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Targeting the Wnt signalling pathway in cancer: prospects and perils

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Summary

The Wnt pathway, involved in cancer development and progression, has for a long time been said to be undruggable, owing to its complexity and involvement in stem cell biology. This mindset has shifted in the last few years as new research and insights into the pathway mechanisms specific to tumour cells become apparent, leading to the development of multiple compounds targeting the pathway. In this review, we introduce the Wnt pathway and its connections to cancer biology and therapy resistance. We further dive into the details of drugs that have entered clinical trials, examining their successes and side effects. We show that these drugs all have one thing in common: in order to be successful, the drugs must target tumour specific activated sub-branches of the pathway, either at the receptor level or at the nuclear transcription level.

Keywords: *Wnt signalling, cancer, drug discovery, stem cells, proliferation, chemoresistance, radioresistance, clinical studies*

The Wnt pathway – a double-edged sword

One of the most fascinating features of multicellular organisms is the precise and tightly controlled communication among cells, necessary for the development, coordination and functioning of the individual organs and the body as a whole. To communicate, the cells employ chemical signals, which, when received by the recipient cells, trigger defined intracellular signalling pathways in order to relay the information and provide the adequate response to the external stimuli. This enables the body to coordinate patterning and organ development during embryogenesis, to keep the organism in homeostasis and to respond to external stresses and inputs, and to regenerate after injury. On the cellular level, a signalling cascade is initiated by secreted ligands (e.g., hormones, cytokines, neurotransmitters, growth factors) produced by one cell, which then bind to a receptor on another cell. The receptors in most cases are located on the cell surface, and the signal is then relayed through intracellular components of the pathway, called transducers and second messengers, resulting in the corresponding cellular effect, for example target gene transcription or changes in an enzymatic activity [1].

The Wnt pathway is one of the most important signalling cascades in the early events of embryonic development, where it controls cell proliferation and differentiation [2, 3]. To date, the Wnt signalling is still not fully understood. This is mainly because it is composed of a complicated network of a total of ten GPCR homologue Frizzled (FZD) receptors [4], three transmembrane tyrosine kinases Ryk, ROR and PTK7, muscle skeletal tyrosine kinase (MuSK) [5], the co-receptors LRP5/6 [6], and 19 glycolipoprotein Wnt ligands [7]. There is a high degree of promiscuity in the ligand-receptor interactions, although certain Wnts have higher affinities to certain FZD receptors and co-receptors [4, 8]. To further complicate matters, there are additionally secreted antagonists such as Secreted FZD-related proteins (Sfrp1, 2, 4 and 5), Wnt inhibitory factor (Wif) and Dickkopf 1 (Dkk1) reducing signalling activity, and the agonists R-spondin 1 to 4 potentiating the Wnt signalling through their receptors Lgr4, 5 and 6 [9, 10].

Wnt signalling is generally divided into three distinct branches: the canonical β-catenin/TCF pathway, the planar cell polarity (PCP) pathway and the Ca^{2+} pathway. Whereas some ligands are attributed to one distinct branch, others are competent to initiate signalling in several branches, depending on the receptor-ligand combination. It has also been demonstrated that under certain circumstances the β-catenin branch and the PCP branch antagonise each other [11].

The by far most studied branch is the canonical β-catenin/TCF pathway. It is characterised by accumulation of cytoplasmic protein β-catenin upon pathway initiation. It further translocates to the nucleus to bind the TCF family of transcription factors, leading to specific gene expression. The Wnt-dependent transcriptional programme in the nucleus – in a manner reminiscent of the complexity at the cell surface – is again controlled in a diversified manner. It has been shown that, depending on which co-activators β-catenin recruits, it will either upregulate genes responsible for self-renewal and proliferation (through, e.g., β-catenin binding to CBP) or will lead to upregulation of genes in-

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volved in differentiation (binding to p300) [12]. In the absence of Wnt ligands, a specific complex containing Axin, APC, CK1 and GSK3β phosphorylates β-catenin, targeting it for degradation. In the adult tissues, Wnt signalling is mainly silent with the exception of stem cells, where the pathway regulates replenishment and regenerative processes, for example in the intestinal crypt [13], haematopoietic stem cells [14] and bone [15]. This vital role of the Wnt pathway in maintaining tissues healthy, as one edge of the sword, stands in a sharp opposition to the other edge, which is the key role of the pathway in disease. If not held in check, aberrant Wnt signalling can lead to uncontrolled cell proliferation and cancer [2, 16].

Unlike the canonical signalling, β-catenin is not part of the PCP and Ca^{2+} pathways. The PCP pathway, involving small GTPases and JUN-N-terminal kinase, controls cell polarity, cytoskeletal remodelling, directional cell migration and c-Jun-dependent transcription. The Ca^{2+} signalling branch leads to activation of phospholipase C (PKC) followed by opening of intracellular stores of Ca^{2+}, in turn leading to activation of downstream effectors such as NFAT and CREB transcription factors, also controlling cell migration and cell survival [17]. As these two branches involve cytoskeletal changes and cell migration, it is not surprising that they have been associated with cell invasion and metastasis in cancer [18–20].

The Wnt signalling-dependent cancers can be divided into those that harbour mutations in components of the pathway, and those cancers that have a dysregulation of Wnt signalling due to epigenetically driven up- or downregulation in expression levels of the pathway components. The most famous example of pathway mutations is that of the Wnt pathway suppressor APC. It was first associated with patients with familial adenomatous polyposis (FAP) and occurs in >80% of colorectal carcinomas [21, 22].

Immunohistological analyses of tissues from colorectal patients show that β-catenin relocalisation is a typical sign of the canonical pathway activation. Indeed, the loss of membrane β-catenin (where it plays Wnt-independent functions) is significantly associated with poor prognosis when using overall survival as the endpoint, as shown in a study of 720 colorectal patient samples [23]. Additional reports have demonstrated that loss of membranous β-catenin is especially prominent in the invasive front in colorectal cancer and that membranous localisation in general and in the invasive front in particular are both prognostic markers for longer disease-free survival [24], whereas high nuclear accumulation in colorectal cancer has been associated with worse disease-free and overall survival and higher probability of developing lymph node metastasis [25, 26].

In additional to mutational activation of the Wnt signalling, the pathway can be aberrantly activated by overexpression of the pathway components, such as Wnts or their FZD receptors [27]. Analysis of tumour tissues of 201 patients with colorectal cancer showed high Wnt1 and low expression of the non-canonical Wnt5a correlating with cytoplasmic and nuclear β-catenin; all three characteristics are indicative of shortened disease-free survival. High Wnt1 and nuclear β-catenin also correlated with lower overall survival [25]. In non-small-cell lung cancer, cytoplasmic Wnt1 is also significantly upregulated and correlates with β-catenin, c-myc and cyclin D1 overexpression. Although there was no link between high Wnt1/β-catenin expression and the disease stage, high expression correlated significantly with a lower 5-year survival rate [28].

FZD expression has also been analysed in various studies (reviewed by [29]). As expected, tumour tissues show an upregulation of FZD receptor expression compared with healthy tissues. The expression is even stronger towards later stages of cancer development. For example, in gastric cancer, high FZD7 expression significantly correlates with tumour invasion, metastasis and late stage cancer. In an analysis of 5-year survival, patients with high FZD7 expression had a 30.3% survival rate (median survival 23.5 months) versus 65.4% in patients with low or no FZD7 expression (median survival 77 months) [30].

Analysis of individual Wnt pathway markers, such as select ligands and receptors, is a useful tool for clinicians to predict prognosis and for researchers to determine the molecular mechanisms behind the tumour. However, such analysis often fails to uncover the whole picture. A broader look at the cancer transcriptome of the whole pathway and its numerous target genes is more suitable in this regard, as we have recently done for breast cancer. Exhaustive analysis of the TCGA and GTex databases has revealed that it is not single gene upregulation that is responsible for the aberrant signalling across the patients, but rather epigenetic dysregulation of the whole Wnt system. Such generalised dysregulation is behind the consistent pathway overactivation leading to uncontrolled cancer cell proliferation in breast cancer patients [27]. Network correlation analysis further permitted us to highlight signalling nodes within the Wnt pathway, which emerge as new promising drug targets and biomarkers in clinical studies and personalised medicine treatments [27].

Stemness and therapy resistance in Wnt dependent cancers

Apart from its involvement in tumourigenesis and cell proliferation, the Wnt pathway contributes to chemoresistance and cancer stem cell (CSC) propagation, the two factors ultimately responsible for tumour recurrence after therapy, metastasis and poor patient survival [31]. CSCs are a subpopulation of cancer cells; similarly to normal stem cells, they can self-renew or differentiate [32]. Being activated in CSCs, the Wnt pathway upregulates transcription of genes necessary for proliferation (such as c-myc) [33], cell cycling (such as cyclin-D) [34], anti-apoptosis (e.g., survivin) [31, 35], metabolic switching to aerobic glycolysis (PDK1, MCT-1) [36, 37], and invasion and metastasis (SLUG, MMP) [38, 39]. The role of active Wnt signalling in chemo- and radio-resistance is linked to the survival of CSCs: being relatively dormant, they can better withstand the therapy to repopulate the shrunken tumour, which results in tumour recurrence. There is also a separate mechanism of involvement of the Wnt pathway in cancer chemoresistence, mediated by the ill-famed multidrug resistance protein 1 (MDR1, also known as ABCB1 or P-glycoprotein) [40]. It was first demonstrated in early colorectal cancer that MDR1 is a target gene of the Wnt/β-catenin/TCF4 pathway, thus activation of the pathway led to increased levels of MDR1, increased drug efflux and drug resistance [41]. Similarly, increased MDR1 expression was found to be mediated by FZD1 in neuroblastoma, and a

significant correlation in expression levels of FZD1 and MDR1 was found in patients relapsed after chemotherapy [42]. Other drug pumps involved in chemoresistance, ABCG2 (BCRP) and MRP2, were also shown to be induced by the Wnt pathway [43–45]. Finally, another contribution of the Wnt signalling to drug resistance is mediated by the DNA repair gene O6-methylguanin-DNA-methyltransferase (MGMT) in CSCs [46–48]. MGMT specifically repairs alkylated DNA and therefore upregulation of the protein leads to inefficiency of DNA alkylating agents and PARP inhibitors [49].

Wnt signalling plays several roles in tumour radioresistance. Firstly, radiotherapy induces upregulation of a panel of growth factors including Wnts, both in the tumour and in the surrounding stroma leading to enrichment of the CSC population [50]. Secondly, the Wnt pathway can directly protect against irradiation-induced DNA damage driving expression of DNA ligase 4 (LIG4) in colorectal cancer cells [51]. Further, histone modifier high-mobility group box 1 protein (HMGB1) involved in chromatin remodelling and DNA repair can be induced by Wnt/TCF4 signalling; blocking HMGB1 in oesophageal squamous cell carcinoma cells was found to suppress the Wnt1-dependent radioresistance [50].

Targeting the Wnt pathway is therefore beneficial at multiple levels: inhibition of tumour growth and survival with minimal effects on somatic cells, inhibition of CSC maintenance (and thus, of tumour relapse), and prevention of the development of tumour resistance to chemo- and radiotherapy. Inhibitors of the Wnt pathway are therefore in high therapeutic demand, and platforms dedicated to the search and development of such inhibitors are needed [52]. Although no Wnt-targeting drugs have yet reached the market, some are in preclinical and early clinical stages of development.

Wnt inhibitors in clinical development

The pathological and physiological roles of Wnt signalling, as well as the complexity of this pathway with its numerous sub-branches utilised in different cell types, underlie the practical difficulties in finding therapeutically relevant Wnt-targeting agents. The total number of Wnt pathway inhibitors active *in vitro* is around fifty [53, 54], many of them having reached different stages of preclinical development, but so far only a few have attained early phase clinical trials.

Figure 1 shows the anti-Wnt agents that have reached clinical trials. It can be appreciated that these agents target the pathway at the levels where the pathway diverges into several sub-pathways (perhaps with the exception of the Porcupine-targeting drugs, but see below). Such diversification into sub-pathways can be found at the level of the plasma membrane, as well as in the nucleus; in contrast, the events in the cytoplasm are poorly diversified and are rather common for all the Wnt signalling subtypes [55, 56]. For a drug candidate being selected for clinical studies, we consider it critical for it to act on Wnt signalling subtypes active specifically in pathological tissues, instead of affecting all Wnt signalling subtypes. Indeed, pan-Wnt inhibitors fail to show acceptable safety profiles at preclinical levels and cannot advance further, as exemplified by attempts to develop tankyrase inhibitors [57, 58] or Dickkopf-1 as a biologic to block the Wnt pathway [59].

Vantictumab, ipafricept and rosmantuzumab

The only agent directly targeting FZDs having entered clinical development is a humanised antibody vantictumab (OMP-18R5). Initially developed against the Wnt-binding CRD-domain of FZD7, it was found to act on FZD1, 2, 5, 7 and 8 – five FZDs out of the ten encoded by the human genome [60]. The preclinical activity profile against a panel of tumour cells [60] prompted it's entry into phase I clin-

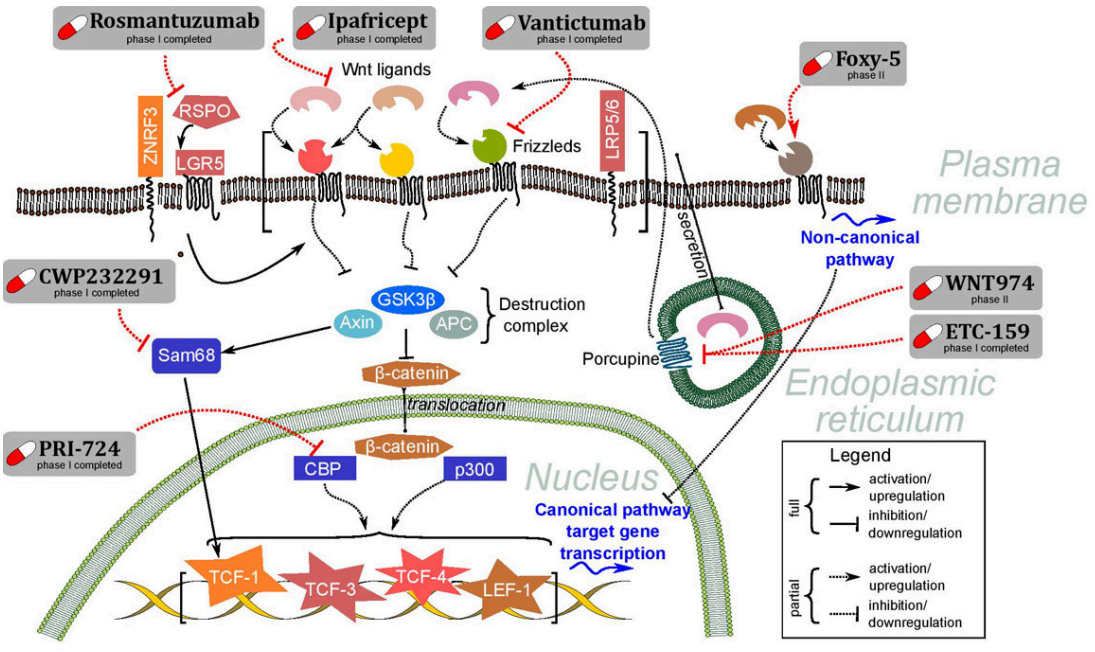

Figure 1: Drug compounds of past or current clinical trials target the Wnt pathway at the ligand/receptor level (rosmantuzumab, ipafricept, vantictumab and Foxy-5) or at the transcriptional level (CWP232291 and PRI-724). Porcupine inhibitors (WNT974 and ETC-159) target Wnt secretion.

ical trials (NCT01345201, NCT01973309, NCT02005315 and NCT01957007). All the trials have been completed by now and reports are available for the first three. The first phase Ia study measured the dose escalation effects following the intravenous administration of doses ranging between 0.5mg/kg weekly and 2.5mg/kg once in 3 weeks. The main finding was bone toxicity manifested as a bone fracture on day 110 in one patient. Other adverse events were fatigue, vomiting, abdominal pain, constipation, diarrhoea and nausea of grades 1 and 2, with grade 3 diarrhoea and vomiting reported in one patient. To tackle bone toxicity, the study monitored β-C-terminal telopeptide (β-CTX), a marker for bone degradation, and was able to manage its levels by administering zolendronic acid [61]. The other two studies, phase Ib on pancreatic and breast cancer using vantictumab in combination with paclitaxel (90 g/m^2) or nab-paclitaxel (125 g/m^2), adopted the same strategy for tackling the bone fragility and reported similar adverse effects of grade 2 observed in phase Ia and few additional grade 3 events (neutropenia, leukopenia, pelvic pain, fatigue and nausea). Both studies used increased vantictumab dosages (between 3.5 and 14 mg/kg) and reported further bone fragility events, which required improvements in the zolendronic acid administration regimen and resulted in a temporary halt of the trials in 2014 [62–64].

Similar results were obtained for ipafricept (OMP-54F28) – another anti-Wnt biologic from OncoMed, representing the FZD8 CRD-domain fused to an IgG1 constant fragment. By mechanism, this compound can be expected to possess a certain selectivity towards a subset of Wnt proteins, although its specificity among the 19 Wnts encoded by the human genome is unclear because of the lack of comprehensive data on mutual affinities of Wnt and FZD proteins. Four clinical trials were launched for ipafricept (NCT01608867, NCT02092363, NCT02069145 and NCT02050178) with two of them reporting the results. As with vantictumab, the trials used the scheme with zolendronic acid to counteract the bone-related adverse effects, apparently with more success since only one fracture was recorded at 20 mg/kg; the on-target dose was estimated to be at >10mg/kg. Non-bone-related adverse events with the compound included grade 1 and 2 dysgeusia, decreased appetite, fatigue, muscle spasms, alopecia and vomiting and grade 3 events such as anaemia hypophosphataemia, neutropenia and weight loss [65, 66].

Finally, Oncomed had one more anti-Wnt compound in its portfolio – the R-spondin 3-targeting antibody rosmantuzumab (OMP-131R10). R-spondins are soluble ligands that enhance Wnt signal transduction, especially the canonical branch, through different mechanisms [10, 67]. The phase Ia/b clinical trial (NCT02482441) of the agent demonstrated a set of adverse effects similar to the other two agents of the company: doses from 2.5 to 15 mg/kg every 2 weeks resulted in nausea, decreased appetite, diarrhoea, vomiting and weight decrease of unspecified grades. Additionally, the treatment resulted in changes in bone turnover markers – which is somewhat unexpected since R-spondin 3 (unlike related R-spondin 1 and 2) is not known to be involved in bone formation and maintenance [68, 69]. This might hint towards insufficient specificity of rosmantuzumab, which is difficult to assess since no preclinical report was published for the agent.

Overall, one may conclude that vantictumab, ipafricept and rosmantuzumab, biologics interfering with Wnt signalling at the level of the ligands, receptors and extracellular enhancers, which have been designed to achieve selectivity in targeting different Wnt signalling subtypes, have ultimately revealed poorer specificity than intended. The similar adverse effects of the three drug candidates in safety clinical trials suggest a too-general wiping out of the Wnt pathway instead of the selective inhibition of the pathway subtype active in the tumour. These adverse effects were likely behind the strategic decisions made regarding the drugs: in 2017, Bayer opted out of licensing vantictumab or ipafricept from Oncomed for “strategic reasons”; rosmantuzumab was stated to have “failed to provide compelling evidence of clinical benefit” [70]. These decisions resulted in discontinuation of the clinical development of the three candidates. Since the molecules did not advance beyond the safety trials, conclusions on compound efficacy in human subjects could not be drawn.

Porcupine inhibitors WNT974 (LKG974) and ETC-159 (ETC-1922159)

Another clinically relevant attempt to inhibit Wnt signalling at the upstream levels is currently spearheaded by two competing inhibitors of Porcupine, the acyltransferase responsible for posttranslational modification of all Wnt proteins. By conception, molecules of this type were supposed to be pan-Wnt inhibitors, preventing both autocrine and paracrine signalling since the acylation is considered an absolute prerequisite for the Wnt protein secretion and activity [71]. However, as described below, both molecules show quite acceptable preclinical and clinical safety profiles, which might be explained by novel insights into the signalling by non-acylated Wnts, meaning that inhibition of acylation might affect the pathway only partially [72]. Both competitors from Novartis (WNT974) and Singapore State D3 consortium (ETC-159) have successfully passed preclinical investigations, with significant reduction of the tumour burden and no toxicity – either overt or at the level of tissue morphology following the analysis of several Wnt-dependent tissues. In phase I clinical trials (NCT01351103 for WNT974 and NCT02521844 for ETC-159), both were tested at similar doses – 5 to 30 mg/day for WNT974 and 1 to 30 mg for ETC-159. The more representative study of WNT974, enrolling 94 patients by 2017, showed that it induces grade 1 and 2 dysgeusia, decreased appetite, nausea, fatigue, diarrhoea, vomiting, hypercalcaemia, alopecia, asthenia and hypomagnesaemia. Additionally, in a small number (3–4%) of patients, grade 3 and 4 adverse events included asthenia, fatigue, decreased appetite and enteritis [73, 74]. Analysis of tumour specimens for various markers has shown a profound Wnt inhibitory effect; moreover, in some patients the compound was used in combination with spartalizumab (an anti-PD-1 antibody), giving a positive outlook on potential combination of the anti-Wnt and immune-therapy. Surprisingly, authors do not report any events or even any attempts to follow bone-related effects, which is in contrast to the ETC-159 trial. The latter enrolled 16 patients and the study reported vomiting, anorexia, fatigue, dysgeusia and constipation as the adverse events of unspecified grade identified in >20% of patients. Beta-CTX levels were analysed and found to be expectedly elevated in two patients with con-

comitant loss in bone density, which was counteracted by vitamin D and calcium supplements [75].

Although that WNT974 was shown to affect bone structure in animals [76, 77], the effect does not seem to manifest clinically. Perhaps this is a reason why WNT974 is currently the most advanced anti-Wnt agent and the only one to have moved to a phase II trial (NCT02649530), and therefore might become the first anti-Wnt agent with a comprehensive assessment of clinical pharmacodynamics.

Wnt5a-mimetic Foxy-5

An interesting approach to Wnt inhibition is employed by the WntResearch start-up company from Sweden, which has identified a Wnt5a-mimicking peptide called Foxy-5 as an efficient anti-metastatic agent [78]. Specific to the compound is its intervention into the non-canonical Wnt pathway, suppressing migration and adhesion of breast cancer cells. Therefore, this approach does not target tumour bulk, but is rather oriented to metastasis prevention and is used in combination with surgery, irradiation and other drugs. The compound has passed a phase I clinical trial [79, 80]. According to the sparse information provided, Foxy-5 was reported to be "non-toxic" at any dose, and showing good pharmacokinetics and stabilisation of the levels of circulating tumour cell in patients with metastatic breast, colon, or prostate cancer [81]. Currently the company has reported recruitment of the first patient for the phase II study. This study will compare patients undergoing colon cancer surgery followed by a 6 month regimen with FOLFOX with patients receiving a treatment of Foxy-5 before and after surgery until starting the FOLFOX regimen (NCT03883802).

Downstream pathway component inhibitors PRI-724 and CWP232291

These two drug candidates make use of the "downstream target window" to achieve the necessary specificity (fig. 1). Both compounds affect the pathway at the transcriptional level, but through entirely different mechanisms: the small molecule PRI-724 affects interaction of β-catenin with transcription co-activator CBP, whereas the peptidomimetic CWP232291 (sometimes called CWP-291) binds to Sam68, an RNA-binding protein that regulates alternative splicing of the TCF-1 transcription factor in a complex with CBP. This selectivity of the compounds towards the Wnt pathway components employed by cancer cells allowed both PRI-724 (as its early analogue ICG-001) [82–84] and CWP232291 [85] to succeed in the preclinical setting and enter phase I clinical trials.

PRI-724 was tested in three phase I trials: in patients with advanced solid tumours (NCT01302405), acute and chronic myeloid leukaemia (NCT01606579), and pancreatic cancer (NCT01764477). In the phase I trials including 18 patients, the compound showed a promising safety profile with only dose-limiting grade 3 hyperbilirubinaemia registered in one patient (out of 7 presenting grade 3 events) at the highest dose of the compound (1280 mg/m^2/day). Grade 2 adverse events included diarrhoea, bilirubin elevation, hypophosphataemia, nausea, fatigue, anorexia, thrombocytopenia and alkaline phosphatase elevation. The compound also showed a decrease in survivin expression in circulating tumour cells as an efficacy readout in colon cancer subjects [86]. At the same dosage, no grade 3 adverse events were recorded for refractory leukaemia patients, with only four cases of grade 1 nausea, vomiting and diarrhoea attributed to the drug. Analysis of patient samples demonstrated a 44% median blast decrease [87]. However, in the third study, when combined with gemcitabine against pancreatic adenocarcinoma, the compound induced seven grade 3 and 4 adverse events in 20 patients, inducing abdominal pain, neutropenia, anaemia, fatigue and alkaline phosphatase rise. Stable disease was observed in 40% of patients. Despite this somewhat worse performance, none of the adverse events met the dose-limiting definition, thus the combination was considered overall safe with "modest clinical activity" [88]. Interestingly, since CBP/β-catenin interaction was found to be important during the onset of liver fibrosis, PRI-724 is in clinical trials against this disease as well, reporting similar adverse reactions against the background of a clinical benefit [89]. This later indication is being continued, as currently a phase I/II study is announced for PRI-724 in fibrosis, whereas for its anti-cancer application no follow-up is in sight.

Peptidomimetic CWP232291 was used in a single phase I trial in patients with relapsed and refractory acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) comprising 56 patients. Grade 3 and 4 events made up 9% of the all recorded adverse events and included fever, nausea and anaphylactic reaction, with the first two being dose limiting. Grade 1 and 2 adverse events included nausea, infusion-related reaction, vomiting, diarrhoea and anorexia. There were also some indications of efficacy, since remission was observed in one patient and reduction in β-catenin and survivin as markers consistently observed in other subjects.

Conclusions and perspectives

The agents described above result from different approaches to inhibiting the Wnt pathway in cancer and are clearly unified by one motif: in order to target the pathway, one needs to identify disease-specific vulnerabilities in it to avoid systemic toxicity. Such specific vulnerabilities in the Wnt pathway are best to be found among its most divergent levels of the pathway – the one at the plasma membrane and the one inside the nucleus [55]. It should be noted that in the current review we have focused on the *de novo* and dedicated Wnt-targeting compounds; however, a wealth of Wnt inhibitors have been found among already approved drugs, prompting attempts to reposition them against Wnt-dependent cancers, as reviewed by us and elsewhere [90, 91]. Our own recent preclinical study shows that clofazimine, known as an anti-leprosy agent with a well-established safety profile, can efficiently inhibit Wnt signalling at the doses comparable to those used against leprosy and is safe to administer in combination with chemotherapy [92, 93]. Other well-known small molecule compounds, such as niclosamide, sulindac, pimozide show promise in various preclinical studies and will hopefully soon appear in clinical studies. Other Wnt inhibitors, including some natural products, may turn out to be promising agents against select Wnt-dependent cancers [94, 95]. Future developments will show whether the new wave of effort to target the "undruggable" Wnt pathway will bear fruit [96]. The main message of our review is that, in order to be suc-

cessful, such efforts should aim not at the Wnt pathway as a whole, but at a particular variant of it, selectively active in a disease state.

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