Review Article
Development of anticancer agents targeting the Wnt/β-catenin signaling

Xiangqian Zhang1, Jijun Hao2,3

1College of Life Science, Yan’an University, Yan’an 716000, Shaanxi, China; 2College of Veterinary Medicine, Western University of Health Sciences, Pomona, CA 91766, USA; 3Graduate College of Biomedical Sciences, Western University of Health Sciences, Pomona, CA, 91766, USA

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Abstract: Wnt/β-catenin signaling plays indispensable roles in both embryonic development and adult homeostasis. Abnormal regulation of this pathway is implicated in many types of cancer. Consequently, substantial efforts have been made to develop therapeutic agents as anticancer drugs by specifically targeting the Wnt/β-catenin pathway. Here we systematically review the potential therapeutic agents that have been developed to date for inhibition of the Wnt/β-catenin cascade as well as current status of clinical trials of some of these agents.

Keywords: Wnt/β-catenin signaling, β-catenin, cancer, small molecules, biologic agents, therapeutic, safety and clinic

Introduction

Wnt/β-catenin signaling is an evolutionarily conserved pathway and it plays indispensable roles in both embryonic development and adult homeostasis. The Wnt/β-catenin network was first reported in 1982 with identification of mouse proto-oncogene int1 (also known as Wnt1). Later the homolog of int1, Wingless (Wg) from Drosophila melanogaster, was identified to promote wing development in fruit flies [1, 2]. Since then, accumulative studies have reported essential roles of the Wnt/β-catenin signaling in development of various organs and tissues such as the brain, spinal cord, kidney, heart, liver, lungs, limbs and eyes [3, 4]. In addition, the Wnt/β-catenin signaling also plays crucial roles in adult homeostasis such as regeneration of skin, gut, hair and bone marrow [5-8].

Aberrant Wnt/β-catenin signaling can lead to developmental malformations and is associated with many types of disease including fibrosis, gastric and colorectal tumors, melanomas and hepatocellular carcinomas [9-15]. Given the critical roles of Wnt/β-catenin pathway in cancer, substantial efforts have been made to develop therapeutic approaches to target this pathway. In this article, we review recent efforts to develop therapeutic agents, with a focus on small molecules, for targeting the Wnt/β-catenin pathway.

The Wnt/β-catenin signaling pathway

β-catenin is the central mediator of the Wnt/β-catenin signaling and it is dynamically distributed in multiple subcellular locations (Figure 1). For instance, β-catenin in adherens junctions is involved in cell-cell contacts, and its levels in cytoplasm are tightly regulated whereas in nucleus, β-catenin is implicated in transcriptional regulation and chromatin modification [16, 17]. In quiescent cells, the cytoplasmic β-catenin is bound to a large protein assembly called ‘destruction complex’ which consists of several proteins including Axin, adenomatous polyposis coli (APC), the Ser/Thr kinases glycogen synthase kinase 3β (GSK3β) and casein kinase Iα (CKIα) [3, 18]. In the destruction complex, β-catenin is initially phosphorylated by CKIα at Ser45 followed by further phosphorylation at Ser33, Ser37 and Thr41 (in human) by GSK3β [19]. Finally the phosphorylated β-catenin is marked with ubiquitin mediated by β-transducin-repeat-containing protein (β-TrCP).
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Abnormal regulation of the Wnt/β-catenin signaling is implicated in various types of cancer. In 1991, genetic mutations in the tumor suppressor APC were first found to be associated with colorectal cancer [20-22]. These mutations typically resulted in truncated APC proteins that are incapable of binding β-catenin and Axin, leading to aberrant activation of the Wnt/β-catenin signaling [23, 24]. Later, mutations in another core component of the destruction complex, Axin, have been reported to display a predisposition for colorectal cancer [25, 26]. Meanwhile genetic mutations of β-catenin that abnormally activate the Wnt/β-catenin signaling were also observed in colorectal cancer [27]. These mutations prevent phosphorylation of the serine and threonine residues of β-catenin targeted by GSK3β or CKIα [27]. Importantly, effects of mutations in the Wnt/β-catenin cascade are not limited to colorectal cancers only. For instance, messenger RNA splicing and mis-sense mutations in the β-catenin gene were described in melanoma progression [28, 29] and other solid tumors such as liver cancer [30], thyroid tumors [31] and ovarian neoplasms [32].

Besides genetic mutations of the Wnt/β-catenin cascade, abnormal expression of the signaling proteins by epigenetic alteration is also involved in various types of cancer. For instance, the reduced activity or absence of extracellular Wnt antagonist, the secreted Frizzled-related proteins (SFRPs) has been reported in colorectal, breast, prostate, lung cancers [33-37]. Furthermore, increased expression of Wnt ligands and Dvl has been demonstrated to be associated with many types of cancer as well [38-42].

Potential therapeutic agents targeting the Wnt/β-catenin cascade

Given the critical roles of abnormal activation of the Wnt/β-catenin signaling in various types of cancer, substantial efforts have been made to develop therapeutic agents including biolog-
Table 1. Selected small molecules that inhibit the Wnt/β-catenin signaling

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Name</th>
<th>Target</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
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<td>DVL</td>
<td>[68]</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>3289-8625</td>
<td>DVL</td>
<td>[70]</td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>J01-017a</td>
<td>DVL</td>
<td>[69]</td>
</tr>
<tr>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>XAV939</td>
<td>Tankyrase</td>
<td>[73]</td>
</tr>
<tr>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>IWR-1</td>
<td>Tankyrase</td>
<td>[75]</td>
</tr>
</tbody>
</table>
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![Chemical structures of WIKI4, JW55, JW74, G007-LK, and Pyrvinium](image)

WIKI4  Tankyrase  [78]

JW55  Tankyrase  [77]

JW74  Tankyrase  [77]

G007-LK  Tankyrase  [79]

Pyrvinium  CKIα  [87]
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LGK-974 Porcupine [84]

IWP2 Porcupine [75]

PNU-74654 β-catenin/TCF [93]

iCRT3 β-catenin/TCF [91]

iCRT5 β-catenin/TCF [91]

iCRT14 β-catenin/TCF [91]
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2,4-diamino-quinazoline derivative β-catenin/TCF [92]

BC21 β-catenin/TCF [94]

Ethacrynic acid LEF [95]

PRI-724 (ICG-001) CBP [104]

Windorphen P300 [103]
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Biological agents

Several biological agents have been studied in cancer by specifically targeting either aberrantly overexpressed Wnt receptors or the Wnt ligands (Figure 1). For instance, inhibition of Wnt/β-catenin signaling by adenovirus-mediated expression of Dickkopf-1 (Dkk-1), a potent secreted Wnt antagonist that interacts with the LRP5/6 co-receptors, has been shown to suppress epithelium proliferation in small intestine and colon [43, 44]. In addition, it has also been shown that Mesd, another LRP5/6 co-receptor inhibitor, effectively inhibits prostate cancer PC-3 cell proliferation in vitro and markedly decreases growth of breast cancer in the mouse mammary tumor virus-Wnt-1 transgenic mice [45, 46]. In addition, OMP-54F28 (also known as FZD8-Fc or F8CRDhFc), a proprietary fusion protein comprised of the cysteine-rich domain (CRD) of frizzled family receptor 8 (Fzd8) fused to the human immunoglobulin Fc domain, was shown to bind to all Wnt ligands to block the Wnt/β-catenin signaling [47]. The clinic Phase I trial of OMP-54F28 is underway.

Moreover, large antibodies and small peptides have been developed to target the Wnt/β-catenin signaling as well. For instance, previous studies have demonstrated that monoclonal antibodies-neutralizing Wnt3a can suppress prostate tumor growth in a mouse model [48], and antibodies targeting Frizzled receptors are effective in various preclinical models including those of breast, colon and liver cancer [49, 50]. Another monoclonal antibody which targets Frizzled receptors, OMP-185, was shown to inhibit tumor growth in mouse xenograft models, reduce tumor-initiating cell frequency and display synergistic activity with chemotherapeutic agents [51]. Other than the large antibodies, small peptides represent another potential therapeutic approach to inhibit the Wnt/β-catenin signaling for cancer therapy. For instance, a hydrocarbon-stapled peptide has been reported to inhibit Wnt/β-catenin signaling by directly targeting β-catenin and interfering with its interaction with TCF proteins [52]. In addition, a stabilized alpha helix of BCL9 (SAH-BCL9) has been developed. The SAH-BCL9 peptide was shown to selectively suppress Wnt signaling by dissociating β-catenin/BCL9 complex, and exhibit antitumor effects in mouse xenograft models of colorectal carcinoma and Interleukin-6-dependent multiple myeloma [53].

Small molecule inhibitors of the Wnt/β-catenin pathway

Compared to biological agents, small molecule drugs exhibit several advantages including lower cost with greater ease of manufacturing, oral bioavailability and ability to penetrate into cells for intracellular targets. Therefore, tremendous research has been performed in the past to develop specific small molecules to target the Wnt/β-catenin pathway. Here we classify the small molecule inhibitors of the Wnt/β-catenin signaling into three groups: small molecules that target cytoplasmic proteins, small molecules that target transcriptional factors and small molecules that target the co-activators (Figure 1 and Table 1).

Small molecules that target cytoplasmic proteins of the Wnt/β-catenin cascade

Dvl: Three Dishevelled isoforms, Dvl1, Dvl2 and Dvl3, have been identified in mammalian species [54-58]. All Dvl proteins contain three functional domains: an N-terminal DIX (Dishevelled/Axin) domain, a central PDZ (Postsynaptic density 95, Discs Large, Zonula occludens-1) domain and a C-terminal DEP domain (Dvl Egl-10, Pleckstrin). The DIX domain is responsible for the polymerization of Dvl in the Wnt signalingosome [59, 60] whereas the DEP domain is suggested to be essential for the DVL binding to membrane lipids during planar epithelial polarization [61-63]. The PDZ domain is a modular protein interaction domain, and it directly interacts with the cytosolic C-terminal tail of the Frizzled to transduce signals from the Frizzled receptor to the downstream signaling cascade [64]. However, this interaction between the Dvl PDZ domain and the Frizzled can be suppressed when the Dvl PDZ domain is bound by the Dapper proteins that promote Dvl lysosomes-mediated degradation [65-67].

The special role of the Dvl PDZ domain in the Wnt pathway makes it an ideal pharmaceutical target. NSC668036, a small molecule Wnt inhibitor by targeting Dvl PDZ domain, was identified from National Cancer Institute small-molecule library by using structure-based virtual
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ligand screening [68]. Based on NSC668036 study, the same research group further developed a more potent small molecule inhibitor of the Dvl PDZ domain, named J01-017a, under guidance of the 3-dimensional quantitative structure-activity relationship analysis [69]. In addition, another small molecule inhibitor of the Dvl PDZ domain, compound 3289-8625, has been identified through structure-based ligand screening and NMR spectroscopy [70]. All three compounds (NSC 668036, J01-07a and 3289-8625) block the Wnt/β-catenin signaling by interacting with the groove of Dvl PDZ domain where the inhibitory Dapper proteins bind.

Tankyrase inhibitors: Tankyrase is a subgroup of Poly (ADP-ribose) polymerases (PARPs) family. Two isoforms of Tankyrase, Tankyrase 1 (PARP5a) and Tankyrase 2 (PARP5b), have been identified to be involved in the Wnt/β-catenin signaling [71, 72]. Both Tankyrase isoforms interact with and poly(ADP-ribosyl)ate Axin to stimulate Axin degradation through the ubiquitin-proteasome pathway [73, 74].

A few small molecule Tankyrase inhibitors have been developed to inhibit the Wnt/β-catenin signaling (Table 1). In 2009, Chen et al. reported the first Tankyrase inhibitor, IWR-1, in screening a diverse synthetic chemical library by using a Wnt luciferase reporter assay [75]. It was shown that IWR-1 stabilized Axin for inhibition of the Wnt/β-catenin signaling by targeting Tankyrases. In the same year, Huang and colleagues identified another Tankyrase inhibitor, XAV939, which functions in a similar way to IWR-1 [73]. Recently, several additional potent and selective tankyrase inhibitors have been reported including WIKI4, JW55, JW74 and G007-LK [76-79].

Porcupine inhibitors: Porcupine is a membrane-bound O-acyltransferase (MBOAT) specific to Wnt post-translational acylation, which is required for subsequent Wnt secretion [80]. Loss of Porcupine leads to inhibition of Wnt ligand-driven signaling activities in knockout mouse models [81, 82]. In humans, loss-of-function mutations in the Porcupine gene lead to focal dermal hypoplasia whose phenotype is consistent with inactivation of the Wnt signaling pathway during embryogenesis and development [29].

Targeting Porcupine for Wnt inhibition may represent a new therapeutic strategy for cancer therapy. In 2009, Chen et al. identified the first Porcupine inhibitor IWP-2 which disrupts Wnt signaling by preventing Porcupine-dependent lipidation of Wnt proteins [75]. Later the same group further developed a number of novel Porcupine inhibitors with diverse chemical structures [83]. In addition, Liu and colleagues recently discovered a new class of specific small-molecule Porcupine inhibitor LGK974 after screening approximately 2.4 million compounds by using Wnt-secreting cells (a stable L-cell line overexpressing Wnt3A) which were co-cultured with the Wnt luciferase reporter cells [84]. LGK974 has been shown to potently inhibit Wnt signaling in vitro, and is efficacious in multiple tumor models including murine and rat mechanistic breast cancer models and a human head and neck squamous cell carcinoma model [84].

Another CK1 kinase isoform, CK1ε, is involved in phosphorylation of E-cadherin upon Wnt binding to Frizzled-LRP5/6 receptor, leading to the release of β-catenin from its complex with E-cadherin and subsequent increase of the cellular threshold of free β-catenin [88]. Recently Cheong and colleagues have identified a small molecule, PF670462, which can potently suppress the Wnt/β-catenin signaling by inhibiting CK1ε activity [89].

Small molecules that target transcriptional factors of the Wnt/β-catenin cascade

As previously described, nuclear β-catenin needs to interact with transcription factor TCF/LEF to regulate the target gene transcription.
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Thus, disrupting the interaction between β-catenin and TCF/LEF in the nucleus represents another therapeutic avenue to block the Wnt/β-catenin signaling pathway.

In a high-throughput enzyme-linked immunosorbent assay (ELISA) screen of a natural product library, eight compounds were identified to exhibit dose-dependent inhibition of the β-catenin/TCF complex formation [90]. Subsequently six of the compounds were shown to block complex formation in the gel retardation assay, inhibit TCF reporter gene activity and down-regulate target gene expression. Three of these six compounds can display efficacy in inhibiting axis duplication induced by β-catenin in the Xenopus [90]. Additionally after screened around 15,000 compounds, Gonsalves and colleagues have identified three new small molecules, iCRT3, iCRT5 and iCRT14, which can disrupt the β-catenin/TCF interaction, down-regulate the Wnt target gene expression and kill colorectal cancer cells [91]. In another high-throughput screen, Chen and colleagues discovered a novel compound, 2,4-diamino-quinazoline, which disrupts the interaction between β-catenin with TCF4. A further structure-activity relationship study yielded a number of new analogues including compound 16k which exhibited good cellular potency, solubility, metabolic stability and oral bioavailability [92].

Other than high-throughput screening, computation and structure-based approaches have also been successfully utilized in developing small molecules to inhibit the β-catenin/TCF interaction. For instance, drug-like TCF-competitive small molecule, PNU-74654, were discovered after a 17,700 compounds subset of the Pharmacia corporate collection was docked to the hot spot of the TCF-binding surface on β-catenin by using the Flo-QXP program [93]. In another crystal structure-based virtual screen of about 1990 small-molecules, BC21 was identified to bind to the armadillo repeat structure of β-catenin and reduce β-catenin/TCF reporter activity [94]. Additionally, the diuretic agent ethacrynic acid (EA) was identified to display an inhibitory effect on the Wnt/β-catenin signaling in a cell-based Wnt reporter assay. Immune co-precipitation experiments demonstrated that EA could directly bind to LEF-1 protein and destabilize the β-catenin/LEF-1 complex [95]. Several more potent EA derivatives were developed and shown to block the Wnt/β-catenin signaling and decrease survival of chronic lymphocytic leukemia cells [96].

Small molecules that target the co-activators of the Wnt/β-catenin cascade

A number of transcriptional co-activators in nucleus are required for Wnt target gene expression. These include CBP, p300, Pygo, BCL-9 and many other basal transcriptional machinery components. CBP and p300 have definitive and distinct roles both in vitro and in vivo [98-100]. Particularly, a new model about unique roles of CBP and p300 in the Wnt/β-catenin signaling cascade for stem cells has been developed: CBP induces a transcriptional program for proliferation and the maintenance of stem cell potency, whereas p300 leads to a transcriptional program for stem cell differentiation [101, 102]. We and others in the field have recently identified small molecules that selectively target CBP and p300 for inhibition of the Wnt/β-catenin signaling [103, 104].

CBP inhibitors: Emami and colleagues have identified the small molecule PRI-724 (also named as ICG-001) that down-regulates the Wnt/β-catenin signaling by specifically binding to CBP [104]. PRI-724 was shown to selectively induce apoptosis in colon carcinoma cells but not in normal colon cells, and exhibit antitumor activity in the mouse xenograft models of colon cancer [104]. Interestingly, PRI-724 binds specifically to the co-activator CBP, but not to the closely related homologue p300.

p300 inhibitors: In a zebrafish-based phenotype screen, we recently discovered a compound named Windorphen that selectively targets p300 histone acetyltransferase for Wnt signal inhibition. Windorphen displays remarkable specificity toward p300, and selectively kills cancer cells that harbor Wnt-activating mutations, supporting the therapeutic potential of Windorphen [103]. In addition, the mechanism study of vitamin A and vitamin D suggested that they may target p300 to inhibit Wnt signal for cancer therapy of the acute promyelocytic leukaemia chemoprevention [105].
### Table 2. Current clinical trials of the potential therapeutic agents that target the Wnt/β-catenin pathway

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Target</th>
<th>Agent Type</th>
<th>Disease</th>
<th>Clinical Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMP18R5 (vantictumab)</td>
<td>OncoMed Pharmaceuticals</td>
<td>frizzled</td>
<td>Biologic agents</td>
<td>Solid tumors</td>
<td>Open-label Phase 1 dose escalation study</td>
</tr>
<tr>
<td>OMP-54F28</td>
<td>OncoMed Pharmaceuticals/Bayer</td>
<td>Wnt</td>
<td>Biologic agents</td>
<td>Solid tumors</td>
<td>Phase I</td>
</tr>
<tr>
<td>LGK974</td>
<td>Novartis Pharmaceuticals</td>
<td>Porcupine</td>
<td>Small Molecule</td>
<td>Melanoma, breast cancer and pancreatic adenocarcinoma</td>
<td>Phase I</td>
</tr>
<tr>
<td>CWP232291</td>
<td>JW Pharmaceutical</td>
<td>β-catenin</td>
<td>Small Molecule</td>
<td>acute myeloid leukemia</td>
<td>Phase I</td>
</tr>
<tr>
<td>PRI-724</td>
<td>Prism/Eisai Pharmaceuticals</td>
<td>β-catenin/β-catenin</td>
<td>Small Molecule</td>
<td>advanced myeloid malignancies</td>
<td>Open-Label Phase 1 dose escalation study</td>
</tr>
</tbody>
</table>
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Safety of targeting the Wnt/β-catenin signaling

Despite the crucial role of aberrant activation of the Wnt/β-catenin signaling in cancer, cautions must be taken when targeting this pathway for cancer therapy because the Wnt/β-catenin pathway is also indispensable in developmental processes and adult tissue homeostasis. A recent review by Kahn provides a detailed discussion of safety concerns targeting of the Wnt pathways [106]. Here, we would like to highlight certain safety issues from the aspect of regenerative biology.

The Wnt signaling plays a central role in stem cell proliferation and pluripotency. For instance, in the intestinal tract, stem cells residing at the most bottom part of the crypt stochastically self-renew and produce the transit-amplifying progenitor cells for intestinal homeostasis [107, 108]. Both genetic disruption of Wnt pathway and ectopic expression of the Wnt antagonist Dkk-1 lead to rapid loss of transient-amplifying cells and crypt structures [6, 43, 109-111]. Conversely, aberrant activation of the Wnt pathway results in an increase of intestinal stem cell numbers and robust proliferation in the crypt [6, 112]. Given the critical role of Wnt signaling in intestinal tract stem cells, targeting this pathway for cancer therapy may cause safety issue. Indeed, disruption of the Wnt/β-catenin signaling by adenovirus-mediated expression of the Wnt antagonist Dkk-1 lead to rapid loss of transient-amplifying cells and crypt structures [6, 43, 109-111].

Therapeutic agents in clinic study

Biological therapeutic agents

A number of biologic therapeutic agents targeting the Wnt pathway have entered clinical trials (Table 2). The clinic Phase I trial of one of these agents, OMP18R5 (also known as Vantictumab, a fully humanized monoclonal antibody that targets frizzled receptor), has recently been completed by OncoMed Pharmaceuticals [116]. 18 patients with solid tumors were treated in 5 dose-escalation cohorts (0.5 and 1 mg/kg weekly; 0.5 mg/kg every 2 weeks; 1 and 2.5 mg/kg every 2 weeks). The most common related adverse events included Grade 1 and 2 fatigue, vomiting, abdominal pain, constipation, diarrhea and nausea. The only potentially drug-related adverse events were dose-limiting toxicities of Grade 1 diarrhea and vomiting in 1 patient treated with 1 mg/kg every week. One patient receiving 0.5 mg/kg every week had a bone fracture on day 110, and three cases exhibited prolonged stable disease in patients with neuroendocrine tumors [116]. The open-label Phase 1 dose escalation study of OMP-18R5 in patients with solid tumors continues and is expected to be completed by June 2016. Another OncoMed agent OMP-54F28, a proprietary fusion protein with Fzd8 that binds to all Wnt ligands, was co-developed with Bayer was initiated recently for solid tumor treatment.
Small molecule therapeutic agents

Other than biological agents, clinical trials of small molecule agents have also been conducted in recent years too (Table 2). For instance, Novartis Pharmaceuticals initiated a Phase I trial of the small molecule Porcupine inhibitor LGK974 for multiple malignancies (melanoma, breast cancer and pancreatic adenocarcinoma) that are associated with aberrant Wnt signaling. It is expected that the Phase I trial to obtain a maximum tolerated dose of LGK974 will be completed in January 2017. In addition, JW Pharmaceutical recently initiated a Phase I clinical study of CWP232291, a small molecule prodrug targeting β-catenin for degradation, in acute myeloid leukemia patients. The clinical trial is expected to be completed at the end of 2015, and no results have been disclosed publicly yet. As described previously, small molecule PRI-724 can block interaction of CBP with β-catenin for Wnt signaling inhibition [104]. The initial results of the Phase I clinical trial of PRI-724 has been disclosed publicly [117]. Overall, PRI-724 was given to 18 patients as a continuous infusion for 7 days, and the drug exhibited an acceptable toxicity profile with only one dose-limiting toxicity of grade 3 reversible hyperbilirubinaemia. An Open-Label dose-escalation phase I/II study of PRI-724 for patients with advanced myeloid malignancies is still ongoing. Additionally, clinical trials of combination of PRI-724 with other therapeutic agents are underway. For instance, a Phase I trial was initiated to treat patient with colorectal cancer by administering PRI-724 in combination with a modified regimen of FOLFOX6 (mFOLFOX 6). Furthermore, a current Phase I trial is testing continuous intravenous doses of PRI-724, in combination with Gemcitabine, to treat patients with advanced or metastatic pancreatic adenocarcinoma.

Concluding remarks

The Wnt/β-catenin signaling is a highly evolutionarily conserved key pathway, and aberrant activation of this pathway is implicated in a broad range of diseases including cancer. Despite extensive studies of the Wnt/β-catenin signaling in almost three decades, targeting this pathway as a therapeutic strategy is still at its infancy. It still remains unclear which targets in the pathway may offer an ideal therapeutic lead for drug discovery. Particularly we shall bear in mind that the Wnt/β-catenin signaling also plays crucial roles in tissue homeostasis and repair, thus successfully targeting aberrant Wnt/β-catenin signaling in cancer will require a fine balancing act. In addition, the fact that several known targets in the Wnt/β-catenin pathway are also implied in other pathways applies another layer of complexity. Despite these complications, our understanding of this pathway in both normal physiology and pathophysiology continues to improve, and significant excitement has been generated to develop therapeutic agents targeting the Wnt/β-catenin signaling for disease treatment. In recent years, a number of small molecule and biologic agents that target the Wnt/β-catenin signaling have entered clinical trials. In the coming years, it shall be clear whether these potential therapeutic agents targeting Wnt/β-catenin pathway will be efficacious to cancer.

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Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

Address correspondence to: Jijun Hao, College of Veterinary Medicine, Western University of Health Sciences, Pomona, CA 91766, USA. Tel: (909) 469-8686; Fax: 909-469-5635; E-mail: jhao@westernu.edu

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