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Mini Review

ROR1 as an emerging therapeutic target in oncology: biology and clinical drug development

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Abstract

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an oncofetal antigen with minimal adult tissue expression but critical roles in cancer progression through Wnt5a, PI3K/AKT, and Hippo-YAP/TAZ pathways. Its selective tumor expression makes ROR1 an attractive therapeutic target across hematologic and solid malignancies. Multiple modalities have advanced clinically, with antibody-drug conjugates (ADC) leading development. Zilovertamabvedotin achieved unprecedented complete response rates in lymphomas, while CAR-T therapies demonstrate efficacy in hematologic cancers with limited solid tumor penetration. Bispecific T-cell engagersand novel platforms including logic-gated CAR-Ts and dual-control ADCs address current limitations. Despite challenges such as on-target/off-tumor effects and heterogeneous expression patterns, ROR1-targeted therapies represent a rapidly evolving precision oncology frontier with transformative potential across ROR1-positive malignancies.

Keywords: ROR1, Zilovertamab, ADC, CAR-T, Targeted therapy

Abbreviations: ADC, Antibody-drug conjugate; AKT, Protein kinase B (serine/threonine kinase); ARHGEFs, Rho guanine nucleotide exchange factors; BC, Breast cancer; BiTEs, Bispecific T-cell engagers; BMI-1, B lymphoma Mo-MLV insertion region 1; BRD4, Bromodomain-containing protein 4; CAR-T, Chimeric antigen receptor T-cell; CLL, Chronic lymphocytic leukemia; CR, Complete response; CRD, Cysteine-rich domain; CRS, Cytokine release syndrome; DACs, Degrader-antibody conjugates; DAR, Drug-to-antibody ratio; DLBCL: Diffuse large B-cell lymphoma; DOCK2, Dedicator of cytokinesis 2; ECD, Extracellular domain; EGFR, Epidermal growth factor receptor; EpCAM, Epithelial cell adhesion molecule; FZD, Frizzled domain; Gα12/13, G-protein subunit alpha 12/13; HS1, Hematopoietic lineage cell-specific protein 1; ICD, Intracellular domain; IG, Immunoglobulin-like domain; IL-6, Interleukin-6; KD, Kringle domain; LATS1/2, Large tumor suppressor kinase 1/2; LUAD, Lung adenocarcinoma; mAbs, Monoclonal antibodies; MCL, Mantle cell lymphoma; MET, Mesenchymal-epithelial transition factor; MMAE, Monomethyl auristatin E; mTOR, Mechanistic target of rapamycin; NbTACs, Nanobody-based proteolysis-targeting chimeras; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NSCLC, Non-small cell lung cancer; ORR: Objective response rate; PBD, Pyrrolobenzodiazepine; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PI3K, Phosphoinositide 3-kinase; PRD, Proline-rich domain; PROTAC, Proteolysis-targeting chimera; R-CHP, Rituximab + cyclophosphamide + doxorubicin + prednisone; Rac1, Ras-related C3 botulinum toxin substrate 1; RhoA, Ras homolog family member A; RNF149, Ring finger protein 149; ROR1: Receptor tyrosine kinase-like orphan receptor 1; S/TRD: Serine/threonine-rich domain; scFv, Single-chain variable fragment; SH3, Src homology 3 domain; STAT3, Signal transducer and activator of transcription 3; TAZ: Transcriptional coactivator with PDZ-binding motif; TKD, Tyrosine kinase domain; TNBC, Triple-negative breast cancer; Wnt, Wingless-related integration site; YAP, Yes-associated protein; mbIL-15: Membrane-bound interleukin-15 (PRGN-3007 engineering).

Introduction

The landscape of precision oncology has witnessed remarkable breakthroughs, with ROR1-targeted therapeutics emerging as a promising frontier. ROR1, first identified in 1992, functions as an oncofetal antigen with high expression in embryonic tissues and diverse malignancies but minimal presence in adult tissues.[1] This differential expression, combined with its critical roles in cancer cell survival, metastasis, and therapy resistance through Wnt5a/ROR1, PI3K/AKT, and Hippo-YAP/TAZ signaling pathways, makes ROR1 an attractive target for precision oncology.[2] Unlike CD19/CD20 targeting that compromises normal immune function, ROR1's absence on mature B cells enables selective tumor targeting while preserving humoral immunity.[3] Multiple therapeutic modalities have rapidly advanced into clinical development, including monoclonal antibodies (mAbs), antibody-drug conjugates(ADCs), CAR-T cells, andbispecific T-cell engagers (BiTEs). Notably,zilovertamabvedotin has demonstrated unprecedented complete response(CR) rates in lymphomas, while next-generation platforms are expanding applications across hematologic and solid malignancies.[4] Despite this progress, ROR1-targeted therapies face distinct challenges. Naked mAbs suffer from insufficient efficacy due to limited signaling inhibition. ADCs are constrained by payload-associated toxicity.BiTEspresent safety concerns including cytokine release syndrome and neurologic toxicity. CAR-T therapies encounter complex limitations including extensive manufacturing requirements and significant toxicity risks. This review provides comprehensive insights into ROR1 structure and signaling pathways, discusses current therapeutic strategies and their clinical prospects, and explores the development of effective small-molecule ROR1 inhibitors to advance next-generation precision therapeutics.

ROR1 structure and biology

ROR1 is a single-pass, type I transmembrane receptor. Its extracellular domain (ECD) comprises an immunoglobulin-like domain (IG), a Frizzled domain (FZD, also known as a cysteine-rich domain [CRD]), and a Kringle domain (KD).[1] The FZD domain is involved in Wnt pathway signaling,[5–7] while the KD facilitates Wnt recognition and engagement with macromolecular complexes and mediates ROR1/ROR2 hetero-oligomerization.[8] The intracellular domain comprises a tyrosine kinase domain (TKD), two serine/threonine-rich domains (S/TRDs), and a proline-rich domain (PRD). S/TRD interacting with adaptor proteins such as 14-3-3ζ for pro-survival signaling,[9,10] and PRD recruit SH3-containing proteins (e.g., HS1, DOCK2, cortactin) for cellular motility and growth. Through its critical roles in multiple signaling pathways, ROR1 critically regulates tumor cell survival, proliferation, migration, and chemotaxis. (Figure 1)

Wnt5a/ROR1 signaling: ROR1 functions as a receptor for Wnt5a, activating non-canonical Wnt signaling pathways rather than the canonical β-catenin pathway. Upon Wnt5a binding, ROR1 can hetero-oligomerize with ROR2, though this interaction is not absolutely required for ROR1 signaling8. Binding of Wnt5a activates RhoA and Rac1 GTPases via ARHGEFs and leads to HS1 phosphorylation, thereby promoting cell migration, particularly in chronic lymphocytic leukemia (CLL).[9] This signaling axis also induces NF-κB activation, which stimulates the production of pro-inflammatory cytokines (e.g., IL-6).[11]

Hippo-YAP/TAZ & BMI-1 pathways: Wnt5a-bound ROR1/FZD complexes activate RhoA via Gα12/13, thereby inhibiting LATS1/2 kinases. This leads to YAP/TAZ dephosphorylation, nuclear translocation, and the transcription of stemness and oncogenic genes. Concurrently, AKT activation by Wnt5a/ROR1 phosphorylates BMI-1, promoting genomic instability, cell proliferation, and resistance to therapy.Notably, YAP/TAZ upregulates ROR1 expression, thereby establishing a feed-forward loop.[12]

PI3K/AKT & SRC/MET pathways: ROR1 directly activates the PI3K/AKT pathway in breast cancer (BC) by recruiting PI3K regulatory subunits (p85) to its intracellular domain, catalyzing PIP_2-to-PIP_3 conversion and driving AKT-dependent survival, proliferation, and metastasis.[13] In lung adenocarcinoma (LUAD), ROR1 scaffolds constitutive complexes with c-Src and MET tyrosine kinases, amplifying c-Src signaling to enhance tumor invasiveness.[7] Notably, ROR1 further potentiates oncogenic signaling by organizing cavin-1/caveolin-1 complexes within lipid rafts, which stabilize AKT activation platforms to suppress apoptosis (e.g., via BAD inactivation) and confer therapy resistance across cancer types.[14]

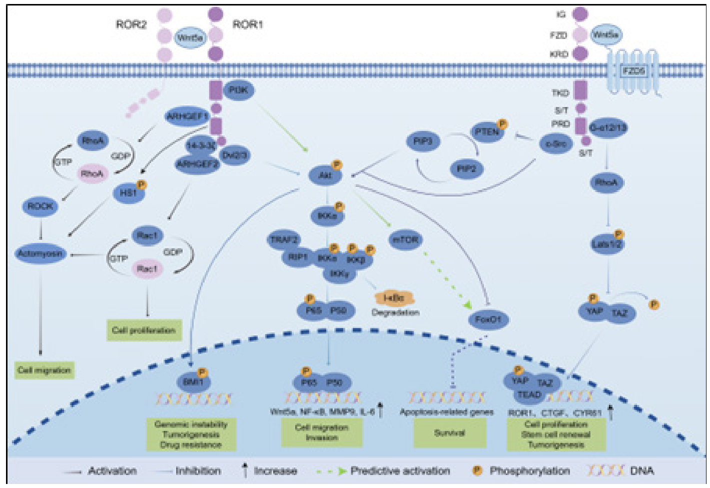

Figure 1: ROR1 signaling pathway and its role in cancer progression.

Schematic representation of ROR1-mediated signaling networks and their cellular outcomes. ROR1 and ROR2 serve as receptors for Wnt5a at the cell membrane, activating multiple downstream pathways including PI3K/Akt, Rho GTPases, and NF-κB signaling cascades. Key signaling nodes include mTOR, PTEN, IKK complex, and YAP/TAZ transcriptional regulators. The integrated pathways ultimately regulate four major cancer-related processes: genomic instability and drug resistance, cell migration and invasion, survival signaling, and cell proliferation with stem cell renewal.

ROR1 as a therapeutic target landscape & clinical progress

ROR1 functions as an oncofetal antigen uniformly expressed in tumor cells of CLL, other B-cell lymphomas, and acute leukemias, while remaining undetectable in postnatal tissues.[15] Unlike CD19/CD20-targeted therapies, which deplete normal B cells and compromise humoral immunity, ROR1 absence on mature B cells preserves immune competence. In solid tumors (e.g., ovarian cancer,[16] triple-negative breast cancer (TNBC),[17] LUAD[18]), ROR1 exhibits homogeneous expression albeit at lower levels (~1,000-10,000 copies/cell) than in CLL. This expression is associated with poorly differentiated, recurrent, and highly metastatic phenotypes.[19] Notably, ROR1 surface density (comparable to CD20's 6,000-14,000 copies/cell) supports antibody-mediated targeting, though its distribution outside lymphoid malignancies require strategic mitigation of on-target/off-tumor risks.[3]Though low-level expression in adipose tissue, intestinal crypts, pancreatic islets, and parathyroid glands necessitates therapeutic window assessment to mitigate on-target/off-tumor risks.

The restricted expression of ROR1 in malignancies versus minimal expression in vital healthy tissues provides a wide therapeutic window. Its rapid internalization upon antibody binding makes it particularly suitable for ADC development. Expression is often maintained upon relapse, potentially reducing the risk of antigen-loss resistance. To date, several therapeutic strategies against ROR1 have been developed and evaluated in clinical trialsand preclinicalstudies.(Table 1)

Table 1 Overview clinicaltrials phase and preclinical studies of ROR1 targeted therapies

Drug type	Preclinical	Phase I	PhaseI/II PhaseII	Phase II/III Phase III	Active Indication
mAb	PB004 ST406			Zilovertamab	Hematologic Neoplasms (MCL, CLL, MZLs, BCL…), Solid tumor (BC…)
ADC	ALM-401 AT-86474 IMD-2607 SKB432 STRO-003 SY-1211 VLS 211 ZL-6301	BR111 CS5001 IM-1021 SYS6005 TQB2101		Zilovertamab vedotin	Hematologic Neoplasms (BCL, ALL, SLL, CLL…), Solidtumor (NSCLC, BC, TNBC…)
BITE	APVO-425 ND-032 NVG-222 ABL-102	EMB-07 NVG-111	GNC-035		Hematologic Neoplasms (DLBCL, ALL, CLL, NHL…), Solid tumor (TNBC, EC, LUAD, BLCA…)
CAR-T	CT-335 CTE-001 Fi-CAR-T(UCL) NVG-333	PRGN 3007 LYL797 (Terminated) ROR1RCAR (UT MDA) ROR1R12 CAR-T	ONCT-808-101		Hematologic Neoplasms (ALL, CLL, DLBCL…), Solid tumor (NSCLC, BC, OV…)
SmallMolecule Inhibitors	KAN0439834 AN0441571C CPD4 24d and 9i				Hematologic Neoplasms (CLL…), Solid tumor (LUAD…)
PROTAC	N16-R14 ROR1DAC				Solid tumor (TNBC…)

Monoclonal antibodies: Zilovertamab (formerly cirmtuzumab; UC-961) and other anti-ROR1 mAbs induce direct cytotoxicity and inhibit oncogenic signaling pathways upon binding to ROR1.[20–22] (Figure 2A) The antibody blocks Wnt5a binding, inhibits tumor cell proliferation, migration, and survival, and induces differentiation.[11,23] In chronic lymphocytic leukemia (CLL), a Phase I study demonstrated zilovertamab's favorable safety and efficacy profile, with significant reduction in tumor cell burden.[24] The drug is also being investigated in mantle cell lymphoma (MCL). Ongoing Phase Ib/I-II trials are evaluating zilovertamab-based combinations specifically in CLL and MCL patients.[25] In breast cancer, zilovertamab is being investigated in combination therapy. In a clinical trial of heavily pretreated patients (median 4 prior therapies), no patient discontinued due to zilovertamab-related toxicity. Among 16 patients, 6 patients(38%) achieved partial response and 6 patients (38%) had stable disease, resulting in 75% disease control rate26.These promising results across both hematologic and solid malignancies support the continued clinical development of zilovertamab as a potentially valuable therapeutic option for ROR1-expressing cancers.

Antibody-Drug conjugates: ROR1-targeted ADCs represent the most clinically advanced and promising therapeutic modality, demonstrating robust anti-tumor activity across both hematologic and solid malignancies (Figure 2B). For example, zilovertamabvedotin (VLS-101/MK2104), comprising the anti-ROR1 monoclonal antibody zilovertamab conjugated to monomethyl auristatin E (MMAE), has established clinical proof-of-concept with impressive efficacy.[27,28] Phase I results demonstrated overall response rates of 47% in MCL and 80% in DLBCL, while the Phase II WaveLINE-007 trial achieved unprecedented 100% CR rate when combined with R-CHP in previously untreated diffuse large B-cell lymphoma (DLBCL) patients.[29] Next-generation ROR1 ADCs are addressing current limitations through innovative platform technologies. BR111 is a biparatopic anti-ROR1 ADC utilizing the CysX™ conjugation platform for stable payload attachment and uniform DAR of 4, demonstrating superior antitumor activity and safety compared to current phase II/III ADCs in preclinical studies.[30] CS5001 (LCB71) features a β-glucuronidase–cleavable linker and a tumor-activated pyrrolobenzodiazepine (PBD) prodrug dimer, which functions as a

DNA cross-linker. This dual-control mechanism is designed to enhance tumor-specific payload release and improve safety. It binds selectively to human ROR1 (but not ROR2), exhibits cross-species reactivity, internalizes rapidly, and demonstrates potent in vitro cytotoxicity, along with dose-dependent in vivo efficacy in lymphoma and BC xenograft models.[31] The clinical success of zilovertamabvedotin, combined with promising next-generation platforms incorporating tumor-selective activation mechanisms and optimized conjugation technologies, positions ROR1 ADCs as leading candidates for transforming treatment paradigms across ROR1-expressing malignancies.

Bispecific antibodies: ROR1-targeted BiTEs represent a transformative immunotherapeutic approach that harnesses endogenous T-cell cytotoxicity, offering off-the-shelf availability and the ability to redirect polyclonal T-cell responses against ROR1-expressing malignancies through localized immune synapse formation. (Figure 2C) First-generation ROR1×CD3 bispecifics have demonstrated clinical feasibility and encouraging activity. NVG-111, targeting the FZD domain of ROR1, has shown manageable safety profiles and promising efficacy in relapsed/refractory CLL and MCL.[32] Similarly, EMB-07 has exhibited favorable tolerability and clinical activity in relapsed/refractory hematologic malignancies.[33] Next-generation platforms are advancing toward multi-specific designs to overcome immune escape mechanisms. GNC-035, a tetra-specific antibody (ROR1×PD-L1×CD3×4-1BB), simultaneously activates T cells through 4-1BB co-stimulation while blocking PD-L1-mediated immune suppression, addressing key limitations of conventional BiTEs. The ongoing Phase I-b study in BC and hematologic malignancies has demonstrated strong efficacy signals with acceptable tolerability.[34] The evolution from conventional BiTEs to multi-specific immune engagers represents a significant advancement in ROR1-targeted immunotherapy, with these platforms positioned to overcome immune escape and establish new therapeutic standards for ROR1-positive malignancies.

CAR-T cell therapies: CAR-T therapies redirect cytotoxic effector functions against tumors by engineering T cells to express synthetic receptors targeting surface antigens. Significant progress in ROR1-targeted CAR-Ttherapies is moving toward clinical validation (Figure 2D). ONCT-808 demonstrates promising early activity in relapsed/refractory B-cell lymphomas, achieving 80% (4/5) metabolic response rate at Month 1, with sustained complete metabolic response observed at 6 months and CAR-T persistence beyond 12 months, while maintaining a manageable safety profile at optimized dosing levels.[35] Additionally, ROR1 CAR-T cells constructed from the R12 scFv, which targets the IG/FZD interface epitope, demonstrated differential efficacy across tumor types. In CLL patients, 67% (2/3) showed robust CAR-T expansion and rapid antitumor responses. However, solid tumor efficacy remained limited, with only 5.5% (1/18) of NSCLC/TNBC patients achieving partial response, attributed to CAR immunogenicity and insufficient tumor infiltration.[36] Lyell Immunopharma's LYL797 demonstrated promising activity in ROR1-positive solid tumors, achieving 40% objective response rate in TNBC patients through advanced engineering with c-Jun overexpression and Epi-R manufacturing.[37] However, clinical development has been discontinued due to toxicity concerns and a narrow therapeutic window. Complementary platforms include Precigen's Phase I candidate PRGN-3007, which co-expresses membrane-bound IL-15 (mbIL-15) and a PD-1 blocker via non-viral delivery.[38] Together, each product has been optimized for different tumor types, reflecting the differentiated development strategies in ROR1 CAR-T therapeutics.

Small molecule inhibitors: Development of small-molecule ROR1 inhibitors is limited by the incomplete characterization of its kinase activity. Nonetheless, several promising preclinical candidates have emerged. Preclinical candidates include KAN0439834 (for CLL and pancreatic cancer),[39] its derivative KAN0441571C (DLBCL),[40] ARI-1 (targets the FZD)41, and strictinin (binds theICD).[42] Recent scaffold optimization of the indole-based LDR102 has yielded two promising candidates: compound 24d (1-methyl-3-(pyridin-3-yl)-1H-indole derivative)43 and compound 9i (N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)benzamide derivative),[44] both demonstrating improved ROR1 selectivity and enhanced anti-tumor efficacy compared to the parent compound. (Figure 2E) Despite these advances, small-molecule ROR1 inhibitors face critical limitations that impede clinical translation. First, these compounds typically demonstrate poor single-agent efficacy and lack immunomodulatory synergy essential for comprehensive cancer therapy. Second, resistance mechanisms emerge rapidly through alternative pathway activation or target mutations. Third, limited target specificity raises off-target toxicity concerns, while suboptimal pharmacokinetic properties (poor bioavailability and solubility) further compromise therapeutic potential. Further mechanistic validation and strategies to address these limitations are essential before clinical translation.

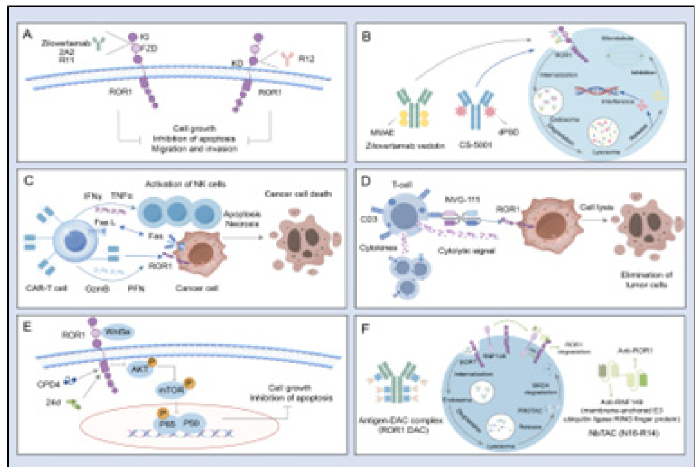

Figure 2: ROR1-targeted therapeutic strategies in clinical development.

(A) Anti-ROR1mAbs bind extracellular IG/FZD and Kringle (KD) domains, suppressing tumor cell growth, inducing apoptosis, and blocking migration/invasion.

(B)ADCs: Zilovertamabvedotin (MMAE payload) and CS-5001 (dPBD payload) undergo ROR1-mediated internalization. Payload release in endosomes disrupts microtubule dynamics (MMAE) or induces DNA crosslinking (dPBD), culminating in lysosomal degradation.

(C) ROR1-directed CAR-T cells recognize surface ROR1, triggering Fas/FasL engagement and release of cytotoxic effectors (granzyme B, perforin) for tumor lysis. Secreted IFNγ/TNFα further activates endogenous NK cells.

(D) BiTEsNVG-111 bridges CD3 on T cells and ROR1 on tumor cells, driving target-specific cytolytic synapse formation and cytokine-mediated tumor elimination.

(E) Small-molecule CPD4 or 24d antagonize Wnt5a-ROR1 signaling, suppressing PI3K/AKT/mTOR activity and NF-κB (p65/p50) signaling, thereby inhibiting proliferation and inducing apoptosis.

(F) Degradation platforms: (i) PROTAC-based DAC recruits RNF149 (membrane-anchored E3 ligase) to ubiquitinate ROR1, promoting endosomal degradation; (ii) NbTAC fuses anti-ROR1 nanobody (N16-R14) to ribonuclease, enabling ROR1-targeted enzymatic degradation.

Emerging ROR1-targeted degradation therapies: Degrader-antibody conjugates (DACs) and nanobody-based proteolysis-targeting chimeras (NbTACs) represent breakthrough strategies to overcome the limitations of conventional ROR1 inhibitors. (Figure 2F) The ROR1-DAC platform links a BRD4-degrading proteolysis-targeting chimeras (PROTAC) to an anti-ROR1 antibody, enabling tumor-specific protein degradation via antibody-mediated delivery.[45] Concurrently, the first ROR1-targeted NbTAC (N16-R14) was developed using phage-derived nanobodies that co-localize membrane-bound ROR1 with the E3 ligase RNF1,[49] inducing clathrin-mediated endocytosis and lysosomal degradation. This approach achieved nanomolar-potency ROR1 depletion and inhibited proliferation in TNBC models.[46] However, clinical translation of PROTAC-based platforms remains challenging due to two primary constraints: suboptimal in vivo efficacy and unfavorable pharmacokinetic profiles. The complex molecular architecture inherently compromises drug-like properties, limiting therapeutic applicability despite promising preclinical results.

Conclusion and future perspectives

ROR1's oncofetal expression pattern, with high expression in malignancies yet minimal presence in adult tissues, and robust clinical validation across multiple therapeutic modalities establish it as a compelling target with an attractive therapeutic window. Zilovertamabvedotin's unprecedented 100% complete response rate in untreated DLBCL exemplifies ADCs' leading potential, while CAR-T therapies demonstrate substantial efficacy in hematologic malignancies (80% metabolic response with ONCT-808) despite persistent challenges in solid tumor penetration. BiTEs like NVG-111 offer off-the-shelf accessibility with manageable safety profiles, and emerging multi-specific platforms (GNC-035) address immune escape mechanisms.

ROR1-targeting in solid tumors faces distinct challenges: tumor microenvironment barriers (physical matrix, immunosuppression), target expression heterogeneity, and suboptimal drug delivery efficiency. These limitations differentially impact on therapeutic modalities. While ADCs achieve better penetration than cellular therapies, they remain vulnerable to heterogeneity; CAR-T cells demonstrate potency but struggle with solid tumor infiltration; small molecules penetrate well but lack specificity. Addressing these challenges requires integrated approaches: drug miniaturization and dual-targeting for enhanced penetration and coverage, tumor microenvironment-targeted delivery systems,[47] and rational combinations with immune checkpoint inhibitors[48] and stromal-modulating agents to optimize therapeutic efficacy in solid tumor contexts.

The heterogeneous nature of ROR1-expressing cancers, ranging from highly responsive lymphomas to resistant solid tumors, necessitates tailored therapeutic architecture rather than universal solutions. Companies must strategically evaluate emerging platforms, including tumor-selective dual-control ADCs[49] and logic-gated CAR-Ts,[50] and develop modular systems enabling 'plug-and-play' customization for specific tumor contexts and patient populations.

Key strategic priorities include advancing tumor-selective platforms (dual-control linker technologies, conditional activation systems) to mitigate on-target/off-tumor toxicity, establishing robust biomarker-driven patient stratification for solid tumor applications, and exploring rational combinations targeting ROR1's signaling crosstalk with immune checkpoints and metabolic pathways. As next-generation agents including novel degrader platforms and multi-specific engagers enter clinical testing, ROR1-targeted therapies are positioned to transform treatment paradigms across ROR1-positive malignancies through precision-tailored therapeutic approaches that address the unique challenges of different cancer types.

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Conflicts of interest

The author(s) report no conflicts of interest in this work.

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