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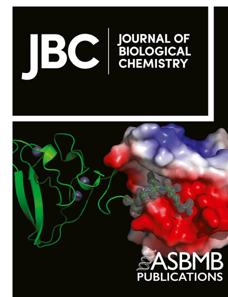

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Thinh-Phat Cao, Adam Shahine, Liam R. Cox, Gurdyal S. Besra, D. Branch Moody, Jamie Rossjohn

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A structural perspective of how T cell receptors recognise the CD1 family of lipid antigen-presenting molecules

Thinh-Phat Cao[1], Adam Shahine[1], Liam R. Cox[2], Gurdyal S. Besra[3], D. Branch Moody[4] & Jamie Rossjohn[1,5*]

[1] Infection and Immunity Program and Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Monash University, Clayton, Victoria, Australia
[2] School of Chemistry, University of Birmingham, Birmingham, United Kingdom
[3] Institute of Microbiology and Infection, School of Biosciences, University of Birmingham, Edgbaston, Birmingham, UK
[4] Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[5] Institute of Infection and Immunity, Cardiff University, School of Medicine, Heath Park, Cardiff, UK
* Corresponding author: Jamie.rossjohn@monash.edu

Running title: *TCR interactions with CD1*

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ABSTRACT

The CD1 family of antigen-presenting molecules adopt a Major Histocompatibility Complex class I (MHC-I) fold. Whereas MHC molecules present peptides, the CD1 family has evolved to bind self- and foreign-lipids. The CD1 family of antigen-presenting molecules comprises four members, CD1a, CD1b, CD1c, CD1d, that differ in their architecture around the lipid-binding cleft, thereby enabling diverse lipids to be accommodated. These CD1-lipid complexes are recognised by T cell receptors (TCRs) expressed on T cells, either through dual recognition of CD1 and lipid or in a new model whereby the TCR directly contacts CD1, thereby triggering an immune response. Chemical syntheses of lipid antigens, and analogues thereof, have been crucial in understanding the underlying specificity of T cell-mediated lipid immunity. This review will focus on our current understanding of how TCRs interact with CD1-lipid complexes, highlighting how it can be fundamentally different from TCR-MHC-peptide co-recognition.

INTRODUCTION

Studies on T cell-mediated immunity have centered on peptide antigen (Ag) display by *Major Histocompatibility Complex* (MHC) proteins. Here, MHC-restricted αβ T cells, *via* their αβ T cell receptor (TCR), play a fundamental role in protective immunity towards pathogens. Conversely, T cells are also associated with aberrant immune responses when recognising self-peptides presented by MHC molecules, leading to immune dysfunction and autoimmune diseases. However, despite the focus on MHC-mediated immunity over the last 40 years, there is another Ag-presenting system, termed CD1, comprising four transmembrane anchored Ag-presenting molecules, (CD1a, CD1b, CD1c, CD1d), along with the soluble CD1e lipid transfer protein, that display Ags to

T cells. Namely, CD1 molecules bind and display lipid-based Ags to T cells. These lipid-reactive T cells are also emerging as key players in protective immunity and immune dysfunction. Whereas nearly all our understanding of T cell Ag-recognition that trigger immune responses are centered on peptides, the discovery of the CD1 family provides a new perspective that cellular, synthetic, and microbial lipids are often overlooked, but potentially relevant Ags for T cells. Moreover, it is now coming to light that lipids can promote inflammation in a CD1-dependent manner and cause aberrant immune responses. Because lipids, one of the four basic biological macromolecules, are structurally stable and cannot undergo point mutations to escape detection like peptide, the lipid Ag-presenting CD1 molecules are non-polymorphic among individuals. In terms of foreign-lipids derived from infectious agents, the lipid structures are unique, as further described in the subsequent part of this review. Thus, it is important to understand the fundamentals underpinning TCR recognition of CD1-presenting lipid Ags, which are universally applicable. Here, we highlight the important role that organic chemistry has played in unravelling the specificity underpinning TCR recognition of lipid Ags.

Structure of CD1 molecules at a glance

CD1a, CD1b, CD1c and CD1d adopt a three-dimensional fold similar to that of MHC class I (MHC-I) molecules. However, unlike MHC molecules, whose Ag-binding clefts are ideally suited to capture peptides, CD1 molecules bind lipids (**Fig. 1**). Structural studies have shown that the shape of the CD1 Ag-binding clefts is different, thereby implying altered modes of lipid Ag display (1). Moreover, each isoform has a specific cell distribution profile and cellular trafficking pathway. For example CD1a, CD1c and CD1d are expressed on non-overlapping subsets of dendritic cells, and each human CD1 protein differs in expression of endosomal recycling motifs in their cytoplasmic tails (2).

The lipids presented by the CD1 system differ in size and composition of their hydrophilic head groups (**Fig. 2**) and each human CD1 isoform has a cleft that likewise differs in size and architecture. Thus, the repertoires of lipids bound by each of the four CD1 isoforms may either overlap or be isoform specific. Examples of pan-CD1 ligands that bind multiple human CD1 isoforms (3) include self-lipids, such as phospholipids, sphingolipids, acylglycerols and fatty acids (4). However, due to the different capacity and characteristics of their binding clefts, even lipid classes that show detectable binding to all four CD1 isoforms can still show marked preferences for specific isoforms. For example, sphingolipids are more efficiently captured by CD1a and CD1d, where CD1a shows a strong preference for molecules with long overall chain length C42 (or greater) (5), whereas efficient sphingomyelin (SM) capture by CD1d does not require long chain length. In terms of exogenous lipids, the presented lipids appear more structurally specific for individual CD1 proteins. Extensive studies described the complex and unique mycobacterial lipids that are presented by each isoform, including dideoxymycobactin (DDM) by CD1a (6), diacylated sulfoglycolipid (SL) (7), mycolic acid (MA) (8) and glucose monomycolate (GMM) (9) by CD1b, and phosphomycoketide (PM) and mannosyl-β1-phosphomycoketide (MPM) by CD1c (10). Additionally, CD1a and CD1c can present several classes of hydrophobic compounds that are small in size and therefore buried inside the CD1 protein, so that TCRs directly contact CD1 itself; these include contact sensitizers, such as farnesol, geranylgeraniol, urushiol, benzyl cinnamate, benzyl benzoate, and

monoacylglycerol (11-13). Another class of non-lipidic small molecule including phenyl pentamethyldihydrobenzosulfonate (PPBF) and its derivatives is presented by CD1d (14,15) to Crohns disease-associated invariant T cells (CAIT) (16,17). Collectively, the structural, biochemical, and cellular studies, including CD1 tetramer and mass spectrometry approaches, were critical to discover the factors within the lipid Ags that drive TCR recognition and downstream T cell responses.

Insights into TCR recognition of CD1 molecules

TCR-peptide-MHC recognition has been extensively studied, and is defined by a central paradigm of 'co-recognition' (18), wherein a TCR epitope is constituted by both the peptide Ag and the polymorphic binding cleft of the MHC molecules. A TCR is a heterodimer of either α and β, or γ and δ chains, which in turn defines the subpopulation to which the expressing T cell belongs. αβ and γδTCRs are indeed identical in their overall structure (**Fig. 3**), except for the highly variable CDR regions, namely CDR3 loops, that constitute the paratope. The same paradigm of co-recognition can be observed in the TCR-CD1-lipid axis but is not universal. As the hydrophobic tails are buried inside the CD1 cleft, the exposed hydrophilic headgroup generally defines the TCR epitope. Presently, two major binding mechanisms are supported by solved ternary crystal structures: 'co-recognition' which occurs for all CD1 isoforms, and 'absence of interference' for CD1a and CD1c, where the lipid is not directly contacted and its role is to permit CD1-TCR contact.

NKT TCR recognition of CD1d

Within the CD1 system, CD1d-lipid recognition by Natural Killer T (NKT) cells has been the most studied molecular paradigm. Two subsets of NKT cells are found, namely: type I NKT cells express invariant TCR α-chain (human TRAV10/TRAJ18, murine TRAV11/TRAJ18) paired with a limited set of β-chains (human TRBV25-1, murine TRBV1, TRBV13-2, or TRBV29) where α–galactosylceramide (α–GalCer) (19) is the prototypical ligand, though other ligands can be recognised (20-27). Type II NKT cells express a diverse repertoire of TCRs and do not recognise α–GalCer, with the most widely studied ligand being sulfatide. CD1d-lipid recognition by the NKT TCRs can adopt distinct interaction modes for each subset: tilted and parallel docking mode over the F' pocket of CD1d for type I NKT TCR, versus orthogonal positioning above the A'-pocket for type II NKT TCR (**Fig. 3A and 3B**). In the type I NKT TCR interaction, the α–GalCer headgroup is solely contacted by the invariant TCR α-chain, while the TCR β-chain contacts the F'-pocket of CD1d. In the type II NKT TCR interaction, the TCR α-chain primarily contacts CD1d while the TCR β-chain interacts with the sulfatide headgroup. However, one type II NKT TCR, namely A11B8.2, interacts with CD1d presenting a mycobacterial lipid adopting a parallel docking mode that resembles type I NKT TCR docking (28), thereby indicating that diverse type II NKT TCR usage can lead to diverse footprints atop CD1d.

Further, a minor subset of NKT cells has been identified as 'atypical', which includes clones whose characteristics fit neither type I nor type II NKT cells. This subset of atypical NKT cells may simultaneously recognise α–GalCer but show diverse range of TCR gene usage. The interaction topology of one such atypical TCR resembles type II NKT TCR-CD1d-sulfatide complex, which mainly binds the A'-roof of CD1d (29). Indeed, in a number of TCR-CD1d structures, the A'-roof of CD1d appears to be the preferable docking platform of the TCRs,

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including γδTCR recognition (30) (**Fig. 3C**). TCR contact with the A' roof is notable because MHC proteins lack a large contact surface that is not occupied by Ag, but the large lipid Ag-free surface of the A' roofs seen in all four human CD1 proteins and mouse CD1d, serves as a landing pad for CD1-autoreactive TCRs (31).

Synthetic α–GalCer analogues

Within these NKT TCR-CD1d-lipid interactions that define co-recognition, the surface area of contact with the lipid is limited when compared to CD1d itself, yet the interaction between TCR and lipid is critical to direct the downstream functional responses. For example, different versions of α–GalCer that activate type I NKT cells with varying potency can lead either to Th1 or Th2 effector responses that promote or inhibit the overall outcome of the immune response (32). Th1 and Th2 subsets are two types of $CD4^+$ T cells that distinguish themselves by two typical patterns of cytokine productions [reviewed in (33)]. Thus, the key purpose is to design analogues that can bias desired pattern towards the desired immune response. Over the past decade, several groups have synthesised 100's of structurally diverse NKT-cell agonists, some of which induce distinct and potentially therapeutically useful immune responses. However, a lack of effective delivery vectors and a tendency for some of the most potent and promising NKT-cell activators to induce NKT-cell anergy and depletion post stimulation, has hindered their development for clinical application. As a result highly efficient synthetic protocols now allow us to access a diverse range of small-molecule NKT-cell activators (see **Fig. 4** for examples), including: (i) glycosyl ceramides (incorporating, for example, amide isosteres, different acyl chains), which represent structural variants of the proto-typical CD1d agonist αGalCer (34-46); (ii) αGalCer dimers used to probe multivalency effects (43); and (iii) non-glycosidic analogues based around the truncated αGalCer analogue, threitol ceramide (ThrCer), which show increased bioavailability (47,48). Many of these molecules are potent NKT-cell activators; some are Th1, Th2 or Th17 cytokine-biasing, and show significant promise as immunomodulatory agents for a variety of therapeutic applications [reviewed in (49-51)]. In addition, the adaptability of the synthetic methodologies have also allowed the late-stage incorporation of a range of molecules, including haptens and labels (biotin, fluorophores, radiolabels), to a diverse range of type I NKT-cell activators (40) (**Fig. 4**). Through careful design, these modifications do not alter appreciably the functionality of the NKT-cell agonist under study and, as a result, these compounds prove to be valuable tools for studying *in vivo* behaviors of the parent antigenic molecules (40,52). This technology has far-reaching implications, linking other molecules (BCG, specific vaccine Ags and TLR ligands) to NKT-cell agonists, allowing the exploitation of multiple pathways of the immune system concurrently. Of particular relevance is recently devised mechanism that enables the chemical conjugation of a lipid Ag to CD1d (**Fig. 4**). Once covalently attached, the Ag cannot dissociate from the CD1d molecule. Consequently, the Ag–CD1d conjugate shows enhanced targeting of NKT cells and reduced off-target effects, in part because immunizing doses can be reduced (53,54).

TCR recognition of CD1b

To date, structures of αβTCR-CD1b-lipid complexes follow the co-recognition paradigm, as lipid-independent TCR activation is not yet clearly demonstrated. In the four ternary structures published, which include both microbial and self-lipids. The TCRs

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consistently sit atop of CD1b, with the α and β chains perpendicularly interacting with the helices α2 and α1, respectively, creating a ‘cationic cup’ to embrace the polar headgroup of the lipid (**Fig. 3D**) (55-58). Upon TCR binding, a slight conformational change of CD1b is seen in each case,mostly due to the remodelling of lipid Ag headgroups. There are also differences of TCR-CD1b footprints, whereby the TCR may or may not fully encase the lipid headgroup (58), which reflects the specificity of each TCR toward its cognate lipid. In one example, TCR docking on top of CD1b-self lipid creates ‘an escape channel’ for the lipid headgroup. This defined mechanism permits TCR cross-reactivity to various self-lipids with different head groups attached to phosphate (56-57), but it still requires the phosphatidyl group, and so is mechanistically distinct from the fully lipid independent absence of interference mechanism.

TCR recognition of CD1a-lipid and CD1c-lipid

There is evidence showing that TCR interactions with CD1a and CD1c also require co-recognition of CD1 and lipid. The identified *M. tuberculosis* lipid Ags including DDM presented by CD1a, or PM and MPM presented by CD1c (**Fig. 2**) are specifically recognised by corresponding T cell lines through TCR contact with the protruding phosphate or mannose unit or both (6,10,59,60). In terms of endogenous lipids, the leukemia-derived methyl-lysophosphatidic acid (**Fig. 2)** presented by CD1c specifically activates T cells (61,62). Although the structural data are yet to be obtained, the biochemical function suggests the existence of direct lipid-TCR contact (61-64).

Notably, TCR recognition of CD1a or CD1c carrying self-lipids can occur without invoking TCR contact with or direct recognition of the lipid. Namely, identification of small headless lipids (65) and the first ternary structure of a TCR-CD1a-lipid complex (66) defined a new structural paradigm, whereby the TCR contacts CD1a without the need to contact the lipid ligand, oleic acid (OLA) or lyso-phosphatidylcholine (LPC) (**Fig. 3E**). Here, the autoreactive TCR binds over the A’-roof of CD1a, thereby ‘missing’ the F’-portal, implying that this mode of direct TCR-CD1a binding would not be impacted by lipids that typically protrude from the F’-portal – these lipids are termed ‘permissive’.However, certain classes of lipids, including sulfatide and sphingomyelin, block the T cell response by altering the structure of the A’-roof of CD1a to disrupt the binding of the TCRs or by showing marked protrusion from the F’ portal to block any TCRs moving toward the A’ roof. Thus, sphingomyelin and sulfatide lipids are termed ‘non-permissive’ as they predominantly block TCR docking. Direct autoreactivity of TCRs to CD1a binding is thought to be a general property of CD1a-restricted T cells in the skin, where CD1a is abundantly expressed (5,67). Moreover, the first structure of a γδTCR-CD1a complex also demonstrates a lipid-independent manner of recognition, which occurs due to a highly lateral approach (**Fig. 3F**) (68).

Similarly, a structure of a TCR-CD1c-lipid complex (12) demonstrated the interaction between the αβTCR with CD1c without contacting the lipid ligands, monoacylglycerol (MAG) or the spacer lipids (**Fig. 3G**). Here, the autoreactive TCR sat directly above the F’-portal of CD1c, and as such lipids with large or charged headgroups such as PM, MPM, phosphatidylcholine (PC), and SM are non-permissive for binding while only small lipids that sit snugly inside the CD1c cleft are permissive (12). Collectively, these related studies of CD1c and CD1a defined an ‘absence of interference’ binding mode for autoreactive αβTCRs.

Conclusions

While there are hundreds of structures of TCR-peptide-MHC complexes, the structural database of TCR-CD1-lipid complexes, with the exception of the NKT TCR-CD1d-lipid structural repertoire, is much less complete. As such, structural models are still evolving. Presently there is only one ternary αβTCR-CD1a and αβTCR-CD1c complex, so the generalities of autoreactive αβTCR-CD1 recognition are unclear. Further how CD1a and CD1c-restricted foreign lipids are recognised by αβTCRs is unknown. The studies on TCR-CD1b-lipid are slightly more advanced, with a few ternary complexes for a foreign lipid and self-lipids being determined. Despite this major knowledge gap, the fundamental principles of TCR-CD1-lipid recognition can deviate from that of TCR-MHC-peptide. Most saliently, this includes breaking of the TCR co-recognition paradigm of MHC-restricted immunity. This lack of co-recognition in CD1a-mediated TCR autoreactivity has led to the discovery of natural lipid blockers, namely sphingomyelins (SMs) (5). Subsequently, this has led to the synthetic design of more potent SM blockers that can reduce the autoreactive CD1a-mediated T cell response in skin, suggesting potential promise as therapeutic agents to treat inflammatory skin conditions. Moreover, monoclonal antibodies directed towards the CD1a A'-roof have shown to be efficacious in reducing inflammation in an *in vivo* mouse model (69). However, a greater understanding of the basic biology of CD1-restricted T cells in humans is required to fully realise its translational potential.

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Conflict of Interest

The authors have patents describing biological and small molecule blockers of the TCR-CD1a response.

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Figure legends

Figure 1. CD1 at a glance

TOP, Structures of four CD1 isoforms in comparison with an MHC-I molecule (HLA-B*57:03). Despite sharing similarity of overall β2M-associated fold, MHC-I has a shallow cleft for peptide binding whereas CD1 molecules possess hydrophobic pockets to accommodate lipids. MIDDLE, Top view to the lipid binding pockets of CD1 molecules in comparison with the peptide binding cleft of MHC-I. The pockets A' and F' in CD1 molecules, corresponding to A and F in MHC-I, are indicated. DOWN, Surface representation demonstrates the full exposure of the peptide in MHC-I whereas only the lipid headgroups can protrude out of the binding pockets in CD1 molecules.

Abbreviations: PG, phosphatidylglycerol; PS, phosphatidylserine; MPM3, difluoro-mannoside phosphomycoketide; αGalCer, α-galactosyl ceramide.

Figure 2. Classes of lipids and hydrophobic compounds presented by CD1. Chemical schematic of different classes of ligands that can bind to CD1

Figure 3. Overall docking topologies of TCR-CD1-lipid. Two paradigms of TCR-lipid-CD1 interactions.
(A) Type I NKT TCR (NKT15) to CD1d-αGalCer (3VWJ (70)). (B) Type II NKT TCR (XV19) to CD1d-sulfatide (4EI5 (71)). (C) 9C2 γδTCR to CD1-αGalCer (4LHU (30)). (D) GEM42 αβTCR to CD1b-GMM (5L2K (55)). (E) BK6 αβTCR to CD1a-oleic acid (4X6D (66)). (F) CO3 γδTCR to CD1a-sulfatide (7RYN (68)). (G) 3C8 αβTCR to CD1c-MAG (6C09 (12)). (H) General structure of a T-cell receptor (TCR).

Figure 4. Strategies for the design of synthetic α−GalCer analogues. Feasible modifications of α−GalCer are indicated in red. α−GalCer can be modified in its headgroup as well as the lipid tails, such as altered chain length, unsaturation, or extra conjugation.

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References

1. Huang, S., Shahine, A., Cheng, T.-Y., Chen, Y.-L., Ng, S. W., Balaji, G. R., Farquhar, R., Gras, S., Hardman, C. S., Altman, J. D., Tahiri, N., Minnaard, A. J., Ogg, G. S., Mayfield, J. A., Rossjohn, J., and Moody, D. B. (2023) CD1 lipidomes reveal lipid-binding motifs and size-based antigen-display mechanisms. *Cell* **186**, 4583-4596.e4513
2. Moody, D. B., and Cotton, R. N. (2017) Four pathways of CD1 antigen presentation to T cells. *Current Opinion in Immunology* **46**, 127-133
3. Shamshiev , A., Gober , H.-J., Donda , A., Mazorra , Z., Mori , L., and De Libero , G. (2002) Presentation of the Same Glycolipid by Different CD1 Molecules. *Journal of Experimental Medicine* **195**, 1013-1021
4. Huang, S., Shahine, A., Cheng, T. Y., Chen, Y. L., Ng, S. W., Balaji, G. R., Farquhar, R., Gras, S., Hardman, C. S., Altman, J. D., Tahiri, N., Minnaard, A. J., Ogg, G. S., Mayfield, J. A., Rossjohn, J., and Moody, D. B. (2023) CD1 lipidomes reveal lipid-binding motifs and size-based antigen-display mechanisms. *Cell* **186**, 4583-4596.e4513
5. Cotton, R. N., Wegrecki, M., Cheng, T.-Y., Chen, Y.-L., Veerapen, N., Le Nours, J., Orgill, D. P., Pomahac, B., Talbot, S. G., Willis, R., Altman, J. D., de Jong, A., Van Rhijn, I., Clark, R. A., Besra, G. S., Ogg, G., Rossjohn, J., and Moody, D. B. (2021) CD1a selectively captures endogenous cellular lipids that broadly block T cell response. *Journal of Experimental Medicine* **218**, e20202699
6. Moody, D. B., Young, D. C., Cheng, T.-Y., Rosat, J.-P., Roura-mir, C., O'Connor, P. B., Zajonc, D. M., Walz, A., Miller, M. J., Levery, S. B., Wilson, I. A., Costello, C. E., and Brenner, M. B. (2004) T Cell Activation by Lipopeptide Antigens. *Science* **303**, 527-531
7. Gilleron, M., Stenger, S., Mazorra, Z., Wittke, F., Mariotti, S., Böhmer, G., Prandi, J., Mori, L., Puzo, G., and De Libero, G. (2004) Diacylated sulfoglycolipids are novel mycobacterial antigens stimulating CD1-restricted T cells during infection with Mycobacterium tuberculosis. *J Exp Med* **199**, 649-659
8. Beckman, E. M., Porcelli, S. A., Morita, C. T., Behar, S. M., Furlong, S. T., and Brenner, M. B. (1994) Recognition of a lipid antigen by CD1-restricted αβ+ T cells. *Nature* **372**, 691-694
9. Moody, D. B., Reinhold, B. B., Guy, M. R., Beckman, E. M., Frederique, D. E., Furlong, S. T., Ye, S., Reinhold, V. N., Sieling, P. A., Modlin, R. L., Besra, G. S., and Porcelli, S. A. (1997) Structural requirements for glycolipid antigen recognition by CD1b-restricted T cells. *Science* **278**, 283-286
10. Ly, D., Kasmar, A. G., Cheng, T. Y., de Jong, A., Huang, S., Roy, S., Bhatt, A., van Summeren, R. P., Altman, J. D., Jacobs, W. R., Jr., Adams, E. J., Minnaard, A. J., Porcelli,

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S. A., and Moody, D. B. (2013) CD1c tetramers detect ex vivo T cell responses to processed phosphomycoketide antigens. *Journal of Experimental Medicine* **210**, 729-741

11. Nicolai, S., Wegrecki, M., Cheng, T. Y., Bourgeois, E. A., Cotton, R. N., Mayfield, J. A., Monnot, G. C., Le Nours, J., Van Rhijn, I., Rossjohn, J., Moody, D. B., and de Jong, A. (2020) Human T cell response to CD1a and contact dermatitis allergens in botanical extracts and commercial skin care products. *Sci Immunol* **5**
12. Wun, K. S., Reijneveld, J. F., Cheng, T.-Y., Ladell, K., Uldrich, A. P., Le Nours, J., Miners, K. L., McLaren, J. E., Grant, E. J., Haigh, O. L., Watkins, T. S., Suliman, S., Iwany, S., Jimenez, J., Calderon, R., Tamara, K. L., Leon, S. R., Murray, M. B., Mayfield, J. A., Altman, J. D., Purcell, A. W., Miles, J. J., Godfrey, D. I., Gras, S., Price, D. A., Van Rhijn, I., Moody, D. B., and Rossjohn, J. (2018) T cell autoreactivity directed toward CD1c itself rather than toward carried self lipids. *Nature Immunology* **19**, 397-406
13. Nicolai, S., Wegrecki, M., Cheng, T.-Y., Bourgeois, E. A., Cotton, R. N., Mayfield, J. A., Monnot, G. C., Le Nours, J., Van Rhijn, I., Rossjohn, J., Moody, D. B., and de Jong, A. (2020) Human T cell response to CD1a and contact dermatitis allergens in botanical extracts and commercial skin care products. *Science Immunology* **5**, eaax5430
14. Van Rhijn, I., Young, D. C., Im, J. S., Levery, S. B., Illarionov, P. A., Besra, G. S., Porcelli, S. A., Gumperz, J., Cheng, T.-Y., and Moody, D. B. (2004) CD1d-restricted T cell activation by nonlipidic small molecules. *Proceedings of the National Academy of Sciences* **101**, 13578-13583
15. Almeida, C. F., Smith, D. G. M., Cheng, T.-Y., Harpur, C. M., Batleska, E., Nguyen-Robertson, C. V., Nguyen, T., Thelemann, T., Reddiex, S. J. J., Li, S., Eckle, S. B. G., Van Rhijn, I., Rossjohn, J., Uldrich, A. P., Moody, D. B., Williams, S. J., Pellicci, D. G., and Godfrey, D. I. (2021) Benzofuran sulfonates and small self-lipid antigens activate type II NKT cells via CD1d. *Proceedings of the National Academy of Sciences* **118**, e2104420118
16. Minervina, A. A., Pogorelyy, M. V., Paysen, S., Luening, U., Degenhardt, F., Franke, A., Thomas, P. G., and Rosati, E. (2024) Crohn's-associated invariant T cells (CAITs) recognise small sulfonate molecules on CD1d. *Gut* **73**, 205-206
17. Rosati, E., Martini, G. R., Pogorelyy, M. V., Minervina, A. A., Degenhardt, F., Wendorff, M., Sari, S., Mayr, G., Fazio, A., Dowds, C. M., Hauser, C., Tran, F., Schönfels, W. v., Pochhammer, J., Salnikova, M. A., Jaeckel, C., Gigla, J. B., Sabet, S. S., Hübenthal, M., Schiminsky, E., Schreiber, S., Rosenstiel, P. C., Scheffold, A., Thomas, P. G., Lieb, W., Bokemeyer, B., Witte, M., Aden, K., Hendricks, A., Schafmayer, C., Egberts, J.-H., Mamedov, I. Z., Bacher, P., and Franke, A. (2022) A novel unconventional T cell population enriched in Crohn's disease. *Gut* **71**, 2194-2204

18. Rossjohn, J., Gras, S., Miles, J. J., Turner, S. J., Godfrey, D. I., and McCluskey, J. (2015) T Cell Antigen Receptor Recognition of Antigen-Presenting Molecules. *Annual Review of Immunology* **33**, 169-200
19. Kawano, T., Cui, J., Koezuka, Y., Toura, I., Kaneko, Y., Motoki, K., Ueno, H., Nakagawa, R., Sato, H., Kondo, E., Koseki, H., and Taniguchi, M. (1997) CD1d-Restricted and TCR-Mediated Activation of Vα14 NKT Cells by Glycosylceramides. *Science* **278**, 1626-1629
20. Uldrich, A. P., Patel, O., Cameron, G., Pellicci, D. G., Day, E. B., Sullivan, L. C., Kyparissoudis, K., Kjer-Nielsen, L., Vivian, J. P., Cao, B., Brooks, A. G., Williams, S. J., Illarionov, P., Besra, G. S., Turner, S. J., Porcelli, S. A., McCluskey, J., Smyth, M. J., Rossjohn, J., and Godfrey, D. I. (2011) A semi-invariant Vα10+ T cell antigen receptor defines a population of natural killer T cells with distinct glycolipid antigen–recognition properties. *Nature Immunology* **12**, 616-623
21. Mattner, J., DeBord, K. L., Ismail, N., Goff, R. D., Cantu, C., Zhou, D., Saint-Mezard, P., Wang, V., Gao, Y., Yin, N., Hoebe, K., Schneewind, O., Walker, D., Beutler, B., Teyton, L., Savage, P. B., and Bendelac, A. (2005) Exogenous and endogenous glycolipid antigens activate NKT cells during microbial infections. *Nature* **434**, 525-529
22. Sriram, V., Du, W., Gervay-Hague, J., and Brutkiewicz, R. R. (2005) Cell wall glycosphingolipids of Sphingomonas paucimobilis are CD1d-specific ligands for NKT cells. *European Journal of Immunology* **35**, 1692-1701
23. Kinjo, Y., Illarionov, P., Vela, J. L., Pei, B., Girardi, E., Li, X., Li, Y., Imamura, M., Kaneko, Y., Okawara, A., Miyazaki, Y., Gómez-Velasco, A., Rogers, P., Dahesh, S., Uchiyama, S., Khurana, A., Kawahara, K., Yesilkaya, H., Andrew, P. W., Wong, C.-H., Kawakami, K., Nizet, V., Besra, G. S., Tsuji, M., Zajonc, D. M., and Kronenberg, M. (2011) Invariant natural killer T cells recognize glycolipids from pathogenic Gram-positive bacteria. *Nature Immunology* **12**, 966-974
24. Kinjo, Y., Tupin, E., Wu, D., Fujio, M., Garcia-Navarro, R., Benhnia, M. R.-E.-I., Zajonc, D. M., Ben-Menachem, G., Ainge, G. D., Painter, G. F., Khurana, A., Hoebe, K., Behar, S. M., Beutler, B., Wilson, I. A., Tsuji, M., Sellati, T. J., Wong, C.-H., and Kronenberg, M. (2006) Natural killer T cells recognize diacylglycerol antigens from pathogenic bacteria. *Nature Immunology* **7**, 978-986
25. Kinjo, Y., Wu, D., Kim, G., Xing, G.-W., Poles, M. A., Ho, D. D., Tsuji, M., Kawahara, K., Wong, C.-H., and Kronenberg, M. (2005) Recognition of bacterial glycosphingolipids by natural killer T cells. *Nature* **434**, 520-525
26. Fischer, K., Scotet, E., Niemeyer, M., Koebernick, H., Zerrahn, J., Maillet, S., Hurwitz, R., Kursar, M., Bonneville, M., Kaufmann, S. H. E., and Schaible, U. E. (2004) Mycobacterial

Journal Pre-proof

phosphatidylinositol mannoside is a natural antigen for CD1d-restricted T cells. *Proceedings of the National Academy of Sciences* **101**, 10685-10690

27. Chang, Y.-J., Kim, H. Y., Albacker, L. A., Lee, H. H., Baumgarth, N., Akira, S., Savage, P. B., Endo, S., Yamamura, T., Maaskant, J., Kitano, N., Singh, A., Bhatt, A., Besra, G. S., Elzen, P. v. d., Appelmelk, B., Franck, R. W., Chen, G., DeKruyff, R. H., Shimamura, M., Illarionov, P., and Umetsu, D. T. (2011) Influenza infection in suckling mice expands an NKT cell subset that protects against airway hyperreactivity. *The Journal of Clinical Investigation* **121**, 57-69
28. Almeida, C. F., Sundararaj, S., Le Nours, J., Praveena, T., Cao, B., Burugupalli, S., Smith, D. G. M., Patel, O., Brigl, M., Pellicci, D. G., Williams, S. J., Uldrich, A. P., Godfrey, D. I., and Rossjohn, J. (2019) Distinct CD1d docking strategies exhibited by diverse Type II NKT cell receptors. *Nature Communications* **10**, 5242
29. Le Nours, J., Praveena, T., Pellicci, D. G., Gherardin, N. A., Ross, F. J., Lim, R. T., Besra, G. S., Keshipeddy, S., Richardson, S. K., Howell, A. R., Gras, S., Godfrey, D. I., Rossjohn, J., and Uldrich, A. P. (2016) Atypical natural killer T-cell receptor recognition of CD1d–lipid antigens. *Nature Communications* **7**, 10570
30. Uldrich, A. P., Le Nours, J., Pellicci, D. G., Gherardin, N. A., McPherson, K. G., Lim, R. T., Patel, O., Beddoe, T., Gras, S., Rossjohn, J., and Godfrey, D. I. (2013) CD1d-lipid antigen recognition by the γδ TCR. *Nature Immunology* **14**, 1137-1145
31. Van Rhijn, I., Godfrey, D. I., Rossjohn, J., and Moody, D. B. (2015) Lipid and small-molecule display by CD1 and MR1. *Nature Reviews Immunology* **15**, 643-654
32. Godfrey, D. I., and Kronenberg, M. (2004) Going both ways: Immune regulation via CD1d-dependent NKT cells. *The Journal of Clinical Investigation* **114**, 1379-1388
33. Liew, F. Y. (2002) TH1 and TH2 cells: a historical perspective. *Nature Reviews Immunology* **2**, 55-60
34. Veerapen, N., Reddington, F., Bricard, G., Porcelli, S. A., and Besra, G. S. (2010) Synthesis and biological activity of α-l-fucosyl ceramides, analogues of the potent agonist, α-d-galactosyl ceramide KRN7000. *Bioorganic & Medicinal Chemistry Letters* **20**, 3223-3226
35. Veerapen, N., Leadbetter, E. A., Brenner, M. B., Cox, L. R., and Besra, G. S. (2010) Synthesis of a Novel α-Galactosyl Ceramide Haptenated-Lipid Antigen, a Useful Tool in Demonstrating the Involvement of iNKT Cells in the Production of Antilipid Antibodies. *Bioconjugate Chemistry* **21**, 741-747
36. Yu, K. O. A., Im, J. S., Molano, A., Dutronc, Y., Illarionov, P. A., Forestier, C., Fujiwara, N., Arias, I., Miyake, S., Yamamura, T., Chang, Y.-T., Besra, G. S., and Porcelli, S. A.

Journal Pre-proof

(2005) Modulation of CD1d-restricted NKT cell responses by using N-acyl variants of α-galactosylceramides. *Proceedings of the National Academy of Sciences* **102**, 3383-3388

37. O'Konek, J. J., Kato, S., Takao, S., Izhak, L., Xia, Z., Illarionov, P., Besra, G. S., Terabe, M., and Berzofsky, J. A. (2013) β-Mannosylceramide Activates Type I Natural Killer T Cells to Induce Tumor Immunity without Inducing Long-Term Functional Anergy. *Clinical Cancer Research* **19**, 4404-4411
38. O'Konek, J. J., Illarionov, P., Khursigara, D. S., Ambrosino, E., Izhak, L., Castillo, B. F., II, Raju, R., Khalili, M., Kim, H.-Y., Howell, A. R., Besra, G. S., Porcelli, S. A., Berzofsky, J. A., and Terabe, M. (2011) Mouse and human iNKT cell agonist β-mannosylceramide reveals a distinct mechanism of tumor immunity. *The Journal of Clinical Investigation* **121**, 683-694
39. Brennan, P. J., Brigl, M., and Brenner, M. B. (2013) Invariant natural killer T cells: an innate activation scheme linked to diverse effector functions. *Nature Reviews Immunology* **13**, 101-117
40. Jervis, P. J., Polzella, P., Wojno, J., Jukes, J.-P., Ghadbane, H., Garcia Diaz, Y. R., Besra, G. S., Cerundolo, V., and Cox, L. R. (2013) Design, Synthesis, and Functional Activity of Labeled CD1d Glycolipid Agonists. *Bioconjugate Chemistry* **24**, 586-594
41. Birkholz, A. M., Girardi, E., Wingender, G., Khurana, A., Wang, J., Zhao, M., Zahner, S., Illarionov, P. A., Wen, X., Li, M., Yuan, W., Porcelli, S. A., Besra, G. S., Zajonc, D. M., and Kronenberg, M. (2015) A Novel Glycolipid Antigen for NKT Cells That Preferentially Induces IFN-γ Production. *The Journal of Immunology* **195**, 924-933
42. Arora, P., Baena, A., Yu, K. O., Saini, N. K., Kharkwal, S. S., Goldberg, M. F., Kunnath-Velayudhan, S., Carreño, L. J., Venkataswamy, M. M., Kim, J., Lazar-Molnar, E., Lauvau, G., Chang, Y. T., Liu, Z., Bittman, R., Al-Shamkhani, A., Cox, L. R., Jervis, P. J., Veerapen, N., Besra, G. S., and Porcelli, S. A. (2014) A single subset of dendritic cells controls the cytokine bias of natural killer T cell responses to diverse glycolipid antigens. *Immunity* **40**, 105-116
43. Jervis, P. J., Graham, L. M., Foster, E. L., Cox, L. R., Porcelli, S. A., and Besra, G. S. (2012) New CD1d agonists: Synthesis and biological activity of 6″-triazole-substituted α-galactosyl ceramides. *Bioorganic & Medicinal Chemistry Letters* **22**, 4348-4352
44. Veerapen, N., Reddington, F., Salio, M., Cerundolo, V., and Besra, G. S. (2011) Synthesis of truncated analogues of the iNKT cell agonist, α-galactosyl ceramide (KRN7000), and their biological evaluation. *Bioorganic & Medicinal Chemistry* **19**, 221-228

Journal Pre-proof

Journal Pre-proof

45. Jervis, P. J., Cox, L. R., and Besra, G. S. (2011) Synthesis of a Versatile Building Block for the Preparation of 6-N-Derivatized α-Galactosyl Ceramides: Rapid Access to Biologically Active Glycolipids. *The Journal of Organic Chemistry* **76**, 320-323

46. Wojno, J., Jukes, J.-P., Ghadbane, H., Shepherd, D., Besra, G. S., Cerundolo, V., and Cox, L. R. (2012) Amide Analogues of CD1d Agonists Modulate iNKT-Cell-Mediated Cytokine Production. *ACS Chemical Biology* **7**, 847-855

47. Jukes, J.-P., Gileadi, U., Ghadbane, H., Yu, T.-F., Shepherd, D., Cox, L. R., Besra, G. S., and Cerundolo, V. (2016) Non-glycosidic compounds can stimulate both human and mouse iNKT cells. *European Journal of Immunology* **46**, 1224-1234

48. Silk, J. D., Salio, M., Reddy, B. G., Shepherd, D., Gileadi, U., Brown, J., Masri, S. H., Polzella, P., Ritter, G., Besra, G. S., Jones, E. Y., Schmidt, R. R., and Cerundolo, V. (2008) Cutting Edge: Nonglycosidic CD1d Lipid Ligands Activate Human and Murine Invariant NKT Cells1. *The Journal of Immunology* **180**, 6452-6456

49. Carreño, L. J., Saavedra-Ávila, N. A., and Porcelli, S. A. (2016) Synthetic glycolipid activators of natural killer T cells as immunotherapeutic agents. *Clinical & Translational Immunology* **5**, e69

50. Kharkwal, S. S., Arora, P., and Porcelli, S. A. (2016) Glycolipid activators of invariant NKT cells as vaccine adjuvants. *Immunogenetics* **68**, 597-610

51. Laurent, X., Bertin, B., Renault, N., Farce, A., Speca, S., Milhomme, O., Millet, R., Desreumaux, P., Hénon, E., and Chavatte, P. (2014) Switching Invariant Natural Killer T (iNKT) Cell Response from Anticancerous to Anti-Inflammatory Effect: Molecular Bases. *Journal of Medicinal Chemistry* **57**, 5489-5508

52. Yuan, W., Qi, X., Tsang, P., Kang, S.-J., Illarionov, P. A., Besra, G. S., Gumperz, J., and Cresswell, P. (2007) Saposin B is the dominant saposin that facilitates lipid binding to human CD1d molecules. *Proceedings of the National Academy of Sciences* **104**, 5551-5556

53. Veerapen, N., Kharkwal, S. S., Jervis, P., Bhowruth, V., Besra, A. K., North, S. J., Haslam, S. M., Dell, A., Hobrath, J., Quaid, P. J., Moynihan, P. J., Cox, L. R., Kharkwal, H., Zauderer, M., Besra, G. S., and Porcelli, S. A. (2018) Photoactivable Glycolipid Antigens Generate Stable Conjugates with CD1d for Invariant Natural Killer T Cell Activation. *Bioconjug Chem* **29**, 3161-3173

54. Kharkwal, S. S., Johndrow, C. T., Veerapen, N., Kharkwal, H., Saavedra-Avila, N. A., Carreño, L. J., Rothberg, S., Zhang, J., Garforth, S. J., Jervis, P. J., Zhang, L., Donda, A., Besra, A. K., Cox, L. R., Almo, S. C., Howell, A., Evans, E. E., Zauderer, M., Besra, G. S., and Porcelli, S. A. (2021) Serial Stimulation of Invariant Natural Killer T Cells with

Covalently Stabilized Bispecific T-cell Engagers Generates Antitumor Immunity While Avoiding Anergy. *Cancer Res* **81**, 1788-1801

55. Gras, S., Van Rhijn, I., Shahine, A., Cheng, T.-Y., Bhati, M., Tan, L. L., Halim, H., Tuttle, K. D., Gapin, L., Le Nours, J., Moody, D. B., and Rossjohn, J. (2016) T cell receptor recognition of CD1b presenting a mycobacterial glycolipid. *Nature Communications* **7**, 13257

56. Shahine, A., Reinink, P., Reijneveld, J. F., Gras, S., Holzheimer, M., Cheng, T.-Y., Minnaard, A. J., Altman, J. D., Lenz, S., Prandi, J., Kubler-Kielb, J., Moody, D. B., Rossjohn, J., and Van Rhijn, I. (2019) A T-cell receptor escape channel allows broad T-cell response to CD1b and membrane phospholipids. *Nature Communications* **10**, 56

57. Farquhar, R., Van Rhijn, I., Moody, D. B., Rossjohn, J., and Shahine, A. (2023) αβ T-cell receptor recognition of self-phosphatidylinositol presented by CD1b. *J Biol Chem* **299**, 102849

58. Shahine, A., Van Rhijn, I., Cheng, T.-Y., Iwany, S., Gras, S., Moody, D. B., and Rossjohn, J. (2017) A molecular basis of human T cell receptor autoreactivity toward self-phospholipids. *Science Immunology* **2**, eaao1384

59. Beckman, E. M., Melián, A., Behar, S. M., Sieling, P. A., Chatterjee, D., Furlong, S. T., Matsumoto, R., Rosat, J. P., Modlin, R. L., and Porcelli, S. A. (1996) CD1c restricts responses of mycobacteria-specific T cells. Evidence for antigen presentation by a second member of the human CD1 family. *J Immunol* **157**, 2795-2803

60. Cheng, J. M. H., Liu, L., Pellicci, D. G., Reddiex, S. J. J., Cotton, R. N., Cheng, T.-Y., Young, D. C., Van Rhijn, I., Moody, D. B., Rossjohn, J., Fairlie, D. P., Godfrey, D. I., and Williams, S. J. (2017) Total Synthesis of Mycobacterium tuberculosis Dideoxymycobactin-838 and Stereoisomers: Diverse CD1a-Restricted T Cells Display a Common Hierarchy of Lipopeptide Recognition. *Chemistry – A European Journal* **23**, 1694-1701

61. Lepore, M., de Lalla, C., Gundimeda, S. R., Gsellinger, H., Consonni, M., Garavaglia, C., Sansano, S., Piccolo, F., Scelfo, A., Häussinger, D., Montagna, D., Locatelli, F., Bonini, C., Bondanza, A., Forcina, A., Li, Z., Ni, G., Ciceri, F., Jenö, P., Xia, C., Mori, L., Dellabona, P., Casorati, G., and De Libero, G. (2014) A novel self-lipid antigen targets human T cells against CD1c+ leukemias. *Journal of Experimental Medicine* **211**, 1363-1377

62. Consonni, M., Garavaglia, C., Grilli, A., de Lalla, C., Mancino, A., Mori, L., De Libero, G., Montagna, D., Casucci, M., Serafini, M., Bonini, C., Häussinger, D., Ciceri, F., Bernardi, M., Mastaglio, S., Bicciato, S., Dellabona, P., and Casorati, G. (2021) Human T cells engineered with a leukemia lipid-specific TCR enables donor-unrestricted recognition of CD1c-expressing leukemia. *Nature Communications* **12**, 4844

Journal Pre-proof

63. Roy, S., Ly, D., Li, N.-S., Altman, J. D., Piccirilli, J. A., Moody, D. B., and Adams, E. J. (2014) Molecular basis of mycobacterial lipid antigen presentation by CD1c and its recognition by αβ T cells. *Proceedings of the National Academy of Sciences* **111**, E4648-E4657

64. Reijneveld, J. F., Marino, L., Cao, T. P., Cheng, T. Y., Dam, D., Shahine, A., Witte, M. D., Filippov, D. V., Suliman, S., van der Marel, G. A., Moody, D. B., Minnaard, A. J., Rossjohn, J., Codée, J. D. C., and Van Rhijn, I. (2021) Rational design of a hydrolysis-resistant mycobacterial phosphoglycolipid antigen presented by CD1c to T cells. *J Biol Chem* **297**, 101197

65. de Jong, A., Cheng, T. Y., Huang, S., Gras, S., Birkinshaw, R. W., Kasmar, A. G., Van Rhijn, I., Peña-Cruz, V., Ruan, D. T., Altman, J. D., Rossjohn, J., and Moody, D. B. (2014) CD1a-autoreactive T cells recognize natural skin oils that function as headless antigens. *Nat Immunol* **15**, 177-185

66. Birkinshaw, R. W., Pellicci, D. G., Cheng, T. Y., Keller, A. N., Sandoval-Romero, M., Gras, S., de Jong, A., Uldrich, A. P., Moody, D. B., Godfrey, D. I., and Rossjohn, J. (2015) αβ T cell antigen receptor recognition of CD1a presenting self lipid ligands. *Nat Immunol* **16**, 258-266

67. Cotton, R. N., Cheng, T.-Y., Wegrecki, M., Le Nours, J., Orgill, D. P., Pomahac, B., Talbot, S. G., Willis, R. A., Altman, J. D., de Jong, A., Ogg, G., Van Rhijn, I., Rossjohn, J., Clark, R. A., and Moody, D. B. (2021) Human skin is colonized by T cells that recognize CD1a independently of lipid. *The Journal of Clinical Investigation* **131**, e140706

68. Wegrecki, M., Ocampo, T. A., Gunasinghe, S. D., von Borstel, A., Tin, S. Y., Reijneveld, J. F., Cao, T. P., Gully, B. S., Le Nours, J., Moody, D. B., Van Rhijn, I., and Rossjohn, J. (2022) Atypical sideways recognition of CD1a by autoreactive γδ T cell receptors. *Nat Commun* **13**, 3872

69. Hardman, C. S., Chen, Y.-L., Wegrecki, M., Ng, S. W., Murren, R., Mangat, D., Silva, J.-P., Munro, R., Chan, W. Y., O'Dowd, V., Doyle, C., Mori, P., Popplewell, A., Rossjohn, J., Lightwood, D., and Ogg, G. S. (2022) CD1a promotes systemic manifestations of skin inflammation. *Nature Communications* **13**, 7535

70. Wun, K. S., Ross, F., Patel, O., Besra, G. S., Porcelli, S. A., Richardson, S. K., Keshipeddy, S., Howell, A. R., Godfrey, D. I., and Rossjohn, J. (2012) Human and mouse type I natural killer T cell antigen receptors exhibit different fine specificities for CD1d-antigen complex. *J Biol Chem* **287**, 39139-39148

71. Patel, O., Pellicci, D. G., Gras, S., Sandoval-Romero, M. L., Uldrich, A. P., Mallevaey, T., Clarke, A. J., Le Nours, J., Theodossis, A., Cardell, S. L., Gapin, L., Godfrey, D. I., and

Journal Pre-proof

Rossjohn, J. (2012) Recognition of CD1d-sulfatide mediated by a type II natural killer T cell antigen receptor. *Nature Immunology* **13**, 857-863

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Figure 1

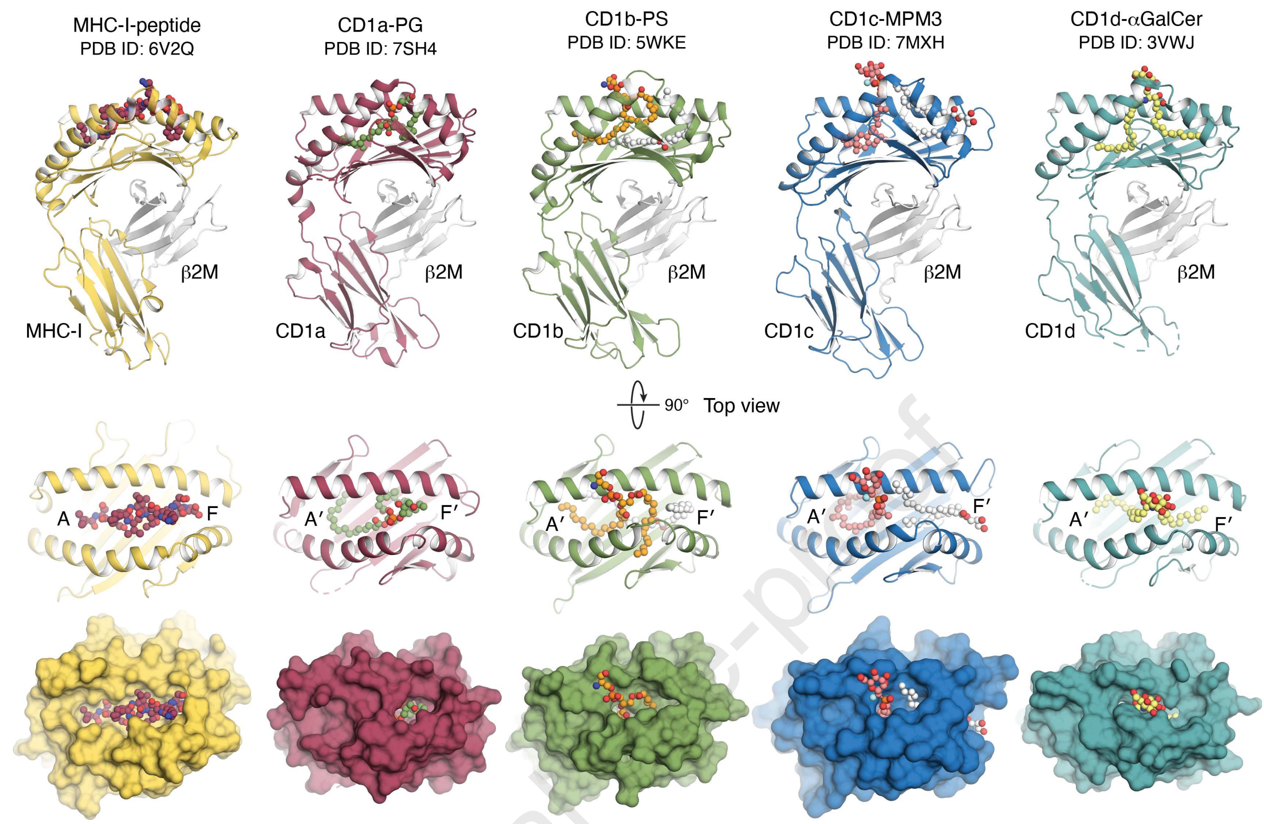

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Figure 2

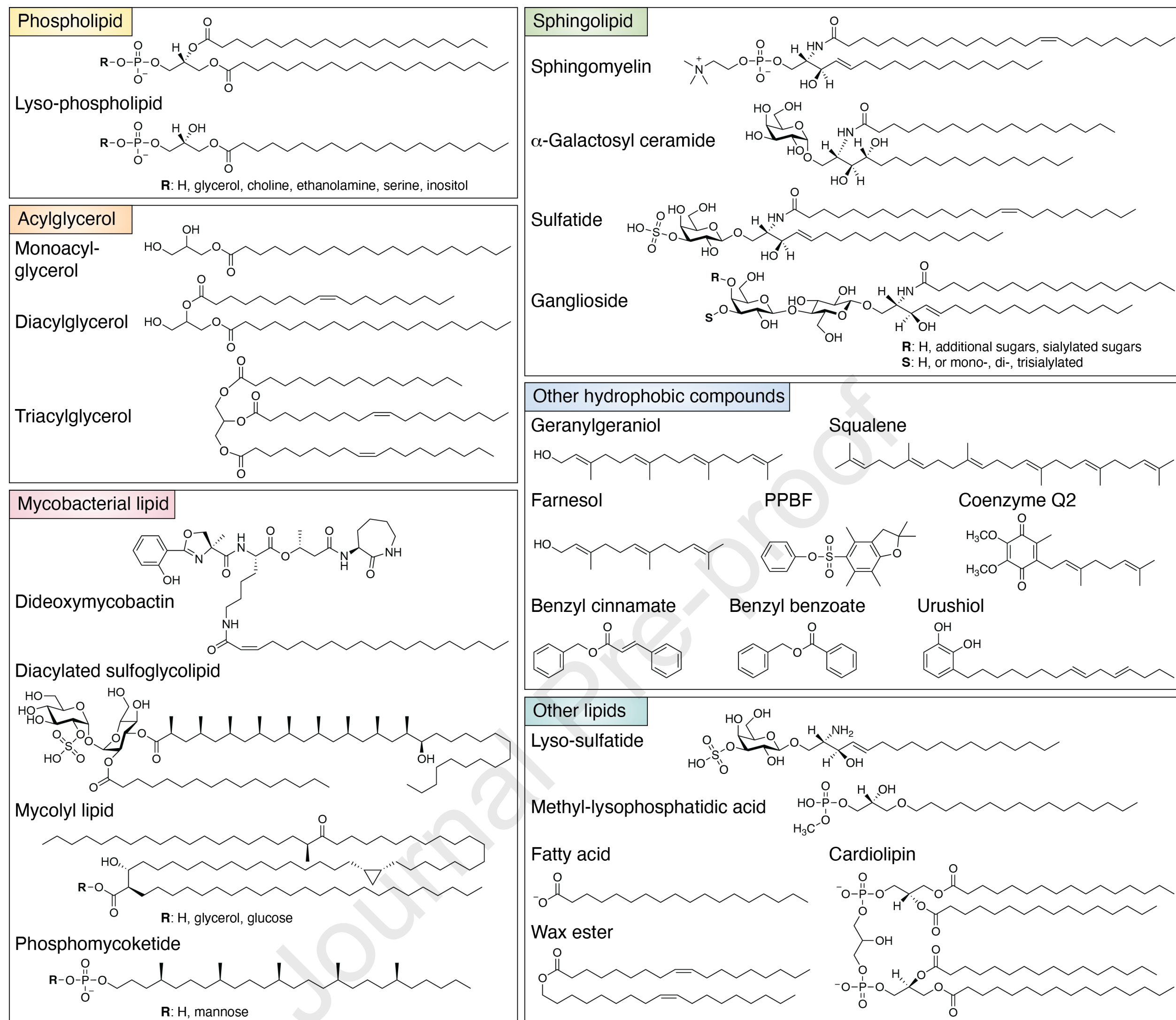

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Figure 3

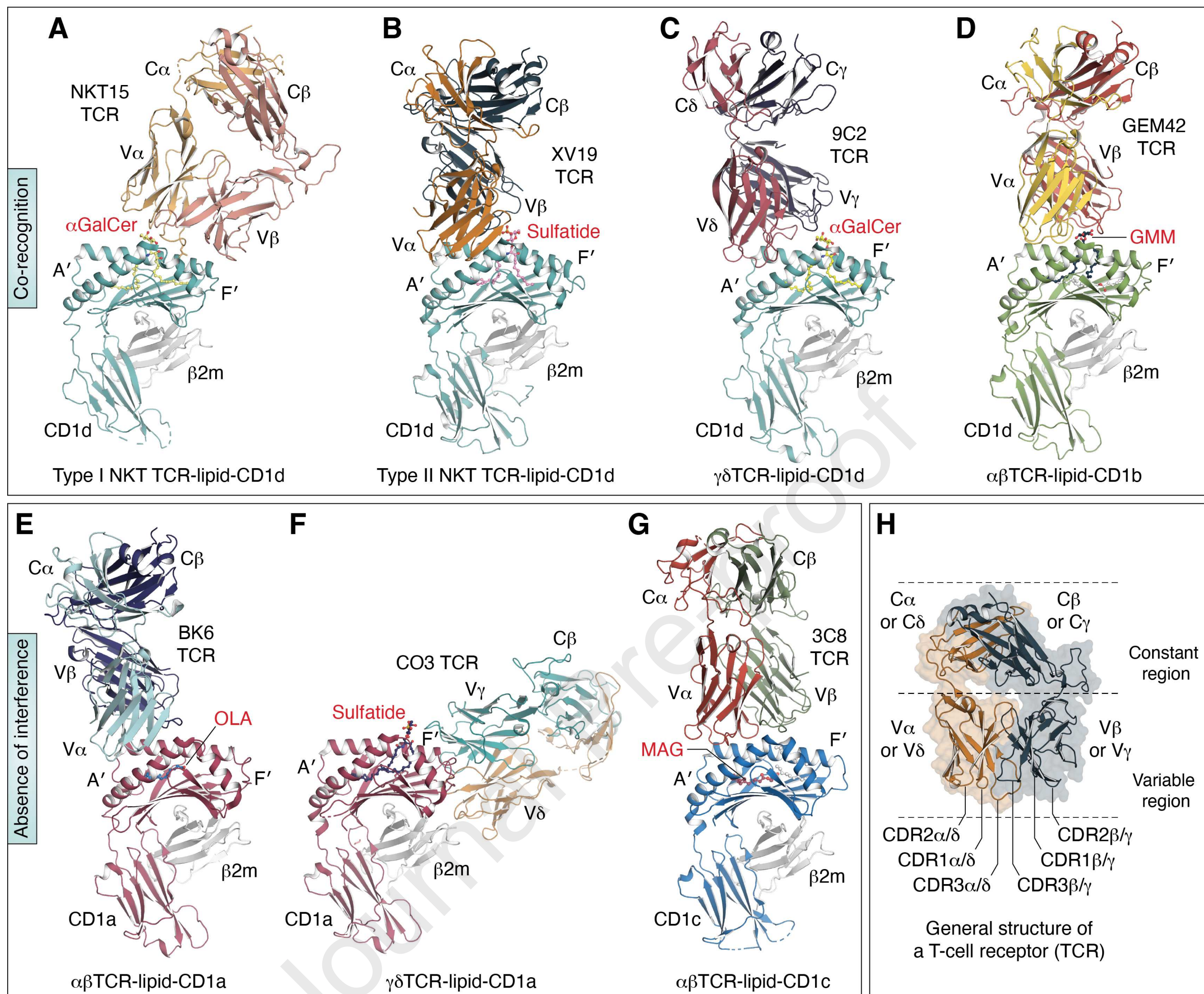

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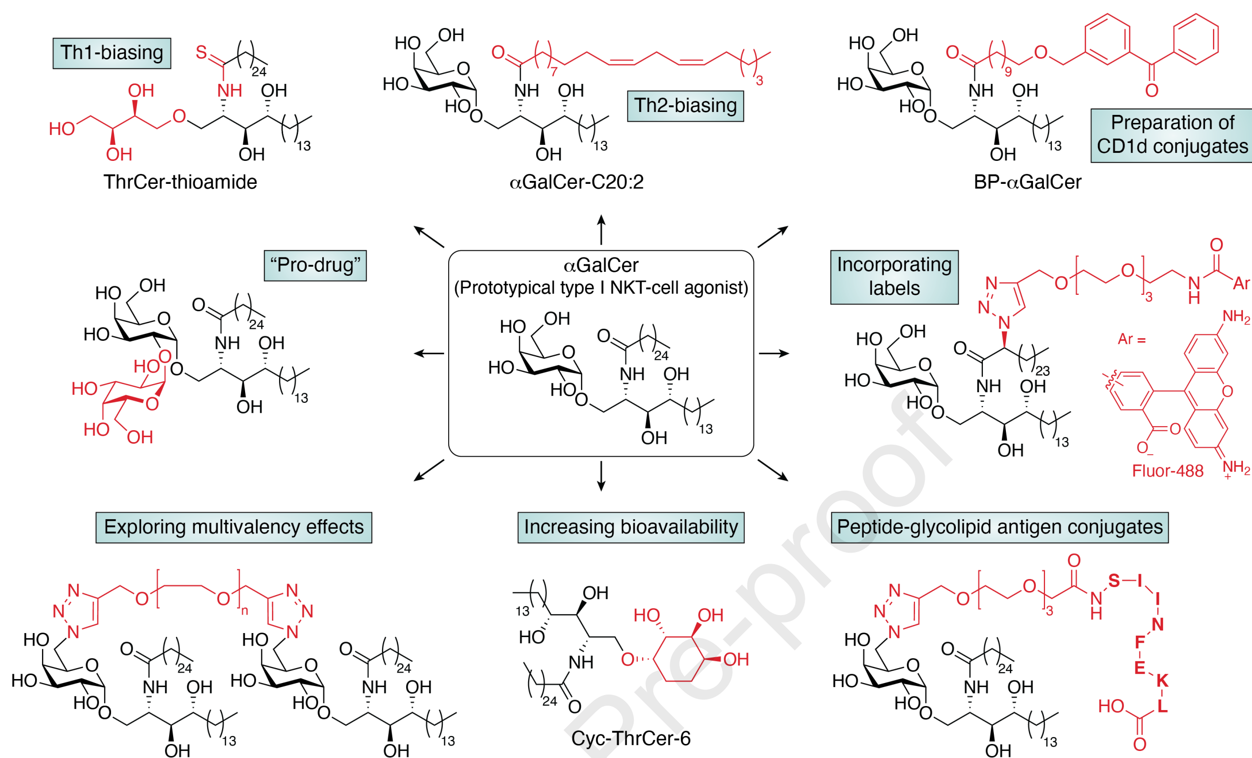
Figure 4



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All authors contributed to the writing and editing of this review

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Conflict of Interest

The authors have patents describing biological and small molecule blockers of the TCR-CD1a response.

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