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Mucosal-associated invariant T-cells in pulmonary pathophysiology

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Purpose of review
Mucosal-associated invariant T-cells (MAIT) have been associated with lung cancer and pulmonary infections. The treatment of patients with cancer or infections includes host-directed therapies (HDTs). MAIT play a role in shaping the 'milieu interne' in cancer and infections and this review addresses the biology of MAIT in pulmonary pathophysiology.

Recent findings
MAIT represent an attractive target for therapy in pulmonary malignancies and infections. T-cells are often difficult to exploit therapeutically due to the diversity of both T-cell receptor (TCR) repertoire and its ligandome. MAIT-cells are restricted by the major histocompatibility complex class I-related gene protein (MR1) that presents nondefined tumor-associated targets, bacterial products, vitamin and drug derivates. Due to their plasticity in gene expression, MAIT are able to conversely switch from IFN-γ to IL-17 production. Both cytokines play a key role in protective immune responses in infections and malignancies. MAIT-derived production of interleukin (IL)-17/TGF-β shapes the tumor micro-environment (TME), including tissue re-modelling leading to pulmonary fibrosis and recruitment of neutrophils. MAIT contribute to the gut-lung axis associated with clinical improved responses of patients with cancer to checkpoint inhibition therapy. MAIT are at the crossroad of HDTs targeting malignant and infected cells. Clinical presentations of overt inflammation, protective immune responses and tissue re-modeling are reviewed along the balance between Th1, Th2, Th9, and Th17 responses associated with immune-suppression or protective immune responses in infections.

Summary
MAIT shape the TME in pulmonary malignancies and infections. Drugs targeting the TME and HDTs affect MAIT that can be explored to achieve improved clinical results while curbing overt tissue-damaging immune responses.

Keywords
host-directed therapy, interleukin-17, lung cancer, mucosal-associated invariant T-cells major histocompatibility complex class I-related gene protein, microbiome

INTRODUCTION/TISSUE MICROENVIRONMENT

Tumors are complex ecosystems composed of neoplastic cells, extracellular matrix and accessory nonneoplastic cells which include inflammatory immune cells. A crosstalk between cancer cells and accessory cells contributes to tumor development. During tumor formation, the tissue architecture evolves into a specialized microenvironment that may either be pro-tumor promoting or antitumor directed.

Conventional αβ T-cells mobilize cellular immune responses by recognizing antigens bound to major histocompatibility complex (MHC) molecules present on the surface of antigen-presenting cells (APCs). MHC I is expressed on all somatic cells with a low expression level in cells of neuronal origin [1,2]. In case of infection or malignant transformation, recognition of an MHC-peptide complex may trigger

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KEY POINTS

- Mucosal-associated invariant T-cells (MAIT) are restricted by the major histocompatibility complex class I-related gene protein (MR1) that presents ill-defined tumor-associated targets, bacterial products, vitamin derivates or drug-compounds, MAIT immune effector functions can also be triggered by viral infections via cytokines, independent of MR1 restriction.
- MAIT exhibit epigenetic plasticity and are able to conversely switch from interferon-γ to interleukin-17 production, there are therefore viable targets for drug interventions tilting the tissue microenvironment to an anti- or pro-inflammatory *milieu*. Cytokine production by MAIT contributes to ICI responses in patients with lung cancer.
- MAIT constitute up to 15% in lung-associated immune cells and play a role in lung cancer, acute bacterial/viral infections, or chronic pulmonary infectious diseases.
- MAIT play a role in pulmonary pathophysiology: preexisting chronic obstructive pulmonary disease -associated MAIT can influence later in life the TME and prognosis of patients with lung cancer.
- Anti-MR1 directed and tumor-specific MAIT-derived T-cell receptors may present viable molecular tools to engineer transgenic cells with a broad application independent of classical MHC molecules since MR1 is commonly shared among humans.

elimination of the target cell by effector mechanisms such as exocytosis of perforin and granzyme granules. The TCR is comprised of an α and β-chain, which are composed of complementary determining loops (CDR1, CDR2 and CDR3) that are collectively unique to every TCR and amount to the rich diversity of TCRs. One of the drawbacks of T-cells limiting their therapeutic use in transgenic cells targeting shared tumor-associated antigens, i.e. KRAS mutations (as used for patients with colorectal cancer or pancreatic ductal adenocarcinoma [3▪▪]), is the diversity of the TCR repertoire that does not allow effective targeting of individual specific clones, if MHC-peptide specific TCRs have been eliminated or negatively selected during thymic education – or that certain tumor-associated targets are limited by the use a very distinct set of MHC restricting elements, as shown for KRAS mutations (e.g. HLA-A3, A11 or Cw0802 or distinct MHC class II molecules) [4]. A crosstalk between cancer cells and accessory cells may contribute to tumor development. Epigenetic changes in transformed and nontransformed cells may either be pro-tumor promoting or antitumor directed (Fig. 1).

Mucosal-associated invariant T-cells (MAIT) represent an attractive population in designing cell therapies since they are restricted by a commonly shared minor histocompatibility antigen MHC class I-like molecule ((MR1). MAIT are a part of the 'unconventional T-cell family', like γδ T-cells, that recognize metabolite antigens presented by MR1 and CD1d, respectively [5,6]. γδ T-cells, in a similar fashion as natural-killer T-cells (NKT), respond to phosphoantigens from infected cells or transformed cells displaying butyrophilin molecules. Like other unconventional T-cell subsets, the MR1-reactive T-cell family is far more complex than initially believed [7,8▪].

MUCOSAL-ASSOCIATED INVARIANT T-CELLS

MAIT were first described in 1993 by Porcelli as $CD4^{-}CD8^{-}$ T-cells purified from peripheral blood of healthy subjects [9]. Porcelli and his team performed TCR cloning intending to better understand the function of those double negative ($CD4^{-}CD8^{-}$) T-cells and identified an enriched expression of a semi-invariant TCR, namely the TRAV1-2TRAJ33 (TCRVα7.2) α-chain. A decade later, Treiner *et al.* [10] showed that these T-cells are preferentially located in mucosal tissues such as the gut lamina propria, dubbing them for the first time as 'mucosal-associated invariant T-cells'. In addition to expressing a semi-invariant α-chain, MAIT also express a limited diversity of TCR β-chains (predominantly TRVβ-6 or TRVβ20 families) and recognize antigens presented by MR1, a minor histocompatibility complex I-(MHC) protein dependent on beta-2 microglobulin [7,11–15].

MR1 is ubiquitously expressed in most nucleated human cells, but surface expression is transient. This monomorphic antigen-presenting molecule is highly preserved throughout mammalian evolution, suggesting an important physiological role in immunity [16▪▪]. MAIT are activated by a wide range of microbial metabolites in a MR1-dependent manner and rapidly mount an inflammatory response. MR1 may act as a pattern recognition receptor since its upregulation triggers an innate-like response. MAIT are capable of recognizing metabolites derived from the biosynthesis of riboflavin (vitamin B2) which is also a broadly conserved pathway among bacterial species and yeast. Microbes, unable to synthesize B2, have evolved into uptaking B2 through transporters, such as *Enterococcus faecalis*. Folate (vitamin B9) and its derivatives are also recognized by MAIT, yet they have been described to be nonagonistic [7,11,14,17,18], at least defined by the immune effector functions

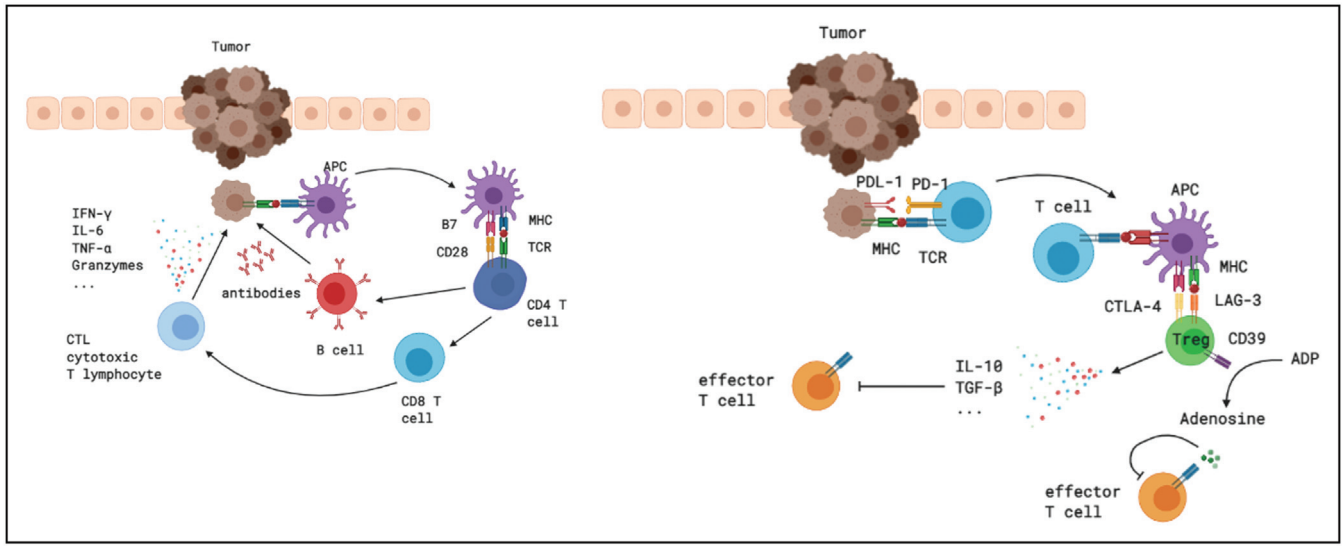

FIGURE 1. Tissue (tumor) microenvironment. Left: complex interplay of antitumor directed antibodies, T-cells and augmentation of immune responses by professional antigen presenting cells, i.e. B-cells and T-cells. MAIT aid in the production of IL-6, TNFα and granzyme B/perforin and they are triggered by bacterial products. Right: Antitumor/pathogen directed immune responses may lead to immune exhaustion and subsequent production of TGFbeta and IL-10, both are immune-suppressive in concert with CD39 which cleaves ATP into immune-suppressive adenosine.

tested up to now. It is believed that this balance between agonistic versus nonstimulatory targets may facilitate the effective surveillance of the breach of barrier function by microflora that activate proinflammatory cytokines – or leads to tissue repair and restauration of barrier integrity [11,14]. Dysbiosis in gut microbiota has been associated with dysfunctional MAIT responses – this may be particularly important in the gut:lung axis shaped by the intestinal microbiome. MAIT are absent in germ-free mice and are restored with the re-introduction of bacteria [7].

The first reported ligand of MR1, 6-formylpterin (6-FP), is a product of the photosynthetic breakdown of folic acid. It has been reported not to stimulate MAIT and displays competitive inhibition with MAIT agonists such as 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) and 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OE-RU) [7,16▪▪], both derivatives from riboflavin. These metabolites form a covalent bond within the MR1 via Schiff base involving a lysine residue at position 43 of MR1 that sits in the binding pocket [7,15,19]. Over more than 20 compounds have been described to bind to MR1 and to modulate MAIT cell activity, including common drugs such as formyl salicylic acids (compound of aspirin) and diclofenac (more commonly known for its muscle relaxant and anti-inflammatory properties) [7,20]. The role of such antidrug directed MAI T-cells in pulmonary pathophysiology has yet to be defined.

While viral pathogens have not been described to be presented by MR1, they can still elicit MAIT activation in a TCR-independent pathway by cytokine [interleukin (IL)-18/IL-12] and/or chemokine production. The MAIT response to pathogens is intensified with cytokine stimulation in concert with MR1-bound antigen recognition [13].

MAIT mount innate-like responses that resemble a 'classical' T-cell maturation / differentiation phenotype. MAIT encompass mainly the costimulatory CD8 molecules, characterized by co-expression of CD26, CD161 (commonly associated NK marker) and CD69 [14,16▪▪,21].

MAIT can produce interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-17A and secrete perforin-granzymes coupled with CD107a, allowing degranulation, conferring either a Th1 or Th17 profile [13,22–24] (Fig. 2). MAIT exhibit a distinct expression of transcription factors: the retinoic related orphan receptor γ (ROR γt) and T-box transcription box factor (Tbet), they may also be stratified into IL-17 and IFN-γ producing lineages [21,23]. MAIT are able to potentiate dendritic cell maturation as well as B cell activation by recruiting other immune cells – and present therefore key players in biologically and clinically relevant immune responses in pulmonary malignancies and infections.

MAIT constitute in humans between 1% and 8% of peripheral blood T-cells, they are greatly enriched in the liver (up to 40% of all T-cell infiltration) and in pulmonary tissue [13,16▪▪,25]. MAIT express chemokine receptors that mediate tissue homing (like CXCR6, CXCR9), which supports with their ability

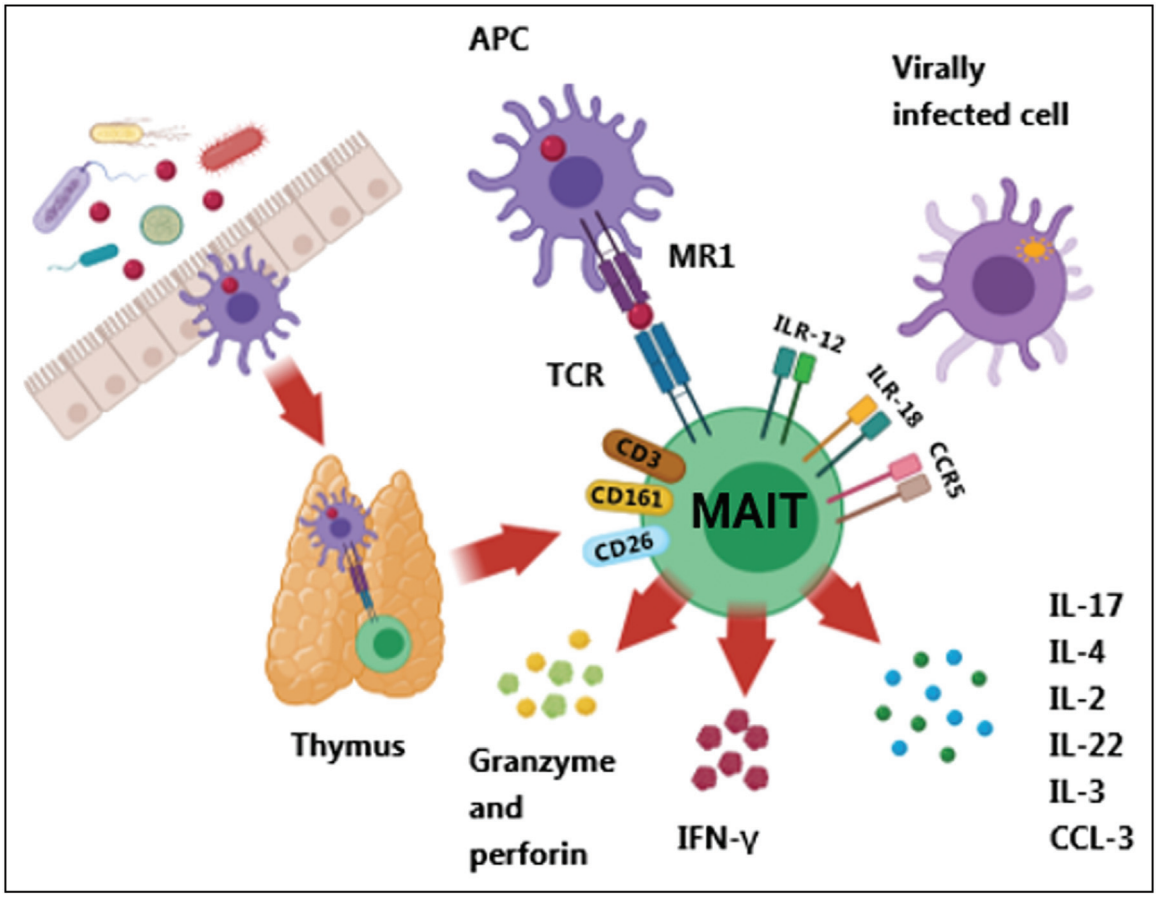

FIGURE 2. Functional MAIT profile. MAIT can be activated via MR1 restricted ligands (Vitamin B derivates, unknown tumor ligands, drug compounds, bacterial products) or – not mutually exclusive - via their cytokine receptors, i.e. IL-18R, IL-12R and CCR5 by factors released by viral infected cells. MAIT are activated by different bacterial pathogens or commensals and produce Th1, Th2 or Th17 – associated cytokines. MAIT are flexible in regard to their unique possibility of epigenetic reprogramming from Th17 to Th1 cells which enables them to orchestrate the local immune response targeting cancer cells or intracellular pathogens. IL-17 production is useful in antifungal responses and to terminate overt inflammatory responses.

to migrate into their target organs [25]. Although MAIT are actively engaged in promoting barrier function and preventing pathogen entry, their function has been extended to immunomodulation in cancer. There is a viable possibility that (cancer – directed) endogenous MR1 ligands are recognized, professional APCs, i.e. dendritic cells and B cells express MR1 [13] and may present engulfed target antigens via MR1. Extracellular expression of MR1 is low in the absence of its nominal ligands and therefore remains intracellularly in an unfolded conformation in the endoplasmic reticulum until it transiently relocates to the surface when antigen binding occurs [13,19].

MUCOSAL-ASSOCIATED INVARIANT T-CELLS IN LUNG PATHOLOGIES

The pulmonary interface is in constant contact with potential pathogens, allergens, smoke, pollutants and other harmful agents. MAIT were found to be enriched in the lung, encompassing up to 15% of the entire tissue resident immune population [26]. MAIT are essential for safeguarding the integrity of the mucosal barrier and homeostasis. Due to their polyfunctional immune effector potency, activated MAIT are linked to a broad clinical spectrum of respiratory disorders, autoimmune disease or cancer [13]. MAIT may not only be stimulated in *situ*, yet they are most likely are influenced by the gut microbiome, which shapes systemic immune responses. A recent preclinical study showed that a gut-derived protozoan imprints the immunological 'milieu' of the lung: airway inflammation was increased, while systemic MTB was prevented [27]. This preclinical study confirmed the biologically and clinically relevant observations that gut-derived *Akkermansia muciniphila* (Akk) has been associated with responses to checkpoint inhibition (ICI) in patients with nonsmall cell lung cancer and a more recent

shotgun-metagenomics-based gut microbiome in patients with NCSLC confirmed the observation that fecal Akk is associated with improved ICI responses in patients associated with an inflamed antitumor directed tumor microenvironment [28▪▪]. The role of MAIT in antitumor directed immune responses, particularly in the gut-lung-axis, needs to be further analyzed. The presence of bacterial species in PDAC has been associated with increased survival, including *Pseudoxanthomas*, *Streptomyces*, *Saccharopolyspora* and *Bacillus* [29] and the role of MAIT is currently being explored in immune responses directed against bacteria that confer increased clinical survival. MAIT have also been proven to be protective in pulmonary infections, they curb off *Mycobacterium tuberculosis* (MTB) and Legionella pneumophila associated with increased IFN-γ, granzyme B and TNF-α production [26]. Perhaps the best example that MAIT may either play a protective or disease – aggravating role is that the link of MAIT with severity of symptoms in SARS-COVID-2 (COVID-19) [30].

MAIT can be activated by viral pathogens in a MR1/TCR independent, cytokine-driven manner, typically with IL-18, IL-15 and IL-12 in a synergistic effect [23], as observed with hepatitis A, B and C virus, dengue virus, HIV and influenza A virus infections. SARS-CoV-2 and other coronaviral species induce production of IL-18 and IL-12 which subsequently activate MAIT and induce production of IFN-γ and TNF-α in order to protect against viral infections [31]. MAIT cytokine release could also assist in tissue repair and recruit neutrophils to the site of infection. However, dysregulated or perpetuated responses could culminate in a cytokine storm, proinflammatory cytokines could lead to toxic shock and tissue damage [32].

Chronic obstructive pulmonary disease (COPD) is characterized by long-term airway inflammation exacerbated by activated CD8+ T-cell infiltration. Nontypeable Haemophilus influenzae (NTHi) is the principal bacterial pathogen during COPD aggravations, and a study by Hinks *et al.* reported that NTHi served as a target for MAIT. The frequency of MAIT is decreased in peripheral blood from patients with COPD as compared with blood from healthy control donors – associated with increased clinical COPD sequelae and lung pathology [33–36]. Migration of MAIT to the inflamed lung tissue is associated with increased COPD symptoms, particularly if MAIT secret predominantly IL-17. Standard corticosteroid administration contributes to functional MAIT dysregulation, this has also been found to be true for cigarette smoke exposure [37,38▪]. A similar pattern concerning MAIT involvement and increased inflammation was seen in asthma [39], cystic fibrosis [37] and lung sarcoidosis [40].

MUCOSAL-ASSOCIATED INVARIANT T-CELLS AND LUNG CANCER

Lung cancer is often diagnosed when curative treatment options are limited. The 5-year survival rate varies from 4% and 17% depending on the disease stage [41▪]. Won *et al.* reported low MAIT cell frequencies in the peripheral circulation of patients with lung cancer and this was further linked with N staging, hypothesizing that MAIT may support tumor progression [42]. In 2020, a study conducted by Yan *et al.*, investigated the interplay of MAIT in a murine model of lung metastasis. MAIT deficient mice showed reduced tumor initiation, development and metastasis by overturning NK cell antitumor capacities in a MR1-dependent fashion [43]. Yet a landmark study by Crowther *et al.* showed in 2021 that MAIT recognized malignant transformed cells, yet not healthy cells [16▪▪]. The combination of a commonly shared restricting element between patients and a commonly shared (not yet defined tumor-associated) target makes MAIT (and a tumor-reactive MAIT-TCR) a viable therapeutic instrument to design cell therapies using smart cell contextual decision making [44▪].

Patients with NSCLC who responded to neoadjuvant immunotherapy, targeting PD-1, exhibited a prominent MAIT infiltrate in the tumor tissue – and this was solely observed in patients who suffer from COPD. One may hypothesize that MAIT associated with COPD have already been present in the tissue and could be re-invigorated upon cancer development and PD-1 therapy joining a biologically relevant anticancer directed immune responses [45▪]. Moreover, Yin and colleagues [45▪], demonstrated that the frequency of MAIT in the peripheral circulation is associated with ICI responses and subsequently increased MAIT functions defined by increased IFN-γ and granzyme B production. These elegant studies suggested that targeting 'exhausted MAIT' may be clinically relevant. Shi *et al.* [46] showed previously similar trends analyzing immune checkpoint inhibitor (ICI) efficacy in patients with NSCLC. MAIT were enriched in tumor lesions and exhibited an exhausted phenotype with upregulated PD-1 and increased IL-17 expression as compared to IFN-γ elaborated *in situ.* Responses to anti-PD1 therapy was associated with MAIT characterized with a Th1 profile (producing IFN-γ) whereas patients resistant to therapy exhibited MAIT with Th17 related gene expression (Fig. 3). This points to the flexibility to reprogram MAIT and to be able to reverse the exhausted phenotype into better treatment outcomes associate with MAIT-derived IFN-γ production. MAIT migrated from peripheral blood via the CCR6–CCL20 axis into the tissue; CCR6 + MAIT have been reported in cancer lesions from patients with

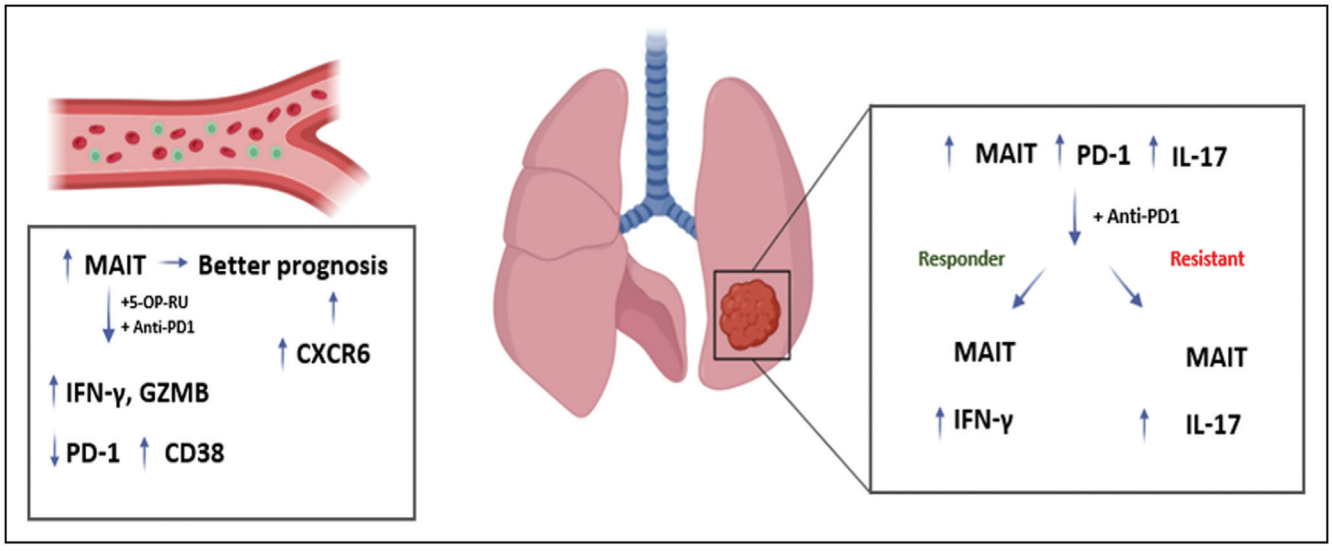

FIGURE 3. MAIT in lung cancer treatment and prognosis. Increased MAIT frequencies, producing IFN−γ and granzyme B in the peripheral circulation along with increased CXCR6 expression, is associated with improved prognosis. Anti-PD1 therapy targeting Th1-MAIT is associated with increased clinical responses and overt IL-17 production with (ICI) therapy resistance.

NSCLC by Ouyang *et al.* [47], most likely representing MAIT which entered the tumor lesion from the blood – and not from tissue resident cells; exhausted MAIT were more prevalent in tumor tissue as compared to peri-tumoral tissue [47] and tumor-associated MAIT produced IL-17.

Zhang *et al.* [48] showed in a pilot study a positive correlation between activated, circulating $CD8^+$ MAIT, expressing $CD38^+$ and a decreased progression-free survival of patients with lung cancer. This was accompanied with high levels IFN-γ, IL-6 and IL-8 -inflammatory cytokines in the serum of these patients. Although this $CD8^+CD38^+$MAIT population has been suggested to serve as a meaningful biomarker for responsiveness to treatment, Sundstrom and coworkers [49▪] were unable to reproduce such a MAIT – associated immune profile in a similar cohort – and could not detect significant differences between ICI- responders and patients with progressive disease. Nonetheless, immune checkpoint blockade facilitated MAIT polyfunctionality with a more pronounced production of IFN-γ and TNF-α.

A more granular analysis of MAIT in ICI responses using single-cell RNA sequencing was directed by Qu and colleagues [50] and this study solidified the increased frequency of activated CD8+MAIT in PBMCs from patients with improved responses to anti-PD-1 therapy. Thus, increased MAIT frequency may serve as predictive biomarker for efficacy of immunotherapy in patients with lung cancer, particularly if MAIT express cytotoxicity-related genes such as CCL4, KLRG1, PRF1, NCR3, NKG7, GZMB and KRK1. The proportion of CXCR6+$CD8^+$MAIT into tissue was proposed to serve as an indicator for progression-free survival. MAIT seem to play an ambiguous role in patients with different cancer histologies along with altered MAIT frequencies in the peripheral circulation and different (Th1/Th17) cytokine profiles. T-cell survival, expansion and cytotoxic profiles are epigenetically imprinted in the TME by cell-to-cell contact, the presence of bacteria and via soluble factors.

MAIT represent an attractive target to consider in combinatorial therapies in patients with lung cancer, particularly in patients with preexisting nonmalignant diseases as discussed above, like COPD, or patients presenting with fibrotic remodeling of the lung and arterial hypertension. There is an unmeted need to use the extraordinary flexibility of MAIT which can be reprogrammed into Th1– cytokine (antitumor directed) producing cells and influenced by pulmonary and gut microbiotic therapeutic interventions. MAIT – with the potential to be reprogrammed into 'pan-cancer' directed cells [51] await further exploitation in phase I/II clinical studies – yet their role in the pathophysiology in anticancer directed and antipathogen directed immune responses in the lung is well established and could be used in smart immunotherapeutic treatment modalities using the commonly shared MR1 molecules as the restricting element [52].

MAIT-DIRECTED PRODUCTS AND CLINICALLY RELEVANT LUNG PATHOPHYSIOLOGY IN TARGETED THERAPY

MAIT play a role in pulmonary pathology, i.e. in lung cancer, acute bacterial and viral pulmonary

infections, or chronic pulmonary infectious diseases such as tuberculosis. Independent of the causative agent for inflammation, a deleterious pathway is certainly the production of fibrotic tissue which appears to be a nonreversible process. Removing systemic IL-17 which attracts immature bone marrow derived cells has already been proposed in the management of SARS-Cov-2 infections using monoclonal antibodies that have been shown to be safe and effective for the treatment of patients with psoriasis [53]. Although causes may be different and patients enjoy the clearance of chronic or acute pulmonary infections, obstructive and fibrotic tissue formations may still be presented after effective pathogen clearance – and MAIT can drive such responses [54].The same is also true for patients with pulmonary cancer where immunotherapy, i.e. checkpoint inhibition and targeted therapies of driver mutations, e.g. gene products coding for anaplastic lymphoma kinase (ALK) or gene fusions or epidermal growth factor receptor (EGFR). These therapies are not able to confer cure yet patients are able to enjoy improved (NSCL)-specific survival [55]. The armentarium in the fight against lung cancer was enriched in November 2023 as the Food and Drug Administration (FDA) approved Repotrectinib, a next generation TKI for certain forms of advanced lung cancers that exhibit a fusion of the ROS1 gene, including those with resistance against mutations which made ROS1 gene targeting resistant to earlier generations of TK1 inhibitions [56▪]. Common pathways in the pulmonary infections and changes in the tumor – microenvironment (TME) involve four different reactivity patterns of the immune system, i.e. the balance of Th1, Th2, Th9 (which plays a role in asthma) and Th17 responses. IL-17 represents a double-edge sword with a protective role in *MTB* infections, fungal infections, protective anti-Yersinia infections [57], yet may also facilitate recruitment of innate cells with immune-suppressive and tissue-restructuring properties. Timing dosing and local versus IL-17 production area is associated with different IL-17 effects: balanced Th1: Th17 responses are associated with protective anti-MTB responses and overt Th17 with tissue-remodeling and damage [57]. IL-17 producing cells can swiftly switch to from IL-17 – producing cells to cells that produce IFN-g resembling Th1 cells, reflecting a high plasticity which may be explored with HDAC inhibitors. IL-17 producing cells can display plasticity in cytokine production in vivo and are able to switch from predominantly producing IL-17 to predominantly producing IFN-γ, thereby resembling Th1 cells [58]. This is of particularly therapeutic interesting since neutrophils from patients with COPD are associated with corticosteroid resistance in part due to interference with HDAC2 promoter activity [59]. Clinically relevant immune responses against MTB is dependent on IL-17, in part via the formation of tertiary lymphoid structures in the lung [60]. Untimely IL-17 blockade may therefore negatively interfere with IL-17-driven protective immune responses, while overt IL-17 production is associated with increased neovascularization and immune-suppression [57]. Since MAIT play a central role in lung homeostasis, a better understanding of MAIT in immunopathology will aid to select repurposed drugs in alleviating treatment- and disease related effects on pulmonary function in patients undergoing treatments for lung cancer or infectious diseases, since MAIT express receptors for chemokines, C-type lectin receptors (CD161), and receptors for IL-12 (Th1 responses), IL-18 and IL-17 [61–63]. Antifibrotic drugs, both approved in 2024 include Pirfenidone [64] and Nintedanib [65] and Saracatinib, a tyrosine kinase inhibitor, appeared to be superior in preclinical studies in reducing inflammation associated pulmonary fibrosis. Sotatercept, a fusion protein acting as a 'neutralizing trap' for selected TGF-β superfamily members has been shown to inhibiting pulmonary growth factors including activins associated with pulmonary tissue remodeling and subsequent pulmonary arterial hypertension [66▪▪]. PDE4B Inhibition has also been shown to be a viable therapy in curbing (idiopathic) pulmonary fibrosis [67]. Mitigating MAIT-associated overt inflammation may include treatment with MSCs (mesenchymal stromal cells), a double-edged sword [68]. Bacterial endotoxin effects on pulmonary injuries has been shown to be mitigated by MSCs, as was the pro-inflammatory, damaging effect in drug-resistant TB using autologous MSCs [69]. Other sequelae affecting patients after severe viral or bacterial, including MTB pneumonia is the formation of bronchiectasis affecting 500/100 000 individuals. Several trials are underway using mesenchymal stromal cells to tune down overt pulmonary inflammation land prevention of (clinically negative) tissue remodeling [70]. These clinical trials addressed the unmet need to mitigate postinfection associated bronchiectasis, where MAIT-derived cellular products are involved in pathophysiology, e.g. the WILLOW phase 2 trial showed using brensocatib (inhibiting dipeptidyl peptidase), as well as the ASPEN trial (NCT04594369). A cathepsin C inhibitor trial (NCT05238675) and an alpha 1-proteinase inhibitors targets airway inflammation neutrophil function (NCT05582798), all of which are affected – in part – by MAIT derived cell products. Timing of cytokine neutralization targeting destructive immune effector functions of MAIT may include neutralizing antibodies directed against IL-17A (CNTO6785, phase 2), anti-Th2 directed immune

responses associated with increased tissue remodeling (anti-IL-5, Mepolizumab, phase 3, IL-5 receptor directed mAb Benralizumab, phase 3), anti-IL-13 (Lebrikizumab, phase 2, anti-IL-4 Receptor, Dupilumab, phase 3) [71]. MAIT are very rich in Granzyme B production, a serine protease leading to DNA damage and apoptosis, leading to tissue remodeling. VTI-1002 is a potent small-molecule candidate of granzyme B inhibition, which has not been tested in phase I clinical trials [72]. Combinatorial therapies for patients with lung cancer, severe pulmonary infections, chronic pulmonary inflammatory diseases, such as COPD, may explore MAIT as biologically relevant surrogate biomarkers to gauge response to therapies, epigenetically versatile cells that can relatively easily switched to a Th1-type, anticancer/pathogen directed response and providers for a selective anti 'pan-cancer' derived immune effector population including the use of a cancer specific, MR1-resctricted TCR to construct smart cell therapies for patients with pulmonary malignancies.

CONCLUSION

Combinatorial therapies for patients with lung cancer, severe pulmonary infections, chronic pulmonary inflammatory diseases, such as COPD, may explore MAIT-cells as biologically relevant surrogate biomarkers to gauge response to therapies. MAIT are epigenetically versatile cells that can relatively easily switched to a Th1-type, i.e. to an anticancer/pathogen directed response. MAIT cells recognizing specifically transformed cells may provide for a selective anti 'pan-cancer' derived immune effector population including the use of a cancer specific, MR1 - restricted TCR to construct smart cell therapies for patients with pulmonary malignancies.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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