**The versatility of the CD1 lipid antigen presentation pathway**

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**Abstract**

The family of non-classical MHC class-I like CD1 molecules has an emerging role in human disease. Group 1 CD1 includes CD1a, CD1b, and CD1c which function to display lipids on the cell surface of antigen presenting cells for direct recognition by T cells. The recent advent of CD1 tetramers and the identification of novel lipid ligands has contributed towards the increasing number of CD1 restricted T cell clones captured. These advances have helped to identify novel donor unrestricted and semi-invariant T cell populations in humans and new mechanisms of T cell recognition. However, while there is opportunity to design broadly acting lipids and harness the therapeutic potential of conserved T cells, knowledge of their role in health and disease is lacking. We briefly summarise the current evidence implicating group 1 CD1 molecules in infection, cancer and autoimmunity and show that although CD1 are not as diverse as MHC, recent discoveries highlight their versatility as they exhibit intricate mechanisms of antigen presentation.

**Introduction**

Cellular adaptive immunity in higher vertebrates is critically dependent on T cells and their specific interactions with antigen presenting molecules on the surface of antigen presenting cells (APCs), including dendritic cells (DC), macrophages, and B cells. The major families of antigen presenting molecules in mammals include the peptide binding major histocompatibility complex (MHC) class I and II molecules, which are highly polymorphic, butyrophillin 3A1 molecules which are thought to mediate phosphoantigen-sensing by γδ T cells (1), the non-polymorphic MR1 which presents small metabolites (2, 3), and the lipid binding CD1 proteins (4). Of the five CD1 isotypes, CD1a, CD1b, CD1c, and CD1d function to present lipid antigen at the cell surface to both  and  T cells (Figure 1). CD1e is not expressed on the cell surface and functions as a lipid transfer protein (5). Group 1 CD1 comprise CD1a, CD1b and CD1c which are not present in mice, whereas group 2 CD1 comprise CD1d, which is found in all mammals (4). Upon recognition of the CD1 ligand complex by the T cell receptor (TCR), CD1 dependent T cells are activated in a variety of immunological contexts.

CD1 restricted T cells can be activated by a range of self and non-self lipids (6). Two broad mechanisms of CD1-lipid/TCR complex interactions have emerged as models of T cell activation. These include highly specific interactions of the antigen surface-exposed polar head-group with the TCR, as is the case for many of the CD1 bound foreign bacterial lipids defined thus far (7, 8). Another mechanism is governed by dominant interactions between the TCR and the CD1 protein, as is the case for the limited number of autoreactive group 1 CD1-restricted TCRs described (9), and for high-affinity human CD1d-restricted TCRs (10). Two mechanisms exist for generating CD1 conformations that induce protein-protein interactions with the TCR. The first is absence of interference as is the case for CD1a (11). The second is conformational remodelling which is driven by ligand binding to CD1c (12), but this model requires further validation. These likely add to the many mechanisms driving CD1 autoreactive T cell activation that include increased CD1 expression, de-novo synthesis of endogenous CD1 lipid antigens, altered cytokine secretion as well as the absence of steric and electrostatic TCR hindrance (13-18). Understanding basic mechanisms of CD1 mediated T cell activation is essential in order to harness their potential in disease treatment. Here, we summarise evidence implicating CD1 molecules in a variety of disease states and review their unique features and emerging concepts of CD1-lipid presentation to T cells, highlighting the versatility of the CD1 system.

**Group 1 CD1 elicit T cell responses in a variety of disease states**

The presentation of lipid antigens by CD1 molecules on the cell surface represents a snapshot of the cell condition. Whether the cell is at homeostasis, infected or under stress; CD1 molecules can report these changes in the lipidome to T cells, and have increasingly recognised roles in many disease states.

*Infection*

The majority of foreign antigens that bind CD1a, CD1b and CD1c have so far been identified as mycobacterial cell wall associated lipids such as: mycolic acid (19), glucose monomycolate (GMM) (7), glycerol monomycolate (GroMM) (20), isoprenoids (21), sulfoglycolipids (22), phosphmycoketides (23, 24), lipoarabinomannan (LAM) (25), phosphatidyliniositol phosphates (PIMs) (26) and dideoxymycobactin (DDM) (27).

CD1 restricted T cells specific for mycobacterial antigens are well described, some of which are being investigated for their role in host immunity against infection. For example, peripheral blood lymphocytes of *Mycobacterium tuberculosis* (Mtb) infected patients, but not those from healthy subjects, proliferate in response to CD1c presented mycobacterial phosphodolichols (21). T cell responses toward CD1b presented mycolates have been broadly characterised and are arguably the current focus of lipid specific T cell investigation in Mtb infection (7, 19, 28-32). Importantly, local expression of CD1b in Mtb infected lung granulomas from tuberculosis patients implies the presentation of CD1b presented lipid antigens, including mycolates, within infected lesions (33). Furthermore, insights from lepromatous dermal lesions showed that lower CD1 expression correlated with a lack of effective cell mediated immunity (34). Once activated, it is possible that lipid specific T cells mediate protection, as they are capable of secreting the anti-microbial cytokines IFN- and TNF-important for APC activation and granuloma formation respectively, among other roles(28, 29, 35, 36). Additionally, polycytotoxic mycolic acid specific T cells isolated from bronchoalveolar fluid in tuberculosis patients are capable of limiting mycobacterial growth *ex vivo* (37). In a humanised CD1 mouse model expressing the mycolic acid specific TCR DN1, T cells were capable of reducing bacterial growth both *in vitro* and *in vivo* (31). Moreover, CD1b tetramers treated with mycobacterial GMM defined two populations of GMM specific T cells within the human CD1b restricted repertoire, the Germline-encoded mycolyl lipid-reactive T cells (GEMs), and the LDN5-like T cells. These T cells produce anti-microbial cytokines and increase in numbers post infection with Mtb (28, 32). Indeed, the presence of conserved GEM T cells in humans with such exquisite specificity, represents possible selective pressure for lipid reactive T cells in mycobacterial infection (28).

Other antigens displayed by CD1 include phospholipids which are shared by both host and pathogens. T cells derived against Staphylococcus and Salmonella antigens were shown to prominently target CD1b presentation of phosphatidylglycerol (PG) and phosphatidylethanolamine (PE) (38). Although abundant in eukaryotic mitochondrial membranes, phospholipids such as PG and PE are also highly expressed by bacterial membranes. As they are only available for loading onto CD1 under conditions of cell stress, damage and infection, the circumstances of their presentation represent a new mechanism of distinguishing between self and non-self (38). Furthermore, solved co-crystal structures prompted speculation that more abundant phospholipids sterically or electrostatically prevented CD1b-restricted autoreactive TCRs from binding, expanding our knowledge regarding regulation of autoreactivity (39). In addition, lipopeptides are also targets for CD1 restricted T cells. DDM is a well characterised mycobacterial CD1a presented antigen which is specifically recognised by T cells (40). Lipo-12, an N-terminally acylated protein similar to the myrisolyated NEF protein from HIV, is also presented by CD1c (41). The recognition of such a ligand by T cells highlights the possibility that viral, ribosomal and mammalian acyl-peptides could be presented by CD1 and demonstrates the flexibility of the CD1 system in reporting infectious disease to T cells.

Due to the tight regulation of group 1 CD1 expression on APC, involvement of CD1a, CD1b and CD1c in infection is confined to their expression. Central to regulating CD1 expression on professional APCs is TLR (18). Bacterial lipids and products trigger group 1 CD1 expression on dendritic cells through TLR2 ligation(13, 42-45)*.* However, regulation of CD1 expression is clearly more complex due to the inconsistencies of expression on various cells types. Macrophages rarely express detectable levels of group 1 CD1, however their expression in macrophages derived from human decidua, and on lipid-laden foam cell macrophages in atherosclerotic tissue suggest that other, as yet unknown mechanisms determine CD1 expression (46, 47).

*Cancer*

A role for CD1b restricted T cells in cancer has only recently been shown, which is highlighted in the double transgenic mouse model which expresses human group 1 CD1 molecules and the CD1b autoreactive HJ1 TCR. The CD1b autoreactive HJ1 T cells recognised several self phospholipids which are known to accumulate in tumours including PE, PG, ether linked PE, phosphatidylcholine (PC), and phosphatidylinositol (PI) (48, 49). HJ1 T cells were more potently activated by tumour-derived self-lipids than those isolated from healthy cells and were able to kill CD1b-expressing tumours. They also exhibited anti-tumour immunity *in vivo,* and their response was enhanced by various TLR agonists and by DC derived IL-12 cytokine secretion. Given that there is little data on the CD1b autoreactive TCR repertoire, and the possible range of self-antigens presented by CD1b, there is potential for CD1b to demonstrate further functions in cancer.

Recently, CD1c restricted T cell clones isolated from different donors recognised several CD1c expressing leukemic cell lines in a CD1c dependent manner (50). Biochemical studies combined with T cell activity data identified methyl-lysophosphatidic acids (mLPAs) as the CD1c presented antigen which was specifically recognised by CD1c autoreactive T cells. mLPA is a self-lipid antigen that accumulates in leukemic cells including primary human leukaemia but not in healthy monocytes or B cells. It potently activated CD1c autoreactive T cell clones *in vivo*, limiting the growth of leukaemic cells in mice with human tumour cell xenografts (50). Therefore, CD1c-mLPA specific TCRs are candidates for adoptive T cell therapy in acute myeloid leukaemia.

*Autoimmunity and allergy*

Presentation of self-lipids to T cells represents a major function of the group 1 CD1 system. CD1 autoreactive T cells, particularly CD1a and CD1c, are abundant among circulating T cells from healthy human adults and neonates (51). In conditions manifesting in hyperthyroidism such as Graves’ disease and the autoimmune condition Hashimoto’s thyroiditis, CD1 has a potential role. B cells positive for CD1c and DCs expressing CD1a, CD1b and CD1c infiltrate afflicted thyroid glands, resulting in major tissue destruction and loss of structure. CD1 autoreactive T cells present within the thyroid are capable of lysing thyroid target cells in a CD1a and CD1c dependant manner (52). In SLE, a systemic autoimmune condition of unknown origin, CD1c autoreactive T cells induce auto-antibody isotype switching on CD1c expressing B cells, leading to an increase in IgM antibody production (53). Potential antigens such as the so-called ‘headless antigens’ derived from self and presented by CD1a have been described, which are present in skin oils (51, 54). In psoriasis, an autoimmune skin condition, neolipid antigens are generated by phospholipase A2 (PLA2), which is found in active psoriasis lesions, implying a pathogenic role in inflammation via CD1a antigen presentation (55). Allergic skin conditions such as atopic dermatitis may also become exacerbated by house dust mite allergen PLA2 through generation of CD1a presented neolipid antigens that cause inflammation (56). Interestingly filaggrin, a skin barrier protein, inhibits PLA2 and therefore prevents development of atopic dermatitis in healthy individuals (56). Furthermore, PLA2 is also found in bee and wasp venom where once delivered sub-cutaneously, generates a local inflammatory response (57). The recent understanding of CD1a presentation of headless antigens that mediate inflammatory skin disorders led to the hypothesis that urushiol, found in poison ivy, can elicit a T cell response in a CD1a dependant manner (58). These studies also demonstrated a role for CD1a in driving psoriatic skin inflammation, and provided a potential therapy for inflammatory skin conditions through targeting CD1a (58).

CD1 lipid antigen presentation therefore, is associated with a wide variety of diseases. New data is consistent with an important role for CD1a, CD1b and CD1c restricted T cells in human immunity to infection, cancer, and autoimmune disease. The small number of CD1 restricted T cell clones and their biased selection in culture, has contributed to our limited knowledge of their overall function in disease. In addition, little attention has been placed upon the translational potential of CD1 and the creation of novel therapeutic treatments. Greater use of humanised mouse models and tetramers for direct *ex vivo* T cell analysis will aid our understanding of the function of the CD1 system in health and disease.

**Unique features allow diverse lipid sampling**

*CD1 structure*

CD1 molecules consist of a heavy chain comprising the α1-α3 domains which non-covalently bind the light chain of -2-microglubulin (2M)(59) (Figure 1). Structural insights of CD1 proteins displaying glycolipids reveal that the antigen binding function of CD1 is embedded within the α1 and α2 domains, which harbour hydrophobic channels that are suited for binding the lipidic parts of CD1 antigens. Polar moieties of lipid antigens are positioned above the binding pocket at the TCR interface for direct recognition by T cells. CD1 isotypes have evolved antigen binding pockets of differing shapes and sizes, presumably to allow them to bind and present a large number of structurally diverse lipids (8, 12, 60, 61). Insights from crystal structures and molecular modelling have greatly contributed to our current understanding of how CD1 proteins bind to a broad range of lipids and glycolipids.

All CD1 proteins have an A’ and an F’ pocket, whereas CD1b has an additional T’ tunnel and a C’ channel (61). In CD1b, the interconnected A’, T’, and F’ pockets form a superchannel, which is a unique feature of human CD1b that enables the presentation of the very long mycolic acids of mycobacteria and nocardia (62). The C’ channel has a C’ portal under the α2 helix which may allow exit of longer hydrocarbon chains. CD1a in comparison, has the smallest groove comprising a short A’ channel that limits the length of alkyl chains able to bind, and it has a less restrictive F’ channel which accommodates larger lipid moieties (60, 63). The A’ and F’ channels of CD1d are ideally suited for binding ceramide lipids such as α-galactosylceramide (α-GC), a potent agonist of invariant natural killer T cells (iNKTs) (8). Lastly, CD1c features an A’ and an F’ channel (12, 64) which can present diverse lipid antigens, including cholesteryl-esters to T cells. The F’ channel of CD1c adopts dramatically different “open” and “closed” conformations depending on ligand occupation (12). Hence, each CD1 isotype has a set of unique antigen binding channels highlighting their ability to bind diverse lipid structures.

*CD1 localisation*

CD1 ensures presentation of a broad range of lipids by surveying distinct cellular subcompartments. Upon assembly in the endoplasmic reticulum (ER), CD1 molecules initially bind polar and non-polar self-lipids, believed to function as stabilising chaperones (65). These include sphingomyelins and phospholipids (66-68), and in the case of CD1b, multiple scaffold ligands are bound (65). Upon correct folding in the ER, CD1 complexes travel though the secretory pathway directly to the plasma membrane. Once expressed, they are internalised into lysosomal compartments where they can encounter self- and bacterial- lipid antigens before recycling back to the plasma membrane (69). The continuous recycling of CD1 molecules from the plasma membrane to lysosomal compartments is regulated by tyrosine-containing motifs in their cytoplasmic tails, with the exception of CD1a, which lacks such a motif (69, 70). CD1a localises predominantly in the early endosomes, and does not require the low pH conditions for lipid loading. CD1b primarily locates to the late endosomes and lysosomes, where the acidic conditions regulate lipid loading by altering ionic tethers in the F’ portal (70-73). CD1c and CD1d recycle to early and late endosomes, as a result of binding adaptor protein 2 (AP-2) via their cytoplasmic tails (74, 75). Additionally, while CD1a, CD1b, CD1c, and CD1d are expressed by myeloid dendritic cells (moDC) (76), they all have niche cellular and tissue expression patterns. CD1d is constitutively expressed on many haematopoietic and non-haematopoietic cells including epithelial cells (76, 77). Whereas CD1a, CD1b and CD1c expression is restricted to professional APCs. CD1c and CD1d are expressed by B cells including leukemic lymphoma cells (50, 78). CD1a and to a lesser extent CD1c are expressed by skin resident Langerhans cells (74, 77, 79). The unique intracellular trafficking routes and cellular expression patterns within different tissues is consistent with a specialised role for each CD1 isotype.

**Diverse mechanisms of antigen display to T cells**

CD1 restricted TCRs recognise a broad range of lipids when bound to CD1 proteins through diverse mechanisms. The TCRs of iNKTs for example, predominantly bind CD1d, while the polar head group of the lipid modulates the interaction. Moreover, recent reports suggest ligands bound to CD1 can modulate TCR interaction even when they are not contacted directly by the TCR (38, 48, 80). Here we describe the possible modes of recognition of CD1 by T cells and mechanisms behind the range of activity that T cells display to CD1 antigens.

The recognition of CD1-lipid complexes by TCRs is regulated by a number of mechanisms. The first and most typical is through T cell specificity for the large lipid head group moieties protruding above the CD1 protein, visible to the TCR (7, 81-84). The best characterised example is recognition of GMMs by CD1b restricted TCRs (7, 85). Here, even the smallest alteration in hydroxyl group orientation on the carbohydrate moiety abrogates TCR binding. This specificity for the head group was recently demonstrated at the molecular level by the structure determination of a GEM TCR in complex with CD1b-GMM. The GEM TCR employs an elegant “tweezer” like mechanism that grips the glucose head group moiety of GMM (85). Another example includes the presentation of mannosyl-β1-phosphomycoketide (MPM) by CD1c. The presence of the polar mannosyl moiety is recognised by the T cell line CD8-1, whose activity is lost upon cleavage of the sugar (21, 86). The discrimination of different head groups is a classical mechanism for differentiating between different lipid ligands by TCRs.

CD1 can also communicate changes in lipid repertoires to T cells through a mechanism coined “absence of interference”. Identification of hundreds of small polar and non-polar CD1a lipid antigens revealed the so called “permissive” or “non-permissive” ligands for the CD1a autoreactive BC2 T cells (11). Generally, permissive ligands were headless antigens as they lacked a polar head group moiety, and were derived from skin oils including squalene and wax esters. CD1a autoreactive T cells were activated in the presence of CD1a bound to headless lipids and not those with large polar head groups (54). Subsequent co-crystal structures revealed the autoreactive BK6 TCR binds the A’ roof without directly contacting the bound lipid cargo (11).

Conformational remodelling, is also employed by CD1 as a mechanism thought to facilitate autoreactive TCR binding (77). Initial CD1c structures were solved, bound to MPM and subsequently phosphomycoketide (PM), which are lipids derived from the cell wall of Mtb(24, 64). These highly methylated and branched lipid molecules sat within the A’ channel, leaving the F’ groove unoccupied, containing only a small spacer lipid likely to have originated from the insect cells from which CD1c was produced. Key features of these CD1c structures included their open F’ groove, reminiscent of the peptide binding grooves of MHC molecules, and two portals, designated D’ and E’, connecting the A’ and F’ channels to the exterior respectively (24, 64). A more recent study reported an entirely different conformation of CD1c, whereby a lipid saturated F’ channel induced extensive remodelling of the protein forming an F’ roof above the F’ channel and a G’ portal, open on the right side of the F’ channel with the apparent loss of the E’ portal (12). Furthermore, aromatic self-ligands including cholesteryl-esters, were able to induce this remodelling which is apparently critical for the binding of some autoreactive TCRs (12). Structural insights of CD1c in complex with autoreactive TCRs will shed further light onto this novel mechanism.

**Buried hydrophobic moieties translate distinct T cell activities**

Identifying mechanisms of ligand recognition by crystal structures are indispensable, yet only describe a snapshot of the interaction. However, to activate T cells, the engagement of the TCR with the CD1-lipid complex must occur over time. Therefore, activation is not only a function of binding affinity and avidity, but also of complex dynamics (87).

T cell activity can be influenced by architecture of the CD1 groove and subtle changes in the structural composition of lipid ligands including the fine structure of lipid tails. This concept was first implied in 2002 with crudely separated classes of mycolate. Stimulation of the mycolic acid specific and CD1b restricted DN1 TCR with - keto- and methoxy classes of mycolate revealed the sensitivity of the TCR towards the fine structure of the long meromycolate chains of mycolic acids (88). Furthermore, MPMs with differing methyl-branching patterns influence the activation levels of CD8-1 T cells when presented by CD1c (84). Another class of lipid, mycobacterial sulfoglycolipids, were shown to alter the potency of the T cell response when the aliphatic hydrocarbon chains were altered (89). This effect was evident when the number of C-methyl substituents within the fatty acid, the positioning and the stereochemistry of the functional groups were changed (89). The iNKT TCR also differentiated between CD1d bound -GC, when the length of the phytosphingosine chain and the extent of saturation was changed (90). These studies suggest that CD1 restricted TCRs are not only influenced by lipid polar head group moieties, but also the fine structure of hydrophobic moieties deeply buried within the CD1 proteins, which are in all cases assumed to be not in direct contact by the TCR.

Until recently, a role for the distal or proximal functional groups of the meromycolate tails of mycolic acids as antigenic determinants were not well understood (88). By treating soluble CD1b molecules with extremely insoluble mycolic acids, Van Rhijn et al. showed definitively, a direct impact of distal meromycolate functional group alteration on TCR recognition (19). Synthetic representatives of the -, keto- and methoxy- mycolic acids that appear on the cell wall of Mtb show clear differential activity on a variety of CD1b-mycolic acid specific T cell clones and lines when presented by CD1b. Furthermore, CD1b tetramers were treated with two forms of mycolic acid classes, the keto- and methoxy-, and tetramer staining revealed differing patterns of binding to T cells. Interestingly, each of the T cell clones recognised distinct classes of mycolates leading to the conclusion that each class of mycolic acid should be considered as separate antigens. Most recently, work investigating GEM TCR activity toward an extensive panel of synthetic mycolates based on natural structures, corroborated this, also showing that both proximal and distal meromycolate functional groups impact T cell responses (33).

A putative mechanism for the differential recognition of hydrocarbon chains, which are expected to lie outside of direct contact by the TCR, was eluded to by computational modelling simulations of lipid/protein interactions (33). These data indicated that meromycolate chain dynamics within the CD1b groove appear to be directly linked to the activity of GEM18-TCR (Figure 2). The result is a range of T cell activities from one TCR against a number of subtly altered mycolic acids of the same class. This model suggests that weakly stimulatory lipid tails are immobile due to the position and nature of their chain substituents caused by functional group ‘trapping’ in hydrophobic crevices within the binding channels of CD1b. This may restrict the head group from adopting positions that facilitate TCR binding. In contrast, strongly stimulatory lipid chain substituents do not ‘catch’ on pocket features and therefore remain fluid. The apparent combination of greater chain fluidity and reduced head group mobility may allow conformations that are more productive for GEM18 TCR binding. The differing activity of diverse CD1b-restricted mycolate-specific TCRs may be because they have different modes of engagement and interaction with the CD1b/mycolic acid complex, and therefore preferentially bind to different classes of mycolic acid that adopt different head group positions (19). However, this model does not account for the ‘combinatorial epitope’ hypothesis, which suggests apparently different conformations of CD1b protein and lipid such that the meromycolate functional groups are displayed directly to the TCR (88). However, given the similarity of lipid structure of mycolic acid to GMM, whose crystal structure has been resolved when bound to CD1b, the required major conformational change is hard to envisage (62). Mutational and structural studies as well as specifically designed mycolic acid analogues will reveal the mechanism behind such enigmatic TCR binding requirements. Elucidation of which will help contribute to the design of lipid vaccines and potential therapies.

**Summary**

The discovery that CD1 is a TCR binding epitope (44), was shortly followed by the recognition that lipid antigens are capable of eliciting specific T cell responses, when presented by CD1 (81). MHC molecules are highly polymorphic and have the capacity to bind and present a vast number of peptide sequences. This results in the generation of an almost infinite number of binding epitopes that can be recognised specifically by TCRs. On the other hand, CD1 molecules are non-polymorphic, therefore CD1 restricted TCRs do not have the luxury of such diverse binding sites or variety of bound lipids. Despite this, CD1 molecules prove highly versatile in lipid presentation and play a role in a number of disease conditions, employing diverse mechanisms to elicit a variety of specific T cell responses. Recent insights suggest multiple modes of TCR engagement to CD1-lipid complexes – head-group discrimination, absence of interference and protein remodelling. Moreover, the hydrophobic groove architecture can communicate subtle differences in lipid structure to T cells, modulating their responses. These features highlight the plasticity of CD1 antigen presentation and supports evolved mechanisms that paints a complete picture of the cellular lipid environment to T cells. Ongoing emphasis on translational research within CD1 will contribute towards the effort to derive new therapeutic targets in cancer, autoimmunity and infectious disease.

**Competing interests**

The authors declare no conflict of interest.

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**Figure 1:** **Structure of human CD1-ligand complexes**. Each Human CD1 protein has a unique lipid binding pocket architecture. CD1a is shown bound to a mycobacterial lipopeptide (60), CD1b is bound to a self-phospholipid, phosphatidylinositol (PI) and two spacer lipids (61), CD1c is shown bound to spacer lipids (stearic and lauric acids) (12), and CD1d is bound to α-galactosylceramide (8).

**Figure 2: Putative dynamics model of CD1b bound mycolic acids.** Representation of the molecular simulation of mycolic acids when bound to CD1b showing the chain functional groups at the start of simulation (*red spheres*) and at the end of simulation (*green spheres*). The model predicts that MAs immunogenic for GEM18 have meromycolate chains that are highly fluid within the CD1b pocket whereas less immunogenic chains are not fluid due to functional group trapping within crevices found in the CD1b pocket (Upper panels). Immunogenic lipids have head groups that are less mobile and “sink” into position to allow GEM18 TCR recognition, whereas less immunogenic lipids have head groups that are mobile or “unstable” which do not position correctly to allow productive GEM18 TCR recognition (Lower panels) (33).