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Targeting the Wnt/beta-catenin Pathway in Cancer: Update on Effectors and Inhibitors

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Targeting the Wnt/beta-catenin Pathway in Cancer: Update on Effectors and Inhibitors
Abstract

The Wnt/beta-catenin pathway is a family of proteins that is implicated in many vital cellular functions like stem cell regeneration and organogenesis. Several intra-cellular signal transduction pathways are induced by Wnt, notably the Wnt/beta-catenin dependent pathway or canonical pathway and the non-canonical or beta-catenin-independent pathway, the latter includes the Wnt/Ca2+ and Planar Cell Polarity pathway (PCP). Wnt activation occurs at the intestinal crypt floor, and is critical to optimal maintenance of stem cells. Colorectal cancers show evidence of Wnt signaling pathway activation and this is associated with loss of function of the tumor regulator APC. Wnt activation has been observed in breast, lung, and hematopoietic malignancies and contributes to tumor recurrence. The Wnt pathway cross talks with the Notch and Sonic Hedgehog pathways, which has implications for therapeutic interventions in cancers. There are significant challenges in targeting the Wnt pathway, including finding agents that are efficacious without damaging the system of normal somatic stem cell function in cellular repair and tissue homeostasis. Here, we comprehensively review the Wnt pathway and its interactions with the Notch and Sonic Hedgehog pathways. We present the state of the field in effectors and inhibitors of Wnt signaling, including updates on clinical trials in various cancers with inhibitors of Wnt, Notch, and Sonic Hedgehog.

Key words: Wnt, beta-catenin, colorectal cancers, gamma secretase, Hedgehog, Targeted therapy
Introduction

The Wnt family is a group of proteins implicated in many cellular functions: organ formation, stem cell renewal, and cell survival [1]. In humans, the Wnt family consists of cysteine rich glycoproteins that act as ligands for as many as fifteen receptors and co-receptors [2]. Extracellular Wnt can trigger varied intra-cellular signal transduction pathways, like the Wnt/beta-catenin dependent or canonical pathway and the beta-catenin-independent or non-canonical pathway (Figure1,2b). Examples of the beta-catenin-independent pathway include the Wnt/Ca 2+ pathway as well as the Planar Cell Polarity pathway (PCP) [3]. The beta-catenin-dependent signaling pathway is triggered by the binding of Wnt ligand to the LRP-5/6 receptors (low-density lipoprotein receptor) and Frizzled receptors. This in turn activates Disheveled (DVL), causing recruitment of the complex (Axin, GSK-3 beta, CK1, APC) to the receptor. [4-6]. The Wnt – Frizzled-Axin -LRP-5/6complex sequesters cytosolic GSK-3 beta rendering it incapable of phosphorylating beta-catenin. There is accumulation of un-phosphorylated beta-catenin in the cytosol which migrates to the nucleus, interacting there with T cell-specific factor(TCF)/ lymphoid enhancer-binding factor(LEF) and co-activators, like Pygopus (Pygo) and Bcl-9, to turn on the Wnt target genes such as c-Myc, cyclin D1 and Cdkn1a [6].

Without Wnt, the beta-catenin in the cytosol undergoes phosphorylation by GSK-3 beta and CK1 and subsequent sequestration in the beta-catenin destruction complex, (APC, GSK-3 beta, CK1, Axin). This phosphorylated complex allows for the E3 ubiquitin ligase called beta-TrCP to attach to the beta-catenin at a binding site, that enhances its ubiquitination leading to subsequent proteasomal degradation [7-8] (Figure 2a). One of the Non-canonical Wnt pathways includes the PCP or Planar cell polarity pathway. This can be initiated by Wnt interaction with Frizzled receptors, with co-
receptors RYK and ROR which control the activity of small GTPases such as RhoA that play a role in regulation of the remodeling of the cytoskeleton [8] (Figure 2b). Wnt interaction with Frizzled leads to Dvl activation [8]. myosin and the Rho-associated kinase (ROCK) are activated by Rho GTPase, altering the mechanism of actin and cytoskeleton rearrangement. There is in tandem activation of Rac GTPase and activated Rac then stimulates JNK activity (c-Jun N-terminal kinase) [9].

In the Wnt/ Ca2+ pathway, activated by Wnt 5A, the frizzled FZD2 cleaves guanine nucleotide binding protein (G-protein), into protein beta/gamma subunits G-protein alpha-t2 causing Ca2+ to be released into the cytosol promoting differentiation in the neuronal system. Calcium activates CaMK II and Calmodulin, enhancing phosphorylation of Tcf/Lef (T-cell factor and lymphoid enhancer factor) thus suppressing the canonical Wnt pathway. The mechanisms by which Wnt5a can also interact via the canonical pathway are not completely mapped out though it is speculated that the LRP5 co-receptor is activated along with FZD4 and FZD5 receptors [10-14].

**Axin and APC- Negative regulators of Wnt**

Axin serves as a scaffold protein recruiting GSK3β and CKIα (caspase kinase alpha) along with APC to form a complex with beta-catenin resulting in beta-catenin phosphorylation, ultimately causing its degradation. Axin also plays a key role in Wnt signaling initiation. PPPSP motifs on the cytoplasmic tail of LRP6 are phosphorylated upon Wnt activation. This in turn causes recruitment of Axin complexes to the membrane destabilizing beta-catenin complex in the cytoplasm. Axin is post translationally modified by phosphorylation/dephosphorylation. Without Wnt, Axin is
phosphorylated, increasing its binding affinity with beta-catenin, leading to stabilization of Axin. When Wnt stimulation is present, Axin is dephosphorylated, resulting in less binding with beta-catenin and consequently Axin degradation [15-18].

APC supplies the framework for a destruction complex together with GSK3β and Axin that promotes phosphorylation and subsequent proteasomal degradation of beta-catenin. In addition, APC enhances export of beta-catenin from the nucleus, which reduces the amount of nuclear beta-catenin for interaction with TCF. Furthermore, APC can bind to beta-catenin, thereby blocking the beta-catenin interaction with TCF/LEF [19-20].

**RNF43 and RSPO signaling modulation of Wnt**

RNF43 (Ring finger protein 43) and the homolog ZNRF3 are transmembrane E3 ligases that dispose of the surface Wnt receptors and promote FZD receptor turnover. R-spondins or RSPO’s are a group of proteins that together bind to the extracellular domains of LGR4/5 and RNF43/ZNRF3, resulting in increased cell surface FZD receptors as this binding causes ubiquitination and clearance of RNF43/ZNRF3[21,22].

**Wnt and Notch signaling pathway cross-talk**

It is thought that the Wnt-beta catenin pathways and Notch pathways interact for Drosophila wing development [23]. Importantly, the Notch target gene Hes1, which encodes a strong basic helix–loop–helix (bHLH) transcriptional repressor, is regulated by beta-catenin-mediated Wnt signaling [24]. There is some evidence that direct interaction between beta-catenin and TCF activates Notch in colorectal cancer cells through regulation of Jagged1 expression. Beta-catenin interaction with Notch-1 leads to decreased Notch-1 ubiquitination, causing Hes-1 expression to increase, which is associated with tumorigenesis. The serine/threonine kinase GSK3β, is an important node in Wnt and Notch signaling crosstalk.
It mediates the phosphorylation of serine and threonine residues of the Notch intracellular domain (NICD-1), which in turn causes it to localize in the nucleus increasing its transcriptional activity and making it more stable [23].

Loss of Notch-1 leads to activation of beta-catenin and increases the transcriptional activity of a beta-catenin-responsive reporter construct, suggesting that Notch dampens betacatenin-mediated responses to Wnt [24]. The non-canonical Wnt/Ca2 + pathway also interacts with Notch signaling. In the non-canonical Wnt/Ca2 + pathway, activation of CamKII by Wnt5a, induces the phosphorylation of the RBP-J-interacting corepressor SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) on serine 1407, resulting in increased promoter activity of a Notch-responsive gene [25] (Figure 2b).

**Wnt- Sonic Hedgehog pathway cross-talk**

The Sonic hedgehog (SHH) pathway plays a vital role in embryogenesis. It has a critical role in the development of neural structures. Activated, the Sonic hedgehog (SHH) attaches to Patch receptors leading to the increased activity of Smoothened receptors(Smo). This in turn causes the transcription of glioma-associated oncogenes homologs (Gli1/2/3) [26]. There is evidence that SHH-mediated tumorigenesis can be inhibited by Wnt. Both GSK3β and CK1α phosphorylate Gli3 that leads to Gli3 ubiquitination. Phosphorylated Gli3 is recognized by β-TrCP (Beta-Transducin Repeat-Containing Protein) and leads to the degradation of C-terminal peptides generating Gli3R, which subsequently inhibits Gli1 activity [27]. Sfrp-1(secreted Frizzled-related protein-1), a suppressor of the Fused kinase, is a negative regulator of both Wnt/beta-catenin and Hedgehog/Gli signaling pathways. Two protein kinases GSK3β and CK1α negatively regulate both beta-catenin and Gli1[28]. Studies have shown an inhibition of SMO could reduce protein levels of active beta-catenin [26] (Figure 3).
Inhibitors of these effectors of the Wnt- beta catenin pathway are summarized in Table1.

**Wnt in Cancers**

Wnt pathway is upregulated in both MSI (microsatellite instable) and MSS (microsatellite stable) colorectal cancers [66]. Normally activated at the bottom of the intestinal crypts, Wnt is critical to cell repair and maintenance of stem cell functions. The primary mechanism of Wnt pathway activation is the loss of function of APC which functions as a negative regulator. Wnt/beta-catenin signaling is activated by truncated APC protein that negates destruction complex-mediated beta-catenin ubiquitination [66].

RNF43 mutations lead to loss of function; they prevent removal of Wnt receptor in the intestinal crypt, thereby causing Wnt signaling activation [21]. They are found in over 18% of colorectal and endometrial cancers [67]. RSPO translocations are noted in 4–18% of patients with gastric, ovarian, and endometrial cancer and about 9% of colorectal cancers. Both RNF43 and R-spondin fusion are mutually exclusive with APC mutations; these alterations may predict for response to inhibitors of Wnt [68].

More than half of breast cancers have activation of Wnt and that is associated with lower overall survival [69]. In a transgenic mouse model inhibition of beta-catenin-dependent signaling in ErbB2-derived cells impaired tumor initiation and metastasis additionally, treatment of ERBB2-overexpressing tumor cells with a selective beta-catenin/CBP inhibitor significantly decreased proliferation and ErbB2 expression [70]. There is an increase in active Wnt signaling in breast cancer stem cells which was confirmed by increased expression of activated beta-catenin protein, both downstream targets AXIN2 and LEF1, and decreased expression of DKK1 protein [69-70].
In non-small cell lung cancer, there is evidence that lung cancer “stemness” is maintained by targeting the negative regulators of Wnt signaling for degradation, thereby increasing beta-catenin mediated Wnt activity [71]. Wnt ligands and receptors were shown to be expressed in the hematopoietic stem cells (HSC) and are found in the bone marrow microenvironment [72]. CML (chronic myeloid leukemia) patients in blast crisis have shown evidence of Wnt activation [73]. Wnt signaling plays a critical role in chemo-resistance in ovarian cancer and is involved in the maintenance and propagation of ovarian cancer stem cells [74]. Desmoid tumors are uncommon malignancies characterized by Wnt/β-catenin activation as the critical step in desmoid tumor formation with tumors almost always showing mutations of the beta-catenin gene or APC [75].

**Wnt-signaling pathway inhibitors in clinical trials for cancer (Table 2).**

**Inhibitors of the Wnt-Receptor Complex**

**Porcupine inhibitors (Figure 2a)**

Porcupine (PORCN) is a membrane-bound O-acyltransferase (MBOAT) important for the secretion of Wnt ligands because it supplies the palmitoyl group to Wnt proteins, a crucial step for Wnt ligand secretion [76].

The Porcupine-selective inhibitor LGK974 blocks Wnt signaling and tumor growth in vivo [40]. Head and neck squamous cell carcinoma (HNSCC) cell lines carrying NOTCH1 mutations that are inactivating are particularly sensitive to inhibition by LGK974 [77]. Porcupine is a Wnt pathway target that is amenable to inhibition while sparing Wnt-dependent tissues. There are ongoing Phase 1/2 trials with LGK974 in metastatic colorectal and head and neck cancers with the characteristic mutations like Rnf43/Znrf3[78], but results are not yet reported (Table 2).
ETC-159 is a small molecule PORCN inhibitor with efficacy in preclinical models of RSPO-translocated colorectal cancer [79]. This molecule has been in Phase I trials since July 2015, with ten patients in the original cohort (9 colorectal cancers and 1 renal) [80]. So far, there are no responses. One patient at 2 mg and 1 at 4 mg remained in the study in stable disease for 6 cycles (Table 2.).

**Antibodies against Wnt family proteins**

Specific Wnt ligands or receptors found to be over expressed in many tumors can also be targeted with agent’s specific to these receptors. Monoclonal antibodies developed against Wnt-1 and Wnt-2 have evidence for Wnt inhibition leading to tumor suppression in melanoma, sarcoma, colorectal cancers, non-small cell lung carcinoma, and mesothelioma [80-81].

OMP-18R5(Vantictumab) manufactured by OncoMed Pharmaceuticals/Bayer is a monoclonal antibody purported to target five of the ten FZD receptors. Safety and efficacy in non-small cell lung cancer, pancreatic and breast cancer are being evaluated alone or combined with chemotherapy [41]. A novel recombinant fusion protein, OMP-54F28 binds Wnt ligands and blocks Wnt signaling through its domain of an extracellular part of human Frizzled 8 receptor (fused to a human IgG1 Fc fragment) [42]. There is concern for Wnt inhibition in bone and five patients had a doubling of a bone turnover marker β-C-terminal telopeptide returning to baseline levels after as single dose of zoledronic acid. There was stable disease for a period of over six months in two patients with desmoid tumors. 4 of 4 patients at 20 mg/kg with ≥1 on-study tumor assessment continue study with stable disease [82]. Three Phase 1b studies are currently in progress in hepatocellular cancer with sorafenib, pancreatic cancer in combined
therapy with nab-paclitaxel and gemcitabine, and in combination with paclitaxel and carboplatin in ovarian cancer [83] (Table 2.).

The first-in-class recombinant fusion protein Ipafricept (OMP-54F28) blocks Wnt signaling through binding of Wnt ligands. In patient-derived ovarian cancer xenografts, this compound has shown activity to decrease the frequency of stem cells, suppress tumor formation and promote differentiation. Interestingly, pretreatment with OMP-54F28 two to three days prior to chemotherapy shows evidence of synergy with taxanes. The first 7 of the 17 patients were dosed in 2 cohorts of q3w IPA/Carboplatin/Paclitaxel (doses of 5 & 10 mg/kg) and the next 10 patients in 2 cohorts of q3w IPA followed by Carboplatin/Paclitaxel (doses of 2 & 4 mg/kg). 6/17 (35%) had complete response (CR), 3 (18%) stable disease and 8 (47%) partial responses (PR). 82% of patients achieved a partial or complete response with main adverse events being grade 3 neutropenia in 3/17, one grade 3 hypophosphatemia and zoledronic acid was used prophylactically in post-menopausal patients [43,84].

**B-Catenin-Destruction Complex Inhibitors**

**Tankyrase inhibitors**

Tankyrase belongs to the Poly (ADP-ribose) polymerases (PARPs) family. There are two isoforms of Tankyrase, Tankyrase 1 (PARP5a) and Tankyrase 2 (PARP5b) associated with the Wnt/beta-catenin signaling. Both these tankyrase isoforms increase the degradation of axin by the ubiquitin-proteasome pathway [85]. Tankyrase inhibitor, XAV939 and IWR-1 regulate Axin by inhibiting Tankyrase 1 and Tankyrase 2[29,30]. Mouse tumor xenografts and patient-derived sphere cultures of patients with colorectal cancer were incubated with a Tankyrase inhibitor, NVP-TNKS656 in addition to AKT and PI3K inhibitors. A high nuclear beta-catenin level predicted for apoptosis with NVP-TNKS656 in combination with
PI3K and AKT inhibitors suggesting the tankyrase inhibitor could overcome resistance to these inhibitors. High FOXO3A (Forkhead box O3) activity was associated with sensitivity to NVP-TNKS656 treatment. Thirteen of forty patients had high nuclear beta-catenin content and had progressed on prior PI3K/AKT/mTOR inhibition [85]. Concerns of gastrointestinal toxicity have arisen in analysis of these inhibitors and further studies are needed [86]. There are currently no ongoing trials with Tankyrase inhibitors.

**Disheveled inhibitors**

Through the PDZ domain, disheveled (DVL) binds to the carboxyl terminal end of the FZD receptors, the common protein-interaction domain. NSC668036, FJ9, and 3289–8625 are some agents that block the FZD and DVL-PDZ interaction leading then to inhibition of the signal transduction pathway [34,87].

**TCF/ beta-catenin Transcription Complex Inhibitors**

There is great variation in Wnt signaling pathway mutations and there is a quest to find agents that can target the downstream effectors. Eight compounds were identified by high-throughput ELISA screening. PFK115-584 and CGP049090 are examples of these and can perturb the beta-catenin/TCF complex in a dose-dependent manner [88]. A major disadvantage is the non-selective nature of the inhibition of beta-catenin/TCF interaction.

**Wnt co-activator antagonist**

PRI-724 is a first-in-class small molecule antagonist that inhibits the interaction between beta-catenin and its transcriptional coactivator CBP (CREB-binding protein) [47]. Preclinical studies of PRI-724 in pancreatic cancer suggest this agent can promote differentiation of chemotherapy-insensitive cancer stem cells and tumor-initiating cells, inhibit stroma formation, and decrease metastatic potential. Patients had progression following 1st-line
treatment with FOLFIRINOX or FOLFOX chemotherapy. A 3+3 dose cohort escalation was done with gemcitabine (1000 mg/m2 on d1, 8, and 15 of 28 d cycle) and increasing doses of PRI-724 administered as a continuous infusion x7 days every other week. 20 patients were enrolled across 3 dose cohorts (doses of PRI-724 at 320, 640 and 905 mg/m2/d). 7/20 had Grade 3/4 adverse events. There was stable disease in 8 pts (40%) and 2 minor responses. 5 of 8 pts (62.5%) with elevated baseline CA19-9 levels showed a marker decline of 30%. Median PFS was 2 months (range, 0.7 to 7.7) [49].

Wnt5a Mimetics

Primary breast carcinomas with low level of Wnt 5a have been found to have a lower disease-free survival suggesting a tumor suppressor role for Wnt 5a. This has been borne out in hematopoietic, prostate, thyroid and colon cancers [89]. Conversely, in melanomas and gastric cancers Wnt 5a expression is associated with increased invasion and metastases [90]. Foxy-5 is a formulated hexapeptide that can mimic the properties of the Wnt5a molecule to impair cancer cell migration in vitro. A phase 1 study of Foxy-5 in patients with metastatic colon, breast, and prostate cancer shows no dose limiting toxicity and a phase 1b trial is ongoing [91].

Gamma Secretase Inhibitors (GSI’s)

There is growing evidence for cross talk between the Notch and Wnt pathways and in a recent study CD44+ CSCs (gastric cancer stem cells) showed high expression of HES-1[92]. Treatment with Gamma secretase inhibitors (GSI) induced apoptosis with demonstrated evidence of inhibition of tumor sphere formation of CD44+ CSCs. Notch1 was thought to be the intermediary in the crosstalk between Wnt-beta-catenin and Notch and these cells [23,24]. Clinical trials with GSI’s have included RO-4929097 with exploratory phase 1 data in pancreatic and colorectal cancer though since discontinued by manufacturer. A more promising molecule is
MK-0752 in combination with ridaforolimus (MK-8669) being investigated in a phase 1 trial of patients with advanced and refractory solid tumors [56,57,93].

There is an ongoing Phase I/II study in patients with locally advanced or metastatic breast cancer of MK-0752 with docetaxel (Table 2). PF-03084014 (Pfizer Inc., Groton, CT, USA) is a selective or Notch-sparing GSI or GS (gamma secretase) modulator [54]. PF-03084014 a small molecule GSI reduced tumor cell migration and mammosphere formation in vitro, reduced tumor cell self-renewal ability in vivo, and decreased mRNA expression of Notch target genes HES-1, HES-4, Notch-1, and HEY-2 in HCC (hepatocellular cancer) xenograft tumors [94].

A Phase 1 trial in triple negative breast cancer in combination with docetaxel had a partial response rate of 4/25 (16%) and 9/25 (36%) with stable disease [54]. Gastrointestinal toxicity is a dose-limiting side-effect with Gamma secretase inhibitors [53-58]. Of interest, gamma secretase showed activity in desmoid tumors (5/9) had an objective response [95].

**Hedgehog Inhibitors**

sFRP-1, a main target gene of the sonic hedgehog pathway, is involved in cross-talk between the hedgehog pathway and the Wnt pathway. Vismodegib is an FDA approved SMO inhibitor that binds directly to SMO; it is currently in use in advanced basal cell cancers. There are also ongoing phase 1/11 trials in cancers like pancreatic gastric, and prostate. Erismodegib (sonidegib) is another FDA-approved, orally bioavailable SMO antagonist used in advanced BCC and there are several ongoing Phase 1/11 trials in other malignancies [62-65]. GLI transcription factors are the terminal effectors of the Shh-SMO signaling pathway and agents called GANTs (GLI antagonists), have shown activity in cell lines and xenografts and arsenic trioxide, a FDA approved drug for acute promyelocytic leukemia, has shown activity as an inhibitor of these transcription factors [96].
Modulating Wnt in the clinical setting

Wnt-targeting therapies are varied and clinical experience nascent. Optimal use of these agents in the future will depend on matching the Wnt inhibitor with responsive alterations. As an example, Porcupine inhibitors act by blocking the secretion of Wnt ligands and may impact tumors carrying alterations e.g., RNF43 and LKB1, acting at the receptor level, in this case, the FZD receptors [78]. In contrast, APC truncating mutations are resistant to Porcupine inhibitors, since loss of APC may activate the pathway independent of Wnt ligands [79]. Tankyrase inhibitors target APC-mutated tumors, which constitute 80% of colorectal cancers, by stabilizing Axin, but gastrointestinal toxicity may limit dose [86].

Wnt inhibitors may work to eradicate the tumor resistant stem cell and thus may overcome resistance to conventional therapy including cytotoxic agents. Such an approach is currently being tested clinically for chronic myeloid leukemia with PRI-724 in combination with the kinase inhibitor Dasatinib [97].

Sorafenib (Tyrosine kinase inhibitor) and refametinib (an MEK inhibitor) inactivate beta-catenin signaling [98]. Since activating mutations in the Wnt/beta-catenin pathway is seen in many patients with HCC [99], combination of sorafenib and refametinib may represent an alternative treatment for beta-catenin-dependent HCC [98]. In desmoid tumors, a phase 1 trial of PF-03084014, an oral Notch inhibitor showed that 5 of 9 patients had a partial response [95,100]. At first glance, the mechanism of action is not apparent because Notch is upstream of beta catenin. However, beta-catenin can directly express HES-1 and activate cell proliferation through it, and HES-1 is induced by Notch and decreased by Notch inhibitors [99]. Molecules such as Sulindac inhibit Wnt signaling, likely by blocking the PDZ domain of the Disheveled
protein and have activity in APC-mutant colorectal cancers, reducing nuclear beta-catenin accumulation [51].

**Challenges to inhibiting the Wnt pathway**

For the last 30 years targeting the Wnt signaling pathway has been an exciting target for inhibition. There is aberrant Wnt signaling in many cancers but thus far, no drugs have been approved to target this pathway, though there are recent clinical trials in a many hematologic and solid malignancies. One area of concern is the Wnt-beta catenin pathway’s role in maintenance of stem cells and regeneration of tissues and organs [72]. There is legitimate concern that inhibition of the Wnt pathway may affect the normal Wnt dependent stem cell population, especially in areas of fast turnover like hair follicles and the gastro-intestinal tract. The preliminary experience with Tankyrase inhibitors suggests dose limiting gastrointestinal toxicity and this may limit use.

The Wnt pathway regulates many aspects of bone formation and agonists have been studied for promoting bone growth. An undesirable side effect of Wnt inhibition is increase in markers of bone turnover though in early trials this effect seems mitigated by single doses of a bisphosphonate [84].

Additionally, an elucidation of the considerable cross talk between the cell signaling pathways will be crucial to designing an efficacious therapeutic approach. The focus of future trials should be using combination therapy with agents that affect these multiple pathways in solid and hematologic malignancies.
Figure Legends

Fig 1. The Wnt pathway can be classified as canonical and non-canonical. In the canonical pathway, Wnt signaling when it is on inhibits the degradation of β-catenin, which can regulate transcription of many genes. Wnt signaling is activated by binding of Wnt proteins to surface receptors composed of the seven transmembrane frizzled proteins and the LRP5/6. Upon binding, the cytoplasmic protein disheveled (Dvl) is activated. Activation of Dvl induces the dissociation of GSK-3β from Axin and leads to the inhibition of GSK-3β. Next, the phosphorylation and degradation of β-catenin is inhibited because of the inactivation of the "destruction complex". Subsequently, stabilized β-catenin translocates into the nucleus leading to transcription of target genes like C-Myc and Cyclin D1. RNF43 (Ring finger protein 43) / ZNRF3 promote FZD receptor turnover. R-spondins or RSPO’s bind to RNF43/ ZNRF3 causing their ubiquitination and clearance, resulting in increased cell surface FZD receptors.

Fig 2a. Canonical Wnt Pathway and Inhibitors of the Wnt/beta-Catenin Signaling Pathway schematic representation of the Canonical Wnt Pathway and pharmacologic inhibitors of the Wnt/beta-catenin signaling pathway.
Fig 2b. Non-Canonical Wnt Pathway and the Notch and Sonic Hedgehog Pathway- The two major non-canonical pathways are Wnt/calcium and Planar Cell Polarity (PCP) pathways. In the Wnt/calcium pathway, Wnt binding to Frizzled activates Dvl, causing calcium release from the endoplasmic reticulum, activating calcium-binding proteins including protein kinase C (PKC) and calmodulin-dependent kinase II (CamKII). Signal transduction through Ca$^{2+}$ activates the nuclear factor of activated T cells (NFAT). The Wnt/PCP pathway is mediated by the GTPases RhoA and Ras, which through the RhoA-Rho-associated kinase (ROCK) axis or JNK, can exert effects on the cytoskeleton. A schematic of the Notch and Sonic Hedgehog pathway is shown.

Fig 3. Cross-Talk between the Wnt, Notch and Sonic Hedgehog Pathways- Beta-catenin can drive activation of Notch signaling by increasing expression of the JAG1 gene, which encodes the Notch ligand Jagged1. Sfrp-1 may be a negative regulator for both SHH and Wnt/beta-catenin pathway.
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Conflict of Interest Statement:

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Wnt/β-Catenin Signaling Pathway-Canonical Wnt Pathway

Figure 1

Wnt Signaling off

Wnt

Frizzled receptors

LRP

AXIN

GK3

β

APC

Beta-Catenin

Proteosomal degradation

Cytosol

Wnt Signaling on

Wnt

Frizzled receptors

LRP

AXIN

GK3

β

DVL

RNF43/ZNRF3

RSPO

RSPO causes clearance of RNF43/ZNRF3

RNF43/ZNRF3 causes Degradation of FZD

Beta-Catenin

Nucleus

CO-ACTIVATORS

CBP

Target genes (C-Myc and Cyclin D1)

TCF/LEF

Beta-Catenin

Target genes (C-Myc and Cyclin D1)
Figure 2 a

Canonical Wnt Pathway and Inhibitors of the Wnt/β-Catenin Signaling Pathway

Wnt Signaling on

- Wnt
- DKK
- LRPs
- Axin
- APC
- TCF/LEF
- CBP
- CO-activators
- Target Genes

Wnt Signaling off

- Frizzled receptors
- IWP-2
- LGK974
- ICG-001
- PRI-724
- PKF115-584
- PKF118-310

Porcupine Inhibitors
- OMP-54 F28
- Decoy receptor
- NCB-0846

Tankyrase Inhibitors - Axin-stabilizers
- Niclosamide
- Sulindac
- NSC668036
- J01-017a

Proteosomal degradation
- Pyrvinium

Beta-Catenin
- CK1

Cytoplasm
- DVL

Nucleus
- TCF/LEF
Figure 2b

Non-Canonical Wnt Pathway and the Notch and Sonic Hedgehog Pathway

Non-Canonical Wnt Pathway

Delta-Notch Signaling

Sonic Hedgehog Pathway

Sonic Hedgehog

Pathway

Vismodegib

Sonidegib

Wnt

Wnt

DVL

DVL

RhoA

Ras

ROCK

PKC

CaMKII

Ca++

NF-AT

Cell adhesion and movement

Cytoskeletal rearrangement

Ras

RhoA

γ-secretase

NICD

Hes 1

Gli1

Gli1act

SUFU

Cell Proliferation

Tumorigenesis

VK1

RO4929097

PF-03084014

Cell adhesion and movement

Cytoskeletal rearrangement

Gamma secretase inhibitors

MK0752
Cross-Talk between Wnt, Notch, and Sonic Hedgehog Pathways

Delta-Notch Signaling

NOTCH

Gamma secretase

NICD

NOTCH

Patch

SMO

Delta-Notch Signaling

Sonic hedgehog Pathway

SHH

Wnt/β-Catenin Signaling Pathway

Wnt

LRP

Frizzled receptors

Jag 1

Gli1 rep

sfrp-1

AXIN

DVL

GK3 β

CRD-BP (coding region determinant-binding protein)

CRD-BP

Stabilizes Gli 1 mRNA

Cell Proliferation
Tumorigenesis
Stem cell Maintenance

Gli1 act

Figure 3
Table 1. Examples of drugs/agents that inhibit Wnt/β-Catenin Signaling

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target/Receptor</th>
<th>Manufacturer/Type of agent/Other targets</th>
<th>Preclinical vs clinical trial (phase) vs FDA approved*</th>
<th>Ref</th>
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<tbody>
<tr>
<td><strong>Tankyrases inhibitors</strong></td>
<td></td>
<td></td>
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<tr>
<td>IWR1</td>
<td>Tankyrases1, 2 inhibitors</td>
<td>Tocris Bioscience/Small Molecule</td>
<td>Preclinical</td>
<td>29</td>
</tr>
<tr>
<td>XAV939</td>
<td>Tankyrases1, 2 inhibitors</td>
<td>Novartis/ Small Molecule</td>
<td>Preclinical</td>
<td>30</td>
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<tr>
<td>NVP-TNKS656</td>
<td>Tankyrases1, 2 inhibitors</td>
<td>AbMole Bioscience/Small Molecule/Parp Inhibitor</td>
<td>Preclinical</td>
<td>31</td>
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<tr>
<td>JW74</td>
<td>Tankyrases1, 2 inhibitors</td>
<td>Tocris Bioscience/Small Molecule</td>
<td>Preclinical</td>
<td>32</td>
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<tr>
<td><strong>Porcupine inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IWP-2</td>
<td>Porcupine inhibitors</td>
<td>Tocris Bioscience/Small Molecule</td>
<td>Preclinical</td>
<td>33</td>
</tr>
<tr>
<td><strong>Disheveled inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSC668036</td>
<td>Disheveled ((Dvl))</td>
<td>Tocris Bioscience/Small Molecule</td>
<td>Preclinical</td>
<td>34</td>
</tr>
<tr>
<td>J01-017a</td>
<td>Binds to PDZ-Dvl</td>
<td>Small Molecule</td>
<td>Preclinical</td>
<td>35</td>
</tr>
<tr>
<td><strong>TCF/beta-catenin Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKF115-584</td>
<td>β-catenin/LEF-1 inhibitor</td>
<td>Novartis/ Small molecule</td>
<td>Preclinical</td>
<td>36</td>
</tr>
<tr>
<td>ICG-001</td>
<td>CREB binding protein/ CBP</td>
<td>Enzo Life Sciences/Small molecule</td>
<td>Preclinical</td>
<td>37</td>
</tr>
<tr>
<td>PKF118-310</td>
<td>Selective inhibitor beta -catenin/TCF</td>
<td>EMD-Millipore/Small Molecule</td>
<td>Preclinical</td>
<td>38</td>
</tr>
<tr>
<td>NCB-0846</td>
<td>TNIK inhibitor</td>
<td>Carna Biosciences/Small molecule</td>
<td>Preclinical</td>
<td>39</td>
</tr>
<tr>
<td><strong>Clinical Trial Phase I/Ia/Ib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LGK974</td>
<td>Porcupine inhibitors</td>
<td>Novartis/ Pyridines; Small molecules</td>
<td>Phase I (NCT01351103) in Melanoma, breast cancer and pancreatic CA</td>
<td>40</td>
</tr>
<tr>
<td><strong>Wnt antibodies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OMP-18R5  (Vantictumab)</td>
<td>Frizzled receptor</td>
<td>Onco Med Pharmaceuticals/ Cellgene</td>
<td>Open –label Phase Ib dose escalation study in solid tumors(NCT01345201), Phase I in breast cancer(NCT01973309), non-small cell lung cancer(NCT01957007) and pancreatic cancer(NCT02005315)</td>
<td>41</td>
</tr>
<tr>
<td><strong>DRT-54 F28</strong>&lt;br&gt;(Ipafircept)</td>
<td><strong>Fzd8-Fc fusion protein</strong>&lt;br&gt;Onco Med Pharmaceuticals/Bayer</td>
<td>Acts as Decoy receptor</td>
<td>Phase I trial in solid tumors(NCT01608867)&lt;br&gt;Phase Ib trial in hepatocellular carcinoma(NCT02069145), ovarian cancer(NCT02092363), and pancreatic cancer(NCT02050178)</td>
<td>42,43</td>
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<tr>
<td>Foxy-5</td>
<td><strong>FZD3 Peptide</strong>&lt;br&gt;WntResearch AB</td>
<td>Phase I in metastatic breast, colorectal, and prostate cancer(NCT02020291)</td>
<td>44</td>
<td></td>
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<tr>
<td>OTSA 101</td>
<td><strong>FZD10 mAb</strong>&lt;br&gt;Centre Léon Bérard, OncoTherapy Science/Monoclonal antibody</td>
<td>Phase I in synovial sarcoma(NCT01469975)</td>
<td>45</td>
<td></td>
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</table>

**Beta-catenin inhibitors**

| **CWP232291** | **Induces beta-catenin degradation**<br>JW Pharmaceuticals/Small molecule | Phase I in Acute Myeloid Leukemia(NCT01498462) | 46 |
| **PRI-724** | **B-catenin/CBP**<br>Prism/Eisai pharmaceuticals/Small molecule | Phase Ia in solid tumors(NCT01302405), Phase Ib in colorectal(NCT0132405) and pancreatic cancer(NCT01764477) | 47 |

**Clinical Trial Phase I/II**

| **DKN-01** | **DKK, dickkopf-related protein**<br>Leap Therapeutics | Phase I/II in Multiple Myeloma(NCT01457417) | 48 |
| **PRI-724** | **Beta-catenin/CBP**<br>Prism/Eisai pharmaceuticals/Small molecule | Phase I/II in Myeloid leukemia(NCT01764477) | 49 |

**FDA approved (off label with preclinical data only)**

| Niclosamide | **Downregulates Dvl-2**<br>Taj Pharma/Anti-helminthic | FDA approved | 50 |
| Sulindac | **PDZ domain of Disheveled(Dvl)**<br>Merck & Co., Inc./Non-steroidal anti-inflammatory drug | FDA approved | 51 |
| Pyrvinium | **CK1α**<br>U.S. Pharmacopeia/Anti-helminthic | FDA approved | 52 |

**Examples of Inhibitors of Notch Signaling**

<p>| MK0752 | <strong>Gamma Secretase Inhibitor (GSI)</strong>&lt;br&gt;Merck/ Small Molecule | Phase 1 advanced solid tumor(NCT00106145) | 53 |
| MK0752 + docelex | GSI | Merck/ Small Molecule | Phase I/II; breast cancer(NCT00645333) | 54 |
| MK0752 + Ge metcatabine | GSI | Merck/ Small Molecule | Phase I/II; pancreatic cancer(NCT01098344) | 55 |
| RO4929097 | GSI | Roche/Small molecule | Phase II, colorectal cancer(NCT01116687) | 56 |
| RO4929097 | GSI | Roche/Small molecule | Phase II; pancreatic cancer(NCT01232829) | 57 |
| PF-03084014 | GSI | Pfizer/ Small molecule | Phase I in Acute T cell lymphoblastic leukaemia/lymphoma and solid tumors(NCT00878189) | 58 |
| BMS-906024 | Pan Notch Inhibitor&lt;br&gt;Bristol-Myers Squibb/Small molecule | Phase I in Acute T cell lymphoblastic leukaemia/lymphoma and solid tumors(NCT01653470, NCT01292655, NCT01363817) | 59 |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Company</th>
<th>Study Details</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDI0639</td>
<td>DLL4-specific Notch antibody</td>
<td>MedImmune</td>
<td>Phase 1 advanced solid tumors (NCT 01577745)</td>
<td>60</td>
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<tr>
<td>OMP-52M51</td>
<td>Notch 1-specific antibody</td>
<td>GlaxoSmithKline/ OncoMed Pharmaceuticals</td>
<td>Phase 1 solid tumors and lymphoid malignancies (NCT 01703572, NCT 01778439)</td>
<td>61</td>
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<tr>
<td></td>
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<td></td>
<td><strong>Examples of Inhibitors of Hedgehog signaling</strong></td>
<td></td>
</tr>
<tr>
<td>Vismodegib</td>
<td>SMO inhibitor</td>
<td>Roche/Genentech</td>
<td>Advanced pancreatic cancer, prostate cancer, gastric cancers(NCT01195415, NCT01088815, NCT00878163)</td>
<td>62</td>
</tr>
<tr>
<td>Erismodegib/Sonidigib</td>
<td>SMO inhibitor</td>
<td>Novartis</td>
<td>Recurrent ovarian cancer, triple negative breast cancer, advanced solid tumors (NCT02195973, NCT02027376, NCT00961896)</td>
<td>63</td>
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<tr>
<td>Glasdegib</td>
<td>SMO inhibitor</td>
<td>Pfizer</td>
<td>Myelofibrosis (NCT02226172)</td>
<td>64</td>
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<tr>
<td>Saridegib(IPI-926)</td>
<td>SMO inhibitor</td>
<td>Infinity</td>
<td>Pancreatic adenocarcinoma (NCT01383538)</td>
<td>65</td>
</tr>
</tbody>
</table>
Table 2. Wnt inhibitors in clinical trials for cancers

Wnt- Receptor Complex Inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Phase of Trial</th>
<th>Manufacturer</th>
<th>Diseases</th>
<th>Concomitant Therapy</th>
<th>Response/Adverse effects</th>
<th>Trial Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGK974 Porcupine inhibitor</td>
<td>1/2</td>
<td>Novartis</td>
<td>Metastatic CRC with Wnt pathway mutations, Head and neck Squamous cell cancers with Notch mutations</td>
<td>Biological: PDR001</td>
<td>No clinical data</td>
<td>NCTO22 78133 NCTO26 49530</td>
<td></td>
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<tr>
<td>ETC 159 Porcupine Inhibitors</td>
<td>1</td>
<td>D3-Institute experimental therapeutics</td>
<td>Refractory solid tumors, 10 patients (9 CRC, 1 Renal)</td>
<td>Oral single agent</td>
<td>2 stable disease (SD).</td>
<td>NCT025 21844</td>
<td></td>
</tr>
<tr>
<td>OMP18RS(V antictumab) Anti Fzd7 antibody</td>
<td>1</td>
<td>Bayer, OncoMed</td>
<td>Non-small cell lung cancer, Pancreatic cancer, Metastatic breast cancer</td>
<td>With Nab-Paclitaxel and Gemcitabine in Pancreatic Ca. With taxanes in Her2 neg MBC and NSCLA</td>
<td>19 pts pancreatic cancer, 8 partial response (PR), 4 SD Prolonged SD in 3 NET’s</td>
<td>NCT019 57007 NCTO20 05315 NCTO19 73309</td>
<td></td>
</tr>
<tr>
<td>OMP-54F28 (Ipafricept) Fad-Fc Decoy receptor</td>
<td>1</td>
<td>Bayer, OncoMed</td>
<td>Hepatocellular carcinoma, ovarian cancer, pancreatic cancer</td>
<td>In ovarian cancer given 2 days before carboplatin and taxol chemotherapy. Trials with Nab-paclitaxel in pancreatic cancer and sorafenib (HCC)</td>
<td>Ovarian cancer 17 patients, 6 (35%) complete response (CR), 8 (47%) (PR) and 3 (18%) SD Pancreatic cancer -14, 4 PR and 7 SD.</td>
<td>NCT0209 2363 NCTO20 0178</td>
<td></td>
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<tr>
<td>OMP131R10 Anti-R-spondin 3 antibody</td>
<td>1</td>
<td>Oncomed/Celgene</td>
<td>RSPO3 positive metastatic Colorectal cancer</td>
<td>FOLFIRI (FOL = Leucovorin Calcium (Folinic Acid)F = Fluorouracil IR1 = Irinotecan Hydrochloride)</td>
<td>No clinical data yet</td>
<td>NCTO24 82441</td>
<td></td>
</tr>
<tr>
<td>OTSA 101 Yttrium90 radiolabeled anti Fzd10 antibody</td>
<td>1</td>
<td>Oncotherapy Science</td>
<td>Synovial Sarcoma</td>
<td>Single agent</td>
<td>1 fatal thrombocytopenia</td>
<td>NCTO14 69975</td>
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</tr>
<tr>
<td>PRI-724 TCF-CBP interaction</td>
<td>1/2</td>
<td>Prism Biolab</td>
<td>Acute and chronic myeloid leukemia, Colorectal cancers,</td>
<td>Gemcitabine in Pancreatic cancer,</td>
<td>8 pts (40%), 2 minor responses. 5 of 8 pts</td>
<td>NCT0176 4477</td>
<td></td>
</tr>
</tbody>
</table>
| inhibitor | pancreatic adeno CA | Dasatinib or Cytarabine in Chronic myeloid leukemia. | (62.5%) | NCTO24 13853  
NCTO16 06579 |
|---|---|---|---|---|

**Foxy 5**

<table>
<thead>
<tr>
<th>1</th>
<th>Wnt Research</th>
<th>Breast cancer, Colorectal cancer, Prostate cancer</th>
<th>Single agent</th>
<th>No dose limiting toxicity in phase 1 trial.</th>
<th>NCTO26 55952</th>
</tr>
</thead>
</table>

**RO4929097**

<table>
<thead>
<tr>
<th>Gamma Secretase Inhibitors</th>
<th>Phase 2</th>
<th>Roche</th>
<th>Pancreatic cancer, metastatic CRC</th>
<th>Single agent</th>
<th>12 patients with pancreatic cancer, 3 SD.</th>
<th>NCTO11 6687</th>
</tr>
</thead>
</table>

**MK0752**

| GSI | Phase 1/2 | Merck | Breast cancer, Pancreatic cancer | Docetaxel in breast cancer  
Gemcitabine in Pancreatic ca | Breast ca in 30 patients, 9 had PR, 8 SD, and 3 PD, RR of 45% | NCT 09645333 |
|---|---|---|---|---|---|---|

**PF-03084014**

<table>
<thead>
<tr>
<th>GSI</th>
<th>Phase 1</th>
<th>Pfizer</th>
<th>Triple negative breast cancer</th>
<th>Docetaxel</th>
<th>Four (16%) of 25 PR; nine (36%) SD.</th>
<th>NCTO187 6251</th>
</tr>
</thead>
</table>

**Abbreviations**

- CBP (CREB- binding protein)
- CRC (colorectal cancer)
- MBC (Metastatic Breast Cancer)
- NET (Neuro-endocrine tumors)
- NSCLCA (Non-small cell lung cancer)
- PFS (Progression free survival)
- RSPO3 (R-spondin 3)
- TCF (T cell factor)
Highlights:

- Wnt is a family of proteins involved in stem cell renewal and organogenesis.
- Wnt pathway activation occurs in many cancers and contributes to tumor recurrence.
- Wnt has significant cross talk with Notch and Sonic Hedgehog pathways.
- Update on clinical trials of agents targeting Wnt, Notch, and Sonic Hedgehog