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Conflict of interest

James McCluskey, Zhenjun Chen and Sidonia BG Eckle are inventors on patents describing MR1 antigens and MR1 tetramers. The other authors have no conflict of interest in relation to this work.

vi. Abstract (word count: 192) **and keywords**

Conventional T cells recognise protein-derived antigens in the context of Major Histocompatibility Complex (MHC) class Ia and class II molecules and provide anti-microbial and anti-tumour immunity. Conventional T cells have also been implicated in type IV (also termed delayed-type or T cell mediated) hypersensitivity reactions in response to protein-derived allergen antigens. In addition to conventional T cells, subsets of unconventional T cells exist, which recognise non-protein antigens in the context of monomorphic MHC class I-like molecules. These include T cells that are

restricted to the cluster of differentiation 1 (CD1) family members, known as CD1-restricted T cells, and mucosal-associated invariant T cells (MAIT cells) that are restricted to the MHC-related protein 1 (MR1). Compared to conventional T cells, much less is known about the immune functions of unconventional T cells and their role in hypersensitivities. Here we review allergen antigen presentation by MHC-I-like molecules, their recognition by unconventional T cells, and the potential role of unconventional T cells in hypersensitivities. We also speculate on possible scenarios of allergen antigen presentation by MHC-I-like molecules to unconventional T cells, the hallmarks of such responses, and the expected frequencies of hypersensitivities within the human population.
Keywords: antigen, CD1, MAIT cells, MR1, NKT cells

vii. Main text (word count: 6,127)

1. Introduction

1.1 Type IV hypersensitivities

According to the type of immune response, four broad subtypes of hypersensitivities can be distinguished based on the traditional classification by Gell and Coombs[1]. Type I-III involve immunoglobulin responses whilst type IV is T cell mediated (also termed delayed-type or T cell mediated hypersensitivity)[1]. Within type IV hypersensitivities, four categories exist, where type IVa is a $CD4^+$ T helper (Th) 1 lymphocyte mediated reaction with activation of macrophages; type IVb is $CD4^+$ Th2 lymphocyte mediated with eosinophilic involvement; type IVc is cytotoxic $CD8^+$ T lymphocyte mediated with involvement of perforin-granzyme B in apoptosis; type IVd is T-cell driven neutrophilic inflammation[2]. Most studies on type IV hypersensitivity[1] have focused on protein allergen-derived peptide antigens (Ags) presented by classical Major Histocompatibility Complex class I or class II (MHC-I or MHC-II) molecules. In contrast, little is known about hypersensitivities caused by non-peptide Ags[3], presented by MHC-I-like molecules, the restriction elements of various subsets of unconventional T cells. Discovered ~ 30 years ago[4–8], unconventional T cells remain an emerging field of research. Despite their higher frequencies and broad tissue distributions[9,10], much less is known about the role and function of unconventional T cell subsets in disease and at steady-state as compared to conventional T cells. Here we provide an overview on possible concepts and review the current knowledge on how MHC-I-like presented allergen Ags cause hypersensitivities.

1.2 Ag presentation by MHC-I-like molecules and their recognition by unconventional T cells

Peptide Ags, presented by classical MHC-I (also termed MHC-Ia) and MHC-II molecules, are recognised by conventional T cells. In contrast, non-peptide Ags are recognised by distinct subsets of unconventional T cells, restricted by a number of Ag presenting molecules that are homologues of classical MHC-I molecules, namely MHC-I-like molecules[9] (Fig. 1). Both conventional and unconventional T cells can express αβ T cell receptors (TCRs), whereas unconventional T cells can alternatively express a γδ TCR[9]. Some γδ TCR^+ unconventional T cells can recognise MHC-I-like molecules, whilst others are not restricted by MHC molecules[9,11] (Fig. 1). In contrast to MHC-Ia and MHC-II molecules which are highly polymorphic and thus present diverse Ags and vary significantly from one individual to the next, MHC-I-like molecules are typically monomorphic[9]. In line with the monomorphic nature of the MHC-I-like molecules, where to date Ag diversity appears limited, unconventional T cells unlike conventional T cells can express limited TCR diversity, often featuring clonally expanded and similar, but nonidentical, TCR sequences (intradonor conservation)[12]. Furthermore, similar TCRs can be found in nearly all individuals (interdonor conservation), allowing for public as compared to private immune responses at the population

level[12]. In the following we describe each set of unconventional T cells. Notably, the characteristics of unconventional T cells, including the breadth of Ags recognised, are an active area of research.

The MHC-I-like molecule MHC-related protein 1 (MR1) is expressed widely amongst nucleated cells and possibly in all tissues based on mRNA[13]. MR1 presents small molecule metabolite Ags, derived from folic acid (non-stimulating)[14,15] and a biosynthetic precursor to microbial riboflavin (stimulating), with 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) being the most potent Ag[16]. MR1 is the restriction element of αβ TCR^+ mucosal-associated invariant T cells (MAIT cells), which are found in most tissues and represent up to 10 % of peripheral blood T cells in humans[17](Fig. 1), and 0.5–2 % of T cells in a broad range of tissues in naïve C57BL/6 and BALB/c mice[18,19] (Table 1). MAIT cells express a semi-invariant TCRα chain, composed of the variable region 1-2 and joining region 33 in humans (TRAV1-2-TRAJ33, and TRAV1-TRAJ33 in mice) (Fig. 1, Table 1), where in humans TRAJ12 and TRAJ20 are also commonly incorporated but less frequently than TRAJ33[20]. Although the repertoire of TCRβ chains of MAIT cells appears skewed, being dominated by TRBV6 and TRBV20 in humans (Fig. 1) and TRBV19 and TRBV13 in mice (Table 1), there is appreciable variation in TCRβ chain usage, especially within the hypervariable loop of the TCR β-chain, the complementarity-determining region 3β (CDR3β) loop[20]. After MR1-mediated stimulation via the TCR, human MAIT cells produce diverse cytokines, including interleukin 2 (IL-2), interferon-γ (IFNγ), tumour necrosis factor (TNF), IL-17A[17] as well as IL-13 during chronic stimulation[21] and can be cytotoxic[22,23] (Fig. 1).

Cluster of differentiation 1 (CD1) molecules CD1a, CD1b, CD1c and CD1d present lipid Ags, with the unique size and architecture of each CD1 cleft, facilitating the capture and presentation of shared but predominantly distinct lipid Ags[12,24,25]. As a whole, CD1a, CD1b and CD1c-restricted T cells range from 0.1-10% of T cells in human blood[9]. CD1a, which amongst the CD1 molecules features the smallest Ag binding cleft and shallow pockets, presents glycolipids as well as 'headless' lipids and lipo-peptides such as dideoxymycobactin (DDM) to αβ TCR^+ CD1a-restricted T cells[9] (Fig. 1). CD1a-reactive cells are particularly abundant in blood and also in the skin where they produce IL-22 (Fig. 1); and CD1a is expressed on dendritic cells and in high levels on Langerhans cells[12]. The TCR usage of CD1a-restricted T cells is largely unexplored, but many of these T cells appear autoreactive and current literature suggests that these cells participate in allergic responses[9], which will be discussed in further detail below.

Other CD1-restricted T cells that play a role in allergic reactions include CD1d-restricted natural killer T (NKT) cells (Fig. 1). CD1d is expressed in many tissues such as the kidney, pancreas, breast and conjunctiva of the eye[26]. CD1d is broadly distributed on many haemopoietic cell types, including monocytes, macrophages, dendritic cells, B cells as well as non-haemopoietic cells such as epithelial cells of the gastrointestinal tract[27], hepatocytes and keratinocytes[28]. CD1d is the restriction element of three subsets of NKT cells: (i) αβ TCR^+ type I NKT, (ii) αβ TCR^+ type II NKT cells and (iii) CD1d-restricted γδ TCR^+ T cells. Type I NKT cells recognise the marine sponge–derived glycolipid α-galactosylceramide (α-GalCer) and other α-linked glycolipids (Fig. 1). Type I NKT cells make up ~0.1 % of T cells in peripheral blood of humans (Fig. 1), ~1 % of T cells in most tissues of mice and up to 50 % of all T cells in mouse liver. Type I NKT cells express an invariant TCRα chain (TRAV10-TRAJ18 in humans (Fig. 1); TRAV11-TRAJ18 in mice (Table 1)) paired with a limited array of TCRβ chains, and hence are also referred to as 'invariant NKT cells' or 'iNKT cells'. Type I NKT cells encompass distinct functional subsets that resemble Th1, Th2 and Th17 cells and predominantly express IFNγ, IL-4 and IL-17, respectively[9] (Fig. 1).

αβ TCR^+ type II NKT cells recognise various lipid Ags presented by CD1d, but not α-GalCer. Type II NKT cells are recognised as T cells that have much greater TCR diversity, compared to type I

NKT cells, and are hence also referred to as 'diverse NKT cells' (Fig. 1). Although type II NKT cells are less-well studied, these cells are thought to outnumber type I NKT cells in humans[29] and some studies suggest that type I and type II NKT cells have opposing roles, reviewed in[30]. A subset of γδ TCR^+ T cells (predominantly $TRDV1^+$ γδ T cells) can also recognise CD1d-α-GalCer[31], while other γδ T cells recognise the endogenous lipid Ag sulfatide[32]. It is unclear if CD1d restricted type II NKT cells and γδ T cells contribute to hypersensitivity; therefore, this review will mainly focus on the role of type I NKT cells in these aberrant immune responses.

In the following we highlight some of the key features of unconventional T cell responses as compared to those by conventional T cells. Precursor frequencies of Ag-specific unconventional T cell subsets in immune tissues are generally much higher (~1-10 × 10^3 per million of human T cells) than those of conventional T cells (1-10 per million of human T cells)[9] (Fig. 1). Furthermore, in non-lymphoid tissues, at the site of infection, unconventional T cells are often present in relatively high frequencies at steady-state[9]. Naïve conventional T cells require Ag contact in secondary lymphoid organs, a process termed priming, which leads to activation followed by clonal T cell expansion and differentiation over the course of 3-7 days[33]. In contrast, driven by the upregulation of the master transcription factor promyelocytic leukemia zinc finger (PLZF) during thymic development[34–36], MAIT cells and type I NKT cells (and possibly other unconventional T cells) acquire a 'preprimed' state, that is somewhere in between the states of a naïve and effector-memory conventional T cell. Whilst this state is not fully characterised, both unconventional T cell subsets express markers broadly consistent with conventional effector-memory T cells (human MAIT cells: $CD45RA^-CD45RO^+CD95^{hi}CD62L^{lo}$ [36–38], human type I NKT cells: $CD45RA^{dim}CD45RO^+CD62L^{-/lo}$ [39]). In particular for MAIT cells, this preprimed state evolves further following thymic egress, when MAIT cells expand in the periphery[36,38], probably in response to commensal flora. In mice, type I NKT cell expansion, lineage commitment and acquisition of a preprimed state occur during thymic development and are independent of exogenous Ag exposure[40,41]. However, for most NKT cells, the upregulation of NK1.1 and further maturation occurs in the periphery[41,42]. Similarly, in humans, the peripheral environment contributes to both maturation and expansion of type I NKT cells[43]. Consistent with their 'preprimed' state, whilst present in low frequencies in naïve mice[18,19], upon Ag exposure MAIT cells rapidly expand to large numbers[44] and produce cytokines[18]. Human MAIT cells also rapidly produce cytokines upon Ag recognition[17,45]. It has further been shown in mice that the MAIT cell effector response involves the formation of a long-lived population with memory-like recall properties, characterised by a polarised and more potent immune response upon restimulation[44,46]. Similarly, mature type I NKT cells expand and produce cytokines rapidly in response to Ag[47–50], however unlike MAIT cells, these cells contract to a pre-stimulation frequency over subsequent days[51], indicating that priming does not lead to memory formation. The development of other CD1-restricted T cells is not well understood, although some studies suggest CD1a-, CD1b- and CD1c-restricted T cells may exit the thymus as naïve T cells ($CD45RA^+CD45RO^-$) and follow a similar pathway as conventional T cells with regards to: priming[52]; clonal expansion[53]; and memory formation[43].

2. Speculation on possible scenarios of allergen Ag presentation by MHC-I-like molecules and T cell recognition

Drawing on a limited number of published examples of allergen Ag presentation by MHC-I-like molecules as well as known concepts of allergen Ag presentation by classical MHC molecules, the following different scenarios of allergen Ag presentation by MHC-I-like molecules can be envisaged: (i) The allergen Ag may displace the microbial or endogenous Ag in the Ag binding cleft (Fig. 2i). This has been demonstrated for MR1 presentation of drugs, drug-metabolites and drug-like molecules[54] as well as for CD1a presentation of the poison ivy allergen derived antigen urushiol[52]

and farnesol present in cosmetics and perfumes[55] (described in detail below). (ii) The allergen Ag and a microbial or endogenous Ag are simultaneously presented, but as distinct entities (Fig. 2ii). This scenario would be similar to the altered repertoire concept for delayed type hypersensitivity (DTH), involving conventional T cell-mediated, drug-specific recall responses[56]: an altered repertoire of endogenous peptides was simultaneously presented with abacavir by the MHC-Ia molecule HLA-B*57:01, and carbamazepine by the MHC-Ia molecule HLA-B*15:02[57].

(iii) In a yet different scenario, the allergen Ag might be directly conjugated to an Ag. Again, the allergen Ag may be conjugated to an Ag selected from the microbial or endogenous Ag repertoire that is either identical or altered to that presented in the absence of the allergen Ag (Fig. 2iii). This scenario would be similar to the hapten concept for DTH, in which a drug covalently bound to a peptide, a drug-haptenated peptide, is presented by the MHC-Ia molecule[56,58]. If not the parent drug itself but a metabolite of the parent drug is bound to the peptide this is referred to the prohapten concept[56].

Whilst scenarios (ii) and (iii) have not been described yet for MR1 or CD1, they may be possible: the Ag binding cleft of MR1 has sufficient plasticity and versatility within the A'-pocket (equivalent to the MHC-Ia pocket that binds the N-terminal peptide residue) to accommodate diverse chemical scaffolds[54]. In addition, Ags or parts of Ags might be accommodated in the F'-pocket of MR1 (equivalent to the MHC-Ia pocket that binds the C-terminal residue of peptides)[20]. Similarly, the Ag binding pockets of the various CD1 molecules are larger in volume than the Ag-binding clefts of MHC and MR1, and are capable of binding multiple lipid species simultaneously, as well as accommodating lipids of greater volume than the Ag-binding pocket itself[12].

(iv) In a last possible scenario, the allergen might elicit presentation of endogenous Ags (in the absence of allergen Ag and referred to as neoantigens), that would not be presented at steady-state or that are presented at very low levels at steady-state (Fig. 2iv). For instance, allergen derived enzymes create neoantigens for presentation by CD1a[59] (see below). Or, as it has been speculated, allergens cause inflammation and dysregulation in the mucosa leading to the release or synthesis of endogenous Ags for Ag display[60].

For any of the given allergen Ag presentation scenarios described above, different scenarios of T cell recognition can be extrapolated from published examples of T cell recognition of allergen Ags presented by MHC-I-like as well as classical MHC molecules. (i) There might be an overlap in the T cell clones that recognise the microbial or endogenous Ags as well as the allergen Ags presented by MHC-I-like molecules, i.e. they cross-react with allergen Ags. The entire repertoire of clonally distributed TCRs or only a subset of TCRs might cross-react with the allergen Ag. For example, only a subset of 5-OP-RU-specific MAIT TCRs cross-reacted with metabolites of the drug diclofenac and responding MAIT cells reacted to different diclofenac metabolites[54]. (ii) Alternatively, a new, distinct repertoire of TCRs might cross-react with the allergen Ag, as seen for recognition of peptides co-presented with abacavir and carbamazepine[57]. (iii) Whilst there are currently no examples of T cell cross-reactivities between classical MHC and MHC-I-like molecules, or amongst different MHC-I-like molecules, these types of cross-reactivity might occur: MR1-reactive MAIT-like cells, atypical MAIT cells and MR1T cells have been described, some of which do not express the invariant MAIT TCR[61,62]. These cells do not possess the same characteristics as invariant MAIT cells and some of these are likely conventional T cells that cross-react with MR1[61]. Interestingly, in MAIT TCR transgenic mice that lack MR1 a significant population of 'MAIT-like' T cells develops, apparently selected by MHC-Ia molecules or CD1d[63]. Similarly, in Mus musculus castaneus (CAST mice), modified to lack MR1, a small population of TRAV1-TRAJ33 expressing cells was identified that was selected by other MHC molecules, possibly MHC-II[64].

3. Recognition of allergen Ags by unconventional T cells

In the following we provide an overview on the current stage of the literature on environmental, food, metal and drug allergen Ag recognition by unconventional T cells, summarised in Table 2.

3.1 Environmental allergens

CD1a-restricted T cell responses to lipid Ags derived from environmental allergens such as bee and wasp venom[59,65], aerosolised extracts from house dust mites (HDM)[66] and tree saps[52] have been described, and may contribute to skin related hypersensitivity reactions in predisposed individuals. During a bee/wasp sting, phospholipase (PLA) enzymes present within venom were introduced in the skin as allergenic products. PLA catalysed the cleavage of host phospholipids into antigenic neolipids, including lysophosphatidylcholine (LPC), that were presented by CD1a (Fig. 3a) and potently stimulated skin-derived CD1a-restricted T cells[59]. Similarly, a skin-topic CD1a-restricted T cell response to HDM extract as allergen has been attributed to both HDM- and host-derived PLA activities[66,67]. CD1a-restricted T cells reactive to bee venom and HDM were more frequent in the peripheral blood of hypersensitive individuals than non-hypersensitive controls[65,66], suggesting that CD1a-restricted T cells may contribute to the hypersensitivity response. In support of this, the frequency of IFNγ producing CD1a-restricted T cells increased significantly in bee sting hypersensitive patients during desensitisation therapy[65]. In addition, HDM-responsive CD1a-restricted T cells were also responsive to bee-derived PLA[66]. These data align closely with another study that identified an increased frequency of autoreactive CD1a-restricted T cells in psoriasis patients compared to controls[68]. Similarly, stimulatory neolipids were generated by host-derived PLA activity, in this case, localised to the dermis of psoriasiform lesions[68]. Thus, the aberrant activity of host-derived PLAs, triggered on an environmental and/or genetic basis, appears to be a shared factor in CD1a-auto- and allergen-reactivity.

Direct recognition of allergen-derived lipids has also been established for CD1a-restricted T cells in response to the poison ivy-derived lipid, urushiol[52]. In sensitised mice, urushiol treatment caused an inflammatory response that was greater in CD1a-transgenic mice compared to CD1a-deficient wild-type mice and was characterised by IL-17 and IL-22 production by clonally expanded (utilising TCRβ-chain TRBV1 or TRBV2 gene segments) $CD4^+$ T cells [52]. Similarly, in hypersensitive donors, urushiol displayed a greater frequency of IL-17 and IL-22 producing CD1a-responsive T cells than control donors[52]. Structural determination of the dominant antigenic species of urushiol (C15:2), presented by CD1a, revealed that the lipid was buried deep within the cleft of CD1a, positioned such that the lipid was only minimally exposed for TCR recognition[52], perhaps indicating a minor role for urushiol in overall TCR binding to CD1a (Fig. 3a). Structural analysis of an autoreactive TCR (isolated from an autoimmune patient) bound to CD1a presenting endogenous lipids revealed that small, solvent protected CD1a binding lipids that did not appreciably alter the conformation of CD1a were permissive of TCR recognition[69]. In contrast, lipids with longer acyl chains or a bulky head group disrupted this interaction[69]. Importantly, the molecular contacts occurred exclusively between TCR and CD1a protein itself, indicating that the lipid Ag was not surveyed by the TCR directly[69] and suggestive of a model of TCR-CD1a recognition described as 'absence of interference'[70]. It is therefore possible that these CD1a-autoreactive T cells may respond to both CD1a-urushiol and other allergenic small lipids that do not disrupt the TCR-CD1a interface.

In support of this hypothesis, several small hydrophobic compounds, derived from cosmetics and perfumes were recently shown to stimulate T cells in a CD1a-dependent manner[55]. This included farnesol, related to farnesyl pyrophosphate, the biosynthetic precursor of the human skin oil

squalene. Farnesol was able to stimulate polyclonal T cells in vitro when presented by CD1a in some donors[55]. Structural analysis revealed farnesol occupied only 36% of the CD1a cleft (Fig. 3a) and was likely protected entirely from TCR surveillance[55]. Despite its small size, farnesol was able to displace larger, amphipathic self-lipids from CD1a, thus restoring 'absence of interference' conducive to TCR recognition[55].

CD1a-restricted T cells and CD1d-restricted NKT cells have also been suggested to play a role in airway hypersensitivity reactions to plant pollens and other aerosolised allergens. In a study examining the cypress pollen, CD1a and CD1d molecules expressed by human pulmonary DCs were able to directly capture the pollen particles[71]. Analysis of the lipids extracted from the cypress pollen revealed a range of phospholipid species, of which phosphatidylcholine (PC) and phosphatidylethanolamine (PE) were demonstrated to be antigenic, and stimulated T cell clones derived from pollen hypersensitive donors in a CD1-dependent manner[71]. Similarly, olive pollen extract upregulated CD1d expression on human monocytes and macrophages, and NKT cells were able to lyse Ag presenting cells (APCs) cultured with olive pollen lipid extract[72], suggesting that pollen-derived lipids may be directly recognised by CD1-restricted T cells. In a mouse model, intranasal administration of the allergen ragweed (RW) pollen in mice deficient of NKT cells reduced the typical hypersensitive response, measured by pulmonary mucus production, serum IgE and circulating eosinophils[73], suggesting that NKT cells are involved in the hypersensitive response to RW pollen. Interestingly, wild-type mice treated with α-GalCer prior to sensitisation with RW further exacerbated the hypersensitive response compared to non-treated mice[73]. Some inroads have been made to identify key factors responsible for regulating NKT cell pathogenicity during hypersensitive responses. Recently, the histone methyltransferase enhancer of zeste homolog 2 (EZH2) was shown to be important in the differentiation of pathogenic NKT cells in an airway hyperresponsiveness (AHR) mouse model[74]. Conditional deletion of EHZ2 in $CD4^+$ T cells induced spontaneous AHR that relied predominantly on NKT cell IL-4 secretion, which was significantly increased in these animals compared to wild-type mice[74]. In humans, expression of EZH2 was shown to be reduced in blood Th1 and Th2 cells of allergic rhinitis (AR) patients compared to controls and EZH2 expression was negatively correlated with serum IL-17A in AR patients challenged with HDM[75]. Thus, EZH2 appears to be important for the epigenetic control of T helper[74,75] and NKT cell differentiation[76] in allergic responses. Similarly, NKT cells were shown to be sensitive to the anti-inflammatory effects of the histamine receptor 2 (H_2R) in AHR mouse models[77]. Pharmacological activation of H_2R attenuated NKT cell lung accumulation and the inflammatory response in AHR, whereas inhibition or genetic deletion of H_2R significantly enhanced NKT cell pathology, suggesting that histamine signalling may be a key modulator of NKT cells during an allergic response[77].

Many studies have examined the role of NKT cells in the development of allergic asthma using an ovalbumin (OVA)-induced mouse model. In sensitised mice, challenge with OVA-induced AHR characterised by airway inflammation, leukocyte infiltration and increased serum IgE[60,78]. Among studies that are reviewed elsewhere[79–81], the consensus is that while OVA-induced AHR is not directly mediated by NKT cells, the disease is significantly attenuated in the absence of NKT cells, such as in $CD1d^{-/-}$ and $J\alpha18^{-/-}$ mice as well as in mice treated with anti-CD1d antibodies to deplete NKT cells[60,78,82]. In spite of these findings, a subset of NKT cells has been described that appears to suppress OVA-induced AHR[83]. This suppressive subset of NKT cells was $CD38^+$ and CD4/CD8 co-receptor deficient and could be expanded in neonatal mice after infection with influenza A virus or upon stimulation with an α-GalCer analogue[83]. In the absence of an exogenously administered lipid Ag in the OVA-induced AHR model, some have speculated that NKT cells may become exposed to antigenic endogenous lipids in the allergen-induced inflammatory mucosal environment[60].

The role of MAIT cells in asthma is unclear, however clinical evidence suggests MAIT cells can be both protective and pathogenic in asthma. In asthmatic adults, disease severity correlated with a lower frequency of MAIT cells in lung biopsies, blood and sputum samples[84]. A potential protective role of MAIT cells in asthma was also observed in a population of infants, whereby lower frequencies of circulating MAIT cells in one-year-old children correlated with the later development of asthma at age 7[85]. However, higher frequencies of circulating IL-17A producing MAIT cells were associated with severe asthma compared to non-severe asthma, suggesting a pathogenic role for this MAIT cell subset[86]. The observed differential roles of MAIT cells in asthma might be related to age, ethnicity and genetic differences, as well as to the exposure of distinct sets of environmental Ags[87,88], which may include unknown MAIT cell Ags.

3.2 Food allergens

NKT cells have been implicated in the recognition of food derived allergens, including from Brazil nuts[89], cow milk[90–92] and other mammal milks[93]. For the study of Brazil nut hypersensitivity, a mouse model of allergic disease has been established[89]. In this model, the purified Brazil nut protein, Ber e 1, acted as a sensitising Ag in conjunction with a fractionated Brazil nut lipid extract to stimulate a Th2-related antibody response[89]. NKT cell deficient mice displayed reduced antibody responses including those specific to Ber e 1, compared to wild-type mice, suggesting a role for NKT cells in the generation of Ber e 1-specific antibodies, possibly involving the secretion of IL-4[89]. Analysis of the lipid fraction revealed a mixture of neutral and polar lipids, including CD1d binding phospholipids[12], of which phosphatidylethanolamine (PE) and phosphatidylinositol (PI) species were most abundant[89]. In nut hypersensitive donors, Brazil nut lipid extract-responsive $CD161^+$ T cells were enriched for NKT cells[89]. Thus, NKT cells may contribute to the hypersensitivity reaction to Brazil nuts in allergic patients, specifically by responding to CD1d-presented lipids derived from the allergen.

A number of studies have assessed the reactivity of NKT cells to common mammalian lipids found in dairy products, most notably cow's milk[90,91], with a focus on two candidates for inducing NKT cell antigenicity: sphingomyelin (SM)[91,94] and β-glucosylceramide (β-GluCer)[90,93]. In one study, NKT cells were found to be significantly less frequent in the peripheral blood of children with a milk allergy compared to non-allergic children and tended to produce more IL-13 in response to a milk-derived SM, suggesting a skewed functional response to milk SM by NKT cells in hypersensitive children[91]. SM was shown to be recognised in the context of CD1d by a modest subset of NKT cells in the peripheral blood of non-allergic donors and was a less potent Ag than α-GalCer[91]. Similarly, in a cohort of children diagnosed with eosinophilia oesophagitis (EoE), an IgE-mediated and food-related atopic disease, NKT cells were less frequent in the peripheral blood of children with active compared to controlled disease or in healthy donors[94]. Further, a greater frequency of NKT cells was reported in oesophageal biopsies from children with active compared to controlled disease[94], indicative of NKT cell recruitment to the oesophagus during active disease. In all children, NKT cells proliferated in response to milk SM, yet significantly more NKT cells from active EoE produced IL-4 and IL-13 than control children[94]. Therefore, NKT cells in two separate cohorts appeared responsive to milk SM, with some evidence of CD1d-dependent recognition.

In terms of cow's milk β-GluCer, it initially appeared that mouse NKT cells were stimulated by β-GluCer in a CD1d dependent manner, and two relevant β-GluCer species were identified as candidate Ags (C12:0 and C24:1)[90]. However, digestion of mouse and human milk lipid extracts with an enzyme that cleaves β-linked GluCer, did not abolish the broad reactivity to the milk lipids displayed by NKT cells, suggesting that the stimulatory response was not caused by β-GluCer, rather, a naturally occurring α-linked lipid present in the milk lipid extract. In a further analysis, the

minor lipid species type 2 α-linked monohexosylceramide was identified from cow's milk which was recognised strongly by a murine type I NKT TCR when bound to CD1d, similarly to α-GalCer bound CD1d[92,95].

Food hypersensitivity has also been associated with γδ T cell recruitment, despite an incomplete understanding of the underlying immunological mechanisms. Biopsies of inflamed gut tissues showed increased infiltration of γδ T cells, predominantly Vδ1, in the terminal ileum and duodenum associated with allergic reactions, when compared to non-allergic and chronic inflammatory diseases[96–99]. Also, increased numbers of intraepithelial γδ T cells have been suggested as a biomarker for the diagnosis of celiac disease when histology is inconclusive[98,100].

However, in a mouse model of food allergy the allergic sensitisation induced by co-administration of cholera toxin and peanut antigens was followed by a decrease of number and proportion of γδ T cells in the intestine[101]. In the same study, the functional depletion of γδ T cells, through co-administration of anti- γδ TCR blocking antibody during the sensitisation, led to a higher production of Th2 cytokines and peanut-specific IgE[101]. While this suggested a protective role for γδ T cells in allergic sensitisation in this model, the involvement of the γδ TCR in the activation of the regulatory response is not clear[101].

Given that MAIT cell Ags are small molecule metabolites, it is tantalising to speculate that MAIT cells might also recognise small molecule food metabolites and this way cause food hypersensitivities or intolerances. Food derived flavonoids, for example, represent likely MR1 Ag candidates due to their chemical structures resembling known MAIT cell Ags. Indeed, dietary isoflavone intake has been associated not only with anti-inflammatory, but also pro-inflammatory effects in the gastrointestinal tract[102–104].

3.3 Metal allergens

Nickel (Ni)-induced allergic contact dermatitis (ACD) is the most common metal allergy in humans[105] and invokes both innate and adaptive immune responses that are not fully understood[106]. During sensitisation, Ni metal ions bind to a histidine rich motif of TLR4 and trigger an inflammatory response[107]. In mice, TLR4 lacks the Ni ion binding site[107]. However, Ni hypersensitivity in mouse models can be induced by co-administration of Ni with a classical TLR4 agonist such as lipopolysaccharide (LPS)[107]. In mice sensitised with Ni and LPS, subsequent footpad challenge with a Ni solution caused a sustained inflammatory response as well as accumulation of T cells in the footpad epithelial basal layer[108]. Analysis of the TCR repertoire from the footpads of challenged mice showed a bias in NKT TCR gene segment usage (TRAV11 and TRBV13-2) and a clonotypic invariant NKT TCR CDR3α chain[108], suggestive of NKT cell accumulation in the inflamed footpad. In another mouse model of Ni hypersensitivity, sensitised NKT cell deficient mice displayed significantly increased ear swelling upon Ni challenge, compared to wild-type mice[109]. The difference in swelling was reduced 96 hours after challenge, suggesting that NKT cells may contribute early in the immune response[109]. Interestingly, when mice were treated with α-GalCer at the same time as receiving Ni challenge, ear swelling induced by Ni was significantly reduced at 24 hours[109]. Together, these data suggest NKT cells may dampen the Ni hypersensitive response, particularly after direct activation with potent Ag.

Further, MAIT cells might be implicated in human Ni hypersensitivity, where preferential activation of human αβ $CD8^+$ T cells expressing a selected TCR-Vβ repertoire, including TRBV6 and TRBV20, has been observed[110] which is typical for MAIT cells; the TCR-Vα repertoire was not

assessed in this study. In this regard, two Ni-reactive $CD8^+$ T cell clones isolated from sensitised patients showed Ni-specific activation independently of MHC-Ia, MHC-II or CD1d. Earlier studies have demonstrated the potential of these clones to proliferate, and to mediate specific cytolysis of different human cell lines in a TCR-dependent way in the presence of Ni-sensitised APCs[111,112].

MHC-Ia-independent activation of $CD8^+$ T cells in response to gold-sensitised APCs is likely related to NKT cell activation[113]. Indeed, in biopsies of skin lesions, NKT cell infiltration was suspected based on increased levels of CD161 and CD1d expression[114]. In addition, in a mouse model of chromium hypersensitivity, NKT cells accumulated in inflamed skin[115]. Together, these results underline the key role that NKT cells play in metal allergy pathogenesis.

3.4 Drug allergens

A study by Moody and colleagues[116] identified a type II NKT cell clone that in the context of CD1d could recognise a non-lipid molecule called phenyl 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonate (PPBF), which resembles sulfa drugs that induce hypersensitivity in some individuals[116]. Data suggested that PPBF bound in or near the CD1d Ag cleft[116]. Precisely how PPBF binds to CD1d and is recognised by the type II NKT cell clone remains unclear.

The capacity of MAIT cells to recognise small molecules, has prompted the proposition that MAIT cells are involved in drug hypersensitivities[54]. Following multiple parallel in silico screens of 6,000 in-house organic compounds and 1,216 drugs (approved by the US Food and Drug Administration), 183 candidate molecules were identified. Of those, 81 were subjected to cellular assays assessing MAIT cell activation and MR1 binding. A quarter of the tested drugs, drug metabolites and drug-like molecules were able to bind to MR1 and/or activate MAIT TCR reporter cell lines[54]. 3-formyl-salicylic acid, a synthetic analogue of salicylate (aspirin) which strongly bound MR1 (Fig. 3b) but did not activate human or mouse MAIT cells, competitively inhibited MAIT cell activation by 5-OP-RU, demonstrating the capacity of drug-like small molecules to modulate MAIT cell function[54]. Consequently, it was demonstrated that MR1 can capture chemically diverse scaffolds. These observations indicate that some drugs and drug-like molecules affect MAIT cell function[54].

Further, MAIT TCR reporter cell lines responded to diclofenac at a concentration that can be achieved in patients after an oral dose[54,117]. The activation of MAIT cells was attributed to diclofenac metabolites, specifically to 4- and 5-hydroxy-diclofenac (4-OH-DCF, 5-OH-DFC) (Fig. 3b). Not all 5-OP-RU specific MAIT TCR reporter cell lines responded to 4-OH-DCF and 5-OH-DCF, suggesting the involvement of specific subsets of MAIT cells in their respective recognition[54]. Hypersensitivity to diclofenac has been attributed to 5-OH-DFC in mouse model studies[118]. Moreover, the cytotoxic activity of diclofenac-activated T cells against sensitised hepatocytes was only partially MHC-Ia-dependent[119], suggesting a potential role for MAIT cells in diclofenac hypersensitivity. Whilst clinical studies are needed it is possible that drugs and drug metabolites modulate MAIT cell function, causing potentially drug hypersensitivities.

4. Speculation on the clinical impact and hallmarks of unconventional T cell mediated hypersensitivities

4.1 Speculations on frequencies of hypersensitivities at the population level, involving allergen Ags presented by MHC-I-like Ag-presenting molecules

Given the donor-unrestricted nature of MHC-I-like molecules and unconventional T cell subsets[12], a given allergen Ag would be predicted to be presented and recognised by most/all donors. Consequently, whilst not enumerated yet, hypersensitivities directed to MHC-I-like molecules

should be more frequent than those directed to classical MHC molecules. Unconventional T cell allergen Ag recognition could however be donor restricted, such as in the following cases:

- A donor-specific microbial or endogenous Ag is presented simultaneously, as per allergen Ag presentation scenarios (ii) and (iii).
- The allergen Ag recognition is mediated by conventional T cells which are donor-restricted, as per allergen Ag T cell recognition scenario (iii).
- Relevant private, donor-specific unconventional T cell repertoires exist.

The latter is exemplified by microbial GMM-reactive CD1b-restricted T cells that in many donors comprise a public TCR repertoire (e.g. GEM T cells) as well as private TCR repertoire[53,120,121]. Further it is unclear which other immunological mechanisms are in place to prevent or encourage reactions to allergens presented by MHC-I-like molecules. Some unconventional T cell responses appear to correlate with genetic polymorphisms established for allergic disease, such as the Filaggrin-null mutation that is associated with atopic dermatitis severity[66]. This also resonates with conventional T cell mediated hypersensitivities. For instance, in the case of abacavir hypersensitivity, ~ 40 % of abacavir treated individuals that are HLA-B*57:01^{+} tolerate abacavir[122]. So, while HLA-B*57:01 is necessary for abacavir hypersensitivity, it is not sufficient to allow for hypersensitivity reactions to occur. In summary, while unconventional T cells are donor-unrestricted, genetic predispositions likely play a major role in the involvement of unconventional T cell in allergic disease. Notably, in the case of drug hypersensitivities, actual frequencies of hypersensitive individuals could be masked as presumably drugs that cause a strong allergic response in most individuals would not pass clinical testing towards drug approval.

4.2 Expected hallmarks of hypersensitivities involving T cell responses to allergen Ags presented by MHC-I-like molecules

In the context of a type IV hypersensitivity, priming of conventional T cells occurs in the lymph nodes upon the first allergen exposure, which is often referred to as Ag sensitisation. Following a second allergen exposure, effector responses are detected with a delay of 24-72 hours, a T cell response termed DTH[123]. In contrast, naïve (or preprimed) MAIT cells and type I NKT cells are present at high frequencies at steady state in most, if not all tissues[9]. Additionally, MHC-I-like molecules are broadly expressed across tissues[13,23,124]. Therefore, one might speculate that MAIT cells and type I NKT cells are poised to encounter allergen Ag directly at these sites. Moreover, given the preprimed nature of these cells, priming might not be needed to the same extent, resulting in a more rapid effector response.

Given the unique chemical properties of the Ag binding clefts of the various MHC-I-like molecules, different classes of non-protein molecules represent allergen Ag candidates for each MHC-I-like molecule. For example, small molecules including pyrimidines, phenols/anilines, enones, aromatic aldehydes, aromatic carboxylates, quinones, flavones, and isoflavones (150-400 Da) can be presented by MR1[20], whilst a diverse repertoire of endogenous lipids can bind mutually to the different CD1 molecules[12,24,125]. The class of allergen Ag in turn is recognised by a subset of T cells restricted by the relevant MHC-I-like molecule, thus eliciting a hypersensitivity reaction, in line with the functional capacity of the relevant T cell subset. Thus, a range of type IV hypersensitivity responses can be envisaged, similar to the existing subgrouping for conventional T cells (type IVa-d)[2]. Type IV hypersensitivities can also be accompanied by IgE production, as described for iNKT cells in the OVA-induced AHR mouse model[60,78].

Box 1: Future Research Perspectives (open areas for future research)

In the last decade there have been significant advances, demonstrating allergen Ag display of lipids by CD1 and small molecules by MR1. Our emerging knowledge of the function of unconventional T cells and development of better reagents will facilitate allergen Ag discoveries and delineation of the

underlying mechanisms governing hypersensitivity responses. More studies into the clinical relevance, especially in the case of potential MAIT cell-mediated hypersensitivities to small molecules, are needed. Could some of the suspected T cell mediated hypersensitivities including those to antibiotics, for which mechanisms are unclear, be mediated by CD1- or MR1-restricted T cells? E.g. metal hypersensitivities have often been described as TCR-dependent but classical MHC-independent, thus not excluding MHC-I-like molecules as targets. T cell immunotherapies with allergen Ags relevant to MHC-I-like molecules would likely apply to the genetically diverse population. Like conventional T cell-based immunotherapies, they would lack IgE binding capacity so that the risk of adverse reactions would be low[3].

viii. References (up to 200)

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ix. Tables

Table 1: Unconventional T cell frequency and TCR usage in mice.

MHC molecules	MR1	CD1d		
	MAIT cell	**Type I NKT cell**	**Type II NKT cell**	**CD1d-restricted γδ T cell**
Cell frequency	0.5-2%	1%	Not well defined	1%?
TCR usage	TRAV1 (Vα19)-TRAJ33 (Jα33) TRBV19 (Vβ6.1)/13 (Vβ8)	TRAV11 (Vα14)-TRAJ18 (Jα18) TRBV13 (Vβ8)/29 (Vβ7)/1(Vβ2)	Predominantly TRAV9(Vα3)/7 (Vα1)-TRAJ7/9 (Jα7/9) TRBV13-3 (Vβ8.1)/ 26 (Vβ3.1)-Jβ2.7	Not defined

Table 2: Hypersensitivities related to allergen recognition by unconventional T cells

Allergen category	**Cell type**	**Potential allergy/allergen**
Environmental	CD1a restricted T cells	Bee/wasp[59,65] House dust mites[66]

		Urushiol[52] Cypress pollen[71]
	CD1d restricted T cells	Cypress pollen[71]
	NKT cells	Olive pollen[72] Ragweed pollen[73] Asthma[60,78–83,126]
	MAIT cells	Asthma[85,86,127]
Food	NKT cells	Brazil nut[89] Cow's milk[90–94]
	γδ T cells	Gluten[97–100] Peanut[101]
Metal	NKT cells	Nickel[109] Chromium[115]
Drug	Type II NKT cells	PPBF[116]
	MAIT cells	Diclofenac[54]

x. Figure legends

Figure 1. Overview of antigen presentation by MHC-I and MHC-I-like molecules and their recognition by T cells.

Row 1 displays top-views onto the antigen cleft based on crystal structures of HLA-A*02:01 in complex with the cytomegalovirus pp65-derived peptide antigen NLV$^{495\text{-}503}$ (PDB ID: 2X4R[127]), as a representative of an MHC-Ia molecule; MR1 in complex with the bacterial/fungal small molecule metabolite antigen 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) derived from a biosynthetic precursor to riboflavin (PDB ID: 4NQC[16]); CD1a in complex with the Mycobacterium tuberculosis lipid antigen Dideoxymycobactin (DDM) (PDB ID: IXZ0[128]); and CD1d in complex with the marine sponge–derived lipid antigen α-galactosylceramide (α-GalCer) (PDB ID: 2PO6[129]) or the endogenous lipid antigen sulfatide (PDB ID: 4MQ7[32]). Row 2 shows chemical structures of the relevant antigens, followed by the name and approximate frequency of the relevant MHC-restricted T cell type in row 3[9]. The frequency of CD1d-restricted γδ T cells, most of which recognise endogenous lipid antigens and sulfatides, is estimated to be 0.05-3.5% of CD1d-α-GalCer reactive cells[31]. Row 4 shows schematics of the antigen presentation by antigen presenting cells (APCs) and their recognition by T cell receptors (TCRs) expressed by T cells. In each case the antigen type, TCR usage and effector function molecules are highlighted[9,16,18,31,37,43,49,130–139]. Row 5 includes phenotypic markers commonly used to identify these cells by flow cytometry[131,140–143].

Figure 2. Possible scenarios of allergen antigen presentation by MHC-I-like molecules.

A schematic of the 4 possible scenarios of allergen antigen display by MHC-I-like molecules in comparison to microbial/endogenous antigen presentation (left column). (i) The allergen antigen replaces the microbial/endogenous antigen. (ii) The allergen antigen and a microbial or endogenous

antigen are simultaneously presented, but as distinct entities. The repertoire of microbial or endogenous antigens may be identical to that presented in the absence of the allergen antigen or distinct. (iii) The allergen antigen is directly conjugated to an antigen (iii), selected from the microbial or endogenous Ag repertoire that is either identical or distinct to that presented in the absence of the allergen antigen. (iv) The allergen might 'act on' endogenous material, eliciting presentation of endogenous antigens (in the absence of allergen antigen and referred to as neoantigens), that would not be presented in steady state or that are normally presented at very low levels.

Figure 3. Allergen antigen presentation by CD1a and MR1. (A) Chemical structures of the Mycobacterium tuberculosis derived antigen Dideoxymycobactin (DDM), the bee/wasp venom allergen derived antigen Lysophosphatidylcholine (LPC), the poison ivy allergen derived antigen urushiol (C15:2) and the allergen antigen farnesol contained in cosmetics/perfumes and their presentation by CD1a (PDB IDs: IXZ0[128], 4X6E[69], 5JIA[52], 6NUX[55]), displaying top-views onto the CD1a-antigen complexes. (B) Chemical structures of the bacterial/fungal riboflavin biosynthesis derived antigen 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), the drug like small molecule antigen 3-formyl-salicylic acid (3-F-SA) and the diclofenac drug metabolite antigen 5-hydroxy-diclofenac (5-OH-DCF) and their presentation by MR1 (PDB IDs: 4NQC[16], 5U6Q[54], 5U72[54]), displaying top-views onto the MR1-antigen complexes.

Figure 1

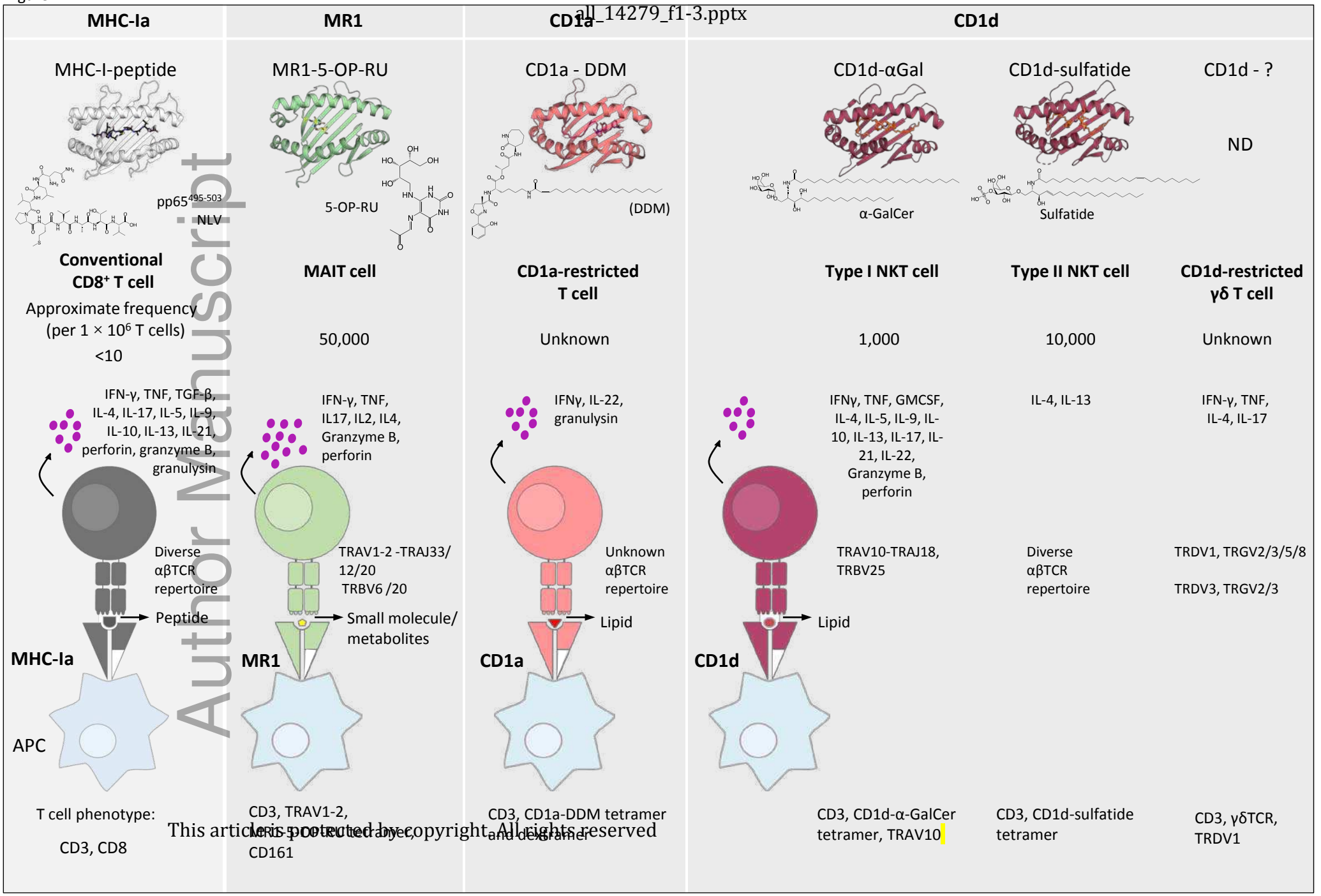

Figure 2

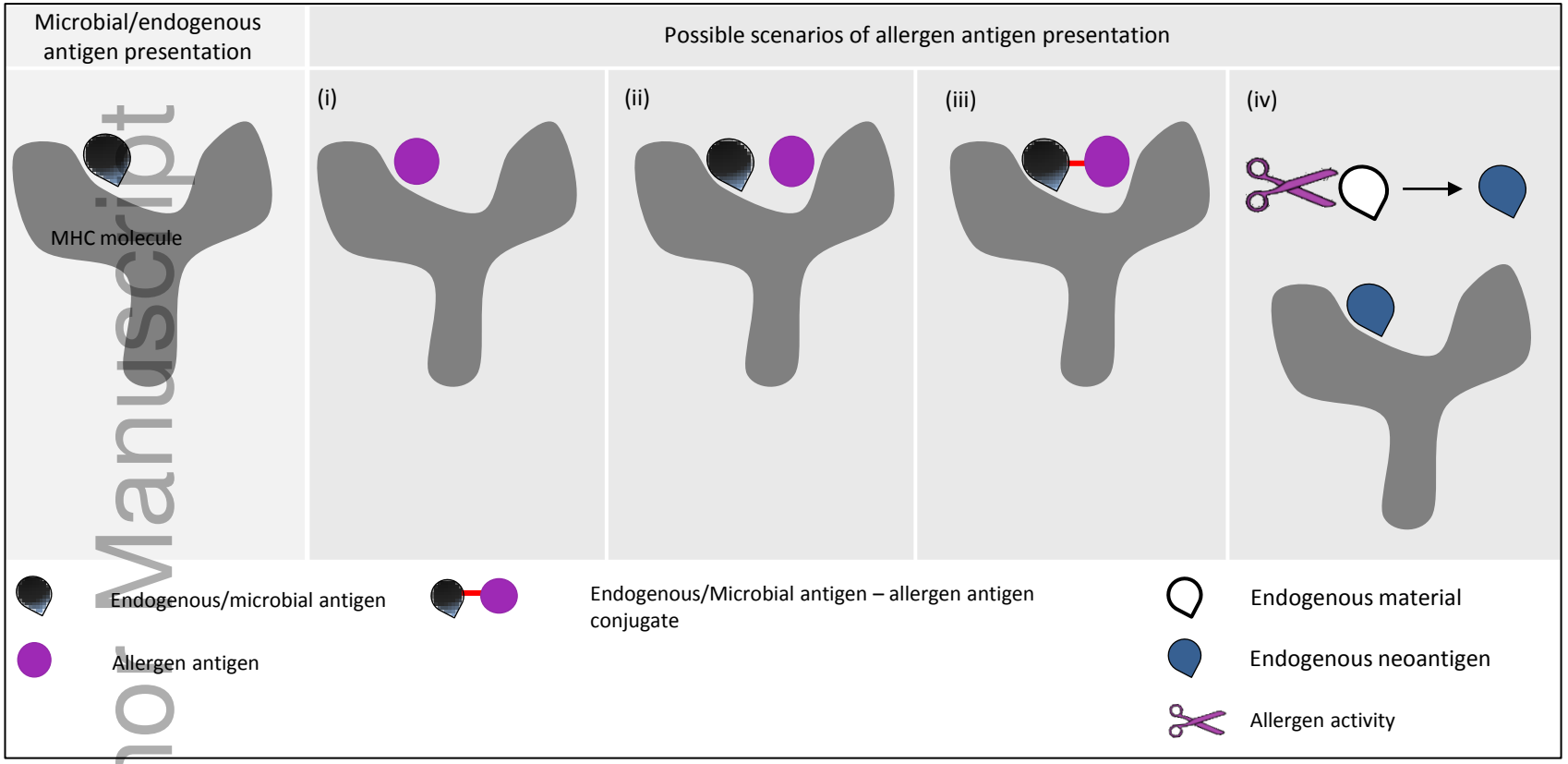

Figure 3