ISSN 2218-4333 (online)

# World Journal of *Clinical Oncology*

*World J Clin Oncol* 2024 May 24; 15(5): 576-666

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

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Monthly Volume 15 Number 5 May 24, 2024

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**Production Editor:** *Yu-Qing Zhao*; **Production Department Director:** *Xu Guo*; **Cover Editor:** *Xu Guo*.

**NAME OF JOURNAL**
*World Journal of Clinical Oncology*

**ISSN**
ISSN 2218-4333 (online)

**LAUNCH DATE**
November 10, 2010

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2218-4333/editorialboard.htm

**PUBLICATION DATE**
May 24, 2024



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*World J Clin Oncol* 2024 May 24; 15(5): 603-613

DOI: 10.5306/wjco.v15.i5.603

ISSN 2218-4333 (online)

*MINIREVIEWS*

# Receptor tyrosine kinase-like orphan receptor 1: A novel antitumor target in gastrointestinal cancers

Zheng-Long Wu, Ying Wang, Xiao-Yuan Jia, Yi-Gang Wang, Hui Wang

**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B
**Novelty:** Grade A
**Creativity or Innovation:** Grade B
**Scientific Significance:** Grade A

**P-Reviewer:** Dharmawansa KVS, Canada

**Received:** January 3, 2024
**Revised:** March 20, 2024
**Accepted:** April 17, 2024
**Published online:** May 24, 2024

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## Abstract

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a member of the type I receptor tyrosine kinase family. ROR1 is pivotal in embryonic development and cancer, and serves as a biomarker and therapeutic target. It has soluble and membrane-bound subtypes, with the latter highly expressed in tumors. ROR1 is conserved throughout evolution and may play a role in the development of gastrointestinal cancer through multiple signaling pathways and molecular mechanisms. Studies suggest that overexpression of ROR1 may increase tumor invasiveness and metastasis. Additionally, ROR1 may regulate the cell cycle, stem cell characteristics, and interact with other signaling pathways to affect cancer progression. This review explores the structure, expression and role of ROR1 in the development of gastrointestinal cancers. It discusses current antitumor strategies, outlining challenges and prospects for treatment.

**Key Words:** Receptor tyrosine kinase-like orphan receptor 1; Gastrointestinal cancers; Therapeutic target; Molecular mechanisms; Antitumor strategies

**Core Tip:** Delve into a comprehensive review spotlighting receptor tyrosine kinase-like orphan receptor 1 (ROR1) pivotal involvement in gastrointestinal cancer advancement and its promising prospects as an anti-tumor remedy. Explore pivotal cellular pathways governing ROR1 regulation and pertinent insights into existing commercial therapeutic offerings. Emphasizing ROR1's crucial role in gastrointestinal cancer treatment, this review offers a nuanced blend of historical context and scientific insight, illuminating the dynamic landscape of this evolving field.

**Citation:** Wu ZL, Wang Y, Jia XY, Wang YG, Wang H. Receptor tyrosine kinase-like orphan receptor 1: A novel antitumor target in gastrointestinal cancers. *World J Clin Oncol* 2024; 15(5): 603-613
**URL:** https://www.wjgnet.com/2218-4333/full/v15/i5/603.htm
**DOI:** https://dx.doi.org/10.5306/wjco.v15.i5.603

## INTRODUCTION

Receptor tyrosine kinase-like orphan receptor (ROR) 1 and ROR2 belong to the ROR subfamily of type I receptor tyrosine kinase (RTK) family. They were first identified in human neuroblastoma cells in 1992 and are termed orphan receptors as their ligands are not known[1-3]. The two proteins share 58% sequence identity. ROR1 has recently been shown to be involved in embryonic development and cancer. It is recognized as a diagnostic biomarker and is a research hotspot for the targeted treatment of various malignancies. ROR1 has two subtypes; an intact membrane receptor and a truncated variant. The truncated versions include a membrane-bound form that lacks an extracellular domain and a soluble form that contains only the extracellular structure[4]. Expression of the soluble isoform does not increase in cancer patients, showing minimal or undetectable levels in the serum that are not dependent on disease progression or severity, whereas expression of the intact membrane-bound isoform increases significantly[5].

ROR1 proteins are found in a variety of species. Drosophila melanogaster has a protein called Dror, which resembles an RTK. The kinase and structural extracellular domains of Dror display 61% and 36% sequence identity, respectively, with the corresponding domains of human ROR1[6], while human and mouse ROR1 are 97% identical. This evolutionary conservation of ROR family proteins indicates the importance of their physiological functions during embryonic and organ development. Many recent studies on ROR1 have demonstrated its aberrant expression in various forms of cancer. Abnormal expression of ROR1 was first observed in chronic lymphocytic leukemia (CLL)[2,7]. Although specific disease-related mutations have yet to be identified in ROR1, it has become a widely studied therapeutic target for localized ischemia, diabetes, and malignancies[8-11].

Gastrointestinal cancers, including liver, gastric, colorectal, and pancreatic cancer, are some of the most frequently diagnosed tumors and contribute significantly to cancer-associated mortality in China and worldwide. Overexpression of ROR1 is seen in many gastrointestinal cancers, where it is linked with poor prognosis, indicating the essential roles of ROR1 in these tumors. This paper reviews the structure and expression patterns of ROR1 in gastrointestinal cancers, as well as its involvement in cancer development. Current antitumor strategies for gastrointestinal cancers involving ROR1 are discussed and the challenges and prospects in treating these diseases are summarized.

## STRUCTURE AND EXPRESSION PATTERNS OF ROR1

ROR1 is a type I transmembrane protein, 937 residues in length, with a molecular weight of approximately 105 kDa. The protein includes extracellular, transmembrane, and intracellular regions (Figure 1). The extracellular region includes several extracellular domains, specifically, immunoglobulin-like (Ig-like), frizzled (FZD), and Kringle (KD) domains. FZD is a cell membrane receptor for the secreted glycoprotein Wnt. It contains a cysteine-rich domain located at the N terminus outside the cell that can bind to Wnt. The FZD domain regulates nonclassical Wnt signaling through interaction with its ligand, Wnt5a, while KD mediates interactions between ROR1 and other receptors, including ROR2. The intracellular domains include three domain types; one tyrosine kinase (TK)-like and two serine/threonine-rich domains, together with a proline-rich domain. The serine/threonine-rich domains bind to bridging proteins such as 14-3-3ζ to prevent apoptosis[12], while the proline-rich domain binds to Src homology 3 (SH3) domains in various proteins, such as hematopoietic lineage cell-specific protein 1 (HS1), dedicator of cytokinesis protein 2 (DOCK2), and cortactin, to promote cell migration and proliferation[13-15]. However, although ROR1 is an RTK, the function of its TK domain remains essentially unknown.

ROR1 expression is primarily limited to embryonic development with low levels seen in postnatal tissue. Nevertheless, some normal tissues, including adipose tissue, endocrine glands, and the gastrointestinal tract, display high levels of ROR1 expression[16,17]. ROR1 knockout is fatal in the embryo, providing evidence of its crucial role in embryonic development[18]. In contrast to the relatively low or minimal expression observed in normal tissues, ROR1 expression increased markedly in a variety of hematological cancers and solid tumors, including CLL, breast cancer, melanoma, and gastrointestinal cancers, such as colorectal cancers and pancreatic ductal adenocarcinomas[19-22]. This feature suggests that ROR1 may be a promising candidate for cancer therapy.

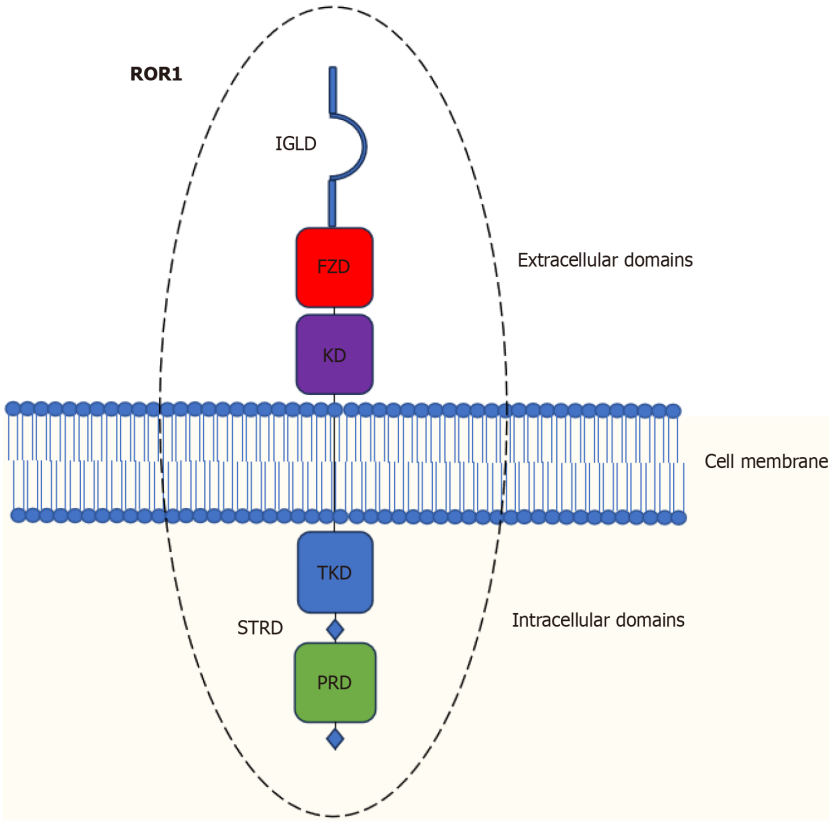


**Figure 1 Diagram of the receptor tyrosine kinase-like orphan receptor 1 domain structure.** IG: Ig-like domain; FZD: Frizzled domain; KD: Kringle domain; TKD: Tyrosine kinase domain; S/T: Serine/Threonine-rich domain; PRD: Proline-rich domain.

## REGULATORY MECHANISMS OF SIGNALING PATHWAYS INVOLVED IN ROR1

Aberrant expression of ROR1 protein in CLL cells was identified using monoclonal antibodies[19]. These authors also found that Wnt5a bound specifically to ROR1 to promote cancer growth and survival, thus ending the orphan status of ROR1. Wnt5a has been shown to activate the non-classical Wnt pathway through interaction with the FZD domain of ROR1[18,23], indicating the potential importance of ROR1 in various biological processes through non-canonical Wnt signaling. Wnt5a is also involved in phosphorylation of the Nuclear Factor-kappa B (NF-κB) subunit p65, activating NF-κB signaling in cancer cells, and thus promoting tumorigenesis, the epithelial-mesenchymal transition (EMT), and metastasis. NF-κB signaling is also closely linked with both inflammation and immune regulation, and shows significant activation in various tumor types.

The Wnt5a pathway is a vital component of the Wnt signaling pathway family and plays a significant role in cancer progression. It affects cell behaviors such as proliferation, differentiation, and migration, which can impact cancer development. Dysregulation of this pathway has been linked to various cancers. By regulating cell cycle and migration, it restricts cancer cell growth and invasion. Additionally, it may impact cancer stem cell characteristics and immune responses within the tumor microenvironment. Furthermore, it interacts with neighboring tissues, promotes angiogenesis, and induces inflammation. Its functions differ among various types of cancer, leading to investigations into its regulatory mechanisms as potential therapeutic targets.

The FZD gene family includes seven transmembrane proteins that are receptors for Wnt ligands. FZD5 appears to be the receptor for Wnt5a. As shown in Figure 2, Wnt5a can activate both FZD5 and ROR1, leading to activation of dishevelled 2/3 (Dvl2/3) and protein kinase B (Akt) phosphorylation. This leads to Akt-mediated phosphorylation of IκB kinase α (IKKα) and activation of IκB kinase (IKK), inducing Inhibitor of kappa B α (IκBα) degradation and NF-κB subunit p65 phosphorylation. After phosphorylation, p65 translocates to the nucleus where it promotes the transcription of various genes including Cyclin D1, cellular myelocytomatosis (c-Myc), matrix metalloproteinase-9, and Vascular Endothelial Growth Factor, as well as Wnt5a to induce an autonomous feedback loop. Continued stimulation of the ROR1/Akt/p65 pathway within this loop further promotes the production of proinflammatory factors such as interleukin-6 (IL-6) and chemokines such as CCL2[24]. Further research found a positive correlation between ROR1 expression and increased transcription of Yes-associated protein/Transcriptional co-Activator with PDZ-binding motif (YAP/TAZ), promoting both tumorigenesis and chemotherapy resistance[25,26]. Complexation of Wnt5a with ROR1/FZD promotes binding between G protein subunit alpha 12/13 (Gα12/13) and the transforming protein Ras homolog gene family, member A (RhoA), inhibiting the activity of large tumor suppressor kinase 1/2 (Lats1/2) and stimulating YAP/TAZ dephosphorylation and nuclear translocation. Gα12/13 belongs to the gα protein family, where it differs from other members of the family, G protein subunit alpha s (Gαs), G protein subunit alpha i (Gαi), and G protein subunit alpha q (Gαq), and modulates cytoskeletal reorganization and morphological changes in the cell by activating the small

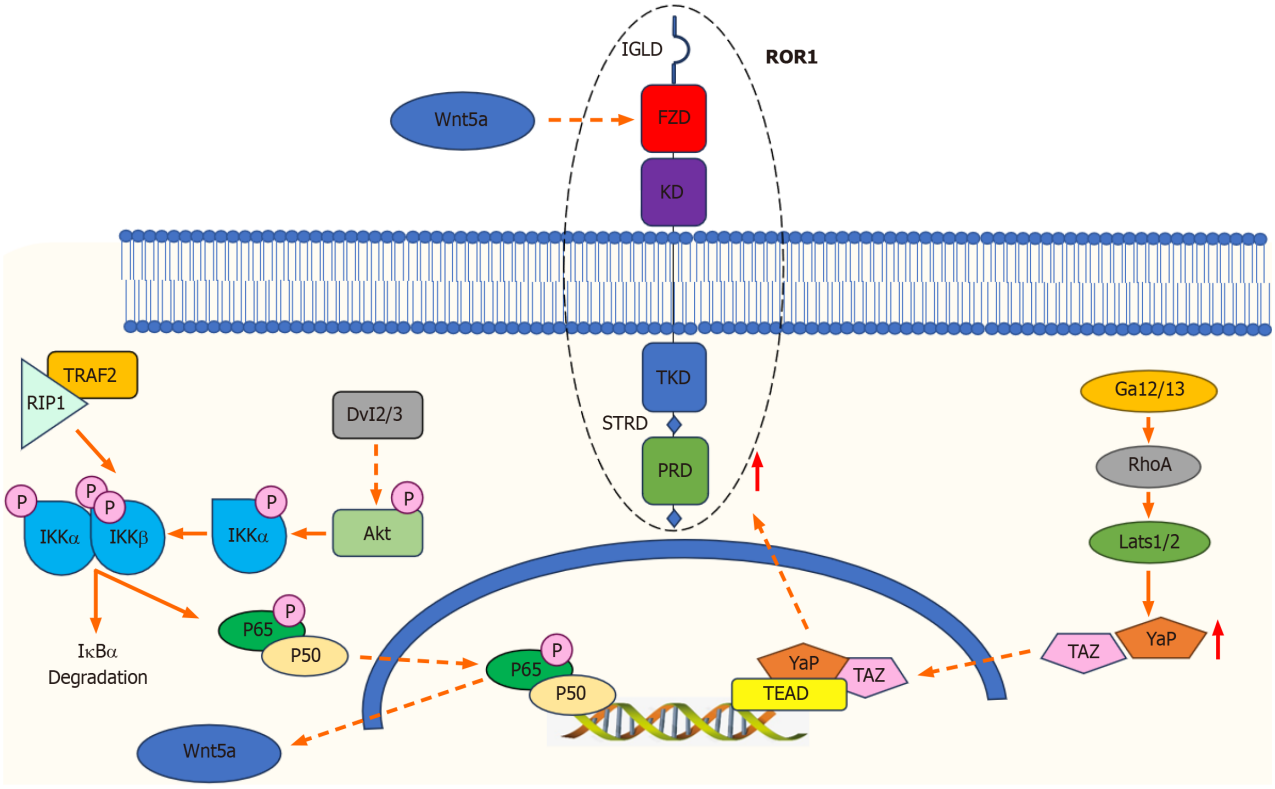


**Figure 2 Signaling pathways regulated by receptor tyrosine kinase-like orphan receptor 1.** Dvl2/3: Dishevelled 2/3; Akt: Protein kinase B; Ikkα: IκB kinase α; IκBα: Inhibitor of kappa B α; p65: Nuclear factor NF-kappa-B p65 subunit; RhoA: Ras homolog gene family, member A; Gα12/13: G protein subunit alpha 12/13; Lats1/2: Large tumor suppressor kinase 1/2; YAP/TAZ: Yes-associated protein/Transcriptional co-Activator with PDZ-binding motif. Binding of Wnt5a to receptor tyrosine kinase-like orphan receptor 1 (ROR1) induces Dvl2/3 activation and Akt phosphorylation, leading to phosphorylation of Ikkα, activation of the IκB kinase complex, degradation of IκBα, and p65 phosphorylation. Subsequently, p65 is transferred to the nucleus where it promotes the transcription of specific genes, including Wnt5a, producing an autonomous feedback loop. Binding between Wnt5a and the ROR1/frizzled complex leads to activation of RhoA *via* Gα12/13. This activation inhibits Lats1/2 activity, leading to the dephosphorylation and nuclear translocation of YAP/TAZ. The binding of YAP/TAZ to transcription enhanced association domain increases the transcription of genes linked to tumorigenesis and stemness while increased levels of YAP/TAZ enhance ROR1 expression.

Guanosine Triphosphatase (GTPase) Rho. Gα12/13 is also involved in processes such as cell proliferation, migration, and apoptosis. Nuclear translocation of YAP/TAZ, together with transcription enhanced association domain (TEAD), increases the transcription of genes associated with stem cell renewal, proliferation, and tumorigenesis. The upregulation of ROR1 expression is, in turn, stimulated by increased YAP/TAZ transcription.

## ROLE OF ROR1 IN GASTROINTESTINAL CANCERS

The mechanisms of ROR1 action in diverse malignancies, encompassing gastrointestinal tumors such as liver, gastric, colorectal, and pancreatic cancer, exhibit heterogeneity. Distinct signaling pathways or processes influenced by ROR1 may be implicated in each specific cancer type. Therefore, it is necessary to discuss the function of ROR1 in these cancers individually.

### *ROR1 and liver cancer*

Liver cancer is one of the six most common cancers worldwide and falls into three main types, namely, hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and mixed cell carcinoma[27]. HCC is the most prevalent and lethal variety, representing approximately 90% of all liver cancers. Liver tumors may also be derived from metastasis of other malignancies, such as lung tumors. Due to its high mortality rate and ease of metastasis, HCC is a subject of significant interest in cancer research[28].

A study by Cetin *et al*[29] assessed ROR1 in HCC, demonstrating its presence in both human and mouse cells, without limitation to metastatic or mesenchymal cell lines. Induction of EMT by transforming growth factor-β (TGF-β) reduced ROR1 levels, while ROR1 knockdown inhibited both the proliferation and migration of HCC cells and increased resistance to apoptosis. Chemotherapeutic agent uptake was modified in ROR1 knockdown epithelial-type HCC cells, leading to resistance to chemotherapy-induced apoptosis. ROR1 has been shown to promote HCC progression through the modulation of various pathways, and changes in ROR1 expression may be useful in diagnosis and prognostic prediction. Meng *et al*[30] reported that ROR1 expression is substantially increased in acid-treated cancer cells and significantly promotes invasion and migration of HCC. ROR1 knockdown through siRNA successfully inhibited acid-

induced tumor cell migration, invasion, and EMT. Nevertheless, the underlying regulatory actions of ROR1 in HCC are not yet clear.

### *ROR1 and gastric cancer*

Gastric cancer (GC) is a heterogeneous disease with a high mortality rate. It is known that infection with *Helicobacter pylori* is both necessary and insufficient for the development of GC[31] which appears to involve a multifactorial and multistep pathogenesis[32].

There is limited information on ROR1 in GC. Kotoh *et al*[33] found an association between Wnt5a and GC invasion and metastasis, showing that Wnt5a bound to FZD/ROR1 and was linked to various signaling pathways including β-catenin-TCF/LEF, Dishevelled–RhoA–Rho-associated protein kinase (DVL–RhoA–ROCK), and mitogen-activated protein kinase kinase kinase 7–nuclear factor-B (MAP3K7–NF-κB) in specific contexts. ROR1 also associates with c-Src, promoting its phosphorylation. C-Src is a non-RTK and known oncogene that has been linked to the development of numerous human cancers, including colon, gastric, lung, breast, and prostate cancers. Once activated, c-Src can regulate a variety of processes, both normal and cancer-associated, including cell survival, proliferation, motility, differentiation, and angiogenesis[34,35].

### *ROR1 and colorectal cancer*

Colorectal cancer (CRC) is among the most prevalent cancer types globally, ranking fifth in incidence in China. Advanced CRC is associated with both recurrence and drug resistance, reducing patient survival. Thus, investigation of the mechanisms underlying CRC is important to improve survival and develop new drugs. Zhou and colleagues investigated expression of ROR1 in CRC[36], observing markedly increased levels in CRC tissues and in approximately 94% of patients with CRC. However, the molecular mechanisms underlying these increases remain unknown.

Wnt signaling is closely associated with regulation of morphogenesis during embryonic development and repair processes. The Wnt ligands are key to these pathways, and are known to bind different receptors, including proteins of the FZD family and ROR1. The interactions trigger downstream cascades involving multiple pathways to influence the arrangement of the cytoskeleton, transcription of genes associated with proliferation and cell growth, and the behavior of intracellular organelles. Dysregulated Wnt signaling has been linked to various malignancies, including CRC, through the modulation of cells associated with the tumor microenvironment (TME)[37].

### *ROR1 and pancreatic cancer*

Pancreatic cancer is an especially lethal form of cancer. Despite significant progress in elucidating its molecular pathology, the prognosis remains extremely poor, mostly due to treatment resistance and the formation of distant metastases in the early stages of the disease[28]. Therefore, uncovering the underlying molecular mechanisms of pancreatic cancer to create new targeted therapeutic strategies remains a pressing research priority.

Yamazaki *et al*[38] demonstrated that ROR1 promotes the proliferation of pancreatic ductal adenocarcinoma (PDAC) by activating E2F *via* c-Myc and inducing expression of aurora kinase B. It was also found that transcription of ROR1 was dependent on the binding of YAP/BRD4 to its promoter region. Prevention of this binding reduced ROR1 expression and inhibited PDAC growth. These findings suggest that increased levels of ROR1 are closely involved in tumorigenesis, highlighting its importance in PDAC progression and its potential as a target for treating the cancer.

## ANTITUMOR STRATEGIES TARGETING ROR1 IN GASTROINTESTINAL CANCERS

There has been an increased focus on ROR1 as a potential antitumor target for gastrointestinal cancers, involving various therapeutic approaches and ongoing clinical trials and preclinical studies. These include the use of monoclonal antibodies (mAbs), antibody–drug conjugates (ADCs), bispecific antibodies, small molecule inhibitors, and chimeric antigen receptor (CAR)-T cell therapies (Table 1).

### *Anti-ROR1 monoclonal antibodies*

The application of anti-ROR1 mAbs to block binding between the receptor and the Wnt5a ligand prevents activation of downstream signaling and activates the immune system to promote removal of tumor cells[39]. Zilovertamab, also known as cirmtuzumab or UC-961, is an mAb targeting ROR1. Zilovertamab binding to ROR1 blocks Wnt5a signaling, thus inhibiting tumorigenic behavior, such as cell growth and survival, and inducing differentiation. This mAb has shown significant antitumor efficacy against both hematological and solid malignancies, such as GC and pancreatic cancer, in Phase I clinical trials, and is currently the only antibody on the market that has undergone clinical evaluations [40]. A phase I/II trial of a combination of zilovertamab and paclitaxel for treating breast cancer is currently underway.

Chen *et al*[24] reported that the Wnt5a/ROR1 axis can activate the NF-κB pathway in tumor cells, resulting in the production of interleukin-6 and signal transducer and activator of transcription 3 phosphorylation. Zilovertamab has the potential to inhibit these processes. According to Hasan *et al*[15], Wnt5a promotes complexation between ROR1 and DOCK2, leading to the activation of Rac1/2. Silencing of DOCK2 specifically reduces Wnt5a-mediated activation of Rac1/2 and tumor cell proliferation. The proline-rich domain (PRD) of ROR1 has been implicated in the Wnt5a interaction with DOCK2 and activation of Rac1/2 in MEC1 CLL cells. This effect is blocked by zilovertamab, which also has the advantages of having a long half-life in the plasma and no dose-limiting toxicity. The use of this antibody showed reductions in the activities of RhoA and HS1, while transcriptome analysis indicates reductions in the expression of stemness genes in CLL *in vivo*. It is apparent that zilovertamab is both safe and effective for the inhibition of ROR1 in

**Table 1 Receptor tyrosine kinase-like orphan receptor 1-targetd therapies in clinical trials or preclinical studies**

| Therapy types | Therapy drugs | Indications | ClinicalTrials.gov Identifier/Ref. |
|---|---|---|---|
| mAb | Zilovertamab | Gastric cancer<br>Pancreatic cancer | [42] |
| ADC | VLS-101 | Solid tumor | NCT04504916 |
| | LCB71 | | NCT05279300 |
| | NBE-002 | | NCT04441099 |
| | miR-29b | | [47] |
| | OSU-2S | | [48] |
| Bispecific antibody | R11×v9-BiAb | Solid tumor | [50] |
| | NVG-111 | | NCT04763083 |
| | SFG.ROR1-BiTE | Pancreatic cancer | [51] |
| Small-molecule inhibitors | KAN0439834 | Pancreatic cancer | [54] |
| | KAN04415711C | | [55] |
| | miR-27b-3p | Gastric cancer | [57] |

mAb: Monoclonal antibodies; ADC: Antibody drug conjugate.

various tumor cells[40].

### *Antibody-drug conjugates*

ADCs involve linkage between mAbs and small cytotoxic molecules *via* specific chemical linkers. ADCs targeting ROR1 are able to transfer cytotoxic agents and regulatory RNAs to ROR1-expressing tumor cells.

VLS-101 (MK-2140) is an ADC consisting of a lead antibody to effectively target ROR1, for treating hematological malignancies and solid tumors. VLS-101 represents a combination of zilovertamab, a lysyl iminohexene-valine-citrulline p-aminobenzoate linker, and a cytotoxic agent monomethyl auristatin E (MMAE) that targets microtubules. Within cells, MMAE is released from the linker to block microtubule polymerization, thus adversely affecting mitosis and cell division [41]. The drug also safely promotes tumor regression in patient-derived xenograft models previously found to be resistant to CAR-T cell, ibrutinib, and/or venetoclax treatment[42]. These findings provide valuable insights into the increasing clinical demand for VLS-101 in gastrointestinal cancers.

LCB71 (CS5001) is an ADC based on an mAb that targets ROR1. LCB71 has a distinctive design involving a unique β-glucosidic acid linker and a pyrrolobenzodiazepine (PBD) pre-toxin dimer. Both the linker and the pretoxin are cleaved by lysosomal β-glucuronidase, an enzyme significantly overexpressed in many types of cancer cells. Thus, LCB71 can eliminate cancerous cells after arrival at the tumor site and cleavage of the linker to release the PBD pre-toxin, which is subsequently activated within the tumor cell. The dual control mechanism of the linker plus precursor toxin resolves typical toxicity issues associated with traditional PBD loads, resulting in an improved safety profile. LCB71 has shown notable dose-dependent antitumor activity in several xenograft tumor models of condylomatous lymphoma and breast cancer and is thus a promising drug candidate with potential for precision therapy in both hematological and solid malignant tumors expressing high levels of ROR1. The ADC NBE-002 is composed of a humanized antibody, huXBR1-402, conjugated to the anthracycline derivative, PNU-159682. HuXBR1-402 is a chimeric rabbit/human mAb identified from a rabbit antibody library using phage display. NBE-002 has been shown to be effective in xenograft models of various human tumors[43]. The drug is currently in a clinical Phase I study. Chiang *et al*[44] connected an anti-ROR1 mAb to a regulatory miRNA (miR-29b). This ADC treatment reduced the expression of the miR-29 targets, DNA methyltransferase (DNMT) 1 and DNMT3A, in cells expressing ROR1. It also led to alterations in global DNA methylation patterns, downregulation of SP1, and upregulation of p21. Another ADC used an mAb against ROR1 linked to nanoparticles containing OSU-2S, a sphingosine analog with anti-tumor capabilities, that activated protein phosphatase 2A and induced SHP1 phosphorylation and nuclear translocation[45], resulting in apoptosis.

### *Bispecific antibody*

Bispecific antibodies (BiAbs) are synthetic antibodies created through cell fusion or recombinant DNA technology. They are formed by two single-chain antibody fragments, or single-chain fragment variable (scFvs), together with different variable regions composed of both heavy and light chains and a common constant region, or Fc. Bispecific T-cell conjugates (BiTes) are fusion proteins composed of two separate scFvs without an Fc. One arm can bind to the Kringle domain on ROR1 while the other interacts with the CD3 subunit of the T cell receptor, thus recruiting polyclonal T cells to the site of the tumor. BiTEs do not rely on antigen presentation and can activate T-cell binding, resulting in the killing of neighboring target cells. Both BiAbs and BiTes can bind simultaneously to two different antigens or epitopes on the same antigen. Due to their specificity and bifunctionality, the use of BiAbs and BiTes is a trending research topic in antibody

engineering and has a broad range of applications in tumor therapy and autoimmune diseases.

Qi *et al*[46] co-conjugated multiple anti-ROR1 single-chain antibodies to a single-chain antibody against CD3 with glycosylated IgG1-Fc, generating various BiAbs. They found that targeting scFv using ROR1 with the proximal epitope R11 of the membrane was the most effective one for recruiting T cells to ROR1-positive solid cancer cell lines. This BiAb exhibited promising antitumor activity both in vitro and *in vivo*. In a similar investigation, Wang *et al*[47] also used a BiAb composed of an scFv and Fc that targeted both ROR1 and CD3; this was termed R11×v9-biAb. When tested on multiple ROR1-positive solid cancer cell lines, the observed cytotoxicity was found to be dependent on the R11×v9-biAb dosage. The BiAb targeted ROR1-positive cancerous cells, induced tumor cell death, and recruited significant numbers of CD4+ and CD8+ T cells to the tumor through the secretion of T-cell-derived proinflammatory factors and promoting perforin production by granzyme B and CD8+ T cells.

NVG-111 is a unique humanized BiTE recognizing both ROR1 and CD3, and is composed of tandem scFvs against ROR1 and CD3. NVG-111 is the first BiAb that utilized the inherent cytotoxicity of T cells. Ongoing clinical trials of NVG-111 have shown promising results in both CLL and solid tumors, with favorable cytotoxicity[48]. Another bispecific T-cell splicer, SFG. ROR1-BITE, includes scFvs targeting the cysteine-rich coiled-coil structural domain of ROR1 and CD3, and showed strong cytotoxicity against pancreatic cancer cells expressing ROR1 at low concentrations, as well as significant tumor reduction in a mouse model of pancreatic tumors[49].

### *Small-molecule inhibitors of ROR1*

The lack of clearly defined kinase activity in ROR1 has limited the identification of small-molecule inhibitors that could target this activity. Although some catalytic activity was observed in immunoprecipitated ROR1 suggesting the possibility of autophosphorylation *in vivo*, this was found to be negligible[50,51].

Nevertheless, Hojjat-Farsangi *et al*[52] identified a promising inhibitor, KAN0439834, against ROR1 by screening a library of 110000 small molecules. This compound targeted the TK domain, preventing phosphorylation of ROR1 by Wnt5a and thus blocking the activation of downstream proteins such as Src, Akt, protein kinase C, and MAPK. Further research demonstrated that KAN0439834 was more effective in inducing apoptosis in cancer cells than mAbs with a potency equivalent to that of venetoclax, an inhibitor of Bcl-2 used for the treatment of patients with CLL. Clinical trials have also shown that combinations of KAN0439834 with erlotinib and ibrutinib, small-molecule inhibitors of epidermal growth factor receptor and Bruton's tyrosine kinase, act synergistically in the treatment of patients with pancreatic cancer [53]. The same group screened KAN04415711C, a second-generation compound targeting ROR1, which was found to be effective against tumors in a zebrafish model[54]. KAN04415711C was also effective in vitro when combined with venetoclax. Its mechanism of action, however, requires further investigation.

### *ROR1-targeted CAR-T cell therapy*

CAR-T therapy involves the transfer of structural domains that specifically recognize antigens and genetic material promoting T cell activation signals into T-cells. This enables the T cells to target the specific antigens on the surfaces of cancer cells, leading to the release of cytotoxic compounds such as perforin and granzyme B. Cytokines may also be released to recruit endogenous immune cells for cotreatment. Additionally, the formation of memory T cells can establish a long-lasting antitumor mechanism *in vivo*[55-57].

ROR1 is currently considered a promising target in the design of CAR-T cell therapy. Hudecek *et al*[58] and Hudecek *et al*[59] designed a range of CAR-T cells targeting ROR1, featuring a concise “hinge-only” extracellular spacer, that was found to be highly effective in destroying ROR1-positive tumor cells and inducing T cell effector functions. The safety of this therapy is currently being evaluated due to concerns about cross-reaction with normal tissues by the scFv[60,61]. Lee *et al*[62] developed two CAR-T cell constructs targeting ROR1 by utilization of the antigen-recognition domains of zilovertamab and different hinge regions on the antibody. It was found that the construct with a truncated IgG4 hinge fragment was the most successful in terms of expression and *in vitro* functionality. Additionally, it effectively controlled tumor growth in xenograft mouse models with no significant toxicity. This study demonstrates the potential of Zilovertamab-derived ROR1 CAR-T for the clinical treatment of solid tumors.

The vast majority of candidate CAR targets in solid tumors, such as HER2, GD2, and mesothelin, are co-expressed in a variety of normal tissues, making off-tumor toxicity a significant risk for immunotherapies targeting these molecules. This makes it crucial to study the toxicity of ROR1 targeted therapy for gastrointestinal tumors, as ROR1 is no exception. SNIP CARs provide a solution to CAR-T therapy toxicities by utilizing a regulated protease-based system controlled by an FDA-approved small molecule. They offer improved potency and safety in various models, enabling remote control over CAR activity for treating solid tumors[63].

A study by Srivastava and colleagues[64] found that ROR1 CAR-T therapy led to fatal bone marrow failure in mice due to the recognition of ROR1-positive stromal cells. To enhance selectivity, they integrated synthetic Notch (synNotch) receptors specifically recognizing epithelial cell adhesion molecule or B7-H3 into T cells. These receptors were expressed on ROR1-positive cancer cells but not on stromal cells expressing ROR1. This induced a selective ROR1 CAR-T effect, leading to successful tumor ablation without toxicity in normal ROR1-positive cells. The study demonstrated that the use of synNotch receptors for combined antigen sensing can prevent CAR-T-cell-mediated lethal toxicity to normal tissue, provided that the tumor and normal tissue were spatially separated. However, if they are highly colocalized at the same site, this approach may not be effective. Moreover, the same group further discovered that ROR1 CAR-T cells showed poor tumor infiltration and malfunctioned. The inclusion of oxaliplatin, however, in the regimen allowed the recruitment of T cells by activated tumor macrophages[65], improving CAR-T-cell infiltration to modify the TME and increasing the sensitivity of the tumor to immunotherapy. Thus, the ROR1 CAR-T combination therapy provides an alternative strategy for the enhancement of CAR-T cell efficacy in clinical settings.

Some metabolites and small-molecule drugs can boost the anticancer actions of CAR-T cells. It was found that some short-chain fatty acids, such as butyrate and valerate, could enhance the actions of cytotoxic T lymphocytes and CAR-T cells through both epigenetic and metabolic means[66]. Furthermore, SD-208, a kinase inhibitor, could enhance the cytolytic activity, cytokine production, viability, and proliferation of ROR1-CAR T cells by blocking TGF-β receptor signaling[67]. These findings underscore the significance of novel combination therapies in enhancing the efficacy of ROR1 CAR T cells for treating gastrointestinal cancers.

## CONCLUSION

ROR1 is a potentially effective therapeutic target for various gastrointestinal cancers. However, high expression of ROR1 on the surface of normal tissues poses potential risks for off-target tumor toxicity. Therefore, the use of treatments targeting ROR1 requires monitoring of potential toxicity to healthy tissues to ensure safety. The effectiveness of mAbs, ADCs, or BiTEs against ROR1 on solid tumors, including gastrointestinal cancers, may be restricted due to the characteristics of the TME and tumor heterogeneity. Therefore, if long-term localized expression of anti-ROR1 BiTEs or mAbs can be induced within tumors, this could recruit and activate tumor-infiltrating lymphocytes for effective antitumor effects. Oncolytic viruses can serve as vectors for delivering ROR1 BiTEs or mAbs, potentially offering a solution to this problem. Our group has constructed a novel oncolytic adenovirus that delivers anti-ROR1-BiTE, which has demonstrated efficient inhibition of the growth of tumor cells in a mouse xenograft model. This highlights the importance of the combination of oncolytic virotherapy with ROR1 CAR T cell therapy. Overall, the in-depth research into the use of treatments targeting ROR1 suggests that better strategies for the clinical treatment of gastrointestinal cancer will be developed in the future.

## FOOTNOTES

**Author contributions:** Wu ZL performed the majority of the writing, prepared the figures and tables; Wang Y coordinated the writing of the paper Wang H provided the input in writing the paper; Jia XY and Wang YG contributed to the conception and design of the paper, literature review, critical revision and approval of the final version.

**Supported by** the Hangzhou Medical Health Science and Technology Project, No. B20220173; the Public Welfare Technology Project of Zhejiang Province, No. LGF21H160033; and Zhejiang Medical Technology Plan Project, No. 2021KY047.

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.



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**S-Editor:** Liu JH
**L-Editor:** A
**P-Editor:** Zhao YQ

## REFERENCES

1 **Casaletto JB**, McClatchey AI. Spatial regulation of receptor tyrosine kinases in development and cancer. *Nat Rev Cancer* 2012; **12**: 387-400 [PMID: 22622641 DOI: 10.1038/nrc3277]
2 **Zhao Y**, Zhang D, Guo Y, Lu B, Zhao ZJ, Xu X, Chen Y. Tyrosine Kinase ROR1 as a Target for Anti-Cancer Therapies. *Front Oncol* 2021; **11**: 680834 [PMID: 34123850 DOI: 10.3389/fonc.2021.680834]
3 **Forrester WC**. The Ror receptor tyrosine kinase family. *Cell Mol Life Sci* 2002; **59**: 83-96 [PMID: 11846036 DOI: 10.1007/s00018-002-8407-9]
4 **Borcherding N**, Kusner D, Liu GH, Zhang W. ROR1, an embryonic protein with an emerging role in cancer biology. *Protein Cell* 2014; **5**: 496-502 [PMID: 24752542 DOI: 10.1007/s13238-014-0059-7]
5 **Baskar S**, Kwong KY, Hofer T, Levy JM, Kennedy MG, Lee E, Staudt LM, Wilson WH, Wiestner A, Rader C. Unique cell surface expression of receptor tyrosine kinase ROR1 in human B-cell chronic lymphocytic leukemia. *Clin Cancer Res* 2008; **14**: 396-404 [PMID: 18223214 DOI: 10.1158/1078-0432.CCR-07-1823]
6 **Wilson C**, Goberdhan DC, Steller H. Dror, a potential neurotrophic receptor gene, encodes a Drosophila homolog of the vertebrate Ror family of Trk-related receptor tyrosine kinases. *Proc Natl Acad Sci U S A* 1993; **90**: 7109-7113 [PMID: 8394009 DOI: 10.1073/pnas.90.15.7109]
7 **Kipps TJ**. ROR1: an orphan becomes apparent. *Blood* 2022; **140**: 1583-1591 [PMID: 35580162 DOI: 10.1182/blood.2021014760]
8 **Stricker S**, Rauschenberger V, Schambony A. ROR-Family Receptor Tyrosine Kinases. *Curr Top Dev Biol* 2017; **123**: 105-142 [PMID:

28236965 DOI: 10.1016/bs.ctdb.2016.09.003]

9 **Heliste J**, Jokilammi A, Paatero I, Chakroborty D, Stark C, Savunen T, Laaksonen M, Elenius K. Receptor tyrosine kinase profiling of ischemic heart identifies ROR1 as a potential therapeutic target. *BMC Cardiovasc Disord* 2018; **18**: 196 [PMID: 30342492 DOI: 10.1186/s12872-018-0933-y]

10 **Kurita Y**, Ohki T, Soejima E, Yuan X, Kakino S, Wada N, Hashinaga T, Nakayama H, Tani J, Tajiri Y, Hiromatsu Y, Yamada K, Nomura M. A High-Fat/High-Sucrose Diet Induces WNT4 Expression in Mouse Pancreatic β-cells. *Kurume Med J* 2019; **65**: 55-62 [PMID: 30853690 DOI: 10.2739/kurumemedj.MS652008]

11 **Sánchez-Solana B**, Laborda J, Baladrón V. Mouse resistin modulates adipogenesis and glucose uptake in 3T3-L1 preadipocytes through the ROR1 receptor. *Mol Endocrinol* 2012; **26**: 110-127 [PMID: 22074948 DOI: 10.1210/me.2011-1027]

12 **Yu J**, Chen L, Chen Y, Hasan MK, Ghia EM, Zhang L, Wu R, Rassenti LZ, Widhopf GF, Shen Z, Briggs SP, Kipps TJ. Wnt5a induces ROR1 to associate with 14-3-3ζ for enhanced chemotaxis and proliferation of chronic lymphocytic leukemia cells. *Leukemia* 2017; **31**: 2608-2614 [PMID: 28465528 DOI: 10.1038/leu.2017.132]

13 **Hasan MK**, Yu J, Chen L, Cui B, Widhopf Ii GF, Rassenti L, Shen Z, Briggs SP, Kipps TJ. Wnt5a induces ROR1 to complex with HS1 to enhance migration of chronic lymphocytic leukemia cells. *Leukemia* 2017; **31**: 2615-2622 [PMID: 28465529 DOI: 10.1038/leu.2017.133]

14 **Hasan MK**, Rassenti L, Widhopf GF 2nd, Yu J, Kipps TJ. Wnt5a causes ROR1 to complex and activate cortactin to enhance migration of chronic lymphocytic leukemia cells. *Leukemia* 2019; **33**: 653-661 [PMID: 30568170 DOI: 10.1038/s41375-018-0306-7]

15 **Hasan MK**, Yu J, Widhopf GF 2nd, Rassenti LZ, Chen L, Shen Z, Briggs SP, Neuberg DS, Kipps TJ. Wnt5a induces ROR1 to recruit DOCK2 to activate Rac1/2 in chronic lymphocytic leukemia. *Blood* 2018; **132**: 170-178 [PMID: 29678828 DOI: 10.1182/blood-2017-12-819383]

16 **Balakrishnan A**, Goodpaster T, Randolph-Habecker J, Hoffstrom BG, Jalikis FG, Koch LK, Berger C, Kosasih PL, Rajan A, Sommermeyer D, Porter PL, Riddell SR. Analysis of ROR1 Protein Expression in Human Cancer and Normal Tissues. *Clin Cancer Res* 2017; **23**: 3061-3071 [PMID: 27852699 DOI: 10.1158/1078-0432.CCR-16-2083]

17 **Hudecek M**, Schmitt TM, Baskar S, Lupo-Stanghellini MT, Nishida T, Yamamoto TN, Bleakley M, Turtle CJ, Chang WC, Greisman HA, Wood B, Maloney DG, Jensen MC, Rader C, Riddell SR. The B-cell tumor-associated antigen ROR1 can be targeted with T cells modified to express a ROR1-specific chimeric antigen receptor. *Blood* 2010; **116**: 4532-4541 [PMID: 20702778 DOI: 10.1182/blood-2010-05-283309]

18 **Nomi M**, Oishi I, Kani S, Suzuki H, Matsuda T, Yoda A, Kitamura M, Itoh K, Takeuchi S, Takeda K, Akira S, Ikeya M, Takada S, Minami Y. Loss of mRor1 enhances the heart and skeletal abnormalities in mRor2-deficient mice: redundant and pleiotropic functions of mRor1 and mRor2 receptor tyrosine kinases. *Mol Cell Biol* 2001; **21**: 8329-8335 [PMID: 11713269 DOI: 10.1128/mcb.21.24.8329-8335.2001]

19 **Fukuda T**, Chen L, Endo T, Tang L, Lu D, Castro JE, Widhopf GF 2nd, Rassenti LZ, Cantwell MJ, Prussak CE, Carson DA, Kipps TJ. Antisera induced by infusions of autologous Ad-CD154-leukemia B cells identify ROR1 as an oncofetal antigen and receptor for Wnt5a. *Proc Natl Acad Sci U S A* 2008; **105**: 3047-3052 [PMID: 18287027 DOI: 10.1073/pnas.0712148105]

20 **Daneshmanesh AH**, Hojjat-Farsangi M, Moshfegh A, Khan AS, Mikaelsson E, Österborg A, Mellstedt H. The PI3K/AKT/mTOR pathway is involved in direct apoptosis of CLL cells induced by ROR1 monoclonal antibodies. *Br J Haematol* 2015; **169**: 455-458 [PMID: 25407287 DOI: 10.1111/bjh.13228]

21 **Daneshmanesh AH**, Hojjat-Farsangi M, Khan AS, Jeddi-Tehrani M, Akhondi MM, Bayat AA, Ghods R, Mahmoudi AR, Hadavi R, Österborg A, Shokri F, Rabbani H, Mellstedt H. Monoclonal antibodies against ROR1 induce apoptosis of chronic lymphocytic leukemia (CLL) cells. *Leukemia* 2012; **26**: 1348-1355 [PMID: 22289919 DOI: 10.1038/leu.2011.362]

22 **Lamers CH**, Sleijfer S, van Steenbergen S, van Elzakker P, van Krimpen B, Groot C, Vulto A, den Bakker M, Oosterwijk E, Debets R, Gratama JW. Treatment of metastatic renal cell carcinoma with CAIX CAR-engineered T cells: clinical evaluation and management of on-target toxicity. *Mol Ther* 2013; **21**: 904-912 [PMID: 23423337 DOI: 10.1038/mt.2013.17]

23 **Mikels AJ**, Nusse R. Purified Wnt5a protein activates or inhibits beta-catenin-TCF signaling depending on receptor context. *PLoS Biol* 2006; **4**: e115 [PMID: 16602827 DOI: 10.1371/journal.pbio.0040115]

24 **Chen Y**, Chen L, Yu J, Ghia EM, Choi MY, Zhang L, Zhang S, Sanchez-Lopez E, Widhopf GF 2nd, Messer K, Rassenti LZ, Jamieson C, Kipps TJ. Cirmtuzumab blocks Wnt5a/ROR1 stimulation of NF-κB to repress autocrine STAT3 activation in chronic lymphocytic leukemia. *Blood* 2019; **134**: 1084-1094 [PMID: 31409670 DOI: 10.1182/blood.2019001366]

25 **Zhang S**, Zhang H, Ghia EM, Huang J, Wu L, Zhang J, Lam S, Lei Y, He J, Cui B, Widhopf GF 2nd, Yu J, Schwab R, Messer K, Jiang W, Parker BA, Carson DA, Kipps TJ. Inhibition of chemotherapy resistant breast cancer stem cells by a ROR1 specific antibody. *Proc Natl Acad Sci U S A* 2019; **116**: 1370-1377 [PMID: 30622177 DOI: 10.1073/pnas.1816262116]

26 **Islam SS**, Uddin M, Noman ASM, Akter H, Dity NJ, Basiruzzman M, Uddin F, Ahsan J, Annoor S, Alaiya AA, Al-Alwan M, Yeger H, Farhat WA. Antibody-drug conjugate T-DM1 treatment for HER2+ breast cancer induces ROR1 and confers resistance through activation of Hippo transcriptional coactivator YAP1. *EBioMedicine* 2019; **43**: 211-224 [PMID: 31085100 DOI: 10.1016/j.ebiom.2019.04.061]

27 **Zhou Y**, Li Y, Zhou T, Zheng J, Li S, Li HB. Dietary Natural Products for Prevention and Treatment of Liver Cancer. *Nutrients* 2016; **8**: 156 [PMID: 26978396 DOI: 10.3390/nu8030156]

28 **Huang F**, Wang BR, Wu YQ, Wang FC, Zhang J, Wang YG. Oncolytic viruses against cancer stem cells: A promising approach for gastrointestinal cancer. *World J Gastroenterol* 2016; **22**: 7999-8009 [PMID: 27672294 DOI: 10.3748/wjg.v22.i35.7999]

29 **Cetin M**, Odabas G, Douglas LR, Duriez PJ, Balcik-Ercin P, Yalim-Camci I, Sayan AE, Yagci T. ROR1 Expression and Its Functional Significance in Hepatocellular Carcinoma Cells. *Cells* 2019; **8** [PMID: 30832318 DOI: 10.3390/cells8030210]

30 **Meng X**, Xu Y, Ning X. Tumor microenvironment acidity modulates ROR1 to promote epithelial-mesenchymal transition and hepatocarcinoma metastasis. *J Cell Sci* 2021; **134** [PMID: 33648935 DOI: 10.1242/jcs.255349]

31 **Ohira M**, Toyokawa T, Sakurai K, Kubo N, Tanaka H, Muguruma K, Yashiro M, Onoda N, Hirakawa K. Current status in remnant gastric cancer after distal gastrectomy. *World J Gastroenterol* 2016; **22**: 2424-2433 [PMID: 26937131 DOI: 10.3748/wjg.v22.i8.2424]

32 **Hong JB**, Zuo W, Wang AJ, Lu NH. Helicobacter pylori Infection Synergistic with IL-1β Gene Polymorphisms Potentially Contributes to the Carcinogenesis of Gastric Cancer. *Int J Med Sci* 2016; **13**: 298-303 [PMID: 27076787 DOI: 10.7150/ijms.14239]

33 **Katoh M**, Katoh M. Transcriptional mechanisms of *WNT5A* based on NF-κB, Hedgehog, TGFβ, and Notch signaling cascades. *Int J Mol Med* 2009; **23**: 763-769 [DOI: 10.3892/ijmm_00000190]

34 **Wheeler DL**, Iida M, Dunn EF. The role of Src in solid tumors. *Oncologist* 2009; **14**: 667-678 [PMID: 19581523 DOI: 10.1634/theoncologist.2009-0009]

35 **Talamonti MS**, Roh MS, Curley SA, Gallick GE. Increase in activity and level of pp60c-src in progressive stages of human colorectal cancer. *J Clin Invest* 1993; **91**: 53-60 [PMID: 7678609 DOI: 10.1172/jci116200]

36 **Zhou JK**, Zheng YZ, Liu XS, Gou Q, Ma R, Guo CL, Croce CM, Liu L, Peng Y. ROR1 expression as a biomarker for predicting prognosis in patients with colorectal cancer. *Oncotarget* 2017; **8**: 32864-32872 [PMID: 28427197 DOI: 10.18632/oncotarget.15860]

37 **Patel S**, Alam A, Pant R, Chattopadhyay S. Wnt Signaling and Its Significance Within the Tumor Microenvironment: Novel Therapeutic Insights. *Front Immunol* 2019; **10**: 2872 [PMID: 31921137 DOI: 10.3389/fimmu.2019.02872]

38 **Yamazaki M**, Hino S, Usuki S, Miyazaki Y, Oda T, Nakao M, Ito T, Yamagata K. YAP/BRD4-controlled ROR1 promotes tumor-initiating cells and hyperproliferation in pancreatic cancer. *EMBO J* 2023; **42**: e112614 [PMID: 37096681 DOI: 10.15252/embj.2022112614]

39 **Nelson AL**, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. *Nat Rev Drug Discov* 2010; **9**: 767-774 [PMID: 20811384 DOI: 10.1038/nrd3229]

40 **Choi MY**, Widhopf GF 2nd, Ghia EM, Kidwell RL, Hasan MK, Yu J, Rassenti LZ, Chen L, Chen Y, Pittman E, Pu M, Messer K, Prussak CE, Castro JE, Jamieson C, Kipps TJ. Phase I Trial: Cirmtuzumab Inhibits ROR1 Signaling and Stemness Signatures in Patients with Chronic Lymphocytic Leukemia. *Cell Stem Cell* 2018; **22**: 951-959.e3 [PMID: 29859176 DOI: 10.1016/j.stem.2018.05.018]

41 **Cui B**, Widhopf GF, Prussak CE, Wu CCN, Sadarangani A, Zhang SP, Lao F, Jamieson CHM, Carson DA, Kipps TJ. Cirmtuzumab Vedotin (UC-961ADC3), An Anti-ROR1-Monomethyl Auristatin E Antibody-Drug Conjugate, Is a Potential Treatment For ROR1-Positive Leukemia and Solid Tumors. *Blood* 2013; **122**: 2 [DOI: 10.1182/blood.V122.21.1637.1637]

42 **Jiang VC**, Liu Y, Jordan A, McIntosh J, Li Y, Che Y, Jessen KA, Lannutti BJ, Wang M. The antibody drug conjugate VLS-101 targeting ROR1 is effective in CAR T-resistant mantle cell lymphoma. *J Hematol Oncol* 2021; **14**: 132 [PMID: 34454548 DOI: 10.1186/s13045-021-01143-w]

43 **Beerli RR**, Waldmeier L, Gébleux R, Pretto F, Grawunder U. NBE-002, an anthracycline-based immune-stimulatory antibody drug conjugate (iADC) targeting ROR1 for the treatment of triple-negative breast cancer. *Cancer Res* 2019; **79**: 2 [DOI: 10.1158/1538-7445.AM2019-LB-197]

44 **Chiang CL**, Goswami S, Frissora FW, Xie Z, Yan PS, Bundschuh R, Walker LA, Huang X, Mani R, Mo XM, Baskar S, Rader C, Phelps MA, Marcucci G, Byrd JC, Lee LJ, Muthusamy N. ROR1-targeted delivery of miR-29b induces cell cycle arrest and therapeutic benefit in vivo in a CLL mouse model. *Blood* 2019; **134**: 432-444 [PMID: 31151986 DOI: 10.1182/blood.2018882290]

45 **Mani R**, Mao Y, Frissora FW, Chiang CL, Wang J, Zhao Y, Wu Y, Yu B, Yan R, Mo X, Yu L, Flynn J, Jones J, Andritsos L, Baskar S, Rader C, Phelps MA, Chen CS, Lee RJ, Byrd JC, Lee LJ, Muthusamy N. Tumor antigen ROR1 targeted drug delivery mediated selective leukemic but not normal B-cell cytotoxicity in chronic lymphocytic leukemia. *Leukemia* 2015; **29**: 346-355 [PMID: 24947019 DOI: 10.1038/leu.2014.199]

46 **Qi J**, Li X, Peng H, Cook EM, Dadashian EL, Wiestner A, Park H, Rader C. Potent and selective antitumor activity of a T cell-engaging bispecific antibody targeting a membrane-proximal epitope of ROR1. *Proc Natl Acad Sci USA* 2018; **115**: E5467-E5476 [PMID: 29844189 DOI: 10.1073/pnas.1719905115]

47 **Wang Y**, Zhang Y, Sun H, Chen J, Yang H, Zhong Z, Xiao X, Li Y, Tang Y, Lu H, Tang X, Zhang M, Wu W, Zhou S, Yang J. Antitumor activity of a ROR1 × CD3 bispecific antibody in non-small cell lung cancer. *Int Immunopharmacol* 2023; **123**: 110686 [PMID: 37499397 DOI: 10.1016/j.intimp.2023.110686]

48 **Granger D**, Gohil S, Barbarulo A, Baccaro A, Muczynski V, Chester K, Germaschewski F, Batten T, Brown K, Cook S, O'Donovan K, Jasani P, Nathwani AC, Phillips P. NVG-111, a novel ROR1xCD3 bispecific antibody for non-Hodgkin lymphoma. *J Clin Oncol* 2021; **39**: 3 [DOI: 10.1200/JCO.2021.39.15_suppl.7549]

49 **Gohil SH**, Paredes-Moscosso SR, Harrasser M, Vezzalini M, Scarpa A, Morris E, Davidoff AM, Sorio C, Nathwani AC, Della Peruta M. An ROR1 bi-specific T-cell engager provides effective targeting and cytotoxicity against a range of solid tumors. *Oncoimmunology* 2017; **6**: e1326437 [PMID: 28811962 DOI: 10.1080/2162402X.2017.1326437]

50 **Hojjat-Farsangi M**, Khan AS, Daneshmanesh AH, Moshfegh A, Sandin A, Mansouri L, Palma M, Lundin J, Österborg A, Mellstedt H. The tyrosine kinase receptor ROR1 is constitutively phosphorylated in chronic lymphocytic leukemia (CLL) cells. *PLoS One* 2013; **8**: e78339 [PMID: 24205204 DOI: 10.1371/journal.pone.0078339]

51 **Gentile A**, Lazzari L, Benvenuti S, Trusolino L, Comoglio PM. Ror1 is a pseudokinase that is crucial for Met-driven tumorigenesis. *Cancer Res* 2011; **71**: 3132-3141 [PMID: 21487037 DOI: 10.1158/0008-5472.CAN-10-2662]

52 **Hojjat-Farsangi M**, Daneshmanesh AH, Khan AS, Shetye J, Mozaffari F, Kharaziha P, Rathje LS, Kokhaei P, Hansson L, Vågberg J, Byström S, Olsson E, Löfberg C, Norström C, Schultz J, Norin M, Olin T, Österborg A, Mellstedt H, Moshfegh A. First-in-class oral small molecule inhibitor of the tyrosine kinase ROR1 (KAN0439834) induced significant apoptosis of chronic lymphocytic leukemia cells. *Leukemia* 2018; **32**: 2291-2295 [PMID: 29725030 DOI: 10.1038/s41375-018-0113-1]

53 **Daneshmanesh AH**, Hojjat-Farsangi M, Ghaderi A, Moshfegh A, Hansson L, Schultz J, Vågberg J, Byström S, Olsson E, Olin T, Österborg A, Mellstedt H. A receptor tyrosine kinase ROR1 inhibitor (KAN0439834) induced significant apoptosis of pancreatic cells which was enhanced by erlotinib and ibrutinib. *PLoS One* 2018; **13**: e0198038 [PMID: 29856777 DOI: 10.1371/journal.pone.0198038]

54 **Ghaderi A**, Daneshmanesh AH, Moshfegh A, Kokhaei P, Vågberg J, Schultz J, Olin T, Harrysson S, Smedby KE, Drakos E, Rassidakis GZ, Österborg A, Hojjat-Farsangi M, Mellstedt H. ROR1 Is Expressed in Diffuse Large B-Cell Lymphoma (DLBCL) and a Small Molecule Inhibitor of ROR1 (KAN0441571C) Induced Apoptosis of Lymphoma Cells. *Biomedicines* 2020; **8**: 170 [PMID: 32586008 DOI: 10.3390/biomedicines8060170]

55 **Davila ML**, Bouhassira DC, Park JH, Curran KJ, Smith EL, Pegram HJ, Brentjens R. Chimeric antigen receptors for the adoptive T cell therapy of hematologic malignancies. *Int J Hematol* 2014; **99**: 361-371 [PMID: 24311149 DOI: 10.1007/s12185-013-1479-5]

56 **Osorio-Rodríguez DA**, Camacho BA, Ramírez-Segura C. Anti-ROR1 CAR-T cells: Architecture and performance. *Front Med (Lausanne)* 2023; **10**: 1121020 [PMID: 36873868 DOI: 10.3389/fmed.2023.1121020]

57 **Peng H**, Nerreter T, Mestermann K, Wachter J, Chang J, Hudecek M, Rader C. ROR1-targeting switchable CAR-T cells for cancer therapy. *Oncogene* 2022; **41**: 4104-4114 [PMID: 35859167 DOI: 10.1038/s41388-022-02416-5]

58 **Hudecek M**, Lupo-Stanghellini MT, Kosasih PL, Sommermeyer D, Jensen MC, Rader C, Riddell SR. Receptor affinity and extracellular domain modifications affect tumor recognition by ROR1-specific chimeric antigen receptor T cells. *Clin Cancer Res* 2013; **19**: 3153-3164 [PMID: 23620405 DOI: 10.1158/1078-0432.CCR-13-0330]

59 **Hudecek M**, Sommermeyer D, Kosasih PL, Silva-Benedict A, Liu L, Rader C, Jensen MC, Riddell SR. The nonsignaling extracellular spacer domain of chimeric antigen receptors is decisive for in vivo antitumor activity. *Cancer Immunol Res* 2015; **3**: 125-135 [PMID: 25212991 DOI: 10.1158/2326-6066.CIR-14-0127]

60 **Broome HE**, Rassenti LZ, Wang HY, Meyer LM, Kipps TJ. ROR1 is expressed on hematogones (non-neoplastic human B-lymphocyte precursors) and a minority of precursor-B acute lymphoblastic leukemia. *Leuk Res* 2011; **35**: 1390-1394 [PMID: 21813176 DOI: 10.1016/j.leukres.2011.06.021]

61 **Berger C**, Sommermeyer D, Hudecek M, Berger M, Balakrishnan A, Paszkiewicz PJ, Kosasih PL, Rader C, Riddell SR. Safety of targeting ROR1 in primates with chimeric antigen receptor-modified T cells. *Cancer Immunol Res* 2015; **3**: 206-216 [PMID: 25355068 DOI: 10.1158/2326-6066.CIR-14-0163]

62 **Lee BK**, Wan Y, Chin ZL, Deng L, Deng M, Leung TM, Hua J, Zhang H. Developing ROR1 Targeting CAR-T Cells against Solid Tumors in Preclinical Studies. *Cancers (Basel)* 2022; **14**: 3618 [PMID: 35892876 DOI: 10.3390/cancers14153618]

63 **Labanieh L**, Majzner RG, Klysz D, Sotillo E, Fisher CJ, Vilches-Moure JG, Pacheco KZB, Malipatlolla M, Xu P, Hui JH, Murty T, Theruvath J, Mehta N, Yamada-Hunter SA, Weber EW, Heitzeneder S, Parker KR, Satpathy AT, Chang HY, Lin MZ, Cochran JR, Mackall CL. Enhanced safety and efficacy of protease-regulated CAR-T cell receptors. *Cell* 2022; **185**: 1745-1763.e22 [PMID: 35483375 DOI: 10.1016/j.cell.2022.03.041]

64 **Srivastava S**, Salter AI, Liggitt D, Yechan-Gunja S, Sarvothama M, Cooper K, Smythe KS, Dudakov JA, Pierce RH, Rader C, Riddell SR. Logic-Gated ROR1 Chimeric Antigen Receptor Expression Rescues T Cell-Mediated Toxicity to Normal Tissues and Enables Selective Tumor Targeting. *Cancer Cell* 2019; **35**: 489-503.e8 [PMID: 30889382 DOI: 10.1016/j.ccell.2019.02.003]

65 **Srivastava S**, Furlan SN, Jaeger-Ruckstuhl CA, Sarvothama M, Berger C, Smythe KS, Garrison SM, Specht JM, Lee SM, Amezquita RA, Voillet V, Muhunthan V, Yechan-Gunja S, Pillai SPS, Rader C, Houghton AM, Pierce RH, Gottardo R, Maloney DG, Riddell SR. Immunogenic Chemotherapy Enhances Recruitment of CAR-T Cells to Lung Tumors and Improves Antitumor Efficacy when Combined with Checkpoint Blockade. *Cancer Cell* 2021; **39**: 193-208.e10 [PMID: 33357452 DOI: 10.1016/j.ccell.2020.11.005]

66 **Luu M**, Riester Z, Baldrich A, Reichardt N, Yuille S, Busetti A, Klein M, Wempe A, Leister H, Raifer H, Picard F, Muhammad K, Ohl K, Romero R, Fischer F, Bauer CA, Huber M, Gress TM, Lauth M, Danhof S, Bopp T, Nerreter T, Mulder IE, Steinhoff U, Hudecek M, Visekruna A. Microbial short-chain fatty acids modulate CD8(+) T cell responses and improve adoptive immunotherapy for cancer. *Nat Commun* 2021; **12**: 4077 [PMID: 34210970 DOI: 10.1038/s41467-021-24331-1]

67 **Stüber T**, Monjezi R, Wallstabe L, Kühnemundt J, Nietzer SL, Dandekar G, Wöckel A, Einsele H, Wischhusen J, Hudecek M. Inhibition of TGF-β-receptor signaling augments the antitumor function of ROR1-specific CAR T-cells against triple-negative breast cancer. *J Immunother Cancer* 2020; **8**: e000676 [PMID: 32303620 DOI: 10.1136/jitc-2020-000676]

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