The role of HLA genes in pharmacogenomics: unravelling HLA associated adverse drug reactions

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Acknowledgments:

PTI is supported by an Australian National Health and Medical Research Council (NHMRC) Early Career Fellowship (1072159). AWP is supported by a NHMRC Senior Research Fellowship (1120467). JMc was supported by a NHMRC Project Grant (1120467) and Program Grant (1113293). Thank you to Julian Vivian and Jamie Rossjohn for assistance with structural figures.

Abstract

Genetic polymorphism in the genes encoding the Human Leukocyte Antigen (HLA) molecules enables presentation of a wide range peptide ligands thus maximising immune surveillance of pathogens. A consequence of the diversification of the HLA Ag-binding pocket is the enhanced opportunity for off-target binding of small drugs by HLA molecules, with subsequent immune reactivity. These potential off-target interactions are 'set up' to generate T cell mediated adverse drug reactions even though the precise mechanisms of most HLA-drug interactions are still poorly understood. The association between abacavir hypersensitivity syndrome and *HLA-B*57:01* is one exception that has been resolved at a molecular and mechanistic level. Here we explore the road to understanding the interaction between abacavir and the HLA-B*57:01 molecule and review the current state of understanding of interactions between other drugs and HLA molecules implicated in adverse drug reactions, which appear to involve multiple mechanisms. The continued expansion of the pharmacopoeia generates an imperative to understand these interactions at the molecular level in order to prevent the continued burden on individuals and the health care system.

Keywords

Human Leukocyte Antigen

Major Histocompatibility Complex

Adverse drug reactions

Antigen processing and presentation

Abacavir

In an ideal world, a therapeutic drug developed to treat a given medical condition would be effective and well tolerated in all patients. However, as with any biological system, drug efficacy can vary greatly between individuals, proving ineffective in some whilst highly effective in others, or, though well tolerated by the major part of the population, causing serious adverse reactions in a subset of individuals. Although many of these differences may be influenced by environmental factors such as concomitant disease or medications, the expanding field of pharmacogenomics aims to understand the genetic factors that influence the outcomes of drug therapy, both beneficial and adverse.

An adverse drug reaction (ADR) is defined by the World Health Organisation as a “response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease”(WHO 1972). ADRs are a leading cause of death in US hospitals (Lazarou et al. 1998) and they impose a significant global economic burden on health care, in part due to extended hospitalisation. The estimated cost of a single ADR is often cited as between US\$2000 and US\$5000 (Bates et al. 1997; Chan et al. 2008), and total costs per annum in Australia and the US have been estimated as AU\$660 million and US\$30.1-136.8 billion respectively (Johnson and Bootman 1995; Roughead and Semple 2009).

Most ADRs are considered predictable (Type A) based on the drug’s known pharmacological action, whilst a lesser number are considered idiosyncratic (Type B) involving drug-induced immune responses and are often termed non-predictable and considered dose-independent (Hunziker et al. 2002; Pichler 2003). Although Type B reactions only constitute about 13 % of ADRs (Hunziker et al. 2002), they are often more severe than Type A reactions generating an impetus to understand their mechanisms and facilitate avoidance. One sub-category of Type B ADRs comprise the T cell-mediated drug hypersensitivities. T cell-mediated reactions have diverse phenotypes, including systemic reactions (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS], also known as Drug-Induced Hypersensitivity Syndrome [DIHS]), as well as cutaneous reactions such as Maculopapular Exanthema (MPE), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) and Acute Generalised Exanthematous Pustulosis (AGEP) (Pichler 2003; Schrijvers et al. 2015). These reactions involve activation of drug-responsive T cells and tend to arise after at least 3-4 days drug treatment, and sometimes much longer exposure times (>30 days). The delayed time course parallels that of a classical T cell response to pathogens; involving a lag phase whilst naïve antigen specific T cells are primed before effecting antigen clearance (or attack on drug exposed cells). Symptoms abate on cessation of drug therapy, consistent with the removal of antigen, however reintroduction of the drug can prove fatal, presumably due to rapid activation of a memory T cell population (Arroyo and de la Morena 2001; Hetherington et al. 2001; Pichler et al. 2002).

Given the role of the Human Leucocyte Antigens or HLA molecules in T cell stimulation, investigators have sought, and found associations between reactions and the highly polymorphic *HLA* genes (Table 1). The most well characterised of these associations are with *HLA class I* alleles; *HLA-B*57:01* and abacavir hypersensitivity syndrome (AHS) (Hetherington et al. 2002; Mallal et al. 2002; Martin et al. 2004; Saag et al. 2008), *HLA-B*15:02* and carbamazepine induced SJS/TEN (Chang et al. 2011; Chung et al. 2004; Genin et al. 2014; Hung et al. 2006; Kulkantrakorn et al. 2012; Locharearnkul et al. 2008; Man et al. 2007; Mehta et al. 2009; Shi et al. 2012; Tangamornsuksan et al. 2013; Tassaneeyakul et al. 2010; Then et al. 2011; Wang et al. 2011; Wu et al. 2010; Zhang et al. 2011), and *HLA-B*58:01* and allopurinol hypersensitivities (Cao et al. 2012; Chiu et al. 2012; Dainichi et al. 2007; Genin et al. 2011; Hung et al. 2005; Kang et al. 2011; Kaniwa et al. 2008; Lonjou et al. 2008; Somkruea et al. 2011; Tassaneeyakul et al. 2009; Tohkin et al. 2013). Furthermore, genome wide association studies continue to highlight the HLA class I, uncovering numerous associations including those between *HLA-B*13:01* and Dapsone hypersensitivity syndrome (Zhang et al. 2013), *HLA-A*31:01* and carbamazepine-induced MPE, DRESS and SJS/TEN (McCormack et al. 2011; Ozeki et al. 2011), and *HLA-B*57:01* and flucloxacillin-induced drug-induced liver injury (DILI) (Daly et al. 2009).

Table 1: Discussed HLA associated ADRs

Drug	Usage	Reaction	HLA allele(s)	Genetic evidence of allele association	Mechanistic Evidence of specific interaction with HLA allotype
Abacavir	Antiretroviral	AHS	<i>B*57:01</i>	Population studies (Hetherington et al. 2002; Mallal et al. 2002; Martin et al. 2004; Saag et al. 2008)	<i>In vitro</i> T cell studies (Chessman et al. 2008; Illing et al. 2012) Structural resolution of interaction of drug and HLA molecule (Illing et al. 2012; Ostrov et al. 2012)
Allopurinol	Uric acid lowering	DRESS MPE SJS/TEN	<i>B*58:01</i>	Population studies (Cao et al. 2012; Chiu et al. 2012; Dainichi et al. 2007; Genin et al. 2011; Hung et al. 2005; Kang et al. 2011; Kaniwa et al. 2008; Lonjou et al. 2008; Ng et al. 2016; Somkruea et al. 2011; Tassaneeyakul et al. 2009; Tohkin et al. 2013)	<i>In vitro</i> T cell studies (Chung et al. 2015b; Lin et al. 2015; Yun et al. 2014; Yun et al. 2013)
Amoxicillin-clavulanate	Antibiotic	DILI	<i>A*02:01</i> <i>A*30:02</i> <i>B*18:01</i> <i>DRB1*15:01-DQB1*0602</i> haplotype	Population studies (Hautekeete et al. 1999; Lucena et al. 2011; Stephens et al. 2013)	<i>In vitro</i> T cell studies (Kim et al. 2015)
Carbamazepine	Anticonvulsant	SJS/TEN	<i>B*15:02</i> (and other alleles of B75 serotype)	Population studies (Chang et al. 2011; Chung et al. 2004; Genin et al. 2014; Hung et al. 2006; Jaruthamsophon et al. 2017; Kaniwa et al. 2010; Kim et al. 2011; Kulkantrakorn et al. 2012; Lochareernkul et al. 2008; Man et al. 2007; Mehta et al. 2009; Shi et al. 2012; Tangamornsuksan et al. 2013; Tassaneeyakul et al. 2010; Then et al. 2011; Wang et al. 2011; Wu et al. 2010; Zhang et al. 2011)	<i>In vitro</i> T cell studies (Ko et al. 2011; Wei et al. 2012)
		DRESS	<i>A*31:01</i>	Population studies (Genin et al. 2014;	Case study (Lichtenfels et al. 2014)

		MPE SJS/TEN		McCormack et al. 2011; Ozeki et al. 2011)	
Dapsone	Antibiotic	Dapsone hypersensitivity syndrome	<i>B*13:01</i>	Population study (Zhang et al. 2013)	
Flucloxacillin	Antibiotic	DILI	<i>B*57:01</i>	Population study (Daly et al. 2009)	<i>In vitro</i> T cell studies (Monshi et al. 2012; Willemin et al. 2013; Willemin et al. 2014; Yaseen et al. 2015)
Lapatinib	Tyrosine kinase inhibitor	DILI	<i>DRB1*07:01</i> <i>DQA1*02:01</i>	Population studies (Schaid et al. 2014; Spraggs et al. 2011)	<i>In vitro</i> T cell studies did not isolate drug responsive T cells (Faulkner et al. 2016)
Oxcarbazepine	Anticonvulsant	DRESS MPE SJS/TEN	<i>B*15:02</i>	Population studies (Chen et al. 2017; Hung et al. 2010)	<i>In vitro</i> T cell studies alongside carbamazepine (Wei et al. 2012)
Pazopanib	Tyrosine kinase inhibitor	DILI	<i>B*57:01</i>	Population study (Xu et al. 2016)	
Phenytoin	Anticonvulsant	SJS/TEN	<i>B*15:02</i>	Population studies (Chang et al. 2017; Hung et al. 2010; Lochareonkul et al. 2008)	
		DRESS	<i>B*56:02</i>	Case reports (indigenous Australians) (Harding et al. 2012) Population study (Thai) (Tassaneeyakul et al. 2016)	

For a more complete list of HLA associations see (Bharadwaj et al. 2012). AHS – abacavir hypersensitivity syndrome, DRESS – Drug reaction with eosinophilia and systemic symptoms, SJS/TEN – Stevens-Johnson syndrome/Toxic epidermal necrolysis, MPE – Maculopapular exanthema, DILI – Drug-induced liver injury.

Based on these data it is hypothesised that associations are the result of specific interactions between the causative drug and the expressed HLA molecule implicated. However, despite a concerted effort within the field, the precise mechanisms of drug-mediated T cell activation have yet to be defined for the majority of associations and a diverse range of mechanisms appear to come into play. To date, only the interaction between abacavir and HLA-B*57:01 has been resolved at a structural and mechanistic level (Chessman et al. 2008; Illing et al. 2012; Ostrov et al. 2012). Here we recount the road to understanding the interaction of HLA-B*57:01 and abacavir and explore the potential modes of HLA-drug interaction proposed in other HLA associated ADRs.

Genetic polymorphism of the HLA and peptide/drug presentation

The function of the classical HLA class I and II molecules is to display peptides derived from the breakdown of proteins produced within the cell (primarily HLA class I) or from the extracellular environment (primarily HLA class II) at the cell surface for immune surveillance. This array, known as the immunopeptidome, serves as a peptide-based summary of the protein production within the cell and its environment that can be accessed and interpreted by circulating T cells via their T cell receptors (TCRs). During infection the immunopeptidome will include pathogen-derived peptides which may be recognised as non-self by circulating T cells and stimulate CD8⁺ T cell responses against presenting cells (class I) or CD4⁺ T cell responses to modulate the immune response to aid pathogen clearance (class II).

Within the Major Histocompatibility Complex (MHC) region of the human genome there are genes encoding 3 classical HLA class I (*HLA-A*, *-B* and *-C*) and 3 classical HLA class II molecules (*HLA-DR*, *-DP* and *-DQ*). The *HLA* genes are highly polymorphic (>8000 functional HLA class I variants and >3000 HLA class II β chain variants) (Robinson et al. 2015) and most polymorphisms map to the antigen-binding cleft, the site of peptide binding (Reche and Reinherz 2003). Peptide binding is facilitated by a mixture of non-covalent interactions between the peptide main chain and conserved residues of the cleft, and sequence dependent contacts between peptide side chains and polymorphic cleft residues. Key in this second form of contacts are the anchor sites, pockets within the antigen-binding cleft that accommodate the side chains of peptide anchor residues. For HLA class I, these pockets are designated A, B, C, D, E and F, and for class II, P1, P4, P6, and P9. The exact topology and electrochemical environment of the anchor pockets, shaped by polymorphic residues of the HLA molecules, favours the binding of peptides containing complementary side chains at these locations and generates an allotype-specific, peptide-binding motif. Thus, the functional effect of HLA polymorphism is to change the array of both self and pathogen derived peptides that can be presented at the cell surface.

HLA associated ADRs, and T cell mediated ADRs in general suggest that HLA ligands may include additional classes of molecules other than just peptides, and that polymorphic residues not only shape the immunopeptidome, but dictate the ability of HLA molecules to interact with small molecules including select members of the pharmacopoeia. However, occupation of the antigen-binding cleft by a peptide is intrinsic to HLA molecule stability and HLA molecules are inefficiently transported from the endoplasmic reticulum (ER, site of HLA class I peptide loading) or endosomal compartment (site of class II loading) without incorporation of a peptide ligand. It is therefore considered unlikely that small molecule drugs (similar in size to 1-2 amino acids) would be able to stabilise HLA molecules alone, and three core hypotheses have been proposed as to how small molecule drugs interact with the HLA-peptide-TCR axis to induce drug specific T cell responses (Fig. 1).

1. Hapten/prohapten concept

The hapten/prohapten concept stems from evidence that certain small molecule drugs can react with specific amino acid side chains to covalently modify proteins. Haptenation of MHC-peptide complexes has been appreciated for many decades, such that specific immune responses to

chemically-modified MHC-peptide complexes have been intensively studied (Martin and Weltzien 1994). For instance, this is one mechanism of skin contact hypersensitivity (Akiba et al. 2002). A long-standing example of systemic drug hypersensitivity involves the β -lactam antibiotics which have been shown to modify proteins *in vitro* and *in vivo*, with numerous reports of drug modified human serum albumin (HSA) isolated from the blood of patients undergoing antibiotic treatment (Jenkins et al. 2009; Meng et al. 2017; Meng et al. 2011; Whitaker et al. 2011). In the hapten model of T cell activation, the reactive drug covalently modifies a cellular protein or peptide that on antigen processing generates a drug-haptenated peptide that can be loaded onto the HLA molecule and presented at the cell surface. A variation of this model is the prohaptent concept, where the parent drug is relatively inert, but metabolism generates a reactive metabolite that can modify proteins (Pichler et al. 2002). Both models require metabolically active antigen presenting cells, and rely on the antigen processing and presentation pathway, resulting in a lag between drug introduction and appearance of immunogenic HLA-peptide-hapten complexes at the cell surface. Alternatively, the drug may haptenate existing HLA-peptide complexes at the cell surface (Fig. 1a). Resulting complexes are as stable as constitutive HLA-peptide complexes and remain intact on removal of soluble drug, or washing of the cells at physiological pH. To date, no covalently drug-modified HLA-peptide complexes have been resolved at a structural level.

2. Non-covalent interaction with immune receptors

The non-covalent interaction with HLA-peptide complexes, sometimes called pharmacological interaction with immune receptors (p.i.), proposes that small molecules or drugs interact non-covalently with the HLA and/or TCR to create neoantigens that engender HLA-TCR ligation and T cell activation (Fig. 1b). Although not drugs per se, Nickel and Beryllium drive hypersensitivity by cationic ligation to HLA-peptide complexes thus creating neoantigens that lead to T cell reactivity (Clayton et al. 2014; Falta et al. 2016; Roediger and Weninger 2011). This model of neoantigen creation is resonant with immunogenicity of drug treated antigen presenting cells that is HLA-dependent, but independent of active metabolism. In this model, activity *in vitro* can be abrogated by washing at physiological pH, implying a labile interaction between the drug and HLA+/- peptide when forming the neoantigen (Schnyder et al. 1997; Zanni et al. 1998). Some formulations of this model speculate, without structural evidence, that the drug is present at the interface of the HLA and TCR interaction. However more recently, a variation has been proposed in which allosteric binding of the drug to the TCR alters TCR conformation promoting HLA-TCR ligation (Fig. 1c) (Watkins and Pichler 2013). Currently, no examples of this form of interaction have been resolved structurally.

3. Altered repertoire model

The altered repertoire model also proposes a non-covalent interaction of the drug and the HLA molecule, however, rather than interacting at the HLA-TCR interface, the drug interacts with the HLA molecule antigen-binding cleft, occupying part of the space normally available to peptide anchor residues. In so doing it alters peptide binding preferences of the HLA molecule, changing the peptide-binding motif, and allowing the entry of a novel array of self-peptides into the immunopeptidome. The resultant HLA-drug-peptide complexes are conformationally distinct from constitutive HLA-peptide complexes and are recognised as foreign by circulating T cells (Fig. 1d). Our initial work on abacavir hypersensitivity demonstrated that systemic reactions to abacavir resulted from drug-specific activation of cytotoxic CD8⁺ T cells that made pro-inflammatory cytokines. Recognition of abacavir *in vitro* required the MHC-I antigen presentation machinery and was restricted by HLA-B*57:01 but not closely related HLA allotypes with polymorphisms in the antigen-binding cleft. Therefore, we reasoned that the strong association of *HLA-B*57:01* with abacavir hypersensitivity reflected specificity through creation of a unique ligand(s) as well as HLA-restricted antigen presentation to CD8⁺ T cells (Chessman et al. 2008). We later proposed that unique ligands were the result of altered HLA-B*57:01 peptide repertoire (Bharadwaj et al. 2012), which was then demonstrated structurally as outlined below (Illing et al. 2012; Norcross et al. 2012; Ostrov et al. 2012). In the abacavir model,

it is presumed that drug-induced conformational changes in the binding of some peptides from the constitutive HLA-B*57:01 repertoire also contributes to the “altered repertoire”. This is consistent with a variation of the altered repertoire model (altered conformation) that has been proposed for allopurinol hypersensitivity in which the drug becomes incorporated in antigen-binding cleft of pre-formed HLA-peptide complexes due to the partial dissociation of the peptide allowing the drug to access the cleft and stabilise a novel peptide conformation (Fig. 1e) (Yun et al. 2014).

The story of Abacavir and the development of the altered repertoire model

Abacavir is a nucleoside reverse transcriptase inhibitor that first came into use in the late 1990s as part of multi-drug therapies to combat infection with Human Immunodeficiency Virus-I (HIV-I). Use was complicated by the development of an idiosyncratic adverse reaction (AHS) involving fever, rash, nausea, vomiting and fatigue in approximately 5% of individuals treated. Developing within the first 6 weeks of treatment (median onset 11 days), reactions ceased on drug withdrawal, and occurred more rapidly, and with greater severity, on re-challenge. Re-challenge proved fatal in several incidences, as did failure to cease drug therapy due to attribution of clinical symptoms to other causes (Easterbrook et al. 2003; Hetherington et al. 2001). A genetic component to AHS was first hinted by increased prevalence in individuals of European as opposed to African descent (Easterbrook et al. 2003), whilst T cell involvement was implicated by correlation of adverse reactions with higher CD8⁺ T cell counts at treatment outset and T cell infiltrate in positive patch test biopsies (Easterbrook et al. 2003; Phillips et al. 2002). These observations prompted GlaxoSmithKline (GSK; developer of abacavir) and Mallal *et al.* to investigate a role for genetic polymorphism in the MHC region of chromosome 6. Strikingly, the HLA class I allele *HLA-B*57:01* was reported in 46 % (39/84) and 78 % (14/18) of AHS patients compared to 4 % (4/113) and 2 % (4/167) of tolerant individuals (Hetherington et al. 2002; Mallal et al. 2002). Later studies, utilising stricter diagnostic criteria and immunological verification by epicutaneous patch testing, reported *HLA-B*57:01* in 100 % of immunologically confirmed AHS cases across ethnicities, although incidence of AHS was higher in individuals of European descent corresponding with higher *HLA-B*57:01* frequency (Mallal et al. 2008; Saag et al. 2008). With odds ratios of >900 quoted, the association of *HLA-B*57:01* and AHS is one of the strongest associations between a *HLA* allele and disease described (Martin et al. 2004; Saag et al. 2008). Indeed, the negative predictive value of 100 % and positive predictive value of approximately 50 % of *HLA-B*57:01* for AHS (Mallal et al. 2008; Saag et al. 2008) has resulted in the implementation of *HLA-B*57:01* screening prior to abacavir therapy (F.D.A 2008; Günthard et al. 2016). The value of *HLA-B*57:01* screening continues to be validated across ethnicities, with incidences of immunologically confirmed AHS reduced to 0 % when screening guidelines are adhered to (Carolino et al. 2017; Small et al. 2017).

The predictive value of *HLA-B*57:01* for AHS strongly suggested a mechanistic role for the *HLA-B*57:01* molecule in drug-induced T cell stimulation and disease progression. Depletion of CD8⁺, but not CD4⁺, T cells from the blood samples of AHS patients reduced abacavir-induced increases in extracellular TNF, and further implicated the HLA class I-CD8 T cell axis (Martin et al. 2004). In 2008 we demonstrated that cytokine producing, abacavir-specific CD8⁺ T cells could be expanded *in vitro* from the peripheral blood mononuclear cells of abacavir hypersensitive, as well as abacavir-naïve, *HLA-B*57:01*⁺ individuals (Chessman et al. 2008). Furthermore, the exquisite specificity of responses for *HLA-B*57:01* was recapitulated *in vitro*. Not only were antigen presenting cells expressing the closely related *HLA-B*57:03* (Asp114Asn and Ser116Tyr substitutions compared to *HLA-B*57:01*) unable to stimulate abacavir responses, a Ser116Tyr substitution alone abrogated immunogenicity. The immunogenic complex was stable at physiological pH and interference with the MHC-I antigen processing and presentation pathway, either through knock out of the chaperone tapasin or inhibition of the transporter associated with antigen processing (TAP), diminished responses. Based on these data it was initially hypothesised that abacavir generated stable

immunogenic complexes by furnishing the HLA with a drug haptenated peptide or peptides (Chessman et al. 2008; Martin et al. 2004).

Conversely, a turning point in our understanding of abacavir-induced T cell activation occurred when we, and two other research groups, sequenced the peptides isolated from HLA-B*57:01 of untreated and abacavir treated antigen presenting cells via liquid chromatography-tandem mass spectrometry (LC-MS/MS). Although no covalently modified peptides were identified, abacavir treatment perturbed self-peptide presentation by altering the C-terminal anchor preferences of HLA-B*57:01. Explicitly, in the absence of abacavir, HLA-B*57:01 ligands terminating in aromatic amino acids (Trp/Phe) predominated, however on abacavir treatment, peptides terminating in Ile/Leu/Val increased in prevalence, and non-covalently bound abacavir co-purified with HLA-B*57:01 (Illing et al. 2012; Norcross et al. 2012; Ostrov et al. 2012). These perturbations increased over time, consistent with *de novo* formation of HLA-drug-peptide complexes and transport from the ER (our unpublished data). Perturbation was consistent with an increase in affinity of Val, Ile and Leu terminating peptides for HLA-B*57:01 in the presence of abacavir, and abacavir co-purification, perturbation of the immunopeptidome, and changes in peptide affinity were unique to HLA-B*57:01 (absent for HLA-B*58:01 and HLA-B*57:03). Crystal structures of HLA-B*57:01, abacavir and three different peptide ligands revealed that abacavir bound within the antigen binding cleft of HLA-B*57:01, underneath the co-occupying peptide, partially occluding the F-pocket binding site of the peptide C-terminal anchor residue (Fig. 2). The intimate association of abacavir with Ser116 and Val97 explained the lack of interaction between abacavir and HLA-B*57:03 and HLA-B*58:01 respectively (Illing et al. 2012; Ostrov et al. 2012) and these structures have been used as a guide for rational redesign of abacavir to remove immunogenicity (Naisbitt et al. 2015).

Consistent with global perturbation of the immunopeptidome, abacavir responsive T cells are polyclonal and TCR usage varies between individuals suggesting that responses are elicited by HLA-drug-peptide complexes containing diverse peptides (Chessman et al. 2008; Illing et al. 2012). Indeed, different abacavir-responsive T cells clones show distinct kinetics of activation (Adam et al. 2012), consistent with altered timelines for accumulation of their target HLA-drug-peptide complexes at the antigen presenting cell surface during abacavir exposure. Together these data form a picture in which abacavir binding to HLA-B*57:01 generates a pseudo-allogeneic HLA molecule furnishing countless new targets for immune recognition and activation of both the naïve and memory T cell populations (Adam et al. 2014). Recent evidence that abacavir can activate the NLRP3 inflammasome suggests that drug-induced stimulation of innate pathways may also contribute to response potency (Toksoy et al. 2017).

The story of abacavir and its link to HLA-B*57:01 has provided the field with a model of how HLA-drug interactions can be resolved, provides a rational basis for HLA screening for avoidance of ADRs and suggests a pathway for potential drug redesign. Hopefully, these lessons, combining cellular, biochemical and structural techniques, provide a roadmap for understanding other associations between HLA and ADRs, mindful that novel mechanisms are likely to be unearthed along the way.

Carbamazepine-induced ADRs: Multiple ADRs, multiple HLA

Carbamazepine is an anticonvulsant used in the treatment of epilepsy. It causes a range of adverse reactions that show T cell involvement in pathophysiology including MPE, DRESS and SJS/TEN (Hari et al. 2001; Nassif et al. 2004). The most severe, SJS/TEN, is a bullous skin disease that is subdivided by severity into SJS, SJS/TEN overlap and TEN, based on the body surface area impacted (<10 %, 10-30 %, >30 % respectively). SJS/TEN has been strongly associated with *HLA-B*15:02* in several Asian populations, with the initial report by in a Han Chinese population finding *HLA-B*15:02* in 100 % (44/44) of SJS patients as compared to 3 % (3/101) of tolerant individuals (Chung et al. 2004; Tangamornsuksan et al. 2013). Interestingly other *HLA-B*15* alleles of the B75 serotype (of which *HLA-B*15:02* is a member), including *HLA-B*15:08*, *-B*15:11*, *-B*15:18* and *-B*15:21*,

have also been implicated in SJS/TEN (Jaruthamsophon et al. 2017; Kaniwa et al. 2010; Kim et al. 2011; Mehta et al. 2009; Shi et al. 2012). MPE and DRESS are not associated with *HLA-B*15:02*, but instead show weaker associations with *HLA-A*31:01* across both European and Asian populations (OR 6.4-57.6) (Genin et al. 2014). *HLA-A*31:01* is also implicated in SJS/TEN in populations where *HLA-B*15:02* is rare (McCormack et al. 2011; Ozeki et al. 2011). As for abacavir these studies have highlighted the need for strict phenotyping of reactions in order to accurately define HLA associations, and difficulties in accurate diagnosis of drug-induced MPE are a suggested cause of inconsistencies between studies characterising *HLA-A*31:01* associations (Yip and Pirmohamed 2017). Currently, screening for *HLA-B*15:02* in individuals of Asian ancestry is strongly recommended, whilst *HLA-A*31:01*⁺ status is flagged as a cause for caution and screening is suggested to be cost-effective (Plumpton et al. 2015).

Interestingly, screening for *HLA-B*15:02* to avoid ADRs has not proved the same universal success as for *HLA-B*57:01*. In Hong Kong, although the incidence of carbamazepine induced reactions has reduced since the implementation of screening recommendations, the reduction appears to have occurred in part due to general avoidance of carbamazepine rather than adherence to screening policy. Given that alternative medications are often more expensive and are also frequent causes of ADRs, in Hong Kong the benefits of screening have so far failed to live up to expectation. Indeed, although carbamazepine induced ADRs have reduced in frequency, reactions to anti-epileptics in general have not, with increased contributions from drugs such as phenytoin (Chen et al. 2014; Chen et al. 2016). Of note, severe cutaneous reactions to phenytoin have also been associated with *HLA-B*15:02* and *HLA-B*15:13* (differs by 5 amino acids) in certain populations (Chang et al. 2017; Lochareonkul et al. 2008). In addition the more distinct *HLA-B*56:02* (14 amino acids difference) has also been implicated in phenytoin induced hypersensitivity syndrome in indigenous Australians (3/3 reported cases compared to population frequency <15 %) (Clemens et al. 2016; Harding et al. 2012) and an association with SJS/TEN is reported in a Thai population (Tassaneeyakul et al. 2016). *HLA-A*31:01* does not appear to confer risk of phenytoin ADRs (McCormack et al. 2012).

Investigations of the mechanisms underlying HLA associations is most progressed in the case of *HLA-B*15:02* and carbamazepine-induced SJS/TEN. Carbamazepine responsive CD8⁺ T cells can be cultured *in vitro* from the blood of *HLA-B*15:02*⁺ SJS patients and are cytotoxic towards *HLA-B*15:02*⁺ B-Lymphoblastoid cells and keratinocytes in the presence of carbamazepine (Ko et al. 2011; Wei et al. 2012). Consistent with association studies, Wei *et al.* found that *HLA-B*15* alleles of the B75 serotype were also immunogenic, whilst those of the B62 and B72 serotypes were unable to elicit responses, suggesting Asn63 at the edge of the cleft of the B75 family members is a requirement for drug presentation (Wei et al. 2012). Drug presentation appears to be labile and independent of antigen processing and presentation machinery and, although non-covalently bound carbamazepine has been isolated with *HLA-B*15:02* of drug treated cells, no major perturbation of the peptide-binding motif has been observed (Illing et al. 2012; Wei et al. 2012; Yang et al. 2007). Activated T cells secrete IFN γ and granulysin matching the pathology of SJS lesions, and can be expanded from the blood of some, but not all, drug naïve *HLA-B*15:02*⁺ donors, but not tolerant individuals (Chung et al. 2008; Ko et al. 2011). Interestingly, cross-reactivity is observed with several structural derivatives of carbamazepine, including the newer antiepileptic oxcarbazepine which can also cause SJS/TEN associated with *HLA-B*15:02*, although at lower incidence and severity than carbamazepine (Chen et al. 2017; Wei et al. 2012).

Although *in silico* analyses have generated many hypotheses for carbamazepine-binding to *HLA-B*15:02* and related molecules (Illing et al. 2012; Jaruthamsophon et al. 2017; Wei et al. 2012; Zhou et al. 2016), to date no crystal structures have been solved. This may be due to the apparent labile interaction with *HLA-B*15:02*, and has led to the proposal that interactions require TCR stabilisation and that the drug may have more intimate contact with the TCR loops than the HLA itself (Zhou et al. 2016). In addition to *HLA-B*15:02*, Ko *et al.* suggested that TCR repertoire may play a role in distinguishing susceptible and tolerant individuals, identifying a common TCR clonotype across

16/19 SJS patients and 4/29 *HLA-B*15:02*⁺ drug naïve donors that was absent in tolerant individuals (Ko et al. 2011). A more drug-centric focus of the TCR may explain this more limited TCR usage by carbamazepine responsive T cells as compared to abacavir responsive T cells, where the drug is buried beneath a broad range of co-binding peptides. Whether the peptide occupying the HLA has any influence on carbamazepine binding or TCR recognition remains to be seen.

Allopurinol hypersensitivities: Exacerbations from gene dosage and drug concentration

Allopurinol is a purine analogue used for the treatment of hyperuricemia and gout. Like carbamazepine, it causes a range of ADRs including MPE, DRESS and SJS/TEN. An association with *HLA-B*58:01* was first reported in the Han Chinese where 100 % of patients (51/51) experiencing SJS/TEN or DRESS in response to allopurinol expressed *HLA-B*58:01*, as compared to 15 % of tolerant individuals (20/135) and 20 % of the population controls (19/93) (Hung et al. 2005). It has since been validated across several ethnicities, although *HLA-B*58:01* was not universally present in patients for all studies (Ng et al. 2016). Interestingly, not only has a gene dosage effect of *HLA-B*58:01* been reported (higher risk for homozygous individuals), but risk of severe reactions is increased in individuals with renal insufficiency which correlates with higher plasma levels of oxypurinol, the major metabolite of allopurinol (Chung et al. 2015a; Ng et al. 2016).

In vitro investigations of T cell responses have isolated CD8⁺ T cells responding to allopurinol or oxypurinol in *HLA-B*58:01*⁺ hypersensitive and drug naïve individuals, and responses appear biased towards oxypurinol (Chung et al. 2015b; Yun et al. 2013). Consistent with increased risk due to higher plasma oxypurinol levels, responses occur more readily at higher concentrations (Chung et al. 2015b; Yun et al. 2013). Furthermore, T cells secrete granulysin in accordance with high levels in patient plasma and the involvement of granulysin in SJS/TEN (Chung et al. 2015a; Chung et al. 2008; Chung et al. 2015b). T cell stimulation lacks the need for active antigen processing pathways within the antigen presenting cell and interactions between allopurinol/oxypurinol and *HLA-B*58:01* appear to be labile, suggesting a non-covalent ligation mechanism (Lin et al. 2015; Yun et al. 2014). Confoundingly, mutagenesis studies suggest that Arg97 in the base of the antigen binding cleft may be required for T cell stimulation and *in silico* docking experiments have placed allopurinol and oxypurinol within the antigen binding cleft reminiscent of the mode of abacavir binding (Lin et al. 2015; Yun et al. 2014). This led Yun *et al.* to propose an adaptation of the non-covalent and altered repertoire models in which allopurinol/oxypurinol can bind the base of the antigen-binding cleft of *HLA-B*58:01* molecules at the cell surface due to the plasticity of the interaction between peptide and HLA. In this model, momentary dissociation of the peptide, or portions of the peptide, grants the drug access to the antigen-binding cleft. On binding, the drug stabilises the HLA-peptide complex in a novel conformation that may be recognised as non-self and stimulate T cell responses (Yun et al. 2014). As yet, no structural data is available to support or contradict this model.

*HLA-B*57:01* – More associations, different mechanisms?

In addition to AHS, *HLA-B*57:01* is implicated in DILI caused by the β -lactam antibiotic flucloxacillin and the tyrosine kinase inhibitor pazopanib. Whilst *HLA-B*57:01*⁺ status is a risk factor for pazopanib DILI, occurring in approximately 10 % of patients with alanine aminotransferase levels more than three times the upper limit of normal (Xu et al. 2016), flucloxacillin DILI has been found to occur primarily in *HLA-B*57:01*⁺ individuals akin to AHS (Daly et al. 2009). Even so, the incidence of flucloxacillin-DILI in *HLA-B*57:01*⁺ individuals is much lower than AHS, occurring in 0.1-0.2 %, as compared to approximately 50 %, of carriers, and the distinct reaction phenotype suggests that the underlying mechanisms may differ.

Although the association of pazopanib-DILI is too recent to have received much scrutiny, efforts to understand how flucloxacillin might interact with *HLA-B*57:01* are progressing. *In vitro* investigations have identified drug responsive CD8⁺ T cells in patients that are restricted to HLA-

B*57:01 and express chemokine receptors such as CCR2 and CCR9 implicated in liver homing and CD8⁺ T cell infiltrate has been observed in the liver of a flucloxacillin-DILI patient (Monshi et al. 2012; WUILLEMIN et al. 2014). Interestingly, HLA interactions appear to lack the same exquisite specificity as abacavir, with the closely related HLA-B*58:01 also able to mediate drug presentation to some HLA-B*57:01 restricted T cell clones (Monshi et al. 2012). Furthermore, different studies have suggested involvement of both stable and labile interactions between flucloxacillin and the HLA (Monshi et al. 2012; WUILLEMIN et al. 2013; Yaseen et al. 2015).

Like many β -lactam antibiotics, flucloxacillin can modify proteins covalently, primarily via lysine residue side chains (Jenkins et al. 2009). Penicillin-G modified synthetic peptides have been shown to elicit T cell responses when presented on HLA class II molecules (Padovan et al. 1997), supporting the idea that flucloxacillin modified peptides might similarly generate stable immunogenic HLA-B*57:01-peptide complexes. However, given the broad distribution of lysine in the human proteome, the potential to generate modified ligands matching diverse HLA peptide-binding specificities is at odds with the apparent bias of flucloxacillin-DILI to *HLA-B*57:01*⁺ individuals. Indeed, investigations of HSA modification by β -lactams *in vitro* and *in vivo*, reveals common binding sites between several antibiotics that cause ADRs, including flucloxacillin, amoxicillin, penicillin-G and piperacillin (Jenkins et al. 2009; Meng et al. 2011; Monshi et al. 2012; Whitaker et al. 2011). Although there is evidence of an association between amoxicillin-clavulanate-induced DILI and several HLA class I and II alleles (Lucena et al. 2011; Stephens et al. 2013), only flucloxacillin-DILI is associated with *HLA-B*57:01*, and modified peptides derived from HSA appear to provide ligands for T cells responding to multiple β -lactams (Brander et al. 1995; Meng et al. 2017). Thus, whether HLA-B*57:01 has increased capacity to present flucloxacillin modified peptides, as compared to other HLA and, if so, why this is specific to flucloxacillin and not other β -lactams is an important point for clarification. Alternatively, direct binding of the native drug to HLA-B*57:01, either covalently or non-covalently, may provide an explanation. The turning of LC-MS/MS techniques to interrogation of peptides presented by HLA-B*57:01 under flucloxacillin treatment, and analysis of the HLA-B*57:01 itself for direct modification, will provide critical insight into these questions.

Class II associations

In comparison to associations with the HLA class I, HLA class II/ADR associations are poorly understood. For example, lapatinib DILI is associated with *HLA-DRB1*07:01* and *-DQA1*02:01*, however drug specific T cell responses could not be elicited *in vitro* as they have for β -lactam-DILI (Faulkner et al. 2016; Schaid et al. 2014). Equally, investigations of amoxicillin-clavulanate-DILI have been performed across individuals with and without risk alleles (Table 1), and the role of *HLA class II* risk alleles is still unclear (Kim et al. 2015). In contrast, recent investigations of Chronic Beryllium Disease, which is associated with HLA-DP molecules containing Glu at position 69 of the β -chain, have shown that T cell responses are elicited by HLA-peptide complexes that incorporate Beryllium ions in a stable fashion within the antigen binding cleft. Interestingly, only a subset of constitutive peptide ligands, bearing acidic residues at p4 and p7, can mediate binding. In addition to β Glu69, these peptide side chains help form an acidic pocket that can incorporate a beryllium ion resulting in an altered HLA-peptide conformation (Clayton et al. 2014). Although mediated by constitutive HLA ligands, as for abacavir this mode of binding shows the importance of the co-binding peptide in ion/drug interactions, and serves as a reminder that, especially for small molecule drugs, peptide must be considered when modelling interactions with the HLA.

Beyond the HLA

Whilst the genetic associations between ADRs and genes of the HLA provide a basis for understanding HLA-drug interactions, the implicated HLA molecule is only part of the story (Fig. 3). For reactions such as AHS, where 100 % of cases occur in individuals with the risk allele, the correct HLA molecule appears essential. However other associations, such as those between pazopanib-DILI and *HLA-B*57:01*, are not as strong, and the implicated HLA appears to be a risk factor, rather than a

requirement, that may be more useful in diagnosis than prediction. Conversely, even for abacavir, 50 % of *HLA-B*57:01*⁺ individuals will tolerate the drug implying that other factors are involved in allowing the reaction to progress. Peripheral tolerance mechanisms usually require a second “danger” signal in addition to TCR ligation for naïve T cell activation. It is unknown whether environmental factors such as disease status or innate stimulation by the drug itself might be needed to break tolerance and stimulate drug responses, contributing to incomplete penetrance of reactions. Furthermore, it is unclear why reactions such as DILI are directed against specific organs and the extent to which tissue specific factors such as distribution of antigen presenting cell subsets, drug metabolism and protein expression impact presentation of drug targets in an immunogenic context.

On the other side of this equation, reactions also rely on the presence of T cells within the circulating T cell pool possessing TCRs capable of interacting with the HLA-drug complex (Fig. 3). For abacavir, both memory and naïve subsets are activated, suggesting the global change in peptide presentation that accompanies abacavir binding provides a large array of targets, some of which mimic previously encountered antigens. For carbamazepine, T cell responses in *HLA-B*15:02*⁺ individuals appear less diverse, and carbamazepine is proposed to interact directly with both HLA and TCR. For such responses, it is conceivable that HLA background and infection history may have greater impact, either through removal of reactive TCRs from the T cell pool, as seen for the public LC13 TCR, which recognises *HLA-B*08:01* presenting the FLRGRAYGL peptide of Epstein Barr virus, and is deleted in individuals who co-express *HLA-B*44:02* against which LC13 is alloreactive (Burrows et al. 1994; Macdonald et al. 2009), or through proliferation of cross-reactive antiviral T cells during prior infections.

Closing remarks:

The genetic diversity of the HLA is driven by the need to bind and present a diverse spectrum of small molecule antigens, usually peptides, to increase the probability of immune responses to a broad array of pathogens. Thus, it seems an almost inevitable consequence that some HLA allotypes will possess the structural requirements to bind and present small molecule drugs. Furthermore, long half-life and maintenance of high serum concentrations, which are desirable qualities of many medications, lend themselves towards off-target interactions. The expansion of the pharmacopoeia therefore generates an impetus to understand how small molecule drugs can interact with the HLA in order to better predict and prevent adverse events.

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Figure Legends:

Fig. 1 Models for interaction between HLA, drugs and T cell receptors in drug-responsive T cell activation

a) Hapten/prohapten model involving covalent modification of cellular proteins which generate haptenated HLA ligands via antigen processing, or direct haptening of HLA-peptide complexes at the cell surface. b) and c) Non-covalent interaction with immune receptors, either at the HLA-TCR interface (b) or allosteric (c). d) The altered repertoire model involving co-occupation of the antigen-binding cleft of the HLA molecule by drug and peptide. Drug presence changes the array of peptides favoured as binders of the HLA. e) Alternatively, drugs may become incorporated by constitutive HLA-peptide complexes to generate conformationally novel complexes.

Fig. 2 Example crystal structure of an HLA-B*57:01-abacavir-peptide complex overlaid with polymorphic residues of HLA-B*57:03/HLA-B*58:01 that impact drug binding

A cut away of the antigen binding cleft of HLA-B*57:01 (yellow) showing the α 1 helix, abacavir (pink), and co-occupying peptide LTTKLTNTNI (orange) (PDB 3VRJ, Illing et al. 2012). The side chains of Val97 and Ser116 are shown as sticks (yellow) overlaid with the Val97Arg polymorphism of HLA-B*58:01 and Ser116Tyr polymorphism of HLA-B*57:03 (transparent cyan) that impact abacavir binding. The conformation of the HIV-Gag peptide TSNLQEQIGW, which binds HLA-B*57:01 in the absence of abacavir, is also shown (cyan), demonstrating a clash of the C-terminal (P Ω) Trp with abacavir (PDB 5T70, Pymm et al. 2017) that would prevent its binding in the presence of the drug. Adapted from (Illing et al. 2012).

Fig. 3 Factors required for drug specific T cell activation

APC – antigen presenting cell

Figure 1

Figure 2

Figure 3

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Title:

The role of HLA genes in pharmacogenomics: unravelling HLA associated adverse drug reactions

Date:

2017-08-01

Citation:

Illing, P. T., Purcell, A. W. & McCluskey, J. (2017). The role of HLA genes in pharmacogenomics: unravelling HLA associated adverse drug reactions. IMMUNOGENETICS, 69 (8-9), pp.617-630. <https://doi.org/10.1007/s00251-017-1007-5>.

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