.8%	99.8%	84	
Efavirenz	Delayed rash	DRB1*01[56]				French
Sulfamethoxazole	SJS/TEN	B*38[43]				European
Amoxicillin-clavulanate	DILI	DRB1*15:01, DRB107 (protective), A*02:01, DQB1*06:02, and rs3135388, a tag SNP of DRB1*15:01-DQB1*06:02[60-62]				European
Lumiracoxib	DILI	DRB1*15:01-DQB1*06:02-DRB5*01:01-DQA1*01:02 haplotype[63]				International, multicenter
Ximelagatran	DILI	DRB1*07 and DQA1*02[64]				Swedish
Diclofenac	DILI	HLA-B11, C-24T, UGT2B7*2, IL-4 C-590-A[65-67]				European
Flucloxacilin	DILI	B*57:01, DRB1*01:07-DQB1*01:03[66,68]	0.12%	99.99%	13,819	European
Lapatinib	DILI	DRB1*07:01-DQA2*02:01-DQA1*02:01[69]				International, multicenter

DILI, Drug-induced liver injury; *HSS*, hypersensitivity syndrome; *MPE*, maculopapular eruption; *NNT*, number needed to test to prevent 1 case of IM-ADR; *NPV*, negative predictive value; *PPV*, positive predictive value; *SNP*, single nucleotide polymorphism.

HLA-B*58:01 or HLA-B*57:03, suggesting that the afferent immune response can only be restricted by HLA-B*57:01.[15,16,112]

Visualization of the molecular composition of the altered peptide repertoire model was provided in 2 simultaneous reports of the crystal structure of HLA-B*57:01 in complex with abacavir and peptide.[102,103] These studies demonstrate metabolism-independent, direct, noncovalent, and dose-dependent association of abacavir with amino acids in the HLA-B*57:01 binding cleft. Furthermore, approximately 20% to 45% of the peptides eluted from abacavir-treated HLA-B*57:01 APCs were distinct from those recovered from untreated cells, illustrating a dramatic shift in the repertoire

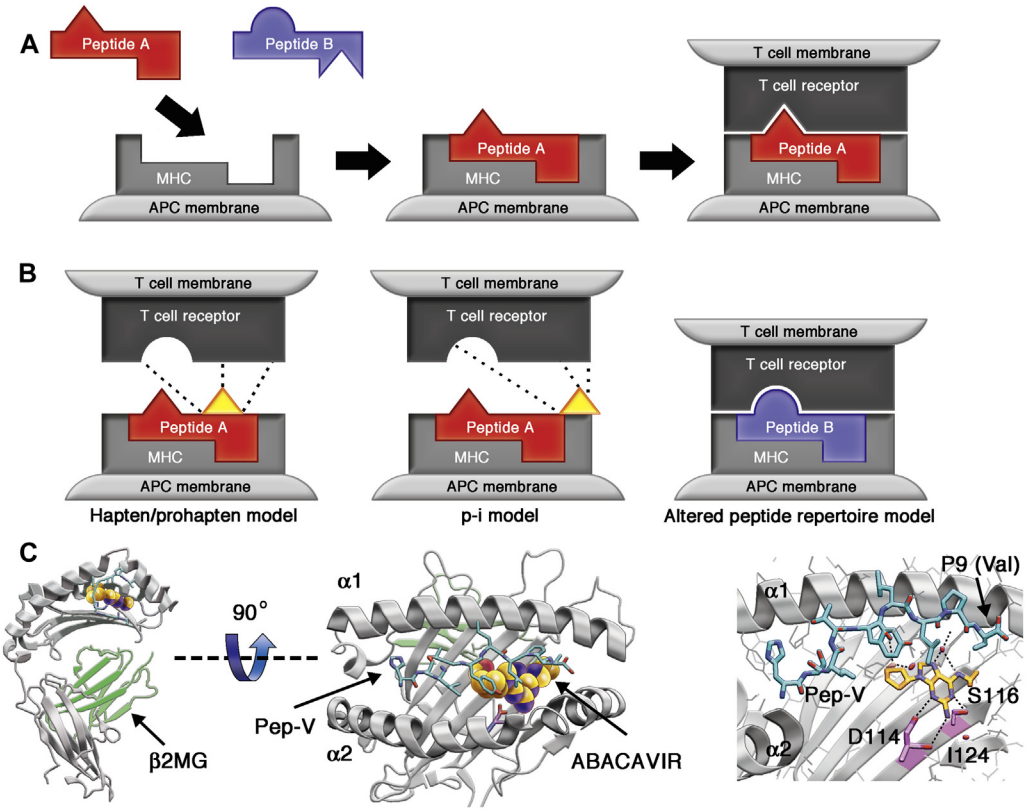

FIG 2. Models of T-cell activation by small molecules. **A,** Peptide selection and presentation by MHC. Peptide antigens are bound to the MHC protein in the intracellular environment and expressed on the surface of the APC. In the example shown, peptide A is able to bind MHC, but peptide B is not; thus peptide B is excluded from the repertoire of ligands presented in the context of this HLA allotype. **B,** Mechanisms 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 to a protein that then undergoes antigen processing to generate haptenated peptides that are presented by MHC. The haptenated peptide is recognized as a neoantigen to stimulate a T-cell response (eg, penicillin binding to serum albumin). The p-i model proposes that a small molecule can bind to HLA or T-cell receptor in a noncovalent manner to directly stimulate T cells. The interaction of allopurinol with HLA-B*58:01 and carbamazepine with HLA-B*15:02 might adhere to the p-i model. The altered peptide model postulates that a small molecule can bind noncovalently to the MHC-binding cleft to alter the specificity of peptide binding. This results in the presentation of novel peptide ligands that are postulated to elicit an immune response. **C,** The abacavir–HLA-B*57:01 interaction demonstrates the altered peptide repertoire model. Shown is the crystal structure of HLA-B*57:01 *(gray)* oriented with the peptide-binding groove facing up in *panel C1* and as viewed from above (bird's-eye view of the peptide-binding groove) in *panel C2*. Abacavir is represented as colored spheres: *orange* for carbon, *blue* for nitrogen, and *red* for oxygen. The peptide HSITYLLPV is shown in *cyan*. Hydrogen bond interactions between abacavir and HLA-B*57:01 and peptides are shown as *black* dashes. The amino acids that differ between HLA-B*57:01 and HLA-B*57:03, which does not participate in abacavir-associated hypersensitivity, are highlighted in *magenta*.[102] A video demonstrating the interactions of abacavir and the HLA-B*57:01 protein is available as Video E1 in this article's Online Repository at www.jacionline.org.

of HLA-B*57:01–bound peptide in the presence of abacavir.[101-103]

Drug-specific models: Aromatic amine anticonvulsants

Carbamazepine is an aromatic amine anticonvulsant used for the treatment of epilepsy, bipolar disorder, and trigeminal neuralgia. The spectrum of IM-ADRs that have been reported after carbamazepine administration is varied and includes SJS/TEN, maculopapular exanthema, and DRESS.[114] In a 2004 study it was demonstrated that carriage of the HLA-B*15:02 allele was associated with carbamazepine-induced SJS/TEN in Han Chinese patients (100% carriage in patients with carbamazepine-associated SJS/TEN vs 3% carriage in carbamazepine-tolerant control subjects; negative predictive value approaches 100%).[17] This association was later confirmed in persons of Thai, Malaysian, and Indian ethnicities.[18-22,115,116] Subsequent studies identified a dominant TCR clonotype, Vβ-11-ISGSY, from 84% of patients with carbamazepine-associated SJS/TEN. This TCR was found in only 14% of carbamazepine-naive healthy control subjects and absent in carbamazepine-tolerant patients.[117] Additionally, T cells derived from carbamazepine-naive, HLA-B*15:02–positive, and TCR Vβ-11-ISGSY–positive patients acquired a cytotoxic phenotype after carbamazepine exposure

in cell-culture experiments that was blocked by the addition of Vβ-11-ISGSY–specific antibody.[117] More recent experiments involving next-generation sequencing of T cells obtained from the blister fluid of 8 Taiwanese patients with HLA-B*15:02–associated carbamazepine-induced SJS/TEN demonstrated a predominance of a T-cell clonotype bearing a separate specific TCR (Hung and Chung, unpublished data). These studies are the first to identify the concomitant involvement of both a specific HLA allotype and TCR clonotype in the pathogenesis of an IM-ADR. However, the structural basis for this association has not been fully characterized.

Carbamazepine presentation in the context of HLA-B*15:02 has been shown to be independent of intracellular drug or antigen processing but does require MHC-peptide binding to stabilize the peptide-MHC complex on the cell surface. *In vitro* studies have demonstrated carbamazepine binding to other members of the HLA class I B75 serotype family, suggesting that residues conserved among B75 alleles are involved in the HLA-carbamazepine interactions.[118] Consistent with this hypothesis, mutagenesis and modeling studies have shown that the carbamazepine-binding site on HLA-B*15:02 maps to the vicinity of the B pocket of the MHC peptide-binding cleft, specifically residues Asn63, Ile95, Leu156, and likely Arg62, many of which are shared by members of the HLA-B75 family.[118] Although the observation that neither drug nor antigen processing is required for T-cell activation might support the p-i concept, a separate study found that approximately 15% of peptides eluted from carbamazepine-treated APCs expressing HLA-B*15:02 were distinct from those bound to HLA-B*15:02 in the absence of carbamazepine exposure, which is consistent with the altered peptide repertoire model of drug-HLA association.[103]

It is important to note that not all patients with carbamazepine-induced SJS/TEN carry the HLA-B*15:02 allele. In Indian, Japanese, and Korean cohorts carbamazepine-induced SJS/TEN has been observed in association with carriage of other HLA alleles in the B75 serotype family, including HLA-B*15:21, HLA-B*15:11, and HLA-B*15:08.[23,24,115] Carbamazepine-induced DRESS/drug-induced hypersensitivity syndrome is not associated with HLA-B*15:02. In addition, separate analyses have demonstrated an association between carbamazepine-induced IM-ADRs and carriage of the HLA-A*31:01 allele in Han Chinese (with DRESS but not SJS/TEN), Northern European, Japanese, and Korean populations.[25-28,119] However, this association was not consistently seen in subsequent studies, many of which also reported a range of phenotypic variation among the carbamazepine-induced IM-ADRs observed.[27,29,120,121] Work to more precisely define these associations and the structural basis for these interactions is ongoing.

Phenytoin, also an aromatic amine anticonvulsant, has been associated with severe cutaneous adverse reactions, including SJS/TEN, DRESS, and maculopapular eruption. A recent genome-wide association study followed by direct sequencing of candidate genes involving 105 cases of phenytoin-associated severe cutaneous reactions (including 61 patients with SJS/TEN, 44 patients with DRESS, and 78 patients with maculopapular eruption), 130 phenytoin-tolerant control subjects, and 3655 population control subjects from Taiwan, Malaysia, and Japan revealed a strong signal at loci in chromosome 10 (CYP2C) but not chromosome 6 (MHC). Further analysis demonstrated that phenytoin-induced severe cutaneous reactions are strongly associated with carriage of the CYP2C9*3 allele (overall odds ratio [OR], 11; 95% CI, 6.2-18; $P < .00001$; OR for SJS/TEN in subgroup analysis, 30).[30] Phenytoin is metabolized to an inactive metabolite by the CYP2C9 enzyme, and variation in this gene was associated with a 93% to 95% reduction in drug clearance in the study population. Additionally, delayed phenytoin clearance was observed in patients with phenytoin-induced ADRs in the absence of CYP2C9 variants, suggesting that other factors contribute to phenytoin accumulation. For example, renal or hepatic insufficiency or drug-drug interactions that inhibit cytochrome p450 likely predispose to phenytoin-induced ADRs, and these adverse reactions are, at least in part, dose dependent. This study also demonstrated a weak association between phenytoin-induced ADRs and carriage of HLA-B*13:01, HLA-B*15:02, and HLA-B*51:01. In a subgroup analysis the OR for HLA-B*15:02 carriage as a predictor of phenytoin-induced SJS/TEN was found to be 5.0 ($P = .25$), and this association has been observed in prior studies.[20,30-32] Combined screening for CYP2C9 variants and HLA-B*15:02 carriage improved the sensitivity for phenytoin-induced SJS/TEN to 62.5% but decreased the specificity (to 86.2% from 97.7% for the CYP2C9 variant alone) of the screening strategy.[30] These findings add to a growing number of observations showing that multiple processes, including pharmacologic and immunologic mechanisms, contribute to ADRs that might be mediated by the parent drug and that dose dependency is likely a key feature of both on-target and off-target ADRs (Fig 1).[33,122-125]

Drug-specific models: Allopurinol

Allopurinol is a xanthine oxidase inhibitor used to treat hyperuricemia and associated with an IM-ADR of variable but primarily cutaneous phenotype in approximately 2% of patients who initiate therapy. In 2005, it was demonstrated that the HLA-B*58:01 genotype is associated with allopurinol-induced SJS/TEN and DRESS in persons of Han Chinese ancestry (100% negative predictive value and 3% positive predictive value).[34] This association has since been identified in Thai, Korean, and Japanese populations, and it is estimated that HLA-B*58:01 explains approximately 60% of allopurinol-induced IM-ADRs in European and Japanese populations.[35,36,126-128]

Unlike abacavir or carbamazepine, both of which drive T-cell reactivity in the absence of drug modification, both allopurinol and its metabolite, oxypurinol, have been shown to contribute to the pathogenesis of allopurinol-induced IM-ADRs. *In vitro* studies have demonstrated that T cells isolated from both allopurinol-naive, HLA-B*58:01-positive subjects and from patients with a history of allopurinol-induced IM-ADRs rapidly proliferate and become activated after exposure to allopurinol or oxypurinol.[129,130] This response occurs within seconds of drug exposure, is not dependent on antigen processing or antigen presentation by APCs, and is abrogated if cells are washed to remove free drug. Taken together, this suggests that the drug-peptide-MHC interaction is noncovalent in nature and occurs after peptide-loaded MHCs are expressed on the surface of the APC. Although the majority of oxypurinol-induced T-cell reactivity was shown to be HLA-B*58:01 restricted, allopurinol-induced T-cell responses occurred in the context of multiple class I HLA alleles. Furthermore, this study also demonstrated polyclonal T-cell reactivity to both allopurinol and oxypurinol.[130] These findings might be explained by a modified version of the p-i hypothesis in which endogenous peptide bound to cell-surface

MHC intermittently and incompletely dissociates from the peptide-binding groove to permit allopurinol or oxypurinol to occupy a site in the binding cleft. This then alters the conformation of the bound peptide to create an antigen that is recognized by T cells to trigger an immune response.[130,131]

The low positive predictive value of HLA-B*58:01 carriage as a predictor of allopurinol-induced IM-ADRs suggests that other factors likely contribute to pathogenesis.[130] Indeed, it is now known that an increased serum oxypurinol concentration is an important risk factor for allopurinol-induced IM-ADRs.[132] The half-life of orally administered allopurinol is only 1 to 2 hours, whereas the half-life of oxypurinol is 15 hours in the setting of normal renal function and longer in the setting of renal insufficiency. Importantly, both impaired renal function and increased plasma concentrations of oxypurinol and granulysin, a known mediator of tissue injury in patients with SJS/TEN, have been shown to correlate with disease severity and mortality in patients with allopurinol-induced SJS/TEN/DRESS, demonstrating the dose dependency of these responses.[132,133]

T-CELL PLASTICITY AND EXPANDED MODELS OF IM-ADR PATHOGENESIS

Protective cellular immunity requires that our T-cell repertoire responds to an extraordinarily large number of potential antigens.[134-136] One way in which our immune system has evolved to contend with this degree of antigenic diversity is through the generation of polyspecific TCRs that are capable of recognizing multiple peptides. Thus a single TCR might recognize peptides derived from more than 1 pathogen, 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.[134,137]

The concept of heterologous immunity is similar to but distinct from that of direct alloreactivity, a setting in which a cross-reactive TCR recognizes peptide antigen presented in the context of non-self MHC. This phenomenon is the basis of acute tissue rejection after solid organ transplantation and graft-versus-host disease after hematopoietic stem cell transplantation. Alloreactivity is a common phenomenon, and multiple studies have demonstrated that alloreactive memory T-cell responses pose a significant barrier to tissue transplantation. These memory responses are derived, at least in part, from heterologous virus-specific memory T cells.[80,137-140] Of the viral pathogens that have been shown to be associated with T-cell alloreactivity, members of the human herpesvirus (HHV) family have been most frequently observed and best characterized.[141] This is not surprising given that heterologous immune responses stem from pre-existing memory T cells and that HHV-specific T cells, such as those directed against EBV and cytomegalovirus (CMV), make up a significant proportion of the memory pool.[142-146]

Multiple models have been experimentally validated to describe the molecular events that form the foundation of cross-reactive T-cell responses. First, a single memory T cell might be expected to recognize peptide-MHC complexes that are structurally similar to the primary peptide-MHC immunogen and in which the molecular contacts are preserved. Interactions such as this are considered examples of molecular mimicry, and it has been shown that neither HLA restriction nor peptide sequence homology are prerequisites for the development of heterologous responses. For instance, the human TCR LC13 recognizes the EBV-immunodominant epitope FLRGRAYGL bound to HLA-B*08:01 but has also been shown to recognize endogenous peptides presented in the context of HLA-B*44:02 and HLA-B*44:05. Crystal structures of each LC13-peptide-MHC complex revealed that the molecular contacts are nearly identical among these pairs despite significant sequence diversity among the HLA proteins and the peptides themselves.[147] Thus conservation of the structural and chemical properties of the contact residues at the TCR-peptide-MHC interface is key to cross-reactivity by the molecular mimicry model.[148]

Another mechanism that might promote TCR cross-reactivity involves the structural flexibility of the TCR protein itself. As discussed previously, the regions of the TCR that mediate contact with peptide-MHC, the α- and β-chain CDR1 through CDR3, rest atop flexible arms in the folded protein. Because of this, the TCR can alter peptide-MHC interactions by shifting the orientation of the CDRs through an "induced fit" mechanism.[80] For example, the murine BM3.3 TCR was shown to recognize 2 antigenically distinct peptides through large conformational shifts in the orientation of the CDR3α loop.[149,150] The 2 peptides used in these studies shared no sequence homology, but both were presented in the context of the mouse HLA homolog H-2K^b. Similarly, large conformational shifts in the orientation of the CDRs have been demonstrated in structural comparisons of free versus bound TCRs in multiple studies (reviewed in Rudolph et al[80]). Furthermore, it has also been shown that some cross-reactive TCRs recognize multiple peptide-MHC complexes through entirely distinct binding orientations with little to no overlap among contact residues at the TCR-peptide-MHC interface.[151] Thus alterations in the protein-protein interactions, either through modulation of flexible domains of the TCR or through an alternate binding strategy, can afford a single TCR the ability to engage multiple ligands.

Unexplained features of T cell–mediated ADRs

Although the existing models that describe drug-peptide-MHC interactions illuminate key features of T cell–associated ADR pathogenesis, many important observations related to these reactions remain unexplained. For example, what might account for the differences among the clinical phenotypes of individual ADRs? Abacavir hypersensitivity syndrome is characterized predominantly by fever and gastrointestinal and respiratory symptoms and is less commonly associated with rash. In contrast, the T cell–mediated hypersensitivity reactions associated with carbamazepine exposure are most commonly severe cutaneous and systemic reactions, such as SJS/TEN and DRESS. Carbamazepine has also been shown to cause the full spectrum of IM-ADRs, and specific phenotypes have been associated with carriage of specific HLA alleles (Table I). There also exists wide variability in the timing of clinical onset of many IM-ADRs. For example, immunologically mediated abacavir hypersensitivity syndrome has been demonstrated to occur within as little as 1.5 days from first exposure to up to 3 weeks after initiation of therapy.[15] Similarly, onset of carbamazepine-induced IM-ADRs has been observed to occur over a broad timeframe, with onset of symptoms generally occurring later, after 2 to 8 weeks of drug therapy.[114]

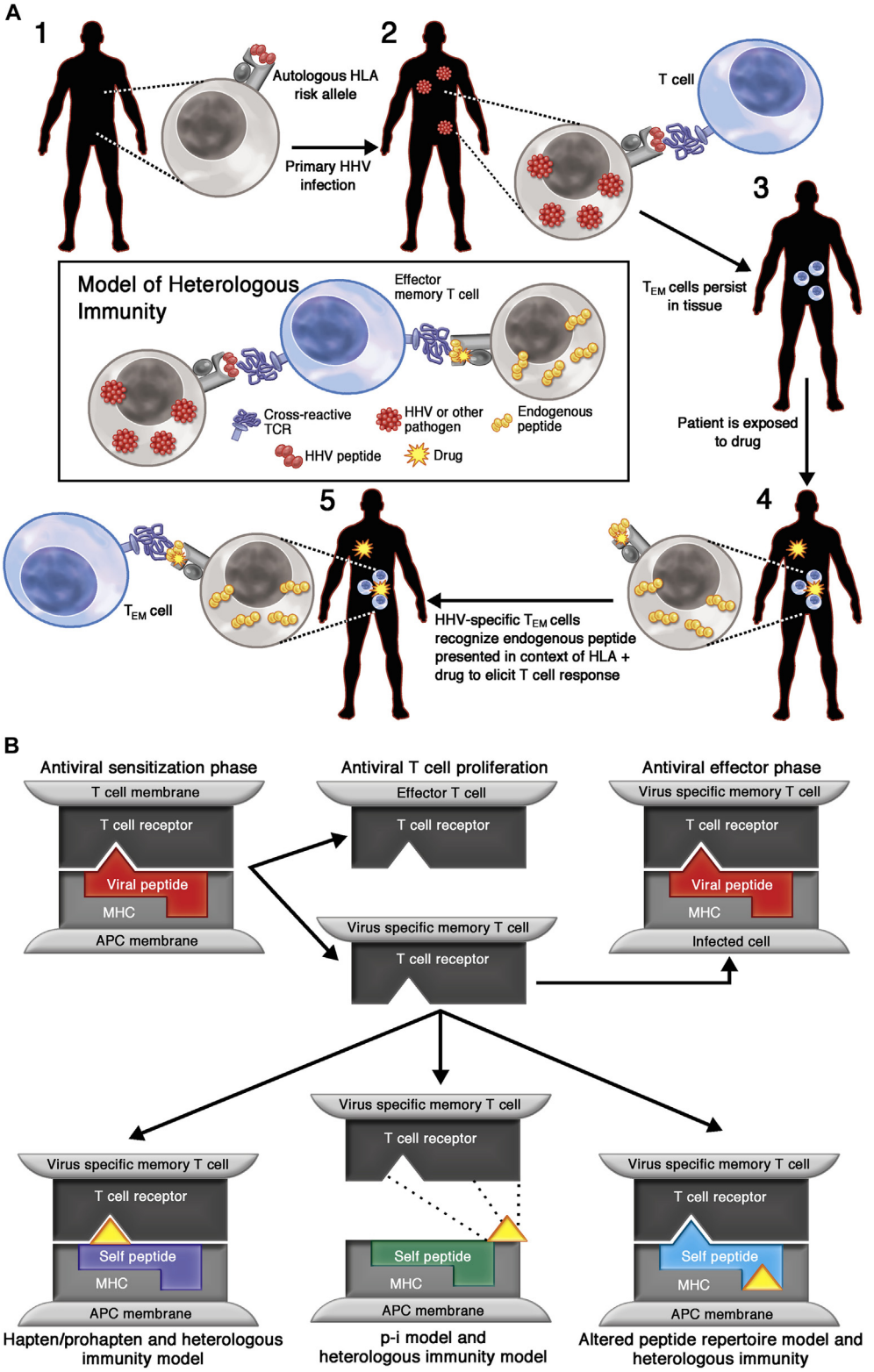

FIG 3. Generation of heterologous immune responses that contribute to the pathogenesis of T cell–mediated ADRs. **A,** Timeline of the generation of IM-ADRs. According to the heterologous immunity model, the generation of an IM-ADR requires the presence of the HLA risk allele, infection by HHV (or other pathogen), and the generation of a pathogen-specific memory T-cell response that is cross-reactive with drug-induced peptide epitopes presented much later. **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 can cross-react with (1) haptenated endogenous peptides presented in the context of the HLA risk allele; (2) drugs that bind the TCR, MHC, or both in a noncovalent manner under the p-i model; or (3) an altered repertoire of endogenous peptides after drug binding to MHC.

Another unexplained outcome, as demonstrated in Table I, is that many of the T cell–mediated ADRs are characterized by a high negative predictive value for HLA association, but paradoxically, the positive predictive values for these associations are much lower. For instance, why is it that 55% of HLA-B*57:01 carriers will have a hypersensitivity reaction in response to abacavir exposure, but only 3% of HLA-B*15:02 carriers exposed to carbamazepine will have SJS/TEN? What are the differences among those subjects who have abacavir hypersensitivity syndrome and carbamazepine-SJS/TEN and those who do not? It is notable that *in vitro* abacavir-specific $CD8^+$ T-cell responses can be elicited from 100% of HLA-B*57:01–positive, abacavir-naive healthy blood donors, but *in vivo* $CD8^+$ T-cell responses, as demonstrated by skin patch testing, occur only in HLA-B*57:01–positive patients with prior abacavir exposure and a history of a hypersensitivity reaction.[112,152] What mechanisms might account for these discrepant observations?

Finally, in some cases, immunologically mediated drug-specific recall reactions have been demonstrated years after drug exposure and withdrawal. For example, it has been shown that abacavir-specific *in vivo* (skin patch test) and *ex vivo* (ELISpot) responses remain positive years after clinical abacavir hypersensitivity syndrome in the absence of subsequent re-exposure to abacavir.[109,110,152] Similarly, long-lived T-cell responses have been observed in patients with a history of carbamazepine-SJS/TEN years after clinical reaction.[153-155] What antigen is maintaining these memory T-cell responses?

Incorporating heterologous immunity into IM-ADR models

We propose that some T cell–mediated hypersensitivity reactions likely represent yet another example of heterologous immunity. According to this model, a substantial proportion of the cross-reactive T-cell responses likely stem from activation of pathogen-specific T_{EM} cells sensitized much earlier that subsequently recognize the neoantigen created by drug exposure (Fig 3, *A*).

Of the microbial pathogens that might prime such heterologous immune responses, the HHVs stand out as likely sources of persistent antigen for the generation of long-lasting cross-reactive T cells. The HHVs are ubiquitous pathogens that are notable for their ability to establish lifelong infection and cellular latency. Periodically, the latent HHVs will turn on transcriptional programs that result in presentation of viral proteins that stimulate the local population of virus-specific memory T cells. Activation of these T-cell responses results in rapid containment of viral replication and forces the virus to return to a quiescent state. A consequence of this intermittent stimulation is the expansion of virus-specific memory T cells without the development of T-cell exhaustion.[156] Multiple studies have demonstrated that CMV-specific $CD4^+$ and $CD8^+$ T cells account for a major proportion of the total memory T-cell repertoire in CMV-seropositive adults and that this proportion increases with aging (estimated to be 10% to 40% of the total $CD4^+$ repertoire and up to 10% of the total $CD8^+$ repertoire).[142-145] Recently, longitudinal studies involving human subjects with a history of genital herpes simplex virus (HSV) infection have demonstrated that HSV-specific $CD8^+$ T cells are retained in the genital mucosa after infection as tissue-resident memory T cells long after active infection is contained. These cells are mostly $CD3^+$ and in human subjects are likely to express CD8αα and CD69 and secrete cytotoxic molecules, such as perforin and granzyme.[75,157]

According to the heterologous immunity model (Fig 3, *A*), the pathogenesis of a T cell–mediated ADR considered over the course of an affected subject's lifetime can be summarized as follows. First, 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.

Second, the subject acquires primary infection by HHVs (or other pathogen). HHV peptides are presented in the context of the HLA risk allele, and a polyclonal $CD8^+$ T-cell response contains the virus. The HHV establishes latency, and the T-cell response contracts.

Third, memory T cells persist at the site of antigen encounter. This cell population is intermittently stimulated by viral antigens during viral reactivation. Activation of T_{EM} cells forces the virus back into latency.

Fourth, later in life, the subject is exposed to the offending drug. The drug interacts with the pathogenic HLA protein through 1 or more mechanisms, as described in the text. This results in either neoantigen formation (as might be seen with haptenated peptide), direct activation of T cells, or presentation of an altered repertoire of endogenous peptides.

Fifth, the peptide-MHC complex is recognized by the TCR that was initially primed against HHV peptide either through molecular mimicry or through an alternate binding strategy. This triggers activation of memory T cells and results in clinical ADRs.

It is important to note that this model includes 2 points of HLA restriction: at the initial encounter with pathogen antigen to generate the primary T-cell response and then again at the time of endogenous peptide presentation in the setting of drug exposure. The requirement for antigen presentation in the context of the same HLA risk allele at 2 distinct steps in this process likely explains the specific HLA restriction that has been observed with clinical IM-ADRs, such as abacavir hypersensitivity syndrome and carbamazepine-induced SJS/TEN. It should also be recognized that the heterologous immunity model does not supplant the existing models that describe drug-peptide-MHC interactions (hapten/prohapten, p-i, and altered peptide repertoire models). Instead, we argue that heterologous immunity likely contributes to IM-ADRs that occur through any (or more than 1) of these models, as depicted in Fig 3, *B*.

Viral replication is not required for IM-ADRs under the heterologous immunity model

The heterologous immunity model is not dependent on the presence of active pathogen replication at the onset of the ADR. Under this model and as described above, the memory T-cell responses that are driving the IM-ADRs are derived from much earlier stimulation by pathogen peptides during active infection, reactivation, or both; are cross-reactive; and are stimulated by endogenous peptide epitopes presented in the context of the drug. At the initiation of IM-ADRs, endogenous peptide drug epitope drives the T-cell response, not pathogen replication, which needs to be distinguished from HHV (HHV-6/7, EBV, and CMV) reactivation that can occur in the setting of DRESS.[158-163] Key to these observations is that HHV replication, as detected by viral DNA PCR, has not been observed early in the clinical course of DRESS,

and generally, viremia is observed more than 2 weeks after symptom onset, suggesting that viral reactivation itself does not mediate DRESS onset.[159-162] Therefore it is possible that this late viral reactivation is the result of general immune dysregulation. Expansion of virus-specific regulatory T cells has been identified late in the course of DRESS, and long-term loss of suppressive function of regulatory T cells on clinical resolution of DRESS has been described.[164,165] HHV reactivation occurs almost exclusively in relation to DRESS and is not seen in patients with SJS/TEN in the absence of severe immunosuppression. Reactivation might be subclinical or could manifest as recurrence of 1 or more DRESS symptoms (eg, hepatitis or rash) in the absence of drug. Reactivation can also manifest as systemic or organ-specific viral disease, and a case report of recurrent CMV colitis on phenytoin rechallenge in a patient with a history of phenytoin-related DRESS 2 years before highlights this reproducibility of tissue-specific viral disease.[166] Autoimmunity can occur as both a subclinical and clinical late complication of DRESS, and this might relate to reactivation of HHV-6 and potentially other HHVs, although the specific immunopathogenesis is currently uncertain.[167,168]

Explaining the unexplained: The consequences of heterologous immunity in IM-ADR pathogenesis

The heterologous immunity model addresses many of the outstanding questions surrounding the pathogenesis of IM-ADRs. For instance, if we suppose that tissue-resident memory T cells that were previously primed against a mucocutaneous HHV, such HSV-1, HSV-2, or varicella zoster virus (VZV), were cross-reactive with peptides presented in the context of HLA-B*15:02 and carbamazepine, then this might explain why the carbamazepine-induced SJS/TEN phenotype is limited to the skin and mucosa. In contrast, the T_{EM} cell clonotype that participates in patients with abacavir hypersensitivity syndrome is likely derived after primary exposure to systemic HHVs, such as CMV, EBV, or HHV-6. This might explain why the abacavir hypersensitivity syndrome phenotype is one in which systemic symptoms and internal organ pathology are dominant features. In addition, tissue-specific expression of endogenous peptides might influence the phenotype restriction of certain ADRs, as has been suggested for tissue rejection after transplantation.[169] For example, it is plausible that the skin and mucous membrane limited phenotype associated with HLA-B*15:02–restricted carbamazepine-induced SJS/TEN might result from T-cell recognition of an endogenous peptide that is preferentially presented by keratinocytes and not by other cell types. It is important to note that the extent of tissue involvement in primary or reactivation HHV infection and in an ADR is a feature of antigen distribution in each case. For example, in the case of VZV reactivation in an immunocompetent subject (shingles), it is common that lesions appear in a dermatomal distribution determined by the site of VZV reactivation. Here the relevant antigen is present only in a limited tissue distribution, and therefore only T cells in the local area are activated. However, in the setting of ADRs, the drug is distributed widely and the relevant drug-induced epitope is presented throughout the body in the context of the MHC class I risk allele. The cross-reactive T-cell clonotype that was initially primed against VZV is now activated by the drug-peptide-MHC epitope, and the ensuing immune response is no longer limited to the site of VZV reactivation; the relevant antigen is now widely distributed, and the T-cell response follows this distribution. This might result in an ADR with expansive tissue involvement, such as SJS/TEN.

The heterologous immunity model might also account for the more rapid development of clinical symptoms observed with certain ADR phenotypes after initial drug exposure (eg, SJS/TEN vs DRESS). As previously described, T_{EM} cells require minimal costimulatory signals for activation and, when exposed to cognate peptide-MHC ligand, have the potential to rapidly proliferate and execute effector functions. This would occur on a timescale consistent with clinical onset and progression of many of the known HLA-associated ADRs. Furthermore, the requirement for both a specific HLA restriction and the use of a specific TCR clonotype that targets a specific pathogen epitope is one potential explanation for the very low positive predictive values observed for HLA carriage as a predictor of a particular ADR.[117] Indeed, a patient's prior history of pathogen exposure shapes which TCRs are present in the memory population. Thus HLA-B*57:01 carriers who do not have a hypersensitivity reaction in response to abacavir exposure might be predicted to have a different repertoire of TCRs that excludes the pathogenic clonotype involved in abacavir hypersensitivity syndrome and possibly a different history of HHV or other pathogen exposures compared with case patients with abacavir hypersensitivity syndrome. Finally, the heterologous immunity model might provide an explanation as to why some drug-specific T-cell responses are particularly durable. As mentioned previously, patients with a history of abacavir hypersensitivity syndrome and those with a history of carbamazepine-induced SJS/TEN have been shown to maintain robust epicutaneous patch test and *ex vivo* responses for years after therapy in the absence of continued drug exposure.[109,110,153-155] Generally, we would expect these responses to wane with time unless there exists a persistent source of antigen from a chronic persistent pathogen, such as HHV, that maintains these specific T-cell populations.

Early data that might support the heterologous immunity model include the identification of abacavir-reactive, pre-existing memory $CD8^+$ T-cell responses in HLA-B*57:01–positive, abacavir-naive healthy donor subjects. These memory T cells respond to abacavir *in vitro* without the need for costimulatory signals or $CD4^+$ T-cell help.[109,113] Additionally, as mentioned previously, analysis of blister fluid from patients with carbamazepine-induced SJS/TEN identified a highly frequent and specific TCR, which showed similarity to the TCR clonotype of the T cells isolated from the genital mucosa of patients with HSV-2 infection (Hung and Chung, unpublished data).[75] Work to define the cross-reactivity of these clonotypes is ongoing.

T-cell plasticity and drug-induced alloreactivity

Although the incorporation of heterologous immunity with the existing models of drug-peptide-MHC interaction provides a biologically plausible hypothesis to explain *in vivo* IM-ADR pathogenesis, it cannot account for all *in vitro* observations. As mentioned previously, recent studies have demonstrated that both memory and naive $CD8^+$ T cells obtained from HLA-B*57:01–positive, abacavir-unexposed subjects are activated after exposure to abacavir-treated cultured APCs independent of costimulatory signals or $CD4^+$ T-cell help.[109,113] About 40% of these cells reacted immediately to the newly formed abacavir-peptide-MHC complex, and a proportion of the abacavir-induced T cells might also cross-recognize peptide antigen

presented in the context of HLA-B*58:01. These findings demonstrate that the abacavir-peptide-MHC complex is capable of inducing the formation of alloreactive T cells *in vitro*, and this highlights the plasticity of the drug-induced T-cell repertoire.[113] However, these results conflict with certain features of clinical IM-ADRs and should therefore be considered with caution as a model for *in vivo* ADRs.

First, the *in vitro* finding that T cells from all HLA-B*57:01 donors, including those obtained from abacavir-naive patients, abacavir-tolerant patients, and patients with a history of abacavir hypersensitivity syndrome, respond to abacavir-stimulated APCs in cell-culture experiments is incompatible with patch test data showing that only patients with a history of abacavir hypersensitivity display *in vivo* T-cell responses to abacavir.[15,16,106-108]

Second, the observed reactivity of abacavir-induced $CD8^+$ T cells against peptide presented in the context of HLA-B*58:01 is inconsistent with epidemiologic data showing that clinical abacavir hypersensitivity syndrome occurs exclusively in the setting of HLA-B*57:01 carriage. Therefore the hypothesis that an alloallele response is mechanistic *in vivo* is incompatible with current clinical data, which show that the alloallele is not present in clinical abacavir hypersensitivity cases.

Finally, the *in vitro* observation that abacavir-induced T cells can react immediately to abacavir-stimulated APCs and that this reactivity can also be induced in the absence of any APCs does not correspond to the timing of the clinical onset of abacavir hypersensitivity syndrome or the requirement for HLA restriction seen in clinical cases. Taken together, these findings offer interesting insight into the polyspecificity of drug-induced T cells,[113,170] but it remains to be proved whether these mechanisms contribute to *in vivo* IM-ADRs.

It should be emphasized that the models presented above, including heterologous immunity and the molecular models of drug-peptide-MHC interaction (hapten/prohapten, p-i, and altered peptide repertoire model), are not mutually exclusive, nor is it requisite that they occur together for each IM-ADR. If the naive T-cell repertoire contributes to clinical IM-ADRs, then it is plausible that these reactions stem from *de novo* responses to the drug-peptide-MHC complex. This might help explain the variability of time to symptom onset for certain clinical syndromes, such as abacavir hypersensitivity syndrome and carbamazepine-induced SJS/TEN. It is possible that pre-existing cross-reactive memory $CD8^+$ T cells are pathogenic in cases of early-onset IM-ADRs through the heterologous immunity model (ie, abacavir hypersensitivity syndrome cases with clinical onset at 1.5 days) and that *de novo* activation of a naive T cell might account for the cases of IM-ADRs with somewhat delayed onset (ie, abacavir hypersensitivity syndrome cases with clinical onset at 3 weeks). Future work to precisely identify the T-cell subsets that participate in patients with clinical IM-ADRs is needed to define the pathogenesis of ADRs.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Predicting risk for ADRs in the clinical setting

The opportunity to identify patients who are at risk for an ADRs through pharmacogenomic screening before drug administration is an attractive concept given the substantial cost, morbidity, and mortality associated with these reactions. After the PREDICT-1 and SHAPE trials in 2008, the US Food and Drug Administration (FDA) issued a black box warning against the use of abacavir in patients known to carry the HLA-B*57:01 allele. Since that time, the US FDA, the US Department of Health and Human Services, the European Medicines Agency, the Clinical Pharmacogenomics Implementation Consortium, and multiple international HIV/AIDS organizations have recommended HLA-B*57:01 genotyping in any patient for whom abacavir therapy is considered and exclusion of abacavir therapy for any patient with a positive test result.[171-175] Similarly, the US FDA recommends screening for carriage of HLA-B*15:02 in persons of Asian ancestry before initiation of carbamazepine 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 an ADR.[176,177] HLA-B*15:02 screening before carbamazepine prescription has been funded and implemented in Taiwan since 2010, and as a result, along with restricted off-label use of carbamazepine, the incidence of carbamazepine-induced SJS/TEN has decreased dramatically, and allopurinol is now the most common cause of SJS/TEN in Taiwan, as well as in many other Asian countries. More recently, the strong association of allopurinol-induced SJS/TEN/DRESS with the HLA-B*58:01 genotype has led the Taiwan Department of Health to recommend screening before initiation of therapy, and a prospective study to evaluate the clinical utility of HLA-B*58:01 screening before allopurinol prescription in Taiwan is ongoing.[178]

Screening for HLA-B*58:01 before initiation of allopurinol has been endorsed by the American College of Rheumatology for those with advanced renal failure and/or from high-risk populations, such as those of Southeast Asian ancestry. A recommendation for HLA-B*58:01 screening has not been adopted by the US FDA or other jurisdictions at this time. The less than 100% negative predictive value and low positive predictive value of HLA-B*58:01 for allopurinol-induced ADRs in European, Japanese, and other non-Southeast Asian populations needs to be considered in the cost-effectiveness equation for HLA-B*58:01 screening.

These examples share key features that facilitate the translation of basic science discoveries into clinical practice. From a drug safety standpoint, the 100% negative predictive value for lack of reaction in the absence of allele carriage in the target population, the low number needed to test to prevent 1 case, and the paucity of safe, efficacious, and effective therapeutic alternatives are critical for incorporation of these screening strategies into clinical care. Additionally, the improved cost, turnaround times, and quality assurance associated with clinical laboratory diagnostic testing has allowed for feasible implementation of screening into clinical algorithms. In contrast, for many other drugs, such as flucloxacillin, a high-utility anti-staphylococcal penicillin used in the United Kingdom and Australia, pretreatment screening appears to be neither cost-effective nor feasible; almost 14,000 patients would need to be screened to prevent 1 case of flucloxacillin-induced drug-induced liver injury.

Given the low positive predictive values for the HLA-associated ADRs defined to date, screening strategies that focus solely on HLA genotyping will inevitably result in denial of therapy to a large number of carriers of HLA risk alleles who would ultimately tolerate the drug in question without complication and benefit from its use. For example, the positive predictive value of HLA-B*58:01 carriage for allopurinol-induced SJS/TEN/DRESS is only 3%. However, this low positive predictive value must be weighed against the extreme short- and long-term morbidity associated with SJS/TEN that is often not accurately

captured in standard cost-effectiveness analyses. In the case of abacavir, carriage of the HLA-B*57:01 gene is associated with a much higher positive predictive value of 55% for abacavir hypersensitivity syndrome. Although true immunologically mediated abacavir hypersensitivity occurs in only 2% to 3% of patients who take abacavir, up to 12% of those treated will have symptoms consistent with abacavir hypersensitivity secondary to a different pathogenic mechanism (eg, viral infection or immune reconstitution after treatment of HIV infection). Before the routine use of HLA-B*57:01 screening, this led to the false diagnosis of abacavir hypersensitivity in these patients and withdrawal of abacavir, a treatment that is safe in this setting, thereby limiting the patient's options for HIV therapy. To explain why a varying percentage of subjects carrying a specific risk allele will have a given IM-ADR, we propose that, in addition to carriage of an HLA risk allele, other factors, such as heterologous immune responses stemming from cross-reactive T cells primed against viral pathogens, are required for the development of some ADRs. Further delineation of the T-cell specificities involved in these reactions will enhance our understanding of pathogenesis and potentially allow us to refine our screening protocols to more precisely identify those patients who are truly at risk of an ADR. Advances in technologies to characterize the TCR repertoire within an individual patient, including deep sequencing techniques that target the TCR Vβ genes, ultrasensitive PCR assays to detect and quantify rare TCR variants, and sequencing assays designed to identify paired TCR α- and β-chain sequences, will enable these discoveries. Furthermore, new computational and experimental methods to identify the HLA-restricted HHV epitopes that prime the cross-reactive pathogenic TCRs in these reactions will shed light on the role of heterologous immunity as a mechanism of drug hypersensitivity.

Drug discovery: Preclinical screening to improve drug safety

IM-ADRs are less common than adverse effects based solely on pharmacology and are typically not recognized during the early phases of drug development. This is particularly true if studies are conducted in populations in which the genetic risk allele or alleles associated with such reactions are not prevalent. These reactions are typically recognized in the 5-year postmarketing phase of drug development after significant investment has been made in research and development. IM-ADRs have contributed to postmarketing drug withdrawal in a significant number of cases. Studies to define the biochemical and structural basis of severe IM-ADRs are providing assays to detect drug-HLA and drug-TCR interactions, as well as the presentation of drug-induced neoantigens by specific HLA alleles. Until we are able to understand and predict the additional factors that are necessary for IM-ADRs to occur, such as heterologous immunity, sole reliance on preclinical biochemical and structural approaches for screening drug compounds is likely to have an unacceptably low positive predictive values for the prediction of IM-ADRs *in vivo*.[179,180] Advances in our understanding of the mechanisms of IM-ADRs will facilitate the development of early screening strategies to identify compounds with high likelihood of eliciting an ADR, and in turn, this will improve drug safety, improve the efficiency of drug design, and reduce the cost of drug development.

What do we know?

- **Certain ADRs are strongly associated with variation in the HLA genes. Examples include associations between carriage of the HLA-B*57:01 allele and abacavir hypersensitivity syndrome, the HLA-B*15:02 allele and carbamazepine-induced SJS/TEN, and the HLA-B*58:01 allele and allopurinol-induced SJS/TEN, among others.**
- **Models that explain how a small-molecule pharmaceutical compound might interact with MHC proteins include the hapten/prohapten model, the p-i model, and the altered peptide repertoire model.**
- **Many of the associations between an ADR and HLA class I and/or II alleles are characterized by a high negative predictive value (approaching 100% in many cases), and this feature makes screening for the risk allele and exclusion of drug therapy for carriers a feasible approach to eliminate these reactions in at-risk populations. This strategy has been applied in the clinical setting for abacavir, carbamazepine, and, more recently, allopurinol, with a marked reduction in the incidence of these ADRs.**
- **The positive predictive values for many of these associations is less than 5%, which suggests that factors other than HLA gene carriage are required for the T cell–mediated drug hypersensitivity reactions to occur.**

What is still unknown?

- **We do not know what factors, in addition to HLA risk allele carriage, are required for a T cell–mediated drug hypersensitivity reaction to occur. An expanded model that incorporates the concepts of heterologous immunity with existing models that describe drug-peptide-HLA interactions (including the hapten/prohapten, p-i, and altered peptide repertoire models) is proposed. Direct evidence for this model is still lacking; however, if proved, it is likely to explain many outstanding observations regarding T cell–mediated drug hypersensitivity reactions, including the incomplete positive predictive value for HLA association, tissue specificity, short latency period (for some ADR), and long-lasting immunity to drugs in the absence of ongoing exposure.**

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