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MINIREVIEWS

Expansion strategies for Vδ2 γδT cells in cancer immunotherapy: Activation, cytokines, and culture conditions

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Abstract

The γδT cells are an emerging class of immune effectors with potent antitumor activity, bridging innate and adaptive immunity. Their unique ability to recognise stress-induced ligands independently of major histocompatibility complex restriction makes them attractive candidates for cancer immunotherapy. However, the clinical application of γδT cells requires efficient *in vitro* expansion strategies to generate large numbers of functional cells. This mini-review explores the latest advancements in γδT cell expansion protocols, focusing on key activation stimuli, cytokine support, and culture conditions that optimise proliferation and cytotoxicity.

Key Words: Vδ2; γδT; Expansion; Immunotherapy; Zoledronate; N-aminobisphosphonates; Mevalonate pathway

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Core Tip: Vδ2 γδT cells hold promise for cancer immunotherapy due to their major histocompatibility complex-independent recognition of phosphoantigens and relative ease of their large scale GMP-compliant expansion *in vitro*. This mini-review outlines current strategies to optimize Vδ2 T cell expansion, highlighting the roles of stimuli, cytokine combinations, and culture conditions. Emerging insights on direct phosphoantigen stimulation and Toll-like receptor-based co-stimulation are also discussed, offering new avenues to enhance γδT cell yield and functionality for therapeutic use.

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INTRODUCTION

Human T cells consist of two major subsets-αβT (90%-95% of total T cells) and γδT (usually up to 5% of total T cells). Human γδT cells are further subdivided into Vδ1, Vδ2, Vδ3, Vδ4, and Vδ5 based on the variable fragment of TCRδ they use[1]. Vδ3-Vδ5 are poorly understood due to several factors, most notably the lack of available antibodies and their scarcity in peripheral blood. Vδ1 cells can be found in substantial numbers in peripheral blood, but are mostly limited to epithelial surfaces[2]. Vδ2 is the dominant subset in peripheral blood, where it usually accounts for 70%-90% of total γδT cells except for newborns and young children, in whom Vδ1 dominates. Both Vδ1 and Vδ2 are naturally cytotoxic against cancerous and viral-infected cells. γδT cells recognise antigens mostly in a major histocompatibility complex-unrestricted manner, thus even allogeneic transfers of γδT cells are immunologically safe[3]. γδT recognise targets *via* a plethora of cytotoxicity receptors *e.g.* natural killer group 2 D (NKG2D), DNAX accessory molecule 1 (DNAM-1), natural killer (NK) p30 and NKp44[1,3].

Vδ2 cells recognise phosphoantigens in a butyrophilin-dependent manner[3]. Phosphoantigens can be of both bacterial and eukaryotic origins. The (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP), a most potent phosphoantigen, is of bacterial origin, while its eukaryotic equivalent isopentenyl pyrophosphate (IPP) is considerably weaker. IPP is commonly accumulated in various tumours due to disruptions in the mevalonate pathway[4]. This can be artificially obtained in *in vitro* cultures by the addition of N-aminobisphosphonates, most commonly zoledronate. N-aminobisphosphonates are thus used to activate and induce the proliferation of Vδ2 from peripheral blood mononuclear cells (PBMCs), where they disrupt the mevalonate pathway of monocytes and induce the accumulation of IPP therein. This results in a culture of approximately 95%-99% pure Vδ2 cells after 2 weeks[5]. Such products were previously tested for immunotherapy[6].

γδT-based immunotherapy of tumours is a promising avenue that requires substantial fine-tuning. Current *in vitro* expansion approaches result in products that are safe even in the case of allogeneic γδT[7]. So far, the clinical studies have yielded unsatisfactory results, mostly partial remission or stable disease, with complete remission only in isolated cases [3]. Nevertheless, current products have severely limited efficacy[8]. Thus, a strong need for optimization exists.

In the current paper, we aim to discuss different approaches to Vδ2 expansion protocols with a final immunotherapeutic aim. Thus, we focus on protocols that may be GMP-compliant and enable good scaling.

CYTOKINE PROFILE

The traditional approach to γδT (Vδ2) *in vitro* expansion is a zoledronate-based stimulation of PBMCs with interleukin (IL)-2 added every 2-3 days[5]. Under those settings, external IL-2 is crucial for the proliferation and survival of Vδ2 cells. IL-2 belongs to the common gamma-chain cytokine family[9]. Thus, some efforts were made to test whether IL-2 could be substituted by other family members: (1) IL-4; (2) IL-7; (3) IL-9; (4) IL-15; and (5) IL-21[10]. IL-4 seems to have a negative impact on γδT cytotoxic potential, while the effect of IL-9 is almost unexplored[10]. IL-9 is only known to activate isolated human γδT cells[11]. Interestingly, IL-33, a member of the IL-1 family, is also capable of sustaining γδT proliferation *in vitro*, although with inferior results to the common gamma-chain cytokines[12,13]. This effect is dependent on conventional T helper (Th) cells, which increased IL-2 production in response to IL-33; at the same time, CD25 was increased on γδT cells. Finally, the addition of IL-33 to IL-2 significantly increased the final yield[13].

The combination of IL-2 and IL-15 significantly improves γδT proliferation in response to zoledronate[14-17]. IL-15 alone promotes the proliferation of γδT cells stimulated with phosphoantigens stronger than IL-2. Moreover, it promotes Th1-related program and improves their cytotoxicity[16,18]. Addition of IL-15 to the standard IL-2 and zoledronate-based expansion protocol does not affect the CD16, CD56, NKG2D, DNAM-1, programmed cell death protein 1 (PD-1), or natural cytotoxicity receptors expression, but it increases the production and release of granzyme B, granulysin, interferon-gamma (IFN-γ), and perforin[18,19]. Interestingly, the addition of IL-15 also increases the Bcl-2 expression and lowers the expression of caspases 3 and 8[20]. IL-15 with zoledronate promotes a shift from late effector memory towards early central memory phenotype in comparison to IL-2 and zoledronate[21]. Moreover, the addition of IL-15 and/or IL-21 facilitates expansion of γδT cells from poorly responding donors[22]. IL-21 seems to have no direct effect on γδT cytotoxic potential, but it promotes IL-10 production and expression of CD73 on γδT cells, thus promoting their regulatory phenotype[22,23]. On the contrary, Thedrez *et al*[24] reported a significantly increased cytotoxicity of γδT cells cultured with IL-21, suggesting that the exact effect may be target-dependent. Similarly, the addition of IL-21 promoted cytotoxicity of γδT cells against some hepatocellular carcinoma cell lines, but not others[25]. Additionally, IL-21 is known for the selective upregulation of chemokine C-C motif ligand (CCL) 13 in expanded γδT cells[26]. CCL13 is an important chemoattractant for T cells, monocytes and eosinophils[27]. Therefore, an increased expression of CCL13 in γδT may further promote their *in vivo* immunotherapeutic potential by increasing the immune-cell infiltration of the tumour. Further studies with the assessment of transcriptional changes by RNAseq could potentially explain those discrepancies

observed for IL-21.

While IL-2 or other common-gamma-chain cytokines are needed to sustain the proliferation, other cytokines may be added to promote certain phenotypes. Preincubation with IL-12 seems to promote CD56 expression and cytotoxic potential of γδT cells[28]. CD56+ γδT cells have superior cytotoxic potential and higher CD16 expression compared to CD56- ones[29]. The addition of IL-12 also promotes a Th1-like program in γδT cells[30]. Finally, IL-12, along with IL-2 at the beginning of zoledronate-induced expansion, seems to further facilitate proliferation and boost cytotoxic potential [31]. IL-12, along with HMBPP, promotes the similar expansion of Vδ2 cells as HMBPP + IL-2, but significantly increases T-bet expression[32]. Similarly, IL-12 together with IL-15 synergistically increases IFN-γ production by Vδ2 cells[33]. IL-12-dependent increase in IFN-γ production by conventional CD8+ T cells is mediated by modulation of downstream T-cell receptor (TCR) signalling[34]. Finally, IL-12 promotes INF-γ and granzyme B production and cytotoxicity of γδT cells when added alone to zoledronate lines at the end of the expansion phase, but induces significant apoptosis when applied together with IL-18[35]. IL-18, along with IL-2 and zoledronate, provides better proliferation than IL-2 and zoledronate alone[36,37]. Moreover, IL-18 promotes higher production of IFN-γ and tumor necrosis factor (TNF)[37]. IL-18 also restores γδT reactivity in human immunodeficiency virus patients and increases their cytotoxic potential[38]. IL-12, along with IL-18, without any TCR stimulation, seems to significantly improve γδT cytotoxicity[39,40] and increase the expression of granzyme B, IFN-γ, and NKG2D on γδT cells[40]. Moreover, the enhanced expression of CD56 upon IL-18 supplementation was noted[41]. On the other hand, a mixture of IL-12 and IL-18 promotes higher T-cell immunoglobulin and mucin domain-3 expression on γδT cells, which may hamper their cytotoxic potential against cancer[42]. The 24-48 hours preincubation of γδT cells with either IL-15 or IL-18 significantly activates γδT cells and increases their cytotoxic potential[17]. Additionally, IL-18 supplemented along with geranylgeranyl pyrophosphate seems to protect γδT cells from zoledronate toxicity[41]. So far, both IL-12 and IL-18 seem to be promising candidates to further increase the cytotoxic potential of γδT cells, but this should be cautiously explored as they may also increase the checkpoint expression.

Transforming growth factor-beta (TGF-β) is another cytokine that was assessed as the co-stimulation factor for γδT cells. TGF-β seems to promote cytotoxic potential and adhesion molecule expression in IL-2 and zoledronate expanded γδT[43,44]. On the other hand, a mixture of IL-2, IL-15, and TGF-β potently promotes the expansion of FoxP3+ regulatory γδT cells[45]. Moreover, according to Capietto *et al*[46], 48 hours preincubation of Vδ2 cells with TGF-β lowers their cytotoxic potential. While some studies claim positive effects, others state the opposite; thus, the impact of TGF-β is uncertain. As a short term preincubation of TGF-β seems to increase γδT cytotoxic potential, the effect seems to be time-dependent, but additional studies are need to fully comprehend this phenomenon.

Other cytokines received severely limited attention. TNF-α, but not IFN-γ, is required for efficient γδT proliferation and IFN-γ production after phosphoantigen stimulation, but TNF-α in this setting is released by stimulated PBMCs[47]. IL-7, a less-known common-gamma-chain cytokine, to a limited degree promotes IL-17 production by human γδT cells[48]. Interesting results were noted for IL-23 and IL-27. IL-27 increases IFN-γ and perforin production by γδT cells and their cytotoxic potential[49]. Recent reports suggest that IL-23, along with phosphoantigen, may promote γδT expansion and increase their cytotoxic potential[50]. Cytokines like IL-23 and IL-27, to some degree, also TNF-α seem to be interesting, but further studies are needed to better understand their function.

Overall, the cytokine milieu during expansion is a key factor influencing both the expansion rate and determining the final phenotype. The optimal cytokine environment likely depends on the intended therapeutic target-different phenotypes may be desirable when manufacturing γδT cells for glioblastoma compared to leukemia. Although significant knowledge has already been gained, further studies are needed to fully understand the impact of specific cytokines on γδT cell phenotype. Major findings are summarized in Table 1[5,11,13,18-24,26,31,33,35-37,41,43,45,46,49,51-58].

IMPACT OF CELL CULTURE MEDIUM

While the cytokine milieu remains a key determinant of γδT cell expansion, it is not the only extrinsic factor influencing this process. Equally important is the choice of culture media, which can substantially affect the magnitude and phenotype of expanded γδT cells. Media composition, including nutrient content, buffering capacity, and serum supplementation, may synergise with cytokine signalling or, in some cases, impose limiting conditions that skew the expansion outcome. According to Peters *et al*[51], different media yield significantly different expansion folds, with RPMI-1640 + 10% foetal bovine serum (FBS) having the best results. Usually, zoledronate and direct phosphoantigens (HMBPP) yield similar expansion rates, but this turned out to differ in serum-free complete media[51]. RPMI-1640 supplemented with 10% human AB plasma provides good expansion, although not compared directly, it seems to be similar to that usually observed with 10% FBS[59].

Serum-free media are especially interesting from the translational perspective-while a wide selection of those is available, only some have been tested. According to Sutton *et al*[60], serum-free media are far less effective for γδT expansion than RPMI-1640 with FBS. On the other hand, Zhou *et al*[61] reported better proliferation in those same serum-free media than in RPMI with FBS. AIM-V gives similar yields to RPMI-1640, while much higher (up to 5-fold) yields were observed for OpTimizer[62]. However, OpTimizer showed approximately 12% of NK cells in the final product and thus had approximately 10% lower purity than the remaining two[62]. At the same time, γδT cells from OpTimizer had a 2-fold higher expression of CD56 (almost 50%), suggesting higher cytotoxic potential[62].

Table 1 Summary of the cytokine milieu used in *in-vitro* expansion of human γδT cells stimulated with N-aminobisphosphonates or phosphoantigens

Cytokine	Impact of cytokine on Vδ2 T expansion		Concentration	Ref.
Common gamma chain				
IL-2	+	Supports robust γδT cell proliferation and enhances cell viability during extended *in vitro* culture. Drives the cytotoxic phenotype, induces CD107a, IFN-γ, and TNF-α expression in a dose-dependent manner, indicating enhanced degranulation and effector function. Upregulation of early activation markers, such as CD69 and CD25, as well as molecules involved in adhesion and cytotoxicity (LFA-1, ICAM-1, NKG2D, CD94). It promotes a proinflammatory effector phenotype (CD27-, CD28-) and CXCL10, but also an increased expression of KLRG1, 2B4. Upregulate expression of Th1-type cytokines and effector molecules, including IFN-γ, TNF-α, GM-CSF, CCL3, IL-5, and IL-13	100-1000 IU/mL	Kondo *et al*[5], Nada *et al*[21], Peters *et al*[51], Mariani *et al*[52], Li and David Pauza[53]
IL-4	+	Enhances the proliferation, however, weaker than IL-2 and IL-15. Upregulation of early activation markers, *e.g.* CD69, and LFA-1, ICAM-1, NKG2D, CD94, CD27, CD269	10 ng/mL	Vermijlen *et al*[26]
IL-9	+/-	Enhances the expression of IL-9R mRNA. Upregulates IL-17 and IFN-γ expression	2 ng/mL	Guggino *et al*[11]
IL-15	+	Promotes γδT cell proliferation and viability, even at low concentrations. Improves survival by increasing Bcl-2 expression and downregulating apoptotic mediators such as caspases 3 and 8, thereby supporting long-term maintenance of γδT cells in culture. Enhances cytotoxic potential by promoting the production and secretion of granzyme B, perforin, and granulysin. Increases the proportion of CD56+ and CD16+ γδT cells. Induces early activation markers, including CD25 and CD69. Favours the development of an early/central memory phenotype (CD27+, CD28+/-) and, when combined with IL-2, further enhances the expression of CCR9, HLA-DR, CD86, and CD70. Notably, while IL-15 does not significantly modulate the surface levels of CD16, CD56, NKG2D, DNAM-1, PD-1, or other natural cytotoxicity receptors, it functionally boosts downstream effector pathways. IL-15-stimulated γδT cells exhibit robust IFN-γ secretion, reportedly higher than in traditional IL-2-based protocols, while lacking expression and secretion of IL-10, IL-13, and IL-17, suggesting a Th1-skewed, non-regulatory profile	2-40 IU/mL	Aehnlich *et al*[18], Dunne *et al*[19], Sawaisorn *et al*[20], Nada *et al*[21], Burnham *et al*[22], Vermijlen *et al*[26], Peters *et al*[43], Chen and Freedman[54], Tyler *et al*[55], Izumi *et al*[56], Guo *et al*[57]
IL-21	+/-	Does not support long-term proliferation of γδT cells following phosphoantigen activation. However, it can enhance expansion in "non-expanders", *i.e.*, donors who respond poorly to conventional protocols. Enhances cytotoxic potential by upregulating CD107a expression and promoting degranulation. Increases expression of key effector molecules, including granzyme A, granzyme B, and perforin. IL-21 induces early activation markers (CD25, CD69) and upregulates surface molecules involved in adhesion and cytotoxicity, such as CD56, LFA-1, ICAM-1, NKG2D, CD94, and CXCL10. Favours an effector memory phenotype and upregulates regulatory and exhaustion-associated molecules (CD244, CD152, KLRG1). Selectively induces expression of CD73 and overexpression of CXCL13. Promotes a proinflammatory Th1-skewed response, though weaker than IL-2. It stimulates secretion of IFN-γ almost exclusively, but also induces IL-8 and IL-10 production.	10-30 ng/mL	Burnham *et al*[22], Barjon *et al*[23], Thedrez *et al*[24], Vermijlen *et al*[26]
Others				
IL-7	+/-	Enhances expanded γδT cells viability. No effect on the induction of naive CD4+ Vγ9/Vδ2 T cells proliferation. Does not induce HLA-DR expression.	20-50 ng/mL	Tyler *et al*[55]
IL-12	+/-	The effects of IL-12 on proliferation are inconsistent. Some studies report limited impact on cell expansion when IL-12 is used alone. However, in specific contexts, particularly when TNF-α is present, IL-12 may support expansion without the need for IL-2. May have dual effects on viability. When combined with IL-18, it induces apoptosis *via* the c-Jun N-terminal kinase signalling pathway. Alone, IL-12 appears less cytotoxic. IL-12 skews the phenotype toward both central and effector memory. When added to already expanded γδT cells, upregulates granzyme B and perforin expression. It also promotes secretion of perforin, indicating heightened degranulation and effector activity. In combination with IL-18, IL-12 upregulates inhibitory and exhaustion-associated markers such as CTLA-4, PD-1, T cell immunoglobulin and mucin-domain-containing-3, and Lymphocyte activation gene-3. Induces robust production of proinflammatory mediators, including CCL4, GM-CSF, IL-1Ra, IL-12 (autocrine loop), IL-13, TNF-α, IFN-γ, and IFN-α	10-25 ng/mL	Assy *et al*[31], García *et al*[33], Song *et al*[35]
IL-18	+/-	Promotes expansion of γδT cells by mitigating zoledronate-induced toxicity, indirectly supporting proliferation. Drives the differentiation toward an effector memory phenotype. Enhances cell survival by increasing anti-apoptotic signalling pathways. Upregulates expression of protein kinase B, Bcl-2, phosphorylated I kappa B, and cellular Fas-associated death domain-like interleukin-1 beta-converting enzyme-like inhibitory protein, while downregulating caspase 3 Levels. The effects on cytotoxicity are somewhat contradictory. While some data report downregulation of granzyme B and IFN-γ at the expression level, IL-18 also promotes the generation of $CD56^{bright}$CD11c+ γδT cells with high cytotoxic cytokine release, co-expressing CD25, CD122, NKG2D, and HLA-DR. Enhances secretion of IFN-γ, TNF-α, and GM-CSF, while not inducing IL-12 production	10-200 ng/mL	Song *et al*[35], Sugie *et al*[36], Li *et al*[37], Nussbaumer *et al*[41], Tsuda *et al*[58]
IL-23	+/-	No conclusive data indicate a direct effect of IL-23 on γδT cell proliferation. Enhances the expression of IL-23R mRNA. Induces elevated IL-17 and IFN-γ expression. Combined with CD26 Ligation, promotes the generation of CD26-negative cytotoxic γδT cells. Enhances CD94, CD226, and granzyme B expression. However, the effect is noted only on CD26-positive cells	10-50 ng/mL	Guggino *et al*[11], Capietto *et al*[46]

IL-27	+	No conclusive data indicate a direct effect of IL-27 on γδT cell proliferation. Enhances cytotoxicity specifically in resting γδT cells, increasing the expression of granzyme A, granzyme B, and perforin. These effects are not observed in already activated or expanded γδT cells. Upregulates CD62 L, suggesting a shift toward a central memory phenotype. It does not affect the expression of CD16 or NKG2A. In activated γδT cells, IL-27 does not affect the secretion of IL-2, IL-4, IL-17A, IFN-γ, IL-10, IL-1β, or TNF-α. In contrast, in resting γδT cells, IL-27 enhances IL-17A secretion. Additionally, it leads to downregulation of Th2-type cytokines	100 ng/mL	Morandi *et al*[49]
IL-33	+	Promote *in vivo* proliferation in dose dose-dependent manner, requiring CD4 T lymphocytes. Exhibit an effector memory phenotype (CD27-, CD45RA-). Elevated cytotoxic potential has been observed, characterised by increased granzyme B, perforin, and CD107a expression. Upregulation of CCR5, CXCR3, NKG2D, CD161, and TNF-related apoptosis-inducing ligand. It does not affect the expression of CD16, CD28, or NKG2S. Moreover, KIR2DL-1, KIR2DL-2, and KIR2DL-3 are not expressed. Promotes secretion of Th1-type cytokines.	100-1000 ng/mL	Duault *et al*[13]
TGF-β	+/-	Shows contradictory effects on γδT cell expansion. In some settings, it supports robust proliferation of purified Vδ2 T cells. However, when added to already expanded γδT cells, it may inhibit proliferation and delay maturation. Promotes differentiation toward central memory (CD27+, CD45RA-) and effector memory (CD27-, CD45RA+) phenotypes. It also supports the emergence of regulatory-like FoxP3+ γδT cells, especially when combined with IL-15. The impact of TGF-β on cytotoxicity is context-dependent. In some studies, it enhances cytotoxic potential and conjugate formation with tumor cells, associated with CD103 upregulation. However, downregulation of CD107a, absence of intracellular granzyme B, perforin, and IFN-γ, and reduced NKG2D expression have also been observed. Upregulates CCR4, CCR7, CXCR3, CXCR4, LFA-1, CD56, and CD103, while downregulating CCR6, CCR10, CD107a, and NKG2D. It also induces expression of FoxP3, CD25, CD69, CTLA-4, HLA-DR, and CD45RA in certain conditions, particularly in combination with IL-15. Promotes secretion of IFN-γ, TNF-α, IL-9, and granzyme B. However, granzyme A expression is reduced, and perforin levels remain comparable to the standard IL-2 + zoledronate protocol	1.7-10 ng/mL	Peters *et al*[43], Casetti *et al*[45], Capietto *et al*[46]
IFN-γ	0	No specific data on proliferation effects have been reported	1-100 ng/mL	Vermijlen *et al*[26]

CCL: C-C motif ligand:; CCR9: C-C chemokine receptor 9; CXCL: C-X-C motif ligand; FoxP3: Forkhead box protein 3; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HLA: Human leukocyte antigen; ICAM-1: Intercellular adhesion molecule-1; IFN-γ: Interferon-gamma; IL: Interleukin; KIR2DL: Killer cell Ig-like receptors; KLRG1: Killer cell lectin-like receptor subfamily G, member 1; LFA-1: Lymphocyte function-associated antigen-1; NKG: Natural killer group; PD-1: Programmed cell death protein 1; TGF-β: Transforming growth factor-beta; Th: T helper; TNF: Tumor necrosis factor; +: Positive; -: Negative; +/-: Ambivalent; 0: No evidence of a significant effect for cancer therapies.

ACTIVATION STRATEGIES

In addition to cytokines and media, the specific stimulation protocol employed plays a prominent role in shaping γδT cell growth. Among these, zoledronate-based and, more broadly, N-aminobisphosphonate-driven protocols are currently the most prevalent due to their simplicity and efficacy. However, alternative strategies are increasingly being explored. The majority of those are based on direct phosphoantigen stimulation-see Table 2[63-67] for the overview of available phosphoantigens and Table 3[68-71] for the comparison of different N-aminobisphosphonates.

In theory, any N-aminobisphosphonate can be used to stimulate γδT expansion from PBMCs. In practice, they differ in their potency of farnesyl pyrophosphate synthase (FPPS) inhibition-the IC_{50} for inhibition is inversely correlated to the expected proliferation response[72]. As mentioned, zoledronate is the most commonly used one and also one of the most potent FPPS inhibitors[62,72]. Titration experiments suggest an optimal concentration of approximately 1-3 μmol/L, both lower and higher doses give inferior results[73,74]. A novel compound, tetrakis-pivaloyloxymethyl 2-(thiazole-2-ylamino)ethylidene-1,1-bisphosphonate, showed very promising results, with far better response than that to zoledronate [75]. Pamidronate, on the other hand, produces unsatisfactory outcome, usually comparable to direct IPP stimulation[76]. Neridronate showed reasonable expansion results, but it was directly compared to zoledronate at suboptimal doses (5-10-fold lower than the optimal)[77]. Alendronate shows expansion similar to that induced by direct phosphoantigen stimulation with bromohydrin pyrophosphate (BrHPP)[78]. To date, there is no direct comparison of various n-aminobisphosphonates at optimal concentration. Thus, it is not possible to draw a definitive conclusion, but it appears that zoledronate is the optimal choice after all.

Different phosphoantigens were tested for γδT expansion *in vitro*. HMBPP is one of the most potent and widely utilised phosphoantigens; it promotes significant proliferation of γδT cells and induces the Th1-like program[65]. Monoethyl phosphate, similarly to other, better-known phosphoantigens, induces the proliferation of Vδ2 cells, comparable to that induced by *Mycobacterium tuberculosis* lysates[67]. A good proliferative response can also be achieved with BrHPP, a synthetic phosphoantigen with a moderate activation strength[79,80]. IPP, the only eukaryotic phosphoantigen, can also be used successfully for γδT expansion *in vitro* with an optimal concentration of approximately 2 μg/mL and IL-2 at around 100 IU/mL. The doses of IL-2 higher than 1000 IU/mL yielded significantly lower final cell counts after 2 weeks, despite initially showing a much better growth rate, an effect that was most likely related to overactivation and activation-induced cell death[81]. Nevertheless, IPP yielded cultures with approximately 50% purity, far inferior to the zoledronate and HMBPP. Interestingly, Nada *et al*[21] observed better proliferation of Vδ2 cells in response to HMBPP than to zoledronate. While this is in contrast to our own observations (unpublished), this may be due to the use of frozen PBMCs. Zoledronate proliferation requires functional myeloid cells[82,83], whereas freezing may significantly impact their viability.

Table 2 Selected phosphoantigens used for *in vitro* activation or expansion of Vδ2 cells

Abbrev name	Full name	Relative strength	Source	Stability in aqueous solution	Ref.
IPP	Isopentenyl pyrophosphate	Approximately 1000 × weaker than HMBPP	Eucaryotic cells	Stable	Latha *et al*[63], Vantourout *et al*[64]
HMBPP	(E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate	Most potent	Prokaryotic cells	Not very stable	Kilcollins *et al*[65]
BrHPP	Bromohydrin pyrophosphate	Stronger than isopentenyl pyrophosphate, weaker than HMBPP	Synthetic	Stable	Sicard *et al*[66]
MEP	Monoethyl phosphate	Unknown	Prokaryotic cells	Stable	Tanaka *et al*[67]

HMBPP: (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate.

Table 3 Comparison of different N-aminobisphosphonates

Name	Food and Drug Administration approval	Water solubility	Relative potency[1]	Ref.
Zoledronate	Yes	4.17 mg/mL	10000 ×	Kondo *et al*[68], Ruggiero *et al*[69]
Pamidronate	Yes	50 mg/mL	100 ×	Ruggiero *et al*[69], Kunzmann *et al*[70]
Alendronate	Yes	20 mg/mL	1000 ×	Ruggiero *et al*[69]
Ibandronate	Yes	72 mg/mL	5000 ×	Ruggiero *et al*[69]
Risedronate	Yes	11 mg/mL	5000 ×	Ruggiero *et al*[69]
Minodronate	No	20 mg/mL[2]	10000 ×	Ohishi and Matsuyama[71]
Neridronate	No	5 mg/mL[2]	100 ×	Ruggiero *et al*[69]
Olpadronate	No	50 mg/mL[2]	1000 ×	Ruggiero *et al*[69]

[1]Relative potency with etidronate (a first-generation bisphosphonate) as the reference compound.
[2]Special conditions may be needed for water solubility, *e.g.*, ultrasonic treatment, heating, pH adjustment.

Stimulation with zoledronate at concentrations exceeding 10 μM significantly decreases the Vδ2 proliferative response after prolonged exposure; however, doses of up to 100 μM can be used if PBMCs are washed with a clear medium after approximately 4 hours[21]. Interestingly, this pulse treatment resulted in an overall similar purity but a higher cell count after 14 days. Notably, the pulse treatment resulted in better degranulation and higher expression of perforin[21]. As recently suggested, blockage of the mevalonate pathway by zoledronate also affects human γδT cells, substantially impacting their cytotoxic potential (Figure 1)[84]. Pulse treatment may be a solution to overcome this impairment.

Finally, apart from the classical approach discussed in the current paper, one can also try conventional T cell expansion protocols that may require prior γδT cell purification or a protocol based on artificial antigen-presenting cells[85,86]. While those approaches may be important, they are not within the scope of the current review.

TOLL-LIKE RECEPTOR AGONISTS FOR CO-STIMULATION

Beyond the foundational cytokine, media, and stimulation components, further optimisation of *in vitro* expansion can be achieved by introducing additional co-stimulatory signals. In our laboratory, we have tested various bacterial lysates with some positive results (unpublished data). Interestingly, this improvement may be mediated *via* Toll-like receptor (TLR). Indeed, TLR agonists [resiquimod (TLR7/8), flagellin from *Salmonella typhimurium* (TLR5), multiple primary lung adenocarcinomas (TLR4), lipopolysaccharide (TLR4), CL429 (TLR2 and nucleotide-binding oligomerization domain 2), PAM3CSK4 (TLR1/2)] improve the proliferative response of Vδ2 after PBMC stimulation with IPP[87]. Resiquimod itself provoked only a very limited proliferative response[87]. Similarly, a better proliferation was observed when resiquimod was added to the anti-TCRγδ antibody[87]. Moreover, Vδ2 cells obtained by IPP + resiquimod stimulation have lower PD-1 expression while at the same time having better degranulation response and higher expression of IFN-γ, TNF-α, and Granzyme B, when compared to both IPP and zoledronate[87]. Moreover, those cells were approximately twice as cytotoxic against melanoma cells, both *in vitro* and *in vivo*, in the orthotopic mouse model[87]. Interestingly, resiquimod, when added along with zoledronate, tended to decrease proliferation[87,88]. Similarly, polyinosinic-polycytidylic acid (TLR3 agonist) significantly improves γδT proliferation in response to IPP. This effect is mediated by dendritic cells and is dependent on IFN-α[89]. This also suggests that some of those results could be mimicked by additional IFN-α added to

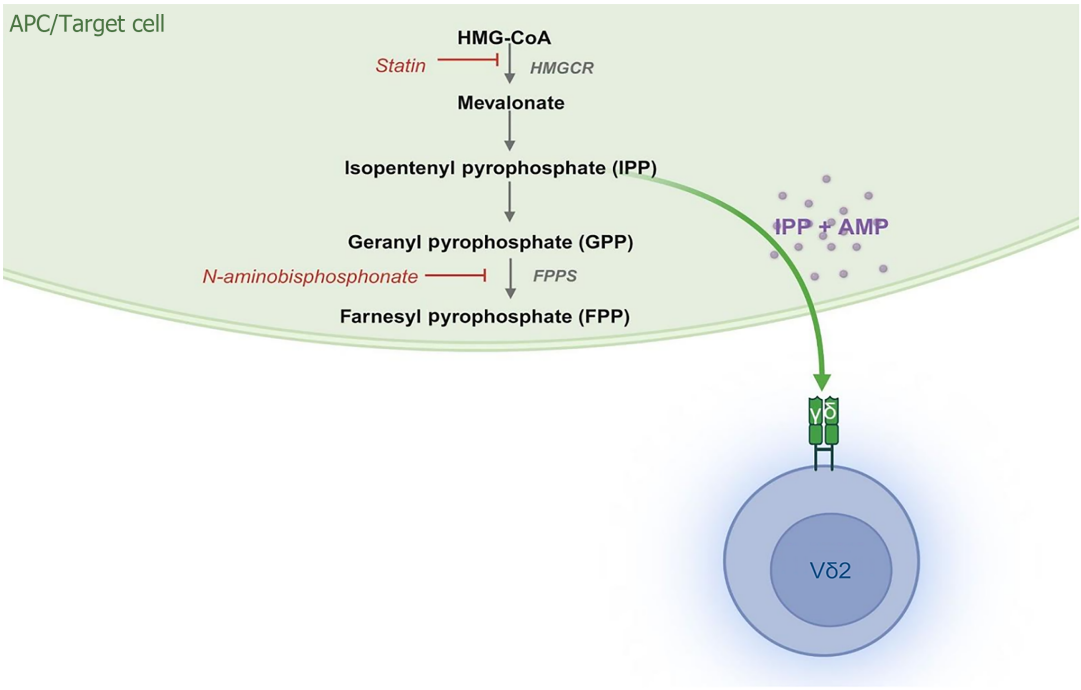


Figure 1 Mevalonate pathway. N-aminobisphosphonates, including zoledronate, inhibit the mevalonate pathway by blocking farnesyl pyrophosphate synthase. This results in intracellular accumulation of isopentenyl pyrophosphate and its metabolites, which are recognized by Vδ2 T cells. APC: Antigen-presenting cell; FFPS: Farnesyl pyrophosphate synthase; HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A; HMGCR: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; IPP: Isopentenyl pyrophosphate.

the culture.

EXPANDERS AND NON-EXPANDERS

Despite these various technical refinements, it is important to acknowledge that expansion outcomes remain highly donor-dependent. Substantial inter-individual variability in γδT cell responsiveness is a well-documented phenomenon [22,87], which may be influenced by prior antigen exposures or intrinsic functional states. This variability represents a key challenge in standardising expansion protocols. Nevertheless, the underlying cause remains largely a mystery. Burnham *et al*[22] attempted to categorise the donors into expanders and non-expanders, observing that non-expanders tended to have a more sedentary lifestyle. Apart from that, they also analysed the expression of chemokine receptors, without noticing any differences. Interestingly, the addition of IL-21 or IL-21 and IL-15 significantly narrowed the proliferative gap between expanders and non-expanders[22]. Interestingly, a high neutrophil-to-lymphocyte ratio predicts poor expansion, at least in cancer patients, where it may be related to granulocyte myeloid-derived suppressor cells[90]. However, if zoledronate-preatreated dendritic cells are used as a stimulus, then proper proliferation is restored, suggesting that, indeed, the problem is not with γδT *per se*[90]. On the other hand, Nicol *et al*[59] observed significant differences in γδT cells before expansion; non-expanders had higher γδT cells with a phenotype of CD45RA+ effector memory and naive T cells, while good responders were skewed towards the effector memory and central memory phenotypes before expansion. Some predictive value also lies in the initial Vδ2 percentage and the age of donors, with better results for young individuals with higher Vδ2 count[91].

The ratio of non-expanders rises in multiple cancers, especially in haematological ones, where over 50% of patients, for chronic lymphocytic leukaemia even over 80%, should be classified as non-responders in contrast to approximately 10% of healthy individuals[92]. This highlights the impact of immunosuppressive microenvironment, possibly also on the dysregulation of butyrophilin, as we have observed in chronic lymphocytic leukaemia patients[93]. Indeed, Tomogane *et al*[94] noted a modest correlation between expansion efficiency and BTN3A1 expression in monocytes. Our own, yet unpublished, data do not support this finding-we have not observed any differences in proliferation between patients with low or high expression of BTN3A, either in monocytes or T cells.

IN VIVO ATTEMPTS

Apart from *in vitro* expansion, there were also attempts to stimulate it *in vivo* in cancer patients. Unfortunately, no proliferation *in vivo* in response to pamidronate and IL-2 was observed in a cohort of haematological cancer patients. Those patients who responded to that treatment showed a clear proliferative response *in vitro* as well. Still, only minimal clinical

efficacy was noted[92]. Similarly, no significant *in vivo* proliferation or satisfactory clinical outcome was observed in renal cell carcinoma and prostate cancer patients treated with zoledronate and IL-2[95,96]. Wilhelm *et al*[97] tried an adoptive transfer of haploidentical αβ-depleted PBMCs to haematological patients after induction chemotherapy. After the transfer, patients were given IL-2 and zoledronate; a notable proliferation of γδT cells was observed, as well as short-term clinical response[97]. While some efficacy was noted, the results of *in vivo* attempts are rather discouraging, possibly due to the highly immunosuppressive environment in cancer patients.

CONCLUSION

Apart from the classical, most widely used, expansion protocol, based on zoledronate and IL-2, there are several alternatives. Despite numerous studies published to date, it is challenging to identify the most effective protocol. Recent data regarding the negative impact of mevalonate blockade on γδT cells adds another layer of complexity; it seems viable to further test direct phosphoantigen stimulation instead of the N-aminobisphosphonate-based one. In parallel, future research should aim to identify predictive biomarkers of γδT cell expandability, which could enable pre-selection of optimal donors and tailoring of expansion strategies. Immunophenotypic features, such as baseline expression of activation or exhaustion markers, as well as metabolic or transcriptomic profiles, may serve as promising candidates and should be systematically investigated.

FOOTNOTES

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