Editorial

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Selecting the Right RORγt Agonist: Implications for Cancer Immunotherapy

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Ligand-responsive transcription factors like nuclear receptors (NRs) play essential roles in regulating diverse biological functions and are common targets for therapeutic compounds [1]. Among the nuclear receptors involved in immune regulation, RAR-related orphan receptor gamma t (RORγt) stands out as a key transcription factor that drives the differentiation of Th17 lymphocytes from naïve CD4+ T cells. It also controls the expression of signature cytokines, including Interleukin (IL)-17A and IL-17F [2]. While Th17 cells contribute significantly to adaptive immunity [3–5], they have also been implicated in the pathogenesis of various autoimmune disorders, including multiple sclerosis, inflammatory bowel disease, and psoriasis [6–8]. As a result, substantial efforts have been made to discover RORγt inverse agonists to suppress its function and thereby reduce the detrimental effects of Th17 cell activity [9]. Although several major pharmaceutical companies have explored this approach, and numerous candidate compounds have been identified, only several have advanced to clinical trials. Moreover, trials for topical application in psoriasis yielded disappointing results, and some compounds exhibited poor specificity or led to adverse effects such as thymic lymphoma in animal models, ultimately causing most development programs to be discontinued [10]. At the same time, accumulating evidence suggests that Th17 cells, along with IL-17-producing CD8+ T cells (Tc17), may enhance anti-tumor immunity in certain cancers. This has sparked increased interest in the development of RORγt agonists, which aim to boost these immune responses and improve the tumor microenvironment. Such agonists may offer new therapeutic avenues in cancer immunotherapy [11].

The ligand-binding domain (LBD) of RORγt consists of a structure made up of 12 alpha-helices (designated H1 through H12) along with a beta-sheet segment (BSR) [12]. Structural analysis through crystallography has shown that this domain contains a largely hydrophobic internal cavity measuring approximately 940 $Å^3$ in volume [13]. In its active state, the RORγt receptor exhibits a stabilized H12 helix, a condition often maintained by specific interactions—such as those involving the amino acid triad His479, Tyr502, and Phe506—with the adjacent H11' helix [13]. This arrangement forms a binding surface that allows coactivator proteins to associate with the receptor. When an inverse agonist binds, it disrupts this interaction, particularly interfering with the His479–Tyr502–Phe506 network, thereby preventing the receptor from adopting its active conformation. In contrast, agonists enhance receptor activation by reinforcing these interactions. They contribute to an extended stabilizing cluster that supports hydrogen bonding between His479 and Tyr502, which in turn secures the positioning of H12 [13]. The degree of this stabilization can vary—being relatively mild in the case of partial agonists, but more robust when full agonists are involved [12].

As previously mentioned, RORγt agonists are emerging as potent immunomodulators with the capacity to boost antitumor immune responses, particularly through the activation of Th17 and Tc17 cells. Their integration into cancer therapy holds significant potential, especially when used alongside immune checkpoint inhibitors targeting cytotoxic T cell antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1). RORγt activation has been shown to suppress *PDCD1* (gene encoding PD-1) expression in Th17 cells, potentially enhancing the efficacy of PD-1 blockade [14]. Moreover, RORγt agonists may reduce regulatory T cell (Treg) populations, thereby shifting the immune balance toward a more pro-inflammatory, antitumor phenotype [15]. In addition to modulating Th17 activity, these compounds increase the expression of chemokine receptor 6 (CCR6) and chemokine (C-C motif) ligand 20 (CCL20) in Th17 cells, and promote the production of interferon-gamma (IFN-γ) and granzyme B within the tumor microenvironment [15]. Furthermore, activation of RORγt in group 3 innate lymphoid cells (ILC3s) enhances C-X-C motif chemokine ligand 10 (CXCL10) secretion, which facilitates the recruitment of both CD4+ and CD8+ T cells into tumors [16]. These immunological shifts not only strengthen the local immune response but also enhance the effectiveness of checkpoint blockade, supporting the use of RORγt agonists as valuable adjuncts in cancer immunotherapy [11]. To support this, it is worth noting that LYC-55716 (WO2015131035A1) was the first RORγt agonist to enter clinical trials, developed through structure-guided optimization of benzoxazine scaffolds [17]. In preclinical models, the compound exhibited significant antitumor activity, leading to its progression into early-phase clinical studies targeting various solid tumors (NCT02929862,

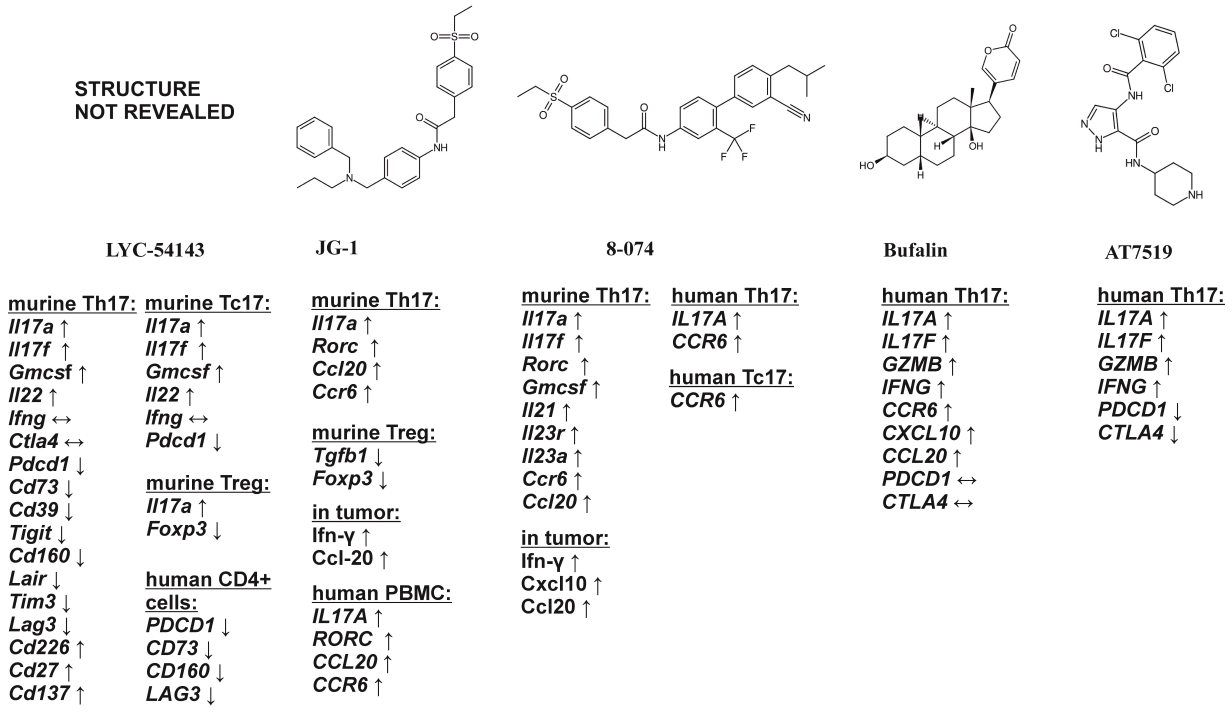

Fig. 1. The structures of selected RAR-related orphan receptor gamma t (RORγt) agonists and their impact on gene expression in immune cells and tumor microenvironment. ↑ indicates increased expression; ↓ indicates decreased expression; ↔ indicates no change.

NCT03396497). The drug exhibited a favorable safety profile, with no dose-limiting toxicities reported. Notably, elevated cytokine levels were observed in 31 of 32 patients. Among 25 patients evaluated for therapeutic response, two (one with non-small cell lung cancer and one with sarcomatoid breast cancer) experienced partial responses, while 11 exhibited stable disease [18]. LYC-55716 has been shown to enhance the antitumor activity of Tc17 cells and promote Tc1 cell recruitment [19].

Despite the large number of identified RORγt receptor agonists, relatively few have been investigated for their anticancer activity [11]. A review of the existing literature suggests that these compounds vary in significance, and importantly, they differ in their ability to induce or inhibit the expression of genes relevant to immunotherapy. For example, LYC-54143 was shown to induce the expression of *IL17A*, *IL17F*, and *IL22*, but not *IFNG* (gene coding IFN-γ) (Fig. 1) in murine Th17 and Tc17 lymphocytes. It also inhibited the expression of the PD-1 receptor on Th17 cells, without affecting CTLA-4 expression and increased the efficacy of anti-PD-1 therapy [14]. JG-1 increased the expression of *IL17A*, *CCL20*, *CCR6*, and increased the efficacy of anti-CTLA-4 therapy [15]. 8-074 upregulated *IL17A*, *IL17F*, *IL21*, *CCL20*, and *CCR6* [20] (Fig. 1). Among various cardiac glycosides tested, bufalin emerged as the most potent RORγt agonist. It strongly induced *IL17A*, *IL17F*, *IFNG*, *CXCL10*, and *CCL20*, as well as *GZMB* (gene coding granzyme B) and *CCR6*, but did not affect the expression of *PDCD1* or *CTLA4* [21]. In contrast, AT7519 not only increased RORγt protein levels, but also significantly upregulated *IL17A*, *IL17F*, *IFNG*, and *GZMB*, while simultaneously suppressing *PDCD1* and *CTLA4* expression [22] (Fig. 1). Thus, although RORγt receptor agonists share similar functions, they differ significantly not only in structure (Fig. 1) but they can have distinct effects on gene expression probably due to several nuanced molecular and biochemical factors, including:

- Differential ligand-induced conformations—Ligand-specific structural changes in RORγt can influence its interaction with coactivators or corepressors, alter DNA-binding affinity and specificity, and affect the recruitment of the transcriptional machinery. For example, agonists typically promote coactivator recruitment, while inverse agonists displace them [23]. Different agonists may therefore recruit distinct coactivators, leading to variations in receptor activity and gene specificity [24]. In the case of RORγt, this is even more plausible, as RORγt interacts with numerous coactivators, including steroid receptor coactivator (SRC)-1 [25], SRC-2 [26], SRC-3 [27,28], p300 [29,30], and transcriptional co-activator with PDZ-binding motif (TAZ) [31].

- Biased agonism—Some agonists display functional selectivity, enhancing specific RORγt-mediated responses (e.g., *IL17* transcription) while having little to no effect on others (e.g., *IFNG*, *PDCD1* or *CTLA4* expression). Similar patterns have been observed with full and

partial peroxisome peroxisome proliferators-activated receptors (PPAR) agonists, which preferentially recruit distinct sets of coactivator peptides [24].

- Response element-dependent coregulator recruitment—The DNA-binding domain may adopt a sequence-specific conformation, suggesting that RORγt can interpret both its ligand-bound and DNA-bound states. Consequently, the DNA sequence influences the ligand-dependent recruitment of coregulatory proteins by RORγt [28].
- Potency and pharmacokinetics—Variations in binding affinity, receptor activation duration, metabolic stability, and cell permeability can influence overall efficacy [32].
- Non-genomic effects or off-target actions—Certain agonists may interact with other nuclear receptors or transcription factors, or modulate signaling pathways indirectly, e.g., digoxin binds or affects the expression of multiple NRs [33].

The differential impact of RORγt agonists on gene expression in immune cells remains a relatively underexplored area of research. This gap is significant, as such variation may be critical for selecting appropriate agonists for clinical development. Moreover, the therapeutic relevance of a given agonist may depend heavily on the type of cancer being targeted. For instance, while low levels of IFN-γ can facilitate tumor progression, higher concentrations are known to exert strong antitumor effects [34,35]. Consequently, RORγt agonists capable of inducing robust IFN-γ expression may offer superior therapeutic benefit in certain malignancies, e.g., bladder cancer [36]. Similarly, compounds that downregulate PD-1 and CTLA-4 expression are likely to be more effective in combination with immune checkpoint inhibitors than those lacking this activity. Agonists that induce granzyme B, other serine protease granzymes, or perforin may enhance the cytotoxic activity of CD4+ and CD8+ T cells, thereby improving their effectiveness in adoptive cell therapy. RORγt agonists can modulate the tumor microenvironment by enhancing the production of cytokines and chemokines, thereby promoting the infiltration of immune cells capable of eradicating tumors. Another promising strategy is adoptive T-cell therapy, which involves isolating lymphocytes from the patient, expanding them *in vitro*—often in the presence of specific or tumor-associated antigens—and reinfusing them to boost the immune system's ability to eliminate cancer cells. RORγt agonists can improve the phenotype and functionality of T-cell subsets such as Th17 and Tc17, potentially increasing their therapeutic efficacy [37]. Moreover, because this procedure involves *ex vivo* manipulation, the compounds can be removed prior to reinfusion, allowing the use of higher or otherwise systemically toxic doses that would not be safe if administered directly to the patient. However, the selection of a specific compound for a given therapeutic approach—whether direct intra-patient administration or adoptive cell therapy—as well as for a particular cancer type, should be guided primarily by cytotoxicity data and the gene expression profile modulated by the agonist. Unfortunately, due to the lack of standardized protocols, comparing the efficacy and safety of different compounds can be challenging. Therefore, I propose that experimental designs for testing RORγt agonists should include the following:

- Cell-based reporter assays using RORγt-expressing cells, such as Jurkat cells, provide a more physiologically relevant assessment of the effective concentration range of a given compound compared to non-cell-based systems, such as coactivator recruitment assays.
- Cytotoxicity assays on differentiating human Th17, Tc17, and, if applicable, Treg cells—preferably during directed differentiation rather than on bulk peripheral blood mononuclear cells (PBMCs) alone. Our team's research has demonstrated, for instance, that Tc17 cells exhibit significantly greater resistance to certain compounds compared to Th17 cells. This may be critical when determining the appropriate compound concentration and choosing between Th17 and Tc17 cells for adoptive therapy. It is important to note that Th17 and Tc17 cells are distinct lymphocyte subsets with different protein repertoires, including coactivator proteins. Therefore, it should not be assumed that RORγt agonists will induce similar effects in both cell types.
- Analysis of the expression of *RORγt*, *IL17A*, *IL17F*, *IFNG*, genes encoding granzymes A and B (*GZMA*, *GZMB*), perforin (*PRF1*), *CCR6*, *CCL20*, *CXCL10*, *PDCD1*, and *CTLA4* in human Th17 and Tc17 lymphocytes following treatment with a RORγt agonist. This analysis is essential for evaluating the agonist's effects on the antitumor potential of these cells (e.g., IL-17A/F, IFN-γ) [14,38–40], their cytotoxic capabilities (granzymes and perforin) [19,41], their ability to modulate the tumor microenvironment through recruitment of other immune cells (CCR6, CCL20, CXCL10) [15,20,42], and their potential influence on immune checkpoint pathways relevant to anti-PD-1 and anti-CTLA-4 therapies (PD-1, CTLA-4) [15,20,22].
- Analysis of *FOXP3*, *IL10*, and *CTLA4* expression in human Tregs following treatment with a RORγt agonist. Since certain RORγt agonists may inhibit Treg activity and reduce their infiltration into tumor tissues [14,20], evaluating the expression of these genes is important to confirm such immunosuppressive modulation.
- If the agonist is intended for direct administration to patients, its stability, pharmacokinetic properties, and potential interactions with other nuclear receptors—such as pregnane X receptor (PXR), which regulates P450 enzymes and plays a role in drug interactions [43–45]—must be thoroughly evaluated.

In summary, our understanding of RORγt receptor agonists remains fragmented, with significant gaps in knowl-

edge regarding the conformational changes induced by different compounds, their impact on coactivator binding and selection, and the resulting effects on the expression of RORγt-regulated genes. Addressing these questions represents a key direction for future research on this critical receptor. Furthermore, existing studies suggest that different agonists can differentially influence the expression of clinically relevant genes. As such, standardized and comparative studies in this field could guide the selection of specific agonists for particular cancer types, therapeutic strategies (e.g., anti-PD-1 or anti-CTLA-4), or treatment approaches, such as direct patient administration or adoptive cell therapy.

Availability of Data and Materials

Not applicable.

Author Contributions

MR performed all literature search, wrote the manuscript, and prepared Fig. 1. MR had been involved in revising it critically and gave final approval of the version to be published. MR agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Given his role as one of the Editorial Board members, Marcin Ratajewski had no involvement in the review of this article and has no access to information regarding its review.

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