

REVIEW

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WNT signaling in cancer: molecular mechanisms and potential therapies

Jiaqi Liang^{1†}, Yiming Pan^{1†}, Jingru Yang¹, Dequan Zeng^{2*} and Jing Li^{1*} 

Abstract

The WNT signaling pathway, a fundamental molecular network regulating cell proliferation, differentiation, and stemness, plays a critical role in tumorigenesis, cancer progression, and therapeutic resistance. Given its crucial regulatory roles in tumors, WNT signaling pathway has been identified as effective targets for cancer treatment. However, the current clinical efficacy of WNT signaling pathway-targeted anti-tumor therapies remains suboptimal. Based on research investigating the role of WNT signaling pathway in cancer, we systematically discuss the molecular mechanisms of WNT signaling in cancer (including both canonical and non-canonical signaling pathways), the role of WNT signaling in different cancer types, highlighting distinct potential therapeutic approaches targeting WNT signaling. We also comprehensively review innovative strategies targeting WNT signaling, including Porcupine (PORCN) inhibitors, Tankyrase (TNKS) inhibitor, Frizzled (FZD)-targeted monoclonal antibodies, β -catenin/TCF transcriptional complex inhibitors, and natural bioactive compounds and drug repositioning etc., critically evaluating their preclinical efficacy and limitations. We emphasize the need for and challenges in developing WNT-targeted therapies including refining the specificity of WNT signaling pathway-targeted therapies, developing biomarkers for patient selection, and exploring synergies between WNT inhibitors and other therapeutic modalities such as immune checkpoint blockers. These advances aim to enable personalized precision therapy and revolutionize cancer treatment paradigms in the future.

Keywords WNT Signaling, FZD, Cancer, Biomarker, Therapeutic targets, Inhibitor

Introduction

The WNT signaling pathway is generally categorized into the canonical pathway and non-canonical pathways. As an evolutionarily conserved signaling pathway, the WNT pathway has been demonstrated to play pivotal roles in the development of multiple tissues and organs, including the skin, eyes, brain, lungs, spinal cord, teeth,

bones, cartilage, kidneys, liver, hematopoietic system, and reproductive organs [1]. Furthermore, the WNT signaling pathway participates in the regulation of tissue homeostasis. For instance, the activation of WNT signaling is observed during tissue repair processes following hepatic and pulmonary injuries. This pathway regulates fundamental cellular behaviors including proliferation, differentiation, apoptosis, and migration [2]. Given the extensive physiological functions of WNT signaling, its dysregulation is closely associated with the pathogenesis of various diseases. An increasing number of studies indicate that aberrant WNT activation contributes to cancer-related mortality by promoting tumorigenesis, cancer cell proliferation, differentiation, metastasis, invasion, and therapeutic resistance [3]. Consequently, the WNT signaling pathway represents a promising therapeutic target in cancer treatment.

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Currently, substantial research efforts have been devoted to developing targeted therapeutics against WNT signaling activation, with several agents undergoing clinical trials. However, despite demonstrating anti-cancer potential in preclinical studies, various WNT inhibitors have exhibited adverse effects in clinical trials, including bone fractures and gastrointestinal toxicity [4]. The primary challenges stem from off-target effects that disrupt physiological WNT signaling in normal tissues and crosstalk between the WNT pathway and other signaling pathways. Balancing therapeutic efficacy with safety profiles remains a critical challenge and research focus for future WNT-targeted therapies. Recent advancements in enhancing therapeutic safety have been reported, encompassing strategies such as improving WNT inhibitor specificity, combinatorial approaches with other pathway inhibitors, and integration with immunotherapies.

In summary, we propose to systematically review the molecular mechanisms of the WNT signaling pathway and its crosstalk with other signaling pathways in cancer. Furthermore, we consolidate the roles of dysregulated WNT signaling in various cancers and categorize distinct types of WNT inhibitors currently under preclinical investigation and in clinical trials. Finally, we highlight existing challenges in targeting the WNT pathway and discuss potential synergies with other therapeutic modalities. We also address the emerging potential of WNT signaling components as biomarkers for diagnosis, therapeutic guidance, and prognostic evaluation.

Molecular mechanisms of WNT signaling in cancer

The molecular mechanisms of the WNT signaling pathway have been extensively studied. Aberrations in components of both canonical and non-canonical pathways have been demonstrated to be closely associated with cancer progression. By comprehensively reviewing the latest advances in WNT signaling mechanisms, we can gain deeper insights into its pivotal role in cancer pathogenesis. Furthermore, the WNT signaling pathway extensively crosstalks with other signaling cascades, and this interplay collectively promotes tumor development. Therefore, we provide an updated overview of WNT signaling mechanisms, systematically summarize the aberrations in WNT signaling contributing to cancer, and highlight the critical network interactions between the WNT pathway and other signaling cascades.

The canonical signaling pathway in cancer

The canonical signaling pathway is one of the most extensively studied signaling pathways (Fig. 1). This pathway can be divided into OFF and ON states, during which different biological events occur. Briefly, after WNT proteins are secreted, they are acylated and released into the

cytoplasm, where they bind to the receptor FZD and the co-receptors low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6). In the OFF state, several proteins form the destruction complex with β -catenin, mediating its subsequent ubiquitination and inactivation. In the ON state, the activation of Dishevelled (DVL) inhibits the formation of the destruction complex, allowing β -catenin to escape inactivation and enter the nucleus. Within the nucleus, β -catenin acts as a transcription factor or other roles, promoting the expression of downstream genes. Next, we will detail the mechanism of action of the canonical WNT pathway by examining its major components involved in the biological events, the mechanisms of dysregulation, and their links to cancer.

WNT

In canonical WNT signaling pathways, WNT proteins act as ligands that bind to cell membrane receptors, triggering intracellular cascade reactions which regulate diverse cellular processes including proliferation, division, stem cell maintenance, and various stages of embryonic development [5]. The WNT family comprises 19 highly hydrophobic secretory glycoproteins, each characterized by their cysteine-rich domains [6]. The canonical signaling pathway is primarily activated by WNT1, WNT2, WNT3, WNT3A, WNT8B, WNT10A, and WNT10B. In the endoplasmic reticulum, WNTs undergo PORCN-mediated palmitoylation, a modification that is indispensable for membrane receptor binding. The p24 protein family subsequently facilitates the transport of lipid-modified WNTs to the Golgi apparatus for further processing. Mature WNTs are ultimately secreted into the extracellular matrix via exosomes. However, WNT proteins do not represent the exclusive ligands for pathway activation [7]. Norrin binding to FZD4 has been demonstrated as an alternative activation mechanism for WNT signaling [8]. Overexpression of WNTs can mediate cancer phenotypes. For example, transgenic mice with mammary-specific overexpression of WNT1, driven by the mouse mammary tumor virus promoter, develop mammary tumors and serve as a model for breast cancer (BC) research [9]. Non-coding RNAs can bind to the mRNA of WNTs, thereby inhibiting WNT expression and subsequently suppressing the canonical pathway [10]. In addition to overexpression, structural alterations in WNTs proteins, which can be induced by missense mutations of genes, have also been reported. Research has shown that missense mutations in WNTs play an important role in cancer process. For WNT1, the Catalogue Of Somatic Mutations In Cancer database contained a total of 83 mutations, most of which were missense mutations [11]. In hepatocellular carcinoma, WNT3 stability and signaling depend on two

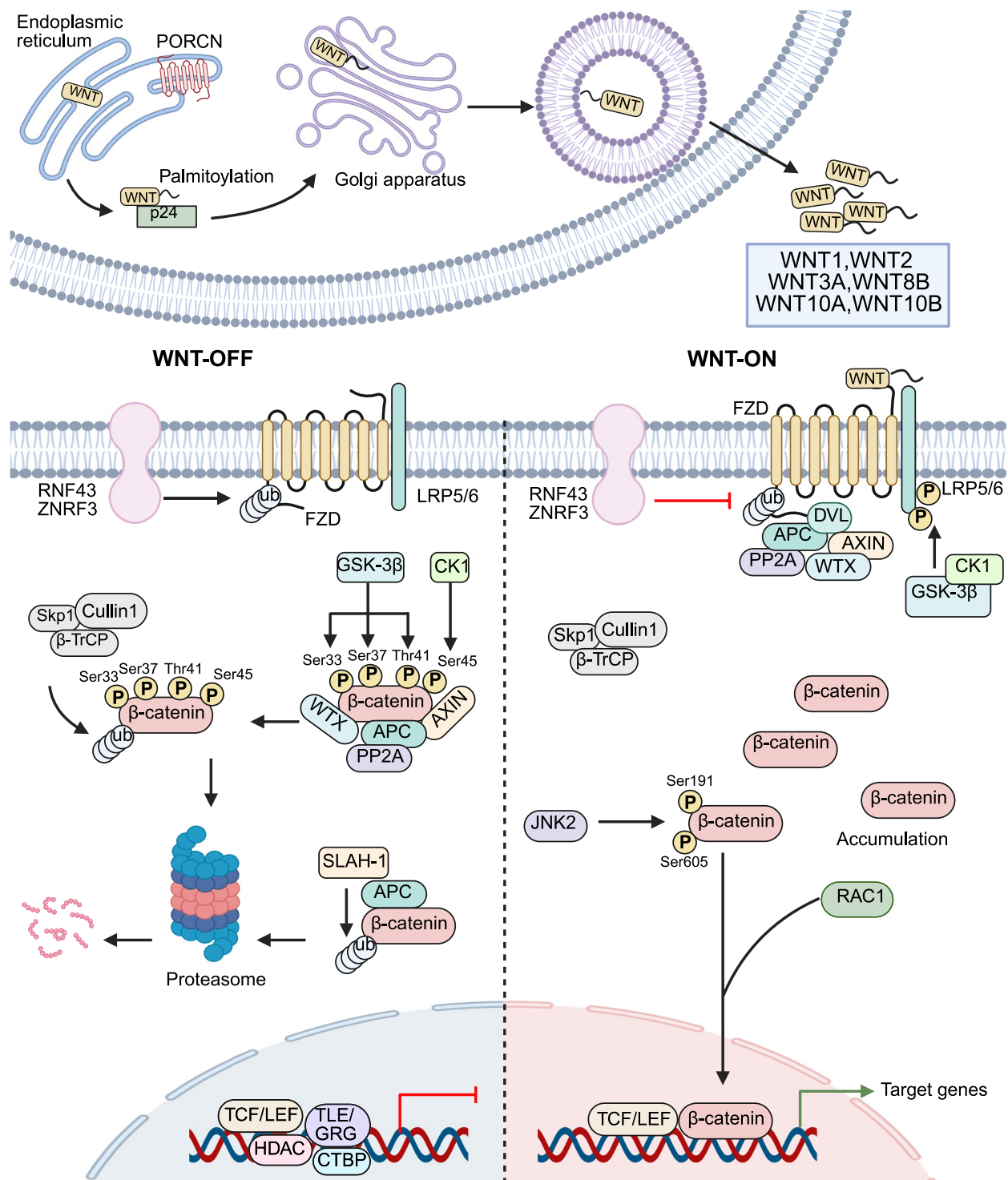


Fig. 1 Signal transduction of the canonical WNT pathway. Under the canonical WNT signaling off conditions, the WNT ligand undergoes palmitoylation modification by PORCN and is secreted from the endoplasmic reticulum into the intracellular space. RNF43/ZNRF3 are actively expressed, ubiquitinating the FZD receptor to maintain low levels of WNT ligand stimulation. The destruction complex assembles and phosphorylates intracellular β -catenin, which is subsequently degraded by ubiquitin ligases such as β -TrCP. In contrast, during canonical WNT signaling activation, FZD is highly expressed and binds overexpressed WNT ligands. Upon receiving this signal, DVL is activated and inhibits the formation of the destruction complex. Meanwhile, CK1 and GSK-3 β phosphorylate the co-receptor LRP5/6. As a result, β -catenin escapes phosphorylation by the destruction complex and is transported into the nucleus via the action of proteins such as JNK2 and RAC1. Once in the nucleus, β -catenin binds to TCF/LEF transcription factors, initiating the transcription of downstream target genes

N-glycosylation sites (asparagine (Asn) 90 and Asn301). Mutation at Asn301 reduces WNT3 stability, while dual mutations at both sites impair its binding to FZD7, downregulate WNT/ β -catenin signaling, and attenuate cancer invasion and proliferation [12].

FZD

FZD, belonging to the G protein-coupled receptor family, is composed of ten highly conserved seven-transmembrane receptors. FZD and co-receptor LRP bind to WNTs to form trimeric complexes, ultimately leading to intracellular β -catenin accumulation [13]. FZD is thought to be a key receptor molecule in the WNT signaling pathway, and their expression levels influence a series of cellular phenotypes, closely associated with cancer development and progression. Abnormal FZD expression can arise from genetic mutations, mRNA alterations, and dysregulated post-translational modifications. Gene amplification, missense mutations, and truncating mutations are major genetic mechanisms driving cancer through FZD dysregulation. In pancreatic cancer (PCA), gene amplification represents the most prevalent form of FZD mutation. Specifically, *FZD3* and *FZD9* demonstrate amplification mutations [14]. FZD expression levels are also regulated by mRNA state. For example, METTL3-mediated N6-methyladenosine modification of *FZD10* mRNA enhances its stability, promoting *FZD10* overexpression and hepatocellular carcinogenesis [15]. Non-coding RNAs can downregulate FZD expression by binding to specific mRNA regions; miR-328-3p, for instance, suppresses cancer phenotypes by targeting the 3'-untranslated region of *FZD7* mRNA [16]. Post-translationally, FZD levels are negatively regulated by RNF43 and ZNRF3-mediated ubiquitination and degradation. Inactivating mutations in RNF43, particularly in ubiquitination functional domains such as the RING domain or phosphorylation switch, impair its ability to degrade FZD, leading to increased their abundance [17]. Similarly, ZNRF3 mutations elevate FZD levels, although these two ubiquitin ligases target distinct FZD subtypes: RNF43 preferentially regulates *FZD1*/*FZD5*/*FZD7*, while ZNRF3 primarily modulates *FZD6* [18]. In addition, the downstream signaling products mediated by FZD can also affect its levels, thereby forming a positive feedback loop. Glenn E. Simmons Jr. et al. demonstrated that β -catenin and c-JUN bind to a region 7 kb upstream of the *FZD7* transcription start site, promoting its expression.

LRP5/6

The coreceptors LRP5/6, belonging to LRP superfamily, can form a trimeric complex with FZD and WNT to regulate the activation of WNT signaling, thereby modulating diverse physiological functions. However,

dysregulation of LRP5/6 can promote cancer initiation and progression. For instance, Cui, B. et al. discovered that butyrate can suppress properties of BC stem cell. As a histone deacetylase inhibitor, butyrate upregulates *ZFP36* expression, which bind to the AU-rich region in the 3'UTR of *LRP5* mRNA, thereby inhibiting *LRP5* expression and consequently suppressing B stem cell traits [19]. Rong, Z. et al. also found that salt-inducible kinase 2, upon interacting with CK1 α , phosphorylates *LRP6* at Ser 1490, thereby promoting *IDH1* expression via the WNT/ β -catenin pathway [20]. In gastric cancer (GC) cells, *LRP5* expression is aberrantly elevated and promotes cancer cell proliferation and metastasis by activating the WNT/ β -catenin signaling pathway. High *LRP5* expression is closely associated with poor prognosis in GC [21]. Epithelial-mesenchymal transition (EMT) is a critical process enabling cancer cell metastasis and invasion. In triple-negative breast cancer (TNBC), overexpressed *LRP6* promotes the EMT process in cancer cells by activating the WNT/ β -catenin signaling pathway, whereas inhibition of *LRP6* using the MESD protein effectively suppresses cell migration and invasion. Furthermore, Ma, J. et al. also identified *S100A4* as a downstream target gene of the WNT/ β -catenin signaling pathway, which is strongly implicated in tumor metastasis [22]. Similarly, overexpression of *LRP6* has been demonstrated to enhance the metastasis and invasion of hepatocellular carcinoma (HCC) cells [23]. In cancer chemotherapy, *LRP5/6* is also implicated in cancer cell drug resistance. FOLFOX (5-FU+oxaliplatin (OXA)+leucovorin) induces the expression of alternatively spliced isoforms of *CD44* containing variable exon 6 (*CD44v6*) in colorectal cancer (CRC), which serves as a marker for colorectal cancer-initiating cells. *CD44v6* forms a complex with *LRP6*, promotes its phosphorylation, and consequently augments WNT3A/ β -catenin signaling and facilitates drug efflux [24].

Destruction complex

When the WNT signaling pathway is inactive due to the absence of WNT ligands, β -catenin, the central component of this pathway, undergoes ubiquitination and proteasomal degradation, maintaining its low cytoplasmic concentration. This process is primarily mediated by the formation of the destruction complex. The widely accepted molecular mechanism involves that casein kinase 1 (CK1) mediates the phosphorylation of Ser45 at the N-terminal domain of β -catenin, followed by the phosphorylation at Thr41, Ser33, and Ser37 residues by glycogen synthase kinase-3 β (GSK-3 β) [25]. These phosphorylation events facilitate the recruitment of a series of proteins comprising adenomatous polyposis coli (APC), AXIN, GSK-3 β , CK1, protein phosphatase 2A (PP2A),

and Wilms tumor gene on the X chromosome (WTX), which orchestrates β -catenin degradation in the cytoplasm. The binding of these proteins to β -catenin marks the formation of the destruction complex. The phosphorylation at Ser33 and Ser37 serves as a recognition signal for β -transducin repeat-containing protein (β -TrCP), enabling subsequent ubiquitination by the Skp1, Cullin1 and β -TrCP ubiquitin ligase complex and proteasomal degradation [26]. In addition, SIAH-1 can also mediate the proteasomal degradation of β -catenin with APC [27].

Aberration of the destruction complex affects the aforementioned steady-state regulation, thereby triggering cancer phenotypes. Next, we will focus on the dysfunction of APC, AXIN, GSK-3 β , and CK1, since they are the typical components of the destruction complex. Apc abnormalities represent the most common cause of excessive WNT signaling activation. Truncating mutations in APC are particularly prevalent. APC mutations are implicated in familial adenomatous polyposis and subsequent CRC, with additional reports of its involvement in HCC and ovarian cancer (OC) [28, 29]. Mechanistically, APC truncations disrupt partial binding sites for β -catenin and AXIN, reducing both the assembly efficiency of the destruction complex and its binding capacity to β -catenin. Notably, there are also extensive evidences confirming APC mutation-mediated carcinogenesis through WNT-independent pathways [30].

AXIN is divided into AXIN1 and AXIN2, which acts as a scaffold in the formation of the destruction complex. AXIN2 is believed to have tumor-suppressive effects, while the tumor-suppressive role of AXIN1 remains controversial. Skeptics highlight the rare observation of significant β -catenin accumulation in AXIN1-mutant HCC, a phenomenon later attributed to compensatory AXIN2 activity mitigating β -catenin elevation [31]. Zhang Ruyi et al. resolved this debate by engineering AXIN1-mutant organoids and employing CRISPR/Cas9-mediated correction, demonstrating that AXIN1 mutations, which destroy the structure of AXIN1, indeed elevate β -catenin levels [32]. Further studies by Zhang's group identified three functional domains in AXIN1 regulating WNT signaling in cancer, with deletions in GSK-3 β or β -catenin-binding domains critically disrupting β -catenin regulation [30]. Collectively, these findings establish AXIN1 mutations as β -catenin-dependent drivers of tumorigenesis.

GSK-3 β , a core destruction complex component, was historically classified as a tumor suppressor. However, emerging evidence paradoxically links GSK-3 β to proliferative effects [33]. Its tumor-promoting activity appears WNT-independent and is not discussed here [34]. Genetic mutations of GSK-3 β are rare in cancers, with most mutations localizing to the kinase domain and

substrate-binding pocket [35]. These likely impair phosphorylation capacity, potentially enabling WNT pathway activation. Additionally, post-translational modifications (e.g., aberrant phosphorylation) may inactivate GSK-3 β to promote malignancy [36].

CK1 exhibits context-dependent roles in cancer, varying by isoform. CK1 α acts as a tumor suppressor, while the oncogenic potential of CK1 δ/ϵ remains controversial. CK1 dysregulation in cancer primarily involves alterations in expression levels rather than structural mutations [37]. Reduced CK1 expression, often mediated by promoter methylation, stabilizes β -catenin to drive tumorigenesis [38].

DVL

DVL is a key cytoplasmic phosphoprotein that mediates signaling in the WNT pathway. Its domains (DIX, PDZ, DEP) enable interactions with multiple partners, making it essential for embryonic development and tissue homeostasis. DVL is a typical positive regulator of the canonical WNT pathway and plays a role in aberrant WNT signal transduction. Specifically, upon activation of the WNT signaling pathway, FZD recruit and activate DVL [39]. With the assistance of the LRP6 phosphorylation events mediated by GSK-3 β and CK1, AXIN is recruited to the plasma membrane and binds to the activated DVL [40]. The disruption of the destruction complex attenuates β -catenin ubiquitination and proteasomal degradation, resulting in cytoplasmic accumulation of β -catenin, which leads to the expression of downstream molecules [41]. In addition to its role at the plasma membrane, DVL can also function within the nucleus, where it interacts with phosphorylated c-JUN and β -catenin to form a DVL-c-JUN- β -catenin-TCF transcriptional complex. For this subcellular localization-dependent regulation, post-translational modifications play indispensable roles. For example, acetylation enhances the nuclear localization of DVL [42]. Another instance is that Foxm1 binds to DVL2 and promotes its nuclear translocation as well as the transcriptional activity of WNT/ β -catenin signaling [43]. In addition to playing important roles in aberrant activation of upstream WNT signaling, dysregulation of DVL itself can also drive cancerous phenotypes. Multiple mechanisms may contribute to DVL overexpression. For instance, the loss of non-coding RNAs such as miR-1247-5p leads to upregulation of DVL1, thereby activating canonical signal transduction [44]. Additionally, DVL is extensively degraded during normal WNT signaling, with various proteins involved in maintaining its low steady-state levels. For example, ASPM interacts with DVL2 and inhibits autophagy-mediated DVL2 degradation by reducing its binding to the lipidated form of microtubule-associated protein 1A/1B light chain 3A.

CYP2E1 enhances the interaction between DVL2 and the E3 ubiquitin ligase KLHL12 in cells, promoting DVL2 ubiquitination [45]. The DVL ubiquitination process mediated by these proteins can be reversed, leading to abnormal activation of the WNT signaling pathway [46].

β-catenin

β-catenin is a multifunctional protein, and its nuclear accumulation represents the central event in canonical WNT signaling transduction. As mentioned above, in the OFF state of WNT signaling, β-catenin undergoes ubiquitination to prevent its accumulation, whereas in the activated state, the stabilized β-catenin translocates to the nucleus. In the nucleus, β-catenin displaces GRG corepressors and binds to TCF/LEF transcription factors, thereby activating target genes including *c-MYC*, *c-JUN*, *AXIN2* [47, 48]. In addition to the activation of upstream WNT signaling leading to increased nuclear translocation of β-catenin, other biological events can also mediate its nuclear accumulation: (1) Interactions of β-catenin with other non-WNT pathway components proteins. In epithelial cells, the linkage between β-catenin and E-cadherin forms the classic structure mediating cell adhesion [49]. Reduced E-cadherin promote the release of β-catenin, and increased nuclear translocation of β-catenin can further mediate the downregulation of E-cadherin [50]. Additionally, other binding proteins regulate β-catenin homeostasis. For example, FAT, a canonical WNT pathway inhibitor in cervical cancer (CC), acts like a “nail” to anchor β-catenin to the cell membrane, preventing its nuclear entry. Thus, reduced FAT levels lead to β-catenin dissociation and nuclear translocation [51]. Beyond ubiquitinases within the WNT pathway components, other proteins can also mediate β-catenin ubiquitination. SORBS3-β can recruit UBA1 to enhance the degradation of β-catenin, thereby inhibiting cancer cell invasion and migration. Suppression of SORBS3-β contributes to the accumulation of β-catenin, promoting invasive phenotypes [52]. (2) Pre-translational modifications driving abnormal β-catenin expression. β-catenin is produced after transcription and translation of *CTNNB1*. Multiple non-coding RNAs regulate *CTNNB1* expression. For instance, miR-129-2-3p binds *CTNNB1* to suppress its transcription, while LINC01006 acts as a sponge for miR-129-2-3p, upregulating *CTNNB1* expression [53]. CPEB4 interacts with *CTNNB1* mRNA to promote β-catenin expression, facilitating EMT [54]. (3) *CTNNB1* mutations mediating aberrant β-catenin nuclear translocation. *CTNNB1* mutations are a major cause of WNT pathway hyperactivation and have been detected in numerous cancers [55–57]. Mutations in *CTNNB1* are highly concentrated in N-terminal residues, which form the functional domain for β-TrCP, CK-1, and GSK-3β

binding. These mutations prevent β-catenin phosphorylation and ubiquitination, enabling escape from degradation and promoting nuclear translocation, ultimately driving oncogenic phenotypes [58]. Notably, certain *CTNNB1*-mutant cancers exhibit distinct histopathological features, such as *CTNNB1*-mutant HCC and trichoblastoma-like high-grade endometrial carcinoma, which may guide precise targeted therapies in clinical practice [59, 60].

The non-canonical signaling pathways in cancer

Non-canonical signaling pathways are β-catenin-independent signaling pathways including the WNT-Ca²⁺ and WNT-planar cell polarity (PCP) signaling pathways. Although the non-canonical and canonical signaling pathways are two entirely distinct branches, they exhibit complex interactions with each other. Experimental evidence demonstrates that both WNT-Ca²⁺ and WNT-PCP pathways antagonize β-catenin-dependent transcription through calcium calmodulin mediated kinase II (CaMKII)- and nuclear factor of activated T cells (NFAT)-mediated transcriptional regulation [61]. Similarly, canonical signaling exerts negative regulation on non-canonical pathways. LRP6, a co-receptor of the canonical signaling pathway, can bind to WNT5A, which preferentially activates the non-canonical signaling pathway, acting as a decoy receptor [62]. Intriguingly, WNT3A, a prototypical canonical ligand, has been shown to activate non-canonical signaling under specific cellular contexts [63]. Given the complex interplay of signaling, it is challenging to study the roles of β-catenin-dependent and β-catenin-independent signaling pathways in cancer independently, although numerous studies have demonstrated the roles of both pathways in promoting and suppressing cancer. Compared with canonical signaling, the molecular mechanisms governing downstream non-canonical signal transduction are still not fully understood. Next, we will describe the currently known molecular mechanisms of the signaling pathways.

The WNT-PCP signaling pathway plays a role in regulating planar cell polarity, manifested by the asymmetric enrichment of proximal and distal transmembrane complexes. Similar to canonical signaling pathways, specific WNTs and FZDs are involved in the activation of the signaling pathway, such as WNT4, WNT5A, WNT5B, WNT7B, and WNT11, as well as FZD3, FZD6, and FZD7 [64]. At the proximal end, the transmembrane complex is primarily composed of Vang-like (VANGL), cadherin EGF LAG seven-pass G-type receptor (CELSR), PRICKLE, inturmed (INTU), and DVL. PRICKLE can bind to DVL to prevent the localization of Inversin (INVS) to the proximal end. At the

distal end, the transmembrane complex mainly consists of FZD, CELSR, INVS, and DVL. Although the components of the transmembrane complex have been identified, the specific mechanisms of by which WNTs bind to CELSR or VANGL remain unclear [65]. Nevertheless, numerous studies have confirmed the role of VANGL and CELSR dysregulation in cancer progression. Studies have reported that overexpression of VANGL1 and VANGL2 enhances the migratory capacity of cancer cells. In addition to VANGL overexpression, the downregulation of inhibitory factors that bind to VANGL can also lead to hyperactivation of non-canonical WNT signaling. For example, loss of Nrdp1 disrupts its interaction with VANGL, thereby inhibiting DVL ubiquitination and upregulating WNT signaling [66]. Interestingly, Anastas et al. identified a complex containing VANGL1, NOS1AP, and Scribble localized at the leading edge of migrating BC cells. Disruption of this complex reduces tumor cell migration. This complex is not expressed in normal tissues. Thus, VANGL1-mediated formation of this ternary complex may signify enhanced migratory capacity in cancer cells [67]. For CELSR, its expression is significantly higher in lung adenocarcinoma tissues than in adjacent normal tissues, associated with high cancer migratory capacity [68].

When the WNT-PCP signaling pathway is activated, INVS is localized at the distal end. DVL is found to be phosphorylated, leading to the formation of the DVL-PAR6 complex and the recruitment of SMURF. Subsequently, PRICKLE bound to PAR6 is ubiquitinated and degraded at the distal end [69] (Fig. 2). Currently, multiple co-receptors have been identified to participate in the activation of the WNT-PCP signaling pathway such as receptor-like tyrosine kinase (RYK), muscle-skeletal receptor Tyr kinase (MUSK), and protein tyrosine kinase 7 (PTK7) [70]. Upon the binding of WNT to FZD, DVL is phosphorylated, subsequently leading to the activation of Dvl-associated activator of morphogenesis (DAAM) and RAC1. On one hand, DAAM activates Ras homolog family member A (RHOA), which in turn activates RHO-associated coiled-coil-containing protein kinase (ROCK) and diaphanous 1 (DIA1), with the latter activating mitogen-activated protein kinase (MLCK) [71]. On the other hand, RAC1 activates JNK, leading to the phosphorylation of c-JUN and CapZ-interacting protein (CapZIP). DIA1, MLCK, and CAPZIP all contribute to actin polymerization. Finally, c-JUN translocates to the nucleus to initiate the transcription of target genes [72] (Fig. 2). Cell polarization and changes in motility are the primary phenotypes associated with the activation of the WNT-PCP pathway [73].

In the aforementioned mechanism, RAC1 and RHOA, members of the small GTPase family, determine the

mutually antagonistic nature of the two branches of the PCP pathway. RAC1 and RHOA act as molecular switches by cycling between GTP-bound active and GDP-bound inactive states, thereby spatiotemporally regulating cytoskeletal dynamics. Dysregulation of the two components is frequently associated with cancer phenotypes. Multiple mechanisms can lead to aberrant activation of RAC1. In addition to enhanced signaling from upstream WNT ligands and FZD overexpression, dysregulation of post-translational modifications is another key contributor to RAC1 hyperactivation and overexpression. Abnormal phosphorylation and ubiquitination of RAC1 disrupt its GTP-binding capacity, thereby inhibiting signal transduction in the non-canonical pathway. Loss-of-function mutations in the tumor suppressor HACE1 result in a sharp reduction in RAC1 ubiquitination, promoting cancer invasion and migration. Furthermore, alternative splicing or mutations in the *RAC1* gene can impede GTP dissociation or enhance GTP-GDP exchange efficiency, leading to persistent WNT pathway activation [74]. Similarly, defective ubiquitination and phosphorylation can cause RHOA hyperactivation. For instance, the inhibition of phosphorylation at the Ser26 site activate RHOA [75]. Unlike *RAC1* mutations, *RHOA* mutations often downregulate WNT signaling output [76]. For example, a glycine-to-valine substitution in RHOA's nucleotide-binding pocket introduces a bulky side chain, reducing GTP-binding capacity [77]. Upstream signals, such as FZD overexpression, may also suppress RAC1- and RHOA-mediated WNT pathway activity. Research by C. Fukukawa et al. demonstrated that FZD10 overexpression downregulates RHOA activity, disrupting actin cytoskeletal structures, but upregulates DVL/RAC1/JNK pathway activity to promote synovial sarcoma progression [78]. This suggests that excessive activation of upstream signaling can promote cancer progression through bidirectional regulation of these two pathways.

The WNT-Ca²⁺ signaling pathway was first reported in the 1990s [79]. WNT5A and FZD2 are primarily involved in the activation of the WNT-Ca²⁺ signaling pathway [80]. FZD activates coupled heterotrimeric G proteins, which in turn stimulate phospholipase C (PLC). This activation results in the generation of inositol 1,4,5-trisphosphate (IP3) and 1,2-diacylglycerol (DAG). IP3 then triggers the release of Ca²⁺ into the cytoplasm, where it accumulates in significant amounts and functions as a second messenger. This Ca²⁺ interacts with CaMKII, calcineurin (CaN), and protein kinase C (PKC) [81]. Subsequently, CaMKII and CaN activate NFAT, leading to the transcription of specific target genes (Fig. 3). During cancer progression, the WNT/Ca²⁺ pathway exerts bidirectional regulatory effects, either promoting or suppressing

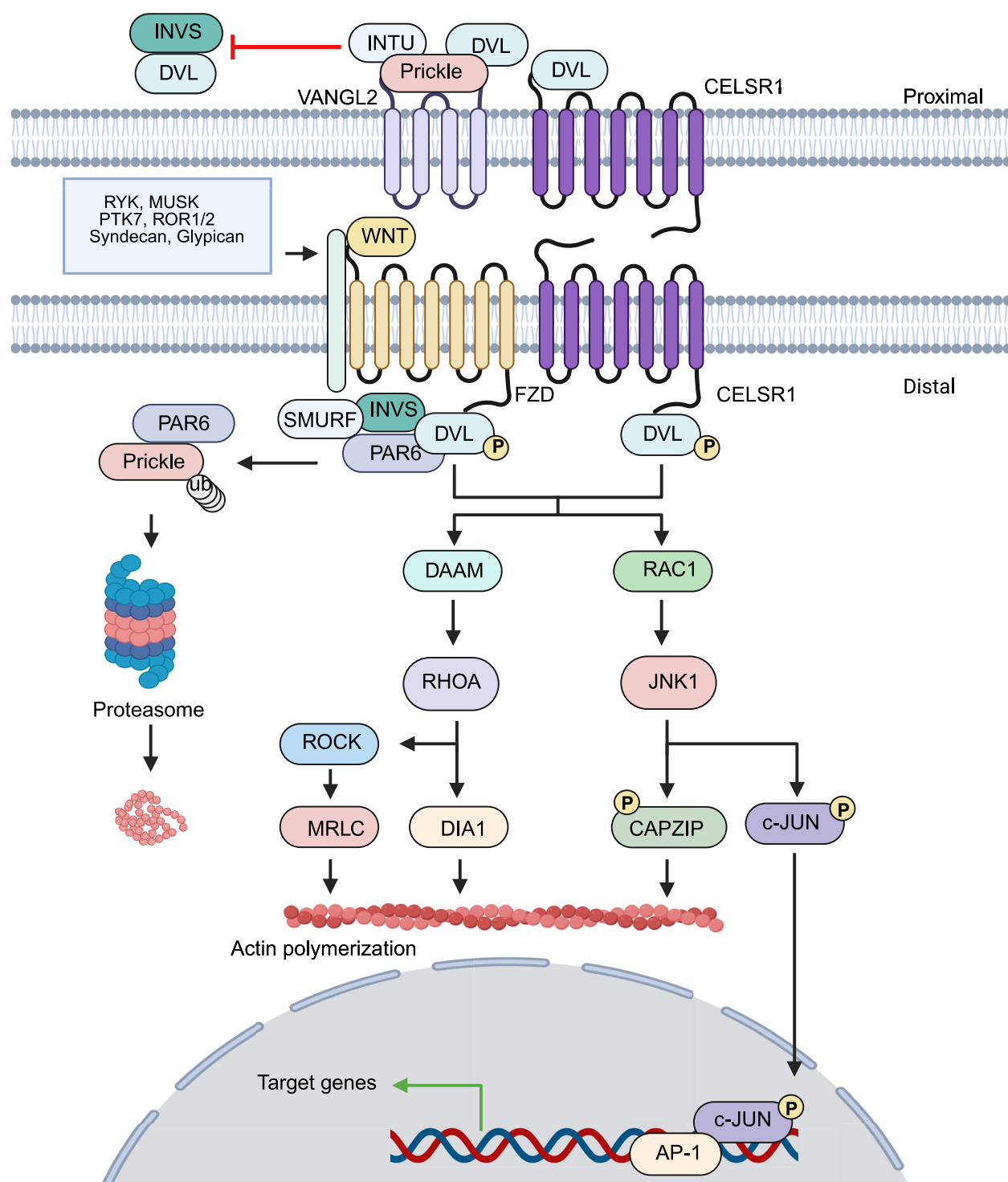


Fig. 2 Signal transduction of the WNT-PCP pathway. The core signaling components of the WNT-PCP, such as VANGL and FZD form asymmetrically distributed transmembrane protein complexes on the cell membrane, regulating cell polarity through spatial arrangement. This process is characterized by FZD binding to DVL to initiate downstream signal transduction, while VANGL remains unbound to DVL. Upon activation by FZD, DVL promotes Daam1-mediated activation of RHOA, which subsequently triggers ROCK activation. Concurrently, DVL activates RAC1, thereby facilitating JNK1-dependent phosphorylation of CAPZIP and c-JUN. The activation of the WNT-PCP pathway orchestrates a cascade of downstream events, including actin phosphorylation and transcriptional regulation of target genes

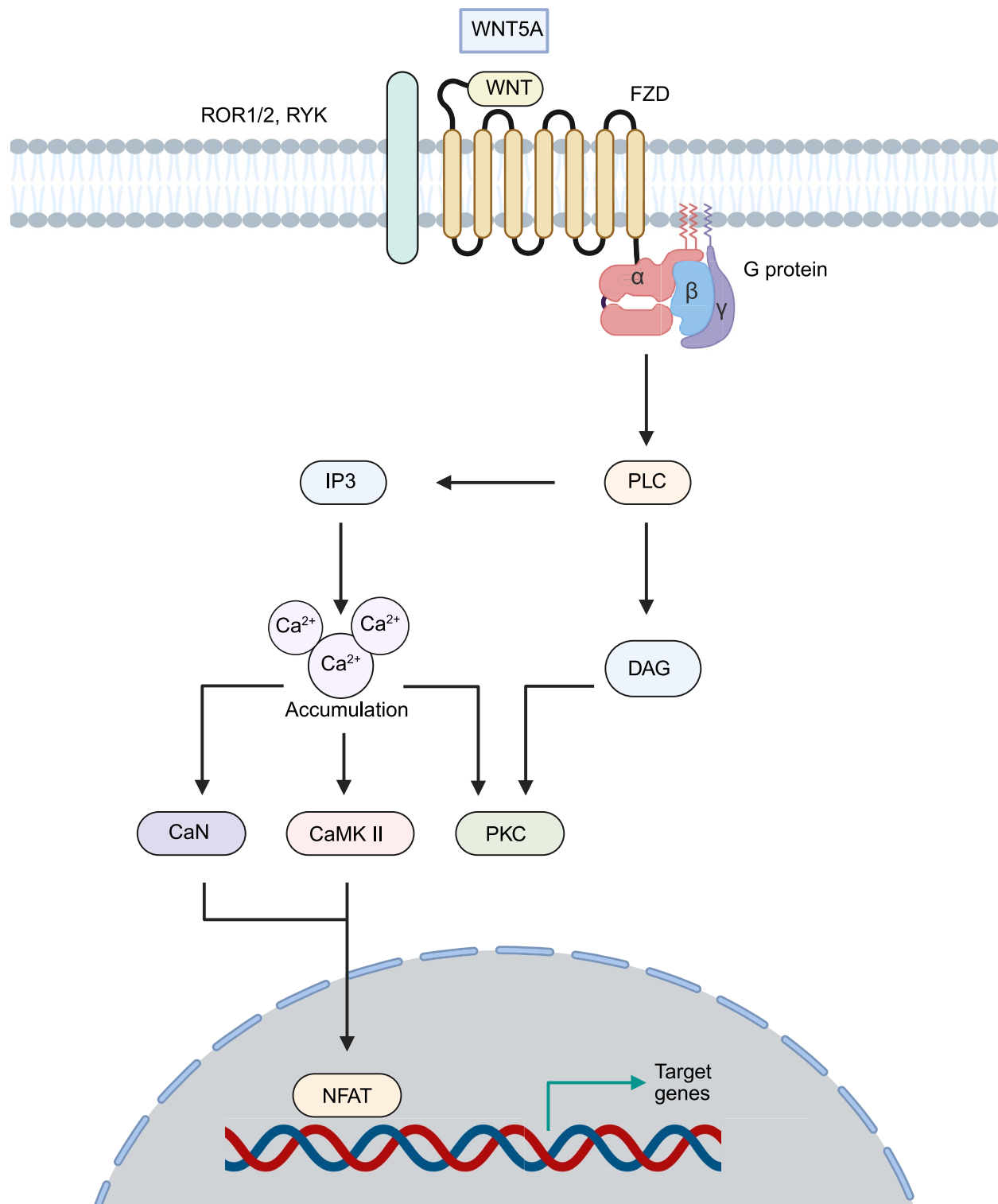


Fig. 3 Signal transduction of the WNT-Ca²⁺ pathway. The WNT ligand binds to FZD and its co-receptor, activating heterotrimeric G proteins. The G proteins then mediate the hydrolysis of PLC into IP₃, triggering Ca²⁺ release, and into DAG, which activates PKC. The released Ca²⁺ further activate CaN, CaMKII, and PKC, while the generated DAG also contributes to PKC activation. These signaling proteins collectively regulate downstream cellular events. Among them, NFAT serves as a transcription factor, whose activity is modulated by CaN and CaMKII, ultimately driving the transcription of target genes

tumorigenesis. Regarding the tumor-suppressive role, WNT5A, a prototypical tumor-suppressive WNT, inhibits cancer progression by activating the WNT/ Ca^{2+} pathway, thereby enhancing CD8^+ T-cell cytotoxicity and improving the tumor immune microenvironment [82]. In OC, the WNT/ Ca^{2+} pathway has been shown to reduce chemotherapy resistance [83]. For the cancer promotion, phosphorylation induces abnormal CaMKII activation, leading to β -catenin phosphorylation and degradation, thereby enhancing cancer cell motility [84]. In prostate cancer (PCa), CaMKII overexpression has been observed. Inhibiting CaMKII reduces PCa cell motility, while CaMKII overexpression also suppresses transcription of β -catenin and its downstream targets [85]. This suggests that the specific role of WNT/ Ca^{2+} pathway hyperactivation in cancer may depend on its degree of suppression of the canonical WNT pathway. However, the specific switching mechanisms remain to be further elucidated.

Non-canonical pathways play crucial roles in regulating cell polarity, promoting cell motility and invasion, and maintaining stem cell populations [86]. Dysregulation of cellular processes caused by aberration in non-canonical signaling pathways serves as a promoter of tumorigenesis and cancer progression [87]. Therefore, continuous refinement of the molecular framework underlying non-canonical signal transduction is essential for strengthening the established link between aberrant WNT signaling and neoplasia.

Crosstalk between WNT signaling and other pathways in cancer

Aberrant activation of the WNT signaling pathway is a key driver in the initiation and progression of various cancers. However, within the complex tumor microenvironment, the WNT pathway does not function in isolation; rather, it engages in extensive crosstalk with other signaling pathways, such as the TGF- β , Hippo, Hedgehog, Notch, and NF- κ B pathways. This inter-pathway communication is mediated through diverse molecular mechanisms. Here, we map the crosstalk between WNT and other signaling pathways based on the components of the WNT cascade, aiming to provide a comprehensive understanding of the underlying mechanisms (Fig. 4). Such intricate crosstalk enables cancer cells to integrate multiple pro-survival signals, enhancing their proliferative capacity, maintaining stemness, promoting EMT, and conferring resistance to apoptosis. Therefore, elucidating the crosstalk mechanisms between WNT and other pathways is critically important theoretically and clinically, as it may facilitate the development of combination anticancer strategies targeting multiple pathways and help overcome resistance to existing targeted therapies.

WNT signaling pathways and TGF- β signaling pathway

The classic transforming growth factor- β (TGF- β) signaling pathway is also known as the SMAD signaling pathway, which acts as the transcription factor for the signaling pathway. TGF- β binds to the Ser/Thr kinase and the tyrosine kinase T β RI and T β RII to form a heteromeric complex, thereby activating the classic TGF- β signaling pathway. Due to conformational changes caused by phosphorylation of T β RI, the GS domain shifts from binding the signaling inhibitor immunophilin FK506 binding protein 1A (FKBP12) to binding the signaling effectors, the receptor-activated SMADs (R-SMADs). The R-SMADs are activated by phosphorylation modification by T β RI and ultimately enter the nucleus to regulate the transcription of target genes. In addition to the classic TGF- β signaling pathway, TGF- β can also regulate SMAD-independent signaling pathways [88]. TGF- β signaling pathway plays a crucial role in promoting cell proliferation, immune regulation, tissue repair, and extracellular matrix regulation [88]. It has been demonstrated that TGF- β and WNT signaling pathways crosstalk through signaling components such as SMAD, AXIN, DVL, and β -Catenin. TGF- β activates the WNT signaling pathway through multiple mechanisms. For example, TGF- β can inhibit the transcription of DKK1 and SFRP1 in a p38-dependent manner, thereby activating the WNT/ β -Catenin signaling pathway [89]. Additionally, TGF- β suppresses the negative regulator Wilms' Tumor 1 of β -catenin, promoting the expression of WNT target genes such as *MMP-9*, *SNAIL1*, *PAI-1*, and *FSP1* [90]. Furthermore, SMAD7 acts as an adaptor protein to recruit p38 MAPK. This recruitment promotes p38 phosphorylation and inhibiting GSK-3 β activity by phosphorylating Ser9. Due to GSK-3 β inactivation, β -catenin accumulates in the cytoplasm. The C-terminus of SMAD7 binds APC, and its N-terminus binds β -catenin, forming a ternary complex. APC anchors the complex to the plus ends of microtubules, promoting polarized extension and migration of tumor cells [91]. In addition to inactivating GSK-3 β to activate β -Catenin, TGF- β can activate the canonical WNT signaling pathway in a β -catenin-independent manner. Experiments have shown that even when LEF1 lacks the β -catenin binding domain (LEF1 Δ 20), TGF- β can still activate the WNT signaling pathway through the interaction between SMAD and LEF1 [92]. On the other hand, the WNT signaling pathway can also regulate TGF- β : the WNT signaling pathway mainly exerts its influence on TGF- β by regulating the SMAD linker region. When the WNT signaling pathway is off, GSK-3 β phosphorylates the SMAD linker region. This phosphorylation promotes ubiquitination and degradation of SMAD proteins, thereby inhibiting the transcription of target genes of the TGF- β signaling

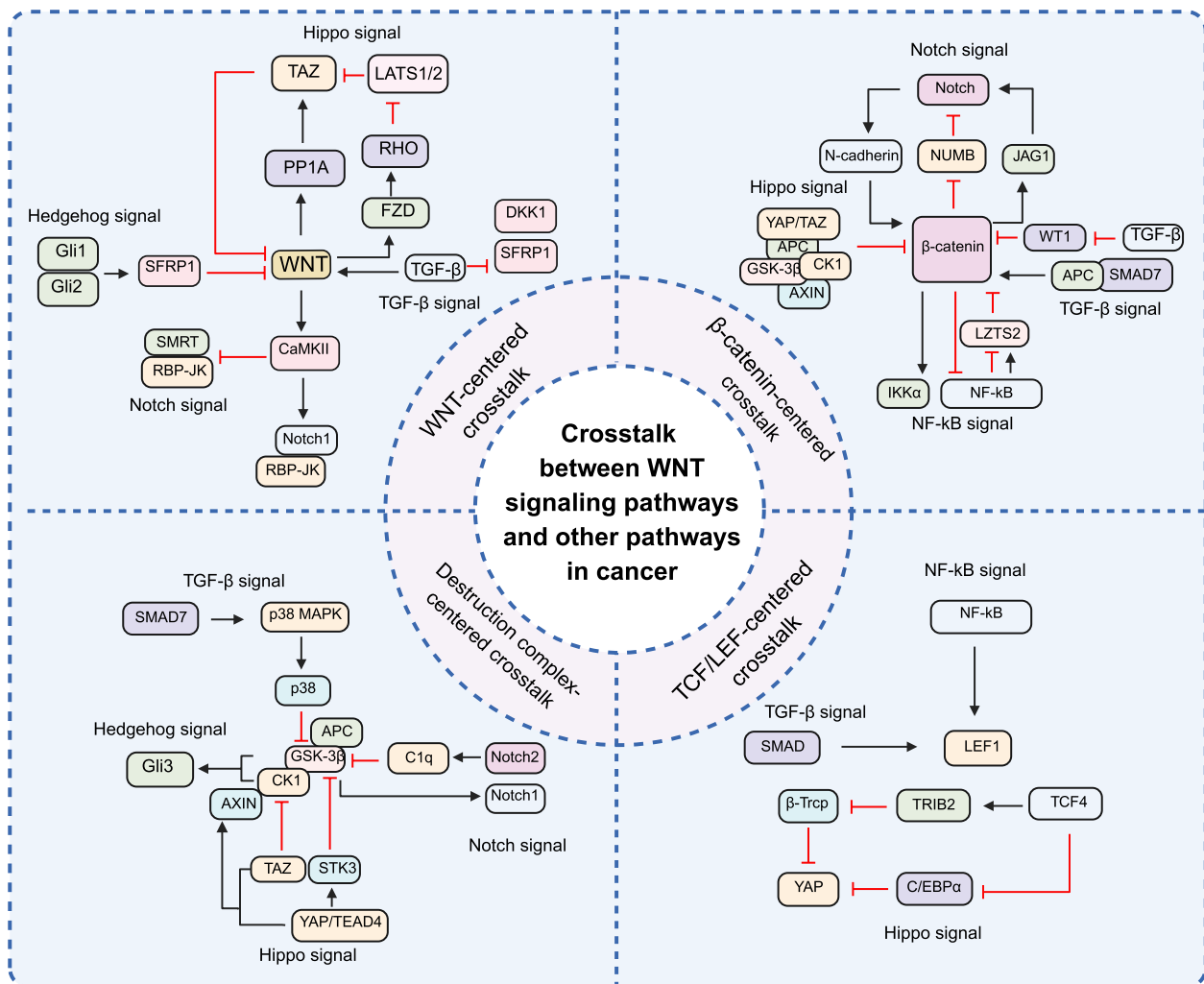


Fig. 4 Crosstalk between WNT signaling and other pathways in cancer. The WNT signaling pathway primarily crosstalks with the TGF- β , Hippo, Hedgehog, Notch, and NF- κ B signaling pathways, mediated by key components including WNT ligands, β -catenin, the destruction complex, and TCF/LEF transcription factors

pathway. Additionally, it has been reported that AXIN, through its C-terminal region interacting with SMAD3, can promote the activation of the SMAD3 protein by TβRI, leading to the dissociation of SMAD3 from AXIN and TβRI [93]. Studies have found that blocking one of the signaling pathways affects the activation of the other. For example, the WNT/β-Catenin inhibitor ICG-001 and its derivatives can block TGF-β-induced SMAD2/3 phosphorylation. Deleting TβRII in epithelial cells simultaneously blocks the WNT/β-Catenin signaling pathway and the TGF-β signaling pathway [90].

WNT signaling pathways and Hippo signaling pathway

The transcriptional coactivators Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding

motif (TAZ) are characteristic components of the Hippo signaling pathway, whose phosphorylation activities regulate the expression of downstream genes of Hippo [94]. Unphosphorylated YAP/TAZ primarily bind to the TEAD family of transcription factors in the nucleus, activating genes associated with cell proliferation and survival. The Hippo and WNT signaling pathways have been shown to crosstalk through signaling components such as YAP/TAZ, β -Catenin, APC, AXIN, and DVL. YAP/TAZ primarily act as inhibitors of the WNT signaling pathway. In BC, TAZ can disrupt the interaction between CK1 and DVL, thereby inhibiting activation of the WNT3A signaling pathway. Upon knockdown of TAZ, β -Catenin accumulates in the cytoplasm and DVL becomes phosphorylated. YAP/TAZ also directly bind to

the N-terminal region of β -catenin through their TEAD-binding domain, preventing β -catenin nuclear translocation and thereby inhibiting WNT target gene expression [95]. However, in GC cells, the Hippo and WNT signaling pathways cooperatively activate each other. The YAP1/TEAD4 complex directly binds to the Serine/threonine kinase 3 (STK3) promoter and promotes its expression, which is a key regulator of the Hippo signaling pathway. STK3 directly binds to the N-terminal domain of GSK-3 β , promoting its phosphorylation at Ser9, leading to its inactivation and the cytoplasmic accumulation of β -catenin, thereby promoting malignant phenotypes and 5-FU resistance in GC [96]. Additionally, YAP/TAZ have been shown to be components of the β -catenin degradation complex in the WNT pathway, and the recruitment of β -TrCP depends on YAP/TAZ. Research has demonstrated that when the WNT signaling pathway is inactive, YAP/TAZ directly bind to AXIN1 to become components of the β -catenin destruction complex, which anchors YAP/TAZ in the cytoplasm, inhibiting their nuclear translocation and activation of downstream genes. Concurrently, knockdown of YAP/TAZ significantly reduces the binding of β -TrCP to the AXIN1 complex, which is essential for the ubiquitin-mediated degradation of β -catenin. However, when WNT signaling is activated, AXIN1 binds to the LRP6 receptor, prompting the dissociation of YAP/TAZ from the destruction complex and their entry into the nucleus. In the nucleus, YAP/TAZ, in complex with TEAD transcription factors, cooperate with β -catenin, which itself functions through TCF/LEF transcription factors, collectively driving cell proliferation, maintaining stem cell properties, and promoting tumor growth [97]. The WNT signaling pathway also activates the Hippo signaling pathway. In HCC cells, upon activation of the WNT/ β -Catenin pathway, the TCF4 transcription factor directly binds to the enhancer region of the TRIB2 gene, driving its expression. This process relies on FoxA factors to maintain an open chromatin state. TRIB2 acts as an adaptor protein, binding the E3 ubiquitin ligase β -TrCP, thereby blocking its ubiquitin-mediated degradation of YAP and consequently enhancing YAP stability. Furthermore, TRIB2 can down-regulate C/EBP α protein levels, relieving the inhibition of YAP transcriptional activity by C/EBP α , thus promoting hepatocyte survival and transformation [98]. Canonical WNT signaling (WNT3A) mediates the dephosphorylation of TAZ at Ser89/306/309 by phosphatase PP1A, inhibiting its binding to 14-3-3 proteins and ubiquitin-mediated degradation, thereby stabilizing TAZ and promoting its nuclear translocation [99]. The β -catenin/TCF complex can bind to a DNA enhancer element within the first intron of the YAP gene, thereby promoting YAP expression. Additionally, a negative feedback mechanism

exists between the non-canonical WNT signaling pathway and the Hippo signaling pathway. WNT3A and WNT5A/B promote YAP/TAZ activity through FZD/ROR-G $\alpha_{12/13}$ -Rho GTPases-Lats1/2, while the activated YAP/TAZ-TEAD complex upregulates the expression of secreted WNT inhibitors, blocking the canonical WNT signaling pathway [100].

WNT signaling pathways and Hedgehog signaling pathway

The Hedgehog signaling pathway has two major receptors: the Patched (PTC) and the Smoothened (SMO). When the Hedgehog signal is off, PTC promotes the phosphorylation of CI/GLI by PKA, GSK3, and CK1, followed by the generation of CIR/GLIR-repressed Hedgehog target genes via the Slimb/ β -TrCP-mediated ubiquitin and proteasome degradation pathway. Conversely, binding of Hedgehog to PTC enables SMO to transduce signals downstream, altering the balance between the activated form (CIA/GLIA) and the repressed form (CIR/GLIR) of CI/GLI proteins. SMO primarily promotes the formation of CIA/GLIA and thus the expression of target genes by inhibiting the production of CIR/GLIR, stimulating Fu/Ulk3/Stk36-mediated phosphorylation of CI/GLI, and antagonizing Sufu [101]. GLIs serve as a pivotal transcriptional regulator within the Hedgehog signaling pathway. The majority of the crosstalk between the Hedgehog and WNTs signaling pathways revolves around GLIs [102]. For instance, the transcription factors GLI1 and GLI2 directly bind to the *sFRP-1* promoter, modulating its expression. Upon activation of the Hedgehog pathway, a significant increase in sFRP-1 mRNA and protein levels is observed. High expression of sFRP-1 can inhibit WNT1-induced cytoplasmic accumulation of β -catenin [103]. On the other hand, Wang B et al. have elucidated the key molecular mechanism of GLS3 protein processed in the Hedgehog signaling pathway that the C-terminal region of GLI3 is sequentially phosphorylated by PKA, CK1, and GSK3. Subsequently, the WD40 domain of β -TrCP specifically binds to the phosphorylated GLI3 fragment, participating in GLI3 processing. GLI3 undergoes polyubiquitination within the cell, and the proteasome may mediate specific cleavage of GLI3 through partial degradation rather than complete destruction [104]. Additionally, CK1 can also activate GLIs. The crosstalk between Hedgehog and WNT signaling pathways also significantly influences the onset and progression of diseases [105]. In osteoarthritis, Hedgehog induces the expression of a dominant negative isoform of *TCF7L2*, selectively inhibiting β -catenin-induced expression of the fibroblast growth factor 18 gene [106]. In CRC cells, inhibition of the Hedgehog pathway using cyclopamine significantly reduces β -catenin-Tcf transcriptional activity, and this effect can

be reversed by exogenous SHH protein, indicating that Hedgehog has a positive regulatory effect on WNT signaling. β -catenin can enhance the transcriptional activity of GLI1, suggesting that WNT signaling may directly regulate the downstream effector of the Hedgehog pathway through β -catenin. Hedgehog-WNT crosstalk drives EMT and tumor invasion cooperatively [107].

WNT signaling pathways and Notch signaling pathway

The Notch signaling pathway exhibits intricate crosstalk with the WNT signaling pathway [108]. On one hand, the Notch signaling pathway can regulate the activity of the WNT signaling pathway. In chronic lymphocytic leukemia (CLL), CLL cells express Notch ligands, which bind to Notch receptors on the surface of bone marrow stromal cells (BMSCs), specifically activating Notch2 in BMSCs. This activation is manifested by elevated levels of the Notch2 intracellular domain (ICD) and increased nuclear localization. Notch2 acts as a transcriptional regulator in BMSCs, inducing the expression of complement factor C1q. This, in turn, inhibits GSK3- β activity and reduces its ubiquitin-mediated degradation, thereby stabilizing β -catenin. Additionally, Notch2 upregulates the expression of N-cadherin in CLL cells, further stabilizing β -catenin and enhancing its nuclear translocation and transcriptional activity through interaction with N-cadherin [109]. However, in CRC, ligand of numb protein-X 2, a regulator of Notch, can enhance the activation of the WNT signaling pathway [110]. Aberrant activation of the Notch pathway can also promote the invasiveness and metastasis of oral squamous cell carcinoma (OSCC) by upregulating the expression of c-MYC and β -catenin genes [111]. On the other hand, the WNT signaling pathway primarily facilitates the activation of the Notch signaling pathway. For instance, *Jagged 1* (*JAG1*) is a direct target gene of β -catenin, which can enhance the activity of the Notch signaling pathway by activating the transcription of *JAG1* [112]. In BC, keratin 19 (KRT19) binds to the β -catenin/Rac1 complex to inhibit NUMB expression, and relieve NUMB-mediated suppression of the Notch pathway, leading to enhanced Notch signaling [113]. Additionally, KRT19 can directly interact with the β -catenin/RAC1 complex, promoting the nuclear translocation of β -catenin. Enhanced nuclear translocation of β -catenin inhibits the Notch signaling pathway by upregulating NUMB expression. Conversely, KRT19 knockdown suppresses β -catenin nuclear translocation, reduces NUMB expression, and activates the Notch pathway. In CD133/CXCR4/ALDH1 cancer stem cell (CSC), the expression of KRT19 is extremely low, leading to reduced β -catenin nuclear translocation, decreased NUMB expression, excessive activation of the Notch pathway, and consequently enhanced stem cell

properties [114]. Gu, B. et al. discovered that the Notch signaling pathway and the WNT/ β -catenin signaling pathway exhibit tight cross-regulation during the lineage differentiation of mammary stem cells (MaSCs), and the chromatin effector PYGO2, acting as a histone methylation reader, is the key molecule mediating this regulation by recruiting β -catenin to bind to the Notch3 gene regulatory region, thereby maintaining a chromatin state at this locus characterized by the simultaneous presence of an activating mark (H3K4me3) and a repressive mark (H3K27me3), thus suppressing aberrant Notch3 activation. Loss of PYGO2 causes a shift in the chromatin state towards activation, releasing Notch3 expression. The WNT/ β -catenin pathway suppresses Notch3 via PYGO2, maintaining the self-renewal and basal cell characteristics of MaSCs [115]. GSK-3 β also mediates the phosphorylation of Ser and Thr on the Notch ICD-1, thereby facilitating its nuclear localization, increasing its transcriptional activity, and enhancing its stability [111]. Beyond the canonical WNT signaling pathway, WNT-Ca²⁺ also interacts with the Notch signaling pathway. WNT5A enhances the transcriptional activity of downstream target genes induced by the Notch1 ICD in a dose-dependent manner, and this process is dependent on CaMKII. Specifically, CaMKII itself can dose-dependently activate the transcription of Notch1 downstream target genes. CaMKII promotes the binding of RBP-Jk to Notch1-IC while inhibiting the binding of RBP-Jk to SMRT by binding to the RID1 domain of SMRT and phosphorylates its Ser-1407 residue, promoting proteasomal degradation of SMRT, thereby enhancing the promoter activity of Notch-responsive genes [116].

WNT signaling pathways and NF- κ B signaling pathway

Both inhibitor of nuclear factor- κ B (NF- κ B) subunit α (IKK α) and β (IKK β) are activators of the NF- κ B signaling pathway. However, they exhibit differences in the regulation of β -catenin. IKK β prevents the nuclear accumulation of β -catenin and inhibits its transcriptional activity, while IKK α promotes its nuclear localization and enhances its transcriptional activity, thereby positively regulating the WNT signaling pathway. The N-terminus of β -catenin contains a conserved sequence DSGXXS, which is the phosphorylation site for IKK [117]. Carayol, N et al. found that IKK α plays an inhibitory role in both the AXIN/APC/GSK-3 β complex-dependent phosphorylation and the non-classical SIAH-1-mediated GSK-3 β -independent β -catenin degradation pathways. IKK α directly interacts with β -catenin, inhibiting its ubiquitination process, thereby blocking the destruction of β -catenin by the ubiquitin-proteasome system in both degradation pathways [118]. Huang, F.I. et al. also found that in HCC cells and BC cells, there are multiple NF- κ B

binding sites upstream of the LEF1 transcription start site. NF- κ B can directly bind to these sites upstream of the LEF1 transcription start site, thereby activating LEF1 transcription [119]. Furthermore, in MCL cells, β -catenin and NF- κ B form a complex through protein–protein interactions, bind to the NF- κ B DNA consensus sequence, and directly promote the transcription of NF- κ B target genes. Ma, B. et al. discovered that NF- κ B regulation of the β -catenin/TCF pathway is cell type-specific: In colon, liver, and BC cells, NF- κ B activation can upregulate LZTS2, which binds to β -catenin, preventing its entry into the nucleus and inhibiting its transcriptional activity. However, in glioma cells, NF- κ B instead downregulates LZTS2 to promote the activity of β -catenin [120]. Chang, J. et al. found that in mesenchymal stem cells (MSCs), the pro-inflammatory factors TNF and IL-17 can activate the IKK–NF- κ B signaling pathway. TNF induces the mRNA expression of SMURF1 and SMURF2 via IKK–NF- κ B, while IL-17 induces SMURF2 in an IKK-dependent manner. After TNF treatment, the NF- κ B subunit p65 directly binds to the promoter regions of SMURF1 and SMURF2 and promotes their expression, which inhibits the WNT/ β -catenin signaling pathway [121]. In addition to its antagonistic role, the Ectodysplasin A (EDA)/EDA receptor/NF- κ B pathway also activates the expression of epithelial Shh and Cyclin D1, which are likewise target genes of the WNT signaling pathway [122]. The WNT signaling pathway also exerts regulatory effects on NF- κ B. In human colon and BC cells, overexpressed β -catenin can form a complex with the RelA and p50 subunits of NF- κ B, reducing NF- κ B's DNA-binding ability and transcriptional activity, thereby inhibiting the expression of its target genes. However, in endometrial cancer (EC) cells, NF- κ B's RelA can compete with β -catenin for binding to the co-activator p300, inhibiting the transcriptional activity of β -catenin/TCF [120]. Researchers have found that WNT/ β -catenin can transcriptionally upregulate coding region determinant-binding protein (CRD-BP), which binds and stabilizes the mRNA of β -TrCP, promoting β -TrCP-mediated degradation of I κ B- α and activating the NF- κ B signaling pathway [123].

Dysregulation of the WNT pathway in oncogenesis across various cancers

The WNT signaling pathway, as a core regulatory hub in tumor progression, is abnormally activated in driving the advancement of 30%–40% of malignant tumors, including BC, CRC, Glioblastoma multiforme (GBM), HCC, and PCa. External stimuli, such as gut microbiota, can induce this abnormal activation, driving oncogene expression through the β -catenin/TCF transcription complex. This pathway exhibits significant tissue-specific

regulatory patterns: in CRC, APC mutations primarily drive pathway activation, while in HCC, *CTNNB1* mutations are more common. Here, we systematically elucidate the mechanistic underpinnings through the lens of both canonical and non-canonical WNT signaling pathways in different cancers.

Breast cancer

Within the canonical WNT/ β -catenin pathway, the aberrant nuclear accumulation of β -catenin represents the central oncogenic event [25]. In BC, this phenomenon is predominantly orchestrated through the dysregulation of three key regulatory nodes: WNT ligands, FZD/LRP receptor complexes, and the β -catenin destruction complex. Sustained activation of WNT ligands not only initiates mammary tumorigenesis but also facilitates metastatic progression [124]. Therapeutic intervention targeting specific FZD receptor subtypes (e.g., FZD1/2/7) effectively attenuates β -catenin nuclear translocation, resulting in significant reduction of tumor-initiating cell populations and suppressed growth of basal-like breast tumor organoids [125]. AXIN, the central scaffolding protein of the destruction complex, undergoes phosphorylation at Ser45, which impairs its function in β -catenin degradation, thereby promoting β -catenin stabilization and nuclear accumulation [126]. β -catenin nuclear translocation can occur via mechanisms that bypass canonical WNT upstream signaling. Recent studies reveal that SHC4 mediates phosphorylation of Src kinase at tyrosine 419, which in turn catalyzes phosphorylation of β -catenin at critical residues that facilitate nuclear translocation. This signaling cascade potently upregulates key mediators of BC invasion and metastasis, including CD44 and MMP-7 [127]. Moreover, the RNA helicase DEAD-box helicase 5 (DDX5) functions as a molecular chaperone that protects β -catenin from proteasomal degradation, while Aurora-A kinase interacting protein 1 (AURKAIP1) enhances this stabilization by preventing ubiquitin-mediated degradation of DDX5. Together, these interactions create a positive feedback loop that amplifies β -catenin signaling and accelerates BC progression [128].

Non-canonical pathways also play crucial roles in BC progression. The WNT-PCP pathway is associated with the efficacy of various BC therapeutics. Upregulation of the WNT-PCP has been demonstrated to correlate with resistance to anti-estrogen therapy and doxorubicin in BC [129]. This doxorubicin resistance may be indirectly mediated through activation of the WNT5A/ROR2/c-JUN signaling axis. Complementary to cellular and molecular studies, bioinformatics analysis identifies WNT5A/ROR2 as a prototypical WNT-PCP pathway in BC, showing significant co-expression with IL16, SULF1, PLXNA2 and RASGRF2, while predicting responsiveness

to MEK1/2 inhibitors [130]. Beyond WNT5A, WNT11 may participate in ROR2-mediated signaling to promote BC invasiveness [131]. The role of WNT- Ca^{2+} signaling in BC development remains controversial. On one hand, WNT- Ca^{2+} signaling suppresses canonical WNT transduction, where elevated cytosolic Ca^{2+} activates CaMKII to promote β -catenin phosphorylation and degradation, consequently reversing EMT [132]. Conversely, calcineurin activation enhances NFATC3 nuclear translocation to stimulate vascular endothelial growth factor expression, angiogenesis and tumor growth [133]. These paradoxical findings underscore the need for more comprehensive investigations into WNT- Ca^{2+} signaling in BC. Elucidation of these mechanisms provides potential therapeutic targets for clinical BC management.

Colorectal cancer

In contrast to BC, aberrant activation of the WNT signaling pathway in CRC predominantly stems from mutations in WNT pathway component genes. These WNT-related gene mutations show the highest incidence in rectal cancers [134]. Luís Nunes et al. established a comprehensive mutational landscape of CRC, revealing recurrent mutations in WNT pathway genes including *APC*, *AXIN2*, *CTNNB1*, *RNF43*, *TCF12* and *TCF7L2* [135]. Another study demonstrated age-dependent mutation patterns, with *RNF43* mutations predominating in early-onset CRC versus *APC* mutations in adult-onset cases [136]. *APC* mutations represent the principal lesions driving WNT hyperactivation in CRC, comprising missense mutations and more prevalent truncating variants [137]. *APC* mutations inactivate the destruction complex, impairing β -catenin degradation and promoting nuclear accumulation [138]. Recent studies have provided mechanistic refinements to this paradigm, demonstrating that AXIN undergoes liquid–liquid phase separation to organize destruction complex condensates under physiological conditions [139]. *APC* truncations disrupt complex assembly by impairing recruitment of GSK-3 β and CK1 α into these liquid droplets [140]. Truncated APC also fails to suppress USP10, which stabilizes β -catenin through direct binding [141]. HMGA1 amplifies WNT signaling output from *APC* mutations, potentiating tumorigenesis [142]. Given its pivotal role, researchers identified a distinct APC truncation (lacking seven 20-amino acid repeats) as a biomarker for β -catenin inhibitor resistance in CRC therapy [143]. The gut microenvironment enables microbial interactions, exemplified by *Clostridium_sensu_stricto_1* correlating with β -catenin, AXIN2 and c-MYC expression [144]. These findings illuminate the multifaceted complexity of canonical WNT dysregulation, particularly through APC mutations, in colorectal carcinogenesis.

There is evidence indicating aberrant activation of non-canonical WNT signaling in CRC. Collagen type I α 1 overexpression enhances c-JUN N-terminal kinase phosphorylation and upregulates RHOA-GTP expression [145]. WNT5A/JNK signaling promotes CSC development with β -catenin activity and modulates tumor microenvironment by regulating M2 macrophage polarization and T-cell differentiation [146]. In colitis-associated CRC, WNT5A activates CaMKII to subsequently stimulate STAT3-mediated tumor progression [147]. These findings demonstrate that both the WNT-PCP and WNT- Ca^{2+} pathways can facilitate CRC progression. However, certain non-canonical pathways exhibit tumor-suppressive effects, as evidenced by Evacetrapib-induced JNK activation inhibiting CRC cell growth [148]. One review article reveals the dual roles of non-canonical signaling in CRC pathogenesis, with tumor suppression mediated through ROR2-dependent signaling, competitive antagonism of canonical pathways, and downstream gene regulation [149]. Intriguingly, patients exhibiting low β -catenin but high TCF12/MALAT1/Cyclin D1 expression demonstrate poorer prognosis, a phenotype strongly associated with non-canonical WNT activation [150]. These observations warrant caution regarding the oncogenic potential of non-canonical WNT signaling in CRC, notwithstanding its duality in modulating cancer progression.

Glioblastoma multiforme

Similar to BC, GBM rarely harbors mutations in core components of the WNT pathway [151]. The GBM phenotype shows strong correlation with hyperactivated WNT signaling, particularly the WNT/ β -catenin axis. Aberrant activation of canonical WNT signaling results from dysregulation at multiple nodal points. Non-coding RNA-mediated pre-translational regulation plays an indispensable role in this process. For instance, circMMD functions as a miR-15b-5p sponge, attenuating miR-FZD6 mRNA interaction to upregulate FZD6 expression. Moreover, circMMD enhances DVL1 expression, dually promoting GBM cell proliferation [152]. RNA-binding proteins like YTHDF2 facilitate β -catenin nuclear translocation by degrading APC and GSK-3 β mRNAs, thereby hyperactivating canonical WNT signaling [153]. Enhanced nuclear β -catenin elevates expression of canonical WNT targets including *c-MYC* and *survivin* [154]. Interestingly, c-MYC acts as a transcription factor for *CTNNB1* in GBM cells, establishing a positive feedback loop [155]. Canonical WNT activation promotes multiple oncogenic phenotypes in GBM cells. The WNT/ β -catenin axis upregulates *neurologin 3* transcription to induce CSC formation in neighboring cells [156]; it also

enhances chemoresistance [154], EMT progression [157], and invasiveness with colony-forming capacity [158].

Therapeutic targeting of canonical WNT signaling in GBM remains largely ineffective, suggesting alternative pathways may drive tumor aggressiveness. Core WNT-PCP components VANGL1, VANGL2, FZD7 and DAAM1 play important roles in GBM progression. DAAM1 demonstrates the most pronounced dysregulation with concomitant upregulation of downstream effectors RHOA, ROCK2 and RAC2 [159]. VANGL1/2 mediate essential physiological functions including ciliary elongation and neural tube patterning via the WNT-PCP signaling [160]. Dreyer et al. demonstrated VANGL1-FZD7 complex formation at leading edges of migrating GBM cells, driving actin cytoskeletal reorganization [161]. Overexpressed VANGL2 promotes migration, invasion, proliferation and tumor sphere formation, representing a potential prognostic biomarker [162]. Emerging evidence implicates WNT- Ca^{2+} signaling in GBM pathogenesis. Huang et al. revealed the dual regulatory role of WNT- Ca^{2+} signaling in GBM cells. FZD6-mediated CaMKII activation upregulates NLK to antagonize canonical WNT, while parallel STAT3/NF- κ B activation sustains tumor growth and renewal [163].

Hepatocellular carcinoma

HCC, a prevalent malignancy of the digestive gland, frequently exhibits WNT pathway dysregulation primarily driven by *CTNNB1* mutations. *CTNNB1* mutagenesis correlates with multiple etiological factors, particularly alcohol consumption, viral infection, and aflatoxin exposure [164]. Recurrent mutations cluster at exon 3 Ser/Thr residues or adjacent amino acids [165], disrupting phosphorylation sites required for β -catenin ubiquitination and proteasomal degradation, thereby stabilizing nuclear β -catenin. *CTNNB1*-mutant HCC constitutes a distinct subtype characterized by well-differentiation, pseudoglandular patterns, cholestasis, and immune exclusion [166]. Mechanistic investigations have elucidated the molecular basis of this unique HCC subtype. T-box transcription factor 3 mRNA is upregulated in *CTNNB1*-mutant HCC, correlating with enhanced differentiation status [167]; β -catenin overexpression induces ATP-binding cassette transporter expression, driving profound cholestasis [168]; Nuclear β -catenin transactivates PF4, expanding myeloid-derived suppressor cell populations while depleting CD8⁺ T cells, potentially mediating immune evasion [169]. However, comprehensive understanding of *CTNNB1*-driven transcriptional programs and their phenotypic consequences remains incomplete, warranting further investigation. Beyond *CTNNB1* mutations, β -catenin hyperactivation occurs through FZD7/10 overexpression [15, 170], destruction complex

phosphorylation [171], and translational dysregulation [172]. This orchestrates oncogenic transcriptional cascades involving YAP-1, c-JUN, CD90, epithelial cell adhesion/activating molecule, CD44, and CD133, enhancing stemness, chemoresistance, and metastatic competence [173].

The role of non-canonical pathways in HCC progression exhibits considerable complexity. The tumor-modulating functions of non-canonical signaling, particularly the WNT-PCP pathway, require further elucidation. The initial 2012 research identified WNT5A/ROR2 downregulation as correlating with poor prognosis [174]. Wakiyaka et al. demonstrated that WNT5A/ROR2 signaling promotes HCC differentiation, with high expression predicting favorable outcomes and WNT5A/ROR2-negative cases showing elevated Alpha-Fetoprotein (AFP) levels [175]. Contrastingly, Huang et al. reported that WNT5A/ROR2 activation suppresses canonical signaling, with this pathway switching mechanism driving HCC progression [176]. Given the limited impact of *CTNNB1*/*AXIN* mutations on downstream WNT targets [164], non-canonical pathways may play a more important role in HCC progression, though whether WNT5A/ROR2 serves as the principal mediator remains unresolved. Beyond WNT5A/ROR2, upregulated FZD2/ROR1 signaling similarly enhances EMT in HCC cells [177]. WNT5A activates this axis, potentially through STAT3 phosphorylation to promote oncogenic phenotypes. FZD2, WNT5A and ROR2 collectively represent potential prognostic biomarkers [175, 178].

Prostate cancer

PCa is one of the most common malignant tumors in men, particularly prevalent among older males. While early-stage PCa typically grows slowly and has a favorable prognosis, advanced or aggressive forms can lead to high mortality rates. Androgen receptor (AR) expression levels determine the efficacy of anti-androgen therapy, a cornerstone treatment for PCa. The WNT signaling pathway modulates AR expression in PCa cells, directly influencing therapeutic resistance. Alterations in canonical WNT components impact AR receptor expression. Beildeck et al. systematically delineated the β -catenin-AR crosstalk. β -catenin potentiates AR transcriptional activity through direct binding, a function mutually exclusive with its canonical TCF/LEF-mediated signaling [179]. This mechanism becomes prominently activated during castration-resistant progression [180]. Beyond AR upregulation, canonical WNT signaling drives metastatic progression through multiple avenues. β -catenin stabilization, FZD/WNT activation, or destruction complex impairment all promote metastasis via WNT hyperactivation [181–183], though definitive pro-metastatic target

genes remain unvalidated. Canonical WNT signaling additionally governs CSC acquisition, EMT progression, and immune microenvironment remodeling [184, 185].

Extensive research has elucidated the multifaceted mechanisms of non-canonical WNT signaling in PCa, which can be categorized as follows. (1) FYN/STAT3 pathway: Representing a distinct non-canonical axis independent of WNT-PCP/ Ca^{2+} signaling, this pathway is activated by FZD2/8 receptors. The scaffolding protein Abi functions as a molecular gatekeeper between FZD2 and FYN/STAT3, critically regulating EMT progression [186, 187]. (2) The WNT-PCP pathway: Core components including ROR1/ROR2 demonstrate overexpression, with the Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealing differential expression of DAAM1/RAC effectors [188, 189]. However, direct experimental validation of complete WNT-PCP cascades and their transcriptional targets remains lacking. (3) The WNT- Ca^{2+} pathway: WNT5A overexpression induces calcium oscillations that activate CaMKII, enhancing wound healing and motility in malignant cells [85]. KEGG data further implicates PLC and calcineurin dysregulation, suggesting concurrent activation of multiple Ca^{2+} -dependent mechanisms [188].

Other relevant cancers

The WNT pathway plays a significant role in various other cancers. Targeting upregulated β -catenin in Renal cell carcinoma (RCC) is considered a promising strategy. Alterations in multiple WNT pathway components, such as WNT9B, FZD2/7, AXIN, and APC, can lead to the upregulation of β -catenin [190–192]. CLIP170, a protein implicated in multiple cancers, promotes the nuclear translocation of β -catenin by directly mediating the reduction of its ubiquitination levels, thereby increasing FOSL1 expression and facilitating the proliferation and growth of RCC cells [193]. Similar to RCC, the canonical WNT pathway also plays a crucial role in melanoma. A recent study demonstrated that WNT3A binds to FZD and LRP6 to promote the nuclear translocation of β -catenin, subsequently enhancing the expression of various oncogenes, including *c-MYC*, *MMP-9*, *SOX10*, and *CD44* [194]. Regarding the progression of melanoma, Pan Song et al. proposed that melanoma employs distinct WNT signaling pathways during its growth [151]. The canonical WNT pathway primarily promotes growth and transformation to enhance proliferative capacity [195], whereas non-canonical WNT signaling appears to facilitate melanoma metastasis and invasion [196]. Additionally, upregulation of WNT5A may enhance the immunogenicity of melanoma [197], though this conclusion remains controversial. For instance, FZD6 upregulation promotes melanoma invasion via the

canonical WNT pathway without affecting proliferation, while FZD3 enhances melanoma growth and metastasis independently of the canonical WNT pathway [198]. Thus, the specific roles of different WNT pathways may still be closely associated with the types of FZD receptors involved [199]. Osteosarcoma (OS) is one of the most metastatic cancers, and the WNT pathway is highly active in its progression. The canonical WNT signaling not only plays a critical role in tumor invasion and EMT but is also closely linked to angiogenesis, cell proliferation, and drug resistance in OS [200]. However, Singla A. et al. suggested that the role of canonical WNT signaling in OS is less defined compared to other cancers [201]. Evidence indicates that DKK-1, an inhibitor of canonical WNT signaling, may paradoxically promote tumor phenotypes, likely due to its low specificity, which enhances other signaling pathways and counteracts the inhibitory effects of canonical WNT signaling [202]. Moreover, since canonical WNT signaling promotes the differentiation of MSCs into osteoblasts in normal human tissues, its inhibition may lead to the acquisition of an MSC-like phenotype, potentially explaining why some researchers consider canonical WNT signaling suppressive in OS progression [203]. Non-canonical WNT signaling also contributes to OS, with evidence suggesting its role in promoting ALDH-1 expression to facilitate cancer phenotypes [203]. The WNT pathway is essential for the development of oral and associated organs [204], and its dysregulation can contribute to oral carcinogenesis. Both canonical and non-canonical pathways play significant roles in oral cancer progression, including metabolic reprogramming, acquisition of cancer stemness, immune microenvironment modulation, and EMT [205–208]. In lung cancer (LCA), WNT signaling is also pivotal. The canonical WNT pathway promotes various tumor phenotypes in non-small cell lung cancer (NSCLC), such as proliferation, migration, and drug resistance [209, 210]. Additionally, multiple non-canonical WNT components have been identified in LCA [211–213], but similar to other cancers, their pro- or anti-tumor effects require further clarification. Furthermore, WNT signaling plays a critical role in the pulmonary metastasis of other cancer types [177, 214, 215].

Potential therapeutic approaches targeting WNT signaling

The aberrant activation of the WNT signaling pathway has been confirmed to be closely associated with the initiation and progression of various malignancies. This discovery has positioned targeting critical regulatory nodes within this pathway as a highly promising anti-cancer strategy. Research indicates that dysregulation of this pathway not only contributes to malignant tumor

transformation but is also implicated in the pathological processes of multiple degenerative diseases. Currently, inhibitors targeting distinct components of the WNT/ β -catenin signaling cascade have shown significant

progress in development, with several drug candidates advancing into preclinical evaluations (Fig. 5) or various phases of clinical trials (Table 1 and Fig. 6). These novel therapeutic agents effectively suppress canonical WNT

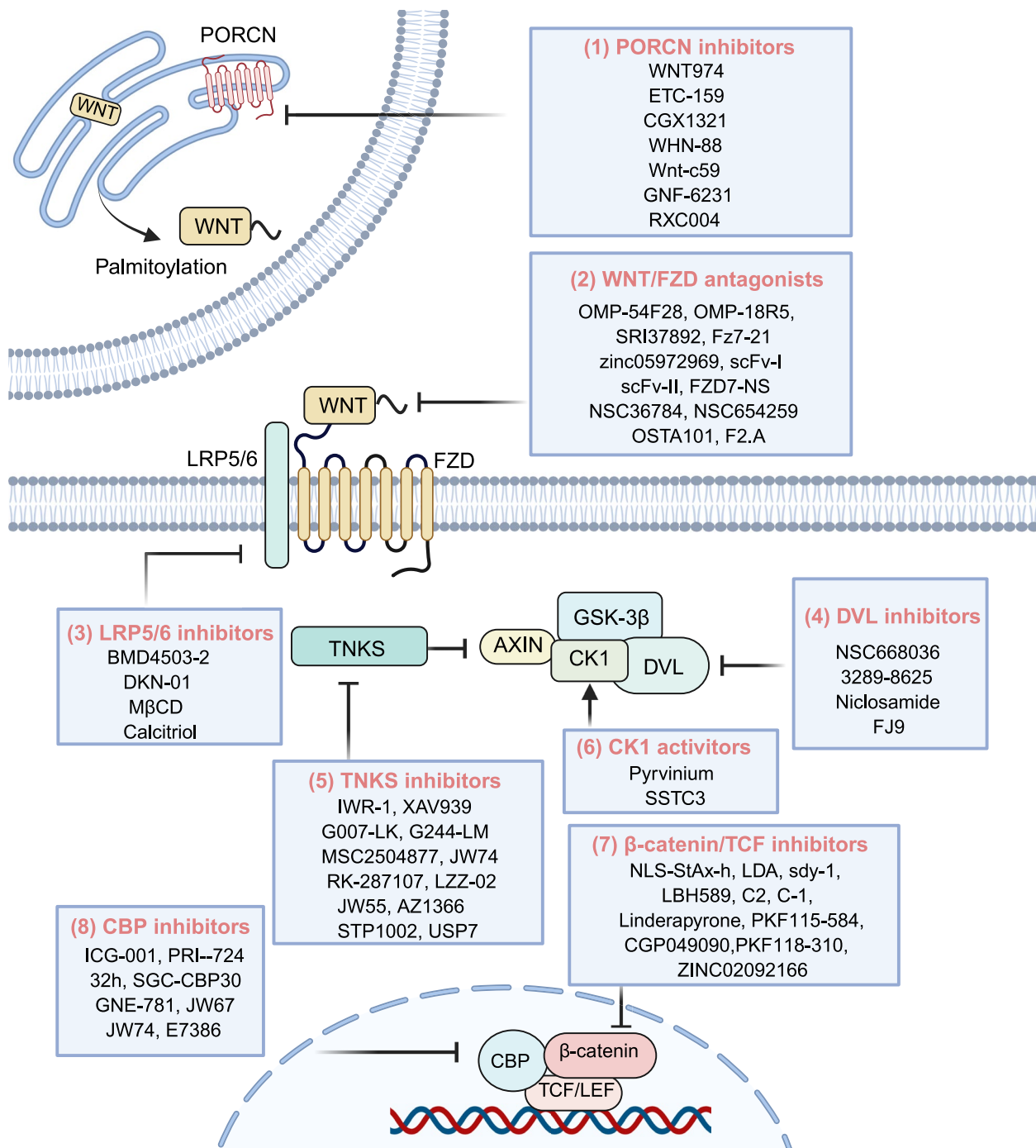


Fig. 5 WNT signaling pathway inhibitors. The WNT signaling pathway is a promising target for cancer therapy. Currently, numerous inhibitors have been reported in both preclinical and clinical trial stages. Based on the targeted components of the WNT pathway, these inhibitors can be categorized into the following classes: (1) Porcupine inhibitors, (2) WNT/FZD antagonists, (3) LRP5/6 inhibitors, (4) DVL inhibitors, (5) TNKS inhibitors, (6) CK1 agonists, and (7) β -catenin/TCF transcriptional complex inhibitors, (8) CBP inhibitors

Table 1 The Summary of Clinical Trials Targeting the WNT Signaling Pathway at Different Stages

Drug	NCT	Phase	Status	Last Update Posted	Cancer Type
WNT947	NCT02649530	Phase 2	Withdrawn	2016/9/30	SCC
WNT947	NCT02278133	Phase 1/2	Completed	2017/10/9	MCRC
WNT947	NCT01351103	Phase 1	Completed	2024/9/19	PCA BRAF Mutant CRC Melanoma
NUC-7738	NCT03829254	Phase 1/2	Recruiting	2024/11/12	Lymphoma
DKN-01	NCT03645980	Phase 1/2	Unknown status	2020/10/22	HCC
DKN-01	NCT01457417	Phase 1	Completed	2016/9/28	Multiple Myeloma NSCLC
DKN-01	NCT04166721	Phase 1/2	Active, not recruiting	2024/8/2	Metastatic EC Metastatic GC
DKN-01	NCT02013154	Phase 1	Completed	2023/11/1	Esophageal Neoplasms Adenocarcinoma of the Gastroesophageal Junction Gastroesophageal Cancer (GEC) SCC GA
DKN-01	NCT04363801	Phase 2	Active, not recruiting	2024/1/22	GC GA GEC
DKN-01	NCT01711671	Phase 1	Completed	2017/3/13	MultipEndometrial Cancerle Myeloma
DKN-01	NCT05761951	Phase 2	Recruiting	2024/11/18	
DKN-01	NCT04681248		Available	2023/9/29	Esophageal Neoplasm Adenocarcinoma of the Gastroesophageal Junction GEC SCC GA EC Uterine Cancer OC Carcinosarcoma GC
DKN-01	NCT02375880	Phase 1	Completed	2018/9/10	Carcinoma of Intrahepatic and Extra-hepatic Biliary System Bile Duct Cancer Carcinoma of Gallbladder Cholangiocarcinoma
DKN-01	NCT03395080	Phase 2	Completed	2023/7/12	EC Uterine Cancer OC Carcinosarcoma
DKN-01	NCT03837353	Phase 1/2	Terminated	2023/12/18	PCa
DKN-01	NCT05480306	Phase 2	Active, not recruiting	2024/9/27	CRC Colorectal Adenocarcinoma Colo-rectal Cancer
DKN-01	NCT03818997	Phase 2	Withdrawn	2020/2/5	EC BTC GEC Hepatobiliary Neoplasm
DKN-01	NCT04057365	Phase 2	Terminated	2024/4/10	BTC
Vantictumab	NCT01957007	Phase 1	Completed	2020/9/9	Solid Tumors
Vantictumab	NCT01973309	Phase 1	Completed	2020/9/9	Metastatic BC
Vantictumab	NCT02005315	Phase 1	Completed	2020/9/9	Stage IV PCA
OMP-54F28	NCT02069145	Phase 1	Completed	2020/8/11	Hepatocellular Cancer HCC
OMP-54F28	NCT02092363	Phase 1	Completed	2020/8/12	OC
OMP-54F28	NCT01608867	Phase 1	Completed	2020/8/11	Solid Tumors
OMP-54F28	NCT02050178	Phase 1	Completed	2020/9/9	Stage IV PCA
RXC004	NCT03447470	Phase 1	Completed	2025/1/29	Cancer Solid Tumor

Table 1 (continued)

Drug	NCT	Phase	Status	Last Update Posted	Cancer Type
XNW7201	NCT03901950	Phase 1	Completed	2023/2/16	Advanced Solid Tumors
FOG-001	NCT05919264	Phase 1/2	Recruiting	2024/12/17	CRC
Sinecatechins	NCT02029352	Phase 2/3	Completed	2016/5/18	Carcinoma, Basal Cell
Calcitriol	NCT01358045	Phase 2	Completed	2015/1/13	Basal Cell Carcinoma
Resveratrol	NCT00256334	Phase 1	Completed	2014/6/20	CRC
PTK7-ADC	NCT03243331	Phase 1	Completed	2021/1/7	TNBC Metastatic BC
ETC-159	NCT06513624	Phase 1	Not yet recruiting	2024/11/29	With MSS/pMMR Advanced, Platinum-resistant OC
ETC-159	NCT02521844	Phase 1	Active, not recruiting	2024/10/8	Solid Tumors
CGX1321	NCT03507998	Phase 1		2020/7/24	Colorectal Adenocarcinoma GA Pancreatic Adenocarcinoma
CGX1321	NCT02675946	Phase 1		2022/1/26	Solid Tumors Gastrointestinal Cancer
OMP-18R5	NCT01345201	Phase 1	Completed	2020/9/9	Solid Tumors
OMP-18R5	NCT02005315	Phase 1	Completed	2020/9/9	Stage IV PCA
OMP-18R5	NCT01957007	Phase 1	Completed	2020/9/9	Solid Tumors
OMP-18R5	NCT01973309	Phase 1	Completed	2020/9/9	Metastatic BC
OMP-131R10	NCT02482441	Phase 1	Completed	2020/8/11	Advanced Relapsed Tumors Refractory Solid Tumors
UC-961	NCT02222688	Phase 1	Completed	2020/8/13	CLL
UC-961	NCT05156905	Phase 1	Terminated	2024/10/9	Metastatic Castration-resistant Prostate Cancer
UC-961	NCT02860676	Phase 1	Completed	2019/3/20	CLL
UC-961	NCT04501939	Phase 2	Active, not recruiting	2023/11/28	CLL
UC-961	NCT02776917	Phase 1	Completed	2024/4/10	Breast Neoplasms
UC-961	NCT03088878	Phase 1/2	Completed	2025/2/12	B-cell CLL SLL MCL Marginal Zone Lymphoma
OTSA101	NCT04176016	Phase 1	Terminated	2024/2/2	Relapsed or Refractory Synovial Sarcoma
Foxy-5	NCT02020291	Phase 1	Completed	2016/2/2	Metastatic BC CRC PCa
Foxy-5	NCT02655952	Phase 1	Completed	2018/12/28	Metastatic BC MCRC Metastatic PCa
Foxy-5	NCT03883802	Phase 2		2022/12/9	CRC
CWP232291	NCT03055286	Phase 1/2		2021/12/13	AML
CWP232291	NCT01398462	Phase 1	Completed	2016/3/8	AML Chronic Myelomonocytic Leukemia Myelodysplastic Syndrome Myelofibrosis
CWP232291	NCT02426723	Phase 1	Completed	2019/5/17	Multiple Myeloma
LY2090314	NCT01287520	Phase 1	Completed	2019/2/25	Advanced Cancer
LY2090314	NCT01632306	Phase 1/2	Terminated	2019/1/15	PCA
LY2090314	NCT01214603	Phase 2	Completed	2018/11/19	Leukemia
Tegavivint	NCT05797805	Phase 1/2	Recruiting	2024/8/27	Advanced HCC
Tegavivint	NCT04874480	Phase 1	Active, not recruiting	2025/1/30	Recurrent Leukemia Refractory Leukemia
Tegavivint	NCT04851119	Phase 1/2	Recruiting	2024/10/26	Colorectal Carcinoma Endometrial Carcinoma Melanoma Neuroblastoma OC PDAC Recurrent Desmoid Fibromatosis/ES/HB/HCC/Malignant Solid Neoplasm/NHL/OS Refractory Desmoid Fibromatosis/ES/HB/HCC/Malignant Solid Neoplasm/NHL/OS Solid Pseudopapillary Neoplasm of the Pancreas Wilms Tumor

Table 1 (continued)

Drug	NCT	Phase	Status	Last Update Posted	Cancer Type
Tegavivint	NCT04780568	Phase 1	Recruiting	2025/1/1	Metastatic NSCLC [Stage IV Lung Cancer AJCC V8 Stage IVA/B Lung Cancer AJCC V8
Tegavivint	NCT03459469	Phase 1	Completed	2023/3/1	Desmoid Tumor
PRI-724	NCT01606579	Phase 1/2	Completed	2017/8/17	AML Chronic Myeloid Leukemia
PRI-724	NCT03620474	Phase 1/2	Completed	2024/10/10	Hepatitis C Hepatitis B Liver Cirrhoses
PRI-724	NCT01764477	Phase 1	Completed	2017/8/17	Advanced PCA Metastatic PCA Pancreatic Adenocarcinoma
PRI-724	NCT02195440	Phase 1	Completed	2022/7/7	Hepatitis C Virus-infected Cirrhosis
PRI-724	NCT01302405	Phase 1	Terminated	2017/8/17	Advanced Solid Tumors
PRI-724	NCT02828254		Completed	2022/7/7	Hepatitis C Virus-infected Cirrhosis
PRI-724	NCT02413853	Phase 2	Withdrawn	2017/4/17	Colorectal Adenocarcinoma Stage IVA CRC Stage IVB CRC
Umbralisib	NCT04163718	Phase 2	Terminated	2023/3/24	CLL
Umbralisib	NCT03364231	Phase 2	Completed	2023/6/23	Marginal Zone Lymphoma Waldenstrom Macroglobulinemia Non Follicular Indolent NHL
Umbralisib	NCT04508647	Phase 2	Completed	2024/3/21	Marginal Zone Lymphoma FL
Umbralisib	NCT03776864	Phase 2	Terminated	2023/5/3	HL
Umbralisib	NCT02742090	Phase 2	Terminated	2024/7/3	CLL
Umbralisib	NCT04149821	Phase 2	Terminated	2023/6/15	CLL SLL
Umbralisib	NCT04692155	Phase 1/2	Terminated	2023/9/28	MCL
Umbralisib	NCT03919175	Phase 2	Terminated	2024/5/8	Lymphoma FL
Umbralisib	NCT03828448	Phase 2	Terminated	2023/7/24	FL SLL
Umbralisib	NCT02793583	Phase 1/2	Terminated	2022/7/21	DLBCL FL Marginal Zone Lymphoma
Umbralisib	NCT03801525	Phase 1/2	Terminated	2024/4/19	CLL SLL
Umbralisib	NCT04783415	Phase 2	Active, not recruiting	2024/12/2	MCL
Umbralisib	NCT05152459	Phase 1/2	Withdrawn	2023/5/31	Recurrent FL Refractory FL
Umbralisib	NCT02656303	Phase 2	Terminated	2023/6/22	CLL
Umbralisib	NCT04624633	Phase 2	Active, not recruiting	2024/12/24	CLL SLL Relapsed CLL
Umbralisib	NCT02535286	Phase 1	Completed	2022/10/20	CLL Richter Syndrome
Umbralisib	NCT04635683	Phase 1	Withdrawn	2022/9/30	Recurrent B-Cell NHL Recurrent Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue Recurrent FL
Umbralisib	NCT03283137	Phase 1	Active, not recruiting	2025/2/7	CLL B-cell NHL
Umbralisib	NCT03379051	Phase 1/2	Terminated	2022/8/22	CLL NHL
Umbralisib	NCT03671590	Phase 1	Terminated	2024/7/19	NHL CLL

Table 1 (continued)

Drug	NCT	Phase	Status	Last Update Posted	Cancer Type
Umbralisib	NCT04016805	Phase 2	Terminated	2023/7/24	CLL
Umbralisib	NCT02268851	Phase 1	Completed	2024/11/15	CLL/SLL MCL
Umbralisib	NCT02612311	Phase 3	Terminated	2024/12/13	CLL
Umbralisib	NCT03207256	Phase 2	Terminated	2022/7/21	CLL NHL
Vantictumab	NCT01345201	Phase 1	Completed	2020/9/9	Solid Tumors
RXC004	NCT04907851	Phase 2	Completed	2024/3/8	Advanced Solid Tumours
RXC004	NCT04907539	Phase 2	Completed	2024/5/3	CRC
Zilovertamab	NCT03833180	Phase 1	Completed	2024/1/12	CLL MCL FL
Zilovertamab	NCT04504916	Phase 2	Terminated	2024/8/15	TNBC Non-squamous NSCLC NSCLC
Zilovertamab	NCT06395103	Phase 1/2	Recruiting	2025/2/18	B-cell Acute Lymphoblastic Leukemia DLBCL Burkitt Lymphoma Neuroblastoma ES
Zilovertamab	NCT05144841	Phase 2	Active, not recruiting	2024/11/8	Relapsed or Refractory DLBCL
Zilovertamab	NCT05431179	Phase 3	Withdrawn	2023/4/21	MCL Lymphoma Lymphoproliferative Disorders Lymphatic Diseases Immunoproliferative Disorders Immune System Diseases Lymphoma, NHL
Zilovertamab	NCT05562830	Phase 1/2	Active, not recruiting	2024/11/20	Urothelial Carcinoma
Zilovertamab	NCT04501939	Phase 2	Active, not recruiting	2023/11/28	CLL
Zilovertamab	NCT05458297	Phase 2	Recruiting	2025/2/20	CLL MCL FL Richter Transformation Lymphoma
Zilovertamab	NCT05406401	Phase 2	Active, not recruiting	2024/10/15	Lymphoma, DLBCL
Zilovertamab	NCT06717347	Phase 3	Recruiting	2025/2/20	DLBCL
Zilovertamab	NCT05139017	Phase 2/3	Recruiting	2025/1/10	DLBCL

Data sources – ClinicalTrials.gov

Abbreviations: SCC squamous cell carcinoma, CRC colorectal cancer, PCA pancreatic cancer, HCC hepatocellular carcinoma, NSCLC non-small cell lung cancer, EC esophageal cancer, GC gastric cancer, GA gastric adenocarcinoma, OC ovarian cancer, BTC biliary tract cancer, BC breast cancer, TNBC triple-negative breast cancer, CLL chronic lymphocytic leukemia, SLL small lymphocytic lymphoma, MCL mantle cell lymphoma, AML acute myeloid leukemia, DLBCL diffuse large B-cell lymphoma, NHL Non-Hodgkin lymphoma, PDAC Pancreatic ductal adenocarcinoma, ES Ewing sarcoma, HB hepatoblastoma, OS osteosarcoma, FL follicular lymphoma, HL Hodgkin's lymphoma, PCa prostate cancer, GEC gastroesophageal cancer, mCRC metastatic colorectal cancer

signal transduction through mechanisms such as selectively interfering with WNT ligand binding, disrupting β -catenin stability, or blocking the formation of transcriptional complexes, thereby achieving targeted regulation of tumor growth.

Preclinical studies and clinical trials of WNT pathway inhibitors

Numerous preclinical studies have demonstrated that targeting components of the WNT signaling pathway can effectively inhibit the activation of the WNT signaling

pathway in cancer. Furthermore, a large number of related clinical trials have reported promising anticancer activity. Below, we describe WNT signaling inhibitors according to the components targeting the signaling pathway.

PORCN inhibitors

WNT palmitoylation is crucial for the activation of its signaling pathway. As an O-acyltransferase localized in the endoplasmic reticulum, PORCN catalyzes the binding of palmitoleic acid to the Ser residue of WNT

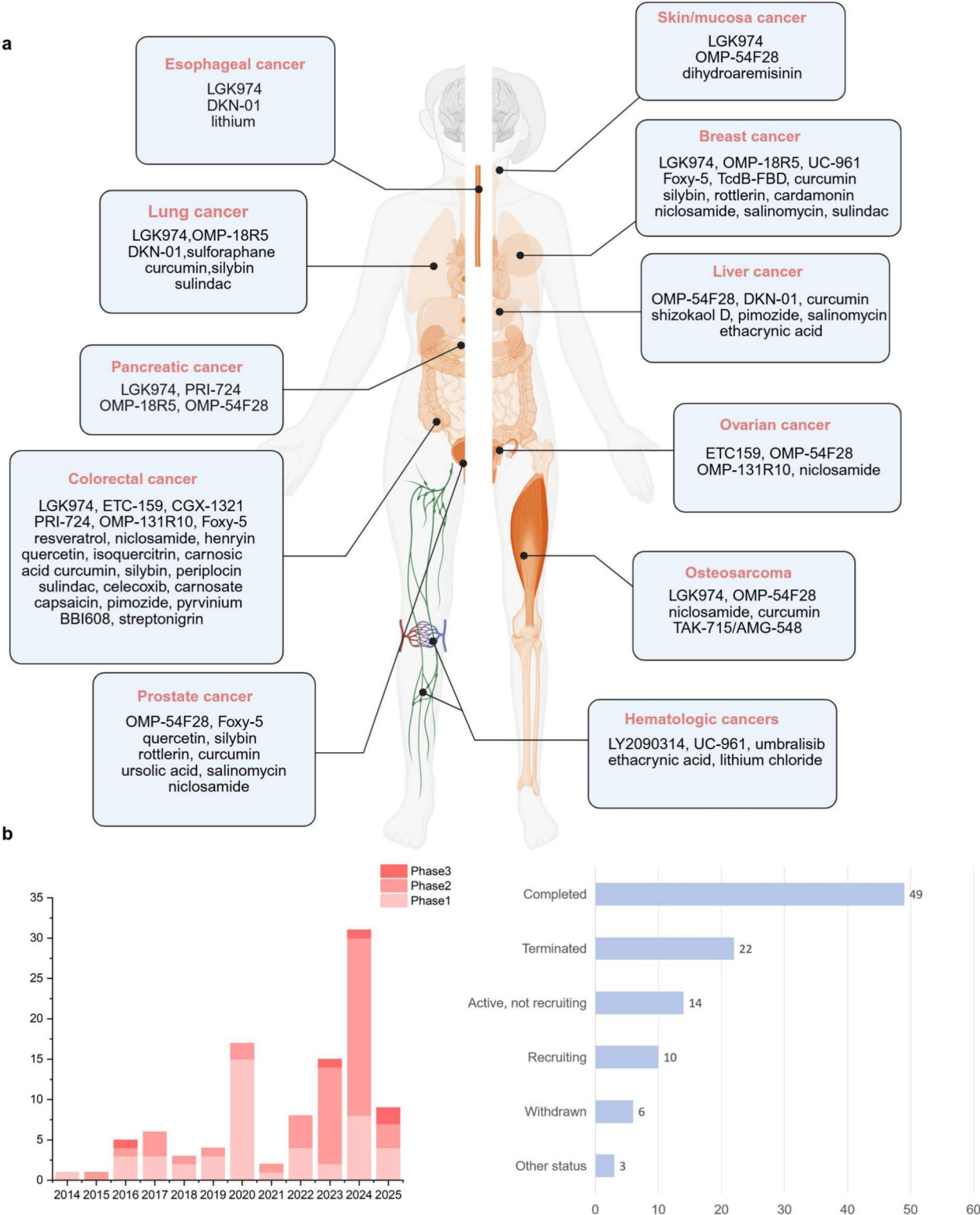


Fig. 6 Comprehensive landscape of clinical trials about WNT pathway inhibitors (data cutoff: March 2025). **a** The summary of the WNT signaling inhibitors currently registered in clinical trials. WNT signaling inhibitors targeting the same type of cancer are grouped within a single diagram. **b** Statistics on clinical trials of currently available WNT signaling pathway inhibitors. Annual distribution of clinical trials, with color coding indicating trial phases: light red for Phase 1, medium red for Phase 2, and dark for Phase 3. Current status of clinical trials, classified into five distinct categories: “Completed” “Terminated” “Active, not recruiting” “Withdrawn” “Other status”

proteins, thereby mediating the palmitoylation modification of the ligand. Therefore, inhibiting PORCN can prevent the secretion of WNT proteins into the extracellular matrix, thereby reducing the excessive accumulation of β -catenin in the cytoplasm to promote the expression of cancer-related genes. Currently, various PORCN inhibitors have been in preclinical studies and clinical trials. For instance, in OC, upregulation of the WNT/ β -catenin pathway is associated with tumor proliferation and chemotherapy resistance. WNT974 (LGK974) blocks the WNT pathway activity by inhibiting PORCN, leading to cell cycle arrest in ascites cells rather than direct cytotoxicity [216]. Additionally, WNT974 has been validated to be effective in head and neck squamous cell carcinoma with aberrant WNT signaling [217]. Several clinical trials have investigated its potential. In a Phase Ib dose-escalation study (NCT02228120), researchers investigated the combination of WNT974 with encorafenib and cetuximab in patients with The B-Raf proto-oncogene (BRAF) V600E-mutant metastatic CRC (mCRC) harboring RNF43 mutations or R-spondin (RSPO) fusions. As a secreted glycoprotein, RSPO binds to LGR4/5/6 receptors and significantly potentiates WNT/ β -catenin signaling pathway. RSPO fusions have been demonstrated to drive hyperactivation of WNT/ β -catenin signaling in multiple cancer types, serving as an oncogenic driver. In the 10 mg WNT974 cohort, bone toxicity occurred in 45% of patients. Although the disease control rate reached 85%, the overall response rate was only 10%, with most patients achieving stable disease. Compared to the historical encorafenib and cetuximab dual regimen, the triple-combination therapy did not demonstrate significantly enhanced antitumor activity. Due to the high incidence of bone toxicity and lack of superior efficacy over the dual regimen, the study was terminated after Phase Ib, and no Phase II trial was initiated. Another Phase I study (NCT01351103) demonstrated that WNT974 monotherapy was well-tolerated in patients with advanced solid tumors. The most common adverse event was dysgeusia (50% of patients), mostly Grade 1–2. Notably, AXIN2 mRNA expression was significantly reduced in 94% of skin biopsies and 74% of tumor biopsies, confirming effective WNT pathway suppression. Despite these findings, WNT974 monotherapy showed limited antitumor efficacy. ETC-159 is an oral PORCN inhibitor that blocks the palmitoylation of WNT proteins to inhibit the secretion and activity of WNTs. ETC-159 can effectively suppress aberrant WNT signaling in CRC and OS [218, 219]. Furthermore, in the treatment of RNF43-mutant PCA, the combination of ETC-159 and the pan-PI3K inhibitor GDC-0941 effectively inhibits the growth of xenografts in vivo [220]. In 2016, ETC-159 was reported in a Phase 1, first-in-human dose-escalation study (NCT02521844)

for solid tumors, evaluating its safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK), and pharmacodynamics. The Phase 1 study demonstrated that ETC-159 had a manageable safety profile and preliminarily validated its inhibitory effect on the WNT pathway, though its single-agent antitumor activity was limited. The study also assessed whether ETC-159, at a dose of 24 mg every other day combined with prophylactic denosumab treatment, resulted in toxicities such as compression fractures, hyperbilirubinemia, and elevated serum b-CTX, which were considered dose-limiting toxicities (DLT) of ETC-159. Subsequently, the results of a Phase Ib dose-escalation study evaluating ETC-159 in combination with pembrolizumab, a programmed death (PD)–1 inhibitor, for the treatment of advanced or metastatic solid tumors were reported. CGX1321 is an orally bioavailable small molecule PORCN inhibitor. In OC, CGX1321 significantly reduces tumor burden, improves survival rates, and the functions of T cells, macrophages, and dendritic cells by inhibiting WNT secretion, transforming the tumor microenvironment into an "immune-hot" state [221]. To enhance the efficacy of CGX1321, it has been encapsulated in liposomes, successfully achieving efficient targeted delivery to tumor tissues while significantly reducing toxicity to normal tissues [222]. Currently, there are two clinical studies underway: a Phase I dose-escalation and dose-expansion study of CGX1321 monotherapy, and a study of CGX1321 in combination with pembrolizumab. The primary objectives are to evaluate the safety, tolerability, and recommended dose of CGX1321, as well as to characterize its antitumor activity, PK profile, and PD responses. In terms of safety, CGX1321—both as monotherapy and in combination—demonstrated a manageable side effect profile, with most adverse events being Grade 1–2 (e.g., mild dysgeusia). Bone resorption could be mitigated with prophylactic denosumab or zoledronic acid. As a monotherapy, CGX1321 achieved disease stabilization in 71% of colorectal or small intestinal cancer patients harboring RSPO fusions or RNF43 mutations, with a median progression-free survival of 112 days. In the combination therapy arm, three patients with RSPO3-fusion tumors achieved partial responses after treatment with CGX1321 plus pembrolizumab. In addition, a small molecule compound 1 has been reported. It is capable of simultaneously inhibiting the WNT and Hedgehog signaling pathways. Mechanistic studies indicate that compound 1 achieves dual inhibition by targeting PORCN and SMO which belongs to the FZD family of seven-transmembrane proteins with a typical G protein-coupled receptor structure and can mediate the activation of the Hedgehog pathway through phosphorylation of its intracellular C-terminal domain. The amino group in the right

tricyclic structure of compound 1 is crucial for Hedgehog inhibition, while the fluorine atom on the left aromatic ring significantly impacts WNT inhibition [223]. Moreover, a novel PORCN inhibitor, WHN-88, can effectively inhibit the palmitoylation of WNT ligands through its unique diiodopyridone structure [224]. Other PORCN inhibitors, including Wnt-c59, pyridylacetamide derivative GNF-6231, and RXC004, have demonstrated therapeutic anti-tumor activity in various cancers [225–227]. RXC004 primarily inhibits PORCN O-acyltransferase and demonstrated favorable safety and tolerability in a Phase I study (NCT03447470) involving patients with advanced solid tumors. Subsequently, between March 24, 2021, and June 30, 2022, 14 unselected patients with advanced solid tumors received RXC004 at doses of 1 mg and 1.5 mg once daily (QD) in combination with nivolumab. The adverse event profile of the combination therapy was generally consistent with that of RXC004 monotherapy, and disease control was observed in some patients in the 1.5 mg QD combination cohort. Following the completion of the Phase I study (NCT03447470), further evaluation of RXC004 was conducted in patients with metastatic microsatellite-stable CRC harboring RNF43 mutations or RSPO fusions (NCT04907539). The monotherapy arm primarily assessed the 16-week disease control rate, while the combination arm with nivolumab focused on objective response rate. Another Phase II study (NCT04907851) is evaluating the efficacy of RXC004 in BTC and RNF43-mutant PCA.

FZD Inhibitors

FZD has emerged as pivotal molecules in cancer research, exerting pleiotropic effects on cancer progression, including modulation of tumor growth, metastasis, drug resistance, and CSC properties. Accumulating studies suggest that overexpressed FZD exerts extensive oncogenic effects through the WNT signaling pathway. Given the crucial regulatory role of FZDs in tumors and their favorable localization on the cell membrane, they have been identified as promising therapeutic targets for cancer treatment. OMP-54F28 (Ipafricept) is a fusion protein consisting of the extracellular domain of FZD8 and IgG1 Fc, which blocks WNT signaling by competitively binding to WNT ligands. Preclinical studies have shown that OMP-54F28 monotherapy significantly inhibits tumor growth, reduces the frequency of CSCs and diminishes metastasis [228]. To date, three Phase 1b studies have been conducted, including evaluating OMP-54F28 in combination with nab-paclitaxel and gemcitabine for PCA (NCT02050178), carboplatin and paclitaxel for OC (NCT02092363), and sorafenib for HCC (NCT02069145). Despite promising therapeutic efficacy, bone toxicity has halted the further development

[80]. OMP-18R5 (Vantictumab) is initially a monoclonal antibody targeting FZD7. Subsequently, OMP-18R5 was found to bind to FZD1/2/5/7/8 and to block the WNT3A signaling pathway [229]. In the first-in-human Phase I trial (NCT01345201), OMP-18R5 demonstrated manageable safety, clear WNT pathway inhibition, and preliminary clinical activity. However, one patient experienced a Grade 2 compression fracture. Preclinical studies suggested enhanced antitumor effects when OMP-18R5 was combined with paclitaxel. In a Phase Ib clinical trial (NCT01973309), 48 patients with locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative BC (45.8% hormone receptor (HR)-positive, 54.2% triple-negative), with a median age of 54 years (66.6% previously treated with metastatic chemotherapy), were enrolled. Multiple cohorts received OMP-18R5 at escalating doses from 3.5 mg/kg (every 2 weeks) up to 8 mg/kg (every 4 weeks) in combination with weekly paclitaxel (90 mg/m²). Despite promising efficacy, serious adverse events—particularly fractures—limited further development of OMP-18R5 in metastatic BC. Another study (NCT02005315) showed that OMP-18R5 was well-tolerated in the Phase Ia trial, though bone-related toxicity was observed. In the Ib dose-escalation phase, OMP-18R5 was administered intravenously every two weeks alongside nab-paclitaxel (125 mg/m²) and gemcitabine (1000 mg/m²). The regimen was later adjusted to a four-week schedule with the addition of zoledronic acid as a preventive measure. This modified dosing strategy effectively reduced fracture risk. Based on structural similarities with the SMO receptor, researchers constructed a homology model of FZD7 transmembrane domain (TMD), revealing two conserved binding pockets composed of hydrophobic residues in the transmembrane region. These binding sites have been targeted for drug design. Molecular docking studies indicate that SRI37892 occupies the hydrophobic core at the bottom of the TMD through a benzimidazole fragment, forming π - π interactions, while its dihydroquinolinone moiety binds to the top hydrophobic region and interacts with Glu492 via hydrogen bonds, enhancing binding stability. SRI37892 exhibits potent efficacy in TNBC cells [230]. In addition to targeting the transmembrane domain of FZD, inhibitors specifically binding to the extracellular cysteine-rich domain (CRD) have been reported. Fz7-21, as the first small molecule ligand targeting the FZD subclass, specifically binds to the CRD and locks the FZD7 in an inactive state by inducing CRD dimerization and altering the conformation of its lipid-binding groove [231]. On this basis, researchers successfully optimize the peptide Fz7-21 by combining structure-based rational design and phage display technology, significantly enhancing its binding affinity and selectivity. Key optimization strategies

include the deletion of two N-terminal residues ($\Delta 2$), critical amino acid substitutions (e.g., S3T, L6Tba, F8F(3-Cl), V12I), and mutations obtained from phage screening (e.g., E7K, F8L). The final peptides (e.g., peptides 32 and 34) effectively block the binding of *Clostridium difficile* toxin B (TcdB) to FZD7 and inhibit the pathogenicity of TcdB by inducing receptor dimerization to create steric hindrance [232]. Additionally, the ligand zinc05972969 can also target the CRD of FZD7, providing a new direction for the treatment of TNBC [233]. Employing a structure-based drug design approach, researchers conducted virtual screening of 10,000 plant-derived compounds and ultimately identified that Cycloatrobiloxanthone (CAX) exhibits high binding affinity to the FZD7-CRD domain. CAX not only demonstrates promising anticancer activity in the treatment of GBM but also possesses favorable oral bioavailability, low toxicity, high gastrointestinal absorption capacity, and the potential to cross the blood–brain barrier [234]. Other inhibitors targeting FZD7 include anti-FZD7 single-chain antibodies (scFv-I and scFv-II), which bind to key regions of FZD7 involved in WNT ligand binding through epitope design [235]. Researchers also conjugate FZD7 antibodies to gold shell nanoparticles (FZD7-NS), significantly enhancing the binding affinity of the antibodies to FZD7 on the surface of TNBC cells by leveraging the multivalent binding effect of nanoparticles [236]. Currently, targeting FZD7 represents a promising therapeutic strategy characterized by low drug toxicity and high anticancer activity. Additionally, compounds such as NSC36784 and NSC654259 effectively inhibit the WNT3A-induced β -catenin signaling pathway [237]. For FZD10, OTSA101 is a humanized monoclonal antibody targeting FZD10. OTSA101-DTPA-90Y is labeled with a β -radiation-emitting yttrium Y90 for OTSA101. OTSA101-DTPA-90Y selectively kills cancer cells overexpressing FZD10 [238]. In addition, some inhibitors exhibit pan-specificity, targeting multiple FZDs. F2.A is a newly developed antibody targeting six out of the ten human FZDs (FZD1/2/4/5/7/8). Researchers first identified a specific anti-FZD antibody (F2) that matches OMP-18R5, and then developed a variant F2.A with specificity for FZD4 using combinatorial antibody engineering. According to their research, F2.A can selectively bind to FZD4 without competing with FZD4-specific ligand Norrin [239]. Additionally, there is an F2 scFv corresponding to the FZD1/2/7 CRD [240].

LRP5/6 inhibitors

LRP5/6 forms a trimer with FZD and WNT, thereby initiating the WNT signaling pathway. Its phosphorylation plays a crucial role in the activation of the pathway. For example, salinomycin inhibits the WNT signaling pathway by interfering with LRP6 phosphorylation [241]. The

proton pump inhibitor pantoprazole can also inhibit the proliferation of GC cells and induce apoptosis by reducing the levels of phosphorylated LRP6 [242]. In addition, an anthelmintic drug niclosamide has been shown to effectively inhibit the expression of LRP6, leading to a reduction in the nuclear accumulation of β -catenin. Currently, niclosamide has demonstrated significant anti-tumor effects in PCa, BC, and CRC [243]. In PCa, MESD is a specific chaperone protein responsible for promoting the folding of the LRP family. MESD inhibits the phosphorylation of LRP5/6 to reduce β -catenin accumulation by binding with high affinity to mature LRP5/6 on the cell surface, thereby inhibiting the proliferation of PCa cells [244]. In addition, through pharmacophore model-guided virtual screening, molecular docking simulations and in vitro experiments, Choi, J et al. first discovered that the quinoxaline derivative BMD4503-2 can serve as a novel inhibitor of the LRP5/6-sclerostin interaction, directly targeting the key node of the WNT/ β -catenin signaling pathway that regulates bone homeostasis. BMD4503-2 competitively binds to the E1 domain of LRP5/6, disrupting the interaction between sclerostin and LRP5/6 [245]. In addition, DKN-01, the cholesterol-depleting agent M β CD, and the vitamin D receptor agonist calcitriol can also inhibit tumors by reducing LRP6 protein levels [246, 247].

DVL inhibitors

DVL is a crucial component of the WNT signaling pathway. DVL recruits the destruction complex to the cell membrane and binds to the cytoplasmic carboxyl terminus of FZD proteins via its PDZ domain. FJ9 is a novel small molecule inhibitor that suppresses the canonical WNT signaling pathway by specifically blocking the interaction between the FZD7 and the PDZ domain of DVL [248]. Additionally, NSC668036 and 3289–8625 can also inhibit WNT signaling by binding to the PDZ domain of DVL [249]. DVL2 is significantly overexpressed in 90% of tumor tissues from hepatoblastoma (HB) patients. Knockdown of DVL2 via shRNA significantly inhibits the proliferation and invasive capabilities of HB cell lines, indicating that DVL2 plays a pro-oncogenic role in HB. Niclosamide can downregulate the expression of DVL2 and β -catenin in a dose-dependent manner, thereby inhibiting the proliferation of HB cells [250].

TNKS inhibitors

TNKS belong to the Poly (ADP-ribose) polymerase (PARPs) family, with two subtypes: TNKS1 (PARP5a) and TNKS2 (PARP5b). TNKS-mediated PARsylation of AXIN induces its degradation via the ubiquitin–proteasome pathway, and subsequent AXIN degradation triggers

the release of β -catenin from the destruction complex into the nucleus. Therefore, TNKS inhibitors typically stabilize AXIN, thereby exerting anti-tumor effects. The TNKS inhibitor IWR-1 inhibits the WNT/ β -catenin pathway by stabilizing AXIN protein, significantly reducing the viability of OS CSCs, inducing cell cycle arrest and triggering mitochondrial-dependent apoptosis. The combination of IWR-1 with doxorubicin exhibits synergistic cytotoxicity, significantly enhancing the sensitivity of CSCs to doxorubicin [251]. In addition, a small molecule compound XAV939 significantly increases AXIN protein levels by inhibiting the activity of TNKS 1 and TNKS 2, thereby enhancing the phosphorylation and degradation of β -catenin [252]. XAV939 and IWR-1 also can inhibit the proliferation of LCA cells in a dose-dependent manner [253]. Additionally, TNKS inhibitors such as G007-LK, G244-LM, MSC2504877, JW74, RK-287107, LZZ-02, JW55, and AZ1366 can significantly reduce nuclear β -catenin levels by stabilizing AXIN protein [254–260]. Researchers also discover that USP7 directly interacts with AXIN through its N-terminal TRAF domain and relies on its deubiquitinating enzyme activity to remove polyubiquitin modifications from AXIN. This process prevents AXIN from being degraded by the proteasome, thereby stabilizing the AXIN protein and negatively regulating the WNT/ β -catenin signaling pathway [261]. STP1002 is a novel oral selective inhibitor of TNKS. It demonstrates good efficacy in APC-mutated CRC [262].

CK1 Agonists

CK1 is a crucial component of the destruction complex and plays a pivotal role in preventing the nuclear localization of β -catenin, indicating that activating CK1 is an attractive therapeutic target. For instance, Pyrvinium, an FDA-approved drug, can directly bind to CK1 α , enhancing its kinase activity through allosteric effects to promote the phosphorylation and degradation of β -catenin [263]. Additionally, Pyrvinium stabilizes CK1 α protein levels by inhibiting the E3 Ubiquitin Ligase Cereblon (CRBN) -mediated degradation which plays a role in substrate recognition within the CRL4^{CRBN} E3 ubiquitin ligase complex, further suppressing WNT signaling [264]. Moreover, SSTC3, a small molecule CK1 α activator, inhibits the WNT signaling pathway through CK1 α activation. Its pharmacokinetic properties are superior to earlier drugs (e.g., Pyrvinium), maintaining effective concentrations in vivo and significantly inhibiting the proliferation of CRC cells and tumor growth [265].

β -catenin/TCF transcriptional complex inhibitors

Currently, several compounds have been reported to block the β -catenin/TCF complex. For example, the

researchers have successfully developed a cell-penetrating stabilized peptide inhibitor named NLS-StAx-h. By integrating the design strategy of cell-penetrating peptides with peptide stabilization technology, they significantly enhance the cellular uptake efficiency and targeting capability of the peptide. This inhibitor effectively suppresses the WNT signaling pathway by specifically blocking the interaction between β -catenin and TCF/LEF transcription factors. Moreover, the intracellular distribution and stability of the peptide were significantly improved through the optimization of the nuclear localization sequence and arginine derivatives [266]. In addition, Tumor necrosis factor receptor-associated factor 2 (TRAF2), a member of the TRAF superfamily of proteins, regulates NF- κ B and MAPK signaling pathways through its E3 ubiquitin ligase activity. TRAF2 positively regulates the WNT/ β -catenin signaling pathway by directly interacting with the N-terminus of β -catenin through its TRAF-C domain, promoting CRC cell proliferation and tumor growth. Liquidambaric acid (LDA) directly targets the TRAF-C domain of TRAF2, disrupting the binding between TRAF2 and β -catenin, thereby inhibiting WNT signaling activity. LDA also blocks the formation of the TRAF2/ β -catenin/TCF4/TNFK complex, which maintains the transcriptional activity of WNT signaling in CRC cells [267]. Demethylsteroid A3 (Sdy-1) is a sterol isolated from the endophytic fungus HQD-6 of the *Rhizophora* genus. Sdy-1 can significantly inhibit the proliferation, migration, and invasion of liver and CC cells, induce apoptosis, and suppress tumor growth by arresting the cell cycle at the G1 phase. Molecular docking experiments reveal that Sdy-1 binds to key sites such as THR-433 of the β -catenin protein. Sdy-1 can directly reduce the mRNA level of β -catenin and block the binding of nuclear β -catenin to TCF/LEF transcription factors, thereby inhibiting the expression of downstream target genes [268]. Panobinostat (LBH589), as a pan-histone deacetylase inhibitor, exerts significant anti-tumor effects in BC treatment by upregulating the expression of the tumor suppressor gene APCL to inhibit the WNT/ β -catenin signaling pathway. Panobinostat activates the transcription of APCL by increasing histone acetylation levels and the upregulation of APCL promotes the ubiquitination and degradation of β -catenin [269]. Luteolin, a flavonoid monomer isolated from *Paulownia* flowers, binds to β -catenin through hydrogen bonds, causing conformational changes (reduced α -helix, increased β -sheet) to inhibit its activity [269]. 4 β -hydroxywithanolide E (4 β HWE) is a natural glycolic acid with a 17 α -oriented side chain. 4 β HWE promotes the phosphorylation of β -catenin at Ser33/Ser37/Thr41 sites to enhance its ubiquitination and degradation [270]. In addition, researchers identified a small molecule inhibitor C2, which

directly targets the allosteric site of β -catenin, alters its conformation, and exposes phosphorylation sites, triggering the degradation of β -catenin via the ubiquitin–proteasome pathway [271]. B-cell lymphoma 9 (BCL9) is a β -transcriptional co-activator. The C-1 inhibits the β -catenin/BCL9 complex, thereby blocking the WNT signaling pathway [272]. Moreover, researchers isolated a novel compound, Linderapyrone, from the stems and branches of *Lindera umbellata*. Experiments show that Linderapyrone, with its pyrone and monoterpene moieties, can effectively block the WNT signaling pathway by inhibiting β -catenin/TCF transcriptional activity [273]. Additionally, small molecule inhibitors of the β -catenin/TCF transcriptional complex, PKF115-584, CGP049090, and PKF118-310, have been shown to significantly inhibit the progression of HCC [274, 275]. In another study, it was found that CGP049090 and PKF115-584 effectively kill CLL cells but exhibit lower toxicity to normal B cells, demonstrating selective anti-cancer activity [276]. Furthermore, researchers identified the compound ZINC02092166 through high-throughput screening, which effectively inhibits β -catenin/TCF. To address the potential reactivity of the acyl hydrazone group that may cause off-target effects, derivatives 26, 33, and 37 were designed by replacing the acyl hydrazone group with chemically more stable structures such as amides or tetrazole rings. These compounds maintain inhibitory activity while significantly reducing off-target effects and enhancing selectivity for β -catenin/TCF [277].

CREB-binding protein (CBP) is a crucial transcriptional coactivator, essential for activating cancer-related WNT genes. ICG-001, a selective CBP/ β -catenin antagonist screened from 5000 secondary structure mimics, specifically binds to CBP, thereby blocking the interaction between CBP and β -catenin. This drug forces CSCs to switch from self-renewal to symmetric differentiation, thereby eliminating CSCs, while normal somatic stem cells, which rely on asymmetric division to maintain homeostasis, are not significantly affected [278]. Moreover, the combination of ICG-001 and ZSTK-474 (a PI3K inhibitor) significantly enhances the cytotoxicity of ICG-001, inducing apoptosis in T-ALL [279]. ICG-001 also exerts anticancer effects in pancreatic ductal adenocarcinoma (PDAC) and tamoxifen-resistant BC cells [280, 281]. PRI-724 is a second-generation small molecule antagonist of CBP/ β -catenin interaction, which inhibits the activity of the WNT/ β -catenin/CBP signaling pathway by blocking the binding of β -catenin to CBP, thereby reversing chemotherapy resistance caused by RBMS3 deficiency. In RBMS3-deficient EOC cells, the combination of PRI-724 and cisplatin significantly enhances chemotherapy sensitivity and apoptosis rates [282]. In a Phase I/IIa study (NCT03620474), PRI-724 administered

at a dose of 280 mg/m² over 4 h (twice weekly via intravenous infusion for 12 weeks) was preliminarily assessed as well-tolerated in patients with liver cirrhosis. Based on liver biopsy evaluations (collagen proportionate area or fibrosis staging), PRI-724 did not significantly reduce hepatic fibrosis area. However, significant improvements were observed in liver stiffness measurement and serum albumin levels after treatment. Through fragment-based virtual screening and structure-guided medicinal chemistry optimization, highly effective and selective compounds (1-(1H-indol-1-yl) ethanone derivatives) are identified. Among them, derivative 32 h exhibits twice the inhibitory activity against the CBP bromodomain compared to the known inhibitor SGC-CBP30 and shows significant selectivity for CBP/EP300 [283]. Other inhibitors include GNE-781, JW67, JW74, and E7386 [284–287].

Advances in WNT-targeted therapies

New therapeutic approaches targeting the WNT signaling pathway are being explored, which may offer new possibilities for enhancing anticancer activity and reducing adverse reactions in future clinical trials, including the combination of WNT signaling pathway targeting with immunotherapy, Antibody–Drug Conjugation, non-coding RNA therapeutics, Antisense Oligonucleotides, Proteolysis Targeting Chimeras and Molecular glues.

Immunotherapy

Deactivation of the immune system constitutes a critical mechanism underlying cancer resistance to immune checkpoint inhibitors. Reactivating the immune system has emerged as a promising antitumor strategy. Currently, multiple studies have shown that the WNT signaling pathway is involved in mediating the regulation of the immune system in cancer. Consequently, combining WNT/ β -catenin pathway inhibitors with immunotherapy may overcome therapeutic resistance and potentiate the antitumor capacity of immune cells. Ganesh, S et al. developed DCR-BCAT, a therapeutic agent employing RNA interference to specifically suppress β -catenin expression. DCR-BCAT remarkably enhances T cell and dendritic cell infiltration in tumor microenvironment, reverses immune "cold" phenotype, and synergizes with anti-PD-1/CTLA-4 checkpoint inhibitors [288]. Another study demonstrates that in patients resistant to PD-1/PD-L1 antibodies, DKN-01 exerts anti-tumor effects primarily through immune activation in combination with pembrolizumab and nivolumab. The tumor suppression effect of DKN-01 combined with anti-PD-1 antibodies is significantly superior to that of monotherapy [289, 290]. Currently, clinical studies on the combination of WNT signaling pathway inhibitors with immune checkpoint

inhibitors are increasing, which may provide new insights for enhancing the efficacy of immunotherapy and overcoming immune resistance in cancer treatment in the future.

Antibody-Drug Conjugation

Antibody-Drug Conjugation (ADC) utilizes antibodies to specifically recognize tumor surface antigens, enabling targeted delivery of cytotoxic agents to cancer cells. Through endocytosis and lysosomal release mechanisms, these conjugates achieve precise drug activation, significantly reducing the off-target toxicity of traditional chemotherapy [291]. Septuximab vedotin (F7-ADC) employs its antibody component to bind the extracellular domain of FZD7, facilitating drug internalization into lysosomes and subsequent release of the cytotoxic payload monomethyl auristatin E (MMAE), thereby selectively eliminating OC cells with high FZD7 expression. Notably, F7-ADC does not interfere with the WNT signaling pathway itself, circumventing the bone-related adverse effects commonly observed with conventional WNT inhibitors [292]. Other ADCs include PF-06647020, LGR5-mc-vc-PAB-MMAE, and LRG5-NMs818 [293, 294].

Non-coding RNA therapeutics

MiRNAs are a type of non-coding RNA that primarily function by interacting with mRNAs. Substantial evidence demonstrates that miRNAs exhibit tumor-suppressive functions in cancers characterized by aberrant activation of the WNT signaling pathway. These regulatory RNAs effectively modulate protein levels in the WNT/ β -catenin pathway, thereby suppressing the expression of molecules associated with tumorigenesis and progression [295]. For instance, miR-384-5p exerts anti-tumor effects by downregulating the expression of FZD1, FZD2, and LRP6 [296]. In addition, another type of non-coding RNA, siRNA, also exhibits anti-tumor potential. Researchers have engineered a novel bioengineered BERA-WNT5A siRNA that inhibits the non-canonical WNT pathway through WNT5A/FZD2 axis suppression, effectively curbing the growth of therapy-resistant PCa [297].

Antisense Oligonucleotides

Antisense Oligonucleotides (ASOs) are synthetic short-chain nucleic acid molecules that selectively target specific RNA or DNA sequences through Watson-Crick base pairing principles. Their primary mechanism involves binding to target mRNA via complementary base pairing, forming duplex structures that either trigger mRNA degradation or block its translation into proteins. ASOs can specifically target oncogenes or modulate aberrant splicing sites, thereby inhibiting tumor growth,

angiogenesis, or metastasis [298]. In one study, lncRNA AC104041.1 is significantly overexpressed in head and neck squamous cell carcinoma. lncRNA AC104041.1 sponges miR-6817-3p, thereby relieving the inhibitory effect of miR-6817-3p on WNT2B, driving tumor growth and metastasis. ASO targeting AC104041.1 effectively inhibits tumor growth and metastasis, while the antibiotic salinomycin further enhances the anti-tumor effect of the ASO by blocking the WNT/ β -catenin signaling pathway [299]. Researchers also used second-generation ASOs to target β -catenin, reducing β -catenin mRNA levels by 70–80% and cytoplasmic/nuclear protein levels in the liver and white adipose tissue, thereby regulating lipid metabolism [300].

Proteolysis Targeting Chimeras

Proteolysis Targeting Chimeras (PROTACs), as an emerging drug development technology, catalyze the degradation of target proteins through the ubiquitin-proteasome system, providing new insights for the treatment of cancer and other diseases. PROTACs are bifunctional small-molecule drugs composed of three parts: (1) a target protein ligand that specifically binds to the target protein; (2) an E3 ubiquitin ligase; and (3) a linker that optimizes the spatial conformation between the two, inducing the proximity of the target protein and the E3 ligase [301]. Currently, researchers have applied PROTACs to target the WNT signaling pathway for cancer treatment. By conjugating the β -catenin-binding peptide xStAx with a VHL E3 ligase ligand, the designed PROTAC peptide xStAx-VHLL achieves sustained degradation of β -catenin through the ubiquitin-proteasome system, with effects significantly superior to those of the xStAx peptide alone or existing small-molecule inhibitors of the WNT signaling pathway (e.g., PRI-724, PNU-74654). However, PROTACs face limitations in binding capacity, specificity, and availability [302]. Therefore, based on the co-crystal structure of the BCL9 protein and β -catenin, researchers design a peptide-based degrader called PepTAC (β CatPepTAC). Utilizing the efficient cellular uptake, stability, and targeting capabilities of lipid nanoparticle carriers, NP-delivered β CatPepTAC significantly degrades β -catenin and inhibits WNT-driven transcriptional activity [303].

Molecular glues

Molecular glues are a class of single-molecule small compounds that reshape the interface of E3 ubiquitin ligases to induce the formation of stable ternary complexes with disease-causing proteins. This process triggers the degradation of the target proteins via the ubiquitin-proteasome pathway. Unlike bifunctional PROTACs, molecular glues do not require linking two ligands.

Instead, they directly enhance the interaction between the E3 ligase and the target protein [304]. Based on the 6-trifluoromethylpyridone and biarylamine scaffolds, compounds such as NRX-252114 and NRX-252262 have been designed as molecular glues. These compounds strengthen the interaction between β -catenin and the SCF β -TrCP E3 ligase, forming a stable ternary complex. The molecular glues promote the ubiquitination of β -catenin, leading to its degradation through the proteasome pathway, thereby exerting anti-cancer effects in CRC [305, 306].

Challenges and future directions

The development of WNT-targeted therapies confronts a tripartite challenge spanning biological complexity, clinical stratification, and therapeutic integration. First, the dual role of WNT signaling in tissue homeostasis and tumorigenesis necessitates precision targeting to avoid catastrophic on-target toxicity, compounded by pathway redundancy and spatial heterogeneity within tumor niches. Second, biomarker innovation must transcend static genomic markers toward dynamic readouts: single-cell spatial transcriptomics could map WNT activity gradients, while liquid biopsy-based DKK1/LGR5 tracking may predict adaptive resistance. Third, rational combination strategies require systems-level optimization—WNT inhibitors with ICBs could reverse T-cell exhaustion via β -catenin/PD-L1 crosstalk blockade, while radiotherapy synergy might exploit WNT-mediated DNA repair vulnerability. Future success hinges on organ-specific pathway mapping and microenvironment-adapted delivery systems.

Challenges of targeting the WNT signaling pathway

The WNT signaling pathway plays a critical role in maintaining normal cellular physiological functions. Aberrant activation or suppression of this pathway is closely associated with cancer initiation and progression. Preclinical studies have demonstrated that targeting the WNT pathway exhibits promising antitumor activity, indicating its key regulatory components as attractive therapeutic targets in malignancies. Therefore, researchers have devoted considerable efforts to developing drugs targeting the WNT signaling pathway [307]. Although several WNT signaling inhibitors have shown favorable outcomes in ongoing clinical trials, no WNT-specific therapeutic agent has received clinical approval to date. A major concern is that targeting the WNT signaling pathway in cancer treatment may induce adverse events. Because the pleiotropic functions of WNT signaling in normal cellular processes are indispensable for tissue homeostasis and repair, pathway inhibition may lead to unintended consequences on normal tissue functions [307]. For

example, the first-generation WNT pathway inhibitors, PORCN inhibitors, such as LGK974 and ETC-159, are pan-WNT pathway inhibitors. When these two PORCN inhibitors are administered to mice, the treatment induces dose-dependent adverse effects, such as reductions in bone volume and density [308]. Another example of WNT pathway inhibitor toxicity is TNKS inhibitors. Despite exhibiting excellent antitumor efficacy in preclinical studies, current TNKS inhibitors manifest multiorgan toxicity, particularly gastrointestinal toxicity, during clinical trials [309]. In addition, studies have shown that inhibiting the WNT pathway may adversely affect normal WNT-dependent stem cell populations. Therefore, next-generation WNT inhibitors must achieve potent antitumor efficacy while preserving physiologically essential WNT signaling. Some researchers believe that the WNT signaling pathway receptor FZD is promising therapeutic targets. On one hand, the FZDs family consists of 10 members, which can be further divided into four subfamilies based on their sequences: FZD1/2/7, FZD4/9/10, FZD5/8, and FZD3/6. FZD exhibits distinct tissue-specific expression patterns and plays a crucial role in initiating multiple WNT signaling branches. On the other hand, in mouse models, FZD7 has been shown to be essential for maintaining intestinal and atrial gastric epithelial cells. FZD7 knockout mice are fertile under basic, non-challenging conditions, indicating that the loss of FZD7 in a developing organism can be compensated for by other mechanisms. Furthermore, in adults, the downregulation of FZD7 does not prevent but rather delays intestinal regeneration [310]. Although the broad-spectrum FZD inhibitor Vantictumab was discontinued in Phase I clinical trials due to an increased frequency of fractures, the lack of FZD specificity—particularly targeting FZD1, FZD4, and FZD8, which are important for bone homeostasis—is a critical factor. Therefore, the development of highly selective inhibitors targeting specific FZD subtypes is a future direction [311]. Zhang, M. et al. have proposed how the widespread presence of drug-targetable allosteric sites in FZD could guide structure- or mechanism-based drug design, and have outlined the therapeutic potential of developing bispecific ligands targeting this receptor family in the future [312]. In addition, mapping the organ-specific pathway is another noteworthy approach. A recent study utilizes machine learning models to quantify T1 relaxation times (a biomarker of interstitial fibrosis) in the liver, pancreas, heart, and kidneys among 43,881 UK Biobank participants. The research revealed both organ-specific and shared cross-organ fibrosis pathways. Through genome-wide association studies, the investigation identified genetic loci associated with fibrosis across these organs, including SLC39A8, HFE, and ABO [313].

Development of WNT pathway biomarkers for patient stratification

The use of biomarkers for the precise stratification of cancer patients has been demonstrated to effectively reduce cancer-related mortality. These biomarkers assist clinicians in selecting appropriate treatment strategies and identifying patients at high or low risk of tumor progression, which allows for the refinement of monitoring and the allocation of early therapeutic interventions. Given that the expression of various components of the WNT signaling pathway is deregulated in many tumor tissues and contributes to tumor proliferation, invasion, and metastasis, the WNT signaling pathway may serve as a potential biomarker [311] (Table 2).

Prognostic biomarkers

Numerous studies have demonstrated that core components of the WNT signaling pathway play a significant role in tumor progression. Abnormal expression of WNT, FZD, β -catenin, and other elements is positively

correlated with poor prognosis in various cancers. The WNT signaling pathway holds potential as a prognostic biomarker. For instance, high expression of β -catenin in CC tissues is significantly associated with tumor metastasis, reduced progression-free survival, and overall survival [323]. Additionally, researchers have explored the value of E-cadherin and β -catenin as prognostic biomarkers in esophageal squamous cell carcinoma, revealing that patients with dual-positive expression have significantly higher survival rates compared to those with single-positive or dual-negative expression [331]. In PDAC, β -catenin is significantly upregulated in metastatic tissues, potentially driving metastasis by promoting EMT and matrix metalloproteinase activity. β -catenin specifically upregulated in metastatic lesions may serve as predictive markers for metastasis [315]. Beyond β -catenin, WNT5A also exhibits potential prognostic value in high-grade serous OC, CRC, PCa, EC, and HCC [314, 318, 320, 321, 332]. For example, the expression rate of WNT5A in HCC tissues is significantly lower than in adjacent

Table 2 The Summary of WNT Signaling Pathway Components as Cancer Biomarkers

Biomarker Type	WNT Signaling Pathway Component	Cancer Type	Role	References
Prognostic Biomarker	WNT5A	HCC	Tumor-suppressive effects	[314]
	β -catenin	PDAC	Promotes metastasis and invasion	[315]
	β -catenin	EC	Inhibits invasion and metastasis	[316]
	WNT8B	HCC	Promotes cancer cell proliferation	[317]
	β -catenin	Endometrioid Endometrial Cancer	Promotes cancer invasion	[318]
	TCF7	GC	Promotes metastasis and invasion	[319]
	WNT5A-S	CRC	Inhibits CRC cell proliferation	[320]
	WNT5A-L	CRC	Promotes CRC cell proliferation	[320]
	WNT5A	OC	Promotes migration and invasion	[321]
	WNT6	CRC, GC, BC, GBM	Promotes metastasis and invasion	[322]
	β -catenin	CC	Promotes infiltration	[323]
	WNT11	CC	Promotes metastasis	[323]
Diagnostic Biomarker	WNT11	SCLC	Promotes proliferation and EMT	[324]
	WNT3A	HCC	Promotes proliferation and differentiation	[325]
	β -catenin	Non-Seminomatous Germ Cell Tumor	Suppresses tumor immunity	[326]
	β -catenin	Desmoid-Type Fibromatosis		[327]
	LEF1	BA, Pancreatic Solid Pseudopapillary Neoplasm		[327]
	LEF1	Sinonasal Hemangiopericytoma		[328]
	β -catenin	OSCC	Promotes EMT	[329]
	APCL	OSCC	Promotes EMT	[329]
	WNT6	OS		[330]
	PORCN	OC	High PORCN expression correlates with sensitivity to WNT974 therapy	[217]
Therapeutic Biomarker	APCL	BC	High APCL expression correlates with sensitivity to Panobinostat therapy	[296]

Abbreviations:PDAC pancreatic ductal adenocarcinoma,EC esophageal cancer,GC gastric cancer,CRC colorectal cancer,OC ovarian cancer,GC gastric cancer,BC breast cancer,SCLC small cell lung cancer,OSCC oral squamous cell carcinoma,OS osteosarcoma,EMT epithelial-mesenchymal transition,LRP low-density lipoprotein receptor-related protein,EC endometrial cancer,GBM Glioblastoma multiforme

tissues, and its expression intensity gradually decreases with clinical stage progression. Low WNT5A expression is significantly correlated with poor prognostic factors, including poorly differentiated tumors, portal vein tumor thrombus, high TNM staging, and reduced 5-year survival rates [314]. Conversely, WNT5A is highly expressed in PCa and CRC [320, 332]. In PCa, WNT5A expression is associated with shorter overall survival, higher Gleason scores, and shorter recurrence times. WNT5A-S is highly expressed in CRC cell lines and tumor tissues, while WNT5A-L is significantly low. WNT5A-S has a pro-cancer effect: knocking down its expression can inhibit CRC cell proliferation and induce apoptosis. WNT5A-L has a tumor-suppressive effect: restoring its expression can enhance apoptosis and inhibit β -catenin expression. The combination of high WNT5A-S expression and low WNT5A-L expression is associated with poor patient prognosis [320]. Moreover, WNT8B has also been reported as a potential prognostic biomarker in HCC. High WNT8B expression is linked to adverse pathological features such as large tumor volume, liver cirrhosis, and high ALT levels. Patients with high WNT8B expression have significantly shorter overall survival and recurrence-free survival [317]. Tulu Hong et al. report that BC tissues exhibit high FZD2 expression, which is closely related to poor distant metastasis-free survival and overall survival [333]. Additionally, FZD2 has the potential to predict patient prognosis in other cancers such as serous OC, HCC, and EC [334–336]. Other FZDs, such as FZD3 and FZD6, have been reported as potential prognostic biomarkers for melanoma and OSCC, respectively [198, 337]. TCF7 is a novel independent prognostic biomarker in GC. High TCF7 expression is closely associated with the invasiveness and metastasis of GC, and patients with high TCF7 expression have significantly lower 5-year survival rates compared to those with low expression [319].

Diagnostic biomarkers

Identifying clinically valuable tumor biomarkers for precise diagnosis is an auxiliary method to achieve ideal clinical outcomes. Researchers have investigated the diagnostic value of WNT11 in SCLC. WNT11 is involved in regulating neuroendocrine differentiation, cell proliferation, and E-cadherin expression in SCLC, suggesting its close association with the malignant phenotype of SCLC. The high expression of WNT11 in the cytoplasm and perinuclear regions of SCLC cells can serve as a pathological diagnostic marker to distinguish SCLC from NSCLC [324]. Other studies have found that WNT3A can promote malignant transformation of hepatocytes by activating the WNT/ β -catenin pathway. WNT3A is significantly upregulated from the early stages of HCC development, and its expression level is positively

correlated with disease progression, the sensitivity of which is even superior to AFP. As a dynamically upregulated molecule during HCC development, WNT3A exhibits high sensitivity and specificity, making it a highly promising biomarker for early diagnosis [325]. In OS patients, serum WNT6 levels are significantly higher than those in ES, osteomyelitis patients, and healthy controls. Serum WNT6 may serve as a diagnostic tool for liquid biopsy to differentiate OS from other bone-related diseases. In neuroblastoma, WNT6 is highly expressed in high-risk neuroblastoma without MYCN amplification, potentially serving as a diagnostic marker for this high-risk subtype [338]. Additionally, β -catenin is also a potential diagnostic biomarker. β -catenin is highly expressed in non-seminomatous germ cell tumors but shows very low expression in seminomas. High expression of β -catenin is also associated with high PD-L1 expression and low SII in tumor cells. β -catenin and LEF1 have been used in combined diagnosis. β -catenin is highly expressed in desmoid-type fibromatosis (DF) but shows low sensitivity in basal cell adenoma (BA), whereas LEF1 has significantly higher sensitivity in BA than β -catenin but lower sensitivity in DF. LEF1 can complement β -catenin as a diagnostic marker, and their combined use significantly improves diagnostic accuracy [326]. In sinonasal glomangiopericytoma (SN-GPC), high nuclear expression of β -catenin and LEF1 is observed. In glomus tumors, LEF1 is negative, while it may be partially positive in some solitary fibrous tumors. Therefore, high expression of β -catenin and LEF1 can be used to distinguish SN-GPC from glomus tumors but cannot differentiate it from some solitary fibrous tumors. Researchers have found that all SN-GPC cases do not express stat6, whereas solitary fibrous tumors show strong positivity for stat6. Stat6 negativity helps exclude solitary fibrous tumors, and the combined detection of β -catenin, LEF1, and stat6 can enhance the specificity of SN-GPC diagnosis [328]. Furthermore, in familial adenomatous polyposis (FAP) screening, germline mutations in the APC gene are the primary genetic cause of FAP, with a very high risk of developing CRC. Early screening and intervention for FAP patients and their family members can be achieved by detecting APC mutations. Biallelic APC mutations are an early driving event in most sporadic CRC and can be detected at the adenoma stage, indicating its potential as a molecular marker for early diagnosis [339].

Therapeutic biomarkers

In OC patients, PORCN as a key enzyme in WNT ligand secretion shows high expression in ascites samples, indicating abnormal activation of the WNT pathway. Studies have demonstrated that high expression of PORCN in OC cells is significantly associated with sensitivity

to WNT974, suggesting its potential use in identifying patient populations suitable for WNT974 treatment [217]. In BC, APC1 is a tumor suppressor gene and inhibits the WNT/ β -catenin signaling pathway by promoting the ubiquitination and degradation of β -catenin. Its upregulation is a crucial mechanism of Panobinostat's therapeutic effect in BC. Kaplan–Meier analysis reveals that high expression of APC1 is significantly correlated with better prognosis in BC patients, particularly in Luminal A, Luminal B, and triple-negative subtypes. The expression level of APC1 is closely related to the efficacy of Panobinostat and patient outcomes, highlighting its potential as a biomarker for selecting patients for Panobinostat treatment [269].

Rational combinations of WNT-targeted therapy with other therapeutic strategies

Cancer is an extremely complex disease, and its development involves a series of multiple consecutive mutations in cells. Additionally, chemotherapy can select for mutations that favor the survival of tumor cells, making drug resistance a significant challenge in cancer treatment. Therefore, when targeting the WNT signaling pathway for therapy, single-pathway inhibition may not be sufficient to induce tumor regression. Furthermore, the adverse effects such as gastrointestinal toxicity and fractures observed in clinical trials of WNT pathway inhibitors emphasize that combining WNT-targeted therapy with other treatment modalities is a promising approach to enhance anti-tumor efficacy and reduce cytotoxicity.

Single-pathway targeted therapies often have limited efficacy due to compensatory activation of other pathways, leading to tumor resistance or recurrence. Therefore, combination therapeutic strategies targeting pathway intersections hold greater potential. For instance, the WNT, Hedgehog, and Notch signaling pathways, which are highly conserved, play critical roles in cancer initiation, progression, and recurrence. These pathways not only independently drive tumor formation but also establish a complex cross-regulatory signaling network that maintains CSC stemness and tumor heterogeneity. Consequently, simultaneous inhibition of WNT and Hedgehog or WNT and Notch can synergistically suppress tumor cell proliferation and eliminate CSCs, thereby reducing the risk of recurrence [340]. In GBM, both the PI3K/AKT/mTOR and WNT/ β -Catenin pathways are aberrantly activated, regulating cell proliferation, metabolism, and the maintenance of stemness, invasion, and chemoresistance. Preclinical studies have shown that combined use of mTOR inhibitors Rapamycin and WNT pathway antagonists β -catenin siRNA synergistically blocks tumor proliferation, stemness, and drug resistance [341]. Additionally, in AML, the AKT/mTOR

and WNT/ β -Catenin signaling pathways are hyperactivated in PRL-3-high cancer cells. The combined use of PI3K/mTOR inhibitors VS-5584 and WNT inhibitors ICG-001 has demonstrated significant synergistic cytotoxic effects, inducing apoptosis in PRL-3-high AML cells [342]. Furthermore, in CRC cells with concurrent WNT pathway activation and KRAS mutations, the combination of β -catenin inhibitors PKF115-584 or pyvinium pamoate and KRAS inhibitors FTS synergistically inhibits cell proliferation and induces apoptosis [343]. Beyond cancer, in non-neoplastic diseases such as ankylosing spondylitis, activation of the WNT and SMAD pathways enhances the osteogenic differentiation capacity of fibroblasts. The combined use of DKK-1 and SIS3, a selective small-molecule inhibitor of SMAD3 that inhibits SMAD3 phosphorylation and attenuates its binding to target DNA, significantly outperforms single inhibitors in suppressing fibroblast proliferation, promoting apoptosis, and inhibiting osteogenic differentiation [344].

The combination of WNT signaling inhibitors with radiotherapy and chemotherapy is also a joint therapeutic strategy. For instance, in CRC, β -catenin is involved in cancer cell resistance to 5-Fluorouracil (5-FU). 4-O-Methylasclochlorin effectively inhibits the viability of 5-FU-resistant cells and reduces drug resistance by downregulating the expression of β -catenin. When 4-O-Methylasclochlorin is used in combination with 5-FU, it significantly enhances the apoptosis of CRC cells, with a superior effect compared to monotherapy [345]. Additionally, carbon dots (A-CDs) with intrinsic WNT/ β -catenin inhibitory capabilities are successfully prepared through a one-step hydrothermal method using aloe. These A-CDs are then used as carriers to load the chemotherapeutic drug 5-FU, forming CDs@5-FU complexes, which are further modified with hyaluronic acid (HA) to achieve tumor targeting (HA-CDs@5-FU). The result shows that HA-CDs@5-FU significantly outperform free 5-FU in inhibiting colon and LCA cells, with lower toxicity to normal liver cells [346]. Niclosamide enhances the binding of the β -catenin destruction complex to β -catenin, promoting its phosphorylation and subsequent ubiquitination, leading to β -catenin degradation via the proteasome, thereby inhibiting the expression of downstream target genes of the WNT/ β -catenin pathway. The combination of niclosamide with gemcitabine significantly enhances the inhibition of PCA cell proliferation, outperforming gemcitabine monotherapy [347]. Furthermore, the combination of ICG-001 with radiotherapy significantly inhibits HCC tumor growth and extends the survival period in mice [348].

Many studies have reported the therapeutic effects of combining WNT signaling inhibitors with immunotherapy. For instance, the RNAi drug DCR-BCAT, which

targets β -catenin, has been shown to significantly inhibit the growth of various types of tumors when used in combination with anti-PD-1/CTLA-4 antibodies [288]. Clofazimine, by inhibiting the WNT6-mediated WNT/ β -catenin signaling pathway, reduces the expression of PD-L1 in tumor cells and suppresses EMT, thereby weakening the tumor's immune escape capability and enhancing the efficacy of anti-PD-1 immunotherapy. The combination of clofazimine and anti-PD-1 has been found to significantly inhibit the proliferation, invasion, and intracranial spread of GBM cells [349]. Additionally, arsenic trioxide has demonstrated significant anti-tumor activity in MCL. The primary mechanisms include the inhibition of the WNT signaling pathway and the suppression of DNA methyltransferase-1 expression, which reactivates silenced tumor suppressor genes or WNT pathway inhibitors through demethylation, further inhibiting tumorigenesis. The combination of arsenic trioxide with the demethylating agent 5-azacytidine has emerged as a potential therapeutic strategy for MCL [350]. Furthermore, a novel WNT signaling inhibitor, Rh-1, has also been reported to exhibit anti-cancer effects when used in combination with PD-1 inhibitors [351].

Inhibitors of the WNT signaling pathway combined with other methods: Researchers investigated the effects of combining Sorafenib and the β -catenin inhibitor FH535 on the metabolism and mitochondrial function of HCC cells. The result shows that Sorafenib alone reduces the glycolytic capacity of HCC cells, while FH535 has no significant effect on this. However, the combination of the two significantly decreases the mitochondrial respiration rate and ATP production, and induces the loss of mitochondrial membrane potential (ΔY_m), ultimately leading to apoptosis of HCC cells. The synergistic effect of Sorafenib and FH535 stems from the dual inhibition of key metabolic pathways in HCC cells, providing a new approach for the treatment of HCC [352]. In another study, researchers combine targeting the WNT signaling pathway with autophagy inhibition for the treatment of TNBC. They use FZD7-NS in combination with the autophagy inhibitor chloroquine (CQ). FZD7-NS significantly inhibits the expression of WNT downstream genes by blocking the interaction between WNT ligands and the FZD7 receptor, while upregulating the autophagy marker LC3. The combination of FZD7-NS and CQ synergistically reduces the expression of genes associated with CSCs and simultaneously inhibit the migration and self-renewal abilities of BC cells [353].

Conclusions and perspectives

Despite extensive and prolonged research on this fundamental and highly conserved WNT signaling pathway, we still lack definitive answers on how to safely target it for

therapeutic purposes. Over the past 15 years, inhibitors targeting various components of the WNT pathway have shown promising results in preclinical studies, yet no FDA-approved drugs targeting WNT are currently available for clinical use. Acceptable safety remains a central challenge in WNT-targeted therapies, and determining how to selectively target WNT components in specific tumor types while optimizing dosage is key to overcoming current limitations.

Nevertheless, given the substantial body of early research demonstrating the therapeutic potential of WNT modulation in cancer—along with the ongoing discovery of new regulatory factors and pathway components—further investigation into WNT-targeted cancer therapies remains highly warranted. Some researchers have proposed shifting the focus of WNT inhibitor development from upstream WNT effectors to specific mutations in cytoplasmic components to improve specificity. Additionally, they suggest that nanoparticle drug delivery systems may offer a novel approach to cancer treatment due to their potential for targeted cell delivery and precise drug release. Others have highlighted that identifying druggable structures and binding sites within WNT components could facilitate the development of more specific therapeutics. Additionally, to optimize cancer therapeutics targeting the WNT signaling pathway, we also propose several promising research directions, including bispecific antibody development, organ-specific pathway mapping and microenvironment-adaptive delivery systems. These approaches demonstrate significant potential for advancing precision oncology while maintaining fidelity to biological mechanisms.

Through this review, we illustrate the cancer-promoting mechanisms of the WNT signaling pathway from different perspectives and comprehensively review the current research status of WNT signaling pathway inhibitors. Finally, we focus on the possible research directions for optimizing WNT signaling pathway inhibitors, hoping to provide new research ideas for future WNT signaling pathway-targeted therapies.

Abbreviations

PCP	Planar cell polarity
FZD	Frizzled
LRP	Low-density lipoprotein receptor-related protein
RNF43	Ring finger protein 43
ZNRF3	Zinc and ring finger 3
CK1	Casein kinase 1
Ser	Serine
Thr	Threonine
GSK-3 β	Glycogen synthase kinase-3 β
APC	Adenomatous polyposis coli
PP2A	Protein phosphatase 2A
WTX	Wilms tumor gene on the X chromosome
β -TrCP	β -Transducin repeat-containing protein
CTBP	C-terminal binding protein
GRG	Groucho

HDACs	Histone deacetylases	HA	Hyaluronic acid
DVL	Dishevelled	CQ	Chloroquine
JNK2	Jun N-terminal kinase 2	Asn	Asparagine
CaMKII	Calcium calmodulin mediated kinase II	CD	Carbon dots
NFAT	Nuclear factor of activated T cells	SLL	Small Lymphocytic Lymphoma
VANGL	Vang-like	OC	Ovarian cancer
CELSR	Cadherin EGF LAG seven-pass G-type receptor	GC	Gastric cancer
INTU	Inturned	BC	Breast cancer
INVS	Inversin	EC	Esophageal cancer
RYK	Receptor-like tyrosine kinase	PDAC	Pancreatic ductal adenocarcinoma
MUSK	Muscle-skeletal receptor Tyr kinase	FL	Follicular lymphoma
PTK7	Protein tyrosine kinase 7	MCL	Mantle cell lymphoma
ROR1/2	Receptor Tyr kinase-like orphan receptor 1/2	ES	Ewing sarcoma
DAAM	Dvl-associated activator of morphogenesis	NHL	Non-Hodgkin lymphoma
RHOA	Ras homolog family member A	GA	Gastric adenocarcinoma
ROCK	RHO-associated coiled-coil-containing protein kinase	SCC	Squamous cell carcinoma
DIA1	Diaphanous 1	HL	Hodgkin's lymphoma
MRLC	Mitogen-activated protein kinase	STK3	Serine/threonine kinase 3
CapZIP	CapZ-interacting protein	BMSC	Bone marrow stromal cell
PLC	Phospholipase C	MaSC	Mammary stem cell
IP3	Inositol 1,4,5-triphosphate	ICD	Intracellular domain
DAG	1,2-Diacylglycerol	PTC	Patched
CaN	Calcineurin	SMO	Smoothed
PKC	Protein kinase C	PORCN	Porcupine
EMT	Epithelial-mesenchymal transition	RSPO	Spondin
TGF- β	Transforming growth factor- β	CRBN	Cereblon
YAP	Yes-associated protein	TRAF2	Tumor necrosis factor receptor-associated factor 2
TAZ	Transcriptional co-activator with PDZ-binding motif	CAX	Cycloatrobiloxanthone
CLL	Chronic lymphocytic leukemia	KRT19	Keratin 19
OSCC	Oral squamous cell carcinoma	CC	Cervical cancer
JAG1	Jagged 1	EC	Endometrial cancer
NF- κ B	Nuclear factor- κ B	PCa	Prostate cancer
EDA	Ectodysplasin A	RCC	Renal cell carcinoma
DDX	DEAD-box helicase 5	LCA	Lung cancer
AURKAIP1	Aurora-A kinase interacting protein 1	PCA	Pancreatic cancer
CRC	Colorectal cancer	PD	Programmed death
GBM	Glioblastoma multiforme	PK	Pharmacokinetics
HCC	Hepatocellular carcinoma	mCRC	Metastatic CRC
AFP	Alpha-Fetoprotein	BRAF	Raf proto-oncogene
AR	Androgen receptor	HER2	Human epidermal growth factor receptor 2
MSC	Mesenchymal stem cell	HR	Hormone receptor
NSCLC	Non-small cell lung cancer	OXA	Oxaliplatin
CSC	Cancer stem cell	CD44v6	CD44 containing variable exon 6
TMD	Transmembrane domain	CRD-BP	Coding region determinant-binding protein
TNBC	Triple-negative breast cancer	GEC	Gastroesophageal cancer
CRD	Cysteine-rich domain		
TcdB	Clostridium difficile toxin B		
HB	Hepatoblastoma		
TNKS	Tankyrase		
PARP	Poly(ADP-ribose) polymerase		
OS	Osteosarcoma		
LDA	Liquidambaric acid		
4 β HWE	4 β -hydroxywithanolide E		
BCL9	B-cell lymphoma 9		
CBP	CREB-binding protein		
AMP	Adenosine monophosphate		
AMPK	Adenosine monophosphate-activated protein kinase		
5-LO	5-lipoxygenase		
ADC	Antibody-Drug Conjugation		
ASO	Antisense Oligonucleotide		
PROTAC	Proteolysis Targeting Chimera		
MTD	Maximum tolerated dose		
DLT	Dose-limiting toxicities		
AML	Acute myeloid leukemia		
BTC	Biliary tract cancer		
DLBCL	Diffuse large B-cell lymphoma		
SCLC	Small cell lung cancer		
DF	Desmoid-type fibromatosis		
BA	Basal cell adenoma		
SN-GPC	Sinonasal glomangiopericytoma		
5-FU	5-Fluorouracil		

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Authors' contributions

J.L. and D.Z. conceived and revised this manuscript. J-Q.L. and Y.P. wrote the manuscript and designed the figures. J.Y. provided substantial ideas and help in manuscript. All authors have read and approved the final manuscript.

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References

- Parsons MJ, Tammela T, Dow LE. WNT as a driver and dependency in cancer. *Cancer Discov*. 2021;11(10):2413–29. <https://doi.org/10.1158/2159-8290.Cd-21-0190>.
- Yu M, Qin K, Fan J, Zhao G, Zhao P, Zeng W, et al. The evolving roles of Wnt signaling in stem cell proliferation and differentiation, the development of human diseases, and therapeutic opportunities. *Genes Dis*. 2024;11(3):101026. <https://doi.org/10.1016/j.gendis.2023.04.042>.
- Onyido EK, Sweeney E, Nateri AS. Wnt-signalling pathways and microRNAs network in carcinogenesis: experimental and bioinformatics approaches. *Mol Cancer*. 2016;15(1):56. <https://doi.org/10.1186/s12943-016-0541-3>.
- Kahn M. Can we safely target the WNT pathway? *Nat Rev Drug Discov*. 2014;13(7):513–32. <https://doi.org/10.1038/nrd4233>.
- Zou G, Park JI. Wnt signaling in liver regeneration, disease, and cancer. *Clin Mol Hepatol*. 2023;29(1):33–50. <https://doi.org/10.3350/cmh.2022.0058>.
- Yu J, Liao PJ, Keller TH, Cherian J, Virshup DM, Xu W. Ultra-large scale virtual screening identifies a small molecule inhibitor of the Wnt transporter Wntless. *iScience*. 2024;27(8):110454. <https://doi.org/10.1016/j.isci.2024.110454>.
- Xu X, Zhang M, Xu F, Jiang S. Wnt signaling in breast cancer: biological mechanisms, challenges and opportunities. *Mol Cancer*. 2020;19(1):165. <https://doi.org/10.1186/s12943-020-01276-5>.
- Bruguera ES, Mahoney JP, Weis WI. The co-receptor Tetraspanin12 directly captures Norrin to promote ligand-specific β -catenin signaling. *Elife*. 2025. <https://doi.org/10.7554/eLife.96743>.
- Yu L, Wei W, Lv J, Lu Y, Wang Z, Cai C. FABP4-mediated lipid metabolism promotes TNBC progression and breast cancer stem cell activity. *Cancer Lett*. 2024;604:217271. <https://doi.org/10.1016/j.canlet.2024.217271>.
- Zhang F, Li Y, Xu W, He L, Tan Y, Xu H. Long non-coding RNA ZFAS1 regulates the malignant progression of gastric cancer via the microRNA-200b-3p/Wnt1 axis. *Biosci Biotechnol Biochem*. 2019;83(7):1289–99. <https://doi.org/10.1080/09168451.2019.1606697>.
- Peng C, Lu Y, Ren X, Wang Y, Zhang S, Chen M, et al. Comprehensive bioinformatic analysis of Wnt1 and Wnt1-associated diseases. *Intractable Rare Dis Res*. 2020;9(1):14–22. <https://doi.org/10.5582/irdr.2020.01018>.
- Zhang XZ, Mo XC, Wang ZT, Sun R, Sun DQ. N-glycosylation of Wnt3 regulates the progression of hepatocellular carcinoma by affecting Wnt/ β -catenin signal pathway. *World J Gastrointest Oncol*. 2024;16(6):2769–80. <https://doi.org/10.4251/wjgo.v16.i6.2769>.
- Schulte G, Scharf MM, Bous J, Voss JH, Grätz L, Kozieliwicz P. Frizzleds act as dynamic pharmacological entities. *Trends Pharmacol Sci*. 2024;45(5):419–29. <https://doi.org/10.1016/j.tips.2024.03.003>.
- Li Y, Liu Z, Zhang Y. Expression and prognostic impact of FZDs in pancreatic adenocarcinoma. *BMC Gastroenterol*. 2021;21(1):79. <https://doi.org/10.1186/s12876-021-01643-6>.
- Wang J, Yu H, Dong W, Zhang C, Hu M, Ma W, et al. N6-methyladenosine-mediated up-regulation of FZD10 regulates liver cancer stem cells' properties and lenvatinib resistance through WNT/ β -catenin and hippo signaling pathways. *Gastroenterology*. 2023;164(6):990–1005. <https://doi.org/10.1053/j.gastro.2023.01.041>.
- Li B, Li X, Jiang Z, Zhou D, Feng Y, Chen G, et al. LncRNA XIST modulates miR-328-3p ectopic expression in lung injury induced by tobacco-specific lung carcinogen NNK both in vitro and in vivo. *Br J Pharmacol*. 2024;181(15):2509–27. <https://doi.org/10.1111/bph.16373>.
- Nag JK, Appasamy P, Malka H, Sedley S, Bar-Shavit R. New target(s) for RNF43 regulation: implications for therapeutic strategies. *Int J Mol Sci*. 2024. <https://doi.org/10.3390/ijms25158083>.
- Bugter JM, van Kerkhof P, Jordens I, Janssen E, Tran Ngoc Minh T, Iglesias van Montfort D, et al. E3 ligases RNF43 and ZNRF3 display differential specificity for endocytosis of Frizzled receptors. *Life Sci Alliance*. 2024;7(9). <https://doi.org/10.26508/lsa.202402575>.
- Cui B, Luo H, He B, Liu X, Lv D, Zhang X, et al. Gut dysbiosis conveys psychological stress to activate LRP5/ β -catenin pathway promoting cancer stemness. *Signal Transduct Target Ther*. 2025;10(1):79. <https://doi.org/10.1038/s41392-025-02159-1>.
- Rong Z, Zhang L, Li Z, Xiao Z, Duan Y, Ren X, et al. SIK2 maintains breast cancer stemness by phosphorylating LRP6 and activating Wnt/ β -catenin signaling. *Oncogene*. 2022;41(16):2390–403. <https://doi.org/10.1038/s41388-022-02259-0>.
- Nie X, Wang H, Wei X, Li L, Xue T, Fan L, et al. LRP5 promotes gastric cancer via activating canonical Wnt/ β -catenin and glycolysis pathways. *Am J Pathol*. 2022;192(3):503–17. <https://doi.org/10.1016/j.ajpath.2021.11.007>.
- Ma J, Lu W, Chen D, Xu B, Li Y. Role of wnt co-receptor LRP6 in triple negative breast cancer cell migration and invasion. *J Cell Biochem*. 2017;118(9):2968–76. <https://doi.org/10.1002/jcb.25956>.
- Tung EK, Wong BY, Yau TO, Ng IO. Upregulation of the Wnt co-receptor LRP6 promotes hepatocarcinogenesis and enhances cell invasion. *PLoS ONE*. 2012;7(5):e36565. <https://doi.org/10.1371/journal.pone.0036565>.
- Ghatak S, Hascall VC, Karamanos N, Markwald RR, Misra S. Chemotherapy induces feedback up-regulation of CD44v6 in colorectal cancer initiating cells through β -catenin/MDR1 signaling to sustain chemoresistance. *Front Oncol*. 2022;12:906260. <https://doi.org/10.3389/fonc.2022.906260>.
- Nusse R, Clevers H. Wnt/ β -catenin signaling, disease, and emerging therapeutic modalities. *Cell*. 2017;169(6):985–99. <https://doi.org/10.1016/j.cell.2017.05.016>.
- Rim EY, Clevers H, Nusse R. The Wnt pathway: from signaling mechanisms to synthetic modulators. *Annu Rev Biochem*. 2022;91:571–98. <https://doi.org/10.1146/annurev-biochem-040320-103615>.
- Liu J, Stevens J, Rote CA, Yost HJ, Hu Y, Neufeld KL, et al. Slah-1 mediates a novel β -catenin degradation pathway linking p53 to the adenomatous polyposis coli protein. *Mol Cell*. 2001;7(5):927–36. [https://doi.org/10.1016/s1097-2765\(01\)00241-6](https://doi.org/10.1016/s1097-2765(01)00241-6).
- Nguyen VHL, Hough R, Bernado S, Peng C. Wnt/ β -catenin signalling in ovarian cancer: insights into its hyperactivation and function in tumorigenesis. *J Ovarian Res*. 2019;12(1):122. <https://doi.org/10.1186/s13048-019-0596-z>.
- Krutsenko Y, Singh AD, Monga SP. β -catenin activation in hepatocellular cancer: implications in biology and therapy. *Cancers (Basel)*. 2021. <https://doi.org/10.3390/cancers13081830>.
- Wang T, Fu J, Huang Y, Fu C. Mechanism of APC truncation involved in colorectal cancer tumorigenesis (Review). *Oncol Lett*. 2025;29(1):2. <https://doi.org/10.3892/ol.2024.14748>.
- Feng GJ, Cotta W, Wei XQ, Poetz O, Evans R, Jardé T, et al. Conditional disruption of Axin1 leads to development of liver tumors in mice. *Gastroenterology*. 2012;143(6):1650–9. <https://doi.org/10.1053/j.gastro.2012.08.047>.
- Zhang R, Li S, Schippers K, Eimers B, Niu J, Hornung BVH, et al. Unraveling the impact of AXIN1 mutations on HCC development: insights from CRISPR/Cas9 repaired AXIN1-mutant liver cancer cell lines. *PLoS ONE*. 2024;19(6):e0304607. <https://doi.org/10.1371/journal.pone.0304607>.
- Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3beta participates in nuclear factor kappaB-mediated gene transcription and cell survival in pancreatic cancer cells. *Cancer Res*. 2005;65(6):2076–81. <https://doi.org/10.1158/0008-5472.Can-04-3642>.
- Tao S, Pu Y, Yang EJ, Ren G, Shi C, Chen LJ, et al. Inhibition of GSK3 β is synthetic lethal with FHIT loss in lung cancer by blocking homologous recombination repair. *Exp Mol Med*. 2025;57(1):167–83. <https://doi.org/10.1038/s12276-024-01374-0>.
- Borden BA, Baca Y, Xiu J, Tavora F, Winer I, Weinberg BA, et al. The landscape of glycogen synthase kinase-3 beta genomic alterations in

- cancer. *Mol Cancer Ther*. 2021;20(1):183–90. <https://doi.org/10.1158/1535-7163.Mct-20-0497>.
36. Zhou J, Wang X, Li Z, Wang F, Cao L, Chen X, et al. PIM1 kinase promotes EMT-associated osimertinib resistance via regulating GSK3 β signaling pathway in EGFR-mutant non-small cell lung cancer. *Cell Death Dis*. 2024;15(9):644. <https://doi.org/10.1038/s41419-024-07039-0>.
 37. Tsai IC, Woolf M, Neklason DW, Branford WW, Yost HJ, Burt RW, et al. Disease-associated casein kinase I delta mutation may promote adenomatous polyps formation via a Wnt/beta-catenin independent mechanism. *Int J Cancer*. 2007;120(5):1005–12. <https://doi.org/10.1002/ijc.22368>.
 38. Schitteck B, Sinnberg T. Biological functions of casein kinase 1 isoforms and putative roles in tumorigenesis. *Mol Cancer*. 2014;13:231. <https://doi.org/10.1186/1476-4598-13-231>.
 39. Wong HC, Bourdela A, Krauss A, Lee HJ, Shao Y, Wu D, et al. Direct binding of the PDZ domain of Dishevelled to a conserved internal sequence in the C-terminal region of Frizzled. *Mol Cell*. 2003;12(5):1251–60. [https://doi.org/10.1016/s1097-2765\(03\)00427-1](https://doi.org/10.1016/s1097-2765(03)00427-1).
 40. Murillo-Garzon V, Kypta R. Wnt signalling in prostate cancer. *Nat Rev Urol*. 2017;14(11):683–96. <https://doi.org/10.1038/nrurol.2017.144>.
 41. Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, et al. Wnt/ β -catenin signaling: function, biological mechanisms, and therapeutic opportunities. *Signal Transduct Target Ther*. 2022;7(1):3. <https://doi.org/10.1038/s41392-021-00762-6>.
 42. Wang L, Zhu R, Wen Z, Fan HS, Norwood-Jackson T, Jathan D, et al. Structural and Functional Insights into Dishevelled-Mediated Wnt Signaling. *Cells*. 2024;13(22). <https://doi.org/10.3390/cells13221870>.
 43. Yang Y, Jiang H, Li W, Chen L, Zhu W, Xian Y, et al. FOXM1/DVL2/Snail axis drives metastasis and chemoresistance of colorectal cancer. *Aging (Albany NY)*. 2020;12(23):24424–40. <https://doi.org/10.18632/aging.202300>.
 44. Zeng B, Li Y, Feng Y, Lu M, Yuan H, Yi Z, et al. Downregulated miR-1247-5p associates with poor prognosis and facilitates tumor cell growth via DVL1/Wnt/ β -catenin signaling in breast cancer. *Biochem Biophys Res Commun*. 2018;505(1):302–8. <https://doi.org/10.1016/j.bbrc.2018.09.103>.
 45. Alshahrani SH, Rakhimov N, Rana A, Alsaab HO, Hjazi A, Adile M, et al. Dishevelled: an emerging therapeutic oncogene in human cancers. *Pathol Res Pract*. 2023;250:154793. <https://doi.org/10.1016/j.prp.2023.154793>.
 46. Jung H, Kim BG, Han WH, Lee JH, Cho JY, Park WS, et al. Deubiquitination of dishevelled by Usp14 is required for Wnt signaling. *Oncogenesis*. 2013;2(8):e64. <https://doi.org/10.1038/oncsis.2013.28>.
 47. Rubinfeld B, Robbins P, El-Gamil M, Albert I, Porfiri E, Polakis P. Stabilization of beta-catenin by genetic defects in melanoma cell lines. *Science*. 1997;275(5307):1790–2. <https://doi.org/10.1126/science.275.5307.1790>.
 48. Molenaar M, van de Wetering M, Oosterwegel M, Peterson-Maduro J, Godsave S, Korinek V, et al. XTcf-3 transcription factor mediates beta-catenin-induced axis formation in *Xenopus* embryos. *Cell*. 1996;86(3):391–9. [https://doi.org/10.1016/s0092-8674\(00\)80112-9](https://doi.org/10.1016/s0092-8674(00)80112-9).
 49. Tian X, Liu Z, Niu B, Zhang J, Tan TK, Lee SR, et al. E-cadherin/ β -catenin complex and the epithelial barrier. *J Biomed Biotechnol*. 2011;2011:567305. <https://doi.org/10.1155/2011/567305>.
 50. Loh CY, Chai JY, Tang TF, Wong WF, Sethi G, Shanmugam MK, et al. The E-cadherin and N-cadherin switch in epithelial-to-mesenchymal transition: signaling, therapeutic implications, and challenges. *Cells*. 2019. <https://doi.org/10.3390/cells8101118>.
 51. Wang D, Wu S, He J, Sun L, Zhu H, Zhang Y, et al. FAT4 overexpression promotes antitumor immunity by regulating the β -catenin/STT3/PD-L1 axis in cervical cancer. *J Exp Clin Cancer Res*. 2023;42(1):222. <https://doi.org/10.1186/s13046-023-02758-2>.
 52. Sun H, Zhang Y, Wang F, Wang Z, Zhang Y, Chen Y, et al. Sorbs3- β suppresses lymph node metastasis in cervical cancer by promoting the ubiquitination of β -catenin. *J Transl Med*. 2025;23(1):406. <https://doi.org/10.1186/s12967-025-06409-2>.
 53. Zhang Y, Liu H, Zhang Q, Zhang Z. Long Noncoding RNA LINC01006 Facilitates Cell Proliferation, Migration, and Epithelial-Mesenchymal Transition in Lung Adenocarcinoma via Targeting the MicroRNA 129–2–3p/CTNNB1 Axis and Activating Wnt/ β -Catenin Signaling Pathway. *Mol Cell Biol*. 2021;41(6):e0038020. <https://doi.org/10.1128/mcb.00380-20>.
 54. Fen L, Yuanwan W, Tian C, Yingying W, Yongping W, Mingwan Z, et al. Molecular network analysis of CPEB4 translational control and targeting CPEB4/ β -catenin to modulate invasion and migration of nasopharyngeal carcinoma cells. *Int J Med Sci*. 2025;22(6):1329–43. <https://doi.org/10.7150/ijms.103024>.
 55. You Z, Sima Z, Guo X, Li X, Feng Y, Du N, et al. Mutational landscape of ameloblastoma: analysis of BRAF and other key mutations in Chinese patients. *Oral Dis*. 2025. <https://doi.org/10.1111/odi.15286>.
 56. Coorens THH, Collord G, Jung H, Wang Y, Moore L, Hooks Y, et al. The somatic mutation landscape of normal gastric epithelium. *Nature*. 2025;640(8058):418–26. <https://doi.org/10.1038/s41586-025-08708-6>.
 57. Ding M, Ma C, Lin Y, Fang H, Xu Y, Wang S, et al. Therapeutic targeting *de novo* purine biosynthesis driven by β -catenin-dependent PPAT upregulation in hepatoblastoma. *Cell Death Dis*. 2025;16(1):179. <https://doi.org/10.1038/s41419-025-07502-6>.
 58. Yan Y, Gong Y, Liang X, Xiong Q, Lin J, Wu Y, et al. Decoding β -catenin associated protein-protein interactions: emerging cancer therapeutic opportunities. *Biochimica et Biophysica Acta (BBA)*. 2025;1880(1):189232. <https://doi.org/10.1016/j.bbcan.2024.189232>.
 59. Lehrich BM, Tao J, Liu S, Hirsch TZ, Yasaka TM, Cao C, et al. Development of mutated β -catenin gene signature to identify CTNNB1 mutations from whole and spatial transcriptomic data in patients with HCC. *JHEP Rep*. 2024;6(12):101186. <https://doi.org/10.1016/j.jhepr.2024.101186>.
 60. Zhou F, Qin L, Huang S, Lin W, Zhang H, Parkash V, et al. Plomatrix-like high-grade endometrial carcinoma: an underdiagnosed entity with aggressive clinicopathologic features. *Am J Surg Pathol*. 2025;49(8):818–29. <https://doi.org/10.1097/pas.0000000000002402>.
 61. Caspi M, Wittenstein A, Kazelnik M, Shor-Nareznay Y, Rosin-Arbesfeld R. Therapeutic targeting of the oncogenic Wnt signaling pathway for treating colorectal cancer and other colonic disorders. *Adv Drug Deliv Rev*. 2021;169:118–36. <https://doi.org/10.1016/j.addr.2020.12.010>.
 62. Ring L, Neth P, Weber C, Steffens S, Faussner A. β -Catenin-dependent pathway activation by both promiscuous “canonical” WNT3a- and specific “noncanonical” WNT4- and WNT5a-FZD receptor combinations with strong differences in LRP5 and LRP6 dependency. *Cell Signal*. 2014;26(2):260–7. <https://doi.org/10.1016/j.cellsig.2013.11.021>.
 63. Pashirzad M, Fiuji H, Khazei M, Moradi-Binabaj M, Ryzhikov M, Shabani M, et al. Role of Wnt3a in the pathogenesis of cancer, current status and prospective. *Mol Biol Rep*. 2019;46(5):5609–16. <https://doi.org/10.1007/s11033-019-04895-4>.
 64. VanderVorst K, Dreyer CA, Konopelski SE, Lee H, Ho HH, Carraway KL 3rd. Wnt/PCP Signaling Contribution to Carcinoma Collective Cell Migration and Metastasis. *Cancer Res*. 2019;79(8):1719–29. <https://doi.org/10.1158/0008-5472.Can-18-2757>.
 65. Torban E, Sokol SY. Planar cell polarity pathway in kidney development, function and disease. *Nat Rev Nephrol*. 2021;17(6):369–85. <https://doi.org/10.1038/s41581-021-00395-6>.
 66. Wald JH, Hatakeyama J, Printsev I, Cuevas A, Fry WHD, Saldana MJ, et al. Suppression of planar cell polarity signaling and migration in glioblastoma by Nrdp1-mediated Dvl polyubiquitination. *Oncogene*. 2017;36(36):5158–67. <https://doi.org/10.1038/onc.2017.126>.
 67. Anastas JN, Biechele TL, Robitaille M, Muster J, Allison KH, Angers S, et al. A protein complex of SCRIB, NOS1AP and VANG1 regulates cell polarity and migration, and is associated with breast cancer progression. *Oncogene*. 2012;31(32):3696–708. <https://doi.org/10.1038/onc.2011.528>.
 68. Li Y, Zhu L, Hao R, Li Y, Zhao Q, Li S. Systematic expression analysis of the CELSR family reveals the importance of CELSR3 in human lung adenocarcinoma. *J Cell Mol Med*. 2021;25(9):4349–62. <https://doi.org/10.1111/jcmm.16497>.
 69. Adler PN, Zhu C, Stone D. Inturned localizes to the proximal side of wing cells under the instruction of upstream planar polarity proteins. *Curr Biol*. 2004;14(22):2046–51. <https://doi.org/10.1016/j.cub.2004.11.007>.
 70. Katoh M. WNT/PCP signaling pathway and human cancer (review). *Oncol Rep*. 2005;14(6):1583–8.
 71. Peng Y, Chen Z, Chen Y, Li S, Jiang Y, Yang H, et al. Rock isoforms differentially modulate cancer cell motility by mechanosensing the substrate stiffness. *Acta Biomater*. 2019;88:86–101. <https://doi.org/10.1016/j.actbio.2019.02.015>.

72. Evers CE, McNeill H, Knebel A, Morrice N, Arthur SJ, Cuenda A, et al. The phosphorylation of CapZ-interacting protein (CapZIP) by stress-activated protein kinases triggers its dissociation from CapZ. *Biochem J*. 2005;389(Pt 1):127–35. <https://doi.org/10.1042/bj20050387>.
73. Semenov MV, Habas R, Macdonald BT, He X. SnapShot: Noncanonical Wnt Signaling Pathways. *Cell*. 2007;131(7):1378. <https://doi.org/10.1016/j.cell.2007.12.011>.
74. Casado-Medrano V, Baker MJ, Lopez-Haber C, Cooke M, Wang S, Caloca MJ, et al. The role of Rac in tumor susceptibility and disease progression: from biochemistry to the clinic. *Biochem Soc Trans*. 2018;46(4):1003–12. <https://doi.org/10.1042/bst20170519>.
75. Tang J, Ip JP, Ye T, Ng YP, Yung WH, Wu Z, et al. Cdk5-dependent Mst3 phosphorylation and activity regulate neuronal migration through RhoA inhibition. *J Neurosci*. 2014;34(22):7425–36. <https://doi.org/10.1523/jneurosci.5449-13.2014>.
76. Olson MF. Rho GTPases, their post-translational modifications, disease-associated mutations and pharmacological inhibitors. *Small GTPases*. 2018;9(3):203–15. <https://doi.org/10.1080/21541248.2016.1218407>.
77. Yoo HY, Sung MK, Lee SH, Kim S, Lee H, Park S, et al. A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. *Nat Genet*. 2014;46(4):371–5. <https://doi.org/10.1038/ng.2916>.
78. Fukukawa C, Nagayama S, Tsunoda T, Toguchida J, Nakamura Y, Katagiri T. Activation of the non-canonical Dvl-Rac1-JNK pathway by Frizzled homologue 10 in human synovial sarcoma. *Oncogene*. 2009;28(8):1110–20. <https://doi.org/10.1038/onc.2008.467>.
79. De AW. Wnt/Ca²⁺ signaling pathway: a brief overview. *Acta Biochim Biophys Sin*. 2011;43(10):745–56. <https://doi.org/10.1093/abbs/gmr079>.
80. Harb J, Lin PJ, Hao J. Recent development of Wnt signaling pathway inhibitors for cancer therapeutics. *Curr Oncol Rep*. 2019;21(2):12. <https://doi.org/10.1007/s11912-019-0763-9>.
81. Mikoshiba K. IP3 receptor/Ca²⁺ channel: from discovery to new signaling concepts. *J Neurochem*. 2007;102(5):1426–46. <https://doi.org/10.1111/j.1471-4159.2007.04825.x>.
82. Zhao Z, Hu Y, Li H, Lu T, He X, Ma Y, et al. Inhibition of stromal MAOA leading activation of WNT5A enhance prostate cancer immunotherapy by involving the transition of cancer-associated fibroblasts. *J Immunother Cancer*. 2025. <https://doi.org/10.1136/jitc-2024-010555>.
83. Huang L, Jin Y, Feng S, Zou Y, Xu S, Qiu S, et al. Role of Wnt/ β -catenin, Wnt/c-Jun N-terminal kinase and Wnt/Ca²⁺ pathways in cisplatin-induced chemoresistance in ovarian cancer. *Exp Ther Med*. 2016;12(6):3851–8. <https://doi.org/10.3892/etm.2016.3885>.
84. Tian S, Hu J, Tao K, Wang J, Chu Y, Li J, et al. Secreted AGR2 promotes invasion of colorectal cancer cells via Wnt11-mediated non-canonical Wnt signaling. *Exp Cell Res*. 2018;364(2):198–207. <https://doi.org/10.1016/j.yexcr.2018.02.004>.
85. Wang Q, Symes AJ, Kane CA, Freeman A, Nariculam J, Munson P, et al. A novel role for Wnt/Ca²⁺ signaling in actin cytoskeleton remodeling and cell motility in prostate cancer. *PLoS ONE*. 2010;5(5):e10456. <https://doi.org/10.1371/journal.pone.0010456>.
86. Akoumianakis I, Polkinghorne M, Antoniadis C. Non-canonical WNT signalling in cardiovascular disease: mechanisms and therapeutic implications. *Nat Rev Cardiol*. 2022;19(12):783–97. <https://doi.org/10.1038/s41569-022-00718-5>.
87. Shah R, Amador C, Chun ST, Ghiam S, Saghizadeh M, Kramerov AA, et al. Non-canonical Wnt signaling in the eye. *Prog Retin Eye Res*. 2023;95:101149. <https://doi.org/10.1016/j.preteyeres.2022.101149>.
88. Deng Z, Fan T, Xiao C, Tian H, Zheng Y, Li C, et al. TGF- β signaling in health, disease, and therapeutics. *Signal Transduct Target Ther*. 2024;9(1):61. <https://doi.org/10.1038/s41392-024-01764-w>.
89. Mitsui Y, Yamabe F, Hori S, Uetani M, Kobayashi H, Nagao K, et al. Molecular mechanisms and risk factors related to the pathogenesis of Peyronie's disease. *Int J Mol Sci*. 2023. <https://doi.org/10.3390/ijms241210133>.
90. Zhang Y, Jin D, Kang X, Zhou R, Sun Y, Lian F, et al. Signaling pathways involved in diabetic renal fibrosis. *Front Cell Dev Biol*. 2021;9:696542. <https://doi.org/10.3389/fcell.2021.696542>.
91. Ekman M, Mu Y, Lee SY, Edlund S, Kozakai T, Thakur N, et al. APC and Smad7 link TGF β type I receptors to the microtubule system to promote cell migration. *Mol Biol Cell*. 2012;23(11):2109–21. <https://doi.org/10.1091/mbc.E10-12-1000>.
92. Letamendia A, Labbé E, Attisano L. Transcriptional regulation by Smads: crosstalk between the TGF- β and Wnt pathways. *J Bone Joint Surg Am*. 2001;83-A Suppl 1(Pt 1):S31–9.
93. Furuhashi M, Yagi K, Yamamoto H, Furukawa Y, Shimada S, Nakamura Y, et al. Axin facilitates Smad3 activation in the transforming growth factor β signaling pathway. *Mol Cell Biol*. 2001;21(15):5132–41. <https://doi.org/10.1128/mcb.21.15.5132-5141.2001>.
94. Sileo P, Simonin C, Melnyk P, Chartier-Harlin MC, Cotelle P. Crosstalk between the hippo pathway and the Wnt pathway in Huntington's disease and other neurodegenerative disorders. *Cells*. 2022. <https://doi.org/10.3390/cells11223631>.
95. Imajo M, Miyatake K, Iimura A, Miyamoto A, Nishida E. A molecular mechanism that links hippo signalling to the inhibition of Wnt/ β -catenin signalling. *EMBO J*. 2012;31(5):1109–22. <https://doi.org/10.1038/emboj.2011.487>.
96. Xie F, Lyu Y, Chen B, Leung HW, Yu P, Feng T, et al. STK3 is a transcriptional target of YAP1 and a hub component in the crosstalk between Hippo and Wnt signaling pathways during gastric carcinogenesis. *Mol Cancer*. 2025;24(1):186. <https://doi.org/10.1186/s12943-025-02391-x>.
97. Azzolin L, Panciera T, Soligo S, Enzo E, Bicciato S, Dupont S, et al. YAP/TAZ incorporation in the β -catenin destruction complex orchestrates the Wnt response. *Cell*. 2014;158(1):157–70. <https://doi.org/10.1016/j.cell.2014.06.013>.
98. Wang J, Park JS, Wei Y, Rajurkar M, Cotton JL, Fan Q, et al. TRB2 acts downstream of Wnt/TCF in liver cancer cells to regulate YAP and C/EBP α function. *Mol Cell*. 2013;51(2):211–25. <https://doi.org/10.1016/j.molcel.2013.05.013>.
99. Byun MR, Hwang JH, Kim AR, Kim KM, Hwang ES, Yaffe MB, et al. Canonical Wnt signalling activates TAZ through PP1A during osteogenic differentiation. *Cell Death Differ*. 2014;21(6):854–63. <https://doi.org/10.1038/cdd.2014.8>.
100. Park HW, Kim YC, Yu B, Moroishi T, Mo JS, Plouffe SW, et al. Alternative Wnt signaling activates YAP/TAZ. *Cell*. 2015;162(4):780–94. <https://doi.org/10.1016/j.cell.2015.07.013>.
101. Jiang J. Hedgehog signaling mechanism and role in cancer. *Semin Cancer Biol*. 2022;85:107–22. <https://doi.org/10.1016/j.semcancer.2021.04.003>.
102. Farahmand L, Darvishi B, Majidzadeh AK, Madjid Ansari A. Naturally occurring compounds acting as potent anti-metastatic agents and their suppressing effects on Hedgehog and WNT/ β -catenin signalling pathways. *Cell Prolif*. 2017;50(1). <https://doi.org/10.1111/cpr.12299>.
103. He J, Sheng T, Stelter AA, Li C, Zhang X, Sinha M, et al. Suppressing wnt signaling by the hedgehog pathway through sFRP-1. *J Biol Chem*. 2006;281(47):35598–602. <https://doi.org/10.1074/jbc.C600200200>.
104. Wang B, Li Y. Evidence for the direct involvement of β cat/Trip in Gli3 protein processing. *Proc Natl Acad Sci U S A*. 2006;103(1):33–8. <https://doi.org/10.1073/pnas.0509927103>.
105. Shin K, Lee J, Guo N, Kim J, Lim A, Qu L, et al. Hedgehog/Wnt feedback supports regenerative proliferation of epithelial stem cells in bladder. *Nature*. 2011;472(7341):110–4. <https://doi.org/10.1038/nature09851>.
106. Rockel JS, Yu C, Whetstone H, Craft AM, Reilly K, Ma H, et al. Hedgehog inhibits β -catenin activity in synovial joint development and osteoarthritis. *J Clin Invest*. 2016;126(5):1649–63. <https://doi.org/10.1172/jci80205>.
107. Qualtrough D, Rees P, Speight B, Williams AC, Paraskeva C. The hedgehog inhibitor cyclopamine reduces β -catenin-tcf transcriptional activity, induces E-cadherin expression, and reduces invasion in colorectal cancer cells. *Cancers (Basel)*. 2015;7(3):1885–99. <https://doi.org/10.3390/cancers7030867>.
108. Gumed DB, Abrahamse H, Houeild NN. Targeting Wnt/ β -catenin signaling and its interplay with TGF- β and Notch signaling pathways for the treatment of chronic wounds. *Cell Commun Signal*. 2024;22(1):244. <https://doi.org/10.1186/s12964-024-01623-9>.
109. Mangolini M, Götte F, Moore A, Ammon T, Oelsner M, Lutzny-Geier G, et al. Notch2 controls non-autonomous Wnt-signalling in chronic lymphocytic leukaemia. *Nat Commun*. 2018;9(1):3839. <https://doi.org/10.1038/s41467-018-06069-5>.
110. Camps J, Pitt JJ, Emons G, Hummon AB, Case CM, Grade M, et al. Genetic amplification of the NOTCH modulator LNX2 upregulates the WNT/ β -catenin pathway in colorectal cancer. *Cancer Res*. 2013;73(6):2003–13. <https://doi.org/10.1158/0008-5472.Can-12-3159>.

111. Patni AP, Harishankar MK, Joseph JP, Sreeshma B, Jayaraj R, Devi A. Comprehending the crosstalk between Notch, Wnt and Hedgehog signaling pathways in oral squamous cell carcinoma - clinical implications. *Cell Oncol (Dordr)*. 2021;44(3):473–94. <https://doi.org/10.1007/s13402-021-00591-3>.
112. Estrach S, Ambler CA, Lo Celso C, Hozumi K, Watt FM. Jagged 1 is a beta-catenin target gene required for ectopic hair follicle formation in adult epidermis. *Development*. 2006;133(22):4427–38. <https://doi.org/10.1242/dev.02644>.
113. Saha SK, Yin Y, Chae HS, Cho SG. Opposing regulation of cancer properties via KRT19-mediated differential modulation of Wnt/ β -catenin/Notch signaling in breast and colon cancers. *Cancers (Basel)*. 2019. <https://doi.org/10.3390/cancers11010099>.
114. Saha SK, Choi HY, Kim BW, Dayem AA, Yang GM, Kim KS, et al. KRT19 directly interacts with β -catenin/RAC1 complex to regulate NUMB-dependent NOTCH signaling pathway and breast cancer properties. *Oncogene*. 2017;36(3):332–49. <https://doi.org/10.1038/ncr.2016.221>.
115. Gu B, Watanabe K, Sun P, Fallahi M, Dai X. Chromatin effector Pygo2 mediates Wnt-notch crosstalk to suppress luminal/alveolar potential of mammary stem and basal cells. *Cell Stem Cell*. 2013;13(1):48–61. <https://doi.org/10.1016/j.stem.2013.04.012>.
116. Ann EJ, Kim HY, Seo MS, Mo JS, Kim MY, Yoon JH, et al. Wnt5a controls Notch1 signaling through CaMKII-mediated degradation of the SMRT corepressor protein. *J Biol Chem*. 2012;287(44):36814–29. <https://doi.org/10.1074/jbc.M112.356048>.
117. Lamberti C, Lin KM, Yamamoto Y, Verma U, Verma IM, Byers S, et al. Regulation of beta-catenin function by the IkappaB kinases. *J Biol Chem*. 2001;276(45):42276–86. <https://doi.org/10.1074/jbc.M104227200>.
118. Carayol N, Wang CY. IKKalpha stabilizes cytosolic beta-catenin by inhibiting both canonical and non-canonical degradation pathways. *Cell Signal*. 2006;18(11):1941–6. <https://doi.org/10.1016/j.cellsig.2006.02.014>.
119. Huang FI, Chen YL, Chang CN, Yuan RH, Jeng YM. Hepatocyte growth factor activates Wnt pathway by transcriptional activation of LEF1 to facilitate tumor invasion. *Carcinogenesis*. 2012;33(6):1142–8. <https://doi.org/10.1093/carcin/bgs131>.
120. Ma B, Hottiger MO. Crosstalk between Wnt/ β -catenin and NF- κ B signaling pathway during inflammation. *Front Immunol*. 2016;7:378. <https://doi.org/10.3389/fimmu.2016.00378>.
121. Chang J, Liu F, Lee M, Wu B, Ting K, Zara JN, et al. NF- κ B inhibits osteogenic differentiation of mesenchymal stem cells by promoting β -catenin degradation. *Proc Natl Acad Sci U S A*. 2013;110(23):9469–74. <https://doi.org/10.1073/pnas.1300532110>.
122. Rishikaysh P, Dev K, Diaz D, Qureshi WM, Filip S, Mokry J. Signaling involved in hair follicle morphogenesis and development. *Int J Mol Sci*. 2014;15(1):1647–70. <https://doi.org/10.3390/ijms15011647>.
123. Elcheva I, Tarapore RS, Bhatia N, Spiegelman VS. Overexpression of mRNA-binding protein CRD-BP in malignant melanomas. *Oncogene*. 2008;27(37):5069–74. <https://doi.org/10.1038/ncr.2008.141>.
124. Herr P, Hausmann G, Basler K. WNT secretion and signalling in human disease. *Trends Mol Med*. 2012;18(8):483–93. <https://doi.org/10.1016/j.molmed.2012.06.008>.
125. He A, Tian S, Kopper O, Horan DJ, Chen P, Bronson RT, et al. Targeted inhibition of Wnt signaling with a *Clostridioides difficile* toxin B fragment suppresses breast cancer tumor growth. *PLoS Biol*. 2023;21(11):e3002353. <https://doi.org/10.1371/journal.pbio.3002353>.
126. Huang H, Jin H, Lei R, He Z, He S, Chen J, et al. LncRNA-WAL promotes triple-negative breast cancer aggression by inducing β -catenin nuclear translocation. *Mol Cancer Res*. 2024;22(11):1036–50. <https://doi.org/10.1158/1541-7786.Mcr-23-0334>.
127. Zhong W, Jian Y, Zhang C, Li Y, Yuan Z, Xiong Z, et al. Shc4 orchestrates β -catenin pathway-mediated metastasis in triple-negative breast cancer by promoting Src kinase autophosphorylation. *Cancer Lett*. 2024. <https://doi.org/10.1016/j.canlet.2023.216516>.
128. Tian W, Tang Y, Luo Y, Xie J, Zheng S, Zou Y, et al. Aurkaip1 actuates tumor progression through stabilizing DDX5 in triple negative breast cancer. *Cell Death Dis*. 2023;14(12):790. <https://doi.org/10.1038/s41419-023-06115-1>.
129. Liu B, Liu Y, Yang S, Ye J, Hu J, Chen S, et al. Enhanced desmosome assembly driven by acquired high-level desmoglein-2 promotes phenotypic plasticity and endocrine resistance in ER(+) breast cancer. *Cancer Lett*. 2024;600:217179. <https://doi.org/10.1016/j.canlet.2024.217179>.
130. Huang Y, Fan M, Liu Y, Jiang X, Du K, Wu A, et al. Novel biomarkers and drug correlations of non-canonical WNT signaling in prostate and breast cancer. *Discov Oncol*. 2024;15(1):511. <https://doi.org/10.1007/s12672-024-01394-2>.
131. Bayerlová M, Menck K, Klemm F, Wolff A, Pukrop T, Binder C, et al. Ror2 signaling and its relevance in breast cancer progression. *Front Oncol*. 2017;7:135. <https://doi.org/10.3389/fonc.2017.00135>.
132. Makena MR, Ko M, Dang DK, Rao R. Epigenetic modulation of SPCA2 reverses epithelial to mesenchymal transition in breast cancer cells. *Cancers (Basel)*. 2021;13(2):259. <https://doi.org/10.3390/cancers13020259>.
133. Siamakpour-Reihani S, Caster J, Bandhu Nepal D, Courtwright A, Hilliard E, Usary J, et al. The role of calcineurin/NFAT in SFRP2 induced angiogenesis—a rationale for calcineurin inhibition with the calcineurin inhibitor tacrolimus. *PLoS ONE*. 2011;6(6):e20412. <https://doi.org/10.1371/journal.pone.0020412>.
134. Ferrell M, Guven DC, Gomez CG, Nasrollahi E, Giza R, Cheng S, et al. Investigating the WNT and TGF- β pathways alterations and tumor mutation burden in young-onset colorectal cancer. *Sci Rep*. 2024;14(1):17884. <https://doi.org/10.1038/s41598-024-68938-y>.
135. Nunes L, Li F, Wu M, Luo T, Hammarström K, Torell E, et al. Prognostic genome and transcriptome signatures in colorectal cancers. *Nature*. 2024;633(8028):137–46. <https://doi.org/10.1038/s41586-024-07769-3>.
136. Busico A, Gasparini P, Rausa E, Cattaneo L, Bozzi F, Silvestri M, et al. Molecular profiling of pediatric and young adult colorectal cancer reveals a distinct genomic landscapes and potential therapeutic avenues. *Sci Rep*. 2024;14(1):13138. <https://doi.org/10.1038/s41598-024-64149-7>.
137. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell*. 1996;87(2):159–70. [https://doi.org/10.1016/s0092-8674\(00\)81333-1](https://doi.org/10.1016/s0092-8674(00)81333-1).
138. Parker TW, Neufeld KL. APC controls Wnt-induced β -catenin destruction complex recruitment in human colonocytes. *Sci Rep*. 2020;10(1):2957. <https://doi.org/10.1038/s41598-020-59899-z>.
139. Nong J, Kang K, Shi Q, Zhu X, Tao Q, Chen YG. Phase separation of Axin organizes the β -catenin destruction complex. *J Cell Biol*. 2021. <https://doi.org/10.1083/jcb.202012112>.
140. Zhang D, Ni QQ, Wang SY, He WF, Hong ZX, Liu HY, et al. APC mutations disrupt β -catenin destruction complex condensates organized by Axin phase separation. *Cell Mol Life Sci*. 2024;81(1):57. <https://doi.org/10.1007/s00018-023-05068-0>.
141. Reissland M, Hartmann O, Tauch S, Bugter JM, Prieto-Garcia C, Schulte C, et al. USP10 drives cancer stemness and enables super-competitor signalling in colorectal cancer. *Oncogene*. 2024;43(50):3645–59. <https://doi.org/10.1038/s41388-024-03141-x>.
142. Luo LZ, Kim JH, Herrera I, Wu S, Wu X, Park SS, et al. HMG1 acts as an epigenetic gatekeeper of ASCL2 and Wnt signaling during colon tumorigenesis. *J Clin Invest*. 2025. <https://doi.org/10.1172/jci184442>.
143. Chen M, Mashima T, Oishi T, Muramatsu Y, Seto Y, Takamatsu M, et al. APC/PIK3CA mutations and β -catenin status predict tankyrase inhibitor sensitivity of patient-derived colorectal cancer cells. *Br J Cancer*. 2024;130(1):151–62. <https://doi.org/10.1038/s41416-023-02484-8>.
144. Di Paola FJ, Alquati C, Conti G, Calafato G, Turrone S, D'Amico F, et al. Interplay between WNT/PI3K-mTOR axis and the microbiota in APC-driven colorectal carcinogenesis: data from a pilot study and possible implications for CRC prevention. *J Transl Med*. 2024;22(1):631. <https://doi.org/10.1186/s12967-024-05305-5>.
145. Zhang Z, Wang Y, Zhang J, Zhong J, Yang R. COL1A1 promotes metastasis in colorectal cancer by regulating the WNT/PCP pathway. *Mol Med Rep*. 2018;17(4):5037–42. <https://doi.org/10.13892/mmr.2018.8533>.
146. Sui H, Deng W, Chai Q, Han B, Zhang Y, Wei Z, et al. YTE-17 inhibits colonic carcinogenesis by resetting antitumor immune response via Wnt5a/JNK mediated metabolic signaling. *J Pharm Anal*. 2024;14(4):100901. <https://doi.org/10.1016/j.jpba.2023.11.008>.
147. Ma X, Meng Z, Jin L, Xiao Z, Wang X, Tsark WM, et al. CAMK2 γ in intestinal epithelial cells modulates colitis-associated colorectal carcinogenesis via enhancing STAT3 activation. *Oncogene*. 2017;36(28):4060–71. <https://doi.org/10.1038/ncr.2017.16>.
148. Hu L, Dong H, He L, Shi M, Xiang N, Su Y, et al. Evacetrapib elicits anti-tumor effects on colorectal cancer by inhibiting the Wnt/ β -catenin

- signaling pathway and activating the JNK signaling pathway. *Biol Pharm Bull.* 2022;45(9):1238–45. <https://doi.org/10.1248/bpb.b22-00053>.
149. Tufail M, Wu C. WNT5A: a double-edged sword in colorectal cancer progression. *Mutat Res.* 2023;792:108465. <https://doi.org/10.1016/j.mrrrev.2023.108465>.
 150. Wu CM, Chen CH, Tsai KW, Tan MC, Tsai FY, Jiang SS, et al. TCF12 and LncRNA MALAT1 cooperatively harness high cyclin D1 but low β -catenin gene expression to exacerbate colorectal cancer prognosis independently of metastasis. *Cells.* 2024. <https://doi.org/10.3390/cells13242035>.
 151. Song P, Gao Z, Bao Y, Chen L, Huang Y, Liu Y, et al. Wnt/ β -catenin signaling pathway in carcinogenesis and cancer therapy. *J Hematol Oncol.* 2024;17(1):46. <https://doi.org/10.1186/s13045-024-01563-4>.
 152. Xu S, Luo C, Chen D, Tang L, Cheng Q, Chen L, et al. CircMMD reduction following tumor treating fields inhibits glioblastoma progression through FUBP1/FIR/DVL1 and miR-15b-5p/FZD6 signaling. *J Exp Clin Cancer Res.* 2023;42(1):64. <https://doi.org/10.1186/s13046-023-02642-z>.
 153. Yu P, Xu T, Ma W, Fang X, Bao Y, Xu C, et al. PRMT6-mediated transcriptional activation of ythdf2 promotes glioblastoma migration, invasion, and emt via the wnt- β -catenin pathway. *J Exp Clin Cancer Res.* 2024;43(1):116. <https://doi.org/10.1186/s13046-024-03038-3>.
 154. Wang Y, Gao G, Wei X, Zhang Y, Yu J. Ube2t promotes temozolomide resistance of glioblastoma through regulating the Wnt/ β -catenin signaling pathway. *Drug Des Devel Ther.* 2023;17:1357–1369. <https://doi.org/10.2147/dddt.S405450>.
 155. Li Y, Zheng X, Wang J, Sun M, Li D, Wang Z, et al. Exosomal circ-AHCY promotes glioblastoma cell growth via Wnt/ β -catenin signaling pathway. *Ann Clin Transl Neurol.* 2023;10(6):865–78. <https://doi.org/10.1002/acn3.51743>.
 156. Yun EJ, Kim D, Kim S, Hsieh JT, Baek ST. Targeting Wnt/ β -catenin-mediated upregulation of oncogenic NLGN3 suppresses cancer stem cells in glioblastoma. *Cell Death Dis.* 2023;14(7):423. <https://doi.org/10.1038/s41419-023-05967-x>.
 157. Huang M, Zhang D, Wu JY, Xing K, Yeo E, Li C, et al. Wnt-mediated endothelial transformation into mesenchymal stem cell-like cells induces chemoresistance in glioblastoma. *Sci Transl Med.* 2020. <https://doi.org/10.1126/scitranslmed.aay7522>.
 158. Li C, Yang J, Lei S, Wang W. Ska3 promotes glioblastoma proliferation and invasion by enhancing the activation of Wnt/ β -catenin signaling via modulation of the Akt/GSK-3 β axis. *Brain Res.* 2021;1765:147500. <https://doi.org/10.1016/j.brainres.2021.147500>.
 159. Shevchenko V, Arnatskaya N, Zaitsev S, Sharma A, Sharma HS, Bryukhovetskiy A, et al. Proteins of Wnt signaling pathway in cancer stem cells of human glioblastoma. *Int Rev Neurobiol.* 2020;151:185–200. <https://doi.org/10.1016/bs.irn.2020.03.006>.
 160. Goodrich LV, Strutt D. Principles of planar polarity in animal development. *Development.* 2011;138(10):1877–92. <https://doi.org/10.1242/dev.054080>.
 161. Dreyer CA, VanderVorst K, Natwick D, Bell G, Sood P, Hernandez M, et al. A complex of Wnt/planar cell polarity signaling components Vangl1 and Fzd7 drives glioblastoma multiforme malignant properties. *Cancer Lett.* 2023;567:216280. <https://doi.org/10.1016/j.canlet.2023.216280>.
 162. Zhao M, Chen S. The role of VANGL2 in glioma oncogenesis and progression: insights into expression profiles and prognostic relevance. *Front Oncol.* 2024;14:1527226. <https://doi.org/10.3389/fonc.2024.1527226>.
 163. Huang T, Alvarez AA, Pangeni RP, Horbinski CM, Lu S, Kim SH, et al. A regulatory circuit of miR-125b/miR-20b and Wnt signaling controls glioblastoma phenotypes through FZD6-modulated pathways. *Nat Commun.* 2016;7:12885. <https://doi.org/10.1038/ncomms12885>.
 164. Idrissi YA, Rajabi MR, Beumer JH, Monga SP, Saeed A. Exploring the impact of the β -catenin mutations in hepatocellular carcinoma: an in-depth review. *Cancer Control.* 2024;31:10732748241293680. <https://doi.org/10.1177/10732748241293680>.
 165. Hwang YJ, Lee Y, Yu SJ, Hong SK, Yi NJ, Choi Y, et al. Correlation between CTNNB1 mutation status and tumour phenotype in hepatitis B virus-related hepatocellular carcinoma. *Histopathology.* 2025;86(4):547–58. <https://doi.org/10.1111/his.15363>.
 166. Dantzer C, Dif L, Vaché J, Basbous S, Billottet C, Moreau V. Specific features of β -catenin-mutated hepatocellular carcinomas. *Br J Cancer.* 2024;131(12):1871–80. <https://doi.org/10.1038/s41416-024-02849-7>.
 167. Liang B, Zhou Y, Qian M, Xu M, Wang J, Zhang Y, et al. TBX3 functions as a tumor suppressor downstream of activated CTNNB1 mutants during hepatocarcinogenesis. *J Hepatol.* 2021;75(1):120–31. <https://doi.org/10.1016/j.jhep.2021.01.044>.
 168. Lemberger UJ, Fuchs CD, Karer M, Haas S, Stojakovic T, Schöfer C, et al. Hepatocyte specific expression of an oncogenic variant of β -catenin results in cholestatic liver disease. *Oncotarget.* 2016;7(52):86985–98. <https://doi.org/10.18632/oncotarget.13521>.
 169. Wang K, Wu J, Yang Z, Zheng B, Shen S, Wang RR, et al. Hyperactivation of β -catenin signal in hepatocellular carcinoma recruits myeloid-derived suppressor cells through PF4-CXCR3 axis. *Cancer Lett.* 2024;586:216690. <https://doi.org/10.1016/j.canlet.2024.216690>.
 170. Gu Y, Wang Z, Liang G, Peng J, Zhang X, Yu T, et al. Sirt7 stabilizes β -catenin and promotes canonical Wnt activation via upregulating FZD7. *Life Sci.* 2024;359:123240. <https://doi.org/10.1016/j.lfs.2024.123240>.
 171. Zhang X, Wu N, Huang H, Li S, Liu S, Zhang R, et al. Phosphorylated PTTG1 switches its subcellular distribution and promotes β -catenin stabilization and subsequent transcription activity. *Oncogene.* 2023;42(32):2439–55. <https://doi.org/10.1038/s41388-023-02767-7>.
 172. Su Z, Lu C, Zhang F, Liu H, Li M, Qiao M, et al. Cancer-associated fibroblasts-secreted exosomal miR-92a-3p promotes tumor growth and stemness in hepatocellular carcinoma through activation of Wnt/ β -catenin signaling pathway by suppressing AXIN1. *J Cell Physiol.* 2024;239(9):e31344. <https://doi.org/10.1002/jcp.31344>.
 173. Jeng KS, Chang CF, Sheen IS, Jeng CJ, Wang CH. Cellular and molecular biology of cancer stem cells of hepatocellular carcinoma. *Int J Mol Sci.* 2023. <https://doi.org/10.3390/ijms24021417>.
 174. Geng M, Cao YC, Chen YJ, Jiang H, Bi LQ, Liu XH. Loss of Wnt5a and Ror2 protein in hepatocellular carcinoma associated with poor prognosis. *World J Gastroenterol.* 2012;18(12):1328–38. <https://doi.org/10.3748/wjg.v18.i12.1328>.
 175. Wakizaka K, Kamiyama T, Kakisaka T, Orimo T, Nagatsu A, Aiyama T, et al. Expression of Wnt5a and ROR2, components of the noncanonical Wnt-signaling pathway, is associated with tumor differentiation in hepatocellular carcinoma. *Ann Surg Oncol.* 2024;31(1):262–71. <https://doi.org/10.1245/s10434-023-14402-6>.
 176. Huang FY, Wong DK, Mak LY, Cheung TT, Zhang SS, Chau HT, et al. FAT4 loss initiates hepatocarcinogenesis through the switching of canonical to noncanonical WNT signaling pathways. *Hepatol Commun.* 2023;7(12). <https://doi.org/10.1097/hc9.0000000000000338>.
 177. Liu Y, Deng H, Liang L, Zhang G, Xia J, Ding K, et al. Depletion of VPS35 attenuates metastasis of hepatocellular carcinoma by restraining the Wnt/PCP signaling pathway. *Genes Dis.* 2021;8(2):232–40. <https://doi.org/10.1016/j.gendis.2020.07.009>.
 178. Asano T, Yamada S, Fuchs BC, Takami H, Hayashi M, Sugimoto H, et al. Clinical implication of Frizzled 2 expression and its association with epithelial-to-mesenchymal transition in hepatocellular carcinoma. *Int J Oncol.* 2017;50(5):1647–54. <https://doi.org/10.3892/ijo.2017.3937>.
 179. Wang G, Wang J, Sadar MD. Crosstalk between the androgen receptor and beta-catenin in castrate-resistant prostate cancer. *Cancer Res.* 2008;68(23):9918–27. <https://doi.org/10.1158/0008-5472.CAN-08-1718>.
 180. Atawia IM, Kushwaha PP, Verma S, Lin S, Shankar E, Abdel-Gawad O, et al. Inhibition of Wnt/ β -catenin pathway overcomes therapeutic resistance to abiraterone in castration-resistant prostate cancer. *Mol Carcinog.* 2023;62(9):1312–24. <https://doi.org/10.1002/mc.23565>.
 181. Broderick A, Pan E, Li J, Chu A, Hwang C, Barata PC, et al. Clinical implications of Wnt pathway genetic alterations in men with advanced prostate cancer. *Prostate Cancer Prostatic Dis.* 2025;28(2):419–26. <https://doi.org/10.1038/s41391-024-00869-1>.
 182. Li W, Yang G, Yang D, Li D, Sun Q. LncRNA LEF1-AS1 promotes metastasis of prostatic carcinoma via the Wnt/ β -catenin pathway. *Cancer Cell Int.* 2020;20(1):543. <https://doi.org/10.1186/s12935-020-01624-x>.
 183. Yang B, Chen W, Tao T, Zhang J, Kong D, Hao J, et al. Ube2n promotes cell viability and glycolysis by promoting Axin1 ubiquitination in prostate cancer cells. *Biol Direct.* 2024;19(1):35. <https://doi.org/10.1186/s13062-024-00469-y>.

184. Wu S, Yue Y, Gu Y, Wang Q, Liu T, Li L, et al. MUC15 loss facilitates epithelial-mesenchymal transition and cancer stemness for prostate cancer metastasis through GSK3 β / β -catenin signaling. *Cell Signal*. 2021;84:110015. <https://doi.org/10.1016/j.cellsig.2021.110015>.
185. Yu G, Corn PG, Mak CSL, Liang X, Zhang M, Troncoso P, et al. Prostate cancer-induced endothelial-cell-to-osteoblast transition drives immunosuppression in the bone-tumor microenvironment through Wnt pathway-induced M2 macrophage polarization. *Proc Natl Acad Sci U S A*. 2024;121(33):e2402903121. <https://doi.org/10.1073/pnas.2402903121>.
186. Nath D, Li X, Mondragon C, Post D, Chen M, White JR, et al. Abi1 loss drives prostate tumorigenesis through activation of EMT and non-canonical WNT signaling. *Cell Commun Signal*. 2019;17(1):120. <https://doi.org/10.1186/s12964-019-0410-y>.
187. Liu RJ, Xu ZP, Huang X, Xu B, Chen M. Yin Yang 1 promotes the neuroendocrine differentiation of prostate cancer cells via the non-canonical WNT pathway (FYN/STAT3). *Clin Transl Med*. 2023;13(10):e1422. <https://doi.org/10.1002/ctm2.1422>.
188. Sennoune SR, Nelius T, Jarvis C, Pruitt K, Kottapalli KR, Filleur S. The Wnt non-canonical signaling modulates cabazitaxel sensitivity in prostate cancer cells. *PLoS ONE*. 2020;15(6):e0234078. <https://doi.org/10.1371/journal.pone.0234078>.
189. Ma F, Arai S, Wang K, Calagua C, Yuan AR, Poluben L, et al. Autocrine canonical Wnt signaling primes noncanonical signaling through ROR1 in metastatic castration-resistant prostate cancer. *Cancer Res*. 2022;82(8):1518–33. <https://doi.org/10.1158/0008-5472.Can-21-1807>.
190. Lasorsa F, Rutigliano M, Milella M, Ferro M, Pandolfo SD, Crocetto F, et al. Cancer stem cells in renal cell carcinoma: origins and biomarkers. *Int J Mol Sci*. 2023. <https://doi.org/10.3390/ijms241713179>.
191. Zhong K, Wang X, Zhang H, Chen N, Mai Y, Dai S, et al. BIRC6 Modulates the Protein Stability of Axin to Regulate the Growth, Stemness, and Resistance of Renal Cancer Cells via the β -Catenin Pathway. *ACS Omega*. 2024;9(7):7782–92. <https://doi.org/10.1021/acsomega.3c07265>.
192. Chi XG, Meng XX, Ding DL, Xuan XH, Chen YZ, Cai Q, et al. HMGAI-mediated miR-671-5p targets APC to promote metastasis of clear cell renal cell carcinoma through Wnt signaling. *Neoplasma*. 2020;67(1):46–53. https://doi.org/10.4149/neo_2019_190217N135.
193. Huang Y, Wen Z, Tao S, Yu Z, Wang X, Li X, et al. CLIP170 enhancing FOSL1 expression via attenuating ubiquitin-mediated degradation of β -catenin drives renal cell carcinoma progression. *Cell Mol Life Sci*. 2024;81(1):467. <https://doi.org/10.1007/s00018-024-05504-9>.
194. Wronski N, Madej E, Grabacka M, Brożyna AA, Wolnicka-Glubisz A, RPK4 downregulation impairs Wnt3A-stimulated invasiveness via Wnt/ β -catenin signaling in melanoma cells and tumor growth in vivo. *Cell Signal*. 2024;113:110938. <https://doi.org/10.1016/j.cellsig.2023.110938>.
195. Da Forno PD, Pringle JH, Hutchinson P, Osborn J, Huang Q, Potter L, et al. WNT5A expression increases during melanoma progression and correlates with outcome. *Clin Cancer Res*. 2008;14(18):5825–32. <https://doi.org/10.1158/1078-0432.Ccr-07-5104>.
196. Weeraratna AT, Jiang Y, Hostetter G, Rosenblatt K, Duray P, Bittner M, et al. Wnt5a signaling directly affects cell motility and invasion of metastatic melanoma. *Cancer Cell*. 2002;1(3):279–88. [https://doi.org/10.1016/s1535-6108\(02\)00045-4](https://doi.org/10.1016/s1535-6108(02)00045-4).
197. Wohlfarth J, Kosnopfel C, Faber D, Berthold M, Siedel C, Bernhardt M, et al. Loss of p14 diminishes immunogenicity in melanoma via non-canonical Wnt signaling by reducing the peptide surface density. *Mol Oncol*. 2024;18(10):2449–70. <https://doi.org/10.1002/1878-0261.13660>.
198. Li C, Nguyen V, Clark KN, Zahed T, Sharkas S, Filipp FV, et al. Down-regulation of FZD3 receptor suppresses growth and metastasis of human melanoma independently of canonical WNT signaling. *Proc Natl Acad Sci USA*. 2019;116(10):4548–57. <https://doi.org/10.1073/pnas.1813802116>.
199. Dong B, Simonson L, Vold S, Oldham E, Barten L, Ahmad N, et al. FZD6 promotes melanoma cell invasion but not proliferation by regulating canonical Wnt signaling and epithelial-mesenchymal transition. *J Invest Dermatol*. 2023;143(4):621–629.e6. <https://doi.org/10.1016/j.jid.2022.09.658>.
200. Ding Y, Chen Q. Wnt/ β -catenin signaling pathway: an attractive potential therapeutic target in osteosarcoma. *Front Oncol*. 2024;14:1456959. <https://doi.org/10.3389/fonc.2024.1456959>.
201. Singla A, Wang J, Yang R, Geller DS, Loeb DM, Hoang BH. Wnt Signaling in Osteosarcoma. *Adv Exp Med Biol*. 2020;1258:125–39. https://doi.org/10.1007/978-3-030-43085-6_8.
202. Bhavanasi D, Speer KF, Klein PS, CKAP4 is identified as a receptor for Dickkopf in cancer cells. *J Clin Invest*. 2016;126(7):2419–21. <https://doi.org/10.1172/jci88620>.
203. Krause U, Ryan DM, Clough BH, Gregory CA. An unexpected role for a Wnt-inhibitor: Dickkopf-1 triggers a novel cancer survival mechanism through modulation of aldehyde-dehydrogenase-1 activity. *Cell Death Dis*. 2014;5(2):e1093. <https://doi.org/10.1038/cddis.2014.67>.
204. Wang J, Feng JQ. Signaling pathways critical for tooth root formation. *J Dent Res*. 2017;96(11):1221–8. <https://doi.org/10.1177/00220345171717478>.
205. Yin C, Miao Y, Lu W, Liu Z. IER3 facilitates tumor progression and aberrant glycolysis via activating wnt/ β -catenin pathway in oral squamous cell carcinoma. *Adv Biol (Weinh)*. 2025;9(7):e2400564. <https://doi.org/10.1002/adbi.202400564>.
206. Li X, Zhao H, Jiang E, Liu P, Chen Y, Wang Y, et al. ITGB1/FERMT1 mecha-noactivation enhances CD44 characteristic stemness in oral squamous cell carcinoma via ubiquitin-dependent CK1 α degradation. *Oncogene*. 2025;44(20):1530–44. <https://doi.org/10.1038/s41388-025-03317-z>.
207. Liu Y, Yang Z, Pu JJ, Zhong J, Khoo US, Su YX, et al. Proteogenomic characterisation of primary oral cancer unveils extracellular matrix remodeling and immunosuppressive microenvironment linked to lymph node metastasis. *Clin Transl Med*. 2025;15(3):e70261. <https://doi.org/10.1002/ctm2.70261>.
208. Wang S, Fan H, Bai J. NKD2 as a mediator of IIFX antioncogene-induced Wnt signalling and epithelial-mesenchymal transition in human OSCC. *J Cell Mol Med*. 2025;29(2):e70342. <https://doi.org/10.1111/jcmm.70342>.
209. You G, Yang Q, Li X, Chen L. TMEM33, an oncogene regulated by miR-214-3p, promotes the progression of lung adenocarcinoma through the Wnt/ β -catenin signaling pathway. *Oncol Res*. 2025;33(4):905–17. <https://doi.org/10.32604/or.2024.052089>.
210. Tong W, Sun J, Shen B, Hu Y, Wang C, Rao M, et al. Transcription factor FOSL1 promotes cisplatin resistance in non-small cell lung cancer cells by modulating the Wnt3a/ β -catenin signaling through upregulation of PLIN3 expression. *Front Biosci (Landmark Ed)*. 2025;30(3):26898. <https://doi.org/10.31083/fbl26898>.
211. Zhao H, Wu G, Luo Y, Xie Y, Han Y, Zhang D, et al. WNT5B promotes the malignant phenotype of non-small cell lung cancer via the FZD3-DVL3-RAC1-PCP-JNK pathway. *Cell Signal*. 2024;122:111330. <https://doi.org/10.1016/j.cellsig.2024.111330>.
212. Vesel M, Rapp J, Feller D, Kiss E, Jaromi L, Meggyes M, et al. ABCB1 and ABCG2 drug transporters are differentially expressed in non-small cell lung cancers (NSCLC) and expression is modified by cisplatin treatment via altered Wnt signaling. *Respir Res*. 2017;18(1):52. <https://doi.org/10.1186/s12931-017-0537-6>.
213. Rapp J, Kiss E, Meggyes M, Szabo-Meleg E, Feller D, Smuk G, et al. Increased Wnt5a in squamous cell lung carcinoma inhibits endothelial cell motility. *BMC Cancer*. 2016;16(1):915. <https://doi.org/10.1186/s12885-016-2943-4>.
214. Zhuang X, Zhang H, Li X, Cong M, Peng F, et al. Differential effects on lung and bone metastasis of breast cancer by Wnt signalling inhibitor DKK1. *Nat Cell Biol*. 2017;19(10):1274–85. <https://doi.org/10.1038/ncb3613>.
215. Zhang J, Zhai J, Wong CC, Chen H, Wang X, Ji J, et al. A novel amplification gene PCI domain containing 2 (PCID2) promotes colorectal cancer through directly degrading a tumor suppressor promyelocytic leukemia (PML). *Oncogene*. 2021;40(49):6641–52. <https://doi.org/10.1038/s41388-021-01941-z>.
216. Liu J, Pan S, Hsieh MH, Ng N, Sun F, Wang T, et al. Targeting wnt-driven cancer through the inhibition of Porcupine by LGK974. *Proc Natl Acad Sci U S A*. 2013;110(50):20224–9. <https://doi.org/10.1073/pnas.1314239110>.
217. Boone JD, Arend RC, Johnston BE, Cooper SJ, Gilchrist SA, Oelschlager DK, et al. Targeting the Wnt/ β -catenin pathway in primary ovarian cancer with the porcupine inhibitor WNT974. *Lab Invest*. 2016;96(2):249–59. <https://doi.org/10.1038/labinvest.2015.150>.
218. Chua K, Sim AYL, Yeo EYM, Bin Masroni MS, Naw WW, Leong SM, et al. ETC-159, an upstream Wnt inhibitor, induces tumour necrosis

- via modulation of angiogenesis in osteosarcoma. *Int J Mol Sci*. 2023;24(5):4759. <https://doi.org/10.3390/ijms24054759>.
219. Madan B, Ke Z, Harmston N, Ho SY, Frois AO, Alam J, et al. Wnt addiction of genetically defined cancers reversed by PORCN inhibition. *Oncogene*. 2016;35(17):2197–207. <https://doi.org/10.1038/ncr.2015.280>.
 220. Zhong Z, Sepramaniam S, Chew XH, Wood K, Lee MA, Madan B, et al. PORCN inhibition synergizes with PI3K/mTOR inhibition in Wnt-addicted cancers. *Oncogene*. 2019;38(40):6662–77. <https://doi.org/10.1038/s41388-019-0908-1>.
 221. Goldsberry WN, Meza-Perez S, Londoño AI, Katre AA, Mott BT, Roane BM, et al. Inhibiting WNT ligand production for improved immune recognition in the ovarian tumor microenvironment. *Cancers (Basel)*. 2020. <https://doi.org/10.3390/cancers12030766>.
 222. Li C, Liang Y, Cao J, Zhang N, Wei X, Tu M, et al. The delivery of a Wnt pathway inhibitor toward CSCs requires stable liposome encapsulation and delayed drug release in tumor tissues. *Mol Ther*. 2019;27(9):1558–67. <https://doi.org/10.1016/j.ymthe.2019.06.013>.
 223. Ma H, Chen Q, Zhu F, Zheng J, Li J, Zhang H, et al. Discovery and characterization of a potent Wnt and hedgehog signaling pathways dual inhibitor. *Eur J Med Chem*. 2018;149:110–121. <https://doi.org/10.1016/j.ejmech.2018.02.034>.
 224. Yang Q, Qin T, An T, Wu H, Xu G, Xiang J, et al. Novel PORCN inhibitor WHN-88 targets Wnt/ β -catenin pathway and prevents the growth of Wnt-driven cancers. *Eur J Pharmacol*. 2023;945:175628. <https://doi.org/10.1016/j.ejphar.2023.175628>.
 225. Paul MA, Wainwright CL, Hector EE, Ryberg E, Leslie SJ, Walsh SK. Short-term oral administration of the Porcupine inhibitor, Wnt-c59, improves the structural and functional features of experimental HFpEF. *Pharmacol Res Perspect*. 2025;13(1):e70054. <https://doi.org/10.1002/prp2.70054>.
 226. Cheng D, Liu J, Han D, Zhang G, Gao W, Hsieh MH, et al. Discovery of pyridinyl acetamide derivatives as potent, selective, and orally bio-available porcupine inhibitors. *ACS Med Chem Lett*. 2016;7(7):676–80. <https://doi.org/10.1021/acsmedchemlett.6b00038>.
 227. Phillips C, Bhamra I, Eagle C, Flanagan E, Armer R, Jones CD, et al. The wnt pathway inhibitor RXC004 blocks tumor growth and reverses immune evasion in wnt ligand-dependent cancer models. *Cancer Res Commun*. 2022;2(9):914–28. <https://doi.org/10.1158/2767-9764.Crc-21-0095>.
 228. Le PN, McDermott JD, Jimeno A. Targeting the Wnt pathway in human cancers: therapeutic targeting with a focus on OMP-54F28. *Pharmacol Ther*. 2015;146:1–11. <https://doi.org/10.1016/j.pharmthera.2014.08.005>.
 229. Gurney A, Axelrod F, Bond CJ, Cain J, Chartier C, Donigan L, et al. Wnt pathway inhibition via the targeting of Frizzled receptors results in decreased growth and tumorigenicity of human tumors. *Proc Natl Acad Sci U S A*. 2012;109(29):11717–22. <https://doi.org/10.1073/pnas.1120068109>.
 230. Zhang W, Lu W, Ananthan S, Suto MJ, Li Y. Discovery of novel frizzled-7 inhibitors by targeting the receptor's transmembrane domain. *Oncotarget*. 2017;8(53):91459–70. <https://doi.org/10.18632/oncotarget.20665>.
 231. Nile AH, de Sousa EMF, Mukund S, Piskol R, Hansen S, Zhou L, et al. A selective peptide inhibitor of Frizzled 7 receptors disrupts intestinal stem cells. *Nat Chem Biol*. 2018;14(6):582–90. <https://doi.org/10.1038/s41589-018-0035-2>.
 232. Hansen S, Nile AH, Mehta SC, Fuhrmann J, Hannoush RN. Lead optimization yields high affinity frizzled 7-targeting peptides that modulate *Clostridium difficile* toxin B pathogenicity in epithelial cells. *J Med Chem*. 2019;62(17):7739–50. <https://doi.org/10.1021/acs.jmedchem.9b00500>.
 233. Alves Pinto I, Freitas Da Silveira NJ. In silico identification of potential inhibitors of the Wnt signaling pathway in human breast cancer. *J Comput Biol*. 2020;27(7):999–1010. <https://doi.org/10.1089/cmb.2019.0311>.
 234. Sun X, Jabeen A, Zhang L, Li C, Serfraz S. G-protein-coupled receptor FZD7 as a therapeutic target in glioblastoma: multi-cohort validation and identification of cycloartobioxanthone as an inhibitor. *Bioorg Chem*. 2025;162:108616. <https://doi.org/10.1016/j.bioorg.2025.108616>.
 235. Zarei N, Fazeli M, Mohammadi M, Nejatollahi F. Cell growth inhibition and apoptosis in breast cancer cells induced by anti-FZD7 scFvs: involvement of bioinformatics-based design of novel epitopes. *Breast Cancer Res Treat*. 2018;169(3):427–36. <https://doi.org/10.1007/s10549-017-4641-6>.
 236. Riley RS, Day ES. Frizzled7 Antibody-Functionalized Nanoshells Enable Multivalent Binding for Wnt Signaling Inhibition in Triple Negative Breast Cancer Cells. *Small*. 2017;13(26). <https://doi.org/10.1002/sml.201700544>.
 237. Lee HJ, Bao J, Miller A, Zhang C, Wu J, Baday YC, et al. Structure-based discovery of novel small molecule Wnt signaling inhibitors by targeting the cysteine-rich domain of Frizzled. *J Biol Chem*. 2015;290(51):30596–606. <https://doi.org/10.1074/jbc.M115.673202>.
 238. Giraudet AL, Cassier PA, Iwao-Fukukawa C, Garin G, Badel JN, Kryza D, et al. A first-in-human study investigating biodistribution, safety and recommended dose of a new radiolabeled MAb targeting FZD10 in metastatic synovial sarcoma patients. *BMC Cancer*. 2018;18(1):646. <https://doi.org/10.1186/s12885-018-4544-x>.
 239. Pavlovic Z, Adams JJ, Blazer LL, Gakhil AK, Jarvik N, Steinhart Z, et al. A synthetic anti-Frizzled antibody engineered for broadened specificity exhibits enhanced anti-tumor properties. *MAbs*. 2018;10(8):1157–67. <https://doi.org/10.1080/19420862.2018.1515565>.
 240. Chen H, Lu C, Ouyang B, Zhang H, Huang Z, Bhatia D, et al. Development of Potent, Selective Surrogate WNT Molecules and Their Application in Defining Frizzled Requirements. *Cell Chem Biol*. 2020;27(5):598–609.e4. <https://doi.org/10.1016/j.chembiol.2020.02.009>.
 241. Lu D, Choi MY, Yu J, Castro JE, Kipps TJ, Carson DA. Salinomycin inhibits Wnt signaling and selectively induces apoptosis in chronic lymphocytic leukemia cells. *Proc Natl Acad Sci U S A*. 2011;108(32):13253–7. <https://doi.org/10.1073/pnas.1110431108>.
 242. Shen W, Zou X, Chen M, Shen Y, Huang S, Guo H, et al. Effect of pan-topirazole on human gastric adenocarcinoma SGC7901 cells through regulation of phospho-LRP6 expression in Wnt/ β -catenin signaling. *Oncol Rep*. 2013;30(2):851–5. <https://doi.org/10.3892/or.2013.2524>.
 243. Lu W, Lin C, Roberts MJ, Waud WR, Piazza GA, Li Y. Niclosamide suppresses cancer cell growth by inducing Wnt co-receptor LRP6 degradation and inhibiting the Wnt/ β -catenin pathway. *PLoS ONE*. 2011;6(12):e29290. <https://doi.org/10.1371/journal.pone.0029290>.
 244. Lu W, Liu CC, Thottassery JV, Bu G, Li Y. Mesd is a universal inhibitor of Wnt coreceptors LRP5 and LRP6 and blocks Wnt/ β -catenin signaling in cancer cells. *Biochemistry*. 2010;49(22):4635–43. <https://doi.org/10.1021/bi1001486>.
 245. Choi J, Lee K, Kang M, Lim SK, Tai No K. In silico discovery of quinoxaline derivatives as novel LRP5/6-sclerostin interaction inhibitors. *Bioorg Med Chem Lett*. 2018;28(6):1116–21. <https://doi.org/10.1016/j.bmcl.2018.01.050>.
 246. Arensman MD, Nguyen P, Kershaw KM, Lay AR, Ostertag-Hill CA, Sherman MH, et al. Calcipotriol targets LRP6 to inhibit Wnt signaling in pancreatic cancer. *Mol Cancer Res*. 2015;13(11):1509–19. <https://doi.org/10.1158/1541-7786.Mcr-15-0204>.
 247. Badana AK, Chintala M, Gavara MM, Naik S, Kumari S, Kappala VR, et al. Lipid rafts disruption induces apoptosis by attenuating expression of LRP6 and survivin in triple negative breast cancer. *Biomed Pharmacother*. 2018;97:359–68. <https://doi.org/10.1016/j.biopha.2017.10.045>.
 248. Fujii N, You L, Xu Z, Uematsu K, Shan J, He B, et al. An antagonist of dishevelled protein-protein interaction suppresses beta-catenin-dependent tumor cell growth. *Cancer Res*. 2007;67(2):573–9. <https://doi.org/10.1158/0008-5472.Can-06-2726>.
 249. Grandy D, Shan J, Zhang X, Rao S, Akunuru S, Li H, et al. Discovery and characterization of a small molecule inhibitor of the PDZ domain of dishevelled. *J Biol Chem*. 2009;284(24):16256–63. <https://doi.org/10.1074/jbc.M109.009647>.
 250. Huang S, Chen J, Tian R, Wang J, Xie C, Gao H, et al. Down-regulation of dishevelled-2 inhibits cell proliferation and invasion in hepatoblastoma. *Pediatr Blood Cancer*. 2018;65(7):e27032. <https://doi.org/10.1002/pbc.27032>.
 251. Martins-Neves SR, Paiva-Oliveira DI, Fontes-Ribeiro C, Bovée J, Cleton-Jansen AM, Gomes CMF. *Cancer Lett*. 2018;414:1–15. <https://doi.org/10.1016/j.canlet.2017.11.004>.
 252. Huang SM, Mishina YM, Liu S, Cheung A, Stegmeier F, Michaud GA, et al. Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. *Nature*. 2009;461(7264):614–20. <https://doi.org/10.1038/nature08356>.

253. Busch AM, Johnson KC, Stan RV, Sanglikar A, Ahmed Y, Dmitrovsky E, et al. Evidence for tankyrases as antineoplastic targets in lung cancer. *BMC Cancer*. 2013;13:211. <https://doi.org/10.1186/1471-2407-13-211>.
254. Menon M, Elliott R, Bowers L, Balan N, Rafiq R, Costa-Cabral S, et al. A novel tankyrase inhibitor, MSC2504877, enhances the effects of clinical CDK4/6 inhibitors. *Sci Rep*. 2019;9(1):201. <https://doi.org/10.1038/s41598-018-36447-4>.
255. Stratford EW, Daffinrud J, Munthe E, Castro R, Waaler J, Krauss S, et al. The tankyrase-specific inhibitor JW74 affects cell cycle progression and induces apoptosis and differentiation in osteosarcoma cell lines. *Cancer Med*. 2014;3(1):36–46. <https://doi.org/10.1002/cam4.170>.
256. Mizutani A, Yashiroda Y, Muramatsu Y, Yoshida H, Chikada T, Tsumura T, et al. RK-287107, a potent and specific tankyrase inhibitor, blocks colorectal cancer cell growth in a preclinical model. *Cancer Sci*. 2018;109(12):4003–14. <https://doi.org/10.1111/cas.13805>.
257. Waaler J, Machon O, Tumova L, Dinh H, Korinek V, Wilson SR, et al. A novel tankyrase inhibitor decreases canonical Wnt signaling in colon carcinoma cells and reduces tumor growth in conditional APC mutant mice. *Cancer Res*. 2012;72(11):2822–32. <https://doi.org/10.1158/0008-5472.Can-11-3336>.
258. Quackenbush KS, Bagby S, Tai WM, Messersmith WA, Schreiber A, Greene J, et al. The novel tankyrase inhibitor (AZ1366) enhances irinotecan activity in tumors that exhibit elevated tankyrase and irinotecan resistance. *Oncotarget*. 2016;7(19):28273–85. <https://doi.org/10.18632/oncotarget.8626>.
259. Lau T, Chan E, Callow M, Waaler J, Boggs J, Blake RA, et al. A novel tankyrase small-molecule inhibitor suppresses APC mutation-driven colorectal tumor growth. *Cancer Res*. 2013;73(10):3132–44. <https://doi.org/10.1158/0008-5472.Can-12-4562>.
260. Li B, Liang J, Lu F, Zeng G, Zhang J, Ma Y, et al. Discovery of novel inhibitor for WNT/ β -catenin pathway by tankyrase 1/2 structure-based virtual screening. *Molecules*. 2020. <https://doi.org/10.3390/molecules25071680>.
261. Ji L, Lu B, Zamponi R, Charlat O, Aversa R, Yang Z, et al. Usp7 inhibits Wnt/ β -catenin signaling through promoting stabilization of Axin. *Nat Commun*. 2019;10(1):4184. <https://doi.org/10.1038/s41467-019-12143-3>.
262. Kim DY, Kwon YJ, Seo WY, Kim UI, Ahn S, Choi SM, et al. Tankyrase-selective inhibitor STP1002 shows preclinical antitumor efficacy without on-target toxicity in the gastrointestinal tract. *Eur J Cancer*. 2022;173:41–51. <https://doi.org/10.1016/j.ejca.2022.06.031>.
263. Fan J, Reid RR, He TC. Pyrvinium doubles against WNT-driven cancer. *J Biol Chem*. 2022;298(10):102479. <https://doi.org/10.1016/j.jbc.2022.102479>.
264. Thorne CA, Hanson AJ, Schneider J, Tahinci E, Orton D, Cselenyi CS, et al. Small-molecule inhibition of Wnt signaling through activation of casein kinase 1 α . *Nat Chem Biol*. 2010;6(11):829–36. <https://doi.org/10.1038/nchembio.453>.
265. Li B, Orton D, Neitzel LR, Astudillo L, Shen C, Long J, et al. Differential abundance of CK1 α provides selectivity for pharmacological CK1 α activators to target WNT-dependent tumors. *Sci Signal*. 2017. <https://doi.org/10.1126/scisignal.aak9916>.
266. Dietrich L, Rathmer B, Ewan K, Bange T, Heinrichs S, Dale TC, et al. Cell Permeable Stapled Peptide Inhibitor of Wnt Signaling that Targets β -Catenin Protein-Protein Interactions. *Cell Chem Biol*. 2017;24(8):958–968.e5. <https://doi.org/10.1016/j.chembiol.2017.06.013>.
267. Yan R, Zhu H, Huang P, Yang M, Shen M, Pan Y, et al. Liquidambaric acid inhibits Wnt/ β -catenin signaling and colon cancer via targeting TNF receptor-associated factor 2. *Cell Rep*. 2022;38(5):110319. <https://doi.org/10.1016/j.celrep.2022.110319>.
268. Sun M, Zhou D, Wu J, Zhou J, Xu J. Sdy-1 executes antitumor activity in HepG2 and HeLa cancer cells by inhibiting the Wnt/ β -catenin signaling pathway. *Mar Drugs*. 2022. <https://doi.org/10.3390/md20020125>.
269. Qin G, Li Y, Xu X, Wang X, Zhang K, Tang Y, et al. Panobinostat (LBH589) inhibits Wnt/ β -catenin signaling pathway via upregulating APC expression in breast cancer. *Cell Signal*. 2019;95:62–75. <https://doi.org/10.1016/j.cellsig.2019.03.014>.
270. Ye ZN, Yuan F, Liu JQ, Peng XR, An T, Li X, et al. *Physalis peruviana*-derived 4 β -hydroxywithanolide E, a novel antagonist of Wnt signaling, inhibits colorectal cancer *in vitro* and *in vivo*. *Molecules*. 2019. <https://doi.org/10.3390/molecules24061146>.
271. Cheltsov A, Nomura N, Yenugonda VM, Roper J, Mukthavaram R, Jiang P, et al. Allosteric inhibitor of β -catenin selectively targets oncogenic Wnt signaling in colon cancer. *Sci Rep*. 2020;10(1):8096. <https://doi.org/10.1038/s41598-020-60784-y>.
272. Tanton H, Sewastianik T, Seo HS, Remillard D, Pierre RS, Bala P, et al. A novel β -catenin/BCL9 complex inhibitor blocks oncogenic Wnt signaling and disrupts cholesterol homeostasis in colorectal cancer. *Sci Adv*. 2022;8(17):eabm3108. <https://doi.org/10.1126/sciadv.abm3108>.
273. Matsumoto T, Kitagawa T, Imahori D, Matsuzaki A, Saito Y, Ohta T, et al. Linderapyrone: a Wnt signal inhibitor isolated from *Lindera umbellata*. *Bioorg Med Chem Lett*. 2021;45:128161. <https://doi.org/10.1016/j.bmcl.2021.128161>.
274. Lepourcelet M, Chen YN, France DS, Wang H, Crews P, Petersen F, et al. Small-molecule antagonists of the oncogenic Tcf/ β -catenin protein complex. *Cancer Cell*. 2004;5(1):91–102. [https://doi.org/10.1016/s1535-6108\(03\)00334-9](https://doi.org/10.1016/s1535-6108(03)00334-9).
275. Yamashita T, Budhu A, Forgues M, Wang XW. Activation of hepatic stem cell marker EpCAM by Wnt- β -catenin signaling in hepatocellular carcinoma. *Cancer Res*. 2007;67(22):10831–9. <https://doi.org/10.1158/0008-5472.Can-07-0908>.
276. Gandhirajan RK, Staib PA, Minke K, Gehrke I, Plickert G, Schlösser A, et al. Small molecule inhibitors of Wnt/ β -catenin/lef-1 signaling induces apoptosis in chronic lymphocytic leukemia cells *in vitro* and *in vivo*. *Neoplasia*. 2010;12(4):326–35. <https://doi.org/10.1593/neo.91972>.
277. Catrow JL, Zhang Y, Zhang M, Ji H. Discovery of selective small-molecule inhibitors for the β -catenin/T-cell factor protein-protein interaction through the optimization of the acyl hydrazone moiety. *J Med Chem*. 2015;58(11):4678–92. <https://doi.org/10.1021/acs.jmedchem.5b00223>.
278. Lenz HJ, Kahn M. Safely targeting cancer stem cells via selective catenin coactivator antagonism. *Cancer Sci*. 2014;105(9):1087–92. <https://doi.org/10.1111/cas.12471>.
279. Evangelisti C, Chiarini F, Cappellini A, Paganelli F, Fini M, Santi S, et al. Targeting Wnt/ β -catenin and PI3K/Akt/mTOR pathways in T-cell acute lymphoblastic leukemia. *J Cell Physiol*. 2020;235(6):5413–28. <https://doi.org/10.1002/jcp.29429>.
280. Arensman MD, Telesca D, Lay AR, Kershaw KM, Wu N, Donahue TR, et al. The CREB-binding protein inhibitor ICG-001 suppresses pancreatic cancer growth. *Mol Cancer Ther*. 2014;13(10):2303–14. <https://doi.org/10.1158/1535-7163.Mct-13-1005>.
281. Won HS, Lee KM, Oh JE, Nam EM, Lee KE. Inhibition of β -catenin to overcome endocrine resistance in tamoxifen-resistant breast cancer cell line. *PLoS ONE*. 2016;11(5):e0155983. <https://doi.org/10.1371/journal.pone.0155983>.
282. Wu G, Cao L, Zhu J, Tan Z, Tang M, Li Z, et al. Loss of RBMS3 confers platinum resistance in epithelial ovarian cancer via activation of miR-126-5p/ β -catenin/CBP signaling. *Clin Cancer Res*. 2019;25(3):1022–35. <https://doi.org/10.1158/1078-0432.Ccr-18-2554>.
283. Xiang Q, Wang C, Zhang Y, Xue X, Song M, Zhang C, et al. Discovery and optimization of 1-(1H-indol-1-yl)ethanone derivatives as CBP/EP300 bromodomain inhibitors for the treatment of castration-resistant prostate cancer. *Eur J Med Chem*. 2018;147:238–52. <https://doi.org/10.1016/j.ejmech.2018.01.087>.
284. Romero FA, Murray J, Lai KW, Tsui V, Albrecht BK, An L, et al. GNE-781, a highly advanced potent and selective bromodomain inhibitor of cyclic adenosine monophosphate response element binding protein, binding protein (CBP). *J Med Chem*. 2017;60(22):9162–83. <https://doi.org/10.1021/acs.jmedchem.7b00796>.
285. Waaler J, Machon O, von Kries JP, Wilson SR, Lundenes E, Wedlich D, et al. Novel synthetic antagonists of canonical Wnt signaling inhibit colorectal cancer cell growth. *Cancer Res*. 2011;71(1):197–205. <https://doi.org/10.1158/0008-5472.Can-10-1282>.
286. Luo Y, Tan W, Jia W, Liu Z, Ye P, Fu Z, et al. The long non-coding RNA LINC01606 contributes to the metastasis and invasion of human gastric cancer and is associated with Wnt/ β -catenin signaling. *Int J Biochem Cell Biol*. 2018;103:125–34. <https://doi.org/10.1016/j.biocel.2018.08.012>.
287. Yamada K, Hori Y, Inoue S, Yamamoto Y, Iso K, Kamiyama H, et al. E7386, a selective inhibitor of the interaction between β -catenin and CBP, exerts antitumor activity in tumor models with activated canonical Wnt signaling. *Cancer Res*. 2021;81(4):1052–62. <https://doi.org/10.1158/0008-5472.Can-20-0782>.

288. Ganesh S, Shui X, Craig KP, Park J, Wang W, Brown BD, et al. RNAi-mediated β -catenin inhibition promotes T cell infiltration and antitumor activity in combination with immune checkpoint blockade. *Mol Ther*. 2018;26(11):2567–79. <https://doi.org/10.1016/j.ymthe.2018.09.005>.
289. Klempner SJ, Bendell JC, Villaflor VM, Tenner LL, Stein SM, Rottman JB, et al. Safety, efficacy, and biomarker results from a phase Ib study of the anti-DKK1 antibody DKN-01 in combination with pembrolizumab in advanced esophagogastric cancers. *Mol Cancer Ther*. 2021;20(11):2240–9. <https://doi.org/10.1158/1535-7163.Mct-21-0273>.
290. Haas MS, Kagey MH, Heath H, Schuerpf F, Rottman JB, Newman W. MDKN-01, a novel anti-DKK1 mAb, enhances innate immune responses in the tumor microenvironment. *Mol Cancer Res*. 2021;19(4):717–25. <https://doi.org/10.1158/1541-7786.Mcr-20-0799>.
291. Parit S, Manchare A, Gholap AD, Mundhe P, Hatvate N, Rojekar S, et al. Antibody-drug conjugates: a promising breakthrough in cancer therapy. *Int J Pharm*. 2024;659:124211. <https://doi.org/10.1016/j.jipharm.2024.124211>.
292. Riccardi F, Dal Bo M, Macor P, Toffoli G. A comprehensive overview on antibody-drug conjugates: from the conceptualization to cancer therapy. *Front Pharmacol*. 2023;14:1274088. <https://doi.org/10.3389/fphar.2023.1274088>.
293. Junttila MR, Mao W, Wang X, Wang BE, Pham T, Flygare J, et al. Targeting LGR5+ cells with an antibody-drug conjugate for the treatment of colon cancer. *Sci Transl Med*. 2015;7(314):314ra186. <https://doi.org/10.1126/scitranslmed.aac7433>.
294. Hirsch D, Ried T. Targeting colorectal cancer (stem-like) cells using LGR5 directed antibody drug conjugates. *Ann Transl Med*. 2016;4(24):508. <https://doi.org/10.21037/atm.2016.11.78>.
295. Rhee CS, Sen M, Lu D, Wu C, Leoni L, Rubin J, et al. Wnt and frizzled receptors as potential targets for immunotherapy in head and neck squamous cell carcinomas. *Oncogene*. 2002;21(43):6598–605. <https://doi.org/10.1038/sj.onc.1205920>.
296. Seo HH, Lee S, Lee CY, Lee J, Shin S, Song BW, et al. Multipoint targeting of TGF- β /Wnt transactivation circuit with microRNA 384–5p for cardiac fibrosis. *Cell Death Differ*. 2019;26(6):1107–23. <https://doi.org/10.1038/s41418-018-0187-3>.
297. Ning S, Liu C, Lou W, Yang JC, Lombard AP, D'Abronzio LS, et al. Bioengineered BERA-Wnt5a siRNA targeting Wnt5a/FZD2 signaling suppresses advanced prostate cancer tumor growth and enhances enzalutamide treatment. *Mol Cancer Ther*. 2022;21(10):1594–607. <https://doi.org/10.1158/1535-7163.Mct-22-0216>.
298. Crooke ST, Baker BF, Crooke RM, Liang XH. Antisense technology: an overview and prospectus. *Nat Rev Drug Discov*. 2021;20(6):427–53. <https://doi.org/10.1038/s41573-021-00162-z>.
299. Li M, Ding X, Zhang Y, Li X, Zhou H, Yang L, et al. Antisense oligonucleotides targeting lncRNA AC104041.1 induces antitumor activity through Wnt2B/ β -catenin pathway in head and neck squamous cell carcinomas. *Cell Death Dis*. 2020;11(8):672. <https://doi.org/10.1038/s41419-020-02820-3>.
300. Popov VB, Jornayvaz FR, Akgul EO, Kanda S, Jurczak MJ, Zhang D, et al. Second-generation antisense oligonucleotides against β -catenin protect mice against diet-induced hepatic steatosis and hepatic and peripheral insulin resistance. *FASEB J*. 2016;30(3):1207–17. <https://doi.org/10.1096/fj.15-271999>.
301. Nalawansa DA, Crews CM. PROTACs: an emerging therapeutic modality in precision medicine. *Cell Chem Biol*. 2020;27(8):998–1014. <https://doi.org/10.1016/j.chembiol.2020.07.020>.
302. Liao H, Li X, Zhao L, Wang Y, Wang X, Wu Y, et al. A PROTAC peptide induces durable β -catenin degradation and suppresses Wnt-dependent intestinal cancer. *Cell Discov*. 2020;6:35. <https://doi.org/10.1038/s41421-020-0171-1>.
303. Goyal A, Murkute SL, Bhowmik S, Prasad CP, Mohapatra P. Belling the "cat": Wnt/ β -catenin signaling and its significance in future cancer therapies. *Biochim Biophys Acta Rev Cancer*. 2024;1879(6):189195. <https://doi.org/10.1016/j.bbcan.2024.189195>.
304. Dong G, Ding Y, He S, Sheng C. Molecular glues for targeted protein degradation: from serendipity to rational discovery. *J Med Chem*. 2021;64(15):10606–20. <https://doi.org/10.1021/acs.jmedchem.1c00895>.
305. Sasso JM, Tenchov R, Wang D, Johnson LS, Wang X, Zhou QA. Molecular glues: the adhesive connecting targeted protein degradation to the clinic. *Biochemistry*. 2023;62(3):601–23. <https://doi.org/10.1021/acs.biochem.2c00245>.
306. Simonetta KR, Taygerly J, Boyle K, Basham SE, Padovani C, Lou Y, et al. Prospective discovery of small molecule enhancers of an E3 ligase-substrate interaction. *Nat Commun*. 2019;10(1):1402. <https://doi.org/10.1038/s41467-019-09358-9>.
307. Krishnamurthy N, Kurzrock R. Targeting the Wnt/ β -catenin pathway in cancer: update on effectors and inhibitors. *Cancer Treat Rev*. 2018;62:50–60. <https://doi.org/10.1016/j.ctrv.2017.11.002>.
308. Madan B, McDonald MJ, Foxa GE, Diegel CR, Williams BO, Virshup DM. Bone loss from Wnt inhibition mitigated by concurrent alendronate therapy. *Bone Res*. 2018;6:17. <https://doi.org/10.1038/s41413-018-0017-8>.
309. Qin D, Lin X, Liu Z, Chen Y, Zhang Z, Wu C, et al. Discovery of orally bioavailable ligand efficient quinazolinones as potent and selective tankyrases inhibitors. *ACS Med Chem Lett*. 2021;12(6):1005–10. <https://doi.org/10.1021/acsmedchemlett.1c00160>.
310. Larasati Y, Boudou C, Koval A, Katanaev VL. Unlocking the Wnt pathway: therapeutic potential of selective targeting FZD(7) in cancer. *Drug Discov Today*. 2022;27(3):777–92. <https://doi.org/10.1016/j.drudis.2021.12.008>.
311. Katoh M. Canonical and non-canonical WNT signaling in cancer stem cells and their niches: Cellular heterogeneity, omics reprogramming, targeted therapy and tumor plasticity (review). *Int J Oncol*. 2017;51(5):1357–69. <https://doi.org/10.3892/ijo.2017.4129>.
312. Zhang M, Chen T, Lu X, Lan X, Chen Z, Lu S. G protein-coupled receptors (GPCRs): advances in structures, mechanisms, and drug discovery. *Signal Transduct Target Ther*. 2024;9(1):88. <https://doi.org/10.1038/s41392-024-01803-6>.
313. Nauffal V, Klarqvist MDR, Hill MC, Pace DF, Di Achille P, Choi SH, et al. Noninvasive assessment of organ-specific and shared pathways in multi-organ fibrosis using T1 mapping. *Nat Med*. 2024;30(6):1749–60. <https://doi.org/10.1038/s41591-024-03010-w>.
314. Wang L, Yao M, Fang M, Zheng WJ, Dong ZZ, Pan LH, et al. Expression of hepatic Wnt5a and its clinicopathological features in patients with hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int*. 2018;17(3):227–32. <https://doi.org/10.1016/j.hbpd.2018.03.005>.
315. Van den Broeck A, Vankelecom H, Van Eijsden R, Govaere O, Topal B. Molecular markers associated with outcome and metastasis in human pancreatic cancer. *J Exp Clin Cancer Res*. 2012;31(1):68. <https://doi.org/10.1186/1756-9966-31-68>.
316. Cai Y, Xia L, Zhu H, Cheng H, Tian Y, Sun L, et al. Mir-3682-3p promotes esophageal cancer progression by targeting FHL1 and activating the Wnt/ β -catenin signaling pathway. *Cell Signal*. 2024;119:111155. <https://doi.org/10.1016/j.cellsig.2024.111155>.
317. Liu Y, Wu D, Cheng H, Chen L, Zhang W, Zou L, et al. Wnt8B, transcriptionally regulated by ZNF191, promotes cell proliferation of hepatocellular carcinoma via Wnt signaling. *Cancer Sci*. 2021;112(2):629–40. <https://doi.org/10.1111/cas.14738>.
318. Liu Y, Patel L, Mills GB, Lu KH, Sood AK, Ding L, et al. Clinical significance of CTNNB1 mutation and Wnt pathway activation in endometrioid endometrial carcinoma. *J Natl Cancer Inst*. 2014;106(9). <https://doi.org/10.1093/jnci/dju245>.
319. Xu X, Liu Z, Tian F, Xu J, Chen Y. Clinical significance of transcription factor 7 (TCF7) as a prognostic factor in gastric cancer. *Med Sci Monit*. 2019;25:3957–63. <https://doi.org/10.12659/msm.913913>.
320. Huang TC, Lee PT, Wu MH, Huang CC, Ko CY, Lee YC, et al. Distinct roles and differential expression levels of Wnt5a mRNA isoforms in colorectal cancer cells. *PLoS ONE*. 2017;12(8):e0181034. <https://doi.org/10.1371/journal.pone.0181034>.
321. Kotrbová A, Ovesná P, Gybel T, Radaszkiewicz T, Bednaříková M, Hausnerová J, et al. WNT signaling inducing activity in ascites predicts poor outcome in ovarian cancer. *Theranostics*. 2020;10(2):537–52. <https://doi.org/10.7150/thno.37423>.
322. Hartmann H, Siddiqui GS, Bryant J, Robbins DJ, Weiss VL, Ahmed Y, et al. Wnt signalosomes: What we know that we do not know. *BioEssays*. 2025;47(2):e2400110. <https://doi.org/10.1002/bies.202400110>.
323. Bahrami A, Hasanazadeh M, ShahidSales S, Yousefi Z, Kadkhodayan S, Farazestanian M, et al. Clinical significance and prognosis value of Wnt signaling pathway in cervical cancer. *J Cell Biochem*. 2017;118(10):3028–33. <https://doi.org/10.1002/jcb.25992>.

324. Tenjin Y, Kudoh S, Kubota S, Yamada T, Matsuo A, Sato Y, et al. Ascl1-induced Wnt11 regulates neuroendocrine differentiation, cell proliferation, and E-cadherin expression in small-cell lung cancer and Wnt11 regulates small-cell lung cancer biology. *Lab Invest*. 2019;99(11):1622–35. <https://doi.org/10.1038/s41374-019-0277-y>.
325. Yao M, Wang JJ, Chen XY, Sai WL, Yang J, Wang DF, et al. Oncogenic Wnt3a is a promising sensitive biomarker for monitoring hepatocarcinogenesis. *Hepatobiliary Pancreat Dis Int*. 2023;22(3):263–9. <https://doi.org/10.1016/j.hbpd.2022.11.004>.
326. Chovanec M, Cierna Z, Miskovska V, Machalekova K, Kalavska K, Rejlekova K, et al. β -catenin is a marker of poor clinical characteristics and suppressed immune infiltration in testicular germ cell tumors. *BMC Cancer*. 2018;18(1):1062. <https://doi.org/10.1186/s12885-018-4929-x>.
327. Maurice MM, Angers S. Mechanistic insights into Wnt- β -catenin pathway activation and signal transduction. *Nat Rev Mol Cell Biol*. 2025;26(5):371–88. <https://doi.org/10.1038/s41580-024-00823-y>.
328. Suzuki Y, Ichihara S, Kawasaki T, Yanai H, Kitagawa S, Shimoyama Y, et al. β -catenin (CTNNB1) mutation and LEF1 expression in sinonasal glomangiopericytoma (sinonasal-type hemangiopericytoma). *Virchows Arch*. 2018;473(2):235–9. <https://doi.org/10.1007/s00428-018-2370-9>.
329. Bai Y, Sha J, Kanno T. The role of carcinogenesis-related biomarkers in the Wnt pathway and their effects on epithelial-mesenchymal transition (EMT) in oral squamous cell carcinoma. *Cancers (Basel)*. 2020. <https://doi.org/10.3390/cancers12030555>.
330. Jiang K, Li S, Li L, Wang X, Gu Y, Jin Z. WNT6 is an effective marker for osteosarcoma diagnosis and prognosis. *Medicine (Baltimore)*. 2018;97(46):e13011. <https://doi.org/10.1097/md.00000000000013011>.
331. Katoh M. Multi-layered prevention and treatment of chronic inflammation, organ fibrosis and cancer associated with canonical WNT/ β -catenin signaling activation (Review). *Int J Mol Med*. 2018;42(2):713–25. <https://doi.org/10.3892/ijmm.2018.3689>.
332. Fisher RR, Pleskow HM, Bedingfield K, Miyamoto DT. Noncanonical Wnt as a prognostic marker in prostate cancer: “you can’t always get what you Wnt.” *Expert Rev Mol Diagn*. 2020;20(2):245–54. <https://doi.org/10.1080/14737159.2020.1702522>.
333. Tuluhong D, Chen T, Wang J, Zeng H, Li H, Dunzhu W, et al. FZD2 promotes TGF- β -induced epithelial-to-mesenchymal transition in breast cancer via activating notch signaling pathway. *Cancer Cell Int*. 2021;21(1):199. <https://doi.org/10.1186/s12935-021-01866-3>.
334. Fu Y, Zheng Q, Mao Y, Jiang X, Chen X, Liu P, et al. WNT2-mediated FZD2 stabilization regulates esophageal cancer metastasis via STAT3 signaling. *Front Oncol*. 2020;10:1168. <https://doi.org/10.3389/fonc.2020.01168>.
335. Ou H, Chen Z, Xiang L, Fang Y, Xu Y, Liu Q, et al. Frizzled 2-induced epithelial-mesenchymal transition correlates with vasculogenic mimicry, stemness, and Hippo signaling in hepatocellular carcinoma. *Cancer Sci*. 2019;110(4):1169–82. <https://doi.org/10.1111/cas.13949>.
336. Luo M, Zhou L, Zhan SJ, Cheng LJ, Li RN, Wang H, et al. *ALPL* regulates the aggressive potential of high grade serous ovarian cancer cells via a non-canonical WNT pathway. *Biochem Biophys Res Commun*. 2019;513(2):528–33. <https://doi.org/10.1016/j.bbrc.2019.04.016>.
337. Sun S, Wang J, Liu J, Yin F, Xin C, Zeng X, et al. MiR-302b suppresses tumor metastasis by targeting Frizzled 6 in OSCC. *J Dent Res*. 2021;100(7):739–45. <https://doi.org/10.1177/0022034520986551>.
338. Ferreira JM, Gonçalves CS, Costa BM. Emerging roles and biomarker potential of WNT6 in human cancers. *Cell Commun Signal*. 2024;22(1):538. <https://doi.org/10.1186/s12964-024-01892-4>.
339. Hankey W, Frankel WL, Groden J. Functions of the APC tumor suppressor protein dependent and independent of canonical WNT signaling: implications for therapeutic targeting. *Cancer Metastasis Rev*. 2018;37(1):159–72. <https://doi.org/10.1007/s10555-017-9725-6>.
340. Chatterjee S, Sil PC. Targeting the crosstalks of Wnt pathway with Hedgehog and Notch for cancer therapy. *Pharmacol Res*. 2019;142:251–61. <https://doi.org/10.1016/j.phrs.2019.02.027>.
341. Daisy Precilla S, Biswas I, Kuduvali SS, Anitha TS. Crosstalk between PI3K/AKT/mTOR and WNT/ β -Catenin signaling in GBM - Could combination therapy checkmate the collusion? *Cell Signal*. 2022;95:110350. <https://doi.org/10.1016/j.cellsig.2022.110350>.
342. Zhou J, Toh SH, Chan ZL, Quah JY, Chooi JY, Tan TZ, et al. A loss-of-function genetic screening reveals synergistic targeting of AKT/mTOR and WTN/ β -catenin pathways for treatment of AML with high PRL-3 phosphatase. *J Hematol Oncol*. 2018;11(1):36. <https://doi.org/10.1186/s13045-018-0581-9>.
343. Mologni L, Brussolo S, Ceccon M, Gambacorti-Passerini C. Synergistic effects of combined Wnt/KRAS inhibition in colorectal cancer cells. *PLoS ONE*. 2012;7(12):e51449. <https://doi.org/10.1371/journal.pone.0051449>.
344. Zeng Y, Wang T, Liu Y, Luo T, Li Q, He Y, et al. Wnt and Smad signaling pathways synergistically regulated the osteogenic differentiation of fibroblasts in ankylosing spondylitis. *Tissue Cell*. 2022;77:101852. <https://doi.org/10.1016/j.tice.2022.101852>.
345. Jo MY, Jeong YJ, Song KH, Choi YH, Kwon TK, Chang YC. 4-O-methylas-cochlorin synergistically enhances 5-fluorouracil-induced apoptosis by inhibiting the Wnt/ β -catenin signaling pathway in colorectal cancer cells. *Int J Mol Sci*. 2024. <https://doi.org/10.3390/ijms25115746>.
346. Yang Z, Zhou M, Yin T, Wang CY, Zhu GY, Bai LP, et al. Functionalized Carbon Dots With Intrinsic Wnt/ β -Catenin Inhibition to Synergistically Promote 5-Fluorouracil Chemotherapy. *Int J Nanomedicine*. 2025;20:1951–64. <https://doi.org/10.2147/ijn.S503540>.
347. Kang HW, Kim JH, Lee DE, Lee YS, Kim MJ, Kim HS, et al. Combination therapy of niclosamide with gemcitabine inhibited cell proliferation and apoptosis via Wnt/ β -catenin/c-Myc signaling pathway by inducing β -catenin ubiquitination in pancreatic cancer. *Cancer Biol Ther*. 2023;24(1):2272334. <https://doi.org/10.1080/15384047.2023.2272334>.
348. Huang Y, Sheng H, Xiao Y, Hu W, Zhang Z, Chen Y, et al. Wnt/ β -catenin inhibitor ICG-001 enhances the antitumor efficacy of radiotherapy by increasing radiation-induced DNA damage and improving tumor immune microenvironment in hepatocellular carcinoma. *Radiother Oncol*. 2021;162:34–44. <https://doi.org/10.1016/j.radonc.2021.06.034>.
349. Zhao Y, Song Y, Li W, Wu J, Zhao Z, Qu T, et al. Clofazimine enhances anti-PD-1 immunotherapy in glioblastoma by inhibiting Wnt6 signaling and modulating the tumor immune microenvironment. *Cancer Immunol Immunother*. 2025;74(4):137. <https://doi.org/10.1007/s00262-025-03994-5>.
350. Li XY, Li Y, Zhang L, Liu X, Feng L, Wang X. The antitumor effects of arsenic trioxide in mantle cell lymphoma via targeting Wnt/ β -catenin pathway and DNA methyltransferase-1. *Oncol Rep*. 2017;38(5):3114–20. <https://doi.org/10.3892/or.2017.5945>.
351. Wang FY, Yang LM, Xiong XL, Yang J, Yang Y, Tang JQ, et al. Rhodium(III) complex noncanonically potentiates antitumor immune responses by inhibiting Wnt/ β -catenin signaling. *J Med Chem*. 2024;67(16):13778–87. <https://doi.org/10.1021/acs.jmedchem.4c00583>.
352. Turcios L, Vilchez V, Acosta LF, Poyil P, Butterfield DA, Mitov M, et al. Sorafenib and FH535 in combination act synergistically on hepatocellular carcinoma by targeting cell bioenergetics and mitochondrial function. *Dig Liver Dis*. 2017;49(6):697–704. <https://doi.org/10.1016/j.dld.2017.01.146>.
353. Wang J, Dang MN, Day ES. Inhibition of Wnt signaling by Frizzled7 antibody-coated nanoshells sensitizes triple-negative breast cancer cells to the autophagy regulator chloroquine. *Nano Res*. 2020;13(6):1693–703. <https://doi.org/10.1007/s12274-020-2795-8>.

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