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Harnessing $\gamma\delta$ T cells in anticancer immunotherapy

Dalil Hannani^{1,2,4}, Yuting Ma^{1,2,4}, Takahiro Yamazaki^{1,2,4}, Julie Dechanet-Merville⁵, Guido Kroemer^{1,3,6,7,8,9} and Laurence Zitvogel^{1,2,4}

¹ Institut Gustave Roussy, Villejuif, France

² INSERM, U1015, F-94805 Villejuif, France

³ INSERM, U848, F-94805 Villejuif, France

⁴ Université Paris Sud-XI, F-94805 Villejuif, France

⁵ CNRS UMR 5164, Université Bordeaux 2, 33076 Bordeaux, France

⁶ Metabolomics Platform, Institut Gustave Roussy, Villejuif, France

⁷ Centre de Recherche des Cordeliers, Paris, France

⁸ Pôle de Biologie, Hôpital Europe en Georges Pompidou, AP-HP, Paris, France

⁹ Université Paris Descartes, Paris 5, Paris, France

$\gamma\delta$ T lymphocytes are involved in the stress response to injured epithelia and in tissue homeostasis by limiting the dissemination of malignant or infected cells and by regulating the nature of the subsequent adaptive immune response. $\gamma\delta$ T cells have potent MHC-unrestricted cytotoxicity, a high potential for cytokine release and broad-spectrum recognition of cancer cells, and as such, are attractive effectors for cancer immunotherapy. Current expectations are going beyond ex vivo manipulation of the V γ 9V δ 2 T subset, and target novel $\gamma\delta$ T cell subsets, properties or receptors, to harness these unconventional T lymphocytes against cancer. This Opinion article discusses novel aspects of $\gamma\delta$ T cell function during the course of anticancer therapies, as well as new avenues for their clinical implementation.

$\gamma\delta$ T cell characteristics

$\gamma\delta$ T cells have several innate cell-like attributes that allow their early and rapid activation following recognition of conserved stress-induced ligands [1,2]. For example, $\gamma\delta$ T cells can be activated by non-self-ligands, such as viral glycoproteins derived from herpes viruses, and phosphoantigens generated either by the isoprenoid pathway used by microorganisms [3] or by the mevalonate pathway in infected or transformed cells [4]. $\gamma\delta$ T cells can also be indirectly activated by proinflammatory cytokines released by Toll-like receptor (TLR)-induced dendritic cells (DCs) [interleukin (IL)-12, IL-23 and type-I interferons (IFNs)], with or without concomitant engagement of T cell receptor (TCR) and/or activating natural killer (NK) cell receptors [5–7]. Both human and mouse CD16-expressing $\gamma\delta$ T cells can also recognize and be activated by antibody-opsonized cells or microorganisms through binding of IgGs, which mediates antibody-dependent cell cytotoxicity (ADCC). On activation, $\gamma\delta$ T cells expand, acquire cytotoxic functions and secrete an array of proinflammatory (Th1) cytokines. Thus, these cells are attractive for cell therapy strategies against cancer.

In humans, $\gamma\delta$ T cells represent 3–5% of blood lymphocytes. Among this population, the V γ 9V δ 2 T cell subset is predominant (>70%), whereas in other tissues such as gut epithelia, dermis, spleen and liver, $\gamma\delta$ T cells mostly express the V δ 1 TCR and to a lesser extent the V δ 3 TCR. The V δ 2⁺ population has received less attention than V γ 9V δ 2 cells, but recent description of their specific anti-cytomegalovirus (CMV) activity and antitumor

crossreactivity has raised a new interest in this subset. Here, we summarize recent advances in our understanding of how the different $\gamma\delta$ T cell subsets contribute to antitumor responses during different cancer therapies, including treatment with bisphosphonates and immunogenic chemotherapy (Box 1). We highlight the potential therapeutic value of combining immunotherapy to target $\gamma\delta$ T cells with chemotherapeutic approaches.

$\gamma\delta$ T cells in cancer immunosurveillance

$\gamma\delta$ T cells can exert cytolytic functions against a variety of premalignant or malignant primary tumor cells and tumor stem cells in an MHC-dependent or -independent manner [8–10]. Activated V γ 9V δ 2 T cells show in vitro cytolytic activity towards myeloma [11–13], lymphoma cell lines [14,15] and solid tumors [16–19]. Ex vivo expanded $\gamma\delta$ T cells from patients with glioblastoma multiforme (GBM) harbor intact killing functions against GBM cells; however, both $\gamma\delta$ T cell counts and the mitogen-stimulated proliferative response of circulating $\gamma\delta$ T cells are decreased when compared to healthy volunteers [20]. In immunocompromised patients, a large number of V δ 2⁺ $\gamma\delta$ T cells, which exert crossreactive recognition of both CMV-infected and transformed epithelial cells, are associated with reduced risk of developing cancer. In a longitudinal case–control study involving 18 immunosuppressed recipients who developed cancer between 2 and 6 years after transplantation and 45 recipients who did not, the median percentage of $\gamma\delta$ T cells among total lymphocytes in patients with malignancies was significantly lower (<4%) before the diagnosis of cancer compared with that in control patients. An increase in V δ 2⁺ $\gamma\delta$ T cell numbers correlates with a lower incidence of cancer only in recipients who experienced pre- or post-graft CMV infection, suggesting a role for the CMV-induced V δ 2⁺ $\gamma\delta$ T cells (mainly V δ 1 $\gamma\delta$ T cells) in protection against tumors. Consistent with this, a retrospective follow-up of kidney recipients for 8 years revealed that CMV-naïve recipients had a fivefold higher risk of developing cancer compared with CMV-seropositive patients [21]. CMV replication is also associated with a decrease in relapse risk in acute myeloid leukemia (AML) patients who undergo allogeneic stem cell transplantation [22]. This might rely on the antileukemic activity capacity of V δ 1 $\gamma\delta$ T cells [23]. Indeed, after bone marrow transplantation in patients suffering from acute lymphoid leukemia (ALL), donor-derived V δ 1 $\gamma\delta$ T cells are activated and proliferate in response to primary recipient ALL blasts. In addition, these cells lyse ALL blasts. Importantly, V δ 1 $\gamma\delta$ T cells do not respond to HLA-mismatch nonleukemic cells, offering promising perspectives for immunotherapy using allogeneic V δ 1 $\gamma\delta$ T cells.

Whether the presence of $\gamma\delta$ tumor-infiltrating lymphocytes (TILs) reflects good or poor prognosis in cancer is still controversial. $\gamma\delta$ TILs from epithelial tumors in breast, prostate or colon cancer belong to the resident V δ 2⁺ population [10,24], whereas in other types of epithelial tumors (such as renal cell carcinoma; RCC) $\gamma\delta$ T cell infiltrates are found to comprise mainly V γ 9V δ 2 T cells [17]. $\gamma\delta$ TILs isolated in various types of cancer, including colorectal, breast, prostate, ovarian and RCC [17,24,25], recognize and kill both the autologous tumor and a broad range of related tumors, presumably via the recognition of shared stress-related ligands, but do not kill nontransformed cells [17,25]. The infiltration of V γ 1 and V δ 1 $\gamma\delta$ T cells into necrotizing melanomas (NMMs) significantly correlates with

increased survival [26], whereas intratumoral $\gamma\delta$ T cell infiltration in RCC tumors does not [27]. These studies suggest that $\gamma\delta$ T cell infiltration might be beneficial; however, the immunoregulatory properties of $\gamma\delta$ T cells should not be ignored [28]. Indeed, in breast and prostate cancer, the $V\delta 1^+$ $\gamma\delta$ T subset of TILs potently suppresses naive and effector T cell responses and blocks the maturation and function of DCs. This suppressive function is reversed by addition of TLR8 ligands [29]. In addition, $\gamma\delta$ T cells could prevent tumor elimination in an IL-10-dependent manner [30].

Mouse models suggest that the contribution of $\gamma\delta$ T cells to anticancer surveillance is nonredundant with ab T cells. Mice lacking $\gamma\delta$ T cells are vulnerable to cutaneous malignancy when inoculated with carcinoma cells, or when induced by chemical carcinogenesis, underlining their crucial role in cancer immunosurveillance [9,31]. $\gamma\delta$ T-cell-deficient mice also show that $\gamma\delta$ T cells strongly contribute to host protection against papillomas, whereas ab T cells have only a moderate effect or even promote the progression of papillomas to carcinomas [9,31]. $\gamma\delta$ T cells that are probably responsible for restraining malignancy are the NKG2D-expressing, skin-associated NKG2D T cells, suggesting that these cells respond very rapidly to stress-ligand-expressing cells (i.e. transformed cells) [9,31]. Using the TRAMP transgenic mouse model of prostate cancer, one group has provided evidence that $\gamma\delta$ T cells can mediate protective immunosurveillance against spontaneously arising cancer [8]. In nude mice inoculated subcutaneously with nasopharyngeal carcinoma cell lines, infused human peripheral $\gamma\delta$ T cells could temporarily accumulate in tumors, causing a transient reduction in tumor growth [32]. In a preclinical breast tumor model, infused $\gamma\delta$ T cells traffic to breast tumors in a TCR-dependent manner and prevent tumor growth [33]. Another study using mice transplanted with HER-2⁺ human breast cancer cell lines has shown that in vivo activation of $\gamma\delta$ T cells (through bisphosphonates) enhances the efficacy of standard immunotherapy (administration of trastuzumab, a monoclonal antibody directed against HER2/neu receptors) [34]. Also, coadministration of zoledronic acid – a synthetic $\gamma\delta$ T cell activator – together with intravesical infusion of $\gamma\delta$ T cells induces antitumor effects against orthotopically inoculated human bladder cancer cells in immunodeficient mice and prolongs survival [35]. CMV-specific $V\delta 2^-$ $\gamma\delta$ T cells can also target cancer cells in vivo. Prophylactic injections of $V\delta 2^-$ $\gamma\delta$ T cell clones in subcutaneous (s.c.) HT29 tumors established in immunodeficient mice prevent the development of these colon tumors, whereas $V\delta 2V\gamma 9$ $\gamma\delta$ T cells fail to do this. More importantly, systemic intraperitoneal (i.p.) treatment with $V\delta 2^-$ $\gamma\delta$ T cell clones delays the growth of HT29 s.c. tumors in a chemokine C-C motif receptor 3 (CCR3)-dependent manner. $V\delta 2^-$ $\gamma\delta$ T cell clones express CCR3 and migrate in vitro in response to chemokines (macrophage inflammatory protein-1 α and monocyte chemoattractant protein-4) secreted by HT29 cells [36]. Taken together, these findings suggest that $\gamma\delta$ T cells can be harnessed for cancer immunotherapy and could synergize with other immunotherapy (such as monoclonal antibodies).

IL-17-producing $\gamma\delta$ T cells ($\gamma\delta$ T17) contribute to the efficacy of anticancer therapies

Bidirectional tumor–host interactions (i.e. tumor-induced immunosuppression vs antitumor immunity) during the course of certain anticancer therapies can influence therapeutic success [37–39]. Indeed, some cytotoxic compounds are capable of triggering an ‘immunogenic’ cell death, in that chemotherapy-induced cell death elicits a tumor-specific immune response that controls residual tumor cells instead of inducing tolerance [40–42]. Failure to activate an antitumor immune response compromises the success of conventional

anticancer chemotherapies. Anthracyclines, oxaliplatin and X-rays can trigger immunogenic cell death. Four major checkpoints dictate the immunogenicity of cell death and how the host immune system recognizes dying tumor cells. First, optimal phagocytosis of dying tumor cells requires the translocation of endoplasmic re-ticulum (ER)-resident calreticulin (CRT) [43] and disulfide isomerase ERp57 [44] to their plasma membrane. The ER stress response, initiated by the phosphorylation of eif2a and culminating in the combined exposure of CRT and ERp57 to the plasma membrane, dictates DC uptake of apoptotic bodies, a crucial step to elicit an immune re-sponse against cancer [41,45]. Second, the chromatin-binding high mobility group box 1 protein (HMGB1) is released by dying tumor cells and binds to TLR4 to facilitate antigen processing and presentation to T cells [46]. Third, release of ATP by dying cells is required to engage the purinergic receptor P2RX7, which triggers IL-1b secretion through a cascade involving the Nlrp3 inflammasome, and culminates with IL-1b-dependent $\gamma\delta$ T cell activation and Tc1 polarization of antigen-specific T cell responses [47,48]. The antitumor effects of anthracyclines, oxaliplatin and X-rays are abrogated in mice devoid of T cells or Th1 cytokines (such as IFN γ and the IFN γ receptor, and IL-1b and IL-1 receptor 1) [47–49].

These data suggest that immunogenic cell death induced by chemotherapy could influence the composition of the immune infiltrate present in tumors, which in turn could affect the therapeutic response. Supporting this, it has recently been reported that $\gamma\delta$ T cells that produce IL-17 ($\gamma\delta$ T17), followed by IFN γ -producing CD8⁺ T cells (CTLs), infiltrate tumor beds post-chemotherapy and both $\gamma\delta$ T cells and CTLs, as well as IL-17 and IFN γ , are essential for the therapeutic success of anthracyclines in several preclinical models [47,49] (Figure 1).

The transcriptional analysis of the cytokine/chemokine profile in regressing tumor beds post-anthracycline treatment has revealed a four- to fivefold increase in the gene products associated with the typical Th1 signature [Eomes, T-bet, IFN- γ , lymphotoxin-b, chemokine C-C motif ligand 5 (Ccl5), chemokine C-X-C motif ligand (Cxcl)10, Cxcl9, and tumor necrosis factor (TNF)- α], as well as gene products encoding IL-7 receptor, IL-21, aryl hydrocarbon receptor (AhR), Cxcl2 and forkhead box p3 (Foxp3). The mandatory role of the IL-17A and IL-17RA pathway has been demonstrated in several transplantable tumor models (EG7 thymoma, MCA205 sarcoma, CT26 colon cancer, and TS/A mammary carcinomas) and in 3-methylcholanthrene (MCA)-induced spontaneous sarcoma [49]. Moreover, doxorubicin treatment increases the proportion of both IFN- γ - and IL-17-producing TILs (which are CD44⁺ CD62L[−] CD69⁺ granzyme B⁺ CD27[−] NKG2D[−] V γ 4⁺ or V γ 6⁺). Eight days post-chemotherapy in MCA205 sarcomas, the major source of IFN- γ is CD8⁺ T cells, whereas that of IL-17 is mostly TCR δ ⁺ T cells rather than CD4⁺ Th17 cells. Doxorubicin-based chemotherapy substantially enhances IFN- γ production by CD8⁺ and CD4⁺ TILs, as well as IL-17 production by $\gamma\delta$ TILs. $\gamma\delta$ TILs invade MCA205 tumor beds within 3 days of treatment, rapidly divide and produce IL-17 shortly after chemotherapy. The early induction of IL-17 contrasts with the later induction of IFN- γ production by CD8⁺ T cells on day 8 post-chemotherapy.

The percentage of $\gamma\delta$ T17 cells correlates with the frequency of IFN- γ -producing CD8⁺ T lymphocytes (Tc1) in the tumor microenvironment. Accordingly, in the absence of $\gamma\delta$ T17 or IL-17, priming of adaptive anticancer Th1/Tc1 responses is hampered, suggesting a helper role of $\gamma\delta$ T17 cells in the context of immunogenic cell death.

The absence of the TCR δ chain, as well as V γ 4 and V γ 6 $\gamma\delta$ T cells, has been found to reduce the efficacy of chemo-therapy. Adoptive transfer of $\gamma\delta$ T cells from naïve mice enhances chemotherapy efficacy and restores the sensitivity of IL-17 knockout mice, provided that these cells express IL-1 receptor 1 and are competent for IL-17 production. $\gamma\delta$ T17 cells respond to ex vivo propagated bone-marrow-derived DCs (but not macrophages) loaded with dying tumor cells (but not live tumor cells) for the production of IL-17 and IL-22 in a manner depending on IL-1b [but not IL-23, transforming growth factor (TGF)- β or IL-6] [47]. It is of note that neutralization of IL-23 fails to abrogate the efficacy of chemotherapy [49]. A beneficial role of $\gamma\delta$ T17 cells in cancer is supported by a study showing that $\gamma\delta$ T17 cells are indispensable for the efficacy of *Mycobacterium bovis* bacillus Calmette–Guerin (BCG) against bladder cancer by recruiting neutrophils [50]. In contrast to these data, IL-17-producing $\gamma\delta$ TILs could support tumor outgrowth by promoting angiogenesis. Such $\gamma\delta$ T17 TILs exhibit low levels of perforin and are stimulated through TCR, NKG2D and receptors for IL-23, IL-6 and TGF- β to produce IL-17 and cyclooxygenase (COX)-2 in tumor beds [51]. In fact, $\gamma\delta$ T17 cells from chemotherapy-treated tumor beds depend upon IL-1 receptor 1 to mediate their immunostimulatory effects (instead of TCR, NKG2D and IL-23, as described in [51]).

These findings unravel the capacity of distinct subsets of $\gamma\delta$ T cells, presumably antigen-naïve (as opposed to self-reactive) and IL-1b-responsive [52], to link innate signals to adaptive immunity during a sterile inflammation such as chemotherapy-induced cell death. Knowing whether human $\gamma\delta$ T cells invade tumor beds at the onset of chemo-therapy and radiotherapy may help in harnessing such effectors to improve conventional therapies of cancer.

Aminobisphosphonates and bromohydrin pyrophosphate: rationale for the utilization of $\gamma\delta$ 2 T cells as antitumor weapons. Synthetic aminobisphosphonates (pamidronate, zoledronate) are well known for treatment of Paget's disease and bone metastases and are potent $\gamma\delta$ T cell stimulatory compounds that induce cytokine secretion and cell-mediated cytotoxicity [13]. The nitrogen-containing bisphosphonate zoledronic acid (ZOL) blocks the mevalonate pathway, leading to intracellular accumulation of isopentenyl pyrophosphate and triphosphoric acid I-adenosin-5'-yl ester 3-(3-methylbut-3-enyl) ester (IPP and Apppl) mevalonate metabolites. V γ 9V δ 2 T cells appear to recognize IPP and Apppl in ZOL-treated cancer cells as tumor phosphoantigens in vitro. These findings may also be significant in vivo because there is a correlation between the ability of V γ 9V δ 2 T cells to kill tumors and the intracellular IPP and Apppl concentrations in ZOL-treated breast cancer cells. In ZOL-treated mice bearing s.c. breast cancer xeno-grafts, V γ 9V δ 2 T cells traffic to tumor beds containing high concentrations of IPP and Apppl, which lead to tumor regression. These findings suggest that cancers producing high amounts of IPP and Apppl after ZOL administration may benefit from V γ 9V δ 2 T-cell-mediated immunotherapy [53].

The antitumor activity of $\gamma\delta$ T cells in vivo was first tested in a clinical trial in 2003 in which recombinant IL-2 (rIL-2) was combined with pamidronate for the treatment of hematological malignancies (non-Hodgkin lymphoma and multiple myeloma) [54–56]. The combination of pamidronate and low-dose IL-2 was well tolerated. Preselection of patients based on 'positive in vitro proliferation of $\gamma\delta$ T cells in response to pamidronate and IL-2' was associated with significant activation/proliferation of $\gamma\delta$ T cells (in 55% of cases) in vivo and

33% of objective responses (tumor regression). In end-stage breast cancer for which administration of zoledronate and rIL-2 was combined, the number of peripheral V γ 9V δ 2 T cells correlated significantly with clinical outcome. The seven patients who failed to sustain V γ 9V δ 2 T cells showed progressive clinical deterioration (PD), whereas three patients who sustained robust peripheral V γ 9V δ 2 cell populations showed declining serum concentrations of the glycoprotein Mucin-

1 (MUC-1) tumor-related marker (CA15.3); one patient showed partial remission (PR) and two exhibited stable disease (SD) [55]. In metastatic hormone-refractory prostate cancers treated with ZOL and rIL-2, the numbers of effector memory $\gamma\delta$ T cells and serum levels of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (produced by activated $\gamma\delta$ T cells) correlated with declining prostate-specific antigen levels and objective clinical responses that comprised three PR and five SD. By contrast, most patients treated only with zoledronate (seven out of nine) failed to sustain either $\gamma\delta$ cell numbers or serum TRAIL and showed PD [56]. This result is in line with a recent report showing no efficacy of ZOL alone in adjuvant breast cancer [57].

Adoptive transfer of $\gamma\delta$ T cells for treatment of some cancers such as metastatic RCC or non-small cell lung carcinoma has been investigated in several clinical trials during the past decade (Table 1). $\gamma\delta$ T cells can either be infused into patients after ex vivo activation and expansion with phosphoantigens, or without experimental manipulation, instead being directly activated in vivo by administration of synthetic aminobisphosphates (such as bromohydrin pyrophosphate, pamidronate or ZOL) and exogenous T cell growth factors [54–56]. These therapies are usually feasible and well tolerated (with the exception of risk for thrombo-embolic events in patients with multiple myeloma [58]), but therapeutic benefits seem only to occur when used in combination with other therapies [16,59], including cytokines (such as IL-2 and IL-21) [54–56,60], traditional chemotherapy or monoclonal antibodies, because $\gamma\delta$ T cells mediate ADCC [61,62].

These studies examining the antitumor activity of $\gamma\delta$ T cells (Table 1) highlight the therapeutic potential of $\gamma\delta$ T cells in patients in whom V γ 9V δ 2 T cells can expand and survive. However, more knowledge is needed of $\gamma\delta$ T cell biology (survival, trafficking patterns, subset variability, ligands and/or TCR identifications) to further such trials [63].

Improving $\gamma\delta$ T cell function for combinatorial regimens with immunotherapy and chemotherapy

V γ 9V δ 2 $\gamma\delta$ T cell-triggering may be ameliorated by combining TCR stimulation with engagement of NK receptors or TLRs [64]. In addition, because $\gamma\delta$ T cells may be inhibited by T regulatory cells [65–67], any therapeutic intervention aimed at reducing T regulatory cell (Treg) immunosuppressive functions could be valuable for restoring $\gamma\delta$ T cell activity.

Although V δ 1 $\gamma\delta$ T cell ligands have not been identified yet, these cells can be triggered using a specific activating anti-V δ 1 TCR antibody coupled with activating signals such as NKG2D ligands (Figure 2). Using this strategy, one group has developed protocols to expand both human peripheral and tumor infiltrating $\gamma\delta$ T cells, which show cytotoxicity and antitumor activity [68–70]. In addition, V δ 1 $\gamma\delta$ T cells that are activated by certain CMV-infected cells or CMV-induced autoantigens display crossreactivity against tumor cells. Thus,

a protocol for V δ 1 $\gamma\delta$ T cell amplification using autologous CMV-infected cells may favor in vivo V δ 1 $\gamma\delta$ T cell antitumor activity [21,71]. In immunocompromised mice, sustained expansion of human peripheral blood $\gamma\delta$ T cells is observed upon stimulation with anti- $\gamma\delta$ TCR antibody (which expands both V δ 1 and V δ 2 subsets of $\gamma\delta$ T cells). Compared to phosphoantigen-stimulated $\gamma\delta$ T cells, the antibody-expanded cells manifest similar functional phenotypes and cytotoxic activity towards tumor cell lines between subsets. V δ 1 T cells are more prone to infiltrate CCL17- or CCL22-expressing lymphomas than V δ 2 T cells because of high expression levels of CCR4 and CCR8 [68]. V δ 1 T cells are also preferentially expanded by extended exposure to concanavalin A in the presence of IL-2. These cells display potent cytotoxicity toward B cell chronic lymphocytic leukemia and represent a new perspective for the treatment of this disease [72].

Similar to conventional T cells, the polarization of $\gamma\delta$ T cells crucially influences the nature of the downstream adaptive immune response. In the context of a combinational regimen using both chemotherapy and immunotherapy, IL-1R1⁺ $\gamma\delta$ T17 cells appear crucial in that they precede and correlate with trafficking of IFN γ ⁺ CD8⁺ T cells to the tumor site [47]. These cells depend on IL-1b for their triggering and therefore administration of an 'immunogenic chemotherapy' (such as oxaliplatin or anthracycline or an X-ray-based regimen) or local delivery of TLR agonists in the tumor microenvironment (which stimulate local DCs, a source of IL-1b) may be instrumental in polarization of these $\gamma\delta$ TILs. It is of note that targeting of TLR1 and TLR2 (by pathogens or synthetic ligands), as well as dectin-1 on $\gamma\delta$ T cells bearing a CCR6⁺ IL-17⁺ phenotype, promotes (alone or in conjunction with rIL-23) their proliferation and increased Th17-like polarization [73]. Alternatively, passive infusion of prepolarized $\gamma\delta$ T17 cells is conceivable. Co-culture of naive V γ 9V δ 2 T cells with phosphoantigens and a cocktail of cytokines (IL-1b, TGF- β , IL-6, and IL-23) leads to selective induction of the transcription factor Retinoic acid receptor-related Orphan nuclear Receptor (ROR γ t) and polarization toward IL-17 production. IL-17⁺ V γ 9V δ 2 T cells express granzyme B, TRAIL, FasL, and CD161 and upon activation, rapidly induce CXCL8-mediated migration of neutrophils in vitro. Interestingly, an increased percentage of circulating IL-17⁺ V γ 9V δ 2 lymphocytes has been found in children with bacterial meningitis [74].

Combinations of cellular immune-based therapies with chemotherapy and other antitumor agents may be of clinical benefit in the treatment of malignancies. High cytotoxicity against solid-tumor-derived cell lines has been reported with combination treatment using V γ 9V δ 2 T cells, chemotherapeutic agents and the bisphosphonate ZOL. Pretreatment with low concentrations of chemotherapeutic agents or ZOL has been shown to sensitize tumor cells to rapid killing by V γ 9V δ 2 T cells. V γ 9V δ 2 T cell cytotoxicity and IFN γ secretion are mediated by perforin following TCR-dependent and isoprenoid-mediated recognition of tumor cells [18].

Concluding remarks

Abundant IFN γ or IL-17 secretion, potent cytotoxicity and MHC-independent targeting of a broad spectrum of tumors make $\gamma\delta$ T cells promising targets for cancer immunotherapy using high-affinity phosphoantigens and/or anti-V δ 1 (or V δ 2⁺ TCR) antibodies. Should human data corroborate the findings in mice, the recent demonstration that $\gamma\delta$ T cells might participate in the efficacy of chemotherapy will open novel avenues of combinatorial

therapies for solid tumors. In the past decade, the safety profile of $\gamma\delta$ T cells and the dose-limiting toxicity of phos-phoantigens and rIL-2 have been demonstrated. Ongoing clinical trials are examining the potential for exploiting the ADCC activity of $\gamma\delta$ T cells. Manipulation of $\gamma\delta$ T cell functions by targeting their activating NKG2D receptor (i.e. by blocking soluble MHC class I chain-related genes (MIC)A/B) or co-stimulatory receptors (CD27, TLR3 or TLR7) or interfering with immunosuppressive check-points [Programmed Death-1 (PD-1) or cytotoxic T lymphocyte antigen (CTLA)4, Tregs] may be of further interest. Finally, it would be interesting to examine the prospect for predicting 'γδ T cell susceptible' hematological malignancies using specific gene signatures in future work [75].

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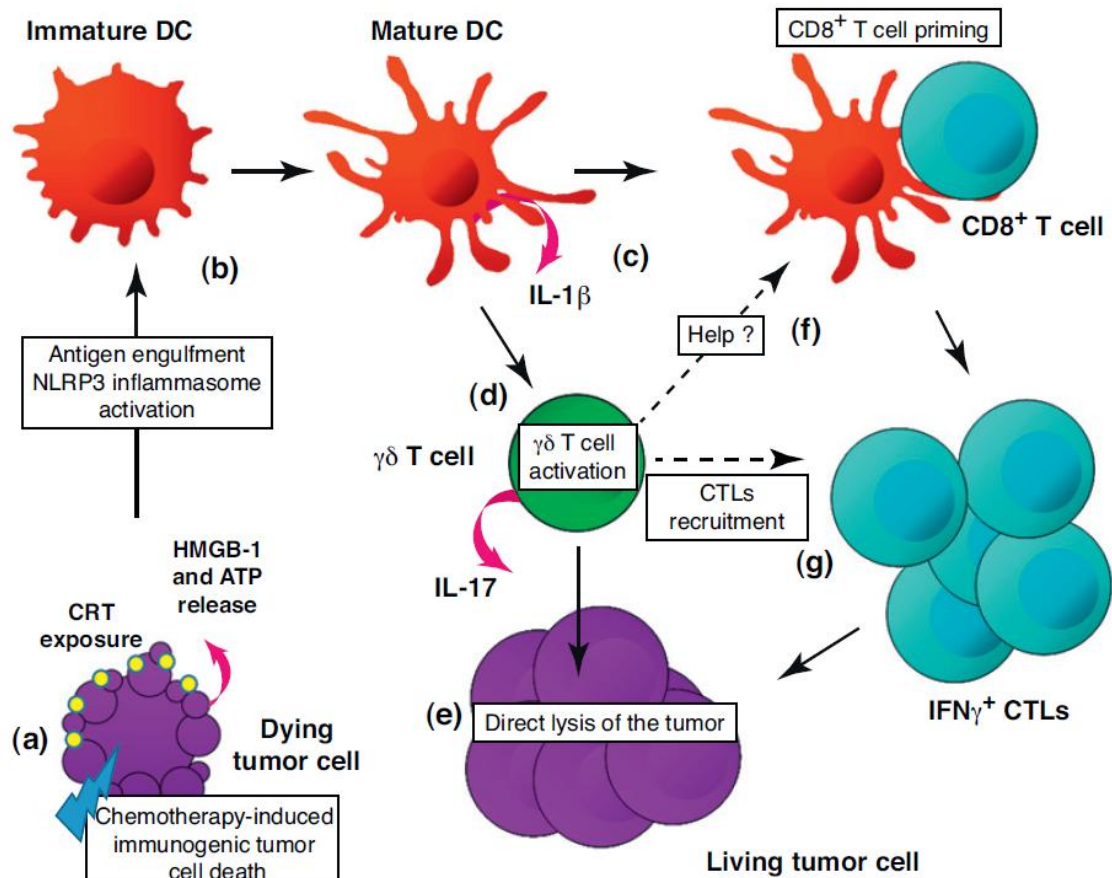


Figure 1. Contribution of IL-17-producing $\gamma\delta$ T cells ($\gamma\delta$ T17) to the efficacy of anticancer chemotherapy. (a) Some chemotherapy regimens induce immunogenic cell death (with release of calreticulin exposure, HMGB1 and ATP by dying tumor cells) leading to (b) tumor cell engulfment by DCs and DC activation through a pathway involving the Nlrp3/Asc/casp-1 inflammasome platform, culminating in (c) IL-1b production by DCs. (d) Within 2–3 days, $\gamma\delta$ T17 are recruited to the tumor bed and activated in an IL-1b-dependent manner. The IL-17-producing $\gamma\delta$ T cells (e) directly contribute to tumor lysis and may help (f) conventional T cell priming by DCs and/or (g) T cell recruitment into the tumor bed because the accumulation of $\gamma\delta$ T17 cells precedes and correlates with rapid IFN γ -producing CTL infiltration, which is also crucial for tumor eradication.

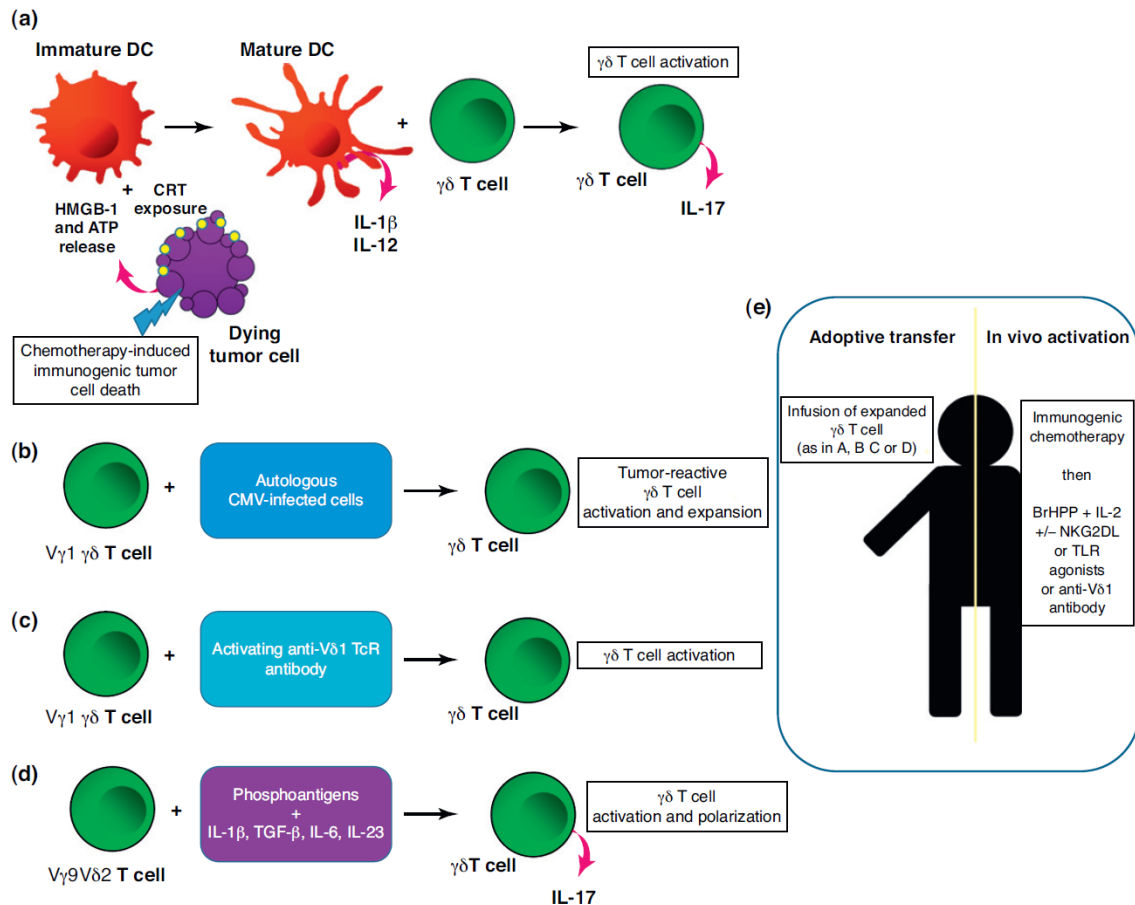


Figure 2. Improving $\gamma\delta$ T cell functions in combinatorial regimen against cancer. $\gamma\delta$ T cells can be infused into patients after ex vivo expansion, activation and polarization.

(a) IL-17-producing $\gamma\delta$ T cells can be generated in co-culture with IL-1 β -secreting DCs exposed to anthracycline-treated tumor cells [47]. (b) $V\gamma 9V\delta 2$ $\gamma\delta$ T cells can be polarized into IL-17-producing cells using phosphoantigens in the presence of cytokines [74]. $V\delta 1$ $\gamma\delta$ T cells can be activated and expanded using either (c) autologous CMV-infected cells [21] or (d) anti-V $\delta 1$ TcR antibody. (e) Patients can be treated either by infusion of ex vivo expanded $\gamma\delta$ T cells (as delineated in a–d) or by direct in vivo $\gamma\delta$ T cell activation using immunogenic chemotherapy followed by BrHPP + rIL-2 (to trigger $V\gamma 9V\delta 2$ $\gamma\delta$ T cell activation), or anti-V $\delta 1$ TcR antibody (to trigger $V\delta 1$ $\gamma\delta$ T cells) and/or NKG2D ligands or TLR agonists.

Table 1. Selection of clinical trials assessing safety and efficacy of $\gamma\delta$ T cell infusions and their stimulatory factors.

Immunotherapy	Cancer type	Treatment arm	No. of patients	PD (%)	SD (%)	PR (%)	CR (%)	Ref.
Autologous $\gamma\delta$ T cell infusions	Metastatic RCC	+rIL-2 +BrHPP	10	40	60			[76]
	Metastatic RCC	+ZOL +rIL-2	1				100	[60]
	Solid tumors	+rIL-2 +BrHPP	28	ND	ND	ND	ND	[77]
	Non-small-cell lung cancer	+ZOL +rIL-2	8	63	37	0		[78]
	Non-small-cell lung cancer	+ZOL +rIL-2	15	60	40			[79]
	Solid tumors	$\gamma\delta$ T alone combination	5 20	40 30	40 5			[80]
	Solid tumors		18	61	17	11	6	[59]
	Refractory low-grade non-Hodgkin lymphoma and multiple myeloma	rIL-2 d6–d8 No preselection	10	80	10			[54]
Bisphosphonate in vivo		rIL-2 d1–d6 Preselection	9	44	22	33		
	Metastatic hormone-refractory prostate cancer	Phase I ZOL Phase I ZOL + rIL-2	9 9	78 33	11 44	11 22		[56]
	Advanced stage IV breast cancer	ZOL+rIL-2 Phase I	10	70	20	10		[55]

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Box 1. Triggering $\gamma\delta$ T-cell-mediated antitumor activity: focus on aminobiphosphonates and chemotherapy

Aminobiphosphonates are synthetic chemical compounds that potently activate $\gamma\delta$ T cells and have shown promising efficacy in the treatment of several types of cancer (RCC, metastatic prostate cancer and breast cancer). So far, only a few drugs have been tested, in particular ZOL, pamidronate and bromohydine pyrophosphate (BrHPP; also known as IPH1101). All these synthetic compounds mimic natural $\gamma\delta$ T cell activating ligands such as IPP or HM-BPP [(E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate].

Some chemotherapy agents (such as doxorubicin and oxaliplatin) have the capacity to induce an immunogenic tumor cell death, which elicits an antitumor immune response that is crucial for tumor eradication and long-term protection against relapse. $\gamma\delta$ T cells are recruited to the tumor bed after immunogenic chemotherapy and appear as crucial contributors to chemotherapy efficacy. Doxorubicin is an anthracycline antibiotic that works by intercalating DNA. Doxorubicin is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas.

Oxaliplatin is a platinum-based anticancer agent. The cytotoxicity of platinum compounds results from inhibition of DNA synthesis. Oxaliplatin is mainly used in the treatment of colorectal carcinoma.