



HAL
open science

Wnt/Planar Cell Polarity Signaling: New Opportunities for Cancer Treatment

A. Daulat, J.P. Borg

► **To cite this version:**

A. Daulat, J.P. Borg. Wnt/Planar Cell Polarity Signaling: New Opportunities for Cancer Treatment. Trends in Cancer, 2017, 3 (2), pp.113-125. 10.1016/j.trecan.2017.01.001 . hal-01790716

HAL Id: hal-01790716

<https://hal.science/hal-01790716v1>

Submitted on 13 May 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 Wnt/Planar Cell Polarity signaling:
2 new opportunities for cancer treatment

3

4 Avais M. Daulat¹ and Jean-Paul Borg¹

5

6

7

8

9

10

11 ¹Centre de Recherche en Cancérologie de Marseille, Aix Marseille Univ UM105, Inst Paoli
12 Calmettes, UMR7258 CNRS, U1068 INSERM, «Cell Polarity, Cell signalling and Cancer -
13 Equipe labellisée Ligue Contre le Cancer », Marseille, France

14

15 * To whom correspondence should be addressed: jean-paul.borg@inserm.fr/Phone 33-4-
16 8697-7201, Fax 33-4-8697-7499

17

18 Keywords: Wnt pathway, non-canonical, planar cell polarity, signaling, therapeutic targets

19

20

21 **Abstract**

22

23 Cancer cells are addicted to a large spectrum of extracellular cues implicated in the initiation,
24 stem cell renewal, tumor growth, dissemination in the body, and resistance to treatment.

25 Among these factors, Wnt ligands and their associated signaling cascades contribute to most
26 of these processes, paving the way for opportunities in therapeutic development. The

27 developmental Wnt/Planar Cell Polarity pathway is the most recently described branch of

28 Wnt signaling for having a strong implication in cancer development at early and late stages.

29 We will depict here some of the latest knowledge accumulated on this pathway and the
30 pending questions, present the most convincing findings about its role in cancer and review

31 the most promising strategies currently designed to target its components.

32

33

34 **Not one but several Wnt signaling pathways**

35 Among the developmental signaling pathways defective in cancer (Hedgehog, Notch, Hippo,
36 Wnt), it recently became clear that Wnt signaling plays a pivotal role in all steps of the
37 disease, from tumor initiation to cancer growth and dissemination. During the past three
38 decades since the discovery of the first Wnt ligand and its implication in cancer (**BOX 1**) [1,
39 2], a large number of genetic, functional and translational studies have greatly improved our
40 knowledge on this pathway. In particular, many important Wnt signaling components have
41 been identified and functionally characterized including a network of 19 Wnt ligands, 10
42 membrane Frizzled receptors (Frizzled) or co-receptors (LRP5/6,...) that trigger intracellular
43 cascades with multiple outputs [3-5] (Figure 1A). Part of the challenge lies in the complexity
44 of the pathway in which multiple combinatorial interactions are generated by the intervening
45 components at the cell surface and inside the cells. Painting a simplistic picture of the
46 pathway, Wnt signaling is classically divided in two branches whose delineation relies on
47 differential requirement for β -catenin, an armadillo-repeat cytoplasmic adaptor protein with
48 membrane and nuclear functions. For many years, Wnt/ β -catenin signaling (also referred as
49 canonical Wnt signaling) has been the most extensively characterized pathway at the
50 molecular level and in human diseases. This has led to major discoveries about its mode of
51 action and its prominent implication in cancer (for review, see [6]). The β -catenin-
52 independent Wnt pathways (hereafter named non-canonical pathways) utilize a different panel
53 of Wnts and (co)receptors compared to the canonical pathway although some Wnt
54 components such as Dishevelled are shared by both pathways. However, depending on the
55 cellular context and expression of particular co-receptors, a given Wnt can activate either β -
56 catenin-dependent or β -catenin-independent Wnt signaling. The non-canonical Wnt pathway
57 is often seen as subdivided in two branches, one using intracellular calcium as a second
58 messenger (Wnt/ Ca^{2+}) and the other one defined by a conserved genetic pathway (Wnt/Planar

59 Cell Polarity or PCP) (Figure 1). However, as discussed below, one can envision these two
60 branches as a single one on the basis of biochemical arguments. Recent reviews have depicted
61 canonical and Wnt/Ca²⁺ pathways in great details (see for example [3]). In this review, we
62 will focus on the Wnt/PCP pathway whose contribution in many cancers has been recently
63 uncovered.

64

65 **The evolutionary conserved Planar Cell Polarity**

66 In 1982, Gubb and Garcia-Bellido studied mutants of the fruit fly (*Drosophila melanogaster*)
67 harboring defects in the orientation of hairs and sensory bristles on the wings, describing for
68 the first time what is now routinely called PCP defects [7]. PCP refers to the organization of
69 the epithelium orthogonal to the apico-basal polarity axis which orients epithelial cells
70 attached to extracellular matrices. Genetic studies in flies further identified a group of genes,
71 so-called core PCP genes, responsible for the establishment and maintenance of PCP in wings
72 and ommatidia [8, 9]. The encoded molecules are evolutionary conserved and are members of
73 diverse family of receptors (Flamingo, Frizzled, Vang-Gogh-like, Ptk7, Ryk, Ror2, Daschous,
74 Fat) and cytoplasmic adaptors (Dishevelled, Prickle, Diego). Asymmetric distribution of PCP
75 components in polarized cells, - Vangl-like, Prickle and Diego localize at the anterior sides of
76 the plasma membrane and Frizzled, Dishevelled and Dachsous at the posterior sides of the
77 plasma membrane -, is inherent to PCP functions, and is achieved through diverse and not
78 completely understood molecular mechanisms [10]. PCP components are highly conserved
79 throughout evolution, from drosophila to humans, albeit one fruit fly gene has usually several
80 paralogs in vertebrates. For example, the drosophila *Vang-Gogh* and *Prickle1* genes have two
81 (*Vangl1* and *Vangl2*) and four (*Prickle1-4*) mammalian paralogs, respectively. In the mouse,
82 PCP is required for orientation of stereocilia in the cochlea, orientation of hairs in the skin and
83 morphogenesis of many organs [11-13]. In the early 2000s, PCP molecules were found

84 implicated in the regulation of convergent extension (C-E), a process characterized by cellular
85 movements controlled by JNK and RHO activities required at early stages of development
86 (gastrulation), and in ciliogenesis in vertebrates [3, 8, 10, 13-15]. The central role of PCP in
87 vertebrate development is further evidenced by the dramatic impact of misexpression of its
88 components in embryos, leading to neural tube defects, - the most obvious and dramatic being
89 craniorachischisis in mice and humans mutant for *Vangl-like* -, and to abnormal formation of
90 the body axis during gastrulation [16]. Work from many laboratories has assigned PCP to a
91 non-canonical Wnt pathway referred thereafter as Wnt/PCP pathway.

92

93 **Wnt/PCP is a β -catenin independent Wnt pathway**

94 Wnts (Wingless/Int-1) are secreted glycoproteins expressed during embryonic development
95 and throughout adult life, acting in diverse processes such as cell proliferation, stem cell
96 maintenance, cell migration, survival, and cell fate determination. In vertebrates, Wnts can
97 activate β -catenin-dependent and -independent pathways, however genetic studies conducted
98 in *Drosophila* concluded that Wingless, the sole fly Wnt, does not control PCP [8].
99 Organization of Wnt pathway is very complex owing to the important number of Wnt ligands
100 and membrane receptors of the seven transmembrane Frizzled family or single-spanning
101 transmembrane (co)receptors able to enter into multiple Wnt/(co)receptor combinations at the
102 plasma membrane [3, 17]. As mentioned above, use of β -catenin defines the canonical and
103 best studied Wnt pathway (**BOX 2**) [3]. Depending on the cellular context, Wnt/PCP pathway
104 can be triggered by various Wnts including some which generally activate the β -catenin
105 dependent pathway. There is a large body of evidence that shows how the presence of co-
106 receptors at proximity of Frizzled receptors orients the decision toward either β -catenin
107 dependent or independent pathways. However, among the Wnts, WNT-5A, WNT-7 or WNT-
108 11 are known to mostly favor Wnt/PCP pathway. In parallel, it is commonly admitted that

109 FRIZZLED-3, -6 and -7 mostly orient toward Wnt/PCP signaling whereas canonical Wnt
110 pathway usually utilizes FRIZZLED-1 and -4. Wnt co-receptors such as tyrosine kinase
111 receptor family members (PTK7, ROR2, RYK) or membrane proteins (CD146, VANGL2,
112 Syndecan, Glypican) have a demonstrated implication in Wnt/PCP pathway [18, 19]. They
113 can directly bind to Wnts (CD146, ROR2, RYK) or facilitate interaction between Wnts and
114 their cognate Frizzled receptors. For example, formation of a Wnt-Frizzled-ROR2 complex
115 triggers Wnt/PCP signaling during development and in cancer cells. The ability of ROR2 to
116 heterodimerize with PTK7, another tyrosine kinase receptor, and to transduce downstream
117 events on its own adds additional layers of complexity to this signaling platform [20-22].
118 Furthermore, oligomerization of Frizzled receptors is not only necessary for their maturation
119 and membrane localization [23] but also represents, as demonstrated for other seven
120 transmembrane proteins [24, 25], an opportunity for the recruitment of signaling molecules
121 implicated in canonical or non-canonical Wnt pathways, increasing again system complexity.
122 Binding of Wnt ligands leads to recruitment of Dishevelled to Wnt/PCP Frizzled receptors
123 and activation of small GTPases of the Rho family (Cdc42, Rac1, RhoA) involved in actin
124 cytoskeleton remodeling and cell contractility, and JNK pathway [14]. In vertebrates, β -
125 catenin independent signaling is traditionally divided into Wnt/ Ca^{2+} and Wnt/PCP JNK-
126 dependent signaling which can be both activated by Wnt5a. However, in *Xenopus*, Randall
127 Moon's team showed that Prickle1 and Dishevelled can trigger JNK (monitored by AP1
128 reporter assays) and calcium (increase of Ca^{2+} dynamics and activation of CAMKII and PKC,
129 two Ca^{2+} dependent kinases) signaling, leaving the possibility open that Wnt/ Ca^{2+} and
130 Wnt/PCP branches function as one signaling pathway or, at least, that they cross-talk [26, 27].
131 None of these biochemical assays have been applied to *Drosophila* where PCP signaling was
132 genetically, not biochemically, defined. Together, these data suggest subtle regulation and
133 overlap between these two Wnt pathways.

134 Canonical Wnt and non-canonical Wnt/PCP pathways are engaged in intimate relationships
135 by sharing common components such as Dishevelled, PTK7 and RYK which can positively or
136 negatively act on both signaling cascades [14, 15]. For example, Wnt-5a can trigger β -catenin
137 dependent or independent pathway [28, 29] and PTK7 can directly interact with β -catenin,
138 promoting a canonical Wnt signaling during *Xenopus* development, or activate Wnt/PCP
139 signaling [20, 30-32]. Finally, like most Wnt/PCP components, Prickle behaves as an
140 inhibitor of β -catenin dependent signaling [3, 33].

141

142 **Deregulation of Wnt/PCP signaling in cancer**

143 Whereas loss of Wnt/PCP signaling, mostly by gene mutations, is linked to human genetic
144 disorders (defects of neural tube closure or palate cleft, kidney diseases, ciliopathies) (for
145 reviews see [8, 9, 14]), up-regulation of Wnt/PCP components is observed in many cancers,
146 this event being most of the time, although not exclusively, associated to a poor prognosis
147 (Table 1). Recent studies have highlighted how these deregulations are associated to the
148 classical features of cancer progression. We will describe thereafter how Wnt/PCP proteins
149 are involved in processes such as cell proliferation, stemness, epithelial-mesenchymal
150 transition (EMT), cell migration, tumor invasiveness and resistance to treatment (Figure 1B).

151 *Cancer cell proliferation and stemness*

152 Involvement of canonical Wnt signaling in the early stages of colon cancer is well established
153 as mutations in up to 90% of colorectal cancers (CRCs) of *APC* (80%), *β -catenin* (10%) or
154 *AXIN* which constitutively activate the pathway were found [3]. A recent study analyzing a
155 large cohort of non-metastatic CRC patients showed that enhanced expression of non-
156 canonical Wnt-5a confers a better clinical outcome [34]. Accordingly, xenografts of colorectal
157 HCT116 cells overexpressing Wnt-5a are less proliferative and less tumorigenic [34]. This
158 tumor suppressing role of Wnt-5a has also been described in other cancer types (lymphoma,

159 thyroid cancer) [35-37] and is due to inhibition of canonical Wnt pathway [29]. Paradoxically,
160 in other studies, Wnt-5a is described as a poor prognosis marker for patients suffering from
161 CRC and gastric cancer and behaves as a pro-migratory and pro-invasive ligand [38, 39].
162 Along the same line, downregulation of the Wnt/PCP receptors PTK7 and
163 VANGL1/VANGL2 impairs cell proliferation of colon and breast cancer cells, respectively
164 [40-43]. A recent report showed that FRIZZLED-7 along with other Wnt/PCP components is
165 upregulated in ovarian cancer cells conferring cell proliferation, cell cycle progression, and
166 stemness mediated in part by RhoA activity [44]. The PDZ protein SCRIBBLE plays a
167 prominent role in apico-basal polarity and behaves as a tumor suppressor in *Drosophila* [45].
168 Its function has somehow diverged along evolution as it participates to Wnt/PCP signaling in
169 vertebrates [46]. However, its tumor suppressing function is conserved in breast and prostate
170 cancer through an increase of cancer cell survival [47, 48], MAPK and Hippo pathways which
171 promote polarity defects, cancer cell proliferation and invasiveness, self-renewal and
172 tumorigenic capacities of cancer stem cells [48-51]. In stark contrast with canonical Wnt
173 pathway, little is known about the transcriptional events and target genes of Wnt/PCP
174 signaling which makes its study difficult. However, GRHL3, a transcription factor involved
175 in epidermal wound repair and acting as a tumor suppressor in squamous cell carcinoma,
176 represents a notable exception [52, 53]. GRHL3 is the orthologous to *Drosophila* Grainy head
177 (Grh), a protein involved in PCP signaling in wing hair formation and ommatidium
178 orientation in flies [54, 55]. Mechanistically, human GRHL3 controls the expression of
179 RhoGEF19, an activator of the small GTPase family RhoA, leading to actin polymerization,
180 cytoskeletal rearrangement and directed migration in wound healing [52]. Recently, Jarid2, a
181 developmental transcription factor member of the Polycomb Repressor complex 2, has been
182 shown to control expression of Wnt/PCP components such as Wnt-9a, Frizzled-2, and
183 Prickle1 which are important for stemness of murine embryonic stem cells [56]. Such a causal

184 link has not been yet established in cancer stem cells; however human JARID2 promotes
185 EMT in hepatocellular, lung and colon cancer cells [57, 58]. Lastly, PTK7 was recently
186 described as a hematopoietic and colon cancer stem cell marker whose function has yet to be
187 determined [59, 60].

188 *Epithelial-Mesenchymal Transition*

189 EMT is a physiological reversible process which describes the transition of epithelial cells
190 from a polarized to a mesenchymal state prone to motility. It occurs during normal embryonic
191 development but also in tumors leading to increased invasion and drug resistance, and is
192 controlled by transcriptional programs driven by many signaling pathways [61]. Up-
193 regulation of Wnt-5a has been observed in cellular systems undergoing EMT such as
194 squamous carcinoma cells [62] and Madin-Darby Canine Kidney (MDCK) cells treated with
195 TGF β [63]. Levels of FRIZZLED-4 and PTK7 receptors are also high in prostate cancer, and
196 in MDCK or human embryonic stem cells in which EMT is triggered [63-65]. Cause or
197 consequence? In melanoma cells, Wnt-5a promotes EMT through a PKC-dependent
198 mechanism, related to Wnt/Ca²⁺ and possibly to Wnt/PCP, which leads to expression of
199 mesenchymal markers such as Snail and Vimentin and decreases E-cadherin expression [66].
200 Recent results attribute to SCRIBBLE a direct role in EMT in normal [67] and tumoral [68]
201 situations through the modulation of SMAD3/SMAD4 and MAPK-ERK activities,
202 respectively. On the other hand, induction of EMT in breast cancer cells delocalizes
203 SCRIBBLE from the plasma membrane inducing a Hippo-dependent pro-metastatic program
204 [50]. Recently, elevated Wnt-5a/Wnt-5b and FRIZZLED-2 levels have been observed in
205 several types of metastatic cancers (liver, lung, colon, and breast) expressing EMT markers.
206 In this study, FRIZZLED-2 is a cornerstone and targetable molecule driving EMT and
207 metastasis through FYN and STAT3, two novel components of Wnt pathways [69].

208 *Cell migration and invasiveness*

209 Extensive data have been accumulated on the role of Wnt/PCP deregulation in tumoral
210 dissemination through *in vitro* and *in vivo* studies [40, 41, 43, 49, 66, 70-73]. In skin cancers
211 such as melanoma, overexpression of Wnt-5a correlates with enhanced cell invasion and
212 metastasis, and with poor outcome [73]. These effects can be mediated by different Wnt
213 receptors including FRIZZLED-3, -5 or ROR2 [73-76]. At the cellular level, stimulation of
214 melanoma cells by Wnt-5a leads to an asymmetrical accumulation of FRIZZLED-3 in
215 intracellular Wnt-mediated receptor-actin-myosin polarity (W-RAMP) structures under the
216 control of two small GTPases, Rab4 and RhoB [77]. Mechanistically, W-RAMPs localize at
217 the trailing edge of migrating cells where they locally activate PKC leading to increased
218 contractility and focal adhesion disassembly rates [78]. Wnt-5a can also control focal
219 adhesion dynamics through FRIZZLED-2, APC and Dishevelled [79]. APC and Dishevelled
220 associate with Focal Adhesion Kinase (FAK) and PAXILLIN which are important for Wnt-
221 5a-dependent focal adhesion turnover. This particular pathway seems initiated through an
222 association between Wnt-5a/FRIZZLED-2 and integrins at the leading edge of migrating
223 cells. In another study, single molecule RNA sequencing of circulating tumor cells (CTCs)
224 from prostate cancer revealed an increase of Wnt-2 driven non-canonical signaling which
225 suppresses anoikis and increases cell motility [80].

226 Genomic analysis led to the stratification of breast cancers into five main classes according to
227 gene expression. Triple negative breast cancers (TNBCs) are the most aggressive entity,
228 lacking expression of HER2 and estrogen/progesterone receptors, with no yet available
229 targeted therapy. Recent data from our lab found that PRICKLE1 and VANGL2 are both
230 overexpressed in TNBCs [43, 70] whereas high expression of VANGL1, a VANGL2
231 homologue, was associated to poor prognosis in estrogen receptor-positive breast cancer
232 patients [81]. PRICKLE1 which is known to interact with VANGL2 [82] is implicated in
233 focal adhesion dynamics [70, 71, 83]. Interestingly, PRICKLE1 downregulation has been

234 reported to strongly impair cell motility via three possible downstream regulators, Akt [70],
235 and Rho-GEF [83] in TNBC cells or LL5 β [71] in other cell systems. Moreover, activation of
236 surviving Akt-dependent mechanism by Wnt/PCP proteins contributes to cancer progression
237 [70, 84]. Since the first observations that elevated amounts of Wnt-5a are found in invasive
238 breast cancers [85] [86], other Wnt/PCP-related molecules have also been proposed as
239 markers of aggressiveness. This is for instance the case of two other Wnt ligands, Wnt-7a and
240 Wnt-11 [72, 87], as well as receptors (FRIZZLED-2, -7, VANGL2) [43, 69] and adaptors
241 (SCRIBBLE, PRICKLE1) [42, 70, 88]. In TNBCs, VANGL2 is thought to act downstream of
242 ROR2 [89] or Frizzled [90] and its overexpression appears to correlate with JNK pathway
243 activation through a direct interaction with the p62/SQSTM1 scaffold [43]. VANGL2 may
244 also promote cell migration through interaction with SCRIBBLE [41]. Altogether these data
245 suggest that VANGL2 act as signaling platform able to mediate downstream signaling events
246 through its interaction with different scaffold proteins (SCRIBBLE, p62/SQSTM1 or
247 PRICKLE1). The finding that, in neuroblastoma and fibrosarcoma cells, *PRICKLE1* and
248 *VANGL2* act as tumor suppressor genes [91, 92] indicates that their implication in cancer
249 might vary depending on the cellular context.

250 First identified in colon cancer cells [93, 94], PTK7 has since been shown to behave as a poor
251 prognosis marker in colon cancer patients and to contribute to the metastatic program [40,
252 95]. This inactive tyrosine kinase receptor is a Wnt-5a co-receptor which forms heterodimers
253 with ROR2 and mediates JNK activation [20, 21]. In other contexts, PTK7 can modulate β -
254 catenin dependent Wnt pathway [30, 31], induce cell migration [40, 96] and associate with
255 diverse cancer-related membrane receptors (VEGFR1, Plexins) [95]. Moreover, upregulation
256 of PTK7 has been reported in Acute Myeloid Leukemia (AML) and T cell acute
257 lymphoblastic leukemia (T-ALL) [96, 97]. High PTK7 levels in AML cells are associated
258 with low circulating blast cell counts most probably because of retention of PTK7 positive

259 cells in the bone marrow [59]. This may well explain the resistance of AML-PTK7 positive
260 patients to chemotherapy as this treatment aims at eliminating circulating cycling blast cells
261 [96]. Other Wnt/PCP components (Wnt-5a, PRICKLE1, VANGL2, CELSR1, FRIZZLED-3,
262 -7) have been also reported to be poor prognosis markers in chronic lymphocytic leukemia
263 (CLL) when overexpressed [98, 99]. Autocrine release of Wnt-5a by CLL cells stimulates
264 ROR1, a ROR2 homologue, and controls the chemotactic response and proliferation by
265 inducing ROR1/ROR2 heterodimerization which activates RhoA and Rac1 [98-100]. This
266 proliferative pathway can be targeted with specific antibodies inducing apoptosis [101].

267

268 **Wnt/PCP pathway in host-tumor interaction**

269 Tumor growth and dissemination is not only governed by genetic alterations of cancer cells
270 but also by an altered deregulated communication with adjacent tissues. In Hodgkin
271 lymphoma, canonical Wnts were shown to be secreted by the endothelial vasculature,
272 promoting chemotaxis and adhesion of lymphoma cells [102]. In prostate cancer, genotoxic
273 treatment leads to WNT16B secretion by the tumor microenvironment which initiates a
274 paracrine activation of canonical Wnt signaling in cancer cells and drug resistance [103].
275 Wnts are secreted, lipid-modified glycoproteins whose maturation in the endoplasmic
276 reticulum relies on Porcupine, an eight transmembrane spanning acyl transferase [28].
277 Inhibition of Porcupine was thus proposed as a strategy to repress Wnt production and treat
278 squamous cell carcinoma and CRCs (Table 2). Several routes involving protein carriers,
279 filipodia or cytomenes and extracellular vesicles such as exosomes are involved in the
280 extracellular transport of Wnts in the hydrophilic extracellular space to generate signaling
281 gradients in tissues [104]. Exosome are 30-150nm vesicles that allow the transfer of proteins,
282 lipids and genetic materials and play a key role in intercellular communication between
283 cancer cells and their microenvironment [105]. In melanoma, Wnt-5a has been shown to

284 induce a calcium dependent release of exosomes that contain IL-6, VEGF and MMP2. This
285 process stimulates the adjacent endothelial cells and favor invasiveness of cancer cells to
286 distant tissues [106]. Recent reports have highlighted the role of Wnt/PCP pathway in cancer-
287 associated fibroblasts (CAFs) which promote breast cancer metastasis. Indeed, Luga et al.
288 have shown that CAFs generate exosomes which are internalized by cancer cells, loaded with
289 Wnt-11, and released by an autocrine loop promoting metastasis through VANGL1,
290 Dishevelled and PRICKLE1 [72]. Conversely, breast cancer cells can secrete Wnt-7a which
291 activates CAFs and promotes invasion through a TGF β -dependent signaling [87]. Wnt/PCP
292 pathway thus plays an important role in tumor-CAFs communication for the regulation of cell
293 motility, invasion and niche formation.

294

295 **Wnt/PCP pathway in resistance to treatment**

296 Wnt/PCP can intervene by different mechanisms on drug resistance either indirectly (for
297 example through its participation to EMT) or directly. In melanoma, hypoxia induces Wnt-5a
298 expression and contributes to resistance to B-RAF inhibitors [84, 107]. The latter mechanism
299 occurs through ROR2 or FRIZZLED-7, RYK and the pro-survival Akt pathway which blocks
300 apoptosis. Elevation of PRICKLE1 expression in poor prognosis breast cancer is correlated
301 with increased Akt activation; however its contribution to drug resistance has not been
302 evaluated [70]. Overexpression of PTK7 is associated with drug resistance through retention
303 of blasts in the bone marrow of AML patients and to resistance anthracycline-based
304 chemotherapy by an unknown mechanism in breast cancer patients [96, 108]. Recently,
305 Wnt/PCP signaling has been shown to be elevated in prostate circulating tumour cells
306 resistant to treatment with enzalutamide, an androgen receptor (AR) inhibitor. Ectopic
307 expression of Wnt-4, -5a, -7b or -11 in LnCAP, an AR-positive cell line, improves cell
308 survival. Interestingly, enzalutamide increases Wnt-5a expression in this cell line suggesting

309 the existence of a positive feedback loop whose knockdown decreases overall cell
310 proliferation [109]. Undoubtedly, examining whether other Wnt/PCP proteins also contribute
311 to drug resistance will deserve further investigation.

312

313 **Concluding Remarks**

314 Despite the progress in understanding how Wnt/PCP deregulation contributes to
315 tumorigenesis, many questions remain to be answered. In particular, the functions of many
316 components that constitute this pathway are still poorly understood both at the molecular and
317 cellular levels. Wnt-5a is by far the most studied Wnt/PCP ligand in cancer. However, other
318 less characterized Wnts such as Wnt-2, -7 or -11 are also playing a crucial role in many steps
319 of tumorigenesis and deserve further attention [72, 80, 87]. Moreover, whereas upregulation
320 of Wnt/PCP components is frequently associated to poor prognosis and drug resistance, an
321 inverse correlation has also been reported in the literature leading to conflicting conclusions
322 as to whether Wnt-5a act as a tumor suppressor or pro-metastatic factor, very much like
323 TGF β [115]. Further contributing to the confusion, Wnt-5a or receptors such as PTK7 have
324 the dual capacity to activate both non-canonical and canonical Wnt pathways. Finally, the
325 frequent repression of canonical Wnt pathway by Wnt/PCP signaling adds an additional layer
326 of complexity. More work is thus needed to further dissect the molecular basis of Wnt/PCP
327 regulation which likely varies with (co)receptors composition at the cell surface (Figure 3)
328 [29].

329 Given the large body of evidence demonstrating the importance of Wnt/PCP signaling in
330 cancer, this pathway is now considered as an attractive target for novel therapeutics. Different
331 strategies are currently explored using chemical- or antibody-based compounds able to inhibit
332 or activate the pathway and the list of ongoing clinical trials is growing (Table 2). However,
333 development of these therapeutics will certainly highly benefit from the identification of

334 reliable biomarkers (assessment of Wnt/PCP component expression levels and/or activation of
335 their associated pathways) able to monitor activation (or inhibition) of the pathway in cells
336 and tissues. Mutations in *PRICKLE1* and *VANGL1* have been recently described in leukemia
337 [116] and squamous cell carcinoma [117]. Interestingly, these mutations lie in regions
338 important for protein-protein interactions. Yet the relevance of these findings will have to be
339 addressed at the functional and clinical levels. During cancer progression, Wnt/PCP
340 molecules can activate signaling pathways that are not classically associated to Wnt signaling
341 such as Akt [70, 84] or Fyn/Stat [69]. Hijacking of these signaling molecules by Wnt/PCP
342 pathway is likely to render cancer cells more efficient at invading tissues or resisting to
343 chemotherapies. Inhibition of Akt or Fyn with available drugs could thus represent a potential
344 strategy to combat Wnt/PCP deregulation in certain cancers. In conclusion, we believe that
345 therapeutics against Wnt/PCP pathway represent an interesting avenue in cancer treatment.

346

347

348 **Figures**

349 **Figure 1** Wnt signaling pathway and cancer progression

350 **Figure 2** Protein composition at the cell surface orients Wnt signaling

351

352 **Table**

353 **Table 1** Deregulation of non-canonical Wnt/PCP signaling components in cancer

354 **Table2:** Clinical trials of compounds targeting Wnt/PCP proteins

355

356 **Text boxes**

357 **BOX 1:** In 1982, Roel Nusse and Harold Varnus published a *Cell* paper using Mouse
358 Mammary Tumour Virus (MMTV) to identify genes involved in tumorigenesis. MMTV is a
359 weak oncogenic milk-transmitted retrovirus causing mammary tumours. The authors found
360 that incorporation of MMTV into the mouse genome led to overexpression of a gene
361 christened *Int-1* (*Integration site-1*) correlated to high occurrence of cancer. A few years later,
362 *Int-1* was recognized as a homologue of the *Drosophila* Wingless ligand and renamed Wnt-1.
363 WNT1 was later on defined as an oncogenic protein in humans and found implicated in the
364 Wnt/ β -catenin pathway.

365

366 **BOX 2:** In the absence of Wnts, β -catenin is associated to a destruction complex comprising
367 adenomatous polyposis coli (APC), Glycogen Synthase Kinase 3 β (GSK3 β) and Axin. β -
368 catenin is phosphorylated by GSK3 β leading to its ubiquitylation by SCF β -TrCP and to its
369 degradation by the 26S proteasome. In the absence of β -catenin, the well-defined transcription
370 factors LEF/TCF bind to a repressor called Groucho which recruits histone deacetylases
371 (HDACs) to repress expression of Wnt-target genes. Wnts such as WNT-3A bind to their

372 cognate (co)receptors and form a Frizzled-LRP5/6-Wnt ternary complex. Dishevelled is then
373 associated to Frizzled at the plasma membrane resulting in the recruitment of GSK3 β and
374 CK1 γ . Both kinases phosphorylate LRP5/6 at the C-terminus resulting in the formation of
375 high affinity binding sites for Axin. Axin sequestration by LRP5/6 competes with the β -
376 catenin destruction complex and leads to accumulation of cytosolic β -catenin and
377 translocation into the nucleus where it displaces Groucho, binds to LEF/TCF and promotes
378 the expression of Wnt-targeted genes.

379

380

381 **References:**

- 382 1. Nusse, R. and H. Varmus, *Three decades of Wnts: a personal perspective on how a*
383 *scientific field developed*. EMBO J, 2012. **31**(12): p. 2670-84.
- 384 2. Tsukamoto, A.S., et al., *Expression of the int-1 gene in transgenic mice is associated*
385 *with mammary gland hyperplasia and adenocarcinomas in male and female mice*.
386 Cell, 1988. **55**(4): p. 619-25.
- 387 3. Angers, S. and R.T. Moon, *Proximal events in Wnt signal transduction*. Nat Rev Mol
388 Cell Biol, 2009. **10**(7): p. 468-77.
- 389 4. Acebron, S.P. and C. Niehrs, *beta-Catenin-Independent Roles of Wnt/LRP6 Signaling*.
390 Trends Cell Biol, 2016.
- 391 5. Anastas, J.N. and R.T. Moon, *WNT signalling pathways as therapeutic targets in*
392 *cancer*. Nat Rev Cancer, 2013. **13**(1): p. 11-26.
- 393 6. Zhan, T., N. Rindtorff, and M. Boutros, *Wnt signaling in cancer*. Oncogene, 2016.
- 394 7. Gubb, D. and A. Garcia-Bellido, *A genetic analysis of the determination of cuticular*
395 *polarity during development in Drosophila melanogaster*. J Embryol Exp Morphol,
396 1982. **68**: p. 37-57.
- 397 8. Zallen, J.A., *Planar polarity and tissue morphogenesis*. Cell, 2007. **129**(6): p. 1051-
398 63.
- 399 9. Yang, Y. and M. Mlodzik, *Wnt-Frizzled/planar cell polarity signaling: cellular*
400 *orientation by facing the wind (Wnt)*. Annu Rev Cell Dev Biol, 2015. **31**: p. 623-46.

- 401 10. Gray, R.S., I. Roszko, and L. Solnica-Krezel, *Planar cell polarity: coordinating*
402 *morphogenetic cell behaviors with embryonic polarity*. Dev Cell, 2011. **21**(1): p. 120-
403 33.
- 404 11. Narimatsu, M., et al., *Regulation of planar cell polarity by Smurf ubiquitin ligases*.
405 Cell, 2009. **137**(2): p. 295-307.
- 406 12. Ezan, J. and M. Montcouquiol, *Revisiting planar cell polarity in the inner ear*. Semin
407 Cell Dev Biol, 2013. **24**(5): p. 499-506.
- 408 13. McNeill, H., *Planar cell polarity: keeping hairs straight is not so simple*. Cold Spring
409 Harb Perspect Biol, 2010. **2**(2): p. a003376.
- 410 14. Sebbagh, M. and J.P. Borg, *Insight into planar cell polarity*. Exp Cell Res, 2014.
411 **328**(2): p. 284-95.
- 412 15. Gao, B., *Wnt regulation of planar cell polarity (PCP)*. Curr Top Dev Biol, 2012. **101**:
413 p. 263-95.
- 414 16. Kibar, Z., et al., *Ltap, a mammalian homolog of Drosophila Strabismus/Van Gogh, is*
415 *altered in the mouse neural tube mutant Loop-tail*. Nat Genet, 2001. **28**(3): p. 251-5.
- 416 17. Kikuchi, A., H. Yamamoto, and S. Kishida, *Multiplicity of the interactions of Wnt*
417 *proteins and their receptors*. Cell Signal, 2007. **19**(4): p. 659-71.
- 418 18. Oishi, I., et al., *The receptor tyrosine kinase Ror2 is involved in non-canonical*
419 *Wnt5a/JNK signalling pathway*. Genes Cells, 2003. **8**(7): p. 645-54.
- 420 19. Niehrs, C., *The complex world of WNT receptor signalling*. Nat Rev Mol Cell Biol,
421 2012. **13**(12): p. 767-79.
- 422 20. Martinez, S., et al., *The PTK7 and ROR2 Protein Receptors Interact in the Vertebrate*
423 *WNT/Planar Cell Polarity (PCP) Pathway*. J Biol Chem, 2015. **290**(51): p. 30562-72.
- 424 21. Podleschny, M., et al., *A PTK7/Ror2 Co-Receptor Complex Affects Xenopus Neural*
425 *Crest Migration*. PLoS One, 2015. **10**(12): p. e0145169.
- 426 22. Green, J., R. Nusse, and R. van Amerongen, *The role of Ryk and Ror receptor tyrosine*
427 *kinases in Wnt signal transduction*. Cold Spring Harb Perspect Biol, 2014. **6**(2).
- 428 23. Kaykas, A., et al., *Mutant Frizzled 4 associated with vitreoretinopathy traps wild-type*
429 *Frizzled in the endoplasmic reticulum by oligomerization*. Nat Cell Biol, 2004. **6**(1): p.
430 52-8.
- 431 24. Maurice, P., et al., *Molecular organization and dynamics of the melatonin MT(1)*
432 *receptor/RGS20/G(i) protein complex reveal asymmetry of receptor dimers for RGS*
433 *and G(i) coupling*. EMBO J, 2010. **29**(21): p. 3646-59.

- 434 25. Angers, S., et al., *Detection of beta 2-adrenergic receptor dimerization in living cells*
435 *using bioluminescence resonance energy transfer (BRET)*. Proc Natl Acad Sci U S A,
436 2000. **97**(7): p. 3684-9.
- 437 26. Sheldahl, L.C., et al., *Dishevelled activates Ca²⁺ flux, PKC, and CamKII in*
438 *vertebrate embryos*. J Cell Biol, 2003. **161**(4): p. 769-77.
- 439 27. Veeman, M.T., et al., *Zebrafish prickle, a modulator of noncanonical Wnt/Fz*
440 *signaling, regulates gastrulation movements*. Curr Biol, 2003. **13**(8): p. 680-5.
- 441 28. Mikels, A.J. and R. Nusse, *Wnts as ligands: processing, secretion and reception*.
442 Oncogene, 2006. **25**(57): p. 7461-8.
- 443 29. Mikels, A.J. and R. Nusse, *Purified Wnt5a protein activates or inhibits beta-catenin-*
444 *TCF signaling depending on receptor context*. PLoS Biol, 2006. **4**(4): p. e115.
- 445 30. Puppo, F., et al., *Protein tyrosine kinase 7 has a conserved role in Wnt/beta-catenin*
446 *canonical signalling*. EMBO Rep, 2011. **12**(1): p. 43-9.
- 447 31. Hayes, M., et al., *Ptk7 promotes non-canonical Wnt/PCP-mediated morphogenesis*
448 *and inhibits Wnt/beta-catenin-dependent cell fate decisions during vertebrate*
449 *development*. Development, 2013. **140**(8): p. 1807-18.
- 450 32. Bin-Nun, N., et al., *PTK7 modulates Wnt signaling activity via LRP6*. Development,
451 2014. **141**(2): p. 410-21.
- 452 33. Chan, D.W., et al., *Prickle-1 negatively regulates Wnt/beta-catenin pathway by*
453 *promoting Dishevelled ubiquitination/degradation in liver cancer*. Gastroenterology,
454 2006. **131**(4): p. 1218-27.
- 455 34. Cheng, R., et al., *Wnt5a suppresses colon cancer by inhibiting cell proliferation and*
456 *epithelial-mesenchymal transition*. J Cell Physiol, 2014. **229**(12): p. 1908-17.
- 457 35. Liang, H., et al., *Wnt5a inhibits B cell proliferation and functions as a tumor*
458 *suppressor in hematopoietic tissue*. Cancer Cell, 2003. **4**(5): p. 349-60.
- 459 36. Kremenevskaja, N., et al., *Wnt-5a has tumor suppressor activity in thyroid carcinoma*.
460 Oncogene, 2005. **24**(13): p. 2144-54.
- 461 37. Dejmek, J., et al., *Expression and signaling activity of Wnt-5a/discoidin domain*
462 *receptor-1 and Syk plays distinct but decisive roles in breast cancer patient survival*.
463 Clin Cancer Res, 2005. **11**(2 Pt 1): p. 520-8.
- 464 38. Bakker, E.R., et al., *Wnt5a promotes human colon cancer cell migration and invasion*
465 *but does not augment intestinal tumorigenesis in Apc1638N mice*. Carcinogenesis,
466 2013. **34**(11): p. 2629-38.

- 467 39. Kurayoshi, M., et al., *Expression of Wnt-5a is correlated with aggressiveness of*
468 *gastric cancer by stimulating cell migration and invasion.* Cancer Res, 2006. **66**(21):
469 p. 10439-48.
- 470 40. Lhoumeau, A.C., et al., *Overexpression of the Promigratory and Prometastatic PTK7*
471 *Receptor Is Associated with an Adverse Clinical Outcome in Colorectal Cancer.* PLoS
472 One, 2015. **10**(5): p. e0123768.
- 473 41. Belotti, E., et al., *The human PDZome: a gateway to PSD95-Disc large-zonula*
474 *occludens (PDZ)-mediated functions.* Mol Cell Proteomics, 2013. **12**(9): p. 2587-603.
- 475 42. Anastas, J.N., et al., *A protein complex of SCRIB, NOS1AP and VANGL1 regulates*
476 *cell polarity and migration, and is associated with breast cancer progression.*
477 Oncogene, 2012. **31**(32): p. 3696-708.
- 478 43. Puvirajesinghe, T.M., et al., *Identification of p62/SQSTM1 as a component of non-*
479 *canonical Wnt VANGL2-JNK signalling in breast cancer.* Nat Commun, 2016. **7**: p.
480 10318.
- 481 44. Asad, M., et al., *FZD7 drives in vitro aggressiveness in Stem-A subtype of ovarian*
482 *cancer via regulation of non-canonical Wnt/PCP pathway.* Cell Death Dis, 2014. **5**: p.
483 e1346.
- 484 45. Bilder, D., M. Li, and N. Perrimon, *Cooperative regulation of cell polarity and growth*
485 *by Drosophila tumor suppressors.* Science, 2000. **289**(5476): p. 113-6.
- 486 46. Montcouquiol, M., et al., *Identification of Vangl2 and Scrb1 as planar polarity genes*
487 *in mammals.* Nature, 2003. **423**(6936): p. 173-7.
- 488 47. Feigin, M.E., et al., *Mislocalization of the cell polarity protein scribble promotes*
489 *mammary tumorigenesis and is associated with basal breast cancer.* Cancer Res,
490 2014. **74**(11): p. 3180-94.
- 491 48. Pearson, H.B., et al., *SCRIB expression is deregulated in human prostate cancer, and*
492 *its deficiency in mice promotes prostate neoplasia.* J Clin Invest, 2011. **121**(11): p.
493 4257-67.
- 494 49. Zhan, L., et al., *Deregulation of scribble promotes mammary tumorigenesis and*
495 *reveals a role for cell polarity in carcinoma.* Cell, 2008. **135**(5): p. 865-78.
- 496 50. Cordenonsi, M., et al., *The Hippo transducer TAZ confers cancer stem cell-related*
497 *traits on breast cancer cells.* Cell, 2011. **147**(4): p. 759-72.
- 498 51. Godde, N.J., et al., *Scribble modulates the MAPK/Fra1 pathway to disrupt luminal*
499 *and ductal integrity and suppress tumour formation in the mammary gland.* PLoS
500 Genet, 2014. **10**(5): p. e1004323.

- 501 52. Caddy, J., et al., *Epidermal wound repair is regulated by the planar cell polarity*
502 *signaling pathway*. Dev Cell, 2010. **19**(1): p. 138-47.
- 503 53. Darido, C., et al., *Targeting of the tumor suppressor GRHL3 by a miR-21-dependent*
504 *proto-oncogenic network results in PTEN loss and tumorigenesis*. Cancer Cell, 2011.
505 **20**(5): p. 635-48.
- 506 54. Lee, H. and P.N. Adler, *The grainy head transcription factor is essential for the*
507 *function of the frizzled pathway in the Drosophila wing*. Mech Dev, 2004. **121**(1): p.
508 37-49.
- 509 55. Mace, K.A., J.C. Pearson, and W. McGinnis, *An epidermal barrier wound repair*
510 *pathway in Drosophila is mediated by grainy head*. Science, 2005. **308**(5720): p. 381-
511 5.
- 512 56. Landeira, D., et al., *Jarid2 Coordinates Nanog Expression and PCP/Wnt Signaling*
513 *Required for Efficient ESC Differentiation and Early Embryo Development*. Cell Rep,
514 2015. **12**(4): p. 573-86.
- 515 57. Tange, S., et al., *JARID2 is involved in transforming growth factor-beta-induced*
516 *epithelial-mesenchymal transition of lung and colon cancer cell lines*. PLoS One,
517 2014. **9**(12): p. e115684.
- 518 58. Lei, X., et al., *JARID2 promotes invasion and metastasis of hepatocellular carcinoma*
519 *by facilitating epithelial-mesenchymal transition through PTEN/AKT signaling*.
520 Oncotarget, 2016.
- 521 59. Lhoumeau, A.C., et al., *Ptk7-Deficient Mice Have Decreased Hematopoietic Stem*
522 *Cell Pools as a Result of Deregulated Proliferation and Migration*. J Immunol, 2016.
523 **196**(10): p. 4367-77.
- 524 60. Jung, P., et al., *Isolation of Human Colon Stem Cells Using Surface Expression of*
525 *PTK7*. Stem Cell Reports, 2015. **5**(6): p. 979-87.
- 526 61. Gonzalez, D.M. and D. Medici, *Signaling mechanisms of the epithelial-mesenchymal*
527 *transition*. Sci Signal, 2014. **7**(344): p. re8.
- 528 62. Taki, M., et al., *Down-regulation of Wnt-4 and up-regulation of Wnt-5a expression by*
529 *epithelial-mesenchymal transition in human squamous carcinoma cells*. Cancer Sci,
530 2003. **94**(7): p. 593-7.
- 531 63. Chen, Y.S., et al., *Proteomics profiling of Madin-Darby canine kidney plasma*
532 *membranes reveals Wnt-5a involvement during oncogenic H-Ras/TGF-beta-mediated*
533 *epithelial-mesenchymal transition*. Mol Cell Proteomics, 2011. **10**(2): p. M110
534 001131.

- 535 64. Gupta, S., et al., *FZD4 as a mediator of ERG oncogene-induced WNT signaling and*
536 *epithelial-to-mesenchymal transition in human prostate cancer cells.* Cancer Res,
537 2010. **70**(17): p. 6735-45.
- 538 65. Chan, D.N., et al., *PTK7 marks the first human developmental EMT in vitro.* PLoS
539 One, 2012. **7**(11): p. e50432.
- 540 66. Dissanayake, S.K., et al., *The Wnt5A/protein kinase C pathway mediates motility in*
541 *melanoma cells via the inhibition of metastasis suppressors and initiation of an*
542 *epithelial to mesenchymal transition.* J Biol Chem, 2007. **282**(23): p. 17259-71.
- 543 67. Yamben, I.F., et al., *Scrib is required for epithelial cell identity and prevents epithelial*
544 *to mesenchymal transition in the mouse.* Dev Biol, 2013. **384**(1): p. 41-52.
- 545 68. Elsum, I.A., C. Martin, and P.O. Humbert, *Scribble regulates an EMT polarity*
546 *pathway through modulation of MAPK-ERK signaling to mediate junction formation.*
547 J Cell Sci, 2013. **126**(Pt 17): p. 3990-9.
- 548 69. Gujral, T.S., et al., *A noncanonical Frizzled2 pathway regulates epithelial-*
549 *mesenchymal transition and metastasis.* Cell, 2014. **159**(4): p. 844-56.
- 550 70. Daulat, A.M., et al., *PRICKLE1 Contributes to Cancer Cell Dissemination through Its*
551 *Interaction with mTORC2.* Dev Cell, 2016. **37**(4): p. 311-25.
- 552 71. Lim, B.C., et al., *Prickle1 promotes focal adhesion disassembly in cooperation with*
553 *the CLASP-LL5beta complex in migrating cells.* J Cell Sci, 2016. **129**(16): p. 3115-29.
- 554 72. Luga, V., et al., *Exosomes mediate stromal mobilization of autocrine Wnt-PCP*
555 *signaling in breast cancer cell migration.* Cell, 2012. **151**(7): p. 1542-56.
- 556 73. Weeraratna, A.T., et al., *Wnt5a signaling directly affects cell motility and invasion of*
557 *metastatic melanoma.* Cancer Cell, 2002. **1**(3): p. 279-88.
- 558 74. Da Forno, P.D., et al., *WNT5A expression increases during melanoma progression*
559 *and correlates with outcome.* Clin Cancer Res, 2008. **14**(18): p. 5825-32.
- 560 75. Dissanayake, S.K., et al., *Wnt5A regulates expression of tumor-associated antigens in*
561 *melanoma via changes in signal transducers and activators of transcription 3*
562 *phosphorylation.* Cancer Res, 2008. **68**(24): p. 10205-14.
- 563 76. O'Connell, M.P., et al., *The orphan tyrosine kinase receptor, ROR2, mediates Wnt5A*
564 *signaling in metastatic melanoma.* Oncogene, 2010. **29**(1): p. 34-44.
- 565 77. Witze, E.S., et al., *Wnt5a control of cell polarity and directional movement by*
566 *polarized redistribution of adhesion receptors.* Science, 2008. **320**(5874): p. 365-9.
- 567 78. Witze, E.S., et al., *Wnt5a directs polarized calcium gradients by recruiting cortical*
568 *endoplasmic reticulum to the cell trailing edge.* Dev Cell, 2013. **26**(6): p. 645-57.

- 569 79. Matsumoto, S., et al., *Binding of APC and dishevelled mediates Wnt5a-regulated focal*
570 *adhesion dynamics in migrating cells*. EMBO J, 2010. **29**(7): p. 1192-204.
- 571 80. Yu, M., et al., *RNA sequencing of pancreatic circulating tumour cells implicates WNT*
572 *signalling in metastasis*. Nature, 2012. **487**(7408): p. 510-3.
- 573 81. Hatakeyama, J., et al., *Vangl1 and Vangl2: planar cell polarity components with a*
574 *developing role in cancer*. Endocr Relat Cancer, 2014. **21**(5): p. R345-56.
- 575 82. Jenny, A., et al., *Prickle and Strabismus form a functional complex to generate a*
576 *correct axis during planar cell polarity signaling*. EMBO J, 2003. **22**(17): p. 4409-20.
- 577 83. Zhang, L., et al., *A lateral signalling pathway coordinates shape volatility during cell*
578 *migration*. Nat Commun, 2016. **7**: p. 11714.
- 579 84. Anastas, J.N., et al., *WNT5A enhances resistance of melanoma cells to targeted BRAF*
580 *inhibitors*. J Clin Invest, 2014. **124**(7): p. 2877-90.
- 581 85. Lejeune, S., et al., *Wnt5a cloning, expression, and up-regulation in human primary*
582 *breast cancers*. Clin Cancer Res, 1995. **1**(2): p. 215-22.
- 583 86. MacMillan, C.D., et al., *Stage of breast cancer progression influences cellular*
584 *response to activation of the WNT/planar cell polarity pathway*. Sci Rep, 2014. **4**: p.
585 6315.
- 586 87. Avgustinova, A., et al., *Tumour cell-derived Wnt7a recruits and activates fibroblasts*
587 *to promote tumour aggressiveness*. Nat Commun, 2016. **7**: p. 10305.
- 588 88. Navarro, C., et al., *Junctional recruitment of mammalian Scribble relies on E-*
589 *cadherin engagement*. Oncogene, 2005. **24**(27): p. 4330-9.
- 590 89. Gao, B., et al., *Wnt signaling gradients establish planar cell polarity by inducing*
591 *Vangl2 phosphorylation through Ror2*. Dev Cell, 2011. **20**(2): p. 163-76.
- 592 90. Kelly, L.K., et al., *Frizzled-Induced Van Gogh Phosphorylation by CK1epsilon*
593 *Promotes Asymmetric Localization of Core PCP Factors in Drosophila*. Cell Rep,
594 2016. **16**(2): p. 344-56.
- 595 91. Dyberg, C., et al., *Planar cell polarity gene expression correlates with tumor cell*
596 *viability and prognostic outcome in neuroblastoma*. BMC Cancer, 2016. **16**: p. 259.
- 597 92. Cantrell, V.A. and J.R. Jessen, *The planar cell polarity protein Van Gogh-Like 2*
598 *regulates tumor cell migration and matrix metalloproteinase-dependent invasion*.
599 Cancer Lett, 2010. **287**(1): p. 54-61.
- 600 93. Mossie, K., et al., *Colon carcinoma kinase-4 defines a new subclass of the receptor*
601 *tyrosine kinase family*. Oncogene, 1995. **11**(10): p. 2179-84.

- 602 94. Jung, J.W., et al., *Cloning and characterization of the full-length mouse Ptk7 cDNA*
603 *encoding a defective receptor protein tyrosine kinase*. *Gene*, 2004. **328**: p. 75-84.
- 604 95. Lhoumeau, A.C., et al., *PTK7: a cell polarity receptor with multiple facets*. *Cell*
605 *Cycle*, 2011. **10**(8): p. 1233-6.
- 606 96. Prebet, T., et al., *The cell polarity PTK7 receptor acts as a modulator of the*
607 *chemotherapeutic response in acute myeloid leukemia and impairs clinical outcome*.
608 *Blood*, 2010. **116**(13): p. 2315-23.
- 609 97. Jiang, G., et al., *PTK7: a new biomarker for immunophenotypic characterization of*
610 *maturing T cells and T cell acute lymphoblastic leukemia*. *Leuk Res*, 2012. **36**(11): p.
611 1347-53.
- 612 98. Kaucka, M., et al., *The planar cell polarity pathway drives pathogenesis of chronic*
613 *lymphocytic leukemia by the regulation of B-lymphocyte migration*. *Cancer Res*, 2013.
614 **73**(5): p. 1491-501.
- 615 99. Janovska, P., et al., *Autocrine Signaling by Wnt-5a Deregulates Chemotaxis of*
616 *Leukemic Cells and Predicts Clinical Outcome in Chronic Lymphocytic Leukemia*.
617 *Clin Cancer Res*, 2016. **22**(2): p. 459-69.
- 618 100. Yu, J., et al., *Wnt5a induces ROR1/ROR2 heterooligomerization to enhance leukemia*
619 *chemotaxis and proliferation*. *J Clin Invest*, 2016. **126**(2): p. 585-98.
- 620 101. Daneshmanesh, A.H., et al., *Monoclonal antibodies against ROR1 induce apoptosis of*
621 *chronic lymphocytic leukemia (CLL) cells*. *Leukemia*, 2012. **26**(6): p. 1348-55.
- 622 102. Linke, F., et al., *Microenvironmental interactions between endothelial and lymphoma*
623 *cells: a role for the canonical WNT pathway in Hodgkin lymphoma*. *Leukemia*, 2016.
- 624 103. Sun, Y., et al., *Treatment-induced damage to the tumor microenvironment promotes*
625 *prostate cancer therapy resistance through WNT16B*. *Nat Med*, 2012. **18**(9): p. 1359-
626 68.
- 627 104. Stanganello, E. and S. Scholpp, *Role of cytonemes in Wnt transport*. *J Cell Sci*, 2016.
628 **129**(4): p. 665-72.
- 629 105. Desrochers, L.M., M.A. Antonyak, and R.A. Cerione, *Extracellular Vesicles:*
630 *Satellites of Information Transfer in Cancer and Stem Cell Biology*. *Dev Cell*, 2016.
631 **37**(4): p. 301-9.
- 632 106. Ekstrom, E.J., et al., *WNT5A induces release of exosomes containing pro-angiogenic*
633 *and immunosuppressive factors from malignant melanoma cells*. *Mol Cancer*, 2014.
634 **13**: p. 88.

- 635 107. O'Connell, M.P., et al., *Hypoxia induces phenotypic plasticity and therapy resistance*
636 *in melanoma via the tyrosine kinase receptors ROR1 and ROR2*. *Cancer Discov*, 2013.
637 **3**(12): p. 1378-93.
- 638 108. Ataseven, B., et al., *PTK7 expression in triple-negative breast cancer*. *Anticancer Res*,
639 2013. **33**(9): p. 3759-63.
- 640 109. Miyamoto, D.T., et al., *RNA-Seq of single prostate CTCs implicates noncanonical Wnt*
641 *signaling in antiandrogen resistance*. *Science*, 2015. **349**(6254): p. 1351-6.
- 642 110. Safholm, A., et al., *The Wnt-5a-derived hexapeptide Foxy-5 inhibits breast cancer*
643 *metastasis in vivo by targeting cell motility*. *Clin Cancer Res*, 2008. **14**(20): p. 6556-
644 63.
- 645 111. Jonsson, M., et al., *Loss of Wnt-5a protein is associated with early relapse in invasive*
646 *ductal breast carcinomas*. *Cancer Res*, 2002. **62**(2): p. 409-16.
- 647 112. Pheesse, T., D. Flanagan, and E. Vincan, *Frizzled7: A Promising Achilles' Heel for*
648 *Targeting the Wnt Receptor Complex to Treat Cancer*. *Cancers (Basel)*, 2016. **8**(5).
- 649 113. Steinhart, Z., et al., *A CRISPR screen reveals a WNT7B-FZD5 signaling circuit as a*
650 *therapeutic opportunity in pancreatic cancer*. *bioRxiv*, 2016.
- 651 114. Masuda, M., et al., *TNIK inhibition abrogates colorectal cancer stemness*. *Nat*
652 *Commun*, 2016. **7**: p. 12586.
- 653 115. Katsuno, Y., S. Lamouille, and R. Derynck, *TGF-beta signaling and epithelial-*
654 *mesenchymal transition in cancer progression*. *Curr Opin Oncol*, 2013. **25**(1): p. 76-
655 84.
- 656 116. Wang, L., et al., *Somatic mutation as a mechanism of Wnt/beta-catenin pathway*
657 *activation in CLL*. *Blood*, 2014. **124**(7): p. 1089-98.
- 658 117. Qin, H.D., et al., *Genomic Characterization of Esophageal Squamous Cell Carcinoma*
659 *Reveals Critical Genes Underlying Tumorigenesis and Poor Prognosis*. *Am J Hum*
660 *Genet*, 2016. **98**(4): p. 709-27.

661

662

663

664 **FIGURE 1: Wnt signaling pathway and cancer progression**

665 **A.** Wnts bind either to Frizzled receptors or to co-receptors leading to activation of diverse
666 intracellular signaling pathways including Wnt/Ca²⁺ or Wnt/ β -catenin and Wnt/PCP which
667 acts through the activation of small G-proteins such as Rho, Rac and Cdc42. Signaling
668 molecules with unknown function in Wnt signaling are in light green.

669 **B. Top panel. Development and progression of epithelium-derived cancer.**

670 After transformation of the cell of origin (green) (a.), cancer stem cells (red) start to
671 proliferate (b.). Cells escape from the site of the primary tumour after gaining cell motility
672 and invasive abilities (c.). Circulating stem cells (red) found in the bloodstream and the
673 lymphatic system invade distal organs and prime sites of metastasis by activating fibroblasts
674 (e.). Some cells can resist to chemotherapy and contribute to patient relapse (f.).

675 **Bottom panel. Contribution of Wnt/ β -catenin and Wnt/PCP signaling in the progression**
676 **of cancer disease.** Wnt/ β -catenin signaling occurs at the early stage of cancer progression
677 providing proliferative cues to cells. Wnt/ β -catenin signaling can be inhibited by components
678 of Wnt/PCP signaling. During cancer progression, a shift of Wnt signaling occurs: Wnt/PCP
679 signaling takes over and contributes to cancer progression by increasing cell motility,
680 invasion, priming metastasis niche and resistance to therapy.

681

682 **FIGURE 2: Protein composition at cell surface orients Wnt signaling**

683 Depending on a particular cellular context (A or B), a given Wnt binds to Frizzled and its co-
684 receptors and activates downstream signaling pathways leading to A or B signaling.

685

686 **Acknowledgments**

687 We would like to sincerely apologize to our colleagues whose contributions were not cited in
688 this review due to manuscript length limitation. The authors wish to thank Eric Bailly,

689 Stéphane Angers and Valerie Ferrier for critical review of the manuscript. JP Borg's lab is
690 funded by La Ligue Nationale Contre le Cancer (Label Ligue J.P.B.), Fondation de France
691 (post-doctoral fellowship to A.M.D.), Fondation ARC pour la Recherche sur le Cancer, Ruban
692 Rose and SIRIC (INCa-DGOS-Inserm 6038, fellowship to A.M.D.). JPB is a scholar of
693 Institut Universitaire de France.
694

Table 1: Deregulation of non-canonical Wnt/PCP signaling components in cancer

Type of cancer	Name of the genes	Features	References
<i>Breast</i>			
	WNT-5A	Increased tumorigenesis	Lejeune S et al., 1995; MacMillan, C.D., et al.,2014
	WNT-11	Increased tumorigenesis	Avgustinova et al., 2016
	WNT-7A	Increased tumorigenesis	Luga V et al., 2012
	FRIZZLED-7	Increased tumorigenesis	Yang et al., 2011
	VANGL-1	Increased tumorigenesis	Anastas et al., 2012
	VANGL-2	Increased tumorigenesis	Purivajessinghe et al., 2016
	SCRIBBLE	Increased tumorigenesis	Anastas et al., 2012
	PRICKLE-1	Increased tumorigenesis	Daulat et al., 2016
	FRIZZLED-2	Increased tumorigenesis	Gujral et al., 2014
	PTK-7	Increased tumorigenesis	Gärtner et al., 2014
	ROR2	Increased tumorigenesis	Henry et al., 2015
	PTK7	Increased resistance to therapy	Ataseven et al., 2013
<i>Ovarian</i>			
	FRIZZLED-7	Increased tumorigenesis	Asad et al., 2014
<i>Squamous carcinoma</i>			
	WNT-5A	Increased tumorigenesis	Taki et al., 2003
	VANGL-1	Increased tumorigenesis	Qin et al., 2016
<i>Neuroblastoma</i>			
	VANGL-2	Decreased tumorigenesis	Dyberg et al., 2016
	PRICKLE-1	Decreased tumorigenesis	Dyberg et al., 2016
<i>Melanoma</i>			
	WNT-5A	Increased tumorigenesis	Dissanyake et al., 2007
	WNT-5A	Increased tumorigenesis	Weeraratna et al., 2002
	WNT-5A	Increased tumorigenesis	Da Forno et al., 2008
	WNT-5A	Increased resistance to therapy	Anastas et al., 2014
	FRIZZLED-7	Increased tumorigenesis	Tiwary et al., Plos One 2016
	FRIZZLED-7	Increased resistance to therapy	Anastas et al., JCI 2014
	SFRP3	Methylation, loss of expression.	Ekström et al., Plos One 2011

		Decreased tumorigenesis	
	FRIZZLED-5	Increased tumorigenesis	Weeraratna et al., 2002
	ROR2	Increased tumorigenesis	O'Connell et al., Oncogene 2010
	ROR1	Increased tumorigenesis	O'Connell et al., Cancer Discovery 2013
<hr/>			
<i>Colorectal</i>	PTK7	Increased tumorigenesis	Lhoumeau et al., Plos One 2015
	ROR2	Increased tumorigenesis	Mei et al., BBRC 2014
	WNT-5A	Tumor suppressor	Cheng et al., J Cell Physiology 2014
	WNT-5A	Increased tumorigenesis	Bakker et al., 2013
<hr/>			
<i>Gastric cancer</i>	WNT-5A	Increased tumorigenesis	Kurayoshi et al., 2006
<hr/>			
<i>Pancreas</i>	FRIZZLED-5	Increased tumorigenesis	Steinhart et al., Biorxiv.org
	FRIZZLED-4	Increased tumorigenesis	Gupta et al., 2010
	WNT-2	Increased tumorigenesis	Yu et al. 2012
	WNT-5A	Increased resistance to therapy	Miyamoto et al., 2015
<hr/>			
<i>Thyroid</i>	WNT-5A	Tumour suppressor	Kremenevskaja et al., 2005
<hr/>			
<i>Leukemia</i>			
<i>CLL</i>			
	PRICKLE1	Increased tumorigenesis	Kaucka et al., 2013
	VANGL2	Increased tumorigenesis	Kaucka et al., 2013
	CELSR1	Increased tumorigenesis	Kaucka et al., 2013
	Frizzled-3	Increased tumorigenesis	Kaucka et al., 2013
	Frizzled-7	Increased tumorigenesis	Kaucka et al., 2013
	Dishevelled 2	Increased tumorigenesis	Kaucka et al., 2013
	Dishevelled 3	Increased tumorigenesis	Kaucka et al., 2013
	Casein kinase 1	Increased tumorigenesis	Kaucka et al., 2013
	ROR1	Increased tumorigenesis	Janovska et al., 2016
	WNT-5A	Increased tumorigenesis	Kaucka et al., 2013
		Increased tumorigenesis	Yu et al., 2016
	WNT-5A	Tumor suppressor	Liang, H et al., 2003
<hr/>			
<i>AML</i>	PTK7	Increased tumorigenesis	Prebet et al., Blood 2010

Table 2: Clinical trials of compounds targeting Wnt/PCP proteins

<i>Target genes</i>	<i>Compound</i>	<i>Cancer</i>	<i>Trial number</i>	<i>Company</i>	<i>Description</i>	<i>Trial phase</i>
<i>WNT-5A</i>	Foxy-5	Breast, Colon and Prostate Cancer	NCT02655 952	WntResearch AB	Establishment of the recommended dose for Phase-II clinical trial	Phase-I completed
<i>Inhibitor of Porcupine</i>	WNT974	Colorectal Cancer with BRAF mutation	NCT02278 133	Array BioPharma / Novartis	In combination with LGX818 (RAF inhibitor) and Cetuximib	Phase-I (WNT974); Phase-II (LGX818)
<i>Inhibitor of Porcupine</i>	WNT974	Squamous Cell Carcinoma, Head And Neck	NCT02649 530	Novartis		Phase-II
<i>PTK7</i>	PF-06647020	Advanced solid tumors	NCT02222 922	Pfizer	In combination with fluconazole. The aim of the study is to assess the maximum tolerated dose.	Phase-I
<i>FRIZZLED-10</i>	SYNFRIZZ	Advanced synovial sarcoma	NCT01469 975	OncoTherapy Science, Inc.	Assesment of biodistribution and tumour uptake	Phase-I completed
<i>FRIZZLED-7</i>	OMP18R5 (Vantictumab)	Non-small cell lung cancer	NCT01957 007	OncoMed Pharmaceuticals, Inc.	In combination with Docetaxel	Phase-I
<i>FRIZZLED-7</i>	OMP18R5 (Vantictumab)	Metastatic Breast cancer	NCT01973 309	OncoMed Pharmaceuticals, Inc.	In combination with Paclitaxel	Phase-I
<i>FRIZZLED-7</i>	OMP18R5 (Vantictumab)	Pancreatic cancer	NCT02005 315	OncoMed Pharmaceuticals, Inc.	In combination with Nab-Paclitaxel and Gemcitabine	Phase-I
<i>FRIZZLED-8</i>	OMP54F28	Ovarian cancer	NCT02092 363	OncoMed Pharmaceuticals, Inc.	In combination with Paclitaxel and Carboplatin	Phase-I
<i>FRIZZLED-8</i>	OMP54F28	Pancreatic cancer	NCT02050	OncoMed	In combination with Nab-	Phase-I

			178	Pharmaceuticals, Inc.	Paclitaxel and Gemcitabine	
<i>FRIZZLED-8</i>	OMP54F28	Hepatocellular Cancer	NCT02069	OncoMed	In combination with	Phase-I
			145	Pharmaceuticals, Inc.	Sorafenib	

Outstanding questions box

- How does the Wnt/PCP pathway function in normal and cancer cells?
- What are the mechanisms that localize and regulate Wnt/PCP molecules at the plasma membrane?
- What is the best readout to monitor Wnt/PCP activation in normal and cancer cells?
- What are the mechanisms that up-regulate expression of Wnt/PCP molecules in cancer cells?
- Are Wnt ligands and receptors mandatory to trigger abnormal activation of Wnt/PCP signaling in cancer cells?
- Which Wnt/PCP components should be targeted in priority in tumors and how?
- Is potential upregulation of canonical Wnt pathway activity upon inhibition of the Wnt/PCP pathway a problem?
- Is it possible to anticipate the side effects of therapeutic inhibition of Wnt/PCP pathway?

FIGURE 1:

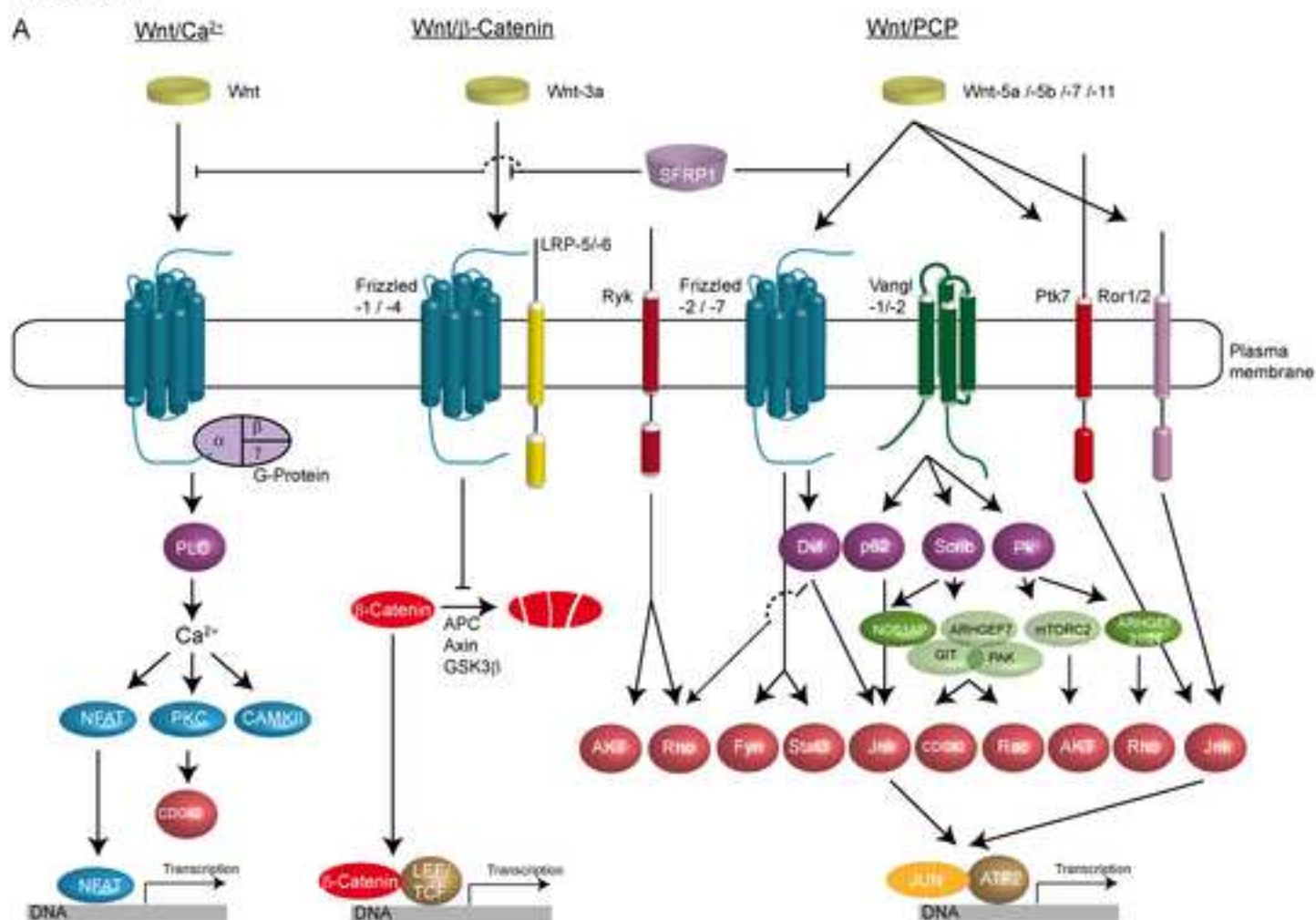
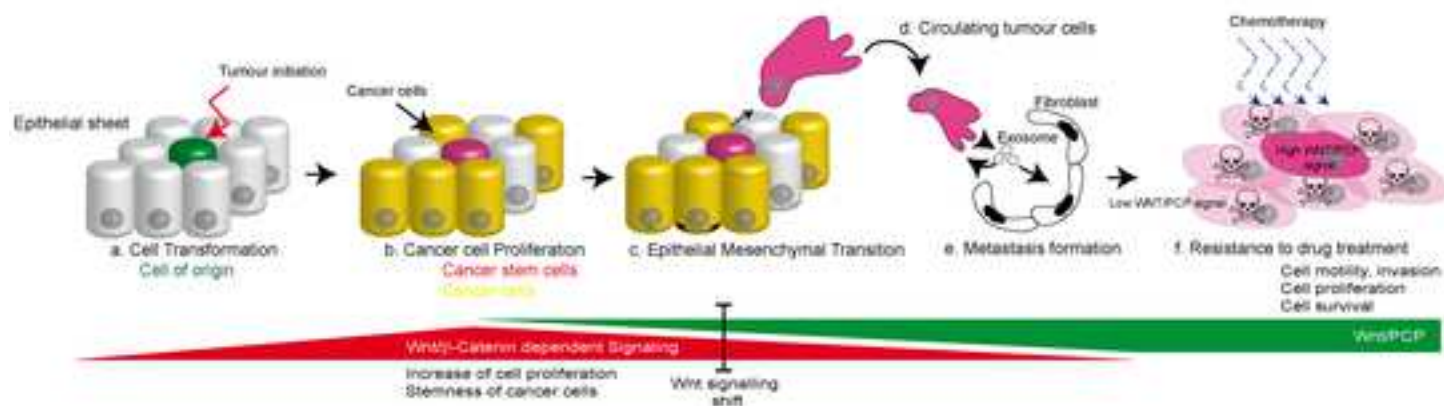
**B**

FIGURE 2:

