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ANNUAL REVIEWS

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Decoding Innate T Cell Functionality in Tumor Immunity and Therapeutic Response

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Keywords

innate T cells, iNKT cells, γδ T cells, MAIT cells, tumor immunity, cancer immunotherapy

Abstract

Innate T cells, including invariant natural killer T (iNKT) cells, mucosal-associated invariant T (MAIT) cells, and γδ T cells, bridge innate and adaptive immunity through rapid responses to nonpeptide antigens, metabolites, and stress-associated signals. In cancer, these populations can promote tumor surveillance through cytotoxicity, type 1 cytokine production, tissue-resident immune monitoring, and activation of broader antitumor networks. However, their functions are highly context dependent. Within suppressive tumor microenvironments, tumor-infiltrating unconventional T cell compartments may contain developmentally programmed innate-like subsets together with recruited or locally differentiated cells displaying

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dysfunctional, regulatory, or IL-17-associated features that support myeloid cell recruitment, chronic inflammation, immune evasion, and therapy resistance. This review discusses the major recognition pathways, functional states, microbiota- and metabolite-dependent regulation, and therapeutic targeting of iNKT, MAIT, and γδ T cells in cancer. We further highlight emerging strategies to harness these cells through endogenous activation, combination immunotherapy, and engineered cell platforms while limiting tumor-promoting inflammatory programs and treatment-associated toxicity.

INTRODUCTION

Tumor immunity is shaped not only by conventional αβ T cells but also by unconventional T lymphocytes that can integrate antigenic, cytokine, metabolic, microbial, and tissue-derived signals within the tumor microenvironment (TME). Among unconventional T cell populations, invariant natural killer T (iNKT) cells, mucosal-associated invariant T (MAIT) cells, and subsets of γδ T cells can acquire innate-like features that position them between innate and adaptive immunity. They express T cell receptors with restricted or semi-invariant recognition features, respond rapidly to nonpeptide antigens or stress-associated cues, and can produce cytokines or cytotoxic mediators without requiring the same priming requirements as conventional T cells (Li et al. 2022, Pinco & Facciotti 2025). These properties allow innate T cells to act as early sensors of tissue perturbation and as regulators of downstream dendritic cell, natural killer (NK) cell, myeloid cell, B cell, and $CD8^+$ T cell responses.

It is important to distinguish unconventional T cells as a broad immunological category from the subset of unconventional T cells that acquire innate-like effector functions during development. Unconventional T cells are commonly defined by nonclassical antigen recognition, restricted or semi-invariant T cell receptor (TCR) usage, or major histocompatibility complex (MHC)-independent recognition pathways and include iNKT cells, MAIT cells, and diverse γδ T cell populations (Godfrey et al. 2018, Hackstein & Klenerman 2023). By contrast, bona fide innate-like T cells acquire rapid effector potential during thymic development or early-life differentiation, often adopting transcriptional and functional programs that resemble helper T cell polarization, including type 1-, type 2-, or type 17-like states (Constantinides & Belkaid 2021, Lee et al. 2020, Parker & Ciofani 2020). This distinction is particularly relevant for γδ T cells, which include both developmentally preprogrammed innate-like subsets and lymphoid, naive-like, or adaptive-like populations that can undergo peripheral differentiation after activation (Jensen et al. 2008, McMurray et al. 2022, Parker & Ciofani 2020). Therefore, throughout this review, we use the term "innate-like T cells" to refer primarily to unconventional T cell subsets or functional states with rapid effector capacity, while recognizing that the broader unconventional T cell compartment is heterogeneous and includes cells with distinct developmental histories, tissue distributions, and differentiation potentials.

Each innate T cell lineage uses distinct recognition pathways that are highly relevant to cancer immunity. iNKT cells recognize lipid antigens presented by CD1d, MAIT cells recognize MR1-presented microbial and metabolite-derived ligands, and γδ T cells sense phosphoantigens, butyrophilin-dependent signals, and stress-associated ligands in a largely MHC-independent manner (Laub et al. 2025, Sanjari Pour et al. 2026). Through these pathways, innate T cells can detect transformed cells, microbial metabolites, dysregulated lipid metabolism, and cellular stress programs that may be missed by classical peptide–MHC surveillance. In tumors, they can

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mediate direct cytotoxicity, promote type 1 inflammation, license antigen-presenting cells, and amplify adaptive antitumor immunity.

However, innate T cells are not uniformly protective. Their functions are highly context dependent and can shift according to tumor type, tissue site, antigen availability, cytokine polarization, microbiota-derived signals, metabolic stress, hypoxia, and checkpoint regulation. In some settings, iNKT, MAIT, and γδ T cells support tumor control through IFN-γ production, cytotoxicity, and immune cell cross talk. In others, tumor-infiltrating unconventional T cell compartments are enriched for cells with dysfunctional, regulatory, or IL-17-associated features that can reinforce inflammation, recruit suppressive myeloid cells, promote angiogenesis, or weaken cytotoxic immunity (Fiala et al. 2024, Hu et al. 2023, Shyanti et al. 2024). Importantly, such diversity should not necessarily be interpreted as direct interconversion among fixed innate-like effector states but may reflect the combined effects of developmental programming, tissue-selective seeding, recruitment of naive-like or adaptive-like unconventional T cells, and local differentiation within evolving TMEs.

Innate-like T cells have attracted increasing therapeutic interest because their tissue-homing properties, rapid effector functions, restricted TCR repertoires, and compatibility with allogeneic or engineered cell platforms may help address antigen heterogeneity and immune suppression (Courtney et al. 2023, X. Fang et al. 2025, Niedzielska et al. 2025). However, their responsiveness to inflammatory and metabolic cues also creates risks, including cytokine toxicity, dysfunction, and reinforcement of tumor-promoting programs.

In this review, we discuss how iNKT, MAIT, and γδ T cell subsets recognize tumors, contribute to distinct tumor-associated functional programs, and are being therapeutically targeted or engineered for cancer immunotherapy. We first summarize the major recognition pathways used by these lineages, including CD1d-restricted lipid recognition; MR1-restricted metabolite sensing; and butyrophilin-, phosphoantigen-, and stress-associated γδ T cell activation. We then examine cytotoxic, tissue-resident, cytokine-driven, dysfunctional, tumor-promoting, and microbiota- or metabolite-regulated states within tumors. Finally, we discuss emerging therapeutic strategies, including endogenous activation, combination approaches, adoptive transfer, chimeric antigen receptor (CAR)-engineered innate T cells, and design principles needed to maximize antitumor activity while minimizing safety risks.

INNATE T CELL RECOGNITION PATHWAYS IN TUMOR IMMUNITY

CD1d-Restricted Lipid Recognition by Invariant Natural Killer T Cells

iNKT cells are innate T cells that recognize lipid antigens presented by the MHC-I-like molecule CD1d, enabling rapid cytokine production and coordination of innate and adaptive immune responses (Godfrey et al. 2010, Rossjohn et al. 2012). Unlike conventional αβ T cells, which recognize peptide antigens presented by MHC molecules, iNKT cells express a semi-invariant TCR composed of an invariant TCR-α chain paired with a limited set of TCR-β chains. In mice, this invariant TCR-α chain is encoded by TRAV11-TRAJ18, whereas in humans it is encoded by TRAV10-TRAJ18. These chains pair with restricted TCR-β usage, most commonly Vβ8.2, Vβ7, or Vβ2 in mice and Vβ11 in humans (Godfrey et al. 2010, Rossjohn et al. 2012). This conserved TCR architecture allows iNKT cells to recognize a range of CD1d-presented lipid antigens, with α-galactosylceramide (α-GalCer) serving as the prototypical experimental agonist (Hayashizaki et al. 2024, Praveena & Le Nours 2024).

iNKT cells can respond to microbial glycolipids, endogenous self-lipids, and synthetic agonists such as α-GalCer. In tumors, the CD1d–iNKT axis is further shaped by antigen-presenting cell

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availability, tumor CD1d expression, lipid–antigen presentation, and local immune suppression, which may either support tumor immunosurveillance or enable immune evasion (Shyanti et al. 2024, Tian et al. 2024). Upon activation, iNKT cells rapidly produce diverse cytokines, including IFN-γ, IL-4, IL-17, and other effector mediators, allowing them to shape dendritic cell activation, NK cell function, $CD8^+$ T cell responses, B cell immunity, and myeloid cell behavior. Thus, iNKT cells act as lipid-sensing immune regulators whose antitumor or immunosuppressive effects depend on antigen context, cytokine polarization, tissue localization, and the surrounding TME.

MR1-Restricted Metabolite Sensing by Mucosal-Associated Invariant T Cells

MAIT cells are a specialized population of innate T lymphocytes characterized by expression of a semi-invariant TCR, typically comprising a conserved TRAV1–2 α-chain paired with a limited repertoire of TCR-β chains (Huang et al. 2009). Unlike conventional αβ T cells, which recognize peptide antigens presented by classical MHC molecules, MAIT cells recognize small-molecule metabolites presented by the nonpolymorphic MHC class I–related molecule MR1. These antigens are primarily derived from the microbial riboflavin (vitamin B2) biosynthetic pathway, which is present in many bacteria and fungi (McWilliam & Villadangos 2020).

Among the most potent MAIT cell agonists identified to date are 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) and the related ligand 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OE-RU) (Corbett et al. 2014). These unstable metabolites are generated through the spontaneous condensation of the riboflavin intermediate 5-amino-6-D-ribitylaminouracil (5-A-RU) with reactive carbonyl compounds such as methylglyoxal and glyoxal. Following ligand formation, MR1 captures and stabilizes these metabolites through formation of a Schiff-base interaction within the MR1 antigen-binding cleft. Ligand binding promotes MR1 folding and trafficking from intracellular compartments to the cell surface, where the MR1-ligand complex can be recognized by MAIT cells (McWilliam et al. 2016).

Butyrophilin-, Phosphoantigen-, and Stress-Associated Recognition by γδ T Cells

γδ T cells are an unconventional subset of T lymphocytes that recognize and kill antigens without MHC restriction, allowing them to respond rapidly against tumor cells that evade immunity by downregulating MHC molecules (Gao et al. 2023). One of the major mechanisms of γδ T cell activation involves phosphoantigen (pAg) sensing by circulating Vγ9Vδ2 T cells (Cieslak & Shahbazi 2025, Gao et al. 2023). Unregulated metabolism in tumor cells results in the accumulation of endogenous pAgs that are detected indirectly through the butyrophilin BTN2A1/BTN3A1 complex (Cieslak & Shahbazi 2025). Binding of pAgs to BTN3A1 induces conformational changes that allow BTN2A1 to transmit activation signals to the Vγ9 chain of the γδ TCR, triggering cytotoxic activation (Cieslak & Shahbazi 2025). This pathway enables Vγ9Vδ2 T cells to recognize metabolic stress and eliminate tumor cells through perforin, granzyme B, and proinflammatory cytokine release (Cieslak & Shahbazi 2025, Herrmann & Karunakaran 2024). Other subsets of γδ T cells recognize stress-associated ligands, rather than pAgs. Tissue-resident Vδ1 T cells respond to ligands such as MICA, MICB, and ULBPs expressed on stressed or transformed cells, often via NKG2D and other NK receptors (Herrmann & Karunakaran 2024). These interactions support tissue immunosurveillance and potent antitumor activity (Herrmann & Karunakaran 2024). Together, BTN-, phosphoantigen-, and stress-associated recognition pathways position γδ T cells as promising targets for cancer immunotherapy.

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FUNCTIONAL STATES OF INNATE T CELLS IN TUMOR MICROENVIRONMENTS

Cytotoxic and Type 1 Antitumor Programs

The recognition pathways described above provide unconventional and innate-like T cells with diverse routes for sensing tumors, but their antitumor relevance ultimately depends on the functional programs represented within the tumor-infiltrating T cell compartment (**Figure 1**). Across iNKT cells, MAIT cells, and γδ T cells, one of the most prominent protective states is a cytotoxic, type 1 inflammatory program characterized by IFN-γ and TNF-α production, expression of cytolytic molecules, and activation of surrounding innate and adaptive immune populations. These programs allow innate T cells to contribute to tumor control not only through direct killing but also by reshaping local immune networks.

iNKT cells also couple cytotoxicity with immunoregulatory functions. Tumor cells expressing CD1d can be directly eliminated through perforin-, granzyme B–, TRAIL-, and Fas/FasL-mediated mechanisms (Bae et al. 2019). Upon activation, iNKT cells secrete large quantities of IFN-γ, TNF-α, GM-CSF, and other cytokines that activate dendritic cells, NK cells, macrophages, and $CD8^+$ T cells, establishing a positive feedback loop that reinforces antitumor immunity (Bae et al. 2019). Recent work has demonstrated that TCR-engineered iNKT cells can simultaneously target malignant cells while remodeling suppressive myeloid populations within the TME, resulting in superior tumor control compared with conventional TCR-engineered $CD8^+$ T cells (Delfanti et al. 2022).

MAIT cells can acquire type 1 effector activity in response to inflammatory cytokines abundant in infected, injured, or malignant tissues. IL-12, IL-18, IL-15, and type I interferons can activate MAIT cells independently of MR1-mediated TCR engagement, inducing rapid production of IFN-γ, TNF-α, granzyme B, and other effector molecules (Choi & Lee 2026). This cytokine-driven responsiveness is particularly relevant in tumors, where antigen presentation may be heterogeneous but inflammatory cues remain available. Tissue-resident MAIT cells, especially in the liver, can also express NK-associated receptors such as CD56 and NKG2D, supporting innate cytotoxicity and responsiveness to stressed target cells (Choi & Lee 2026). Experimental evidence demonstrates that activated MAIT cells can directly inhibit tumor growth and lyse human colon cancer cells, accompanied by increased production of antitumor cytokines and recruitment of immune effector populations (Cheng et al. 2024).

γδ T cells similarly occupy cytotoxic and type 1 functional states within tumors. Rather than restating their recognition mechanisms, their antitumor activity can be understood as the functional consequence of stress-associated tumor alterations. Activated γδ T cells release perforin and granzymes to induce tumor cell apoptosis and produce IFN-γ and TNF-α, which can directly limit tumor proliferation while enhancing the activity of nearby immune cells (Zhu et al. 2024). In addition to direct cytotoxicity, γδ T cells act as immunologic amplifiers within the TME. Through secretion of IFN-γ, TNF-α, and GM-CSF, they promote activation of macrophages, monocytes, and dendritic cells; support reciprocal interactions with plasmacytoid dendritic cells; and strengthen Th1-skewed antitumor responses (Gao et al. 2023). These functions can enhance antigen presentation, costimulatory signaling, and downstream adaptive immunity, positioning γδ T cells as both tumor-killing effectors and coordinators of broader immune activation.

Tissue-Resident and Barrier-Associated Programs

Tissue-resident and barrier-associated programs represent tissue-imprinted configurations in which unconventional and innate-like T cells localize to peripheral tissues and tumor sites, often through developmental seeding, early-life niche establishment, and local retention rather than

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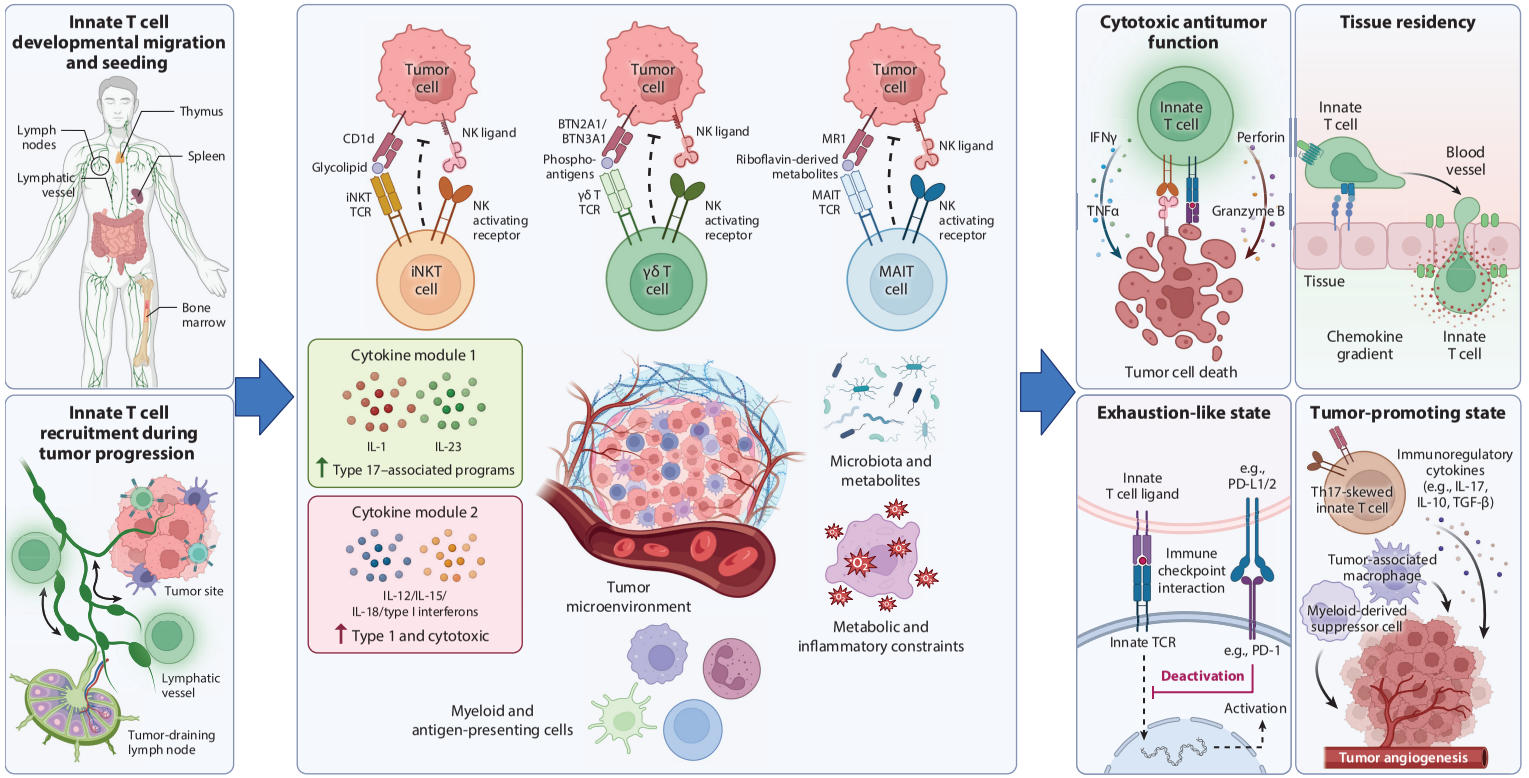

Figure 1

Developmental origin, tumor sensing, and functional programming of innate T cells in cancer. Innate T cell compartments in tumors are shaped by both preexisting developmental programs and tumor-derived environmental cues. During development and early-life tissue seeding, innate T cells distribute to peripheral organs and barrier sites, where they establish tissue-biased populations before tumor initiation. During tumor progression, these resident or tissue-associated cells may be supplemented by recruited innate T cells that traffic through lymphatic vessels, tumor-draining lymph nodes, blood, and tumor tissues. Within the tumor microenvironment, iNKT cells, γδ T cells, and MAIT cells sense tumor-associated signals through CD1d-presented glycolipids, BTN2A1/BTN3A1- associated phosphoantigen recognition, MR1-presented riboflavin-derived metabolites, and NK receptor–ligand interactions. These recognition pathways are integrated with cytokine modules, microbiota-derived metabolites, myeloid and antigen-presenting cells, metabolic and inflammatory constraints, and tissue-associated programs. IL-1/IL-23-associated signals favor type 17–associated programs, whereas IL-12/IL-15/IL-18/type I interferon–associated signals support type 1 and cytotoxic programs. Depending on developmental origin, tissue context, recruitment, and local tumor cues, tumor-associated innate T cells may contribute to cytotoxic antitumor activity, tissue residency or recirculation, checkpoint-associated dysfunction, or inflammatory/regulatory programs that can lead to myeloid recruitment, tumor angiogenesis, and immune suppression. Abbreviations: iNKT, invariant natural killer T; MAIT, mucosal-associated invariant T; NK, natural killer; TCR, T cell receptor. Figure adapted from images created in BioRender; Chen Y. 2026. **https://www.biorender.com/4mcq0k8**.

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continuous recirculation alone (Sun et al. 2019). These populations are often enriched at epithelial and barrier surfaces, such as the gut, lung, liver, and skin, which are common sites of tumor development and chronic inflammation (Sun et al. 2019). Within TMEs, these tissue compartments provide specialized niches that shape innate T cell location, activation state, and functional specialization, resulting in resident populations that differ significantly across organ and tumor sites (J. Li et al. 2025). Thus, these functional states represent dynamically regulated functional adaptations of their local microenvironment, rather than fixed lineage-defined cell states.

A developmental perspective is essential for interpreting tissue-resident unconventional T cells in tumors. Several innate-like T cell populations are not generated within tumors but are seeded into peripheral tissues during fetal, neonatal, or early-life windows, where they occupy tissue niches before tumor initiation. This principle is particularly well-established for γδ T cells, which arise in developmental waves and distribute to barrier tissues with subset-specific functional biases. IL-17-producing γδ T cell populations are enriched in barrier tissues such as skin and mucosa, where they are poised to respond to IL-1- and IL-23-associated inflammatory cues, whereas type 1–biased innate-like populations, including NKT1, MAIT1, and γδT1 cells, are more prominent in tissues such as liver and spleen and are associated with T-bet expression, IFN-γ production, and cytotoxic activity (Constantinides & Belkaid 2021, Haas et al. 2012, Jensen et al. 2008, Khairallah et al. 2018). Therefore, the innate-like T cell compartment encountered during early tumor development may reflect preexisting developmental and tissue-imprinted programs rather than tumor-induced differentiation alone. As tumors progress, however, these resident populations can be supplemented by circulating, lymphoid, or naive-like unconventional T cells that are recruited into tumor tissues and draining lymph nodes, where local antigenic, cytokine, microbial, and metabolic signals may further shape their differentiation and effector function. This framework helps distinguish preexisting tissue-imprinted innate-like programs from tumor-associated recruitment and local differentiation and avoids assuming direct interconversion among fixed innate-like effector states.

Importantly, tissue association should not be interpreted as absolute tissue confinement. Although some unconventional T cell populations display bona fide tissue residency, other tissue-associated innate-like or unconventional T cells may recirculate through lymphatic vessels, draining lymph nodes, and blood; this has been shown most clearly for human MAIT cells that are detectable in lymph draining from peripheral tissues, indicating that at least part of the MAIT cell compartment can exit tissues and reenter circulation under steady-state conditions (Voillet et al. 2018). More broadly, tissue-associated T cells can exist along a continuum between stable residency and recirculation, with lymphatic egress allowing cells activated in peripheral tissues to access draining lymph nodes and potentially influence antigen presentation, immune priming, memory maintenance, and systemic redistribution (Masopust & Soerens 2019, Piconese et al. 2020). In cancer, this concept suggests that unconventional T cells may contribute not only within the tumor parenchyma but also in tumor-draining lymph nodes, where they could shape dendritic cell activation, cytokine availability, and recruitment or expansion of additional effector populations. Thus, tissue-resident and recirculating unconventional T cell compartments should be considered together when evaluating how innate-like T cells sustain or limit antitumor immunity.

Tissue residency is maintained through the coordinate regulation of trafficking and retention pathways (J. Li et al. 2025). Resident innate T cells exhibit downregulation of egress-associated molecules, such as S1PR1 and CCR7, which limit tissue release and systemic recirculation, and upregulation of retention markers, including CD69, CD103, and CD49a (J. Li et al. 2025, Y.-R. Li et al. 2025a). These retention markers promote adhesion and localization and suppress egress signaling (Sun et al. 2019). Tissue residency is also stabilized by key regulators, such as Hobit, Blimp-1, and Runx3, which aid in long-term persistence and self-renewal capacity in tissues by

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repressing recirculation-associated genes (J. Li et al. 2025, Sun et al. 2019). However, the expression of residency-associated markers should be interpreted together with developmental history, tissue localization, and functional evidence of retention or egress. Together, these transcriptional and receptor networks support sustained local immune surveillance within tumors while coexisting with recirculating unconventional T cell populations that may connect tumor tissues, draining lymph nodes, and blood.

Cytokine Modules and Antigen-Independent Activation

Although TCR-dependent recognition remains central to iNKT, MAIT, and γδ T cell biology, these populations can also respond to cytokine-defined inflammatory modules that partially bypass antigen recognition. These modules should not be viewed as generic activation signals, because different cytokine combinations promote distinct effector outputs. One major axis involves IL-1 family cytokines together with IL-23, which supports type 17–associated programs characterized by IL-17A, IL-17F, GM-CSF, and/or IL-22 production. This pathway is particularly relevant for γδT17 cells and other barrier-associated innate-like populations, where IL-1β and IL-23 can amplify preexisting type 17 programs or promote extrathymic differentiation of IL-17-producing γδ T cells during inflammation (Chien et al. 2014, Muschaweckh et al. 2017, Parker & Ciofani 2020, Sutton et al. 2009). In tumors, such IL-1/IL-23-dependent circuits may reinforce neutrophil and myeloid cell recruitment, angiogenesis, and inflammatory immune suppression, although their consequences remain highly tissue and context dependent.

A second cytokine module involves IL-18 combined with STAT-activating cytokines such as IL-12, IL-15, or type I interferons. This axis preferentially promotes type 1 and cytotoxic outputs, including IFN-γ production and, in some contexts, granzyme B or perforin expression. In MAIT cells, IL-12 or IL-15 together with IL-18 can induce antigen-independent IFN-γ production and cytotoxic mediator release, while type I interferon–driven MAIT cell activation is often amplified by cooperation with IL-12 or IL-18 to generate robust effector responses (Camard et al. 2025, Hinks & Zhang 2020, Ussher et al. 2014). Similar cytokine-dependent activation has been reported for iNKT cells and γδ T cells. In iNKT cells, IL-12, IL-18, and type I interferon–associated inflammatory signals can promote IFN-γ production independently of direct microbial lipid recognition or strong TCR ligation under infectious or inflammatory conditions (Reilly et al. 2010, Subleski et al. 2011, Tyznik et al. 2008). In γδ T cells, cytokines including IL-2, IL-15, IL-12, IL-18, and IL-21 can promote IFN-γ production, cytotoxic mediator expression, or type 1 differentiation, in part through MAPK/ERK- and T-bet/Eomes-associated pathways (Ribot et al. 2014, Silva-Santos et al. 2019). These pathways are relevant to cancer because tumor-associated dendritic cells, macrophages, epithelial cells, and stromal cells can generate inflammatory cytokine milieus capable of shaping unconventional T cell activation even when CD1d-, MR1-, or γδ TCR–dependent antigen recognition is limited or heterogeneous.

Cytokine-mediated and TCR-mediated activation are not functionally equivalent. TCR ligation provides antigen-specific signals that can induce outputs not fully reproduced by cytokines alone, and the relative contribution of TCR versus cytokine signaling differs across lineages and functional states. For example, robust iNKT cell IL-4 production is most commonly associated with CD1d-dependent TCR engagement by glycolipid antigens such as α-GalCer, whereas cytokine-driven activation through IL-12 and IL-18 more strongly favors IFN-γ-dominant responses (Kohlgruber et al. 2016, Reilly et al. 2010, Subleski et al. 2011). In MAIT cells, cytokine stimulation can induce rapid IFN-γ and cytotoxic programs, whereas TCR stimulation through MR1-presented ligands can elicit broader inflammatory cytokine and chemokine responses depending on costimulation and cytokine context (Hinks & Zhang 2020, Ussher et al. 2014).

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Therefore, cytokine-driven activation should not be described simply as weaker or stronger than TCR ligation. Rather, these pathways generate qualitatively different response programs that may cooperate, diverge, or compete within the TME.

Dysfunction, Checkpoint Regulation, and Exhaustion-Like States

Chronic antigen exposure, persistent inflammatory signaling, metabolic stress, and inhibitory receptor engagement can impair the effector functions of unconventional and innate-like T cells within tumors. However, it remains unclear whether these changes represent an exhaustion program analogous to that described in conventional $CD8^+$ T cells. In conventional T cells, exhaustion is defined not simply by reduced cytokine production or checkpoint receptor expression but by coordinated transcriptional, epigenetic, developmental, and functional remodeling that accompanies chronic antigen stimulation. Although tumor-infiltrating iNKT, MAIT, and γδ T cells frequently exhibit features consistent with dysfunction, including reduced cytokine production, impaired cytotoxicity, altered tissue localization, and increased expression of inhibitory receptors, the extent to which these cells undergo a comparable exhaustion program remains an active area of investigation. Therefore, checkpoint expression and functional impairment should be distinguished from T cell exhaustion unless supported by additional mechanistic evidence.

For iNKT cells, tumor-associated dysfunction has been linked to reduced frequency, impaired cytokine production, and increased expression of inhibitory receptors such as PD-1, TIM-3, and TIGIT in several cancer settings (Balasko et al. 2023, Zhang et al. 2019). These changes may limit IFN-γ production, dendritic cell licensing, NK cell activation, $CD8^+$ T cell recruitment, and type 1 antitumor immunity. However, inhibitory receptor expression should not by itself be interpreted as evidence of exhaustion, because these molecules may also reflect recent activation, tissue adaptation, or regulatory feedback. Repeated stimulation with potent CD1d agonists such as α-GalCer can induce anergy-like iNKT cell states associated with impaired secondary cytokine responses and PD-1/PD-L1 signaling, but such anergy-like hyporesponsiveness should be distinguished from the broader transcriptional and epigenetic exhaustion programs defined in conventional T cells (Parekh et al. 2009, Wang et al. 2020).

MAIT cells also show evidence of checkpoint-associated dysfunction in tumors. In colorectal liver metastases, tumor-infiltrating MAIT cells are reduced in frequency and exhibit impaired IFN-γ production despite preserved expression of IL-12Rβ1 and IL-18Rα, suggesting functional impairment that is not explained simply by loss of cytokine receptor expression (Shaler et al. 2017). In hepatocellular carcinoma, tumor-infiltrating MAIT cells have been reported to display impaired infiltration and activation/dysfunction-associated features, including increased PD-1, CD25, and HLA-DR expression, as assessed by flow cytometry, single-cell RNA sequencing, imaging, and computational analyses (Ruf et al. 2023). These observations support the presence of dysfunctional or checkpoint-regulated MAIT cell states in tumors. However, whether these states correspond to conventional T cell exhaustion remains unresolved, because many studies do not yet establish the full transcriptional, epigenetic, metabolic, and developmental criteria used to define exhaustion in conventional $CD8^+$ T cells (Blank et al. 2019).

γδ T cells are similarly susceptible to functional impairment within suppressive TMEs. In preclinical three-dimensional spheroid and organoid tumor models, tumor-infiltrating γδ T cells showed increased expression of CTLA-4, PD-1, and PD-L1 compared with control conditions (Ou et al. 2022). Hypoxic tumor regions and metabolic stress can further reduce γδ T cell proliferation, cytotoxicity, and effector differentiation, while some inflammatory environments favor IL-17A-producing γδ T cell programs (Corsale et al. 2021, Sureshbabu et al. 2020). These findings indicate that γδ T cells can become functionally constrained by checkpoint, metabolic,

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and cytokine-mediated signals in tumors. Nevertheless, increased checkpoint expression, reduced cytotoxicity, or type 17 skewing should be interpreted as evidence of altered functional state or dysfunction rather than definitive exhaustion unless supported by integrated molecular and functional analyses (Blank et al. 2019).

Regulatory phenotypes also require careful interpretation. IL-10-producing NKT10-like cells have been described as a distinct regulatory iNKT cell subset under some conditions (Sag et al. 2014). However, IL-10 expression should not be treated as equivalent to exhaustion or uniformly immunosuppressive activity. In cancer, IL-10 can have context-dependent effects, including immunoregulatory functions, as well as potential support of antitumor $CD8^+$ T cell activity and tumor immune surveillance (Dennis et al. 2013, Salkeni & Naing 2023). Therefore, IL-10-producing unconventional T cell states should be discussed in terms of their cellular source, tumor context, and functional consequences rather than being automatically classified as exhausted or tumor promoting.

Collectively, current evidence indicates that unconventional T cells frequently exhibit checkpoint-associated dysfunction within TMEs. However, caution is warranted when applying the terminology of T cell exhaustion to these populations. Unlike conventional $CD8^+$ T cells, for which exhaustion is supported by well-defined transcriptional, epigenetic, metabolic, and developmental programs, comparable evidence remains limited for iNKT, MAIT, and γδ T cells. Many studies rely primarily on inhibitory receptor expression or reduced cytokine production, which alone are insufficient to establish an exhaustion state. Future work will be required to determine whether innate-like T cells undergo exhaustion or instead adopt distinct dysfunctional states unique to their developmental origin, tissue context, and activation biology.

Tumor-Promoting and Immunoregulatory Programs

Innate T cells exhibit substantial functional plasticity within the TME, where chronic antigen exposure, metabolic stress, hypoxia, and suppressive cytokine networks can drive the acquisition of tumor-promoting and immunoregulatory phenotypes. Although iNKT, MAIT, and γδ T cells possess potent antimicrobial and cytotoxic functions under physiological conditions, evidence indicates that these populations can be reprogrammed within tumors to support cancer progression.

Among MAIT cells, multiple studies have identified enrichment of IL-17A-producing subsets within solid tumors, including colorectal cancer, breast cancer, non-small-cell lung cancer, and hepatocellular carcinoma (Choi & Lee 2026, Yigit et al. 2024). IL-17A contributes to tumor progression through several mechanisms, including the recruitment and expansion of myeloid-derived suppressor cells, promotion of angiogenesis through vascular endothelial growth factor (VEGF)-associated pathways, and establishment of a chronic inflammatory environment favorable to tumor growth (X. Zhang et al. 2025). In addition, tumor-infiltrating MAIT cells frequently exhibit altered transcriptional profiles characterized by expression of immunoregulatory and exhaustion-associated genes and chemokines such as IL-8 and CXCL12, suggesting functional reprogramming (Choi & Lee 2026, Duan et al. 2019).

Inflammatory γδT17 populations represent another major source of IL-17A in several tumor settings and have been implicated in the recruitment or functional polarization of neutrophils and myeloid-derived suppressor cells (MDSCs) (Cieslak & Shahbazi 2025, Fiala et al. 2024, Hu et al. 2023). Expansion or enrichment of these cells has been associated with tumor-promoting inflammation in colorectal cancer, hepatocellular carcinoma, breast cancer, ovarian cancer models, and other malignancies, although much of the evidence remains tumor and model dependent (Fiala et al. 2024, Hu et al. 2023, Luo et al. 2024). Recent evidence further suggests that

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IL-17-producing γδ T cells can contribute to therapy resistance by recruiting MDSCs and suppressing T cell–mediated antitumor immunity following radiotherapy (Deng et al. 2025, Galluzzi & Celià-Terrassa 2025). These findings support the concept that type 17–skewed innate T cells can promote tumor-associated inflammation and immunosuppression, although their effects remain context dependent and vary by tumor type, tissue site, and local cytokine milieu.

Context-dependent protumor or immunosuppressive activity has also been reported within iNKT cells. Although iNKT cells are classically associated with rapid cytokine production, dendritic cell licensing, NK cell activation, and antitumor immunity, their function can be redirected or impaired within suppressive TMEs. In some settings, altered CD1d–lipid antigen presentation, chronic stimulation, inhibitory receptor expression, and myeloid cell interactions can limit iNKT cell activation and intratumoral motility, thereby weakening tumor immunosurveillance (Shyanti et al. 2024, Tian et al. 2024). iNKT cells may also acquire regulatory features, including IL-10-producing NKT10-like states, which can dampen inflammatory immune responses and reduce antitumor effector activity under some conditions (McEwen-Smith et al. 2015, Sag et al. 2014). Together, these observations emphasize that iNKT cells should not be viewed as uniformly protective. Rather, their function is shaped by tissue context, lipid–antigen availability, cytokine polarization, metabolic stress, and the suppressive architecture of the TME.

Microbiota and Metabolite Control of Innate T Cell Responses

Microbial communities and metabolic signals can shape innate-like T cell function within tumors by altering antigen availability, inflammatory cytokine responses, and metabolic fitness. Human tumor–infiltrating MAIT cells in colorectal cancer exhibit evidence of TCR-dependent activation by bacterial antigens, including those derived from *Fusobacterium nucleatum*, a species enriched in colorectal tumors relative to other cancers (Li et al. 2020). These findings suggest that tumor-associated microbiota can directly shape MAIT cell activation and function through the MR1–TCR axis. Consistent with this concept, administration of the potent MAIT cell agonist 5-OP-RU increased MR1-dependent antigen presentation by melanoma cells and enhanced MAIT-mediated tumor control in vivo, highlighting the therapeutic potential of manipulating microbial metabolite recognition pathways (Petley et al. 2021). The gut microbiome can also influence MAIT cell activity indirectly. In patients with metastatic renal cell carcinoma, fecal microbiota transplantation increased MAIT cell activation, reduced PD-1 expression, and enhanced cytokine production following stimulation, indicating restoration of functional responsiveness despite cancer-associated immunosuppression (Ninkov et al. 2023).

Metabolic signals within the TME further shape MAIT cell responses. In hepatocellular carcinoma, tumor-derived kynurenine promotes differentiation of $CD4^+$ MAIT cells toward an IL-17-producing phenotype through activation of the aryl hydrocarbon receptor and glycolytic pathways, establishing a metabolic cross talk that supports tumor growth and progression (Fu et al. 2026). In contrast, lactate conditioning can enhance MAIT cell oxidative metabolism; mitochondrial respiration; and production of IFN-γ, TNF-α, and granzymes, thereby strengthening cytotoxic function (Berisha et al. 2026). However, chronic exposure to polyunsaturated fatty acids can induce lipid peroxidation, metabolic exhaustion, and ferroptosis in MAIT cells, resulting in impaired antitumor activity and poorer outcomes in hepatocellular carcinoma (Deschler et al. 2025).

Microbiota-dependent regulation also extends to γδ T cells and iNKT cells. Commensal bacteria are essential for maintaining antitumor γδ T cell responses in the lung, as antibiotic-mediated depletion impairs γδT17 cell activity and increases susceptibility to tumor development (Cheng et al. 2014). However, under certain conditions, local microbiota may promote tumor progression

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by stimulating IL-1β- and IL-23-dependent activation of IL-17-producing γδ T cells, thereby creating a protumor inflammatory environment (Jin et al. 2019). Similarly, microbial metabolites regulate hepatic iNKT cell responses through bile acid metabolism. Secondary bile acids generated by intestinal bacteria suppress iNKT cell accumulation and antitumor activity, whereas depletion of bile acid–producing bacteria enhances hepatic iNKT cell recruitment and reduces tumor burden (Gonzatti & Keller 2025). Beyond microbial metabolites, tumor-associated metabolic remodeling can directly impair iNKT cell function. Lactic acid can reduce lipid biosynthesis, mTORC1 signaling, and IFN-γ production in intratumoral iNKT cells, while long-chain acylcarnitines enriched in HBV-associated hepatocellular carcinoma have been linked to premature iNKT cell senescence and impaired responsiveness to activating stimuli (Bai et al. 2023, Cheng et al. 2023, Fu et al. 2020).

THERAPEUTIC TARGETING AND ENGINEERING

Innate T Cells as Biomarkers of Therapeutic Response

Innate T cells may provide clinically useful biomarkers for therapeutic response (Y. Fang et al. 2025b, Y.-R. Li et al. 2025b). Because iNKT, MAIT, and γδ T cells integrate antigenic, cytokine, microbial, and tissue-derived cues, their abundance and functional states can reflect broader immune competence within the TME. For example, circulating MAIT cells were reported to be enriched in metastatic melanoma patients responding to anti-PD-1 therapy, with responder-associated MAIT cells showing increased CXCR4 expression and granzyme B production (De Biasi et al. 2021). In non-small-cell lung cancer, MAIT cell subsets also showed predictive relevance, with cytotoxic IFN-responsive MAIT states enriched in responsive tumors and exhausted/Th17-like MAIT states associated with nonresponsive tissues (Shi et al. 2023). γδ T cells may similarly carry prognostic and predictive information. Pan-cancer γδ TCR analyses have revealed cancer-type-specific clonotype diversity and suggested that γδ TCR signatures derived from bulk RNA-sequencing may serve as prognostic biomarkers (Yu et al. 2024). Innate T cell biomarkers' predictive value also depends on tissue localization, activation state, checkpoint expression, cytokine profile, and spatial proximity to tumor, stromal, and myeloid compartments, consistent with evidence that the prognostic and therapeutic relevance of immune infiltrates is shaped by tumor immune contexture and spatial organization (Fridman et al. 2012, Fu et al. 2021). Future biomarker strategies should integrate peripheral immune monitoring with single-cell and spatial profiling of tumor tissues (Y.-R. Li et al. 2026a, W. Liu et al. 2024).

Pharmacologic Activation of Endogenous Innate T Cells

Pharmacologic activation of endogenous innate T cells offers an attractive strategy to amplify antitumor immunity without the complexity of cell manufacturing. One established example is activation of iNKT cells with α-GalCer, a potent CD1d-presented glycolipid agonist. α-GalCer and α-GalCer-pulsed dendritic cells have been evaluated in multiple cancer trials and are generally well-tolerated, but clinical efficacy has been modest, likely reflecting limited iNKT cell abundance, impaired antigen presentation, suboptimal tissue delivery, and tumor-induced immune suppression (Ishikawa et al. 2005, Toyoda et al. 2020, Zhang et al. 2019). These limitations have motivated next-generation glycolipid formulations, dendritic cell–based delivery, and combination approaches designed to improve iNKT activation while avoiding rapid anergy or systemic cytokine toxicity (Y.-R. Li et al. 2026b, Thapa et al. 2009, Zhang et al. 2019). γδ T cells can also be pharmacologically expanded or activated in vivo using aminobisphosphonates such as zoledronate, which increase intracellular phosphoantigen accumulation and stimulate Vγ9Vδ2 T cells, often together with IL-2 (Chen et al. 2025b, Revesz et al. 2024). Early clinical studies demonstrated

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feasibility and immune activation, although objective responses have been variable (Dieli et al. 2007, Lang et al. 2011). In contrast, pharmacologic activation of MAIT cells remains less clinically mature. MR1 ligands provide a conceptual route to modulate MAIT cell activity, but the dual antitumor and tumor-promoting roles of MAIT cells indicate that ligand-based strategies will require careful control of tissue context, cytokine milieu, and functional polarization (Laub et al. 2025, Vacchini et al. 2020). Overall, endogenous activation strategies must move beyond global stimulation toward targeted delivery, rational combinations, and state-selective reprogramming.

Combination Strategies to Reprogram Innate T Cell States

Since innate T cell function is shaped by antigenic, cytokine, metabolic, and spatial cues, combination therapies may be necessary to convert dysfunctional or tumor-promoting states into productive antitumor programs (**Supplemental Table 1**). For iNKT cells, α-GalCer-based activation may be enhanced by checkpoint blockade, as PD-1/PD-L1 signaling contributes to α-GalCer-induced iNKT anergy and limits repeated stimulation. Blocking this pathway can preserve type 1–skewed iNKT responses and improve antitumor activity in preclinical models (Ribas et al. 2018, Wang et al. 2020). Clinically, α-GalCer-pulsed antigen-presenting cells have been evaluated in recurrent or advanced non-small-cell lung cancer, including a phase 2 study showing acceptable safety but limited objective response, underscoring the need for combinations that improve antigen-presenting cell activation, tumor delivery, and downstream recruitment of NK and $CD8^+$ T cells (Toyoda et al. 2020).

Similar logic applies to γδ T cells. Aminobisphosphonate- or phosphoantigen-based activation can expand Vγ9Vδ2 T cells, but durable tumor control may require checkpoint inhibition, cytokine support, or strategies that improve trafficking and persistence in suppressive solid tumors. Recent reviews emphasize that although zoledronate plus IL-2 remains the most common clinical strategy for in vivo γδ T cell expansion, its efficacy has been limited by suboptimal agonist delivery, variable pharmacodynamic responses, insufficient solid tumor infiltration, and immunosuppressive TMEs (Luo et al. 2024, Revesz et al. 2024). In multiple myeloma, a phase 2 maintenance trial of IL-2 plus zoledronate after autologous transplantation found that the regimen was feasible but showed only modest activity, where γδ T cells increased after treatment, but later cycles were associated with reduced γδ T cell expansion and increased regulatory T cells (Fazzi et al. 2021). These clinical and translational observations support the concept that γδ T cell activation alone is unlikely to be sufficient and may need to be paired with interventions that relieve checkpoint-mediated dysfunction, improve tumor trafficking, or remodel suppressive myeloid and stromal niches (J. Liu et al. 2024, Revesz et al. 2024).

Cytokine combinations are also attractive. IL-15 can support survival, proliferation, and cytotoxic function of innate lymphocytes, whereas IL-12 and IL-18 can promote IFN-γ production and antigen-independent activation (Baughan et al. 2025, Camard et al. 2025, Hinks & Zhang 2020, Nakanishi 2018). However, systemic cytokine toxicity, pleiotropic immune effects, and compensatory immunosuppression remain major barriers, motivating localized delivery, engineered cytokines, masked cytokine prodrugs, and cell-targeted cytokine formulations (An et al. 2026, Salazar et al. 2025, Song et al. 2025, Wang et al. 2026). Recent cytokine engineering reviews highlight this shift toward tumor-localized or immune cell–directed delivery for IL-12, IL-15, and related cytokines (Dong et al. 2024, Fu et al. 2023, Pousse et al. 2025, Salazar et al. 2025). More broadly, clinical experience with innate immune agonists supports the feasibility of combining innate activation with checkpoint blockade. Intratumoral TLR9 agonists have provided clinically relevant examples: Vidutolimod/CMP-001 with or without pembrolizumab showed acceptable safety and promising activity in PD-1 blockade-resistant melanoma, and a phase 1b/2 study of cavrotolimod with anti-PD-1 antibodies evaluated safety, efficacy, and immune effects in advanced

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solid tumors (Milhem et al. 2025a,b). Stimulator of interferon genes (STING) agonists have also been tested clinically with PD-1 blockade. MIW815/ADU-S100 plus spartalizumab was well-tolerated in advanced/metastatic cancers, including anti-PD-1-refractory disease, but produced minimal antitumor responses, while newer ulevostinag data suggest that intratumoral STING agonism can be combined with pembrolizumab, although efficacy and toxicity require further optimization (Harrington et al. 2025, Meric-Bernstam et al. 2023). Together, these examples support state-selective reprogramming rather than nonspecific immune activation.

Adoptive Transfer and CAR-Engineered Innate T Cells

Innate T cells are emerging as promising platforms for next-generation adoptive cell therapies. Compared with conventional αβ T cells, these populations possess restricted TCR repertoires, reducing the risk of graft-versus-host disease (GvHD) and eliminating the need for extensive endogenous TCR editing in allogeneic settings (Y.-R. Li et al. 2025b). In addition, their innate tumor-recognition mechanisms, efficient tissue infiltration, and ability to modulate the TME provide advantages that may help overcome limitations of conventional CAR-T therapies, particularly in solid tumors (Y.-R. Li et al. 2025b, Mathew et al. 2026).

CAR-iNKT cells combine antigen-specific CAR recognition with endogenous CD1d-restricted and NK-like cytotoxic functions, enabling dual targeting of tumor cells and immunosuppressive myeloid populations within the TME (X. Li et al. 2026, Mathew et al. 2026). This strategy has demonstrated potent antitumor activity in preclinical models and encouraging clinical activity in patients with neuroblastoma and metastatic renal cell carcinoma, while maintaining favorable safety profiles and low rates of cytokine release syndrome (CRS) and neurotoxicity (Niedzielska et al. 2025, Tsahouridis et al. 2025).

γδ T cells have likewise emerged as attractive CAR platforms because they retain their innate, MHC-independent tumor recognition after genetic modification. CAR-γδ T cells targeting CD19, CD20, CD38, GD2, and prostate stem cell antigen have demonstrated potent antitumor activity in both hematologic and solid tumor models (X. Li et al. 2026, Mathew et al. 2026, Qin et al. 2021). Importantly, CAR engineering enhances antigen-specific killing while preserving the intrinsic ability of γδ T cells to recognize stressed or antigen-loss tumor variants, potentially reducing the risk of immune escape (Qin et al. 2021). Early clinical studies of allogeneic CAR-γδ T cells have reported favorable safety profiles, complete remissions in B cell malignancies, and no evidence of GvHD (Tsahouridis et al. 2025).

MAIT cells are also being explored as CAR carriers. CAR-MAIT cells targeting CD19, HER2, and mesothelin exhibit potent cytotoxicity comparable to conventional CAR-T cells while maintaining activity in immunosuppressive tumor models (X. Li et al. 2026, Mathew et al. 2026). Notably, CAR-MAIT cells produce lower levels of proinflammatory cytokines and may therefore reduce the risk of treatment-associated toxicities such as CRS (X. Li et al. 2026). Collectively, these studies highlight innate T cells as versatile and potentially safer platforms for off-the-shelf CAR-based immunotherapies capable of combining direct tumor killing with modulation of the TME (X. Li et al. 2026, Y.-R. Li et al. 2025b, Mathew et al. 2026, Niedzielska et al. 2025, Qin et al. 2021, Tsahouridis et al. 2025).

Safety Risks and Therapeutic Design Principles

Unlike conventional αβ T cells, iNKT cells, MAIT cells, and γδ T cells can respond rapidly to antigenic and cytokine-mediated stimulation, enabling potent antitumor activity while increasing the risk of unintended immune activation. Consequently, careful therapeutic design is required to maximize efficacy while minimizing treatment-associated toxicities.

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Among innate T cell platforms, iNKT cell therapies have demonstrated favorable safety profiles and a low propensity to induce GvHD, making them attractive candidates for allogeneic cellular therapies. However, excessive stimulation with potent agonists such as α-GalCer may induce CRS, highlighting the importance of optimizing dosing schedules and routes of administration during clinical development (Jassaud et al. 2026, Sanjari Pour et al. 2026, Wang & Zhang 2025). Although uncommon, severe adverse events including fatal hyperleukocytosis have also been reported following CAR-iNKT cell therapy (Tian et al. 2025). Similar safety considerations apply to MAIT cell and γδ T cell therapies, as all three populations possess robust cytokine-producing capacity that may contribute to inflammatory toxicities if activation is not tightly controlled (Y. Fang et al. 2025b, Klenerman et al. 2021).

Furthermore, under chronic inflammatory and suppressive conditions, these cells may acquire exhausted, regulatory, or IL-17-producing phenotypes that have been associated with impaired antitumor immunity and, in some contexts, tumor progression. However, the precise contribution of IL-17-producing innate T cell subsets remains under active investigation (Saura-Esteller et al. 2022). Consequently, therapeutic targeting of the IL-17 pathway has emerged as a promising strategy to mitigate tumor-promoting inflammatory programs while preserving beneficial antitumor immunity (Kim et al. 2016, Vitiello & Miller 2019).

Accordingly, the next generation of innate T cell–based therapies should incorporate design principles that improve spatial precision, functional durability, and controllability (**Supplemental Figure 1**). First, activation should be tuned by optimizing agonist dose, schedule, and route of delivery, because systemic stimulation may broaden immune activation beyond the intended effector population. Local or tumor-targeted delivery of cytokines, glycolipid agonists, or innate immune agonists may widen the therapeutic window by concentrating immune activation within tumor tissues while reducing systemic inflammatory toxicity (Fu et al. 2023, Salazar et al. 2025). Second, adoptive and engineered cell products should be designed to improve tumor trafficking and persistence without promoting uncontrolled expansion. For solid tumors, this may require selection of tissue-homing subsets, chemokine receptor engineering, cytokine support, or armoring strategies that enhance survival within metabolically and immunologically suppressive TMEs (X. Fang et al. 2025, Revesz et al. 2024). Third, therapeutic potency should be balanced with built-in safety controls. Suicide switches, inducible activation systems, transient engineering approaches, and careful control of cytokine-armored constructs may help limit severe inflammatory toxicities while preserving antitumor activity (Tian et al. 2025). Fourth, since antigen escape and functional plasticity remain major barriers, future platforms may benefit from combinatorial recognition strategies, including dual-antigen CARs, CAR designs paired with native innate recognition, or combinations with checkpoint blockade and innate immune agonists. Recent reviews emphasize that antigen loss, antigen heterogeneity, and suppressive TME adaptation are major causes of CAR therapy resistance and that multitargeted CAR designs, endogenous immune reprogramming, and engineered innate platforms may help reduce reliance on a single tumor antigen (Chen et al. 2025a, B. Zhang et al. 2025). Finally, clinical translation will require standardized manufacturing, release criteria, potency assays, and longitudinal monitoring of infused cells, cytokines, and tumor immune states (Y. Fang et al. 2025a,c; Simon et al. 2025). Together, these principles support a shift from broad innate T cell activation toward state-selective, spatially controlled, and safety-tuned therapeutic programming.

CONCLUSIONS AND FUTURE PERSPECTIVES

Innate-like T cells challenge simple classifications of immune cells as either antitumor or tumor-promoting. iNKT cells, MAIT cells, and γδ T cells are defined by distinct recognition

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systems, including CD1d-restricted lipid recognition; MR1-restricted metabolite sensing; and butyrophilin-, phosphoantigen-, or stress-associated γδ T cell activation, but their behavior in tumors is shaped by much more than antigen recognition alone (Li et al. 2022, Sanjari Pour et al. 2026). These cells act as environmental interpreters, integrating lipid and metabolite availability, microbial signals, cytokine polarization, tissue residency, metabolic stress, hypoxia, and checkpoint signaling. As a result, the same lineage can mediate cytotoxic immunity, coordinate adaptive responses, enter dysfunctional states, or amplify tumor-promoting inflammation, depending on the tumor ecosystem (Fiala et al. 2024, Hu et al. 2023, Shyanti et al. 2024).

A major priority for the field is to move from lineage-based descriptions toward state-resolved and context-aware models of innate T cell function. Cell frequency alone is unlikely to explain clinical outcome or therapeutic response. Instead, future studies should define which combinations of tissue localization, antigen-presenting context, TCR clonotype, transcriptional state, cytokine profile, metabolic program, and neighboring cell interactions distinguish protective from pathogenic innate-like T cell states. Single-cell and spatial multiomics, when integrated with TCR sequencing, lipidomics, metabolomics, microbiome profiling, and spatial mapping of CD1d, MR1, butyrophilin molecules, stress ligands, and suppressive myeloid niches, will be essential for resolving these functional circuits in situ (Shi et al. 2025, Soundararajan et al. 2025).

Therapeutically, the goal should not be only global activation but precise state programming. Agonists, cytokines, checkpoint blockade, and engineered cell therapies can unleash potent innate T cell responses, but nonspecific stimulation risks anergy, toxicity, or reinforcement of tumor-promoting inflammation (X. Fang et al. 2025, Niedzielska et al. 2025). Future strategies should therefore emphasize spatially controlled delivery, rational combinations, functional perturbation screens, and engineered circuits that preserve cytotoxic or type 1 programs while limiting dysfunctional, regulatory, or IL-17-skewed states. Ultimately, innate T cell immunotherapy will require not only stronger immune activation but a deeper ability to read and rewrite the tissue signals that determine immune cell function within tumors.

DISCLOSURE STATEMENT

L.Y. is a scientific advisor to AlzChem and Amberstone Biosciences. None of the declared companies contributed to this study. The other authors declare no competing interests.

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LITERATURE CITED

An H, Oh J, Bae J. 2026. Advances in IL-2 family cytokine-based cancer therapies: overcoming challenges through molecular engineering and delivery strategies. *Immune Netw.* 26:e6

Bae E-A, Seo H, Kim I-K, Jeon I, Kang C-Y. 2019. Roles of NKT cells in cancer immunotherapy. *Arch. Pharm. Res.* 42:543–48

Review in Advance. Changes may still occur before final publication.

Downloaded from www.annualreviews.org. University of California - Los Angeles UCLA (ar-382234) IP: 149.142.187.196 On: Wed, 28 Oct 2026 22:09:53

Bai S, Wu Q, Zhu S, Zhang Y, Chen X, et al. 2023. Vam6 reduces iNKT cell function in tumor via modulating AMPK/mTOR pathways. *Front. Immunol.* 13:1051045

Balasko AL, Kowatsch MM, Graydon C, Lajoie J, Fowke KR. 2023. The effect of blocking immune checkpoints LAG-3 and PD-1 on human invariant natural killer T cell function. *Sci. Rep.* 13:10082

Baughan SL, Folsom T, Johnson M, Kreuger J, Webber B, Moriarity BS. 2025. IL-15 cytokine-armored NK cells as ready-to-use immunotherapy for diverse malignancies: therapeutic potential and toxicity risks. *Front. Immunol.* 16:1704404

Berisha A, Jenkins BJ, Kedia-Mehta N, Ryan EK, Mayock S, et al. 2026. Lactate conditioning reprograms mucosal-associated invariant T cell metabolism boosting effector function. *J. Immunol.* 215:vkag073

Blank CU, Haining WN, Held W, Hogan PG, Kallies A, et al. 2019. Defining 'T cell exhaustion'. *Nat. Rev. Immunol.* 19:665–74

Camard L, Bianchi E, Rogge L. 2025. Control of MAIT cell functions by cytokines in health and disease. *Front. Immunol.* 16:1594712

Chen Y, Niu S, Li Y-R, Yang L. 2025a. Innovative gene engineering strategies to address tumor antigen escape in cell therapy. *J. Transl. Med.* 23:1227

Chen Y, Zhu Y, Li Y-R. 2025b. The role of innate T cells in cancer. In *Cancer Immunology: The Immune System and Tumor*, ed. N Rezaei. Springer

Cheng M, Qian L, Shen G, Bian G, Xu T, et al. 2014. Microbiota modulate tumoral immune surveillance in lung through a γδT17 immune cell-dependent mechanism. *Cancer Res.* 74:4030–41

Cheng OJ, Lebish EJ, Jensen O, Jacenik D, Trivedi S, et al. 2024. Mucosal-associated invariant T cells modulate innate immune cells and inhibit colon cancer growth. *Scand. J. Immunol.* 100:e13391

Cheng X, Tan X, Wang W, Zhang Z, Zhu R, et al. 2023. Long-chain acylcarnitines induce senescence of invariant natural killer T cells in hepatocellular carcinoma. *Cancer Res.* 83:582–94

Chien Y-h, Meyer C, Bonneville M. 2014. γδ T cells: first line of defense and beyond. *Annu. Rev. Immunol.* 32:121–55

Choi J, Lee YJ. 2026. Dual roles of MAIT cells in the tumor microenvironment: implications for cancer immunity and therapy. *Immune Netw.* 26:e8

Cieslak SG, Shahbazi R. 2025. Gamma delta T cells and their immunotherapeutic potential in cancer. *Biomarker Res.* 13:51

Constantinides MG, Belkaid Y. 2021. Early-life imprinting of unconventional T cells and tissue homeostasis. *Science* 374:eabf0095

Corbett AJ, Eckle SB, Birkinshaw RW, Liu L, Patel O, et al. 2014. T-cell activation by transitory neo-antigens derived from distinct microbial pathways. *Nature* 509:361–65

Corsale AM, Di Simone M, Lo Presti E, Picone C, Dieli F, Meraviglia S. 2021. Metabolic changes in tumor microenvironment: How could they affect γδ T cells functions? *Cells* 10:2896

Courtney AN, Tian G, Metelitsa LS. 2023. Natural killer T cells and other innate-like T lymphocytes as emerging platforms for allogeneic cancer cell therapy. *Blood* 141:869–76

De Biasi S, Gibellini L, Lo Tartaro D, Puccio S, Rabacchi C, et al. 2021. Circulating mucosal-associated invariant T cells identify patients responding to anti-PD-1 therapy. *Nat. Commun.* 12:1669

Delfanti G, Cortesi F, Perini A, Antonini G, Azzimonti L, et al. 2022. TCR-engineered iNKT cells induce robust antitumor response by dual targeting cancer and suppressive myeloid cells. *Sci. Immunol.* 7:eabn6563

Deng Y, Liu X, Yang X, Wei W, Wang J, et al. 2025. IL-17-producing γδ T cells in the tumor microenvironment promote radioresistance in mice. *J. Clin. Investig.* 135:e193945

Dennis KL, Blatner NR, Gounari F, Khazaie K. 2013. Current status of interleukin-10 and regulatory T-cells in cancer. *Curr. Opin. Oncol.* 25:637–45

Deschler S, Pohl-Topcu J, Ramsauer L, Meiser P, Erlacher S, et al. 2025. Polyunsaturated fatty acid-induced metabolic exhaustion and ferroptosis impair the anti-tumour function of MAIT cells in MASLD. *J. Hepatol.* 83:1364–78

Dieli F, Vermijlen D, Fulfaro F, Caccamo N, Meraviglia S, et al. 2007. Targeting human γδ T cells with zoledronate and interleukin-2 for immunotherapy of hormone-refractory prostate cancer. *Cancer Res.* 67:7450–57

Review in Advance. Changes may still occur before final publication.

Downloaded from www.annualreviews.org. University of California - Los Angeles UCLA (ar-382234) IP: 149.142.187.196 On: Wed, 28 Oct 2026 22:09:53

Dong C, Tan D, Sun H, Li Z, Zhang L, et al. 2024. Interleukin-12 delivery strategies and advances in tumor immunotherapy. *Curr. Issues Mol. Biol.* 46:11548–79

Duan M, Goswami S, Shi J-Y, Wu L-J, Wang X-Y, et al. 2019. Activated and exhausted MAIT cells foster disease progression and indicate poor outcome in hepatocellular carcinoma. *Clin. Cancer Res.* 25:3304–16

Fang X, Yan S, He L, Deng C. 2025. CAR-γδ T cells: a new paradigm of programmable innate immune sentinels and their systemic applications in cancer and beyond. *Front. Immunol.* 16:1735763

Fang Y, Chen Y, Li Y-R. 2025a. Engineering the next generation of allogeneic CAR cells: iPSCs as a scalable and editable platform. *Stem Cell Rep*. 20:102515

Fang Y, Chen Y, Niu S, Lyu Z, Tian Y, et al. 2025b. Biological functions and therapeutic applications of human mucosal-associated invariant T cells. *J. Biomed. Sci.* 32:32

Fang Y, Chen Y, Zhu Y, Tian Y, Li Y-R, Yang L. 2025c. Protocol to generate allorejection-resistant universal CAR-NKT cells and evaluate their efficacy, mechanism of action, safety, and immunogenicity. *STAR Protoc.* 6:103810

Fazzi R, Petrini I, Giuliani N, Morganti R, Carulli G, et al. 2021. Phase II trial of maintenance treatment with IL2 and zoledronate in multiple myeloma after bone marrow transplantation: biological and clinical results. *Front. Immunol.* 11:573156

Fiala GJ, Lücke J, Huber S. 2024. Pro-and antitumorigenic functions of γδ T cells. *Eur. J. Immunol.* 54:2451070

Fridman WH, Pagès F, Sautès-Fridman C, Galon J. 2012. The immune contexture in human tumours: impact on clinical outcome. *Nat. Rev. Cancer* 12:298–306

Fu S, He K, Tian C, Sun H, Zhu C, et al. 2020. Impaired lipid biosynthesis hinders anti-tumor efficacy of intratumoral iNKT cells. *Nat. Commun.* 11:438

Fu S, Tang M, Zhao C, Chen S, Su M, et al. 2026. MAIT cell plasticity generates $CD4^+$ MAIT cells that promote HCC progression via metabolic crosstalk with tumor cells. *Cell. Mol. Immunol.* 23:491–504

Fu T, Dai L-J, Wu S-Y, Xiao Y, Ma D, et al. 2021. Spatial architecture of the immune microenvironment orchestrates tumor immunity and therapeutic response. *J. Hematol. Oncol.* 14:98

Fu Y, Tang R, Zhao X. 2023. Engineering cytokines for cancer immunotherapy: a systematic review. *Front. Immunol.* 14:1218082

Galluzzi L, Celià-Terrassa T. 2025. IL17-producing γδ T cells promote radioresistance via immunosuppression. *Trends Cancer* 11:1134–36

Gao Z, Bai Y, Lin A, Jiang A, Zhou C, et al. 2023. Gamma delta T-cell-based immune checkpoint therapy: attractive candidate for antitumor treatment. *Mol. Cancer* 22:31

Godfrey DI, Le Nours J, Andrews DM, Uldrich AP, Rossjohn J. 2018. Unconventional T cell targets for cancer immunotherapy. *Immunity* 48:453–73

Godfrey DI, Pellicci DG, Patel O, Kjer-Nielsen L, McCluskey J, Rossjohn J. 2010. Antigen recognition by CD1d-restricted NKT T cell receptors. *Semin. Immunol.* 22:61–67

Gonzatti MB, Keller AC. 2025. Invariant natural killer T lymphocytes as natural sensors for microbes: a two-edged sword in liver diseases. *Front. Immunol.* 16:1662906

Haas JD, Ravens S, Düber S, Sandrock I, Oberdörfer L, et al. 2012. Development of interleukin-17-producing γδ T cells is restricted to a functional embryonic wave. *Immunity* 37:48–59

Hackstein C-P, Klenerman P. 2023. MAITs and their mates: "innate-like" behaviors in conventional and unconventional T cells. *Clin. Exp. Immunol.* 213:1–9

Harrington KJ, Champiat S, Brody JD, Cho BC, Romano E, et al. 2025. Phase I and II clinical studies of the STING agonist ulevostinag with and without pembrolizumab in participants with advanced or metastatic solid tumors or lymphomas. *Clin. Cancer Res.* 31:3400–11

Hayashizaki K, Kamii Y, Kinjo Y. 2024. Glycolipid antigen recognition by invariant natural killer T cells and its role in homeostasis and antimicrobial responses. *Front. Immunol.* 15:1402412

Herrmann T, Karunakaran MM. 2024. Phosphoantigen recognition by Vγ9Vδ2 T cells. *Eur. J. Immunol.* 54:2451068

Hinks TS, Zhang X-W. 2020. MAIT cell activation and functions. *Front. Immunol*. 11:1014

Hu Y, Hu Q, Li Y, Lu L, Xiang Z, et al. 2023. γδ T cells: origin and fate, subsets, diseases and immunotherapy. *Signal Transduct. Target. Ther.* 8:434

Huang S, Martin E, Kim S, Yu L, Soudais C, et al. 2009. MR1 antigen presentation to mucosal-associated invariant T cells was highly conserved in evolution. *PNAS* 106:8290–95

Review in Advance. Changes may still occur before final publication.

Downloaded from www.annualreviews.org. University of California - Los Angeles UCLA (ar-382234) IP: 149.142.187.196 On: Wed, 28 Oct 2026 22:09:53

Ishikawa A, Motohashi S, Ishikawa E, Fuchida H, Higashino K, et al. 2005. A phase I study of α-galactosylceramide (KRN7000)-pulsed dendritic cells in patients with advanced and recurrent non-small cell lung cancer. *Clin. Cancer Res.* 11:1910–17

Jassaud M, Ziane-Chaouche L, Duhamel M, Salzet M. 2026. Innate immune cells in chimeric antigen receptor therapy. *Mol. Ther.* 34:97–116

Jensen KD, Su X, Shin S, Li L, Youssef S, et al. 2008. Thymic selection determines γδ T cell effector fate: antigen-naive cells make interleukin-17 and antigen-experienced cells make interferon γ. *Immunity* 29:90–100

Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, et al. 2019. Commensal microbiota promote lung cancer development via γδ T cells. *Cell* 176:998–1013.e16

Khairallah C, Chu TH, Sheridan BS. 2018. Tissue adaptations of memory and tissue-resident gamma delta T cells. *Front. Immunol.* 9:2636

Kim B-S, Park Y-J, Chung Y. 2016. Targeting IL-17 in autoimmunity and inflammation. *Arch. Pharm. Res.* 39:1537–47

Klenerman P, Hinks TS, Ussher JE. 2021. Biological functions of MAIT cells in tissues. *Mol. Immunol.* 130:154–58

Kohlgruber AC, Donado CA, LaMarche NM, Brenner MB, Brennan PJ. 2016. Activation strategies for invariant natural killer T cells. *Immunogenetics* 68:649–63

Lang JM, Kaikobad MR, Wallace M, Staab MJ, Horvath DL, et al. 2011. Pilot trial of interleukin-2 and zoledronic acid to augment γδ T cells as treatment for patients with refractory renal cell carcinoma. *Cancer Immunol. Immunother.* 60:1447–60

Laub A, Rodrigues de Almeida N, Huang S. 2025. Unconventional T cells in anti-cancer immunity. *Front. Immunol.* 16:1618393

Lee M, Lee E, Han SK, Choi YH, Kwon D-i, et al. 2020. Single-cell RNA sequencing identifies shared differentiation paths of mouse thymic innate T cells. *Nat. Commun.* 11:4367

Li J, Xiao C, Li C, He J. 2025. Tissue-resident immune cells: from defining characteristics to roles in diseases. *Signal Transduct. Target. Ther.* 10:12

Li S, Simoni Y, Becht E, Loh CY, Li N, et al. 2020. Human tumor-infiltrating MAIT cells display hallmarks of bacterial antigen recognition in colorectal cancer. *Cell Reports Med.* 1:100039

Li X, Lin H, Liang J, Jin X, Shen T, et al. 2026. CAR-X cell engineering. *Nat. Rev. Bioeng.* **https://doi.org/10.1038/s44222-026-00430-w**

Li Y-R, Li M, Chen Y, Leng H, Zhu Y, et al. 2026a. Spatiotemporal profiling reveals distinct dynamics and checkpoint regulations of CAR-T and CAR-NKT cells against solid tumors. *Signal Transduct. Target. Ther.* 11:92

Li Y-R, Li Z, Zhu Y, Li M, Chen Y, et al. 2025a. Overcoming ovarian cancer resistance and evasion to CAR-T cell therapy by harnessing allogeneic CAR-NKT cells. *Med* 6:100804

Li Y-R, Nan H, Liu Z, Fang Y, Zhu Y, et al. 2026b. Engineering an in vivo charging station for CAR-redirected invariant natural killer T cells to enhance cancer therapy. *Nat. Biomed. Eng.* **https://doi.org/10.1038/s41551-026-01629-3**

Li Y-R, Wilson M, Yang L. 2022. Target tumor microenvironment by innate T cells. *Front. Immunol.* 13:999549

Li Y-R, Zhu Y, Chen Y, Yang L. 2025b. The clinical landscape of CAR-engineered unconventional T cells. *Trends Cancer* 11:520–39

Liu J, Wu M, Yang Y, Wang Z, He S, et al. 2024. γδ T cells and the PD-1/PD-L1 axis: a love-hate relationship in the tumor microenvironment. *J. Transl. Med.* 22:553

Liu W, Puri A, Fu D, Chen L, Wang C, et al. 2024. Dissecting the tumor microenvironment in response to immune checkpoint inhibitors via single-cell and spatial transcriptomics. *Clin. Exp. Metastasis* 41:313–32

Luo X, Lv Y, Yang J, Long R, Qiu J, et al. 2024. Gamma delta T cells in cancer therapy: from tumor recognition to novel treatments. *Front. Med.* 11:1480191

Masopust D, Soerens AG. 2019. Tissue-resident T cells and other resident leukocytes. *Annu. Rev. Immunol.* 37:521–46

Mathew AA, Raheja R, Ramalingam K. 2026. Redefining cell therapy: CAR-engineered innate immune cells to conquer solid and hematologic malignancies. *Mol. Biol. Rep.* 53:254

Review in Advance. Changes may still occur before final publication.

Downloaded from www.annualreviews.org. University of California - Los Angeles UCLA (ar-382234) IP: 149.142.187.196 On: Wed, 28 Oct 2026 22:09:53

McEwen-Smith RM, Salio M, Cerundolo V. 2015. The regulatory role of invariant NKT cells in tumor immunity. *Cancer Immunol. Res.* 3:425–35

McMurray JL, von Borstel A, Taher TE, Syrimi E, Taylor GS, et al. 2022. Transcriptional profiling of human Vδ1 T cells reveals a pathogen-driven adaptive differentiation program. *Cell Rep*. 39:110858

McWilliam HE, Eckle SB, Theodossis A, Liu L, Chen Z, et al. 2016. The intracellular pathway for the presentation of vitamin B-related antigens by the antigen-presenting molecule MR1. *Nat. Immunol.* 17:531–37

McWilliam HE, Villadangos JA. 2020. MR1: a multi-faceted metabolite sensor for T cell activation. *Curr. Opin. Immunol.* 64:124–29

Meric-Bernstam F, Sweis RF, Kasper S, Hamid O, Bhatia S, et al. 2023. Combination of the STING agonist MIW815 (ADU-S100) and PD-1 inhibitor spartalizumab in advanced/metastatic solid tumors or lymphomas: an open-label, multicenter, phase Ib study. *Clin. Cancer Res.* 29:110–21

Milhem MM, Wise-Draper TM, Chandra S, Hanna GJ, Laux DE, et al. 2025a. Phase 1b/2 study evaluating safety, efficacy and immune effects of TLR9 agonist cavrotolimod with anti-PD-1 antibodies among patients with advanced solid tumors. *J. Immunother. Cancer* 13:e011651

Milhem MM, Zakharia Y, Davar D, Buchbinder EI, Medina T, et al. 2025b. Intratumoral vidutolimod as monotherapy or in combination with pembrolizumab in patients with programmed cell death 1 blockade-resistant melanoma: final analysis from a phase 1b study. *Cancer* 131:e70022

Muschaweckh A, Petermann F, Korn T. 2017. IL-1β and IL-23 promote extrathymic commitment of $CD27^+$ $CD122^-$ γδ T cells to γδT17 cells. *J. Immunol.* 199:2668–79

Nakanishi K. 2018. Unique action of interleukin-18 on T cells and other immune cells. *Front. Immunol.* 9:763

Niedzielska M, Chalmers A, Popis MC, Altman-Sharoni E, Addis S, et al. 2025. CAR-iNKT cells: redefining the frontiers of cellular immunotherapy. *Front. Immunol.* 16:1625426

Ninkov M, Schmerk CL, Moradizadeh M, Parvathy SN, Figueredo R, et al. 2023. Improved MAIT cell functions following fecal microbiota transplantation for metastatic renal cell carcinoma. *Cancer Immunol. Immunother.* 72:1247–60

Ou L, Wang H, Huang H, Zhou Z, Lin Q, et al. 2022. Preclinical platforms to study therapeutic efficacy of human γδ T cells. *Clin. Transl. Med.* 12:e814

Parekh VV, Lalani S, Kim S, Halder R, Azuma M, et al. 2009. PD-1/PD-L blockade prevents anergy induction and enhances the anti-tumor activities of glycolipid-activated invariant NKT cells. *J. Immunol.* 182:2816–26

Parker ME, Ciofani M. 2020. Regulation of γδ T cell effector diversification in the thymus. *Front. Immunol.* 11:42

Petley EV, Koay H-F, Henderson MA, Sek K, Todd KL, et al. 2021. MAIT cells regulate NK cell-mediated tumor immunity. *Nat. Commun.* 12:4746

Piconese S, Campello S, Natalini A. 2020. Recirculation and residency of T cells and Tregs: lessons learnt in anacapri. *Front. Immunol.* 11:682

Pinco P, Facciotti F. 2025. Unconventional T cells' role in cancer: unlocking their hidden potential to guide tumor immunity and therapy. *Cells* 14:720

Pousse L, Manchala A, Klein C, Codarri Deak L. 2025. Advanced cytokine-based immunotherapies: targeted cis-delivery strategies for enhanced anti-tumor efficacy and reduced toxicity. *mAbs* 17:2590250

Praveena T, Le Nours J. 2024. State of play in the molecular presentation and recognition of anti-tumor lipid-based analogues. *Front. Immunol.* 15:1479382

Qin VM, D'Souza C, Neeson PJ, Zhu JJ. 2021. Chimeric antigen receptor beyond CAR-T cells. *Cancers* 13:404

Reilly EC, Wands JR, Brossay L. 2010. Cytokine dependent and independent iNKT cell activation. *Cytokine* 51:227–31

Revesz IA, Joyce P, Ebert LM, Prestidge CA. 2024. Effective γδ T-cell clinical therapies: current limitations and future perspectives for cancer immunotherapy. *Clin. Transl. Immunol.* 13:e1492

Ribas A, Medina T, Kummar S, Amin A, Kalbasi A, et al. 2018. SD-101 in combination with pembrolizumab in advanced melanoma: results of a phase Ib, multicenter study. *Cancer Discov.* 8:1250–57

Ribot JC, Ribeiro ST, Correia DV, Sousa AE, Silva-Santos B. 2014. Human γδ thymocytes are functionally immature and differentiate into cytotoxic type 1 effector T cells upon IL-2/IL-15 signaling. *J. Immunol.* 192:2237–43

Review in Advance. Changes may still occur before final publication.

Downloaded from www.annualreviews.org. University of California - Los Angeles UCLA (ar-382234) IP: 149.142.187.196 On: Wed, 28 Oct 2026 22:09:53

Rossjohn J, Pellicci DG, Patel O, Gapin L, Godfrey DI. 2012. Recognition of CD1d-restricted antigens by natural killer T cells. *Nat. Rev. Immunol.* 12:845–57

Ruf B, Bruhns M, Babaei S, Kedei N, Ma L, et al. 2023. Tumor-associated macrophages trigger MAIT cell dysfunction at the HCC invasive margin. *Cell* 186:3686–705.e32

Sag D, Krause P, Hedrick CC, Kronenberg M, Wingender G. 2014. IL-10-producing NKT10 cells are a distinct regulatory invariant NKT cell subset. *Curr. Opin. Oncol.* 124:3725–40

Salazar U, Cioffi P, Taskoparan B, Moraga I, Mitra S, vom Berg J. 2025. Protein engineering to overcome limitations of key cytokines in cancer immunotherapy: current approaches and future perspectives. *Immuno-Oncol. Technol.* 28:101064

Salkeni MA, Naing A. 2023. Interleukin-10 in cancer immunotherapy: from bench to bedside. *Trends Cancer* 9:716–25

Sanjari Pour M, Nasimian A, Kazi JU. 2026. Innate-like T cell biology in the tumor microenvironment implications for cancer immunotherapy. *Cells* 15:402

Saura-Esteller J, De Jong M, King LA, Ensing E, Winograd B, et al. 2022. Gamma delta T-cell based cancer immunotherapy: past-present-future. *Front. Immunol.* 13:915837

Shaler CR, Tun-Abraham ME, Skaro AI, Khazaie K, Corbett AJ, et al. 2017. 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.* 66:1563–75

Shi L, Lu J, Zhong D, Song M, Liu J, et al. 2023. Clinicopathological and predictive value of MAIT cells in non-small cell lung cancer for immunotherapy. *J. Immunother. Cancer* 11:e005902

Shi W, Zhang Z, Xu X, Tian Y, Feng L, et al. 2025. Single-cell and spatial transcriptomics integration: new frontiers in tumor microenvironment and cellular communication. *Front. Immunol.* 16:1649468

Shyanti RK, Haque M, Singh R, Mishra M. 2024. Optimizing iNKT-driven immune responses against cancer by modulating CD1d in tumor and antigen presenting cells. *Clin. Immunol.* 269:110402

Silva-Santos B, Mensurado S, Coffelt SB. 2019. γδ T cells: pleiotropic immune effectors with therapeutic potential in cancer. *Nat. Rev. Cancer* 19:392–404

Simon CG Jr., Bozenhardt EH, Celluzzi CM, Dobnik D, Grant ML, et al. 2025. Analysis of the measurements used as potency tests for the 31 US FDA-approved cell therapy products. *J. Transl. Med.* 23:259

Song L, Qi G, Shi W, Zeng Q, Qin Y, et al. 2025. Universal Fab-Fc masked cytokine prodrug platform: αPD-L1/IL-15 prodrug activates $CD44^+$ $CD8^+$ T cells in tumor-draining lymph nodes to enhance antitumor immunity. *J. Immunother. Cancer* 13:e011944

Soundararajan R, Maurin MM, Rodriguez-Silva J, Upadhyay G, Alden AJ, et al. 2025. Integration of lipidomics with targeted, single cell, and spatial transcriptomics defines an unresolved pro-inflammatory state in colon cancer. *Gut* 74:586–602

Subleski JJ, Hall VL, Wolfe TB, Scarzello AJ, Weiss JM, et al. 2011. TCR-dependent and-independent activation underlie liver-specific regulation of NKT cells. *J. Immunol.* 186:838–47

Sun H, Sun C, Xiao W, Sun R. 2019. Tissue-resident lymphocytes: from adaptive to innate immunity. *Cell. Mol. Immunol.* 16:205–15

Sureshbabu S, Chaukar D, Chiplunkar S. 2020. Hypoxia regulates the differentiation and anti-tumor effector functions of γδT cells in oral cancer. *Clin. Exp. Immunol.* 201:40–57

Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KH. 2009. Interleukin-1 and IL-23 induce innate IL-17 production from γδ T cells, amplifying Th17 responses and autoimmunity. *Immunity* 31:331–41

Thapa P, Zhang G, Xia C, Gelbard A, Overwijk WW, et al. 2009. Nanoparticle formulated alpha-galactosylceramide activates NKT cells without inducing anergy. *Vaccine* 27:3484–88

Tian C, Wang Y, Su M, Huang Y, Zhang Y, et al. 2024. Motility and tumor infiltration are key aspects of invariant natural killer T cell anti-tumor function. *Nat. Commun.* 15:1213

Tian G, Courtney AN, Yu H, Bhar S, Xu X, et al. 2025. Hyperleukocytosis in a neuroblastoma patient after treatment with natural killer T cells expressing a GD2-specific chimeric antigen receptor and IL-15. *J. Immunother. Cancer* 13:e010156

Toyoda T, Kamata T, Tanaka K, Ihara F, Takami M, et al. 2020. Phase II study of α-galactosylceramide-pulsed antigen-presenting cells in patients with advanced or recurrent non-small cell lung cancer. *J. Immunother. Cancer* 8:e000316

Review in Advance. Changes may still occur before final publication.

Downloaded from www.annualreviews.org. University of California - Los Angeles UCLA (ar-382234) IP: 149.142.187.196 On: Wed, 28 Oct 2026 22:09:53

Tsahouridis O, Xu M, Song F, Savoldo B, Dotti G. 2025. The landscape of CAR-engineered innate immune cells for cancer immunotherapy. *Nat. Cancer* 6:1145–56

Tyznik AJ, Tupin E, Nagarajan NA, Her MJ, Benedict CA, Kronenberg M. 2008. Cutting edge: the mechanism of invariant NKT cell responses to viral danger signals. *J. Immunol.* 181:4452–56

Ussher JE, Bilton M, Attwod E, Shadwell J, Richardson R, et al. 2014. CD 161^{++} CD 8^{+} T cells, including the MAIT cell subset, are specifically activated by IL-12+ IL-18 in a TCR-independent manner. *Eur. J. Immunol.* 44:195–203

Vacchini A, Chancellor A, Spagnuolo J, Mori L, De Libero G. 2020. MR1-restricted T cells are unprecedented cancer fighters. *Front. Immunol.* 11:751

Vitiello GA, Miller G. 2019. Targeting the interleukin-17 immune axis for cancer immunotherapy. *J. Exp. Med.* 217:e20190456

Voillet V, Buggert M, Slichter CK, Berkson JD, Mair F, et al. 2018. Human MAIT cells exit peripheral tissues and recirculate via lymph in steady state conditions. *JCI Insight* 3:e98487

Wang S, Yao L, Cai J, Gao H, Zhou F. 2026. Immunocytokines in cancer immunotherapy: opportunities and challenges. *Front. Oncol.* 15:1716612

Wang Y, Bhave MS, Yagita H, Cardell SL. 2020. Natural killer T-cell agonist α-galactosylceramide and PD-1 blockade synergize to reduce tumor development in a preclinical model of colon cancer. *Front. Immunol.* 11:581301

Wang Z, Zhang G. 2025. CAR-iNKT cell therapy: mechanisms, advantages, and challenges. *Curr. Res. Transl. Med.* 73:103488

Yigit M, Basoglu OF, Unutmaz D. 2024. Mucosal-associated invariant T cells in cancer: dual roles, complex interactions and therapeutic potential. *Front. Immunol.* 15:1369236

Yu X, Song L, Cen L, Cao B, Tao R, et al. 2024. Pan-cancer γδ TCR analysis uncovers clonotype diversity and prognostic potential. *Cell Rep. Med.* 5:101764

Zhang B, Wu J, Jiang H, Zhou M. 2025. Strategies to overcome antigen heterogeneity in CAR-T cell therapy. *Cells* 14:320

Zhang X, Li B, Lan T, Chiari C, Ye X, et al. 2025. The role of interleukin-17 in inflammation-related cancers. *Front. Immunol.* 15:1479505

Zhang Y, Springfield R, Chen S, Li X, Feng X, et al. 2019. α-GalCer and iNKT cell-based cancer immunotherapy: realizing the therapeutic potentials. *Front. Immunol.* 10:449638

Zhu D, Ren X, Xie W, Chen J, Liang S, et al. 2024. Potential of gamma/delta T cells for solid tumor immunotherapy. *Front. Immunol.* 15:1466266

Review in Advance. Changes may still occur before final publication.