Unconventional T cell targets for cancer immunotherapy

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Abstract

The vast majority of studies regarding the immunotherapeutic potential of T cells have focussed on CD8 and CD4 T cells that recognise tumor-associated peptide antigens (Ag) presented by polymorphic major histocompatibility complex (MHC) class I and MHC class II molecules, respectively. However, unconventional T cells, which interact with MHC class Ib and MHC-I like molecules, are also implicated in tumor immunity, although their role here is unclear. These include unconventional T cells targeting MHC class Ib molecules such as HLA-E and its murine orthologue Qa-1b. Moreover, Natural Killer T (NKT) cells and Mucosal Associated Invariant T (MAIT) cells are activated by lipids and vitamin B metabolite Ags when presented by the MHC-class I-like molecules CD1 and MR1, respectively. Additionally, γδ T cells represent a distinct T cell lineage that interacts with a range of ligands spanning MHC molecules, stress-induced MHC class I-like molecules, CD1 molecules and butyrophylins. Considering that unconventional T cells frequently have repeated and predictable patterns of T cell receptor gene usage in unrelated individuals, and interact with monomorphic Ag-presenting molecules, they have broad clinical potential regardless of patient MHC genotype. Here, we review these unconventional T cells with a focus on the evidence that they can inhibit tumor growth and discuss why further studies into the immunotherapeutic potential of these cells is warranted.

Introduction

T lymphocytes are a key component of the immune system and a major focus for cancer immunotherapy. The vast majority of studies into the immunotherapeutic potential of T lymphocytes have focussed on conventional CD8 T cells that recognise peptide Ags presented by MHC class I molecules. Following activation, clonal expansion and differentiation, these cells become cytotoxic T lymphocytes (CTL) with the ability to target and kill tumor cells when they encounter specific tumor peptide-MHC class I complexes. These responses can also be enhanced by engagement of CD4 T cell help against MHC class II restricted tumor peptide Ags (Coulie et al.,

2014; van der Burg et al., 2016). Approaches to harness anti-tumor CD8 T cell responses using tumor Ag-based vaccines have yielded some, albeit limited success, in part due to tumor instability, peptide stability(Purcell et al., 2007) and the tendency of tumors to modulate expression of tumor Ags and MHC molecules (Coulie et al., 2014; van der Burg et al., 2016). Another important obstacle to harnessing CD4 and CD8 T cell immunity is the polymorphic nature of the MHC (human leucocyte antigen (HLA)) proteins, which means any tumor protein or peptide Ag must contain epitopes that can be presented by the patient's HLA type. Further, the polymorphic nature of the MHC often infers a diverse responding T cell repertoire that is difficult to predict, monitor and control. For example, polymorphic HLA genotypes also limit the potential for the use of 'off the shelf' T cell or chimeric Ag receptor (CAR) T cell therapy because of the danger of graft-versus-host disease. Here, we will review the field of tumor immunity with a focus on the role, and under-explored therapeutic potential, of unconventional T cells that can target monomorphic Ag-presenting molecules and other ligands. This includes the MHC class Ib-restricted T cells, CD1 and MR1 restricted T cells, and γδ T cells (Figure 1). Such unconventional T cells, which are often characterised by repeated patterns of TCR usage in unrelated individuals, have long been implicated in tumor recognition and destruction.

MHC class Ib-restricted T cells

MHC class Ib molecules are structurally similar to classical MHC class I (MHC class Ia) molecules, but are essentially monomorphic. Further, unlike MHC class Ia, MHC class Ib molecules show tissue-restricted expression, the capacity to assemble in the absence of peptide, or a propensity to present "non-standard" peptides (Rodgers and Cook, 2005). Collectively, these features imbue MHC class Ib molecules with the capacity to perform specialised functions that control immune responses, potentially including anti-tumor responses, in unique ways.

Owing to their orthologous nature (Joly and Rouillon, 2006), the most widely studied MHC class Ib molecules are HLA-E in humans and Qa-1b in mice. Following their genetic identification over thirty years ago (Koller et al., 1988; Stanton et al., 1978), both of these molecules were subsequently shown to acts as ligands for members of the NKG2-CD94 NK receptor family (Braud et al., 1998a; Vance et al., 1998). We now understand that the function of HLA-E and Qa-1b is the presentation of peptides from leader sequences that are largely, but not exclusively, derived from MHC class Ia molecules (Braud et al., 1997; Braud et al., 1998b). Presentation of these peptides by HLA-E and Qa-1b allows the immune system a secondary means to monitor cellular health and homeostasis via detection of ongoing MHC class I biosynthesis. Under normal conditions, the presentation of these peptides by HLA-E or Qa-1b results in ligation of NKG2A-CD94 receptors and the transmission of an inhibitory signal via immunoreceptor tyrosine-based inhibitory motifs (ITIM), preventing immune activation. In this setting, it is easy to envision that, by promoting the expression of HLA-E, tumors would be able to escape immune detection. However, HLA-E and Qa-1b are also ligands for activating NKG2C-CD94 complexes, an interaction that leads to immune activation and target elimination. Thus, HLA-E and Qa-1b provide inhibitory and activating signals depending on the context of the receptor that is engaged. This understanding provides a rationale for the contrasting observations that HLA-E expression is associated with poor outcome in breast and cervical cancer (de Kruijf et al., 2010; Gooden et al., 2011) yet can be used as a good prognostic indicator in glioblastoma (Kren et al., 2011), colorectal and renal cell carcinoma (Benevolo et al., 2011; Kren et al., 2012). These data suggest that, by itself, HLA-E may not be a useful parameter for prognosis but should be used in concert with the levels of infiltrating leukocytes expressing activating or inhibitory forms of NKG2-CD94 (Versluis et al., 2017).

Another human MHC class Ib molecule, HLA-G, is normally restricted in its expression to extravillous trophoblast cells where it is thought to play an important role in immune tolerance during pregnancy (Ellis et al., 1990; Ferreira et al., 2017; Kovats et al., 1990). HLA-G can be spliced into multiple isoforms that produces 4 membrane-bound and 3 soluble molecules (Carosella et al., 2015). The major soluble (sHLA-G1 and HLA-G5) and membrane bound HLA-G (HLA-G1) molecules are able to bind inhibitory receptors: Ig-like transcript-2 (ILT2) and ILT4, which in turn transmit inhibitory signals via ITIMs (Shiroishi et al., 2003). In contrast to HLA-E, there is no opposing receptor that transmits an activating signal, which could make increased HLA-G an opportunistic mechanism for tumor immune evasion. Indeed, the potential for HLA-G to regulate tumour immunity is highlighted by the observation that, during neoplastic transformation and growth, HLA-G becomes prominent in hepatocellular carcinoma (Catamo et al., 2014; Lin et al., 2010; Park et al., 2012; Teixeira et al., 2013), colorectal and renal cancers (Rouas-Freiss et al., 2017; Swets et al., 2016), chronic myeloid leukaemia (CML) (Caocci et al., 2017) and glioma (Wang et al., 2015). However, the current data implicating HLA-G in tumour evasion is unclear. Meta-analysis of a mutation that increases HLA-G mRNA stability, the 14bp ins/del (Rousseau et al., 2003), has no prognostic value for hepatocellular carcinoma(Coelho et al., 2016). Furthermore, while increased levels of soluble HLA-G have been identified as a potential prognostic indicator during colorectal cancer progression (Kirana et al., 2017; Li et al., 2017), it is unclear whether increased soluble HLA-G in this setting plays a role in suppressing the immune response. Modelling the immunosuppressive effects of HLA-G in mouse models is hampered by the fact that no homologue exists, hence, more sophisticated methods, including humanised mice (Nguyen-Lefebvre et al., 2016), are required.

Animal models of cancer and MHC class Ib are confounded by the fact that mice have ten times more MHC class Ib genes than humans. Furthermore, only HLA-E/Qa-1b demonstrate sufficient convergent evolution that their functionality is largely unchanged, yet this is complicated by the observation that a duplicate of Qa-1b exists, H2-T11, which has almost identical functionality (Chen et al., 2014). Despite this, studies have shown that Qa-1b plays a critical role in the detection of cells that demonstrate Ag-processing defects. Using cells in which the TAP pathway has been disrupted, Qa-1b is capable of presenting a wide range of peptides and becomes a target for tumor control and CTL activity (Oliveira et al., 2010). This suggests that Qa-1b may act to prevent cancer by limiting neoplastic transformation of cells with Ag-processing defects. While HLA-E can present HLA-A-like peptides in the absence of TAP (Lampen et al., 2013), the role of HLA-E-restricted T cells in tumors is yet to be explored. While patients with TAP deficiency present with chronic bacterial infections of the airways, they are capable of mounting robust CD8 T cell responses and there is no evidence to suggest increased cancer burden in these individuals (Zimmer et al., 2005). Interestingly, TAP-deficient patients demonstrate an increase in $NKG2C^{+}$ NK cells (Béziat et al., 2015), providing a potential clue as to the mechanism by which these patients control viral infections and, potentially, cancer.

With respect to other members of the mouse MHC class 1b family, H2-M3 plays an important role in cancer progression through the education of specific subsets of NK cells (Andrews et al., 2012). In the absence of H2-M3, Ly49A expressing NK cells do not reach their full potential, a process termed licensing, and are unable to contribute to the control of metastatic melanoma and chemically-induced fibrosarcoma (Andrews et al., 2012). At the other end of the mouse MHC class Ib family, Qa-2 can play contrasting roles in the control of cancer. In one setting, Qa-2 acts as a potent CD8

restriction element and allows the generation of functionally protective memory CTL (Chiang and Stroynowski, 2004), while also acting to prevent NK cell control of tumors (Chiang et al., 2002). These two opposing effects provide a conundrum for immune editing of tumors whereby elimination of Qa-2 expression will prevent recognition by CTL but also removes a potential inhibitory ligand for a receptor found on NK cells and activated/memory CTL (Coles et al., 2000; Held et al., 1995).

Given the expression of human MHC class Ib molecules by tumors and their capacity to impair immune responses through specialised pathways, targeting these molecules as a cancer therapeutic offers potential. However, translating observations from mouse models is limited due to species-based differences in expression and function of these molecules. As more sophisticated models of human MHC class Ib become available, our understanding of the role these molecules play in modulating anti-tumor T cells will increase, which could ultimately lead to their assessment in clinical cancer trials.

CD1d restricted NKT cells

The CD1 family of Ag-presenting molecules is divided into two groups: CD1a, CD1b, CD1c Ag-presenting molecules, collectively known as group 1 CD1 molecules, and CD1d (group 2) (Godfrey et al., 2015; Van Rhijn et al., 2015). CD1 molecules are MHC class I-like, but in contrast to MHC molecules, these possess hydrophobic Ag-binding clefts and present lipid-based Ags to the immune system (Van Rhijn et al., 2015). The human immune system harbors populations of T cells with the ability to recognise diverse lipid Ags presented by each CD1 family member (Godfrey et al., 2015; Van Rhijn et al., 2015). While many of the lipid-based Ags described thus far are of microbial origin, a growing list of non-microbial Ags, including tumor-derived lipid Ags, are presented by group 1 and group 2 CD1 family members. The majority of studies have focussed on Ag recognition in association with CD1d, partly because mice express this family member but not the group 1 CD1 molecules, and partly because the production of CD1d tetramers 17 years ago has facilitated the study of CD1d-restricted T cells (Godfrey et al., 2004).

CD1d-restricted T cells are known as Natural Killer T (NKT) cells, in part due to earlier studies that flagged the expression of NK cell molecules such as NK1.1/CD161 by these T cells (Godfrey et al., 2004). NKT cells can be divided into two broad types – based on their TCR usage and lipid Ag specificity. Type I NKT cells typically express semi-invariant TCRs comprised of TRAV11 TRAJ18 paired with a limited array of TCR-β chains, highly enriched for TRBV13, TRBV29 or TRBV1 in mice, or the orthologous TRAV10 TRAJ18 paired with TRBV25 in humans. These type I NKT cells are all strongly reactive to the glycosphingolipid Ag α-galactosylceramide (α-GalCer). Conversely, type II NKT cells represent a broad collection of T cells, excluding α-GalCer-reactive cells with the invariant TCR-α chain, and encompassing all other CD1d-restricted $\alpha\beta$ T cells (Godfrey et al., 2004). Some other 'atypical' NKT TCRs, including $\alpha\beta$ (Le Nours et al., 2016; Uldrich et al., 2011), $\gamma\delta$ (Uldrich et al., 2013) and hybrid $\delta\alpha\beta$ TCRs (Pellicci et al., 2014) can also facilitate recognition of α-GalCer in mice and humans, although these are relatively minor subsets of α-GalCer-reactive T cells.

Type I NKT cells are abundant in mice, representing 1% or more of T cells, while in humans they are much less frequent, typically ranging between 0.01 and 0.1% of T cells (Godfrey et al., 2015). Many studies have demonstrated the potential for type I NKT cells to inhibit tumor growth in mice (recently reviewed in (McEwen-Smith et al., 2015; Nair and Dhodapkar, 2017)). Indeed, the α-GalCer Ag, originally derived from a marine sponge extract, first captured the attention of

immunologists because of its potent anti-tumor potential in mouse tumor models (Kobayashi et al., 1995). Only subsequent to this was it determined that α-GalCer functioned by binding to CD1d and stimulating type I NKT cells (Figure 2) (Kawano et al., 1997). When presented by CD1d, α-GalCer activates type I NKT cells which rapidly produce high levels of a range of cytokines such as IFNγ, TNF, IL-4, IL-13; IL-17; IL-21; IL-22 (Coquet et al., 2008; Salio et al., 2014). Activated NKT cells also express cytotoxic factors such as perforin, granzymes, FAS-ligand and TRAIL (McEwen-Smith et al., 2015; Nair and Dhodapkar, 2017), and are capable of directly lysing tumors (Metelitsa et al., 2001; Nicol et al., 2000; Smyth et al., 2002) although this is not the only means by which NKT cells mediate anti-tumor activity (Hayakawa et al., 2001; Metelitsa, 2011; Smyth et al., 2002). Activated NKT cells in turn activate many other cells of the immune system, and in particular, dendritic cells (DC) where a multifactorial cross talk involving CD40L-CD40, IFNγ and IL-12 production leads to increased expression of CD80, CD86, CD70 and IL-12 production by the DC. This translates to more potent activation of conventional CD4 and CD8 T cells (Fujii et al., 2003; Hermans et al., 2003; Shimizu et al., 2007; Silk et al., 2004; Taraban et al., 2008). Type I NKT cells may also promote an altered DC chemokine profile with CCL17 and CCL22 production driving the recruitment of functionally distinct $CCR4^+$ CD8 T cells (Semmling et al., 2010). In addition, other bystander cells are activated in this environment that contribute to tumor rejection, including NK cells (Hayakawa et al., 2001; Smyth et al., 2002), and γδ T cells (Paget et al., 2012), leading to enhanced effector function at many levels. Consequently, targeting type I NKT cells appears to engage several arms of the immune system at once, reducing the potential for tumor escape from a more focussed immune response. Type I NKT cells can also target tumor-associated macrophages (TAMs) (Song et al., 2009), myeloid-derived suppressor cells (MDSC) (De Santo et al., 2008), IL-10-secreting neutrophils (De Santo et al., 2010) and 'Nurse-like cells' associated with CLL (Gorini et al., 2017) thereby indirectly attacking tumors by eliminating immunosuppressive stromal support.

The adjuvant-like activity of α-GalCer can be harnessed by loading it directly onto DC or tumor cells in vitro and transferring these cells injected back into mice, which promotes more potent anti-tumor immunity by conventional CD8 T cells compared to injecting this Ag as a free molecule (Shimizu et al., 2007). Tumors can also be directly targeted in vivo using fusion proteins combining α-GalCer-CD1d to scFv fragments from tumor-specific antibodies (Stirnemann et al., 2008), focussing the NKT cell response to the tumor site, leading to strong inhibition of pre-established tumors compared to injection of α-GalCer alone (Stirnemann et al., 2008). Another approach to combine the adjuvant activity of α-GalCer to adaptive CD8 T cell immunity is to directly conjugate α-GalCer to tumor peptide Ag, focussing both NKT cells and Ag-specific CD8 T cells on the same Ag-presenting cells, again leading to enhanced CD8 T cell-mediated tumor rejection compared to α-GalCer alone or α-GalCer mixed with, but not conjugated to, peptide Ag (Anderson et al., 2015; Speir et al., 2017).

Type I NKT cells can contribute to tumor surveillance even in the absence of exogenous Ag such as α-GalCer. CD1d deficient and/or Jα18 (TRAJ18) deficient mice that lack type I NKT cells can be more susceptible to tumor development and growth including: carcinogen-induced sarcoma (Nishikawa et al., 2005; Smyth et al., 2000; Swann et al., 2009); TRAMP-induced carcinoma (Bellone et al., 2010); transferred GM-CSF-secreting melanoma (Gillessen et al., 2003) and transferred B lymphoma (Renukaradhya et al., 2008). These findings suggest a natural protective role for type I NKT cells against a range of cancer types in mice. However, some caveats have subsequently emerged with the use of CD1d and Jα18-deficient mice: one study did not detect differential

susceptibility to carcinogen-induced sarcoma development in these mice (Kammertoens et al., 2011), which they suggested may be due to either environment or genetic drift between strains; CD1d-deficient mice unexpectedly harbour increased numbers of MAIT cells compared to wildtype mice (Koay et al., 2016), which may have their own immunomodulatory effects and; the original line of Jα18-deficient mice has a defect in the use of other Jα genes upstream of Jα18 (Bedel et al., 2012), which will impact on general TCR diversity. Future tumor immunosurveillance studies with CD1d-deficient where MR1 is blocked using anti-MR1 antibody (Huang et al., 2005), or the use of CD1d-MR1 double-deficient mice, will test for a possible influence of expanded MAIT cells in these studies. New lines of Jα18-deficient mice that do not have off-target defects in the use of upstream Jα genes (Chandra et al., 2015; Dashtsoodol et al., 2016; Zhang et al., 2016) will also be valuable for future studies. Nonetheless, there is also evidence that type I NKT cells play a naturally protective role in human cancer. Several studies have shown that subnormal type I NKT cell frequencies are associated with poor prognosis in cancer patients: for example, in head and neck carcinoma (Molling et al., 2007); acute myeloid leukemia (Najera Chuc et al., 2012), neuroblastoma (Hishiki et al., 2018) and chronic lymphocytic leukemia (Gorini et al., 2017). Indeed, in the latter study (Gorini et al., 2017), low blood NKT cell frequency and high CD1d expression on CLL cells were significant predictors of CLL progression that, if combined with current prognostic factors such as CD38 expression by CLL cells, may improve prognostic accuracy in this type of cancer. Conversely, a higher degree of NKT cell infiltration in colorectal cancer patients was associated with improved survival (Tachibana et al., 2005).

Collectively, these reports raise the important question of what tumor-associated Ags are the type I NKT cells responding to in these settings? For many years, α-GalCer was viewed only as a foreign microbial Ag that NKT cells were unlikely to encounter. However, it is now clear that this glycolipid is produced by natural gut flora such as *Bacteroides fragilis* (Wieland Brown et al., 2013), and similar molecules such as α-psychosine (Kain et al., 2014) and α-Glucosylceramide (Brennan et al., 2014) are produced in multiple mammalian tissues and can also be detected in cow's milk (Brennan et al., 2017). Thus, it is now apparent that α-linked type I NKT cell ligands are present in normal healthy individuals. Furthermore, several studies have shown that tumor cells modulate lipid Ag production resulting in overrepresentation of some lipids that may be antigenic for NKT cells when presented in the context of CD1d, such as isoglobotrihexosylceramide (iGb3) (Dias et al., 2009), the gangliosides GD3 and GM3 (Park et al., 2008; Wu et al., 2003), and α-fucosylceramides that are associated with various types of human cancer including adenocarcinoma, colonic, gastric and pancreatic carcinomas(Veerapen et al., 2010) (Figure 1).

While type I NKT cells are known for their ability to enhance immunity to tumors and some types of infection, they also have great immunosuppressive potential. Indeed, some of the earliest studies of type I NKT cells were focussed on their ability to inhibit autoimmune diseases such as autoimmune (type 1) diabetes and experimental autoimmune encephalomyelitis (EAE), and to prevent graft versus host disease (Godfrey and Kronenberg, 2004). Accordingly, in two studies of haematological malignancies in mice, type I NKT cells appeared to inhibit tumor rejection (Bjordahl et al., 2012; Renukaradhya et al., 2006). The paradoxical ability of type I NKT cells to either promote, or suppress, cell-mediated immunity may be partly associated with diverse cytokine production by functionally distinct subsets of these cells in response to α-GalCer. These include IFNγ–producing 'NKT1' cells, IL-4-producing 'NKT2' cells, IL-10-producing 'NKT10' cells and IL-17-producing 'NKT17' cells (Lee et al., 2013; Sag et al., 2014), although a recent study has shown that IL-4, IL-10 and IL-13 can be produced at similar levels by NKT1, NKT2 and NKT17 cells (Cameron and

Godfrey, 2018). These subsets have not been separately tested for their anti-tumor potential. However, in order to promote stronger tumor rejection, many studies have explored the potential of synthetic analogues of α–GalCer to drive a type I NKT cell response that is biased toward either pro-inflammatory/cell mediated outcomes, or anti-inflammatory immunosuppressive responses.

Structurally, α-GalCer consists of a α-D-galactose headgroup that is covalently linked to both fatty acid and phytosphingosine chains via a O-glycosidic bond (Figure 2). The first crystal structures of hCD1d-α-GalCer (Koch et al., 2005), mCD1d-α-GalCer analogue (Zajonc et al., 2005), type I NKT TCR-hCD1d-α-GalCer and type I NKT TCR-mCD1d-α-GalCer complexes (Borg et al., 2007; Pellicci et al., 2009) (Figure 2) provided detailed insights into the molecular basis that underpins the presentation by CD1d of the lipid-based antigen α-GalCer and its subsequent recognition by an type I NKT TCR. In brief, the structural studies revealed that the fatty acid and phytosphingosine chains of α-GalCer sit deep within the hydrophobic A′- and F′-pockets of CD1d, respectively, while the polar galactose moiety protrudes out of the CD1d binding cleft for recognition by the type I NKT TCR (Figure 2), which adopted a highly conserved parallel docking mode over the F′-pocket of the CD1d binding groove whereby the invariant TCR α-chain made key interactions with the 2′-, 3′- and 4′-hydroxyls of α-GalCer and CD1d, while the NKT TCR β-chain mediated interactions exclusively with CD1d. A number of CD1d residues also interacted closely with the O-glycosidic oxygen, the 2′- and 3′-hydroxyls of α-GalCer, and thus stabilizing the Ag within the CD1d cleft. These structural insights into the CD1d-α-GalCer-type I NKT TCR molecular interactions provided a highly valuable rational basis to design novel classes of α-GalCer analogues (Figure 2) that impact the type I NKT TCR recognition and direct a more favourable Th1 skewed immune response for cancer therapy. Indeed, presently the molecular presentation and/or recognition of total of over 20 α-GalCer analogues have been investigated structurally although fine specificity differences between mouse and human type I NKT cells may complicate translation of findings from mouse to human-based studies (Birkholz et al., 2015; Li et al., 2009; Wun et al., 2012). In brief, the introduced chemical modifications have been mainly targeting three distinct parts of the α-GalCer molecule that included the O-glycosidic bond, the glycolipid hydrophobic tails, and the galactose C6′ hydroxyl (Figure 2). Collectively, these approaches have resulted in new glycolipid analogues such as α-C-GalCer (Patel et al., 2011; Schmieg et al., 2003), aminocyclitolic ceramide (Kerzerho et al., 2012), β-mannosylceramide (O'Konek et al., 2011), Nu-α-GalCer (Aspeslagh et al., 2011), PyrC-α-GalCer (Aspeslagh et al., 2013), α-GalCer analogues with aromatic rings in their acyl or sphingosine tails (Chang et al., 2007), and ABX196, an α-GalCer analogue with an acetamide group appended to the galactosyl C6 (Tefit et al., 2014) (Figure 2) that lead to improved pro-inflammatory cytokine polarization, cell-mediated immunity and anti-tumor potential.

A number of clinical trials have explored α-GalCer-type I NKT cell-based immunotherapy (Table 1). Early trials where α-GalCer was injected in soluble form (Giaccone et al., 2002) or pulsed onto DC (Chang et al., 2005; Ishikawa et al., 2005; Nieda et al., 2004), demonstrated that these agents, which were generally well-tolerated with no serious complications, could induce type I NKT cell expansion, cytokine production and activation of bystander cells. One of these studies also reported that α-GalCer-pulsed mature DC led to long term enhanced production of CMV and influenza virus Ag specific memory T cells (Chang et al., 2005). However, these interventions had, at best, a transient stabilizing effect on tumor growth in a subset of patients. More recent trials using α-GalCer loaded DC injected i.v. or into tissues (Kurosaki et al., 2011; Nagato et al., 2012; Nicol et al., 2011a; Richter et al., 2012; Uchida et al., 2008) have further demonstrated that this form of

therapy has the potential to cause tumor regression or stabilise cancer growth in a subset of patients. In one study, α-GalCer was pulsed onto autologous IL-2 and GMCSF-cultured PBMC, which were then injected back into patients with advanced non-small cell lung cancer (NSCLC). In the majority (10 out of 17) of patients where a strong IFNγ response was observed, their median survival time was 31.9 months, compared to ~10 months for the poor responders, which is closer to expected for standard care for patients with advanced NSCLC (Motohashi et al., 2009). An additional approach has been to inject in vitro expanded and activated autologous NKT cells (Motohashi et al., 2006) sometimes in combination with α-GalCer loaded dendritic cells (Kunii et al., 2009; Yamasaki et al., 2011). A recent clinical trial has been reported where α-GalCer was combined with a defined tumor protein Ag, NY-ESO-1, both loaded onto DC and injected into melanoma patients (Gasser et al., 2017). This induced a sustained increase in NY-ESO-1 responsive CD4 and CD8 T cells in 7 of 8 subjects, highlighting the potential benefits of targeting type I NKT cells in association with tumor Ag vaccines. While these reports are typically from small-scale pilot studies or phase I or II trials, they are nonetheless providing encouraging results with tumor stabilisation and in some cases, tumor regression (Table 1). The first clinical trial with an enhanced potency α-GalCer analogue (ABX196) as an adjuvant for a prophylactic HepB vaccine was recently reported (Tefit et al., 2014). This work showed that type I NKT cell targeting with this analogue could induce a potent anti-HepB antibody response from a single injection, comparable to the prime and boost response with the existing HepB vaccine with conventional Alum adjuvant. As HepB infection is associated with an increased risk of hepatocellular carcinoma, this highlights another potential means by which NKT cell targeting can be employed as a cancer immunotherapeutic. Moreover, the successful use of the ABX196 analogue in this setting flags the importance of testing this and other α-GalCer analogues in direct anti-tumor clinical trials. The research and clinical community is awaiting larger scale clinical trials that are underway, to more confidently determine the potential of type I NKT cell-based immunotherapy.

Another interesting development in the use of type I NKT cells for immunotherapy is the generation of chimeric antigen receptor expressing NKT (CAR-NKT) cells (Heczey et al., 2014; Tian et al., 2016). Human type I NKT cells engineered to express a CAR specific for the GD2 ganglioside that is highly expressed in neuroblastoma (NB) were cytotoxic against human NB cells *in vitro* and *in vivo* in a humanised NOD-SCID-IL2Rγ^{null} (NSG) mouse tumor model. Moreover, while both GD2-specific CAR-T cells and CAR-NKT cells were capable of infiltrating the NB tumors, the CAR-NKT cells did this more effectively. Furthermore, CAR-T cells generated from an allogeneic donor caused severe GVHD in the NSG mice, whereas this did not happen with GD2-specific CAR-NKT cells (Heczey et al., 2014). This highlights the advantage of using NKT cells, and potentially other unconventional T cells, for 'off the shelf' therapy because they are unlikely to mount allogeneic responses against host MHC.

Unlike type I NKT cells that have repeated patterns of TCR usage, the type II NKT cell repertoire is very diverse, and there is no universal type II NKT cell antigen that can be used to study this population of T cells. Consequently, the functional role of these type II NKT cells is less clear (recently reviewed in (Dhodapkar and Kumar, 2017)), although important to establish as they may be more prevalent in humans than type I NKT cells(Exley et al., 2001). While only a few investigations into the role of type II NKT cells in cancer have been published, most studies suggest these cells inhibit anti-tumor immunity. In a series of mouse-based studies comparing tumor growth in CD1d-deficient (lacking both type I and type II NKT cells) to Jα18-deficient (lacking type I but retaining type II NKT cells), notwithstanding the above-mentioned caveats with these mice, the

data suggested that type II NKT cells suppress tumor rejection through the production of IL-13 (Terabe et al., 2005). In further support for an immunosuppressive function for type II NKT cells, when tumor bearing mice are treated with the glycolipid Ag sulfatide, which is presented by CD1d to a subset of type II NKT cells, tumor growth was exacerbated through production of IL-13 (Ambrosino et al., 2007). Moreover, type II NKT cell-mediated suppression can antagonise the protective effects induced by α-GalCer-mediated type I NKT cell stimulation (Ambrosino et al., 2007; Halder et al., 2007). A more recent study suggested that type II NKT cells and Treg cells both play an immunosuppressive role and that blockade of both cell types was necessary to prevent tumor immunosuppression when type I NKT cells are absent (Izhak et al., 2013). Another mechanism by which type II NKT cells may suppress tumor immunity is via induction of MDSC (Renukaradhya et al., 2008), which notably contrasts with the inhibitory effect of Type I NKT cells on MDSC (De Santo et al., 2008). In a study of multiple myeloma patients (Chang et al., 2008a), the phospholipid Ag lysophosphatidylcholine was detected at increased levels of blood plasma, as well as an increased population of type II NKT cells that produced IL-13 in response to this Ag, compared to healthy individuals. It was suggested that this response might inhibit cell-mediated tumor immunity and promote tumor growth in these patients (Chang et al., 2008a). While there are only a few studies into type II NKT cells, further investigation these cells and the role they play in human cancer should be carried out as they may represent an important checkpoint that could be inhibited with CD1d-blocking antibodies.

Group 1 CD1-restricted T cells.

It is well known that CD1a, CD1b and CD1c restricted T cells are capable of presenting mycobacterial lipid Ags to human T cells (Van Rhijn et al., 2015). Furthermore, recent studies have demonstrated that some T cells are capable of interacting with self-lipid Ags (Birkinshaw et al., 2015; de Jong et al., 2010; de Lalla et al., 2011; Shahine et al., 2017; Van Rhijn et al., 2016; Wun et al., 2018), including skin-derived lipids (de Jong et al., 2014) presented by group 1 CD1 molecules. Moreover, some appear to interact solely with CD1a and CD1c in a response that is indirectly modulated by the bound lipid Ag (Birkinshaw et al., 2015; Wun et al., 2018). Furthermore, CD1a, b and c are expressed by human DC, so these molecules are present in the tumor and/or tumor draining lymph node environment. This raises the question of whether Group I CD1 restricted T cells might recognise tumor-derived lipid Ags and/or whether they represent new targets for cancer immunotherapy. In one study (Lepore et al., 2014), CD1c restricted T cells were found to recognise the self-lipid Ag methyl-lysophosphatidic acid (mLPA) (Figure 2) that is overrepresented in human leukemia cells. These T cells were capable of killing human leukemia cells in vitro, and in a xenogeneic mouse tumor transplantation model. In another study, using mice that transgenically expressed group 1 CD1 molecules, CD1b-self-phospholipid-reactive T cells were capable of responding to tumor-derived phospholipids and conferred protection against a CD1b-transfected T cell lymphoma (Bagchi et al., 2016). Even if specific tumor lipid Ags do not exist for each of the group 1 CD1 molecules, the existence of known foreign agonist ligands raises the possibility that group 1 CD1-restricted T cells could be targeted for cancer immunotherapy, much the same way that type I NKT cells can be targeted with the α-GalCer. For example, most humans harbour a population of CD1b-restricted T cells known as 'germline encoded mycolyl-reactive' (GEM) T cells that express an invariant TRAV1-2-TRAJ9 TCR-α chain (Van Rhijn et al., 2013). This TCR imbues these cells with specificity for the mycobacterial lipid Ag glucose monomycolate, and these cells rapidly produce IFNγ upon Ag encounter. It is noteworthy that glucose monomycolate is present in the mycobacterial bacillus Calmette Guerin (BCG) vaccine strain, and that BCG-based therapy for non-muscular bladder cancer has been successfully for many years(Morales et al., 1976). Given that

the mechanism of action for BCG-based immunotherapy is unclear, but involves both $CD4^+$ and $CD8^+$ T cells (Redelman-Sidi et al., 2014) and that the majority of BCG-responsive CD8 T cells are CD1a, b or c restricted (Kawashima et al., 2003), the potential for mycobacterial lipid-based immunotherapy to target group 1 restricted T cells like GEM T cells is worthy of further exploration.

While group 1 CD1 restricted T cells are prevalent in humans, their role in immunity and tumor immunology, is not well-understood, principally as group 1 CD1 molecules are not present in mice and group 1 CD1 tetramers to identify these cells have only become available in the last few years ((Kasmar et al., 2011; Kasmar et al., 2013; Ly et al., 2013), see http://tetramer.yerkes.emory.edu/). Considering the well-established role that the type I NKT cells play in tumor immunity, further investigations in humans, and in group 1 CD1 transgenic mice, are required in order to determine the cancer immunotherapeutic potential of group 1 CD1-restricted T cells.

Mucosal associated invariant T (MAIT) cells

MAIT cells are innate-like T cells found in mammals, whose frequency varies between species (Godfrey et al., 2015). For example, whilst abundant in humans they are much less frequent in laboratory strains of mice (Rahimpour et al., 2015; Reantragoon et al., 2013; Tilloy et al., 1999). MAIT cells reside, as their name implies, in the mucosa, and are also found in the peripheral blood, and organs such as the liver. Although the physiological and pathophysiological roles for MAIT cells are unclear, it is known that many bacteria and yeast activate MAIT cells via the MAIT TCR-MR1 axis(Gold et al., 2010; Le Bourhis et al., 2010). Moreover, MAIT cells can be activated by viruses in a MAIT TCR-independent manner (Loh et al., 2016; van Wilgenburg et al., 2016). MAIT cells are thought to play a role in protective immunity to bacteria (Chen et al., 2016; Howson et al., 2018; Meierovics et al., 2013), and are reported to be depleted during infection by viruses(Ussher et al., 2018), which is considered to increase host susceptibility to opportunistic infections. In addition, MAIT cells are also implicated in several autoimmune disorders (Godfrey et al., 2015), including diabetes (Magalhaes et al., 2015; Rouxel et al., 2017).

In some regards, MAIT cells are reminiscent of type I NKT cells, rapidly secreting cytokines including IFN-γ, TNF and, in some situations IL-17, following TCR-mediated activation (Salio et al., 2014). In line with their innate-like phenotype, the majority of MAIT cells typically possess a highly biased TCR repertoire, characterised by a near-invariant TCR α-chain (TRAV1-2-TRAJ33 or TRAJ12 or TRAJ20) and a biased usage of TCR β chains (TRBV6 or TRBV20), although the CDR3β loop is hypervariable(Eckle et al., 2014; Porcelli et al., 1993; Reantragoon et al., 2013; Tilloy et al., 1999). In contrast to type I NKT TCR, the MAIT TCR recognises the MHC-I related molecule, MR1(Treiner et al., 2003). However, while MR1 is expressed in all cell types, endogenous MR1 cell surface expression is low, and it is known that the presence of MR1 ligands are required to enable MR1 egress to the cell surface(McWilliam et al., 2016). These MR1 ligands were identified as vitamin B-related ligands that bound MR1 and activated MAIT cells with varying potencies (Figure 3). Specifically, while MR1 bound to pterins (metabolites of folic acid (vitamin B9)) such as 6-FP and the synthetic analogue acetyl-6-FP (Ac-6-FP), they typically do not activate MAIT cells (Awad et al., 2018). In contrast, ribityllumazines (precursors to riboflavin (vitamin B2)) bind MR1 and also activate MAIT cells weakly, while the most potent agonists were derived through condensation of an intermediate (5-amino-6-D-ribitylaminouracil, 5-A-RU) in riboflavin biosynthesis with glycolysis metabolites produced by bacteria and humans to form ribityluracils (e.g. 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil, 5-OP-RU) (Corbett et al., 2014; Kjer-Nielsen et al., 2012; Patel et al., 2013). Further, it has recently been demonstrated that MR1 can present a

broader range of chemical scaffolds, including drugs and drug-like molecules(Keller et al., 2017), which suggest that other endogenous ligands, can modulate MAIT cell function in an MR1-dependent manner. Using these 5-OP-RU and 6-FP/Ac-6-FP ligands, MR1-Ag tetramers have been generated that permit MAIT cell phenotyping *ex vivo* in an Ag-specific manner (Corbett et al., 2014; Rahimpour et al., 2015; Reantragoon et al., 2013). Using these tetramers (which are now readily available from the NIH tetramer facility, http://tetramer.yerkes.emory.edu/), previously unrecognised subsets of MAIT cells are being identified, including immature precursors (Ben Youssef et al., 2018; Koay et al., 2016) and MR1-restricted TRAV1-2$^-$ T cells that bind to 5-OP-RU and/or folate-derived ligands 6-FP and Ac-6-FP (Gherardin et al., 2016). Further, the use of MR1 tetramers has enabled the division of human MAIT cells in peripheral blood into five subsets (CD4+CD8α-; CD4+CD8α+; CD4-CD8α-; CD4-CD8α+CD8β-; CD4-CD8α+CD8β+) and that CD4+CD8α-MAIT cells are phenotypically and functionally distinct from other MAIT cell subsets (Gherardin et al., 2018b; Kurioka et al., 2017). These reports should provide a valuable baseline for future studies examining MAIT cells in human cancers.

While there are no known MR1-binding tumor Ags that activate MAIT cells, it is conceivable that MAIT cells may encounter microbial Ags in tumor types, such as mucosal cancers, where bacterial infiltrates are likely to be present. Furthermore, as observed in viral infections (Ussher et al., 2018), MAIT cells can be activated in the presence of inflammatory cytokines, such as IL-12 and IL-18, without specific Ag stimulation. TRAV1-2The first report to document the presence of MAIT cells in human cancers showed the presence of TRAV1-2-TRAJ33 transcripts that were enriched in brain and kidney tumors (Peterfalvi et al., 2008). More recently, in a study of cancer patients with a variety of cancer types, MAIT cells (defined by co-expression of surrogate markers TRAV1-2 and CD161 or CD218) were found to be diminished in the circulation of mucosal-associated cancers (gastric, colon and lung), but not in association with non-mucosal cancers (breast, liver and thyroid) (Won et al., 2016). Furthermore, in a group of colon cancer patients, where circulating MAIT cells were diminished, increased MAIT cell frequencies were detected amongst the tumor infiltrating cells suggesting that they were recruited from blood to the tumor site (Won et al., 2016). Similar findings have been reported in other studies of MAIT cells in colorectal cancer patients (Ling et al., 2016; Sundstrom et al., 2015; Zabijak et al., 2015), where increased MAIT cells are observed in the tumor infiltrate compared to adjacent healthy colon. Moreover, patients with a higher degree of infiltrating MAIT cells had a significantly worse prognosis (Zabijak et al., 2015).

Because MAIT cells are highly abundant in human liver (Dusseaux et al., 2011; Tang et al., 2013), the role that these might play in liver-localised cancers is of particular interest. One study reported that MAIT cells are present in both the healthy parts of liver as well as the tumor infiltrate in colorectal liver metastasis patients, but those isolated from the tumor margin, or from within the tumor, were functionally impaired in their ability to produce IFN-γ (Shaler et al., 2017). Along similar lines, a single cell sequencing study of hepatocellular carcinoma patient liver samples, MAIT cells were found to be abundant in healthy liver tissue, but diminished in number in the tumour site (Zheng et al., 2017). Moreover, reduced MAIT cell frequencies appeared to correlate with poor prognosis in these patients (Zheng et al., 2017). These studies suggest that inhibition of MAIT cell infiltration and/or function may be important for tumor survival. In multiple myeloma patients, MAIT cells are also numerically and functionally diminished in blood and bone marrow (tumor bed), although in part this may reflect the older ages of these patients (Gherardin et al., 2018a). This study also showed that myeloma cell lines expressed cell surface MR1, which was increased in the presence of the MR1-binding antigen 6-FP, and MAIT cells were capable of targeting and killing

myeloma cell lines pulsed with the agonist ligand 5-OP-RU, highlighting the anti-tumor potential of MAIT cells (Gherardin et al., 2018a). Interestingly, the immunomodulatory drugs lenalidomide and pomalidomide, used to treat multiple myeloma patients, inhibited MAIT cell activation in vitro, which may be an undesirable effect of these drugs. Considering that infection is a major problem for multiple myeloma patients, the impact of diminished MAIT cell numbers and function should be further investigated.

The central mechanistic questions in the MAIT-MR1-cancer axes are: (1) Can MR1 present tumor-associated antigens to MAIT cells; (2) Is MR1 is overexpressed in certain tumor types and is there stress-induced expression of MR1 in transformed cells; (3) Do MAIT cells play a pro- or anti-tumor role in the response to cancer; and (4) Do MAIT cells respond directly to tumors or do they modulate the activity of other immune cells. Further studies could compare tumor development in MR1-deficient mice that lack MAIT cells to wildtype MAIT cell-sufficient mice. Mice that have increased MAIT cells such as C57BL/6^{CAST} congenic mice (Cui et al., 2015b), or where MAIT cells have been expanded in vivo (Chen et al., 2017) may provide a better indication of the role that MAIT cells play in cancer, whereas Va19 TCR transgenic mice might not be helpful for these studies as their MAIT cells appear to be developmentally and functionally altered compared to those in non-transgenic mice (Koay et al., 2016). Complementing the use of different MAIT-deficient or sufficient mouse strains, the use of MAIT cell agonist ligands such as 5-OP-RU (Corbett et al., 2014) to activate MAIT cells in the context of tumor development *in vivo* is also a logical approach to investigating the anti-tumor potential of these cells. Addressing such questions will ultimately enable one to consider using MAIT cells, or CAR-MAIT cells, or MAIT cell ligands, in novel forms of tumor immunotherapy.

γδ T cells

γδ T cells represent ~1-5% of circulating human T cells, and in humans they can be broadly divided into two subsets based on their TCR δ-chain V region usage: TRDV2^{+} cells, which co-express TRGV9, and TRDV2^{-} cells, which pair with an array of TRGV genes. TRDV2^{+} cells are normally more abundant in the circulation and react to small phosphorylated metabolite Ags, known as phosphoantigens, that are typically derived from foreign pathogens, but are also produced by mammalian cells and can lead to increased expression by tumor cells. The TRDV2^{-} cells often utilize TRDV1^{+} or TRDV3^{+} TCRs and localize to peripheral sites such as skin and large intestine. There is only limited knowledge about their Ag reactivity, although some can react with MHC-I like molecules such as MICA, CD1 and EPCR, or soluble Ags in the absence of Ag-presentation, in sharp contrast to other types of T cells (reviewed in (Godfrey et al., 2015; Vantourout and Hayday, 2013)). Interestingly, some TRDV1^{+} γδ T cells can respond to α-GalCer presented by CD1d in humans(Uldrich et al., 2013), which may be relevant in human trials involving this Ag. While γδ T cells in mice share some common innate-like functions with human γδ T cells, they notably differ significantly with respect to TCR specificity and tissue homing. In mice, γδ T cell subsets are normally defined by TCRγ chain usage, and typically enriched in peripheral sites such as skin, intestine, liver, lungs and reproductive tract (Godfrey et al., 2015).

While the major focus for the function of γδ T cells has been their role in homeostasis, wound repair and infection (Nielsen et al., 2017), there is also great interest in the role that these cells play in cancer, especially as intratumoral γδ T cells represents the most favorable prognostic indicator across diverse cancers (Gentles et al., 2015). γδ T cells possess unique properties that make them highly amenable for immunotherapy. They are relatively abundant in human blood and tissue so it

is possible to isolate them in relatively large numbers and most have a Th1-type cytokine bias (strong IFN-γ production) and potent cytotoxicity potential, attributes that are closely correlated with tumor destruction. They readily expand following TCR stimulation in vitro, thereby increasing the feasibility of their usage in adoptive transfer models of therapy and furthermore, many γδ T cells have unique homing properties compared to αβ T cells, typically migrating to peripheral sites, such as epithelial tissues and solid tumors. Finally, like other unconventional T cells, γδ T cells are not MHC restricted, so there are no genetic constraints to their antigen specific activation, and transferred γδ T cells from an MHC mismatched background do not cause overt graft-versus-host disease (GVHD) which can be a life-threatening complication with adoptive transfer of conventional αβ T cells (Godder et al., 2007; Lamb et al., 1996).

Evidence for a role of γδ T cells in cancer surveillance first arose from studies using γδ T cell-deficient mice. These studies indicated a significantly elevated incidence of tumors in models of chemically-induced cutaneous malignancies (Gao et al., 2003; Girardi et al., 2001) and spontaneous prostate adenocarcinoma (Liu et al., 2008), compared to control wild-type mice. Experimental transfer of established tumor cell lines derived from melanoma (Gao et al., 2003) and B cell lymphoma (Street et al., 2004) also confirmed a beneficial role of γδ T cells (reviewed in (Silva-Santos et al., 2015)). Consistent with animal studies, human γδ T cells can also elicit strong anti-tumor responses in vitro. Activated TRDV2$^+$ γδ T cells recognize and kill a broad range of tumor target cells in vitro (Bouet-Toussaint et al., 2008; Corvaisier et al., 2005; Kunzmann et al., 2000; Lanca et al., 2010; Liu et al., 2005; Viey et al., 2005). Likewise, activated TRDV1$^+$ cells can also recognize and kill diverse tumor lines representing many cancer types (Choudhary et al., 1995; Cordova et al., 2012; Correia et al., 2011; Groh et al., 1999; Lamb et al., 2001; Maeurer et al., 1996).

The association between γδ T cells and tumor progression and/or patient survival has been examined in a range of different human tumor settings, with contrasting results. Bialasiewicz et al. ((Bialasiewicz et al., 1999)) found that γδ T cells amongst tumor-infiltrating lymphocytes (TILs) were positively associated with patient survival in choroidal melanoma. Another study of melanoma patients found that TRDV2$^+$ γδ T cells were positively associated with survival at an early stage of disease (Cordova et al., 2012), and a follow up study extended this correlation with overall patient survival (Toia et al., 2016). Studies of patient cohorts that received allogeneic bone marrow transplantation revealed a strong correlation between γδ T cell abundance and overall survival or disease-free survival in cohorts of ALL or acute myeloid leukemia (AML), or chronic myeloid leukemia (CML) patients (Godder et al., 2007; Lamb et al., 1996). Moreover, activated donor-derived γδ T cells, which were predominantly TRDV1$^+$, were cytotoxic against recipient ALL tumors (Lamb et al., 2001) in vitro, suggesting a potentially important role for γδ T cells in immune surveillance against leukemia. Despite these promising findings, in some settings γδ T cells do not appear to be a useful prognostic marker (Inman et al., 2008; Kuriyama et al., 2000), or are even associated with poor outcome or tumor burden, indicative of a pro-tumorigenic role. For instance, in rectal cancer patients, while TRDV1$^+$ γδ T cells amongst TILs positively correlated with tumor burden, TRDV2$^+$ cells negatively correlated, indicating a differential role of these subsets (Rong et al., 2016). Another study also found an association between IL17-producing γδ T cells and poor survival in gall bladder patients (Patil et al., 2016), and in primary breast cancer patients, γδ T cells were associated with more severe disease and reduced overall survival, indicating a pro-tumor role (Ma et al., 2012). In support of this notion, Peng et al. (Peng et al., 2007) isolated a regulatory population of TRDV1$^+$ γδ T cells from breast cancer TILs that specifically recognized a tumor epitope

via the γδTCR, and exhibited immune-suppressive functions that could be reversed in vitro using TLR8 ligands.

Further insight into the pro- versus anti- tumor role of γδ T cells can be gleaned from mouse studies. In many cases, the protective mechanisms appeared to involve interaction with NK cell receptors such as NKG2D, which can recognize stress-associated receptors on transformed cells, along with IFNγ production, which promotes Th1 responses that are generally favorable in an anti-cancer immunotherapeutic setting. Another population of clonally expanded TRDV5$^+$ γδ T cells isolated from a CMV-infected patient was capable of killing tumor lines through recognition of the MHC-I like molecule EPCR (Willcox et al., 2012), suggesting that this ligand may be involved in γδ T cell-mediated immunosurveillance, although further investigation is required. Whilst in some studies, γδ T cell-derived IL-17 exhibited anti-tumor effects (Ma et al., 2011; Takeuchi et al., 2011), it has also been associated with pro-tumor responses, along with regulatory cell-like functions, enhanced angiogenesis, and neutrophil or MDSC recruitment (reviewed in (Fleming et al., 2017)). Collectively these studies highlight the importance of further research to understand the key factors involved in driving pro- versus anti-tumor immunity by γδ T cells.

There have now been ~19 clinical studies examining the anti-cancer potential of TRDV2$^+$ γδ T cells in a range of cancer settings (Abe et al., 2009; Aoki et al., 2017; Bennouna et al., 2008; Bennouna et al., 2010; Cui et al., 2015a; Dieli et al., 2007; Izumi et al., 2013; Kobayashi et al., 2011; Kobayashi et al., 2007; Kunzmann et al., 2012; Lang et al., 2011; Meraviglia et al., 2010; Nakajima et al., 2010; Nicol et al., 2011b; Pressey et al., 2016; Sakamoto et al., 2011; Wada et al., 2014; Wilhelm et al., 2003; Wilhelm et al., 2014) (Table 2). These trials typically involved either in vitro or in vivo expansion of TRDV2$^+$ γδ T cells using aminobisphosphonates, such as zoledronate, which cause an accumulation of the phosphoantigen isopentenyl pyrophosphate (IPP); or phosphoantigens directly. Whilst there were no significant adverse effects of therapy in these studies, complete or even partial responses were relatively infrequent, although of note, Wilhelm et al. ((Wilhelm et al., 2014)) transferred HLA-half-matched, CD4 and CD8-depleted cells into 4 patients with haematological malignancies, followed by in vivo γδ T cell activation using zoledronate and IL-2, of which 3 achieved a complete response. Kobayashi et al. also reported a patient that achieved complete remission from renal cell carcinoma-derived lung metastases following zoledronate and IL-2 therapy (Kobayashi et al., 2010).

To date there have been no clinical trials performed using TRDV1$^+$ γδ T cells, although they were therapeutically beneficial in a xenogeneic model of human ovarian cancer, where adoptively transferred activated TRDV1 cells were largely protective (Deniger et al., 2014a), suggesting that clinical studies may be warranted. Clearly more research is required to understand the functional properties of γδ T cells, including their survival, homing, cytotoxic capacity and natural ligands (reviewed in (Deniger et al., 2014b)), prior to realizing their therapeutic potential. Future therapies such CAR γδ T cell therapy, and combination therapies, hold much promise as improved treatment regimes.

Concluding remarks

Unconventional T cells and immunotherapeutic potential in humans: future prospects

It has long been recognised that unconventional T cells can promote tumor rejection, and there are many reasons why it is of value to translate these studies to clinical trials. Unconventional T cells offer several advantages that may lead to improved T cell immunotherapy for human cancer. These

include the ability to release a rapid burst of cytokines without the need for clonal expansion and differentiation, in part due to the presence of far higher numbers of Ag-specific cells that exist in a poised, memory-like state (Godfrey et al., 2015). For example, Ag-specific NKT cells, MAIT cells and $V\delta2^+$ $\gamma\delta$ T cells outnumber pMHC-specific CD8 T cells by 2-4 orders of magnitude in humans (Godfrey et al., 2015). Furthermore, the adjuvant-like effects and strong cytokine responses upon activation of some of these cells, such as type I NKT cells, engages multiple arms of the immune system that should help to guard against the formation of tumor escape variants. The Ag-presenting molecules for unconventional T cells are monomorphic and thus Ag-based vaccines targeting these cells could be universally effective with respect to human cancer patients. This also means that their TCRs, which are not directed toward polymorphic MHC molecules, will be unlikely to mount alloreactive responses and cause GVHD, making these cells more amenable to off the shelf cellular therapy such as CAR-NKT cell therapy (Heczey et al., 2014; Tian et al., 2016). Further, many of these unconventional T cells express TCRs with repeated patterns of TCR usage in unrelated individuals, which means that they could also potentially represent targets for immunotherapeutic intervention, or diagnostic monitoring in tumor settings. Moreover, the non-peptidic nature of CD1 and MR1 ligands make them less likely to be targets of mutational escape within the tumor, thereby providing more stable Ags to target therapeutically. Lastly, in contrast to most $\alpha\beta$ T cells, unconventional T cells such as $\gamma\delta$ T cells, MAIT cells and NKT cells naturally home to non-lymphoid tissue sites which is an important characteristic to exploit for targeting solid tumors in non-lymphoid locations.

While many clinical trials on unconventional T cells have focussed on the use of α-GalCer to stimulate type I NKT cells, future studies exploring the new lipid analogues (Figure 2) should provide improved clinical outcomes. Moreover, while targeting Ags recognised by group 1 CD1-restricted T cells is in its infancy this also warrants further investigation in the context of tumor immunotherapy. Clinical trials targeting $TRDV1^+$ $\gamma\delta$ T cells may offer improved outcomes over those targeting $TRDV2^+$ $\gamma\delta$ T cells, because the former tend to localise to non-lymphoid tissue locations more so than the latter, suggesting they may be better at invading non-lymphoid tumors. The challenge with the $TRDV1^+$ cells is to determine which Ags they respond to and how they can best be harnessed for immunotherapy. MAIT cells have potential as targets for immunotherapy due to their high frequency in humans, their tissue homing characteristics, and the existence of potent Ags like 5-OP-RU that can target these cells in all individuals. Studies using MR1 restricted Ags in conjunction with tumor vaccines are required to determine if MAIT cells have similar adjuvant-like activity to type I NKT cells. Based on the promising results using in vitro expanded CAR-NKT cells in humanised mouse models, similar studies using CAR-MAIT cells, CAR-$\gamma\delta$ T and CAR MHC class Ib-restricted T cells are also worthy of investigation.

Checkpoint blockade therapy using anti-PD1 and anti-CTLA-4 based drugs to inhibit tumor-mediated immunosuppression is proving to be a very powerful approach to treating some types of cancer (Melero et al., 2015). While this therapy is usually assumed to act primarily via enhanced CD8+ T cell-mediated tumor destruction, the potential role that unconventional T cells play should be considered, given that they also express the inhibitory receptors such as PD1 upon activation and that blockade of these receptors can enhance their cytokine production and anti-tumor capacity (Chang et al., 2008b; Durgan et al., 2011; Iwasaki et al., 2011; Jiang et al., 2014). Moreover, as one of the key resistance genes associated with checkpoint blockade therapy is β2M (Zaretsky et al., 2016) which is associated with MHC class-Ia, MHC class-Ib, MR1 and CD1 family members, studies into the role that each of these T cell lineages play in this therapy is warranted.

These are exciting times in the field of T cell immunotherapy for cancer, and the incorporation of unconventional T cells into these studies has the potential to provide novel approaches to this important area of medicine.

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Conflict of interest declaration
DIG is chair of the scientific advisory board for Avalia Immunotherapies.

Figure legends

Figure 1. Unconventional T cell types.
Unconventional T cells, divided into groups based on their restriction elements. 5-OP-RU, 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil; 6-FP, 6-formylpterin; Ag, antigen; α-GalCer, α-galactosylceramide; GEM, germline encoded mycolyl lipid-reactive; mLPA, methyl lysophosphatidic acid; MAIT, mucosal-associated invariant T; NKT, natural killer T; semi inv, semi-invariant; ? = insufficient or very limited data; 1 = mostly protective but suppressive in some cases.

Figure 2. CD1-restricted lipid-based Ags
Top left panel. A cartoon of a type I NKT cell recognising α-GalCer presented by a CD1d+ Ag presenting cell. The ternary crystal structure of the TCR-CD1d-α-GalCer complex is shown in the inset. Top right panel. A sample of synthetic lipid analogues that have the ability to provide enhanced and/or Th1-biased type I NKT cell responses. Bottom panel. Examples of tumor-derived lipid Ags that are capable of being recognised by CD1d-restricted T cells, with the exception of mLPA that is recognised by CD1c-restricted T cells. α-GalCer, α-galactosylceramide; mLPA, methyl lysophosphatidic acid; NKT, natural killer T

Figure 3. MR1-restricted vitamin B metabolite Ags
Left panel. A cartoon of a MAIT cell recognising a vitamin B metabolite presented by an MR1+ Ag presenting cell. The ternary crystal structure of the MAIT TCR-MR1-Ag complex is shown in the inset. Right panel. Some examples of vitamin-B derivative Ags that have the ability to bind to MR1 and, with varying degrees of potency, to stimulate MAIT cells via their TCR. The exceptions are 6-FP and Acetyl-6-FP (Ac-6-FP) which bind MR1, but are not stimulatory for the majority of MAIT cells. 5-OP-RU, 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil; 6-FP, 6-formylpterin; Ag, antigen; MAIT, mucosal-associated invariant T

Table 1. NKT cell clinical studies.

Study	Tumor type (N)	Treatment	Clinical outcome (N = %)
(Giaccone et al., 2002)	Solid tumors (24) [not defined]	α-GalCer (i.v.) Every 4 weeks for 1-6 cycles	OR (0), SD (7 =29%)
(Nieda et al., 2004)	Solid tumors (12) [Breast cancer (1), Colon cancer (1), Liver cancer (1), Melanoma (2), peritoneal/lung AC (4), RCC (3)]	α-GalCer/immature MoDC (i.v.) Up to 3 cyles separated by several months, each with 2 infusions	OR (N.D.) Reduction in tumor markers or mass (3 = 25%)
(Nicol et al., 2011a)	As above	α-GalCer/immature MoDC (i.v. and intradermal) 2 cycles for each injection route over 2 months	OR [3 = 25% (PR 3)], SD (3 = 25%)
(Chang et al., 2005)	MM (3), RCC (1), Anal SCC (1)	α-GalCer/mature MoDC (i.v.) Every month for 2 cycles	OR (N.D.) Reduction in tumor markers or stable metastatic disease (4 = 80%)
(Ishikawa et al., 2005)	NSCLC (9) [lung AC, SCC, LCC]	α-GalCer/immature DC-enriched PBMC 2 cycles separated by 6 weeks, each with 2 infusions	OR (0), SD (5 = 56%)
(Motohashi et al., 2006)	NSCLC (6) [AC (4), SCC (2)]	α-GalCer/IL-2-expanded PBMC (i.v.) Every week for 2 cycles	OR (0), SD (4 = 67%)
(Uchida et al., 2008)	Head and neck SCC (9)	α-GalCer/immature DC-enriched PBMC (nasal submucosa) Every week for 2 cycles	OR [(1 = 11% (PR 1)], SD (5 = 56%)
(Motohashi et al., 2009)	NSCLC (17) [AC (14), SCC (3)]	α-GalCer/immature DC-enriched PBMC (i.v.) 2 cycles separated by 6 weeks, each with 2 infusions	SD (5 = 29%)
(Kunii et al., 2009)	Head and neck SCC (8)	α-GalCer/immature DC-enriched PBMC (nasal submucosa) + α-GalCer/IL-2-expanded PBMC (arterial infusion) Every week for 2 cycles	OR [3 = 38% (PR 3)], SD (4 = 50%)
(Yamasaki et al., 2011)	Head and neck SCC (10)	α-GalCer/immature DC-enriched PBMC (nasal submucosa) + α-GalCer/IL-2-expanded PBMC (arterial infusion) + surgery Enriched NKT injected 1 week after APCs, followed by surgery	OR [5 = 50% (PR 5)], SD (5 = 50%)
(Kurosaki et al., 2011)	Head and neck SCC (17)	α-GalCer/immature DC-enriched PBMC (nasal or oral submucosa) Undefined number of injections	OR (N.D.) Increased NKT number in PBMC
(Nagato et al., 2012)	NSCLC (4) [AC 1, SCC 3]	α-GalCer/immature DC-enriched PBMC (i.v.) Single injection 2 weeks prior to surgery	OR (N.D.) Increased NKT infiltration of TILs
(Richter et al., 2012)	Asymptomatic MM (6)	α-GalCer/mature MoDC (i.v.) + lenalidomide (i.v.) Every 4 weeks for 3 cycles	OR (N.D.) Reduction in tumor markers (3 = 50%)

NKT cells used in cancer clinical studies, listing tumor time, treatment and clinical outcome

Table 2. γδ T cell clinical studies.

Study	Tumor type (N)	Treatment	Clinical outcome (N = %)
(Wilhelm et al., 2003) cohort A	MM (3), FCL (0), CLL (4), MZL (1), IC (1)	Pamidronate (i.v. day 0) + IL-2 (24h infusion i.v. day 3-8) 1-6 cycles	OR (0), SD (1 = 13%)
(Wilhelm et al., 2003) cohort B	MM (4), FCL (4), CLL (0), MZL (1), IC (0)	Pamidronate (i.v. day 0) + IL-2 (6h infusion i.v. days 1-6) 1-9 cycles	OR [3 = 33% (PR 3)], SD (2 = 22%)
(Dieli et al., 2007) cohort A	HRPC (9)	Zol (i.v.) Every 3 weeks for up to 1 year.	OR [1 = 11% (PR 1)], SD (1 = 11%)
(Dieli et al., 2007) cohort B	HRPC (9)	Zol (i.v.) + IL-2 (s.c.) Every 3 weeks for up to 1 year.	OR [2 = 22% (PR 2)], SD (4 = 44%)
(Kobayashi et al., 2007)	RCC (7)	pAg/IL-2-expanded PBMC (i.v.) + IL-2 (i.v.) Every 1-2 weeks for 6-12 cycles.	OR (N.D.) Tumor doubling time prolonged in 3 patients.
(Bennouna et al., 2008).	RCC (10)	pAg/IL-2-expanded PBMC (i.v.) + IL-2 (s.c.) Every 3 weeks for 3 cycles.	OR (0), SD (6 = 60%)
(Abe et al., 2009)	MM (6)	Zol/IL-2-expanded PBMC (i.v.) Every 2 weeks for 4-8 cycles	OR (0), SD (4 = 67%)
(Bennouna et al., 2010)	RCC (18), Colon cancer (3), Esophagus carcinoma (3), Breast cancer (2), Ovarian cancer (1), Gastric cancer (1)	pAg (i.v.) + IL-2 (s.c.) Every 3 weeks for up to 5 cycles	OR (0), SD (12 = 43%)
(Meraviglia et al., 2010)	Breast cancer (10)	Zol (i.v.) + IL-2 (s.c.) 3 week cycles for up to 1 year	OR [1 = 10% (PR 1)], SD (2 = 20%)
(Nakajima et al., 2010)	NSCLC (10) [AC (8), SCC (1), LCC (1)]	Zol/IL-2-expanded PBMC (i.v.) Every 2 weeks for 3-12 cycles	OR (0), SD (3 = 30%)
(Kobayashi et al., 2011)	RCC (11)	pAg-expanded PBMC (i.v.) + Zol (i.v.) + IL-2 Every 4 weeks for 1-6 cycles	OR [(1 = 9% (CR 1)], SD (5 = 45%)
(Lang et al., 2011)	RCC (11)	Zol (i.v.) + IL-2 (s.c.) Every 4 weeks for 1-10 cycles	OR (0), SD (2 = 22%)
(Nicol et al., 2011b) cohort A/B	Melanoma (7), Ovarian cancer (2), Colon/duodenal-cancer (4), Bone AC (1), Cholangiocarcinoma (1)	Zol/IL-2-expanded PBMC (i.v.) + Zol (i.v.) 6-8 cycles	OR (0), SD (3 = 20%)
(Nicol et al., 2011b) cohort C	Breast cancer (2), Cervical cancer (1)	Zol/IL-2-expanded PBMC (i.v.) + Zol (i.v.) + conventional therapy 7-8 cycles	OR [3 = 100% (CR 1, PR 2)]
(Sakamoto et al., 2011)	NSCLC (15) [AC (11), SCC (2), LCNEC (1), , LCC (1)]	Zol/IL-2-expanded PBMC (i.v.) 6 cycles	OR (0), SD (6 = 40%)
(Kunzmann et al., 2012)	RCC (7) Melanoma (6) AML (8)	Zol (i.v.) + IL-2 (s.c.) Every 4 weeks for 1-6 cycles	OR [(2 = 10% (PR 2)], SD (6 = 29%)
(Izumi et al., 2013)	CRC (6)	Zol/IL-2-expanded PBMC (i.v.) Every week for 8 cycles	OR (N.D.)
(Wilhelm et al., 2014)	T-NHL (1), AML (1), SPL (1), MM (1)	Conditioning chemotherapy + CD4/CD8-depleted half-matched PBMC (i.v.) + Zol (i.v.) + IL-2 (s.c.)	OR [3 = 75% (CR 3)]
(Wada et al., 2014)	Gastric cancer (7)	Zol/IL-2-expanded PBMC (i.p.) + Zol (i.v. and i.p.) Every week for 4 cycles	OR (N.D.) Reduction in tumor ascites
(Cui et al., 2015a)	Gastric cancer (30)	Chemotherapy + γδ T/NK/cytokine-induced killer therapy Up to 6 infusions every 3 weeks	Significant improvement in progression-free survival over chemotherapy alone
(Pressey et al., 2016)	Neuroblastoma (4)	Zol i.v. + IL-2 s.c. Every 4 weeks for 1-3 cycles	OR (0), SD (1 = 25%)
(Aoki et al., 2017)	Pancreatic adenocarcinoma (28)	Chemotherapy + Zol/IL-2-expanded PBMC Every 4 weeks for 6 cycles	No improvement over chemotherapy alone

γδ T cells used in cancer clinical studies, listing tumor time, treatment and clinical outcome

Abbreviations: Objective response (OR), partial remission (PR) and stable disease (SD) defined by criteria in each study. Acute myeloid leukemia (AML), adenocarcinoma (AC), Chronic lymphocytic leukemia (CLL), Follicle center lymphoma (FCL), hormone-refractory prostate cancer (HRPC), immunocytoma (IC), large-cell carcinoma (LCC), large cell neuroendcrine carcinoma (LCNEC), mantle zone lymphoma (MZL), multiple myeloma (MM), non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma (SCC), Secondary Plasma Cell Leukaemia (SPL), T-cell Non-Hodgkin lymphoma (T-NHL), zoledronate (Zol). ND, not determined; pAg, phosphoantigen; ip, intra-peritoneal; iv, intra-venous; sc, sub-cutaneous; TILs, tumor-infiltrating lymphocytes.

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