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Unconventional guardians of the brain: MAIT cells as emerging players in glioblastoma immunity

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Glioblastomas (GBM) are an aggressive form of brain cancer with no curative treatment options. While T cell therapies have demonstrated substantial success in combatting blood cancers, their application for solid tumours, including GBM, is hampered by the immunosuppressive tumour microenvironment and scarcity of tumour antigen-specific targets. There is an urgent need to better understand the immune response to GBM to enable the development of new therapeutic approaches. Recently, a resident population of mucosal-associated invariant T (MAIT) cells in the brain has been described, which may perform critical immune surveillance functions. Recent research also suggests that MAIT cells play diverse roles in anti-tumour immunity, and there is much interest in exploring the potential of MAIT cells in immune therapy by harnessing their cytotoxic capacity and tissue homing properties. However, findings on the role of MAIT cells in cancer are conflicting, while many basic questions regarding MAIT-tumour cell interactions remain. Here we review the challenges for GBM treatment, as well as the potential of unconventional T cells in cancer immunotherapy, with a focus on MAIT cells, their potential role in cancer, and their suitability as novel therapeutic targets in solid tumours such as GBM.

KEYWORDS

brain, GBM, glioblastoma, immune therapy, MAIT cells

Introduction: glioblastoma overview and challenges

Gliomas as a group account for over 80% of all malignant brain tumours and encompass both high-grade malignancies and low-grade tumours (1). Glioblastomas (GBMs) are classified by the World Health Organisation (WHO) as high grade (grade IV) gliomas. Recently, GBM nomenclature has been updated by the WHO to include molecular markers including isocitrate dehydrogenase (IDH) mutation status, categorising GBM tumours as IDH-wildtype or IDH-mutant (2). IDH mutations correlate with an improved chance survival of survival, however, a majority of GBM tumours are IDH-wildtype (3).

GBM is a relatively rare cancer, affecting approximately 7 individuals per 100,000 people in western populations (4, 5). However, GBM accounts for approximately half of malignant brain tumours, and exhibits disproportionately high mortality rates – the median survival time of 15 months from diagnosis (6), and a 5-year survival rate of 4.6%, which is markedly lower than other brain cancer types averaging 22.1% (5). Standard treatment for GBM, which typically combines surgical resection, radiotherapy and adjuvant chemotherapy (7), is

largely ineffective at preventing recurrence, which is generally considered inevitable within 12 months. Overall, there is a clear need for more effective treatment options for GBM to improve patient outcomes and prevent tumour recurrence.

Epidemiology and aetiology of GBM development

While no clear patterns of inherited susceptibility contribute substantially to GBM pathogenesis, several genetic risk factors have been identified. Oncogenic germline variants are estimated to be present in approximately 13% of individuals with GBM (8). Common mutations in GBM tumours include cyclin-dependent kinase inhibitor A2 (CDKN2A) and protein kinase B-Raf, which may be useful biomarkers to predict disease severity and treatment response (8, 9).

Regarding environmental contributions, ionising radiation is the only clearly established risk factor for GBM development, though the correlation is stronger in younger demographics (10). While some researchers report a correlation between mobile phone use and glioma development, a paucity of data prevents any robust conclusions being drawn (11, 12). Interestingly, a history of allergy, particularly respiratory allergies, correlates with a reduced risk of developing glioma, however no clear mechanism has been attributed to this correlation (13, 14).

Tumour pathogenesis

GBM pathophysiology is both complex and variable, with tumours able to arise in any lobe of the brain parenchyma. GBM is characterised by invasive growth into normal brain tissue, whereby tumour cells interact with the extracellular matrix (ECM) (15, 16) and adjacent cells to degrade the ECM, facilitating spread of the tumour and simultaneously damaging brain tissue (17). This invasive pattern of growth into vital brain structures typically makes complete surgical resection impossible thus contributing to an extremely high rate of tumour recurrence (18).

Most GBM tumours harbour genetic and epigenetic alterations that disrupt cell-cycle control, drive over-expression of growth factors and promote rapid proliferation, angiogenesis, migration and invasion of surrounding tissue (19, 20). Mutations to the p53 gene (19, 21) are the most common in oncogenesis of GBM, with the gene being responsible for regulating normal cell proliferation (22). Loss of cell cycle control in GBM occurs due to loss of normal p53 function, as well as through disruption to the p16^{INK4a} pathway, both of which contribute to major cell proliferation checkpoints at which a cell commits to division (23–25). Alterations to the epidermal growth factor receptor (EGFR), and downstream signalling molecules phosphatidylinositol-3-OH kinase (PIK3) the negative regulator phosphatase and tensin homologue (PTEN), which are important for controlling cell proliferation and apoptosis, are frequent in GBM (23, 25). The potential to utilise these mutations as therapeutic targets in GBM has been reviewed elsewhere (26). It should be noted that after initial loss of cell cycle control, rapidly

proliferating cells exhibit a high level of genetic, molecular and metabolic heterogeneity, making tumour cells a difficult target for local immune surveillance due to inherent variability (21, 27). Indeed, the degree of hypermutation is such that recurrent GBM tumours are often genetically unrecognisable from the initial tumour (28).

The formation and development of tumour tissue is highly dependent on the secretion of IL-6, which is derived from various sources but most notably from the tumour cells themselves (29) and tumour-associated macrophages (TAMs) (30). A vital step for tumour progression is the ‘angiogenic switch’, at which point tumour vasculature is established by gaining access to the normal tissue blood supply via disruption of blood vessel membranes and generation of intra-tumoral blood vessels (17, 31). Compared to most other solid tumours, GBM tumours are highly vascularised, which may allow for increased invasive growth (17, 32). Vascularisation is further driven by hypoxic conditions, which activate the hypoxia-induced factor 1 (HIF1)-vascular endothelial growth factor (VEGF) pathway, promoting endothelial cell proliferation and migration, thereby facilitating neovascularisation (27, 32). Tumour cells also undergo metabolic reprogramming to utilise aerobic glycolysis, characterised by rapid uptake of surrounding metabolites, in response to the hypoxic and a nutrient-poor tumour microenvironment (TME). This is triggered by HIF1a activation and NF-κB signalling, and subsequent upregulation of glucose transporter GLUT1 (33). In addition to hypoxia, this further destabilises surrounding healthy tissue due to poor nutrient availability (27). Ongoing hypoxia and necrosis in the tumour core result in damage to healthy brain tissue, leading to the accumulation of necrotic tissue mass and cell debris, as well as thrombosis in the tumour vasculature (27).

Immune suppression in the GBM TME

A weak immune response to GBM is a major driver of poor clinical outcomes. Several factors allow GBM tumours to resist anti-tumour immunity, including restricted immune cell infiltration due to the blood brain barrier (BBB), a high level of tumour heterogeneity, and the immunosuppressive GBM TME (34, 35). GBM tumours are known as immunologically ‘cold’ tumours characterised by infiltration of immunosuppressive macrophages and myeloid cells, with poor lymphocyte infiltration (15, 36).

Under homeostatic conditions, the BBB prevents the transport of most molecules from the vasculature into the brain parenchyma (36–38). It is maintained by astrocytes, which cover the vasculature in the brain and maintain tight endothelial junctions to prevent unwanted transfer across the membrane (37). While the barrier can be partially disrupted in disease settings, including GBM (37), the BBB reduces the infiltration of tumour-targeted immune cells, effectively providing protection for tumour cells from immune detection (36, 38). Delivery of therapeutics across the BBB is also challenging, requiring specific barrier permeability enhancers that allow drug delivery without causing long-term damage (18, 39).

While small populations of tissue-resident T cells have been defined in the brain (40–42), generation of tumour-specific responses is hampered by the high level of tumour heterogeneity

reducing the potential of tumour clearance in response to any single GBM antigen (21, 27, 43, 44). Additionally, tumour-infiltrating lymphocytes (TILs) can become exhausted or anergic in GBM and fail to respond to the tumour (43, 45). T cells isolated from individuals with GBM are poor producers of the T cell survival cytokine IL-2, and exhibit an exhausted phenotype characterised by expression of programmed cell death 1 (PD-1), T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), T cell immunoreceptor with Immunoglobulin and ITIM domains (TIGIT), and Lymphocyte-activation gene 3 (LAG-3) (46), indicating severe and possibly irreversible exhaustion (47). While recent approaches to treating tumours aim to target and reverse exhaustion in cytotoxic T cells, the upregulation of multiple checkpoints, as well as the terminal exhaustion phenotype, has impeded their success in GBM (34, 43, 47), thus necessitating alternative approaches.

T cell activation within the tumour is also impeded by tumour-derived signals suppressing activation of dendritic cells, thereby impairing tumour antigen presentation (48). These immunosuppressive signals include cell surface inhibitory proteins cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-L1, which are expressed on GBM tumour cells and directly impair both dendritic cell and T cell activation (34, 44). Additionally, unusually high proportions of tolerance-inducing T_{reg} cells have been reported in GBM, reaching over a quarter of TILs in some cases (46, 49).

Myeloid cells including monocytes, macrophages and microglia are the most abundant population of tumour-infiltrating immune cells in GBM and contribute to the immunosuppressive TME in several ways (43). Myeloid-derived suppressor cells (MDSCs) are a phenotypically distinct population of neutrophils and monocytes, which exert potent immunosuppressive signals (50), and are associated with more advanced tumours and poor clinical outcomes in GBM (51). TAMs also represent a major subset of infiltrating immune cells, which lack of expression of co-stimulatory markers CD40 and CD86, required for initiation of T cell responses (43). In GBM, TAMs are clinically important as they are associated with poorer overall survival outcomes (52).

In addition to an immunosuppressive TME, systemic treatment-induced immunosuppression is common in individuals with GBM. Dexamethasone, a corticosteroid commonly used to attenuate the side effects of radiation therapy, has been strongly associated with systemic adverse effects and decreased overall survival in GBM (53, 54), likely due to the immunosuppressive properties of corticosteroids (55). There is also increasing evidence that corticosteroid use may interfere with current immunotherapies including checkpoint inhibition (53–55). Temozolomide, the most commonly used chemotherapy drug for GBM, is a powerful inhibitor of lymphocyte expansion, and systemic temozolomide may decrease efficacy of anti-PD-1 treatment as it resulted in severe depletion of TILs in a pre-clinical GBM model (56). Moreover, dosage and timing of each individual therapeutic will be critical to the successful implementation of combination immunotherapy treatments as they progress into the clinic.

Immunotherapies for GBM

The standard treatment protocol for GBM, named the ‘Stupp protocol’, involves maximal safe surgical resection (57) followed by radiotherapy and concurrent treatment with adjuvant chemotherapy, most commonly temozolomide (58–60). However, even in combining radiotherapy and chemotherapy after surgical resection there is only a modest increase in the 5-year survival rate to 11% (58, 59). Almost all individuals on this combination therapy experience recurrent tumour growth within 6–7 months (61). Bevacizumab, a monoclonal therapy targeting VEGF-A has been shown to extend progression-free survival, but not overall survival, and is approved as a second-line treatment for recurrent GBM (62–64). A recent trial demonstrated improved progression-free and overall survival for individuals receiving temozolomide in combination with Bevacizumab in individuals with high cyclooxygenase-2 (COX-2) expression (65). Given the overall poor prognosis, many treatments for individuals with GBM are instead focussed on symptomatic relief to promote quality of life, as disease progression can include serious comorbidities (66–69).

Advances in understanding of both cancer biology and cancer immunobiology have led to the development of several new immune-based therapeutic approaches for cancers, over the last decade. The most notable immunotherapy approaches gaining traction are monoclonal antibodies and more recently, cell-based therapies including chimeric antigen receptor T (CAR-T) cells (Table 1). However, the prohibitive immunological landscape and potential interactions with existing treatments have significantly hampered efficacy of these immunotherapies in GBM.

Chimeric antigen receptor T cells

Autologous chimeric antigen receptor T (CAR-T) cell therapies utilise an individual’s own T cells, which are engineered *ex vivo* to express a receptor complex (CAR) targeted towards a marker expressed by the tumour cells, then re-infused into the patient (70). Multiple generations of CAR have been developed with more recent generation CARs including co-stimulatory molecules such as CD28 and 4-1BB (CD137) to enhance the T cell response (reviewed in (71)). To date, most CAR-T cell therapies have been developed for, and shown efficacy in, haematological cancers. Several CAR-T cell treatments have now been FDA-approved – for example Axicabtagene (Yescarta; Kite Pharma) (72), and Tisagenlecleucel (Kymriah; Novartis) (73), targeting CD19, the first of several such treatments to be made available in 2017 and 2018, respectively. CAR-T therapy does, however, present several limitations. Serious adverse events such as cytokine release syndrome and CAR-T cell related encephalopathy syndrome have hampered the success of some therapeutics in the clinic, particularly those that utilise CD28 or 4-1BB as a co-stimulatory factor. While these conditions often resolve without intervention, in some cases they have had severe clinical manifestations and can lead to death, highlighting the critical need to monitor toxicity (71).

TABLE 1 Active or recruiting trials of GBM immunotherapies as of May 2026.

ClinicalTrials.gov ID	Phase	Therapeutic
Antibody therapies		
NCT05432518	Early phase I	Afatinib, Dasatinib, Palbociclib or Oloparib
NCT06917885	Phase I	HLA-peptide and IL-2 fusion protein
NCT06258018	Phase I/II	Niraparib
NCT06630260	Phase I/II	Avutometinib + Defactinib
NCT05734560	Phase I/II	D2C7-immunotoxin (anti-EGFR) <i>plus</i> 2141-V11 (anti-CD40)
NCT06336291	Phase II	L19-TNF (anti-fibronectin-TNF fusion protein)
NCT06816927	Phase II	Nivolumab + Relatimab
NCT04559230	Phase II	Sacituzumab
NCT03970447	Master protocol adaptive phase II/III platform trial	Regorafenib or Paxalisib
NCT05235737	Phase IV	Neoadjuvant Pembrolizumab
Cell-based therapies		
NCT07343986	Phase I	Autologous anti-EGFR anti-tumour CAR T cells
NCT05353530	Phase I	Autologous IL-8 receptor modified CD70-specific CAR T cells
NCT04003649	Phase I	Autologous IL13R α 2-specific, 4-1BB co-stimulatory, CD19 truncated expressing CAR T cells
NCT04165941	Phase I	Autologous genetically modified chemotherapy resistant $\gamma\delta$ T cells
NCT04991870	Phase I	Allogenic genetically modified TGF β R2- NR3C1-natural killer cells
Vaccination based therapies		
NCT04573140	Phase I	Autologous total tumour mRNA lipid nanoparticle vaccine
NCT06805305	Phase II	Tumour antigen pulsed dendritic cells + pegylated IFN

Efficacy of CAR-T cell therapy in solid tumours is vastly reduced due to poor tumour infiltration, tumour heterogeneity, and immunosuppressive signals in the TME (74). Currently, there are four active trials evaluating CAR-T cells in GBM (Table 1) (75). Attempts to develop GBM-specific CAR-T cells have generated a treatment targeted towards epidermal growth factor receptor (EGFR) variant 3 (EGFRvIII) (76), a GBM-evaluation is ongoing (NCT07343986). Recently, Choi et al. treated three individuals with GBM using EGFRvIII-targeted CARs, observing tumour regression following intraventricular infusion of the CAR-T cells (77). However, in this trial the durability of the treatment was only sustained for greater than 150 days in one of the three enrolled individuals (77). Other approaches have targeted CARs to IL-13R α 2, a high-affinity IL-13 receptor. Brown et al. demonstrated that IL-13R α 2 CARs displayed transient anti-tumour activity (78), but ultimately patient outcomes did not improve, likely due to downregulation of the target receptor (79).

Lastly, targeting human epidermal growth factor receptor 2 (HER2), which is expressed by ~80% of GBMs (80) with CAR-T cells has shown promise *in vitro* (81), and while HER2 is also expressed in healthy tissue (82) a phase I clinical trial using HER2-engineered virus-specific T cells was well tolerated and showed clinical benefits in some patients (83). CAR-NK cells may have some advantages over CAR-T cells, offering the potential for “off-

the-shelf” therapies (reviewed in (84)). For example, CAR-NK cells targeting HER2 (NK-92/5.28.z, derived from the NK-92 cell line), in combination with immune checkpoint blockade, have shown some promise in orthotopic mouse models of GBM, and are currently in Phase I trials (85). Overall, while initial results indicate CAR-T and CAR-NK cell therapies could be a promising avenue for new GBM therapeutics, further research is required.

Immune checkpoint blockade

Exhausted T cells in individuals with cancer display increased expression of immune checkpoint markers – inhibitory regulators of activation – such as PD-1, CTLA-4 and TIM-3. Targeting these markers with monoclonal antibody therapies (immune checkpoint blockade) has proven effective in restoring T cell function in a range of cancers, reducing tumour burden and improving clinical outcomes. A range of FDA-approved checkpoint blockade therapies are in use including Ipilimumab and Tremelimumab targeting CTLA-4, and Nivolumab, Pembrolizumab and Cemiplimab targeting PD-1, for the treatment of melanoma, lymphoma and a range of other cancers (86). Further research is ongoing for other checkpoints, including TIM-3, VISTA and TIGIT (86). Combined therapies targeting more than one immune checkpoint have synergistic effects, for example, combination therapy of ipilimumab and

nivolumab synergistically increased their efficacy in individuals with advanced melanoma (87).

Checkpoint blockade therapies have several limitations. The first is that some patients do not respond to treatment, most likely due to either an absence of antigen expression, genetic mutation to evade T cell responses, or an overwhelming immunosuppressive signal in the TME (88). Second is that adverse effects are common and discourage individuals from maintaining their treatment (89). While toxicity usually resolves, up to 10% of cases require medical intervention (89). Investigation into these mechanisms of therapeutic failure and adverse events, and the design of strategies to overcome these issues will be essential to improving treatment outcomes.

Clinical trials to date have assessed the efficacy of both intravenous and local delivery of immune checkpoint therapies as an addition to standard treatment in GBM. The anti-PD-1 monoclonal antibody Pembrolizumab has shown improvement in specific and systemic anti-tumour immune responses, evidenced by increased migration and infiltration of TILs, but when administered alone these did not translate to improved clinical outcomes (90, 91). A peptide inhibitor of CD200, another checkpoint implicated in GBM, showed some effect of overcoming immune tolerance induced by CD200 expression on tumour cells (92). A phase I trial assessing combined intracerebral delivery of combined α PD-1 and α CTLA-4 therapy showed good tolerance and promising clinical outcomes, although direct comparison of this approach with single-target therapies or standard treatment was not performed (93). Recently, neoadjuvant immune checkpoint inhibitor therapy, with administration of nivolumab (α PD-1), ipilimumab (α CTLA-4) and relatlimab (α LAG3) checkpoint inhibitors as a first line procedure prior to resection has shown promising results for one patient (94) and is currently in clinical trials for newly diagnosed GBM (Table 1). Collectively, new immunotherapy approaches still face significant challenges in GBM but present a promising approach to improve clinical outcomes for individuals with GBM.

Unconventional T cells; a new promise for cancer immunotherapies

Unconventional T cells comprise several subsets including invariant natural killer T (iNKT) cells, $\gamma\delta$ T cells, and mucosal-associated invariant T (MAIT) cells. These ‘innate-like’ T cells exhibit both innate and adaptive immune features that offer potential advantages to overcome the limitations of conventional T cell-based therapies. They have limited repertoires of T cell receptors (TCRs), which are restricted to antigen presenting molecules that, unlike the Major Histocompatibility Complex (MHC) Class I and II molecules, have limited polymorphism, thus reducing the likelihood of off-target reactivity. The rapid activation and effector functions of these cells are reminiscent of innate immune cells, as they can perform both cell signalling functions via cytokine release, and directly target antigen presenting cells with cytotoxic molecules (95). Thus, unconventional T cells are of interest for the

development of both autologous and allogenic ‘off-the shelf’ therapies (96).

Invariant NKT (iNKT) cells use a semi-invariant $\alpha\beta$ TCR comprising V α 14 joined to J α 18 TCR α chain, paired with a limited range of TCR β chains in mice, and V α 24-J α 18 TCR α chain paired with a V $\alpha\beta$ 11 TCR β chain in humans. These TCRs allow recognition of lipid antigens produced by microbes, presented by the MHC class I-like molecule CD1d (97). iNKT cells display innate-like functions, rapidly producing a high level of cytotoxic molecules, including perforin and granzymes, upon antigen recognition. They are also capable of performing functions similar to T helper cell subsets; NKT1 cells have been shown to perform similar immune responses as Th1 cells, with other subsets releasing cytokines to recruit other immune cells including IL-17A (NKT17 cells), as well as anti-inflammatory IL-4 and IL-10 (NKT2) (98).

Invariant NKT cells are of interest in cancer immunotherapy due to their restricted antigen recognition and short *in vivo* lifespan, which together limit their potential for off-target toxicity. Development of iNKT-based immunotherapies has been conducted with mixed success. These therapies have shown great success in treating blood cancers, with a CD19 targeting allogenic CAR NKT cell therapy, showing up to a 43% complete response rate in trials of individuals with relapsed or refractory lymphoma (NCT03774654). In contrast, NKT cell therapies have shown only modest success in the treatment of solid cancers. A CAR-NKT cell therapy developed by Xu et al. in 2019 (99), showed limited success in phase I clinical trials, with injection of autologous NKT cells targeted to GD2 ganglioside – a molecule composed of glycosphingolipids linked with sialic acid chains, which is expressed by neuroblastoma cells – reducing metastatic bone lesions in 25% of neuroblastoma patients, and achieving complete response in 1 of 12 participants (100). In pre-clinical mouse models of orthotopic GBM, intra-tumoral injection of human stem-cell derived iNKT cells increased survival and decreased tumour volume (101). Similarly, CAR-NKT cells directed against EGFRvIII showed increased survival and decreased tumour volume in mice receiving human xenograft (102). Therefore, NKT cells present as a promising avenue for the development and refinement of both autologous and off-the-shelf allogenic therapeutic strategies, especially in seeking to treat cancers with unmet clinical need.

Gamma delta T cells constitute up to 5% of circulating T cells in humans (103). They use a limited number of TCR γ and δ chains, and exhibit reactivity to phosphoantigens (103). Populations of $\gamma\delta$ T cells have been identified in barrier tissues, where their potent cytotoxic response and production of interferon (IFN)- γ confers protection against infection (104). $\gamma\delta$ T cells have also generated interest in cancer research, due to their independence from MHC, their ability to recognise and lyse tumour cell lines in a TCR-dependent manner *in vitro* and demonstrated capacity to negatively regulate growth of tumours (105–107). A recent study characterised $\gamma\delta$ T cells in GBM samples from 40 individuals, finding that $\gamma\delta$ T cells could recognise and lyse autologous tumour tissue, while highlighting heterogeneity in the potency of responses between individuals (108). However, some studies have shown that a subset of IL-17 producing cells $\gamma\delta$ T cells may promote tumour growth,

creating ambiguity as to whether their role is protective or pathogenic (105, 109). While very few $\gamma\delta$ T cell products have reached clinical trials, the development and potential of $\gamma\delta$ CAR T cells as a therapeutic avenue for cancer treatments remains of interest and has been recently reviewed (110, 111).

Mucosal-associated invariant T cells

The MHC class I-related protein (MR1) antigen presenting molecule has limited polymorphism, is highly conserved throughout evolution, and can be expressed by all nucleated cell types (112, 113). The best described and most abundant subset of MR1-reactive T (MR1T) cells in humans are MAIT cells, an innate-like subset of unconventional T cells, which use a semi-invariant TCR α chain comprised of the TCR α gene segment TRAV1-2 (also referred to as V α 7.2) joined to TRAJ33, TRAJ12 or TRAJ20, paired with a limited number of TCR β chains (114). MAIT cells recognise metabolite antigens presented by MR1. The most potent MAIT antigens derive from the vitamin B2 synthesis pathway, which is essential for the metabolism of many bacteria and fungi. 5-(2-oxopropylideneamino)-6-D-ribitylamouracil (5-OP-RU), the most potent known MAIT antigen, is formed by condensation of the riboflavin biosynthesis precursor 5-amino-6-D-ribitylamouracil (5-A-RU) with the ubiquitous small metabolite methylglyoxal (115, 116).

In addition to 5-OP-RU, MR1 is known to accommodate molecularly diverse compounds including folates (6-formyl pterin; 6-FP, acetyl-6-FP) (116), drugs and drug derivatives (e.g., diclofenac, and aspirin analogue 3-formylsalicylic acid) (117), sulphated bile acids (118), and vitamin B6 form pyridoxal (119), which are either antigens and non-agonistic/inhibitory compounds. While limited, the diversity in both TCR α and β chains used by MAIT cells can impact MR1-Ag recognition (120–122). Recent studies have also identified much smaller subsets of non-MAIT “MR1-reactive T cells (MR1T cells)” in human blood, that exhibit a more diverse TCR repertoire, and potentially heterogeneous effector functions (123). Some MR1T cells phenotypically resemble MAIT cells with high expression of CD161, IL-18R and promyelocytic leukaemia zinc finger (PLZF) (124, 125), and some TRAV1-2⁺ cells are not reactive to MR1-5-OP-RU tetramers but bind to 6-FP, microbial antigens, or are MR1 autoreactive T cells (123). Lastly, there are small numbers of TRAV1-2⁺ T cells that bind MR1-5-OP-RU tetramers, albeit with varying degrees of affinity (124). Notably, residual populations of MR1-5-OP-RU reactive cells also exist in *Traj33*^{−/−} mice, and like canonical TRAJ33⁺ MAIT cells (126), were shown to expand in response to bacterial infection (125). Recently, MR1T cells have been identified that appear to recognise endogenous or altered-self antigens and thus may be relevant to tumour cell immune recognition (127–129). MR1T cell clone MC.7.G5 by Crowther et al. was initially reported to recognise cancer cells via an unknown antigen and exert cytotoxic effector functions against a broad range of cancer cells, but not healthy cells, in an MR1-dependent manner (130). However, the specificity of this clone for tumour cells was challenged in subsequent studies (131). While

their study is difficult given their low abundance in humans, identification of antigens is just emerging, and specific tools to allow accurate study of this population are yet to be developed, there is much interest in the potential recognition of tumour cells by non-MAIT MR1T cells.

The strong tissue-homing characteristics of MAIT cells may provide benefits for solid or non-circulating tumour applications, while the greater abundance of MAIT cells compared to iNKT could offer further advantages in terms of isolation and scale-up for clinical development. The anti-tumour properties of MAIT cells have generated strong interest despite a limited body of work to confirm their role in cytotoxicity of tumour cells, reviewed previously (95, 132). While currently there are few MAIT-targeted immunotherapies in development, MAIT cells represent a physiologically important and highly promising candidate for further development in this area.

MAIT cells in infections and non-infectious pathologies

MAIT cells undergo TCR-mediated activation following recognition of MR1 bound metabolite antigens, with activation also dependent on co-stimulatory signals (126, 133, 134) and cytokines (134, 135). TCR-activated human MAIT cells rapidly secrete cytokines such as IFN- γ and tumour necrosis factor (TNF) (133, 136) and can lyse cells infected with bacteria (137, 138). MAIT cells play an important role in defence against bacterial infection as most clearly demonstrated in mouse models (reviewed elsewhere (139)). Conversely, they can drive pathology in chronic *Helicobacter pylori* infection (140) and in chronic sinus inflammation (141).

MAIT cells are also implicated in control of viral infections, including influenza (142, 143) and COVID-19 (144, 145). While viruses cannot produce riboflavin-based antigens, MAIT cells appear to be activated during viral infections in a TCR-independent manner by cytokines (143, 146) with their response slower and more limited than TCR-mediated activation (147). In patients with severe viral infections MAIT cells are reduced in number and functionally impaired (143, 146, 148, 149), and restoring their function may be of therapeutic interest (148).

A growing body of evidence implicates MAIT cells in immune-mediated pathologies including inflammatory bowel diseases, autoimmune diseases, and asthma and allergies (reviewed in (150)). MAIT cells also possess tissue repair functions (151, 152) and can accelerate wound healing in mice (153, 154). Furthermore, a role in maintenance of barrier homeostasis is now considered an important MAIT cell function (155), including an intriguing association with maintenance of meningeal barrier integrity (156).

Mucosal-associated invariant T cell distribution and phenotype in humans and mice

MR1-5-OP-RU tetramers (115, 122) are now the gold standard reagents to specifically identify and isolate MAIT cells and have greatly improved accuracy of MAIT cell studies. Prior to their development, studies relied on surrogate markers such as CD3,

TRAV1–2 and CD161, which are also expressed by other T cells and, in the case of CD161, not expressed at all stages of MAIT cell development (114, 122), and do not match MR1-tetramer reactivity, particularly in tissues (157). Notably, no surrogate markers for MAIT cells exist in mice. TCR transgenic, *Mr1*^{−/−} and *Traj33*^{−/−} mouse lines have been developed (125, 158, 159). These, along with methods for sterile antigen-dependent expansion of MAIT cells *in vivo* (126, 135, 160, 161), and classical tools such as adoptive transfer of MAIT cells, have allowed the assessment of MAIT cells in various infection and disease contexts.

While MAIT cells comprise on average 3–5% of total circulating $\alpha\beta$ T cells in human blood (162), they are also found in both mucosal and non-mucosal sites including the lung, intestines, stomach, oral mucosa, genital tract, skin, thymus, liver, kidneys, lymphoid tissue, and central nervous system (114, 163). While circulating MAIT cell frequencies peak in early adulthood and decline with age (162), populations of tissue-resident MAIT cells remain relatively stable over the lifespan of individuals (164).

Most studies of human MAIT cells in disease have analysed circulating MAIT cells, but they also exhibit tissue-specific phenotypes (Figure 1). For example, MAIT cells residing in the liver are predominately CD8⁺, express the NK cell marker CD56 and display effector responses with a high level of polyfunctionality (164–167). In other tissues, such as the intestines (164), more potent anti-inflammatory and anti-microbial activity is observed, while a phenotypic bias towards IL-17 and IL-22 production is seen in MAIT cells residing in the cervix and endometrial tissue (168).

MAIT cells in laboratory mice are rarer than in humans but are nonetheless found at similar tissues site (139, 169). Both C57BL/6

and BALB/c mouse strains maintain populations of MAIT cells in the thymus, lymph nodes, liver and lungs; with notably higher MAIT cell frequencies in C57BL/6 mice (169). In most cases, frequencies are lower than the corresponding human tissue, for example in the lungs (126, 161, 170), liver (171, 172), and circulation (169). However, some tissues have higher frequencies in mice, for example in the skin, where MAIT cells comprise up to 40% of T cells compared to 2% in humans (154).

MAIT cells in the brain

The first observation hinting at the presence of MAIT cells in the brain was in 2008, when Peterfalvi and colleagues reported V α 7.2 transcripts in biopsies of brain tumours (173). Subsequent studies have identified MAIT cells in the mouse brain and meninges (42, 156, 174), and showed that astrocytes and microglia can present antigen via MR1 to induce TCR-dependent MAIT cell activation (174). These findings collectively indicate a potential for MAIT cell activation and function within the brain, potentially reducing the limitations to immune therapy imposed by the BBB. Zhang et al. demonstrated that meningeal MAIT cells express antioxidant molecules and play a role in the homeostatic maintenance of meningeal barrier integrity, which was found to be greatly reduced in the MAIT-deficient *Mr1*^{−/−} mouse strain (156). Interestingly, adoptive transfer of MAIT cells into *Mr1*^{−/−} mice restored homeostatic and anti-inflammatory functions (156), suggesting that MAIT contributions to maintaining barrier function may be independent of MR1. In contrast, in a Vietnamese cohort, an *MR1* intronic polymorphism affecting expression was strongly associated with the

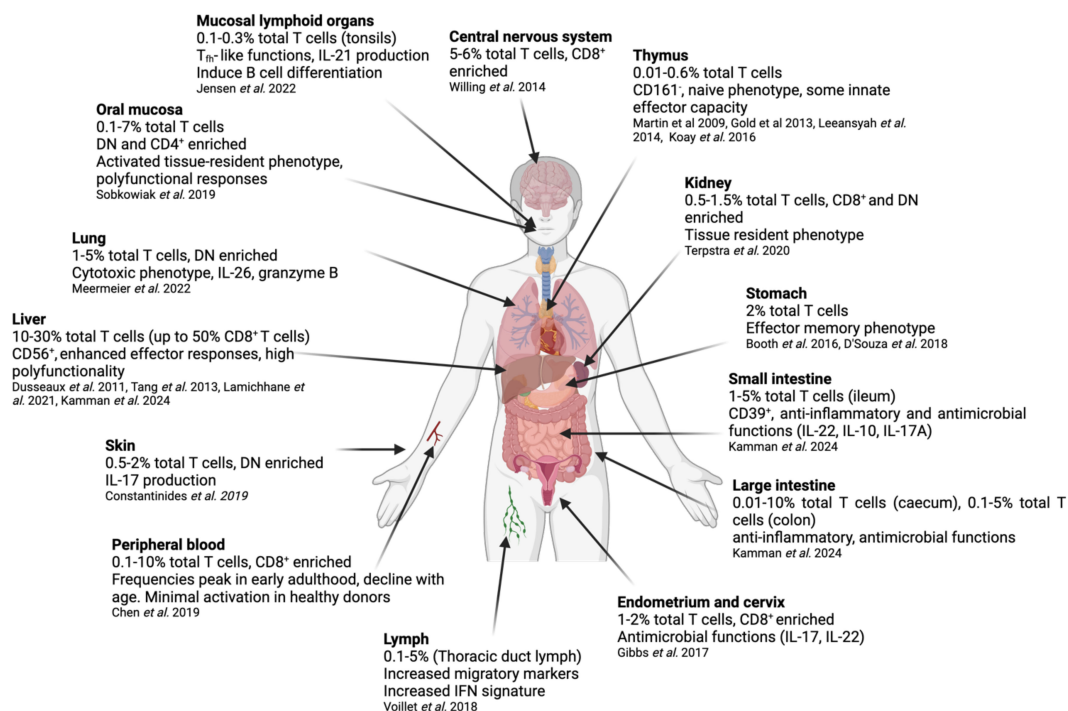


FIGURE 1

Distribution and phenotype of MAIT cells in humans. Frequencies and phenotypic traits of MAIT cells in healthy human tissues, as reported in the cited studies. Studies have defined MAIT cells as V α 7.2⁺ CD161^{hi} T cells or as MR1-5-OP-RU tetramer reactive T cells. Figure created with BioRender (235).

development of meningeal tuberculosis (175). Thus, the role of MR1 in driving MAIT cell immunity in the brain may be context dependent.

Despite the identification of MAIT cells in brain tissue, few studies have investigated MAIT cells in the context of diseases affecting the brain and central nervous system. In individuals with multiple sclerosis (MS), MAIT cells decrease in the circulation but are detected in the cerebrospinal fluid and white matter lesions (176–180), suggesting their migration towards MS lesions. Circulating MAIT cells in individuals with MS exhibit a pro-inflammatory profile including production of IFN- γ and IL-17 (177, 178). Importantly, MS lesions were found to over-express MR1 and displayed elevated IL-18 and IL-23, congruent with a pro-inflammatory environment capable of eliciting TCR-dependent MAIT cell activation (179). Elevated expression of *MR1* was reported in the brain of people with Alzheimer's disease (AD), and the accumulation of amyloid-beta plaques was reduced in the absence of MR1 in a the 5XFAD mouse model (181), suggesting a possible role for MAIT cells in AD. Circulating MAIT cells displayed an activated and exhausted phenotype with reduced IFN- γ producing capacity in people with Parkinson's disease (182). Mouse models of ischaemic stroke indicated a reduction in infarct volume and improved recovery from neurological impairment in *Mr1*^{-/-} mice or mice treated with the MR1 ligand 6-FP, which competitively inhibits MAIT cell activation, hinting that neurological damage may be exacerbated by activated MAIT cells (183). Finally, high expression of *MR1* has been reported in both high- and low-grade gliomas and is associated with poor clinical outcomes (42, 184). Intriguingly, activated MAIT cells appear to be protective in glioma, but the role of MR1-mediated MAIT cell activation in this setting is unclear (42). Collectively, these studies suggest that MAIT cells may be important for maintaining homeostatic functions in a healthy brain, while activated and inflammatory MAIT cells can contribute to either immune protection or drive pathology in disease states.

MAIT cells in cancer

Over the past decade, MAIT cells have been examined in several cancer types, with most studies focussed on mucosal cancers (185–189). However, current research has not reached consensus as to whether MAIT cells potentiate protective or pathogenic effector functions in tumour development, the factors that drive these divergent roles and how they may be harnessed for therapeutic benefit.

Observations from human studies

Studies of mucosal cancers of the colon mostly demonstrate a decrease in the frequency of circulating MAIT cells in people with cancer compared to healthy participants (185–187), with MAIT cells exhibiting an increase in expression of migratory markers and a higher overall abundance compared to adjacent healthy tissue (186, 188, 189). However, this trend is not recapitulated across all

cancer types. For example, patients with hepatocellular carcinoma were found to have both reduced circulating MAIT cells compared to healthy donors, and a lower percentage of MAIT cells in tumour tissue than healthy livers (187).

In several studies, an increase in intra-tumoral MAIT cell abundance was found to correlate with poor patient prognosis (187, 189–191). Large-scale transcriptomic analysis of a range of cancers by Yao et al. revealed either no correlation or a negative correlation between MAIT numbers and clinical outcome in a range of cancer types (192). In contrast, a higher frequency of MAIT cells has been found to correlate with improved clinical outcomes in several cancers, particularly blood cancers (193–195). In some cases, MAIT cells have been observed at higher frequencies in the early stages of tumour development but decline as the tumour progresses (196–198).

Circulating MAIT cells isolated from people with a range of cancers are functionally exhausted (Table 2), having impaired production of IFN- γ and TNF, and increased expression of exhaustion marker CD39 (199) alongside immune checkpoint molecules PD-1, CTLA-4 and TIM-3 (185, 187). These findings indicate susceptibility of MAIT cells to immunosuppressive signals in the TME, which prevent anti-tumour functions, and which may contribute to the correlations with poor prognosis in some cancers (191, 200, 201). *In lieu* of functional T_H1-like responses, MAIT cells have been reported to instead demonstrate T_H17-like or immunoregulatory roles in cancer. Indeed, populations of CD4⁺ FoxP3⁺ MAIT cells have been described in samples collected from patients with colorectal cancer and hepatocellular carcinoma, and these cells have further been shown to suppress anti-tumour functions of CD8⁺ T cells, and thus drive tumour progression (188, 199). MAIT cells can produce IL-17 to as an effector response, but whether IL-17 plays protective or pathogenic role in tumorigenesis remains unclear. The extent of IL-17 production is variable across cancer types, with some studies observing increased IL-17 production (185, 196, 200), and others showing decreased IL-17 production (188, 195, 202). Findings by Ling et al. suggest that elevated IL-17 contributes to MR1-driven tumour suppression in colorectal cancer (185), but others indicate that skewing towards an IL-17 dominant response contributes to tumorigenesis (200). Overall, these studies suggest nuanced roles for MAIT cells between different tumour types, likely driven by signals specific to the tissue of origin and TME.

Importantly, MAIT cells have been implicated in driving responses to several immune modulating treatments. Indeed, the abundance and activation state of MAIT cells has been correlated with responsiveness to anti PD-1 therapy in the context of both blood cancers and solid tumours (190, 193, 194, 200, 201, 203, 204). MAIT cell frequency has been proposed as a potential biomarker to predict responsiveness to anti-PD-1 therapy in melanoma patients (193, 203). Characterisation of functional subsets suggest that T_H1-like functions, rather than T_H17-like functions in tumour-infiltrating MAIT cells drive this correlation (201), and assessment of the effect of α PD-1 combined with MR1 ligands (for example, 5-A-RU plus methylglyoxal) demonstrate enhanced anti-tumour cytotoxicity by MAIT cells *in vitro*, although it's important to note that this was demonstrated with circulating MAIT cells

TABLE 2 Analysis of MAIT cells in clinical samples from people with cancer.

Cancer type	MAIT cell source	MAIT populations	MAIT cell activation	Association with clinical outcomes	Other observations	References
Acute Myeloid Leukaemia	Blood and bone marrow	Circulating MAITs ↓	Immune checkpoints ↑ IL-17 ↑ IFN-γ and TNF ↓	Higher MAIT frequency correlated with improved prognosis	MAIT frequency ↓ during chemotherapy, recovered post-treatment.	(194, 228)
Breast cancer	Tumour samples	Tumour-infiltrating MAITs detected	IL-17 ↑	Unknown	MR1-dependent activation in response to tumour cells.	(229)
Cervical cancer	Blood samples	Circulating MAITs ↓		Fewer circulating MAIT cells correlated with disease progression.		(198)
Colorectal cancer	Blood and tumour tissue	Circulating MAIT cells reported as ↑ or ↓ Tumour-infiltrating MAIT cells detected. MAIT proliferation ↑ Migratory markers↑	Type I responses ↓ or maintained. IL-17 ↓ Exhaustion ↑ Activation enhanced by bacterial infiltration into tumours. Subset of CD4 ⁺ FoxP3 ⁺ MAIT cells detected	MAIT cells induced tumour cell cycle arrest. Higher MAIT frequency associated with poor prognosis.	Cell cycle arrest abrogated by anti-MR1. Effector function can be restored by anti-PD-1.	(185, 186, 189, 190, 199, 230, 231)
Hepatocellular carcinoma	Blood and liver tissue	Circulating and liver resident MAIT cells ↓ Migratory marker CXCR3 ⁺ ↑	Activation ↓ Exhaustion ↑ Immunoregulatory functions	Increased MAITs associated with poor prognosis.		(187, 191, 232)
Melanoma	Blood and tumour tissue	Circulating MAITs ↓ Tumour-infiltrating MAIT cells detected.	Activation ↓ PD-1 ↑	Higher MAIT cell frequencies correlated with successful anti-PD-1 treatment and improved survival outcomes.	Circulating MAIT populations restored by anti-PD-1.	(193, 203)
Metastatic colorectal cancer (Hepatic)	Peripheral blood, healthy liver and tumour tissue	Tumour infiltrating MAITs ↓ compared to healthy liver	IFN-γ ↓ Effector response to MR1-dependent stimuli ↓ No change with chemotherapy.			(233)
Multiple myeloma	Blood and bone marrow samples	Circulating MAITs ↓	Impaired MAIT functionality. PD-1 ↑		Function restored with anti-PD-1 treatment	(204, 207)
Non-small cell lung cancer	Blood and tumour tissue	Circulating MAIT cells unchanged or ↓, Tumour-infiltrating MAIT cells detected Migratory markers ↑ CXCR6 ⁺ MAIT cells identified	Exhaustion markers ↑ IL-17 ↑	CD8 ⁺ MAIT and IFN-γ responses correlate with response to anti-PD-1 therapy. Higher proportion of MAIT17 type responses in non-responders	MAIT frequencies higher in stage I compared to stage IV tumours	(196, 200, 201)
Oesophageal cancer	Blood and tissue samples	Circulating MAIT cells ↓, tumour-infiltrating MAITs detected	Activation ↓ PD-1 ↑	MAIT cell frequency ↑ in patients with less advanced tumours		(197)
Ovarian cancer	Blood, ascites and tumour tissue	Tumour-infiltrating MAIT cells detected Migratory markers ↑	Activation and cytotoxic potential	Activated MAIT cells correlated with response to chemotherapy	Tumour-infiltrating MAITs capable of response to MR1 dependent and independent stimuli	(195, 202)

(Continued)

TABLE 2 Continued

Cancer type	MAIT cell source	MAIT populations	MAIT cell activation	Association with clinical outcomes	Other observations	References
Prostate cancer	Blood samples	MAIT frequency unchanged compared to healthy controls	Response to <i>in vitro</i> stimuli ↓ PD-L1 and PD-L1 upregulation in response to stimuli ↑		MR1-dependent stimulation + anti-PD-1 therapy associated with tumour control <i>in vitro</i>	(205)
Renal carcinoma	Blood samples	MAIT frequency unchanged compared to healthy controls. CD4+ MAIT% ↑	Activation ↓ PD-1 ↑	Activation restored, exhaustion reversed by faecal microbiota transplant (FMT).	MAIT cells important in favourable response to FMT therapy.	(206)
T cell non-Hodgkin's lymphoma	Lymphoma biopsies	MAIT cells detected in ~25% of lymphoma samples			Some variation in TCR clonality between patients.	(234)

isolated from healthy donors, which may not represent functional capacity of MAIT cells in people with cancer (205). Characterisation of MAIT cell responses in renal carcinomas before and after faecal microbiota transplant showed restoration of markers of MAIT cell activation and effector functions, as well as reversal of exhaustion as indicated by PD-1 expression (206), suggesting MAIT cells respond favourably to faecal microbiota transplant therapy. Favreau et al. reported greater activation in MAIT cells from people with multiple myeloma following *in vitro* treatment of the PBMCs with anti-PD-1 and iNKT activating antigen α -GalCer – also highlighting a potential synergistic relationship between MAIT and iNKT cells in this context (204). Collectively, these findings demonstrate important roles for MAIT cells in immune modulating cancer therapies, highlighting the possibility that they may be a useful therapeutic target. Clinical findings to date and the roles of MAIT cells in various tumour types are summarised in Table 2. How MAIT cells are affected, and how they impact the overall immune response to immune checkpoint inhibition warrants further investigation.

Assessment of MAIT cell anti-tumour functions *in vitro*

In vitro studies of human MAIT cells from healthy donors have demonstrated cytotoxic capacity against various tumour cell lines (Table 3). In these studies, MAIT cells were pre-activated and expanded with 5-OP-RU and pro-inflammatory cytokines (207), PMA and ionomycin (186) or IL-12 and IL-18 (197). Cytotoxicity of MAIT cells against GBM tumour cells has been reported, albeit these results follow extensive expansion with MR1-5-OP-RU tetramer conjugated to anti-CD28 beads, and co-culture of tumour cell lines with fixed *Escherichia coli* (208). MAIT cells isolated from healthy liver tissue also demonstrate cytotoxicity against K562 cells that is further enhanced by IL-15 (209). However, few studies have detailed the cytotoxic function of naïve tissue-resident MAIT cells, due to their scarcity and the complexity of these models. Further work is needed to examine the *in vivo* phenotypes and effector functions of MAIT cells in the TME, especially to understand the underlying mechanisms driving MAIT activation in this context and establish whether such activation is dependent on MR1.

Findings from *in vivo* models

To date, few published studies have examined MAIT cell functions in murine tumour models (Figure 2). Petley and colleagues demonstrated that MAIT cell deficient *Mr1*^{-/-} mice showed reduced tumour burdens compared to WT mice, in a model of B16.F10 metastatic melanoma (210), suggesting MAIT cells are detrimental in this model. However, the same study showed reduced metastasis by pulsing the B16.F10 tumour cells with 5-OP-RU prior to intravenous injection (210), indicating a protective effect of MAIT cell activation. In another study, the activation and boosting of MAIT cells *in vivo* with CpG and 5-OP-RU also conferred a protective effect in reducing tumour burden and increasing survival in models of intrahepatic, subcutaneous and metastatic lung tumours (211). Systemic MAIT cell boosting with 5-OP-RU and adjuvants was also shown to increase MAIT cell

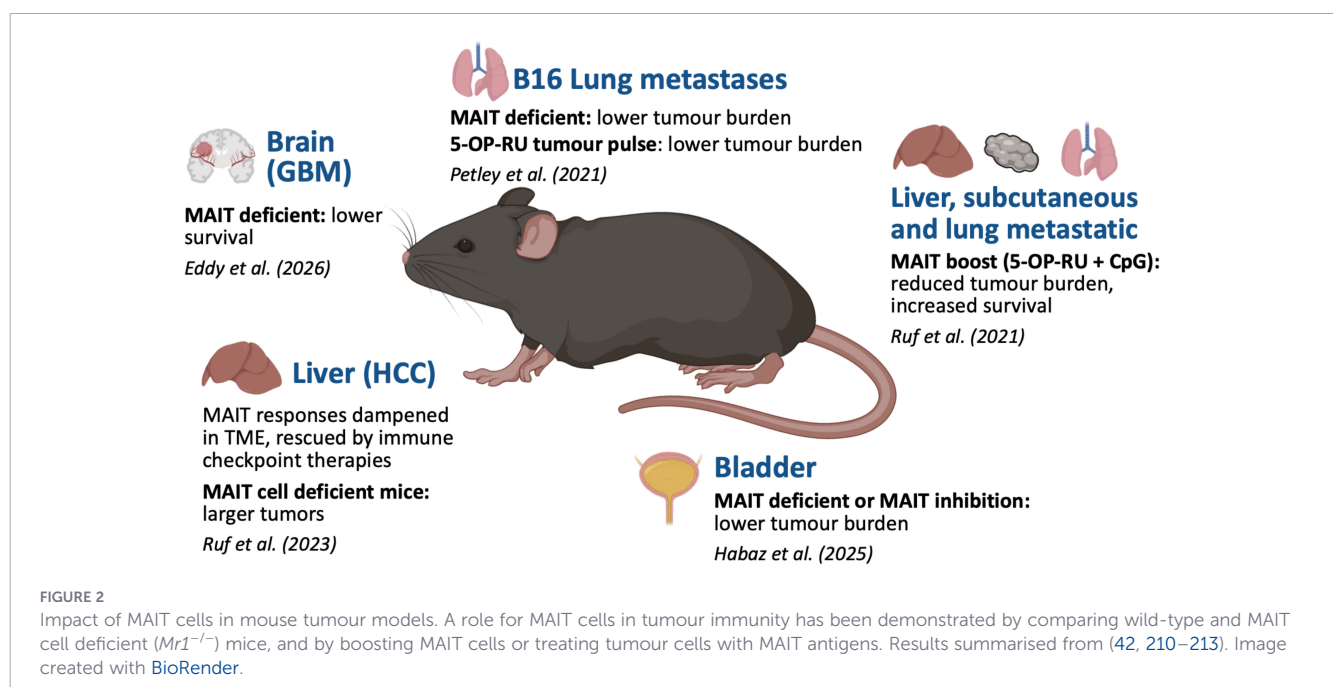
TABLE 3 Evidence of MAIT anti-tumour cytotoxicity *in vitro*.

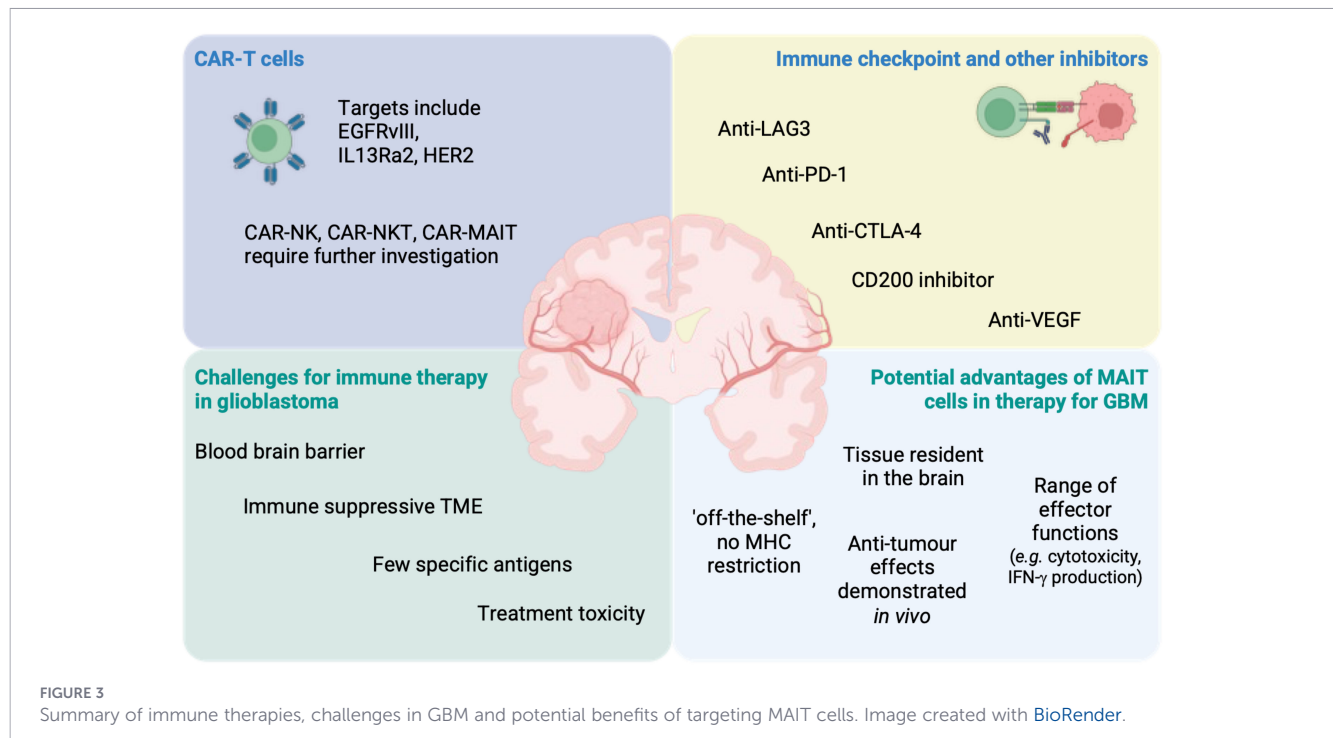
MAIT cell origin	MAIT cell stimulation	Target cell	Time period for killing	MR1 dependence	Reference
Healthy donor blood	PMA/ionomycin during coculture	K562 leukaemia cell line	4 hours	Not tested	(186)
Healthy donor blood	21-day expansion with 5-OP-RU, IL-2, IL-7, IL-12, IL-15, IL-18	RPMI-8226 and U266 (multiple myeloma cell lines)	20 hours	MR1 dependent	(207)
Healthy donor blood	TCR stimulation beads, IL-12 and IL-18	OE33 oesophageal cancer cell line	4 hours	Not tested	(197)
Healthy donor liver tissue	48-hour incubation with IL-15	K562 leukaemia cell line	12 hours	MR1 independent	(209)
Healthy donor blood	21-day expansion with IL-2, 5-OP-RU-MR1 tetramer/CD28 beads	T98G GBM cell line	12 hours	Partially MR1-dependent	(208)
Healthy donor blood	5-A-RU + methylglyoxal, anti-PD-1	PC3 prostate cancer cell line	> 48 hours	Inconclusive	(205)

abundance and modulate their function in the brain (42), but whether 5-OP-RU directly penetrates the brain to locally expand cells was not investigated in this study. MAIT cell cytotoxic effector functions and cytokine secretion were dampened in response to tumour growth and interactions with tumour-associated macrophages (TAMs) in models of hepatocellular carcinoma (212). However, these were somewhat rescued following treatment with immune checkpoint therapies (212). MAIT cell deficient mice had larger tumours in this study, suggesting a role in controlling tumour growth. In contrast MAIT cell deficient mice, or mice treated with acetyl-6-FP which can inhibit MAIT cell activation, showed lower tumour burdens in a model of bladder cancer, suggesting a detrimental role in combatting tumour growth (213). Taken together, potential anti-tumour functions of MAIT cells may depend on their activation state and may require MR1-dependent activation.

Potential of MAIT cells as immunotherapy targets

As development of cell-based cancer immunotherapies progresses, a strong interest in harnessing unconventional T cells for both autologous and off-the-shelf allogenic approaches has emerged (previously reviewed (95, 214, 215)). Unconventional CAR-T approaches currently in clinical trials include NKT cells (216) and $\gamma\delta$ T cells (Table 1). MAIT cells also present as an attractive candidate for immune cell-based therapies for several reasons (Figure 3). MAIT cells are relatively abundant T cells with rapid effector functions including cytotoxicity that also been successfully targeted towards tumour cells *in vitro* (186, 207, 209). Their restriction to the almost monomorphic MR1 protein due to their semi-invariant TCRs limits the variability of antigen recognition, and suggest a more predictable response can be achieved, as well as





reducing the risk of alloreactive immune responses, allowing development of 'off-the-shelf' therapies that may negate the need for developing personalised treatment for each patient (95).

Detailed functional analyses of MAIT cells, including their capacity to restrain tumour growth or reduce tumour volumes, requires *in vivo* models. While the low abundance of MAIT cells in wild-type mice presents a challenge for such studies, investigative tools including MAIT-deficient knockout mouse strains (158, 217), MAIT cell-enriched mouse strains (218, 219) and models to boost MAIT abundance via vaccination (126), assist in establishing robust pre-clinical models to study MAIT cell function in cancer settings.

Initial evidence of MAIT cell infiltration into brain tumours was described by Peterfalvi and colleagues, who identified populations of tumour-infiltrating MAIT cells following detection of V α 7.2-J α 33 transcripts in GBM patient tumour samples, which were negative for NK cell marker CD56 (173), implying that tumour-infiltrating MAIT cells may not have a cytotoxic phenotype. Multi-omics analysis of the Cancer Genome Atlas (TCGA) revealed that high *MR1* expression can be observed relative to healthy individuals in both high- and low-grade gliomas, and *MR1* upregulation was associated with poor clinical outcomes, identifying a potential biomarker for predicting clinical outcomes (184), a finding since verified by further studies (42, 220). However, whether the correlation with poor overall survival is due to interactions between MAIT cells and MR1, which could influence MAIT cell activation state in the TME is less clear. As with other cancers, circulating MAIT cells were reduced in people with GBM compared to healthy controls (220). In GBM tumours, transcriptional signatures of MAIT cells were found to be associated with poor patient prognosis (220), but signatures of activated, rather than naïve, MAIT cells were associated with longer survival (42), suggesting therapies that activate MAIT cells may be beneficial. An *in vitro* study of MAIT-tumour interactions indicated that activated MAIT cells display

partially MR1-dependent cytotoxic capacity against GBM cells (208), suggesting the potential of targeting MAIT cells therapeutically in GBM by harnessing existing cytotoxic functions. In the GL261 mouse model of GBM, *Mr1*^{-/-} mice, which lack MAIT cells, had reduced survival (42), suggesting a beneficial effect for MAIT cells in the context of brain tumours. In both humans and mice, MAIT cells in GBM displayed a Th17-like phenotype (42, 220), but the mechanisms behind MAIT cell protective effects in GBM remain unclear. Overall, more detailed characterisation of how MAIT cell phenotype and function is altered in the context of GBM could reveal a new therapeutic angle for disease treatment.

Conclusions and remaining questions

While there is promise in exploring MAIT and other unconventional T cells as therapeutic targets in GBM, the methods by which these cells could be targeted in this setting is not yet clear. The *in vivo* phenotypes and effector functions of MAIT cells in the GBM TME first need to be defined, as well as the mechanisms (MR1-dependent or independent) driving MAIT cell activation. The potential direct anti-tumour functions of MAIT cells may depend on their activation through MR1. However, it is unclear if direct cytotoxic functions are required, and the complex interactions with other immune cells in the brain are yet to be examined.

While activated MAIT cells appear to be beneficial, MR1 expression is associated with worse outcomes. This apparent contradiction will be important to decipher in future studies. With the finding that MR1 expression is associated with poor survival, the inhibition or further modulation of MAIT cell activation through MR1, such as by the provision of non-agonist compounds [e.g., 6-FP (116)] as has been performed in models of

inflammatory bowel disease, metabolic disease and atopic dermatitis (221–223) should also be explored in pre-clinical models of GBM.

An important unanswered question is whether common GBM-associated genetic alterations influence MAIT cell biology through changes in tumour metabolism, MR1 ligand availability, antigen presentation, or the broader immune microenvironment. Defining these relationships may identify novel opportunities to incorporate MAIT cells into future precision immunotherapy strategies for GBM.

In a mouse model, MAIT cells were enriched to high numbers in the brain by systemic delivery of 5-OP-RU with adjuvants (42). Whether MAIT cells were expanded locally or trafficked from the periphery to the brain was not tested in this study. The small size of 5-OP-RU may suggest it could diffuse across the blood brain barrier. However, 5-OP-RU is chemically unstable, and thus, may require modification for use in therapeutic applications (224, 225). Formally testing the ability of MAIT antigens or antagonists to cross the BBB and understanding the ability of activated MAIT cells to enter the brain parenchyma, may be critical to understanding the therapeutic potential of MAIT cells in this setting.

In this light, it is considered that the tissue homing properties of MAIT cells, along with their cytotoxic capacity, may offer some benefits over conventional T cells in developing CAR-T therapies (CAR-MAIT) for solid tumours. The development of CAR-MAIT cells has not been reported but would be an interesting avenue to explore in GBM.

Finally, there is some evidence that MAIT cell abundance correlates with response to anti-PD-1 therapy in other cancers (193, 203), but this has not yet been explored in GBM. Other immune checkpoints such as CTLA-4 and LAG-3 should also be tested, as expression may differ between MAIT cells and other T cell subsets (226, 227). The mechanisms behind MAIT cell response to immune checkpoint inhibition warrant further investigation.

MAIT cells are relatively recently described and best known for their response to bacterial infections. However, the full scope of their contributions to immunity, including diverse functions in barrier integrity, anti-viral response and tumour immunity is rapidly emerging. Although many basic biological questions are yet to be addressed, their unique characteristics suggest they may provide benefits and new directions in tackling the challenges of GBM.

Author contributions

EE: Conceptualization, Writing – original draft, Writing – review & editing. TP: Writing – review & editing. AB: Conceptualization, Supervision, Writing – review & editing. AC: Conceptualization, Supervision, Writing – review & editing.

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Figure 1 was previously used in a PhD Thesis by Dr Eleanor Eddy (235).

Conflict of interest

AC is an inventor on patents describing MR1 ligands and MR1 tetramers patent families WO/2015/149130 and WO/2014/005194, with MR1 tetramers licensed for commercial use to Immudex and for nonprofit use to the NIH Tetramer Core Facility.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- Lerner A, Palmer K, Campion T, Millner TO, Scott E, Lorimer C, et al. Gliomas in adults: Guidance on investigations, diagnosis, treatment and surveillance. *Clin Med (Lond)*. (2024) 24:100240. doi: 10.1016/j.clinme.2024.100240
- Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol*. (2021) 23:1231–51. doi: 10.1093/neuonc/noab106
- Liu Y, Lang F, Chou FJ, Zaghloul KA, Yang C. Isocitrate dehydrogenase mutations in glioma: Genetics, biochemistry, and clinical indications. *Biomedicines*. (2020) 8:294. doi: 10.3390/biomedicines8090294
- Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro Oncol*. (2017) 19:v1–v88. doi: 10.1093/neuonc/nox158
- Sim HW, Nowak AK, Lwin Z, Khasraw M. Management of glioblastoma: an Australian perspective. *Chin Clin Oncol*. (2021) 10:42. doi: 10.21037/cco.2020.02.05
- Schaff LR, Mellinghoff IK. Glioblastoma and other primary brain Malignancies in adults: A review. *JAMA*. (2023) 329:574–87. doi: 10.1001/jama.2023.0023
- Chen JY, Hovey E, Rosenthal M, Livingstone A, Simes J. Neuro-oncology practices in Australia: a Cooperative Group for Neuro-Oncology patterns of care study. *Asia Pac J Clin Oncol*. (2014) 10:162–7. doi: 10.1111/ajco.12079
- Jonsson P, Lin AL, Young RJ, DiStefano NM, Hyman DM, Li BT, et al. Genomic correlates of disease progression and treatment response in prospectively characterized gliomas. *Clin Cancer Res*. (2019) 25:5537–47. doi: 10.1158/1078-0432.ccr-19-0032
- Tataranu LG, Turliuc S, Rizea RE, Dricu A, Alexandru O, Staicu GA, et al. A synopsis of biomarkers in glioblastoma: Past and present. *Curr Issues Mol Biol*. (2024) 46:6903–39. doi: 10.3390/cimb46070412
- Braganza MZ, Kitahara CM, Berrington de Gonzalez A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. *Neuro Oncol*. (2012) 14:1316–24. doi: 10.1093/neuonc/nos208
- Yang M, Guo W, Yang C, Tang J, Huang Q, Feng S, et al. Mobile phone use and glioma risk: A systematic review and meta-analysis. *PloS One*. (2017) 12:e0175136. doi: 10.1371/journal.pone.0175136
- Weed DL. Do cell phones cause brain tumors? Another piece of the puzzle. *J Natl Cancer Inst*. (2022) 114:643–4. doi: 10.1093/jnci/djac043
- Ostrom QT, Adel Fahmideh M, Cote DJ, Muskens IS, Schraw JM, Scheurer ME, et al. Risk factors for childhood and adult primary brain tumors. *Neuro Oncol*. (2019) 21:1357–75. doi: 10.1093/neuonc/noz123
- Amirian ES, Zhou R, Wrensch MR, Olson SH, Scheurer ME, Il'yasova D, et al. Approaching a scientific consensus on the association between allergies and glioma risk: A report from the Glioma International Case-Control Study. *Cancer Epidemiol Biomarkers Prev*. (2016) 25:282–90. doi: 10.1158/1055-9965.epi-15-0847
- Dinevska M, Widodo SS, Furst L, Cuzcano L, Fang Y, Mangiola S, et al. Cell signaling activation and extracellular matrix remodeling underpin glioma tumor microenvironment heterogeneity and organization. *Cell Oncol (Dordr)*. (2023) 46:589–602. doi: 10.1007/s13402-022-00763-9
- Day ZI, Roberts-Thomson S, Nouri YJ, Dalton NS, Wang SS, Davenport A, et al. Defining the extracellular matrix for targeted immunotherapy in adult and pediatric brain cancer. *NPJ Precis Oncol*. (2025) 9:184. doi: 10.1038/s41698-025-00956-z
- Onishi M, Ichikawa T, Kurozumi K, Date I. Angiogenesis and invasion in glioma. *Brain Tumor Pathol*. (2011) 28:13–24. doi: 10.1007/s10014-010-0007-z
- Mathew EN, Berry BC, Yang HW, Carroll RS, Johnson MD. Delivering therapeutics to glioblastoma: Overcoming biological constraints. *Int J Mol Sci*. (2022) 23:1711. doi: 10.3390/ijms23031711
- Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. *Am J Pathol*. (2007) 170:1445–53. doi: 10.2353/ajpath.2007.070011
- Esemen Y, Awan M, Parwez R, Baig A, Rahman S, Masala I, et al. Molecular pathogenesis of glioblastoma in adults and future perspectives: A systematic review. *Int J Mol Sci*. (2022) 23:2607. doi: 10.3390/ijms23052607
- Leung SY, Yuen ST, Chan TL, Chan AS, Ho JW, Kwan K, et al. Chromosomal instability and p53 inactivation are required for genesis of glioblastoma but not for colorectal cancer in patients with germline mismatch repair gene mutation. *Oncogene*. (2000) 19:4079–83. doi: 10.1038/sj.onc.1203740
- Chen X, Zhang T, Su W, Dou Z, Zhao D, Jin X, et al. Mutant p53 in cancer: from molecular mechanism to therapeutic modulation. *Cell Death Dis*. (2022) 13:974. doi: 10.1038/s41419-022-05408-1
- Kita D, Yonekawa Y, Weller M, Ohgaki H. PIK3CA alterations in primary (de novo) and secondary glioblastomas. *Acta Neuropathol*. (2007) 113:295–302. doi: 10.1007/s00401-006-0186-1
- Nakada M, Kita D, Watanabe T, Hayashi Y, Teng L, Pyko IV, et al. Aberrant signaling pathways in glioma. *Cancers (Bsl)*. (2011) 3:3242–78. doi: 10.3390/cancers3033242
- Cancer Genome Atlas Research. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. (2008) 455:1061–8. doi: 10.1038/nature07385
- Tang J, Karbhar N, Campian JL. Therapeutic targets in glioblastoma: Molecular pathways, emerging strategies, and future directions. *Cells*. (2025) 14(7):494. doi: 10.3390/cells14070494
- Vartanian A, Singh SK, Agnihotri S, Jalali S, Burrell K, Aldape KD, et al. GBM's multifaceted landscape: highlighting regional and microenvironmental heterogeneity. *Neuro Oncol*. (2014) 16:1167–75. doi: 10.1093/neuonc/nou035
- Johnson BE, Mazar T, Hong C, Barnes M, Aihara K, McLean CY, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. *Science*. (2014) 343:189–93. doi: 10.1126/science.1239947
- Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. *Nat Rev Immunol*. (2018) 18:773–89. doi: 10.1038/s41577-018-0066-7
- Radharani NNV, Yadav AS, Nimma R, Kumar TV, Bulbule A, Chanukuppa V, et al. Tumor-associated macrophage derived IL-6 enriches cancer stem cell population and promotes breast tumor progression via Stat-3 pathway. *Cancer Cell Int*. (2022) 22:122. doi: 10.1186/s12935-022-02527-9
- Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. *Nat Rev Cancer*. (2003) 3:401–10. doi: 10.1038/nrc1093
- Lindsey S, Langhans SA. Crosstalk of oncogenic signaling pathways during epithelial-mesenchymal transition. *Front Oncol*. (2014) 4:358. doi: 10.3389/fonc.2014.00358
- Wang X, Liu R, Qu X, Yu H, Chu H, Zhang Y, et al. Alpha-ketoglutarate-activated NF-kappaB signaling promotes compensatory glucose uptake and brain tumor development. *Mol Cell*. (2019) 76:148–62.e7. doi: 10.1016/j.molcel.2019.07.007
- Habashy KJ, Mansour R, Moussalem C, Sawaya R, Massaad MJ. Challenges in glioblastoma immunotherapy: mechanisms of resistance and therapeutic approaches to overcome them. *Br J Cancer*. (2022) 127:976–87. doi: 10.1038/s41416-022-01864-w
- Jackson CM, Choi J, Lim M. Mechanisms of immunotherapy resistance: lessons from glioblastoma. *Nat Immunol*. (2019) 20:1100–9. doi: 10.1038/s41590-019-0433-y
- Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. *Cancer Cell*. (2017) 31:326–41. doi: 10.1016/j.ccell.2017.02.009
- Watkins S, Robel S, Kimbrough IF, Robert SM, Ellis-Davies G, Sontheimer H. Disruption of astrocyte-vascular coupling and the blood-brain barrier by invading glioma cells. *Nat Commun*. (2014) 5:4196. doi: 10.1038/ncomms5196
- Sarkaria JN, Hu LS, Parney IF, Pafundi DH, Brinkmann DH, Laack NN, et al. Is the blood-brain barrier really disrupted in all glioblastomas? A critical assessment of existing clinical data. *Neuro Oncol*. (2018) 20:184–91. doi: 10.1093/neuonc/nox175
- Luo H, Shusta EV. Blood-brain barrier modulation to improve glioma drug delivery. *Pharmaceutics*. (2020) 12:1085. doi: 10.3390/pharmaceutics12111085
- Pappalardo JL, Zhang L, Pecsok MK, Perlman K, Zografou C, Raddassi K, et al. Transcriptomic and clonal characterization of T cells in the human central nervous system. *Sci Immunol*. (2020) 5. doi: 10.1126/sciimmunol.abb8786
- Croese T, Castellani G, Schwartz M. Immune cell compartmentalization for brain surveillance and protection. *Nat Immunol*. (2021) 22:1083–92. doi: 10.1038/s41590-021-00994-2
- Eddy EM, Khan M, Patton T, Moi D, Wang H, Le JP, et al. Brain-resident MAIT cells infiltrate GL261 tumors, and activated MAIT cell signatures are associated with improved outcomes in glioma. *Neurol Neuroimmunol Neuroinflamm*. (2026) 13:e200546. doi: 10.1212/xxi.000000000000200546
- Chuntova P, Chow F, Watchmaker PB, Galvez M, Heimberger AB, Newell EW, et al. Unique challenges for glioblastoma immunotherapy-discussions across neuro-oncology and non-neuro-oncology experts in cancer immunology. Meeting report from the 2019 SNO Immuno-Oncology Think Tank. *Neuro Oncol*. (2021) 23:356–75. doi: 10.1093/neuonc/noaa277
- Woroniecka KI, Rhodin KE, Chongsathidkiet P, Keith KA, Fecci PE. T-cell dysfunction in glioblastoma: Applying a new framework. *Clin Cancer Res*. (2018) 24:3792–802. doi: 10.1158/1078-0432.ccr-18-0047
- Grabowski MM, Sankey EW, Ryan KJ, Chongsathidkiet P, Lorrey SJ, Wilkinson DS, et al. Immune suppression in gliomas. *J Neuro-Oncol*. (2021) 151:3–12. doi: 10.1007/s11060-020-03483-y
- Woroniecka K, Fecci PE. T-cell exhaustion in glioblastoma. *Oncotarget*. (2018) 9:35287–8. doi: 10.18632/oncotarget.26228
- Ott M, Prins RM, Heimberger AB. The immune landscape of common CNS Malignancies: implications for immunotherapy. *Nat Rev Clin Oncol*. (2021) 18:729–44. doi: 10.1038/s41571-021-00518-9
- Pinzon-Charry A, Maxwell T, Lopez JA. Dendritic cell dysfunction in cancer: a mechanism for immunosuppression. *Immunol Cell Biol*. (2005) 83:451–61. doi: 10.1111/j.1440-1711.2005.01371.x

49. El Andaloussi A, Lesniak MS. An increase in CD4+CD25+FOXP3+ regulatory T cells in tumor-infiltrating lymphocytes of human glioblastoma multiforme. *Neuro Oncol.* (2006) 8:234–43. doi: 10.1215/15228517-2006-006
50. Veglia F, Sanseviero E, Gabilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol.* (2021) 21:485–98. doi: 10.1038/s41577-020-00490-y
51. Alban TJ, Bayik D, Otvos B, Rabljenovic A, Leng L, Jia-Shiun L, et al. Glioblastoma myeloid-derived suppressor cell subsets express differential macrophage migration inhibitory factor receptor profiles that can be targeted to reduce immune suppression. *Front Immunol.* (2020) 11:1191. doi: 10.3389/fimmu.2020.01191
52. Gu G, Gao T, Zhang L, Chen X, Pang Q, Wang Y, et al. NKAP alters tumor immune microenvironment and promotes glioma growth via Notch1 signaling. *J Exp Clin Cancer Res.* (2019) 38:291. doi: 10.1186/s13046-019-1281-1
53. Roth P, Happold C, Weller M. Corticosteroid use in neuro-oncology: an update. *Neuro-Oncol Pract.* (2015) 2:6–12. doi: 10.1093/nop/npu029
54. Upadhyayula PS, Higgins DM, Argenziano MG, Spinazzi EF, Wu CC, Canoll P, et al. The sledgehammer in precision medicine: Dexamethasone and immunotherapeutic treatment of glioma. *Cancer Invest.* (2022) 40:554–66. doi: 10.1080/0737907.2021.1944178
55. Tokunaga A, Sugiyama D, Maeda Y, Warner AB, Panageas KS, Ito S, et al. Selective inhibition of low-affinity memory CD8(+) T cells by corticosteroids. *J Exp Med.* (2019) 216:2701–13. doi: 10.1084/jem.20190738
56. Mathios D, Kim JE, Mangraviti A, Phallen J, Park CK, Jackson CM, et al. Anti-PD-1 antitumor immunity is enhanced by local and abrogated by systemic chemotherapy in GBM. *Sci Transl Med.* (2016) 8:370ra180. doi: 10.1126/scitranslmed.aag2942
57. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the extent of resection with survival in glioblastoma: A systematic review and meta-analysis. *JAMA Oncol.* (2016) 2:1460–9. doi: 10.1001/jamaoncol.2016.1373
58. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* (2005) 352:987–96. doi: 10.1201/9781003416197-1
59. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* (2009) 10:459–66. doi: 10.1016/s1470-2045(09)70025-7
60. Fisher JP, Adamson DC. Current FDA-approved therapies for high-grade Malignant gliomas. *Biomedicines.* (2021) 9:324. doi: 10.3390/biomedicines9030324
61. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA.* (2017) 318:2306–16. doi: 10.1001/jama.2017.18718
62. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. *Oncologist.* (2009) 14:1131–8. doi: 10.1634/theoncologist.2009-0121
63. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* (2009) 27:4733–40. doi: 10.1200/jco.2008.19.8721
64. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* (2009) 27:740–5. doi: 10.1200/jco.2008.16.3055
65. Kesumayadi I, Kambe A, Kanda H, Hosoya T, Sakamoto M, Kurosaki M. Bevacizumab enhances overall survival in newly diagnosed glioblastoma patients with high COX-2 expression. *Sci Rep.* (2026) 4974. doi: 10.1038/s41598-026-35550-1
66. Avila EK, Chamberlain M, Schiff D, Reijneveld JC, Armstrong TS, Ruda R, et al. Seizure control as a new metric in assessing efficacy of tumor treatment in low-grade glioma trials. *Neuro Oncol.* (2017) 19:12–21. doi: 10.1093/neuonc/now190
67. Lote K, Stenwig AE, Skullerud K, Hirschberg H. Prevalence and prognostic significance of epilepsy in patients with gliomas. *Eur J Cancer.* (1998) 34:98–102. doi: 10.1016/s0959-8049(97)00374-2
68. Walbert T, Harrison RA, Schiff D, Avila EK, Chen M, Kandula P, et al. SNO and EANO practice guideline update: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. *Neuro Oncol.* (2021) 23:1835–44. doi: 10.1093/neuonc/noab152
69. Perry JR. Thromboembolic disease in patients with high-grade glioma. *Neuro Oncol.* (2012) 14 Suppl 4iv73–80. doi: 10.1093/neuonc/nos197
70. Petty AJ, Heyman B, Yang Y. Chimeric antigen receptor cell therapy: Overcoming obstacles to battle cancer. *Cancers (Bsl).* (2020) 12:842. doi: 10.3390/cancers12040842
71. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. *Blood Rev.* (2019) 34:45–55. doi: 10.1016/j.blre.2018.11.002
72. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* (2017) 377:2531–44. doi: 10.1056/nejmoa1707447
73. Maude SL. Tisagenlecleucel in pediatric patients with acute lymphoblastic leukemia. *Clin Adv Hematol Oncol.* (2018) 16:664–6. doi: 10.1038/s41375-022-01550-z
74. Azeez SS, Yashooa RK, Smail SW, Salihi A, Ali AS, Mamand S, et al. Advancing CAR-based cell therapies for solid tumours: challenges, therapeutic strategies, and perspectives. *Mol Cancer.* (2025) 24:191. doi: 10.1186/s12943-025-02386-8
75. Park S, Maus MV, Choi BD. CAR-T cell therapy for the treatment of adult high-grade gliomas. *NPJ Precis Oncol.* (2024) 8:279. doi: 10.1038/s41698-024-00753-0
76. O'Rourke DM, Nasrallah MP, Desai A, Melenhorst JJ, Mansfield K, Morrisette JJD, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci Transl Med.* (2017) 9. doi: 10.1126/scitranslmed.aaa0984
77. Choi BD, Gerstner ER, Frigault MJ, Leick MB, Mount CW, Balaj L, et al. Intraventricular CARv3-TEAM-E T cells in recurrent glioblastoma. *N Engl J Med.* (2024) 390:1290–8. doi: 10.1056/nejmoa2314390
78. Brown CE, Badie B, Barish ME, Weng L, Ostberg JR, Chang WC, et al. Bioactivity and safety of IL13Ralpha2-redirected chimeric antigen receptor CD8+ T cells in patients with recurrent glioblastoma. *Clin Cancer Res.* (2015) 21:4062–72. doi: 10.1158/1078-0432.ccr-15-0428
79. Brown CE, Alizadeh D, Starr R, Weng L, Wagner JR, Naranjo A, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. *N Engl J Med.* (2016) 375:2561–9. doi: 10.1056/nejmoa1610497
80. Liu G, Ying H, Zeng G, Wheeler CJ, Black KL, Yu JS. HER-2, gp100, and MAGE-1 are expressed in human glioblastoma and recognized by cytotoxic T cells. *Cancer Res.* (2004) 64:4980–6. doi: 10.1158/0008-5472.can-03-3504
81. Shen L, Li H, Bin S, Li P, Chen J, Gu H, et al. The efficacy of third generation anti-HER2 chimeric antigen receptor T cells in combination with PD1 blockade against Malignant glioblastoma cells. *Oncol Rep.* (2019) 42:1549–57. doi: 10.3892/or.2019.7263
82. Press MF, Cordon-Cardo C, Slamon DJ. Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues. *Oncogene.* (1990) 5:953–62.
83. Ahmed N, Brawley V, Hegde M, Bielamowicz K, Kalra M, Landi D, et al. HER2-specific chimeric antigen receptor-modified virus-specific T cells for progressive glioblastoma: A phase I dose-escalation trial. *JAMA Oncol.* (2017) 3:1094–101. doi: 10.1001/jamaoncol.2017.0184
84. Burger MC, Zhang C, Harter PN, Romanski A, Strassheimer F, Senft C, et al. CAR-engineered NK cells for the treatment of glioblastoma: Turning innate effectors into precision tools for cancer immunotherapy. *Front Immunol.* (2019) 10:2683. doi: 10.3389/fimmu.2019.02683
85. Strassheimer F, Elleringmann P, Ludmirski G, Roller B, Macas J, Alekseeva T, et al. CAR-NK cell therapy combined with checkpoint inhibition induces an NKT cell response in glioblastoma. *Br J Cancer.* (2025) 132:849–60. doi: 10.1038/s41416-025-02977-8
86. Arafat Hossain M. A comprehensive review of immune checkpoint inhibitors for cancer treatment. *Int Immunopharmacol.* (2024) 143:113365. doi: 10.1016/j.intimp.2024.113365
87. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* (2013) 369:122–33. doi: 10.1056/nejmoa1302369
88. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell.* (2017) 168:707–23. doi: 10.1016/j.cell.2017.01.017
89. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science.* (2018) 359:1350–5. doi: 10.1126/science.aar4060
90. Cloughesy TF, Mochizuki AY, Orpilla JR, Hugo W, Lee AH, Davidson TB, et al. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. *Nat Med.* (2019) 25:477–86. doi: 10.1038/s41591-018-0337-7
91. Schalper KA, Rodriguez-Ruiz ME, Diez-Valle R, Lopez-Janeiro A, Porciuncula A, Idoate MA, et al. Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma. *Nat Med.* (2019) 25:470–6. doi: 10.1038/s41591-018-0339-5
92. Xiong Z, Ampudia-Mesias E, Shaver R, Horbinski CM, Moertel CL, Olin MR. Tumor-derived vaccines containing CD200 inhibit immune activation: Implications for immunotherapy. *Immunotherapy.* (2016) 8:1059–71. doi: 10.2217/imt-2016-0033
93. Duerinck J, Schwarze JK, Awada G, Tijtgat J, Vaeyens F, Bertels C, et al. Intracerebral administration of CTLA-4 and PD-1 immune checkpoint blocking monoclonal antibodies in patients with recurrent glioblastoma: A phase I clinical trial. *J Immunother Cancer.* (2021) 9. doi: 10.1136/jitc-2020-002296
94. Long GV, Shklovskaya E, Satgunaseelan L, Mao Y, da Silva IP, Perry KA, et al. Neoadjuvant triplet immune checkpoint blockade in newly diagnosed glioblastoma. *Nat Med.* (2025) 31:1557–66. doi: 10.12103/rs.3.rs-4255559/v1
95. Godfrey DI, Le Nours J, Andrews DM, Uldrich AP, Rossjohn J. Unconventional T cell targets for cancer immunotherapy. *Immunity.* (2018) 48:453–73. doi: 10.1016/j.immuni.2018.03.009
96. Perez C, Gruber I, Arber C. Off-the-shelf allogeneic T cell therapies for cancer: Opportunities and challenges using naturally occurring "universal" donor T cells. *Front Immunol.* (2020) 11:583716. doi: 10.3389/fimmu.2020.583716

97. Rossjohn J, Pellicci DG, Patel O, Gapin L, Godfrey DI. Recognition of CD1d-restricted antigens by natural killer T cells. *Nat Rev Immunol.* (2012) 12:845–57. doi: 10.1038/nri3328
98. Fujii SI, Shimizu K. Immune networks and therapeutic targeting of iNKT cells in cancer. *Trends Immunol.* (2019) 40:984–97. doi: 10.1016/j.it.2019.09.008
99. Xu X, Huang W, Heczey A, Liu D, Guo L, Wood M, et al. NKT cells coexpressing a GD2-specific chimeric antigen receptor and IL15 show enhanced *in vivo* persistence and antitumor activity against neuroblastoma. *Clin Cancer Res.* (2019) 25:7126–38. doi: 10.1158/1078-0432.ccr-19-0421
100. Heczey A, Xu X, Courtney AN, Tian G, Barragan GA, Guo L, et al. Anti-GD2 CAR-NKT cells in relapsed or refractory neuroblastoma: Updated phase 1 trial interim results. *Nat Med.* (2023) 29:1379–88. doi: 10.1038/s41591-023-02363-y
101. Ozaki K, Aoki T, Kobayashi M, Takami M, Kobayashi M, Ito T, et al. Anti-tumor effect of intratumoral administration of induced pluripotent stem cell-derived NKT cells on glioblastoma through CD155/DNAM-1 interaction. *Stem Cells Transl Med.* (2025) 14:szaf036. doi: 10.1093/stcltm/szaf036
102. Li YR, Zhu Y, Li Z, Shen X, Halladay T, Tse C, et al. Allogeneic stem cell-engineered EGFRvIII-specific CAR-NKT cells for treating glioblastoma with enhanced efficacy and safety. *Mol Ther.* (2025) 33:6041–62. doi: 10.1016/j.yimthe.2025.09.026
103. Bialy S, Bogunia-Kubik K. Uncovering the mysteries of human gamma delta T cells: from origins to novel therapeutics. *Front Immunol.* (2025) 16:1543454. doi: 10.3389/fimmu.2025.1543454
104. Hu Y, Hu Q, Li Y, Lu L, Xiang Z, Yin Z, et al. Gammadelta T cells: origin and fate, subsets, diseases and immunotherapy. *Signal Transduct Tgt Ther.* (2023) 8:434. doi: 10.1038/s41392-023-01653-8
105. Silva-Santos B, Serre K, Norell H. Gammadelta T cells in cancer. *Nat Rev Immunol.* (2015) 15:683–91. doi: 10.1038/s41573-019-0038-z
106. Girardi M, Oppenheim DE, Steele CR, Lewis JM, Glusac E, Filler R, et al. Regulation of cutaneous Malignancy by gammadelta T cells. *Science.* (2001) 294:605–9. doi: 10.1126/science.1063916
107. Cieslak SG, Shahbazi R. Gamma delta T cells and their immunotherapeutic potential in cancer. *biomark Res.* (2025) 13:51. doi: 10.1186/s40364-025-00762-6
108. Nicolaisen MJT, Gatti LC, Gasull-Celades L, Brazda P, Botas M, Zawal D, et al. Autologous profiling reveals inter-patient heterogeneity in Vdelta2(+)gammadeltaTIL responses to glioblastoma driven by extracellular matrix-BTN3A axis. *J Immunother Cancer.* (2025) 13. doi: 10.1136/jitc-2025-013018
109. Wu P, Wu D, Ni C, Ye J, Chen W, Hu G, et al. GammadeltaT17 cells promote the accumulation and expansion of myeloid-derived suppressor cells in human colorectal cancer. *Immunity.* (2014) 40:785–800. doi: 10.1016/j.immuni.2014.03.013
110. Fang X, Yan S, He L, Deng C. CAR-gammadelta T cells: a new paradigm of programmable innate immune sentinels and their systemic applications in cancer and beyond. *Front Immunol.* (2025) 16:1735763. doi: 10.3389/fimmu.2025.1735763
111. Ganapathy T, Radhakrishnan R, Sakshi S, Martin S. CAR gammadelta T cells for cancer immunotherapy. Is the field more yellow than green? *Cancer Immunol Immunother.* (2023) 72:277–86. doi: 10.1007/s00262-022-03260-y
112. Huang S, Gilfillan S, Cella M, Miley MJ, Lantz O, Lybarger L, et al. Evidence for MR1 antigen presentation to mucosal-associated invariant T cells. *J Biol Chem.* (2005) 280:21183–93. doi: 10.1074/jbc.m501087200
113. Huang S, Martin E, Kim S, Yu L, Soudais C, Fremont DH, et al. MR1 antigen presentation to mucosal-associated invariant T cells was highly conserved in evolution. *Proc Natl Acad Sci USA.* (2009) 106:8290–5. doi: 10.1073/pnas.0903196106
114. Godfrey DI, Koay HF, McCluskey J, Gherardin NA. The biology and functional importance of MAIT cells. *Nat Immunol.* (2019) 20:1110–28. doi: 10.1038/s41590-019-0444-8
115. Corbett AJ, Eckle SB, Birkinshaw RW, Liu L, Patel O, Mahony J, et al. T-cell activation by transitory neo-antigens derived from distinct microbial pathways. *Nature.* (2014) 509:361–5. doi: 10.1038/nature13160
116. Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, et al. MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature.* (2012) 491:717–23. doi: 10.1038/nature11605
117. Keller AN, Eckle SB, Xu W, Liu L, Hughes VA, Mak JY, et al. Drugs and drug-like molecules can modulate the function of mucosal-associated invariant T cells. *Nat Immunol.* (2017) 18:402–11. doi: 10.1038/ni.3679
118. Ito E, Inuki S, Izumi Y, Takahashi M, Dambayashi Y, Ciacchi L, et al. Sulfated bile acid is a host-derived ligand for MAIT cells. *Sci Immunol.* (2024) 9:eade6924. doi: 10.1126/sciimmunol.ade6924
119. McInerney MP, Awad W, Souter MNT, Kang Y, Wang CJH, Chan Yew Poa K, et al. MR1 presents vitamin B6-related compounds for recognition by MR1-reactive T cells. *Proc Natl Acad Sci USA.* (2024) 121:e2414792121. doi: 10.1073/pnas.2414792121
120. Patel O, Kjer-Nielsen L, Le Nours J, Eckle SB, Birkinshaw R, Beddoe T, et al. Recognition of vitamin B metabolites by mucosal-associated invariant T cells. *Nat Commun.* (2013) 4:2142. doi: 10.1038/ncomms3142
121. Eckle SB, Birkinshaw RW, Kostenko L, Corbett AJ, McWilliam HE, Reantragoon R, et al. A molecular basis underpinning the T cell receptor heterogeneity of mucosal-associated invariant T cells. *J Exp Med.* (2014) 211:1585–600. doi: 10.1084/jem.20140484
122. Reantragoon R, Corbett AJ, Sakala IG, Gherardin NA, Furness JB, Chen Z, et al. Antigen-loaded MR1 tetramers define T cell receptor heterogeneity in mucosal-associated invariant T cells. *J Exp Med.* (2013) 210:2305–20. doi: 10.1084/jem.20130958
123. Awad W, Abdelaal MR, Letoga V, McCluskey J, Rossjohn J. Molecular insights into MR1-mediated T cell immunity: lessons learned and unanswered questions. *Immunol Rev.* (2025) 331:e70033. doi: 10.1111/imr.70033
124. Gherardin NA, Keller AN, Woolley RE, Le Nours J, Ritchie DS, Neeson PJ, et al. Diversity of T cells restricted by the MHC class I-related molecule MR1 facilitates differential antigen recognition. *Immunity.* (2016) 44:32–45. doi: 10.1016/j.immuni.2015.12.005
125. Koay HF, Gherardin NA, Xu C, Seneviratna R, Zhao Z, Chen Z, et al. Diverse MR1-restricted T cells in mice and humans. *Nat Commun.* (2019) 10:2243. doi: 10.1038/s41467-019-10198-w
126. Chen Z, Wang H, D'Souza C, Sun S, Kostenko L, Eckle SB, et al. Mucosal-associated invariant T-cell activation and accumulation after *in vivo* infection depends on microbial riboflavin synthesis and co-stimulatory signals. *Mucosal Immunol.* (2017) 10:58–68. doi: 10.1038/mi.2016.39
127. Vacchini A, Chancellor A, Yang Q, Colombo R, Spagnuolo J, Berloff G, et al. Nucleobase adducts bind MR1 and stimulate MR1-restricted T cells. *Sci Immunol.* (2024) 9:eadn0126. doi: 10.1126/sciimmunol.adn0126
128. Chancellor A, Constantin D, Berloff G, Yang Q, Nosi V, Loureiro JP, et al. The carbonyl nucleobase adduct M(3)Ade is a potent antigen for adaptive polyclonal MR1-restricted T cells. *Immunity.* (2025) 58:431–47:e10. doi: 10.1016/j.immuni.2024.11.019
129. Dolton G, Thomas H, Tan LR, Rius Rafael C, Doetsch S, Ionescu GA, et al. MHC-related protein 1-restricted recognition of cancer via a semi-invariant TCR-alpha chain. *J Clin Invest.* (2025) 135:e181895. doi: 10.1172/jci181895
130. Crowther MD, Dolton G, Legut M, Caillaud ME, Lloyd A, Attaf M, et al. Genome-wide CRISPR-Cas9 screening reveals ubiquitous T cell cancer targeting via the monomorphic MHC class I-related protein MR1. *Nat Immunol.* (2020) 21:178–85. doi: 10.1038/s41590-019-0578-8
131. Suckling RJ, Pamukcu C, Simmons RA, Fonseca D, Grant E, Harrison R, et al. Molecular basis underpinning MR1 allomorph recognition by an MR1-restricted T cell receptor. *Front Immunol.* (2025) 16:1547664. doi: 10.3389/fimmu.2025.1547664
132. Rudak PT, Choi J, Haeryfar SMM. MAIT cell-mediated cytotoxicity: roles in host defense and therapeutic potentials in infectious diseases and cancer. *J Leukoc Biol.* (2018) 104:473–86. doi: 10.1002/jlb.4ri0118-023r
133. Turtle CJ, Delrow J, Joslyn RC, Swanson HM, Basom R, Tabellini L, et al. Innate signals overcome acquired TCR signaling pathway regulation and govern the fate of human CD161(hi) CD8alpha(+) semi-invariant T cells. *Blood.* (2011) 118:2752–62. doi: 10.1182/blood-2011-02-334698
134. Slichter CK, McDavid A, Miller HW, Finak G, Seymour BJ, McNeven JP, et al. Distinct activation thresholds of human conventional and innate-like memory T cells. *JCI Insight.* (2016) 1:e86292. doi: 10.1172/jci.insight.86292
135. Wang H, Kjer-Nielsen L, Shi M, D'Souza C, Pediongo TJ, Cao H, et al. IL-23 costimulates antigen-specific MAIT cell activation and enables vaccination against bacterial infection. *Sci Immunol.* (2019) 4:eaaw0402. doi: 10.1126/sciimmunol.aaw0402
136. Lepore M, Kalinichenko A, Calogero S, Kumar P, Paleja B, Schmalzer M, et al. Functionally diverse human T cells recognize non-microbial antigens presented by MR1. *Elife.* (2017) 6:e24476. doi: 10.7554/elife.24476
137. Kurioka A, Ussher JE, Cosgrove C, Clough C, Fergusson JR, Smith K, et al. MAIT cells are licensed through granzyme exchange to kill bacterially sensitized targets. *Mucosal Immunol.* (2015) 8:429–40. doi: 10.1038/mi.2014.81
138. Le Bourhis L, Dusseaux M, Bohineust A, Bessoles S, Martin E, Premel V, et al. MAIT cells detect and efficiently lyse bacterially-infected epithelial cells. *PLoS Pathog.* (2013) 9:e1003681. doi: 10.1371/journal.ppat.1003681
139. Wang H, Chen Z, McCluskey J, Corbett AJ. Mouse models illuminate MAIT cell biology. *Mol Immunol.* (2020) 130:55–63. doi: 10.1016/j.molimm.2020.12.007
140. D'Souza C, Pediongo T, Wang H, Scheerlinck JY, Kostenko L, Esterbauer R, et al. Mucosal-associated invariant T cells augment immunopathology and gastritis in chronic *Helicobacter pylori* infection. *J Immunol.* (2018) 200:1901–16. doi: 10.4049/jimmunol.1701512
141. Ye X, Li Y, Fang B, Yuan Y, Feng D, Chen H, et al. Type 17 mucosal-associated invariant T cells contribute to neutrophilic inflammation in patients with nasal polyps. *J Allergy Clin Immunol.* (2023) 152:1153–66:e12. doi: 10.1016/j.jaci.2023.06.021
142. van Wilgenburg B, Loh L, Chen Z, Pediongo TJ, Wang H, Shi M, et al. MAIT cells contribute to protection against lethal influenza infection *in vivo*. *Nat Commun.* (2018) 9:4706. doi: 10.1038/s41467-018-07207-9
143. Loh L, Wang Z, Sant S, Koutsakos M, Jegaskanda S, Corbett AJ, et al. Human mucosal-associated invariant T cells contribute to antiviral influenza immunity via IL-18-dependent activation. *Proc Natl Acad Sci USA.* (2016) 113:10133–8. doi: 10.1073/pnas.1610750113
144. Parrot T, Gorin JB, Ponzetta A, Maleki KT, Kamman T, Emgard J, et al. MAIT cell activation and dynamics associated with COVID-19 disease severity. *Sci Immunol.* (2020) 5. doi: 10.1126/sciimmunol.abe1670

145. Deschler S, Kager J, Erber J, Fricke L, Koyumdzheva P, Georgieva A, et al. Mucosal-associated invariant T (MAIT) cells are highly activated and functionally impaired in COVID-19 patients. *Viruses*. (2021) 13:241. doi: 10.3390/v13020241
146. van Wilgenburg B, Scherwitzl I, Hutchinson EC, Leng T, Kurioka A, Kulicke C, et al. MAIT cells are activated during human viral infections. *Nat Commun*. (2016) 7:11653. doi: 10.1038/ncomms11653
147. Lamichhane R, Schneider M, de la Harpe SM, Harrop TWR, Hannaway RF, Dearden PK, et al. TCR- or cytokine-activated CD8(+) mucosal-associated invariant T cells are rapid polyfunctional effectors that can coordinate immune responses. *Cell Rep*. (2019) 28:3061–76.e5. doi: 10.1016/j.celrep.2019.08.054
148. Leeansyah E, Svard J, Dias J, Buggert M, Nystrom J, Quigley MF, et al. Arming of MAIT cell cytolytic antimicrobial activity is induced by IL-7 and defective in HIV-1 infection. *PLoS Pathog*. (2015) 11:e1005072. doi: 10.1371/journal.ppat.1005072
149. Tang X, Zhang S, Peng Q, Ling L, Shi H, Liu Y, et al. Sustained IFN- γ stimulation impairs MAIT cell responses to bacteria by inducing IL-10 during chronic HIV-1 infection. *Sci Adv*. (2020) 6:eaz0374. doi: 10.1126/sciadv.aaz0374
150. Toubal A, Nel I, Lotersztajn S, Lehuen A. Mucosal-associated invariant T cells and disease. *Nat Rev Immunol*. (2019) 19:643–57. doi: 10.1038/s41577-019-0191-y
151. Hinks TSC, Marchi E, Jabeen M, Olshansky M, Kurioka A, Pediongco TJ, et al. Activation and *in vivo* evolution of the MAIT cell transcriptome in mice and humans reveals tissue repair functionality. *Cell Rep*. (2019) 28:3249–62.e5. doi: 10.1016/j.celrep.2019.07.039
152. Leng T, Akther HD, Hackstein CP, Powell K, King T, Friedrich M, et al. TCR and inflammatory signals tune human MAIT cells to exert specific tissue repair and effector functions. *Cell Rep*. (2019) 28:3077–91.e5. doi: 10.1016/j.celrep.2019.08.050
153. du Halgouet A, Darbois A, Alkobaftawi M, Mestdagh M, Alphonse A, Premel V, et al. Role of MR1-driven signals and amphiregulin on the recruitment and repair function of MAIT cells during skin wound healing. *Immunity*. (2023) 56:78–92.e6. doi: 10.1016/j.immuni.2022.12.004
154. Constantinides MG, Link VM, Tamoutounour S, Wong AC, Perez-Chaparro PJ, Han SJ, et al. MAIT cells are imprinted by the microbiota in early life and promote tissue repair. *Science*. (2019) 366:eaax6624. doi: 10.1126/science.aax6624
155. Hinks TSC, Zhang XW. MAIT cell activation and functions. *Front Immunol*. (2020) 11:1014. doi: 10.3389/fimmu.2020.01014
156. Zhang Y, Bailey JT, Xu E, Singh K, Lavaert M, Link VM, et al. Mucosal-associated invariant T cells restrict reactive oxidative damage and preserve meningeal barrier integrity and cognitive function. *Nat Immunol*. (2022) 23:1714–25. doi: 10.1038/s41590-022-01349-1
157. Boonpattananon N, Kongkaew T, Sengprasert P, Souter MNT, Lakananurak N, Rerknimitr R, et al. Human mucosal Valpha7.2(+) CD161(hi) T cell distribution at physiologic state and in *Helicobacter pylori* infection. *J Leukoc Biol*. (2022) 112:717–32. doi: 10.1002/JLB.4A0421-223RR
158. Treiner E, Duban L, Bahram S, Radosavljevic M, Wanner V, Tilloy F, et al. Selection of evolutionarily conserved mucosal-associated invariant T cells by MR1. *Nature*. (2003) 422:164–9. doi: 10.1038/nature01433
159. Martin E, Treiner E, Duban L, Guerri L, Laude H, Toly C, et al. Stepwise development of MAIT cells in mouse and human. *PLoS Biol*. (2009) 7:e54. doi: 10.1371/journal.pbio.1000054
160. Wang H, Nelson AG, Wang B, Zhao Z, Lim XY, Shi M, et al. The balance of interleukin-12 and interleukin-23 determines the bias of MAIT1 versus MAIT17 responses during bacterial infection. *Immunol Cell Biol*. (2022) 100:547–61. doi: 10.1111/imcb.12556
161. Zhao Z, Wang H, Shi M, Zhu T, Pediongco T, Lim XY, et al. Francisella tularensis induces Th1 like MAIT cells conferring protection against systemic and local infection. *Nat Commun*. (2021) 12:4355. doi: 10.1038/s41467-021-24570-2
162. Gherardin NA, Souter MN, Koay HF, Mangas KM, Seemann T, Stinear TP, et al. Human blood MAIT cell subsets defined using MR1 tetramers. *Immunol Cell Biol*. (2018) 96:507–25. doi: 10.1111/imcb.12021
163. Nel I, Bertrand L, Toubal A, Lehuen A. MAIT cells, guardians of skin and mucosa? *Mucosal Immunol*. (2021) 14:803–14. doi: 10.1038/s41385-021-00391-w
164. Kammann T, Cai C, Sekine T, Mouchtaridi E, Boulouis C, Nilsen V, et al. MAIT cell heterogeneity across paired human tissues reveals specialization of distinct regulatory and enhanced effector profiles. *Sci Immunol*. (2024) 9:eadn2362. doi: 10.1126/sciimmunol.adn2362
165. Dias J, Leeansyah E, Sandberg JK. Multiple layers of heterogeneity and subset diversity in human MAIT cell responses to distinct microorganisms and to innate cytokines. *Proc Natl Acad Sci USA*. (2017) 114:E5434–43. doi: 10.1073/pnas.1705759114
166. Tang XZ, Jo J, Tan AT, Sandalova E, Chia A, Tan KC, et al. IL-7 licenses activation of human liver intrasinusoidal mucosal-associated invariant T cells. *J Immunol*. (2013) 190:3142–52. doi: 10.4049/jimmunol.1203128
167. Lamichhane R, Munro F, Harrop TWR, de la Harpe SM, Dearden PK, Vernal AJ, et al. Human liver-derived MAIT cells differ from blood MAIT cells in their metabolism and response to TCR-independent activation. *Eur J Immunol*. (2021) 51:879–92. doi: 10.1002/eji.202048830
168. Gibbs A, Leeansyah E, Introini A, Paquin-Proulx D, Hasselrot K, Andersson E, et al. MAIT cells reside in the female genital mucosa and are biased towards IL-17 and IL-22 production in response to bacterial stimulation. *Mucosal Immunol*. (2017) 10:35–45. doi: 10.1038/mi.2016.30
169. Rahimpour A, Koay HF, Enders A, Clanchy R, Eckle SBG, Meehan B, et al. Identification of phenotypically and functionally heterogeneous mouse Mucosal Associated Invariant T cells using MR1 tetramers. *J Exp Med*. (2015) 20:1095–108. doi: 10.1084/jem.20142110
170. Wang H, D'Souza C, Lim XY, Kostenko L, Pediongco TJ, Eckle SBG, et al. MAIT cells protect against pulmonary *Legionella longbeachae* infection. *Nat Commun*. (2018) 9:3350. doi: 10.1038/s41467-018-05202-8
171. Hegde P, Weiss E, Paradis V, Wan J, Mabire M, Sukriti S, et al. Mucosal-associated invariant T cells are a profibrogenic immune cell population in the liver. *Nat Commun*. (2018) 9:2146. doi: 10.1038/s41467-018-04450-y
172. Li Y, Huang B, Jiang X, Chen W, Zhang J, Wei Y, et al. Mucosal-associated invariant T cells improve nonalcoholic fatty liver disease through regulating macrophage polarization. *Front Immunol*. (2018) 9:1994. doi: 10.3389/fimmu.2018.01994
173. Peterfalvi A, Gomori E, Magyarlaci T, Pal J, Banati M, Javorhazy A, et al. Invariant Valpha7.2-Jalpha33 TCR is expressed in human kidney and brain tumors indicating infiltration by mucosal-associated invariant T (MAIT) cells. *Int Immunol*. (2008) 20:1517–25. doi: 10.1093/intimm/dxn111
174. Priya R, Brutkiewicz RR. Brain astrocytes and microglia express functional MR1 molecules that present microbial antigens to mucosal-associated invariant T (MAIT) cells. *J Neuroimmunol*. (2020) 349:577428. doi: 10.1016/j.jneuroim.2020.577428
175. Seshadri C, Thuong NT, Mai NT, Bang ND, Chau TT, Lewinsohn DM, et al. A polymorphism in human MR1 is associated with mRNA expression and susceptibility to tuberculosis. *Genes Immun*. (2017) 18:8–14. doi: 10.1038/gene.2016.41
176. Willing A, Leach OA, Ufer F, Attfield KE, Steinbach K, Kursawe N, et al. CD8(+) MAIT cells infiltrate into the CNS and alterations in their blood frequencies correlate with IL-18 serum levels in multiple sclerosis. *Eur J Immunol*. (2014) 44:3119–28. doi: 10.1002/eji.201344160
177. Carnero Contentti E, Farez MF, Correale J. Mucosal-associated invariant T cell features and TCR repertoire characteristics during the course of multiple sclerosis. *Front Immunol*. (2019) 10:2690. doi: 10.3389/fimmu.2019.02690
178. Abrahamsson SV, Angelini DF, Dubinsky AN, Morel E, Oh U, Jones JL, et al. Non-myeloablative autologous haematopoietic stem cell transplantation expands regulatory cells and depletes IL-17 producing mucosal-associated invariant T cells in multiple sclerosis. *Brain*. (2013) 136:2888–903. doi: 10.1093/brain/awt182
179. Salou M, Nicol B, Garcia A, Baron D, Michel L, Elong-Ngon A, et al. Neuropathologic, phenotypic and functional analyses of Mucosal Associated Invariant T cells in Multiple Sclerosis. *Clin Immunol*. (2016) 166:167:1–11. doi: 10.1016/j.clim.2016.03.014
180. Gargano F, Guerrero G, Piras E, Serafini B, Di Paola M, Rizzetto L, et al. Proinflammatory mucosal-associated invariant CD8+ T cells react to gut flora yeasts and infiltrate multiple sclerosis brain. *Front Immunol*. (2022) 13:890298. doi: 10.3389/fimmu.2022.890298
181. Wyatt-Johnson SK, Kersey HN, Codocedo JF, Newell KL, Landreth GE, Lamb BT, et al. Control of the temporal development of Alzheimer's disease pathology by the MR1/MAIT cell axis. *J Neuroinflamm*. (2023) 20:78. doi: 10.1186/s12974-023-02761-6
182. Figliomeni A, Winter S, Abonne M, Kenna J, Lodge S, Whitley L, et al. Immune and metabolic signatures characterise constipation-driven endophenotypes in Parkinson's disease. *NPJ Parkinsons Dis*. (2025) 12:2. doi: 10.1038/s41531-025-01212-8
183. Nakajima S, Tanaka R, Yamashiro K, Chiba A, Noto D, Inaba T, et al. Mucosal-associated invariant T cells are involved in acute ischemic stroke by regulating neuroinflammation. *J Am Heart Assoc*. (2021) 10:e018803. doi: 10.1161/jaha.120.018803
184. Kubica P, Lara-Velazquez M, Bam M, Siraj S, Ong I, Liu P, et al. MR1 overexpression correlates with poor clinical prognosis in glioma patients. *Neuro-Oncol Adv*. (2021) 3:vdab034. doi: 10.1093/onoajnl/vdab034
185. Ling L, Lin Y, Zheng W, Hong S, Tang X, Zhao P, et al. Circulating and tumor-infiltrating mucosal associated invariant T (MAIT) cells in colorectal cancer patients. *Sci Rep*. (2016) 6:20358. doi: 10.1038/srep20358
186. Won EJ, Ju JK, Cho YN, Jin HM, Park KJ, Kim TJ, et al. Clinical relevance of circulating mucosal-associated invariant T cell levels and their anti-cancer activity in patients with mucosal-associated cancer. *Oncotarget*. (2016) 7:76274–90. doi: 10.18632/oncotarget.11187
187. Duan M, Goswami S, Shi JY, Wu LJ, Wang XY, Ma JQ, et al. Activated and exhausted MAIT cells foster disease progression and indicate poor outcome in hepatocellular carcinoma. *Clin Cancer Res*. (2019) 25:3304–16. doi: 10.1158/1078-0432.ccr-18-3040
188. Sundstrom P, Ahlmanner F, Akeus P, Sundquist M, Alsen S, Yrlid U, et al. Human mucosa-associated invariant T cells accumulate in colon adenocarcinomas but produce reduced amounts of IFN-gamma. *J Immunol*. (2015) 195:3472–81. doi: 10.4049/jimmunol.1500258

189. Zabijak L, Attencourt C, Guignant C, Chatelain D, Marcelo P, Marolleau JP, et al. Increased tumor infiltration by mucosal-associated invariant T cells correlates with poor survival in colorectal cancer patients. *Cancer Immunol Immunother.* (2015) 64:1601–8. doi: 10.1007/s00262-015-1764-7
190. Rodin W, Sundstrom P, Ahlmanner F, Szeponik L, Zajt KK, Wettergren Y, et al. Exhaustion in tumor-infiltrating Mucosal-Associated Invariant T (MAIT) cells from colon cancer patients. *Cancer Immunol Immunother.* (2021) 70:3461–75. doi: 10.1007/s00262-021-02939-y
191. Fu S, Liu M, Zhu C, Zhang H, Zhao C, Xie Y, et al. Regulatory mucosa-associated invariant T cells controlled by beta1 adrenergic receptor signaling contribute to hepatocellular carcinoma progression. *Hepatology.* (2023) 78:72–87. doi: 10.1097/hep.0000000000000014
192. Yao T, Shoostari P, Haeryfar SMM. Leveraging public single-cell and bulk transcriptomic datasets to delineate MAIT cell roles and phenotypic characteristics in human Malignancies. *Front Immunol.* (2020) 11:1691. doi: 10.3389/fimmu.2020.01691
193. De Biasi S, Gibellini L, Lo Tartaro D, Puccio S, Rabacchi C, Mazza EMC, et al. Circulating mucosal-associated invariant T cells identify patients responding to anti-PD-1 therapy. *Nat Commun.* (2021) 12:1669. doi: 10.1038/s41467-021-21928-4
194. Comont T, Nicolau-Travers ML, Bertoli S, Recher C, Vergez F, Treiner E. MAIT cells numbers and frequencies in patients with acute myeloid leukemia at diagnosis: association with cytogenetic profile and gene mutations. *Cancer Immunol Immunother.* (2022) 71:875–87. doi: 10.1007/s00262-021-03037-9
195. Zheng X, Wang X, Cheng X, Liu Z, Yin Y, Li X, et al. Single-cell analyses implicate ascites in remodeling the ecosystems of primary and metastatic tumors in ovarian cancer. *Nat Cancer.* (2023) 4:1138–56. doi: 10.1038/s43018-023-00599-8
196. Ouyang L, Wu M, Zhao J, Jiang L, Shen Z, Cheng X, et al. Mucosal-associated invariant T cells reduce and display tissue-resident phenotype with elevated IL-17 producing capacity in non-small cell lung cancer. *Int Immunopharmacol.* (2022) 113:109461. doi: 10.1016/j.intimp.2022.109461
197. Melo AM, O'Brien AM, Phelan JJ, Kennedy SA, Wood NAW, Veerapen N, et al. Mucosal-associated invariant T cells display diminished effector capacity in oesophageal adenocarcinoma. *Front Immunol.* (2019) 10:1580. doi: 10.3389/fimmu.2019.01580
198. Huang WC, Hsiao YC, Wu CC, Hsu YT, Chang CL. Less circulating mucosal-associated invariant T cells in patients with cervical cancer. *Taiwan J Obstet Gynecol.* (2019) 58:117–21. doi: 10.1016/j.tjog.2018.11.022
199. Li S, Simoni Y, Becht E, Loh CY, Li N, Lachance D, et al. Human tumor-infiltrating MAIT cells display hallmarks of bacterial antigen recognition in colorectal cancer. *Cell Rep Med.* (2020) 1:100039. doi: 10.1016/j.xcrm.2020.100039
200. Shi L, Lu J, Zhong D, Song M, Liu J, You WH, et al. Clinicopathological and predictive value of MAIT cells in non-small cell lung cancer for immunotherapy. *J Immunother Cancer.* (2023) 11:e005902. doi: 10.1136/jitc-2022-005902
201. Qu J, Wu B, Chen L, Wen Z, Fang L, Zheng J, et al. CXCR6-positive circulating mucosal-associated invariant T cells can identify patients with non-small cell lung cancer responding to anti-PD-1 immunotherapy. *J Exp Clin Cancer Res.* (2024) 43:134. doi: 10.21239/ssrn.4718402
202. Yao T, Rudak PT, Laumont CM, Michaud AR, Rashu R, Knier NN, et al. MAIT cells accumulate in ovarian cancer-elicited ascites where they retain their capacity to respond to MRI ligands and cytokine cues. *Cancer Immunol Immunother.* (2022) 71:1259–73. doi: 10.1007/s00262-021-03118-9
203. Vorwald VM, Davis DM, Van Gulick RJ, Torphy RJ, Borgers JS, Klarquist J, et al. Circulating CD8(+) mucosal-associated invariant T cells correlate with improved treatment responses and overall survival in anti-PD-1-treated melanoma patients. *Clin Transl Immunol.* (2022) 11:e1367. doi: 10.1002/cti.1367
204. Favreau M, Venken K, Faict S, Maes K, De Veirman K, De Bruyne E, et al. Both mucosal-associated invariant and natural killer T-cell deficiency in multiple myeloma can be countered by PD-1 inhibition. *Haematologica.* (2017) 102:e266–70. doi: 10.3324/haematol.2017.163758
205. Jarvis EM, Collings S, Authier-Hall A, Dasyam N, Luey B, Nacey J, et al. Mucosal-associated invariant T (MAIT) cell dysfunction and PD-1 expression in prostate cancer: implications for immunotherapy. *Front Immunol.* (2021) 12:748741. doi: 10.3389/fimmu.2021.748741
206. Ninkov M, Schermer CL, Moradzadeh M, Parvathy SN, Figueredo R, Burton JP, et al. Improved MAIT cell functions following fecal microbiota transplantation for metastatic renal cell carcinoma. *Cancer Immunol Immunother.* (2023) 72:1247–60. doi: 10.1007/s00262-022-03329-8
207. Gherardin NA, Loh L, Admojo L, Davenport AJ, Richardson K, Rogers A, et al. Enumeration, functional responses and cytotoxic capacity of MAIT cells in newly diagnosed and relapsed multiple myeloma. *Sci Rep.* (2018) 8:4159. doi: 10.1038/s41598-018-22130-1
208. Priya R, Brutkiewicz RR. MRI tetramer-based artificial APCs expand MAIT cells from human peripheral blood that effectively kill glioblastoma cells. *Immunohorizons.* (2021) 5:500–11. doi: 10.4049/imunohorizons.2100003
209. Rha MS, Han JW, Kim JH, Koh JY, Park HJ, Kim SI, et al. Human liver CD8+ MAIT cells exert TCR/MRI-independent innate-like cytotoxicity in response to IL-15. *J Hepatol.* (2020) 73:640–50. doi: 10.1016/j.jhep.2020.03.033
210. Petley EV, Koay HF, Henderson MA, Sek K, Todd KL, Keam SP, et al. MAIT cells regulate NK cell-mediated tumor immunity. *Nat Commun.* (2021) 12:4746. doi: 10.1038/s41467-021-25009-4
211. Ruf B, Catania VV, Wabitsch S, Ma C, Diggs LP, Zhang Q, et al. Activating mucosal-associated invariant T cells induces a broad antitumor response. *Cancer Immunol Res.* (2021) 9:1024–34. doi: 10.1158/2326-6066.cir-20-0925
212. Ruf B, Bruhns M, Babaei S, Kedei N, Ma L, Revsine M, et al. Tumor-associated macrophages trigger MAIT cell dysfunction at the HCC invasive margin. *Cell.* (2023) 186:3686–705.e32. doi: 10.1016/j.cell.2023.07.026
213. Habaz IA, Ou X, Wang NI, Schincaglia A, Shydlouskaya V, Mahendran A, et al. MAIT cells promote cancer progression and regulatory T cell accumulation in bladder tumor microenvironment. *J Immunother Cancer.* (2025) 13:e012496. doi: 10.1136/jitc-2025-012496
214. Lukasik Z, Elewaut D, Venken K. MAIT cells come to the rescue in cancer immunotherapy? *Cancers (Bsl).* (2020) 12:413. doi: 10.3390/cancers12020413
215. Bayatipoor H, Mehdizadeh S, Jafarpour R, Shojai Z, Pashangzadeh S, Motallebnezhad M. Role of NKT cells in cancer immunotherapy-from bench to bed. *Med Oncol.* (2022) 40:29. doi: 10.1007/s12032-022-01888-5
216. Maakaron JE, Olszewski AJ, Waller EK, Rajneesh Nath R, Herrera AF, Holmes H, et al. Administration of Low-Dose, Subcutaneous (SC) Interleukin-2 (IL-2) Markedly Enhances the Pharmacokinetic (PK) Profile of Azercabtagene Zaprelucel (azer-cel), an Allogeneic Anti-CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy, without Compromising Safety and Early Evidence of Clinical Activity in Patients with Diffuse Large B-Cell Lymphoma (DLBCL) Who Have Relapsed after Prior CD19-Directed CAR T-Cell Products. *Transplant Cell Ther.* (2025) 31:S222. doi: 10.1016/j.jtct.2025.01.340
217. Rouxel O, Da Silva J, Beaudoin L, Nel I, Tard C, Cagninacci L, et al. Cytotoxic and regulatory roles of mucosal-associated invariant T cells in type 1 diabetes. *Nat Immunol.* (2017) 18:1321–31. doi: 10.1038/ni.3854
218. Cui Y, Franciszkiewicz K, Mburu YK, Mondot S, Le Bourhis L, Premel V, et al. Mucosal-associated invariant T cell-rich congenic mouse strain allows functional evaluation. *J Clin Invest.* (2015) 125:4171–85. doi: 10.1172/jci82424
219. Loh L, Orlicky D, Spengler A, Levens C, Celli S, Domenico J, et al. MAIT cells drive chronic inflammation in a genetically diverse murine model of spontaneous colitis. *Mucosal Immunol.* (2023) 18(4):958–72. doi: 10.1016/j.mucimm.2025.05.006
220. Keretsu S, Hana T, Lee A, Kedei N, Malik N, Kim H, et al. Characterization of MAIT cells in glioblastoma reveals a potential immunosuppressive role through a MAIT-neutrophil axis. *Neuro-Oncol Adv.* (2025) 7:vdafl73. doi: 10.1093/onoan/vdafi73
221. Yasutomi Y, Chiba A, Haga K, Murayama G, Makiyama A, Kuga T, et al. Activated mucosal-associated invariant T cells have a pathogenic role in a murine model of inflammatory bowel disease. *Cell Mol Gastroenterol Hepatol.* (2022) 13:81–93. doi: 10.1016/j.jcmgh.2021.08.018
222. Toubal A, Kiaf B, Beaudoin L, Cagninacci L, Rhimi M, Fruchet B, et al. Mucosal-associated invariant T cells promote inflammation and intestinal dysbiosis leading to metabolic dysfunction during obesity. *Nat Commun.* (2020) 11:3755. doi: 10.1038/s41467-020-17307-0
223. Naidoo K, Woods K, Pellefigues C, Cait A, O'Sullivan D, Gell K, et al. MRI-dependent immune surveillance of the skin contributes to pathogenesis and is a photobiological target of UV light therapy in a mouse model of atopic dermatitis. *Allergy.* (2021) 76:3155–70. doi: 10.1111/all.14994
224. Mak JY, Xu W, Reid RC, Corbett AJ, Meehan BS, Wang H, et al. Stabilizing short-lived Schiff base derivatives of 5-aminouracils that activate mucosal-associated invariant T cells. *Nat Commun.* (2017) 8:14599. doi: 10.1038/ncomms14599
225. Mak JYW, Rivero RJD, Hoang HN, Lim XY, Deng J, McWilliam HEG, et al. Potent immunomodulators developed from an unstable bacterial metabolite of vitamin B2 biosynthesis. *Angew Chem Int Ed Engl.* (2024) 63:e202400632. doi: 10.1002/anie.202400632
226. Berkson JD, Slichter CK, DeBerg HA, Delaney MA, Woodward-Davis AS, Maurice NJ, et al. Inflammatory cytokines induce sustained CTLA-4 cell surface expression on human MAIT cells. *Immunohorizons.* (2020) 4:14–22. doi: 10.4049/imunohorizons.1900061
227. Clutter CH, Re A, Jacobson K, Clement K, Aube J, O'Connell RM, et al. Immune checkpoint expression in mucosal-associated invariant T cells is stimulus-dependent. *J Leukoc Biol.* (2025) 118:qiaf177. doi: 10.1093/jleuko/qiaf177
228. Peng Q, Huang R, Wang H, Xiao H, Wang Y, Zhai Z, et al. Immune characteristics and prognostic implications of mucosal-associated invariant T cells in acute myeloid leukemia. *Cancer Immunol Immunother.* (2023) 72:4399–414. doi: 10.1007/s00262-023-03574-5
229. Zumwalde NA, Haag JD, Gould MN, Gumperz JE. Mucosal associated invariant T cells from human breast ducts mediate a Th17-skewed response to bacterially exposed breast carcinoma cells. *Breast Cancer Res.* (2018) 20:111. doi: 10.1186/s13058-018-1036-5
230. Mo J, Zheng L, Gao Z, Wu J, Bao Y. The study of mucosal-associated invariant T cells in colon cancer and roles in immune activities. *Onco Targets Ther.* (2021) 14:5263–73. doi: 10.2147/ott.s332822

231. Sundstrom P, Szeponik L, Ahlmanner F, Sundquist M, Wong JSB, Lindskog EB, et al. Tumor-infiltrating mucosal-associated invariant T (MAIT) cells retain expression of cytotoxic effector molecules. *Oncotarget*. (2019) 10:2810–23. doi: 10.18632/oncotarget.26866
232. Zheng C, Zheng L, Yoo JK, Guo H, Zhang Y, Guo X, et al. Landscape of infiltrating T cells in liver cancer revealed by single-cell sequencing. *Cell*. (2017) 169:1342–56.e16. doi: 10.1016/j.cell.2017.05.035
233. Shaler CR, Tun-Abraham ME, Skaro AI, Khazaie K, Corbett AJ, Mele T, et al. Mucosa-associated invariant T cells infiltrate hepatic metastases in patients with colorectal carcinoma but are rendered dysfunctional within and adjacent to tumor microenvironment. *Cancer Immunol Immunother*. (2017) 66:1563–75. doi: 10.1007/s00262-017-2050-7
234. Torre P, Brescia A, Giurato G, D'Auria R, Rizzo F, Motta BM, et al. Mucosal-associated invariant T cells in T-cell non-hodgkin lymphomas: A case series. *Cancers (Bsl)*. (2022) 14:2921. doi: 10.3390/cancers14122921
235. Eddy E. Investigating the role of mucosal-associated invariant T (MAIT) cells in brain cancer [PhD Thesis]. University of Melbourne (2004). Available online at: <https://hdl.handle.net/11343/356418>.