IUPHAR/BPS Guide to Pharmacology CITE
https://doi.org/10.2218/gtopdb/F25/2025.3

Class Frizzled GPCRs in GtoPdb v.2025.3

Elisa Arthofer[1], Jacomijn Dijksterhuis[2], Lukas Grätz[2], Belma Hot[2], Julia Kinsolving[2], Paweł Kozielewicz[2], Matthias Lauth[3], Jessica Olofsson[2], Julian Petersen[2], Tilman Polonio[2], Gunnar Schulte[2], Katerina Strakova[2], Jana Valnohova[2] and Shane Wright[2]

1. National Institute of Child Health and Human Development, USA
2. Karolinska Institutet, Sweden
3. Philipps-Universität Marburg, Germany

Abstract

Receptors of the Class Frizzled (FZD, **nomenclature as agreed by the NC-IUPHAR subcommittee on the Class Frizzled GPCRs [184]**), are GPCRs highly conserved across species and were originally identified in *Drosophila* [21]. While SMO shows structural resemblance to the 10 FZDs, it is functionally separated as it is involved in Hedgehog signaling [184]. SMO exerts its effects by activating heterotrimeric G proteins or stabilization of GLI by sequestering catalytic PKA subunits [191, 6, 62]. While SMO itself is bound by sterols and oxysterols [28, 96], FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins with fundamental functions in ontogeny and tissue homeostasis. FZD signaling was initially divided into two pathways, being either dependent on the accumulation of the transcription regulator β-catenin or being β-catenin-independent (often referred to as canonical *vs.* non-canonical WNT/FZD signaling, respectively). Nevertheless, it makes pharmacologically more sense to define downstream signaling by transducer coupling to either DVL or heterotrimeric G proteins [185]. WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors *LRP5* (O75197) and *LRP6* (O75581), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β-catenin and subsequently its translocation to the nucleus. β-catenin, in turn, modifies gene transcription by interacting with TCF/LEF transcription factors. WNT/β-catenin-dependent signalling can also be activated by FZD subtype-specific WNT surrogates [142]. β-catenin-independent FZD signalling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the activation of heterotrimeric G proteins [35, 188, 159], the elevation of intracellular calcium [194], activation of cGMP-specific PDE6 [2] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [61]. Novel resonance energy transfer-based tools have allowed the study of the GPCR-like nature of FZDs in greater detail. Upon ligand stimulation, FZDs undergo conformational changes and signal *via* heterotrimeric G proteins [248, 249, 110, 183, 108, 56, 13]. Furthermore, the phosphoprotein Dishevelled constitutes a key transducer in WNT/FZD signaling towards planar-cell-polarity-like pathways. Importantly, FZDs adopt distinct conformational landscapes that regulate pathway selection [249, 54]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [24], as well as for β-catenin-dependent [15] and -independent [93, 16] signalling. The pattern of cell signalling is complicated by the presence of additional ligands, which can enhance or inhibit FZD signalling (secreted Frizzled-related proteins (sFRP), Wnt-inhibitory factor (WIF), sclerostin or Dickkopf (DKK)), as well as modulatory (co)-receptors with Ryk, ROR1, ROR2 and PTK7, which may also function as independent signaling proteins. An important FZD_4-selective non-WNT agonist is the norrin cysteine knot protein, which is a key player in FZD_4-mediated vascularization for example in the retina and which is functionally related to familial exudative vitreoretinopathy (FEVR).

Contents

This is a citation summary for Class Frizzled GPCRs in the Guide to Pharmacology database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

GtoPdb is an expert-driven guide to pharmacological targets and the substances that act on them.

GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts. For further details see [17].

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

Class Frizzled GPCRs
https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=25
Introduction to Class Frizzled GPCRs
https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=25

Receptors

- FZD_1
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=229
- FZD_2
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=230
- FZD_3
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=231
- FZD_4
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=232
- FZD_5
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=233
- FZD_6
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=234
- FZD_7
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=235
- FZD_8
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=236
- FZD_9
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=237
- FZD_{10}
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=238
- SMO
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=239

References

1. Acevedo VD, Gangula RD, Freeman KW, Li R, Zhang Y, Wang F, Ayala GE, Peterson LE, Ittmann M and Spencer DM. (2007) Inducible FGFR-1 activation leads to irreversible prostate adenocarcinoma and an epithelial-to-mesenchymal transition. *Cancer Cell* **12**: 559-71 [PMID:18068632]
2. Ahumada A, Slusarski DC, Liu X, Moon RT, Malbon CC and Wang HY. (2002) Signaling of rat Frizzled-2 through phosphodiesterase and cyclic GMP. *Science* **298**: 2006-10 [PMID:12471263]
3. Albers J, Schulze J, Beil FT, Gebauer M, Baranowsky A, Keller J, Marshall RP, Wintges K, Friedrich FW and Priemel M *et al.*. (2011) Control of bone formation by the serpentine receptor Frizzled-9. *J Cell Biol* **192**: 1057-72 [PMID:21402791]
4. Angers S and Moon RT. (2009) Proximal events in Wnt signal transduction. *Nat Rev Mol Cell Biol* **10**: 468-77 [PMID:19536106]
5. Arthofer E, Hot B, Petersen J, Strakova K, Jäger S, Grundmann M, Kostenis E, Gutkind JS and Schulte G. (2016) WNT Stimulation Dissociates a Frizzled 4 Inactive-State Complex with Gα12/13. *Mol Pharmacol* **90**: 447-59 [PMID:27458145]
6. Arveseth CD, Happ JT, Hedeen DS, Zhu JF, Capener JL, Klatt Shaw D, Deshpande I, Liang J, Xu J and Stubben SL *et al.*. (2021) Smoothened transduces Hedgehog signals via activity-dependent sequestration of PKA catalytic subunits. *PLoS Biol* **19**: e3001191 [PMID:33886552]
7. AstraZeneca. AZD8542. http://openinnovation.astrazeneca.com/what-we-offer/compound/azd8542/. Accessed on 12/09/2014.
8. Bao X, Peng Y, Lu X, Yang J, Zhao W, Tan W and Dong X. (2016) Synthesis and evaluation of novel benzylphthalazine derivatives as hedgehog signaling pathway inhibitors. *Bioorg Med Chem Lett* **26**: 3048-3051 [PMID:27180012]

9. Bengochea A, de Souza MM, Lefrançois L, Le Roux E, Galy O, Chemin I, Kim M, Wands JR, Trepo C and Hainaut P *et al.*. (2008) Common dysregulation of Wnt/Frizzled receptor elements in human hepatocellular carcinoma. *Br J Cancer* **99**: 143-50 [PMID:18577996]
10. Bethge N, Honne H, Hilden V, Trøen G, Eknæs M, Liestøl K, Holte H, Delabie J, Smeland EB and Lind GE. (2013) Identification of highly methylated genes across various types of B-cell non-hodgkin lymphoma. *PLoS ONE* **8**: e79602 [PMID:24260260]
11. Borello U, Berarducci B, Murphy P, Bajard L, Buffa V, Piccolo S, Buckingham M and Cossu G. (2006) The Wnt/beta-catenin pathway regulates Gli-mediated Myf5 expression during somitogenesis. *Development* **133**: 3723-32 [PMID:16936075]
12. Borello U, Buffa V, Sonnino C, Melchionna R, Vivarelli E and Cossu G. (1999) Differential expression of the Wnt putative receptors Frizzled during mouse somitogenesis. *Mech Dev* **89**: 173-7 [PMID:10559494]
13. Bowin CF, Kozielewicz P, Grätz L, Kowalski-Jahn M, Schihada H and Schulte G. (2023) WNT stimulation induces dynamic conformational changes in the Frizzled-Dishevelled interaction. *Sci Signal* **16**: eabo4974 [PMID:37014927]
14. Bravo DT, Yang YL, Kuchenbecker K, Hung MS, Xu Z, Jablons DM and You L. (2013) Frizzled-8 receptor is activated by the Wnt-2 ligand in non-small cell lung cancer. *BMC Cancer* **13**: 316 [PMID:23815780]
15. Bryja V, Gradl D, Schambony A, Arenas E and Schulte G. (2007) Beta-arrestin is a necessary component of Wnt/beta-catenin signaling in vitro and in vivo. *Proc Natl Acad Sci USA* **104**: 6690-5 [PMID:17426148]
16. Bryja V, Schambony A, Cajánek L, Dominguez I, Arenas E and Schulte G. (2008) Beta-arrestin and casein kinase 1/2 define distinct branches of non-canonical WNT signalling pathways. *EMBO Rep* **9**: 1244-50 [PMID:18953287]
17. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
18. Byrne EFX, Sircar R, Miller PS, Hedger G, Luchetti G, Nachtergaele S, Tully MD, Mydock-McGrane L, Covey DF and Rambo RP *et al.*. (2016) Structural basis of Smoothened regulation by its extracellular domains. *Nature* **535**: 517-522 [PMID:27437577]
19. Canny CL and Oliver GL. (1976) Fluorescein angiographic findings in familial exudative vitreoretinopathy. *Arch Ophthalmol* **94**: 1114-20 [PMID:947162]
20. Carmon KS and Loose DS. (2008) Secreted frizzled-related protein 4 regulates two Wnt7a signaling pathways and inhibits proliferation in endometrial cancer cells. *Mol Cancer Res* **6**: 1017-28 [PMID:18567805]
21. Chan SD, Karpf DB, Fowlkes ME, Hooks M, Bradley MS, Vuong V, Bambino T, Liu MY, Arnaud CD and Strewler GJ *et al.*. (1992) Two homologs of the Drosophila polarity gene frizzled (fz) are widely expressed in mammalian tissues. *J Biol Chem* **267**: 25202-7 [PMID:1334084]
22. Chen JK, Taipale J, Young KE, Maiti T and Beachy PA. (2002) Small molecule modulation of Smoothened activity. *Proc Natl Acad Sci USA* **99**: 14071-6 [PMID:12391318]
23. Chen M, Wang J, Lu J, Bond MC, Ren XR, Lyerly HK, Barak LS and Chen W. (2009) The anti-helminthic niclosamide inhibits Wnt/Frizzled1 signaling. *Biochemistry* **48**: 10267-74 [PMID:19772353]
24. Chen W, Kirkbride KC, How T, Nelson CD, Mo J, Frederick JP, Wang XF, Lefkowitz RJ and Blobe GC. (2003) Beta-arrestin 2 mediates endocytosis of type III TGF-beta receptor and down-regulation of its signaling. *Science* **301**: 1394-7 [PMID:12958365]
25. Chen W, ten Berge D, Brown J, Ahn S, Hu LA, Miller WE, Caron MG, Barak LS, Nusse R and Lefkowitz RJ. (2003) Dishevelled 2 recruits beta-arrestin 2 to mediate Wnt5A-stimulated endocytosis of Frizzled 4. *Science* **301**: 1391-1394 [PMID:12958364]
26. Chien AJ, Conrad WH and Moon RT. (2009) A Wnt survival guide: from flies to human disease. *J Invest Dermatol* **129**: 1614-27 [PMID:19177135]
27. Clevers H and Nusse R. (2012) Wnt/β-catenin signaling and disease. *Cell* **149**: 1192-205 [PMID:22682243]
28. Corcoran RB and Scott MP. (2006) Oxysterols stimulate Sonic hedgehog signal transduction and proliferation of medulloblastoma cells. *Proc Natl Acad Sci USA* **103**: 8408-13 [PMID:16707575]
29. Criswick VG and Schepens CL. (1969) Familial exudative vitreoretinopathy. *Am J Ophthalmol* **68**: 578-94 [PMID:5394449]
30. Dann CE, Hsieh JC, Rattner A, Sharma D, Nathans J and Leahy DJ. (2001) Insights into Wnt binding and signalling from the structures of two Frizzled cysteine-rich domains. *Nature* **412**: 86-90 [PMID:11452312]
31. Daudet N, Ripoll C, Molès JP and Rebillard G. (2002) Expression of members of Wnt and Frizzled gene families in the postnatal rat cochlea. *Brain Res Mol Brain Res* **105**: 98-107 [PMID:12399112]
32. DeAlmeida VI, Miao L, Ernst JA, Koeppen H, Polakis P and Rubinfeld B. (2007) The soluble wnt receptor Frizzled8CRD-hFc inhibits the growth of teratocarcinomas in vivo. *Cancer Res* **67**:

5371-9 [PMID:17545618]
33. Deshpande I, Liang J, Hedeen D, Roberts KJ, Zhang Y, Ha B, Latorraca NR, Faust B, Dror RO and Beachy PA *et al.*. (2019) Smoothened stimulation by membrane sterols drives Hedgehog pathway activity. *Nature* **571**: 284-288 [PMID:31263273]
34. Dickins EM and Salinas PC. (2013) Wnts in action: from synapse formation to synaptic maintenance. *Front Cell Neurosci* **7**: 162 [PMID:24223536]
35. Dijksterhuis JP, Petersen J and Schulte G. (2013) WNT/Frizzled signaling: receptor-ligand selectivity with focus on FZD-G protein signaling and its physiological relevance. *Br J Pharmacol* [PMID:24032637]
36. Dufourcq P, Leroux L, Ezan J, Descamps B, Lamazière JM, Costet P, Basoni C, Moreau C, Deutsch U and Couffinhal T *et al.*. (2008) Regulation of endothelial cell cytoskeletal reorganization by a secreted frizzled-related protein-1 and frizzled 4- and frizzled 7-dependent pathway: role in neovessel formation. *Am J Pathol* **172**: 37-49 [PMID:18156211]
37. Endo Y, Beauchamp E, Woods D, Taylor WG, Toretsky JA, Uren A and Rubin JS. (2008) Wnt-3a and Dickkopf-1 stimulate neurite outgrowth in Ewing tumor cells via a Frizzled3- and c-Jun N-terminal kinase-dependent mechanism. *Mol Cell Biol* **28**: 2368-79 [PMID:18212053]
38. Favre CJ, Mancuso M, Maas K, McLean JW, Baluk P and McDonald DM. (2003) Expression of genes involved in vascular development and angiogenesis in endothelial cells of adult lung. *Am J Physiol Heart Circ Physiol* **285**: H1917-38 [PMID:12842817]
39. Fischer T, Guimera J, Wurst W and Prakash N. (2007) Distinct but redundant expression of the Frizzled Wnt receptor genes at signaling centers of the developing mouse brain. *Neuroscience* **147**: 693-711 [PMID:17582687]
40. Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M and Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]
41. Fröjmark AS, Schuster J, Sobol M, Entesarian M, Kilander MB, Gabrikova D, Nawaz S, Baig SM, Schulte G and Klar J *et al.*. (2011) Mutations in frizzled 6 cause isolated autosomal-recessive nail dysplasia. *Am J Hum Genet* **88**: 852-60 [PMID:21665003]
42. Fujimoto T, Tomizawa M and Yokosuka O. (2009) SiRNA of frizzled-9 suppresses proliferation and motility of hepatoma cells. *Int J Oncol* **35**: 861-6 [PMID:19724923]
43. Fukukawa C, Hanaoka H, Nagayama S, Tsunoda T, Toguchida J, Endo K, Nakamura Y and Katagiri T. (2008) Radioimmunotherapy of human synovial sarcoma using a monoclonal antibody against FZD10. *Cancer Sci* **99**: 432-40 [PMID:18271942]
44. Fukukawa C, Nagayama S, Tsunoda T, Toguchida J, Nakamura Y and Katagiri T. (2009) Activation of the non-canonical Dvl-Rac1-JNK pathway by Frizzled homologue 10 in human synovial sarcoma. *Oncogene* **28**: 1110-20 [PMID:19137009]
45. Gao Y and Wang HY. (2006) Casein kinase 2 Is activated and essential for Wnt/beta-catenin signaling. *J Biol Chem* **281**: 18394-400 [PMID:16672224]
46. Gao Y and Wang HY. (2007) Inositol pentakisphosphate mediates Wnt/beta-catenin signaling. *J Biol Chem* **282**: 26490-502 [PMID:17595165]
47. Gazit A, Yaniv A, Bafico A, Pramila T, Igarashi M, Kitajewski J and Aaronson SA. (1999) Human frizzled 1 interacts with transforming Wnts to transduce a TCF dependent transcriptional response. *Oncogene* **18**: 5959-66 [PMID:10557084]
48. Generoso SF, Giustiniano M, La Regina G, Bottone S, Passacantilli S, Di Maro S, Cassese H, Bruno A, Mallardo M and Dentice M *et al.*. (2015) Pharmacological folding chaperones act as allosteric ligands of Frizzled4. *Nat Chem Biol* **11**: 280-6 [PMID:25751279]
49. Gitter KA, Rothschild H, Waltman DD, Scott B and Azar P. (1978) Dominantly inherited peripheral retinal neovascularization. *Arch Ophthalmol* **96**: 1601-5 [PMID:687201]
50. Golan T, Yaniv A, Bafico A, Liu G and Gazit A. (2004) The human Frizzled 6 (HFz6) acts as a negative regulator of the canonical Wnt. beta-catenin signaling cascade. *J Biol Chem* **279**: 14879-88 [PMID:14747478]
51. Gordon MD and Nusse R. (2006) Wnt signaling: multiple pathways, multiple receptors, and multiple transcription factors. *J Biol Chem* **281**: 22429-22433 [PMID:16793760]
52. Gorojankina T, Hoch L, Faure H, Roudaut H, Traiffort E, Schoenfelder A, Girard N, Mann A, Manetti F and Solinas A *et al.*. (2013) Discovery, molecular and pharmacological characterization of GSA-10, a novel small-molecule positive modulator of Smoothened. *Mol Pharmacol* **83**: 1020-9 [PMID:23448715]
53. Gow J and Oliver GL. (1971) Familial exudative vitreoretinopathy. An expanded view. *Arch Ophthalmol* **86**: 150-5 [PMID:5571414]
54. Grätz L, Kowalski-Jahn M, Scharf MM, Kozielewicz P, Jahn M, Bous J, Lambert NA, Gloriam DE and Schulte G. (2023) Pathway selectivity in Frizzleds is achieved by conserved micro-switches defining pathway-determining, active conformations. *Nat Commun* **14**: 4573 [PMID:37516754]
55. Grätz L, Sajkowska-Kozielewicz JJ, Wesslowski J, Kinsolving J, Bridge LJ, Petzold K, Davidson G, Schulte G and Kozielewicz P. (2024) NanoBiT- and NanoBiT/BRET-based assays allow the analysis of binding kinetics of Wnt-3a to endogenous Frizzled 7 in a colorectal cancer model. *Br*

J Pharmacol **181**: 3819-3835 [PMID:37055379]
56. Grätz L, Voss JH and Schulte G. (2024) Class-Wide Analysis of Frizzled-Dishevelled Interactions Using BRET Biosensors Reveals Functional Differences among Receptor Paralogs. *ACS Sens* **9**: 4626-4636 [PMID:39213612]
57. Gregorieff A, Pinto D, Begthel H, Destrée O, Kielman M and Clevers H. (2005) Expression pattern of Wnt signaling components in the adult intestine. *Gastroenterology* **129**: 626-38 [PMID:16083717]
58. Gregory MA, Phang TL, Neviani P, Alvarez-Calderon F, Eide CA, O'Hare T, Zaberezhnyy V, Williams RT, Druker BJ and Perrotti D *et al*.. (2010) Wnt/Ca2+/NFAT signaling maintains survival of Ph+ leukemia cells upon inhibition of Bcr-Abl. *Cancer Cell* **18**: 74-87 [PMID:20609354]
59. Guo N, Hawkins C and Nathans J. (2004) Frizzled6 controls hair patterning in mice. *Proc Natl Acad Sci USA* **101**: 9277-81 [PMID:15169958]
60. Gurney A, Axelrod F, Bond CJ, Cain J, Chartier C, Donigan L, Fischer M, Chaudhari A, Ji M and Kapoun AM *et al*.. (2012) Wnt pathway inhibition via the targeting of Frizzled receptors results in decreased growth and tumorigenicity of human tumors. *Proc Natl Acad Sci USA* **109**: 11717-22 [PMID:22753465]
61. Hansen C, Howlin J, Tengholm A, Dyachok O, Vogel WF, Nairn AC, Greengard P and Andersson T. (2009) Wnt-5a-induced phosphorylation of DARPP-32 inhibits breast cancer cell migration in a CREB-dependent manner. *J Biol Chem* **284**: 27533-43 [PMID:19651774]
62. Happ JT, Arveseth CD, Bruystens J, Bertinetti D, Nelson IB, Olivieri C, Zhang J, Hedeen DS, Zhu JF and Capener JL *et al*.. (2022) A PKA inhibitor motif within SMOOTHENED controls Hedgehog signal transduction. *Nat Struct Mol Biol* **29**: 990-999 [PMID:36202993]
63. Heinonen KM, Vanegas JR, Lew D, Krosl J and Perreault C. (2011) Wnt4 enhances murine hematopoietic progenitor cell expansion through a planar cell polarity-like pathway. *PLoS ONE* **6**: e19279 [PMID:21541287]
64. Hendrickx M and Leyns L. (2008) Non-conventional Frizzled ligands and Wnt receptors. *Dev Growth Differ* **50**: 229-43 [PMID:18366384]
65. Hoch L, Faure H, Roudaut H, Schoenfelder A, Mann A, Girard N, Bihannic L, Ayrault O, Petricci E and Taddei M *et al*.. (2015) MRT-92 inhibits Hedgehog signaling by blocking overlapping binding sites in the transmembrane domain of the Smoothened receptor. *FASEB J* **29**: 1817-29 [PMID:25636740]
66. Holcombe RF, Marsh JL, Waterman ML, Lin F, Milovanovic T and Truong T. (2002) Expression of Wnt ligands and Frizzled receptors in colonic mucosa and in colon carcinoma. *MP, Mol Pathol* **55**: 220-6 [PMID:12147710]
67. Hot B, Valnohova J, Arthofer E, Simon K, Shin J, Uhlén M, Kostenis E, Mulder J and Schulte G. (2017) FZD10-Gα13 signalling axis points to a role of FZD10 in CNS angiogenesis. *Cell Signal* **32**: 93-103 [PMID:28126591]
68. Hsieh JC, Rattner A, Smallwood PM and Nathans J. (1999) Biochemical characterization of Wnt-frizzled interactions using a soluble, biologically active vertebrate Wnt protein. *Proc Natl Acad Sci USA* **96**: 3546-51 [PMID:10097073]
69. Hsieh M, Boerboom D, Shimada M, Lo Y, Parlow AF, Luhmann UF, Berger W and Richards JS. (2005) Mice null for Frizzled4 (Fzd4-/-) are infertile and exhibit impaired corpora lutea formation and function. *Biol Reprod* **73**: 1135-46 [PMID:16093361]
70. Huang P, Zheng S, Wierbowski BM, Kim Y, Nedelcu D, Aravena L, Liu J, Kruse AC and Salic A. (2018) Structural Basis of Smoothened Activation in Hedgehog Signaling. *Cell* **174**: 312-324.e16 [PMID:29804838]
71. Hughes KR, Sablitzky F and Mahida YR. (2011) Expression profiling of Wnt family of genes in normal and inflammatory bowel disease primary human intestinal myofibroblasts and normal human colonic crypt epithelial cells. *Inflamm Bowel Dis* **17**: 213-20 [PMID:20848536]
72. Ide M, Muratake T, Yamada K, Iwayama-Shigeno Y, Iwamoto K, Takao H, Toyota T, Kaneko N, Minabe Y and Nakamura K *et al*.. (2004) Genetic and expression analyses of FZD3 in schizophrenia. *Biol Psychiatry* **56**: 462-5 [PMID:15364045]
73. Inestrosa NC and Arenas E. (2010) Emerging roles of Wnts in the adult nervous system. *Nat Rev Neurosci* **11**: 77-86 [PMID:20010950]
74. Ishikawa T, Tamai Y, Zorn AM, Yoshida H, Seldin MF, Nishikawa S and Taketo MM. (2001) Mouse Wnt receptor gene Fzd5 is essential for yolk sac and placental angiogenesis. *Development* **128**: 25-33 [PMID:11092808]
75. Janda CY, Waghray D, Levin AM, Thomas C and Garcia KC. (2012) Structural basis of Wnt recognition by Frizzled. *Science* **337**: 59-64 [PMID:22653731]
76. Janssens N, Andries L, Janicot M, Perera T and Bakker A. (2004) Alteration of frizzled expression in renal cell carcinoma. *Tumour Biol* **25**: 161-71 [PMID:15557753]
77. Jiang Y, Dunbar A, Gondek LP, Mohan S, Rataul M, O'Keefe C, Sekeres M, Saunthararajah Y and Maciejewski JP. (2009) Aberrant DNA methylation is a dominant mechanism in MDS progression to AML. *Blood* **113**: 1315-25 [PMID:18832655]

78. Kang G, Yue W, Zhang J, Huebner M, Zhang H, Ruan Y, Lu T, Ling Y, Zuo Y and Zhang D. (2008) Two-stage designs to identify the effects of SNP combinations on complex diseases. *J Hum Genet* **53**: 739-46 [PMID:18584117]
79. Karasawa T, Yokokura H, Kitajewski J and Lombroso PJ. (2002) Frizzled-9 is activated by Wnt-2 and functions in Wnt/beta -catenin signaling. *J Biol Chem* **277**: 37479-86 [PMID:12138115]
80. Kasai K, Takahashi M, Osumi N, Sinnarajah S, Takeo T, Ikeda H, Kehrl JH, Itoh G and Arnheiter H. (2004) The G12 family of heterotrimeric G proteins and Rho GTPase mediate Sonic hedgehog signalling. *Genes Cells* **9**: 49-58 [PMID:14723707]
81. Katanaev VL and Buestorf S. Frizzled Proteins are *bona fide* G Protein-Coupled Receptors. http://precedings.nature.com/documents/2765/version/1. Accessed on 31/07/2014.
82. Katsu T, Ujike H, Nakano T, Tanaka Y, Nomura A, Nakata K, Takaki M, Sakai A, Uchida N and Imamura T *et al.*. (2003) The human frizzled-3 (FZD3) gene on chromosome 8p21, a receptor gene for Wnt ligands, is associated with the susceptibility to schizophrenia. *Neurosci Lett* **353**: 53-6 [PMID:14642436]
83. Kaucká M, Plevová K, Pavlová S, Janovská P, Mishra A, Verner J, Procházková J, Krejcí P, Kotasková J and Ovesná P *et al.*. (2013) The planar cell polarity pathway drives pathogenesis of chronic lymphocytic leukemia by the regulation of B-lymphocyte migration. *Cancer Res* **73**: 1491-501 [PMID:23338609]
84. Kawasaki A, Torii K, Yamashita Y, Nishizawa K, Kanekura K, Katada M, Ito M, Nishimoto I, Terashita K and Aiso S *et al.*. (2007) Wnt5a promotes adhesion of human dermal fibroblasts by triggering a phosphatidylinositol-3 kinase/Akt signal. *Cell Signal* **19**: 2498-506 [PMID:17804197]
85. Kaykas A, Yang-Snyder J, Héroux M, Shah KV, Bouvier M and Moon RT. (2004) Mutant Frizzled 4 associated with vitreoretinopathy traps wild-type Frizzled in the endoplasmic reticulum by oligomerization. *Nat Cell Biol* **6**: 52-58 [PMID:14688793]
86. Keay SK, Szekely Z, Conrads TP, Veenstra TD, Barchi Jr JJ, Zhang CO, Koch KR and Michejda CJ. (2004) An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. *Proc Natl Acad Sci USA* **101**: 11803-8 [PMID:15282374]
87. Kemp CR, Willems E, Wawrzak D, Hendrickx M, Agbor Agbor T and Leyns L. (2007) Expression of Frizzled5, Frizzled7, and Frizzled10 during early mouse development and interactions with canonical Wnt signaling. *Dev Dyn* **236**: 2011-9 [PMID:17576136]
88. Khan NI, Bradstock KF and Bendall LJ. (2007) Activation of Wnt/beta-catenin pathway mediates growth and survival in B-cell progenitor acute lymphoblastic leukaemia. *Br J Haematol* **138**: 338-48 [PMID:17614820]
89. Kikuchi A, Yamamoto H and Kishida S. (2007) Multiplicity of the interactions of Wnt proteins and their receptors. *Cell Signal* **19**: 659-71 [PMID:17188462]
90. Kilander MB, Dahlström J and Schulte G. (2014) Assessment of Frizzled 6 membrane mobility by FRAP supports G protein coupling and reveals WNT-Frizzled selectivity. *Cell Signal* **26**: 1943-9 [PMID:24873871]
91. Kilander MB, Dijksterhuis JP, Ganji RS, Bryja V and Schulte G. (2011) WNT-5A stimulates the GDP/GTP exchange at pertussis toxin-sensitive heterotrimeric G proteins. *Cell Signal* **23**: 550-4 [PMID:21070854]
92. Kilander MB, Petersen J, Andressen KW, Ganji RS, Levy FO, Schuster J, Dahl N, Bryja V and Schulte G. (2014) Disheveled regulates precoupling of heterotrimeric G proteins to Frizzled 6. *FASEB J* **28**: 2293-305 [PMID:24500924]
93. Kim GH and Han JK. (2007) Essential role for beta-arrestin 2 in the regulation of Xenopus convergent extension movements. *EMBO J* **26**: 2513-26 [PMID:17476309]
94. Kim M, Lee HC, Tsedensodnom O, Hartley R, Lim YS, Yu E, Merle P and Wands JR. (2008) Functional interaction between Wnt3 and Frizzled-7 leads to activation of the Wnt/beta-catenin signaling pathway in hepatocellular carcinoma cells. *J Hepatol* **48**: 780-91 [PMID:18313787]
95. King TD, Zhang W, Suto MJ and Li Y. (2012) Frizzled7 as an emerging target for cancer therapy. *Cell Signal* **24**: 846-51 [PMID:22182510]
96. Kinnebrew M, Woolley RE, Ansell TB, Byrne EFX, Frigui S, Luchetti G, Sircar R, Nachtergaele S, Mydock-McGrane L and Krishnan K *et al.*. (2022) Patched 1 regulates Smoothened by controlling sterol binding to its extracellular cysteine-rich domain. *Sci Adv* **8**: eabm5563 [PMID:35658032]
97. Kinsolving J, Bous J, Kozielewicz P, Košenina S, Shekhani R, Grätz L, Masuyer G, Wang Y, Stenmark P and Dong M *et al.*. (2024) Structural and functional insight into the interaction of Clostridioides difficile toxin B and FZD_7. *Cell Rep* **43**: 113727 [PMID:38308843]
98. Kinsolving J, Grätz L, Voss JH, Löw B, Shorter E, Jude B, Lanner JT, Löber S, Gmeiner P and Schulte G. (2024) A Putative Frizzled 7-Targeting Compound Acts as a Firefly Luciferase Inhibitor. *J Med Chem* **67**: 22332-22341 [PMID:39670643]
99. Kirikoshi H, Koike J, Sagara N, Saitoh T, Tokuhara M, Tanaka K, Sekihara H, Hirai M and Katoh M. (2000) Molecular cloning and genomic structure of human frizzled-3 at chromosome 8p21. *Biochem Biophys Res Commun* **271**: 8-14 [PMID:10777673]
100. Kirikoshi H, Sagara N, Koike J, Tanaka K, Sekihara H, Hirai M and Katoh M. (1999) Molecular

cloning and characterization of human Frizzled-4 on chromosome 11q14-q21. *Biochem Biophys Res Commun* **264**: 955-61 [PMID:10544037]
101. Kirikoshi H, Sekihara H and Katoh M. (2001) Up-regulation of Frizzled-7 (FZD7) in human gastric cancer. *Int J Oncol* **19**: 111-5 [PMID:11408930]
102. Klein D, Demory A, Peyre F, Kroll J, Augustin HG, Helfrich W, Kzhyshkowska J, Schledzewski K, Arnold B and Goerdt S. (2008) Wnt2 acts as a cell type-specific, autocrine growth factor in rat hepatic sinusoidal endothelial cells cross-stimulating the VEGF pathway. *Hepatology* **47**: 1018-31 [PMID:18302287]
103. Kolben T, Peröbner I, Fernsebner K, Lechner F, Geissler C, Ruiz-Heinrich L, Capovilla S, Jochum M and Neth P. (2012) Dissecting the impact of Frizzled receptors in Wnt/β-catenin signaling of human mesenchymal stem cells. *Biol Chem* **393**: 1433-47 [PMID:23152409]
104. Kondo H, Hayashi H, Oshima K, Tahira T and Hayashi K. (2003) Frizzled 4 gene (FZD4) mutations in patients with familial exudative vitreoretinopathy with variable expressivity. *Br J Ophthalmol* **87**: 1291-5 [PMID:14507768]
105. Kondo H, Qin M, Tahira T, Uchio E and Hayashi K. (2007) Severe form of familial exudative vitreoretinopathy caused by homozygous R417Q mutation in frizzled-4 gene. *Ophthalmic Genet* **28**: 220-3 [PMID:18161623]
106. Koval A and Katanaev VL. (2011) Wnt3a stimulation elicits G-protein-coupled receptor properties of mammalian Frizzled proteins. *Biochem J* **433**: 435-40 [PMID:21128903]
107. Koval A, Purvanov V, Egger-Adam D and Katanaev VL. (2011) Yellow submarine of the Wnt/Frizzled signaling: submerging from the G protein harbor to the targets. *Biochem Pharmacol* **82**: 1311-9 [PMID:21689640]
108. Kowalski-Jahn M, Schihada H, Turku A, Huber T, Sakmar TP and Schulte G. (2021) Frizzled BRET sensors based on bioorthogonal labeling of unnatural amino acids reveal WNT-induced dynamics of the cysteine-rich domain. *Sci Adv* **7**: eabj7917 [PMID:34757789]
109. Kozielewicz P, Bowin CF, Turku A and Schulte G. (2020) A NanoBRET-Based Binding Assay for Smoothened Allows Real-time Analysis of Ligand Binding and Distinction of Two Binding Sites for BODIPY-cyclopamine. *Mol Pharmacol* **97**: 23-34 [PMID:31707356]
110. Kozielewicz P, Turku A, Bowin CF, Petersen J, Valnohova J, Cañizal MCA, Ono Y, Inoue A, Hoffmann C and Schulte G. (2020) Structural insight into small molecule action on Frizzleds. *Nat Commun* **11**: 414 [PMID:31964872]
111. Kumar S, Zigman M, Patel TR, Trageser B, Gross JC, Rahm K, Boutros M, Gradl D, Steinbeisser H and Holstein T *et al.*. (2014) Molecular dissection of Wnt3a-Frizzled8 interaction reveals essential and modulatory determinants of Wnt signaling activity. *BMC Biol* **12**: 44 [PMID:24885675]
112. Laeremans H, Hackeng TM, van Zandvoort MA, Thijssen VL, Janssen BJ, Ottenheijm HC, Smits JF and Blankesteijn WM. (2011) Blocking of frizzled signaling with a homologous peptide fragment of wnt3a/wnt5a reduces infarct expansion and prevents the development of heart failure after myocardial infarction. *Circulation* **124**: 1626-35 [PMID:21931076]
113. Lapointe E, Boyer A, Rico C, Paquet M, Franco HL, Gossen J, DeMayo FJ, Richards JS and Boerboom D. (2012) FZD1 regulates cumulus expansion genes and is required for normal female fertility in mice. *Biol Reprod* **87**: 104 [PMID:22954793]
114. Larasati Y, Boudou C, Koval A and Katanaev VL. (2022) Unlocking the Wnt pathway: Therapeutic potential of selective targeting FZD_7 in cancer. *Drug Discov Today* **27**: 777-792 [PMID:34915171]
115. Le Grand F, Jones AE, Seale V, Scimè A and Rudnicki MA. (2009) Wnt7a activates the planar cell polarity pathway to drive the symmetric expansion of satellite stem cells. *Cell Stem Cell* **4**: 535-47 [PMID:19497282]
116. Li B, Zhong L, Yang X, Andersson T, Huang M and Tang SJ. (2011) WNT5A signaling contributes to Aβ-induced neuroinflammation and neurotoxicity. *PLoS ONE* **6**: e22920 [PMID:21857966]
117. Li C, Wu Y, Wang W, Xu L, Zhou Y, Yue Y, Wu T, Yang M, Qiu Y and Huang M *et al.*. (2023) Structure-Based Ligand Discovery Targeting the Transmembrane Domain of Frizzled Receptor FZD7. *J Med Chem* **66**: 11855-11868 [PMID:37669317]
118. Liu C, Wang Y, Smallwood PM and Nathans J. (2008) An essential role for Frizzled5 in neuronal survival in the parafascicular nucleus of the thalamus. *J Neurosci* **28**: 5641-53 [PMID:18509025]
119. Liu T, Liu X, Wang Hy, Moon RT and Malbon CC. (1999) Activation of rat frizzled-1 promotes Wnt signaling and differentiation of mouse F9 teratocarcinoma cells via pathways that require Galpha(q) and Galpha(o) function. *J Biol Chem* **274**: 33539-44 [PMID:10559239]
120. Lu D, Zhao Y, Tawatao R, Cottam HB, Sen M, Leoni LM, Kipps TJ, Corr M and Carson DA. (2004) Activation of the Wnt signaling pathway in chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* **101**: 3118-23 [PMID:14973184]
121. Lu J, Zhang S, Nakano H, Simmons DG, Wang S, Kong S, Wang Q, Shen L, Tu Z and Wang W *et al.*. (2013) A positive feedback loop involving Gcm1 and Fzd5 directs chorionic branching morphogenesis in the placenta. *PLoS Biol* **11**: e1001536 [PMID:23610556]
122. Lu X, Peng Y, Wang C, Yang J, Bao X, Dong Q, Zhao W, Tan W and Dong X. (2017) Design,

synthesis, and biological evaluation of optimized phthalazine derivatives as hedgehog signaling pathway inhibitors. *Eur J Med Chem* **138**: 384-395 [PMID:28688278]
123. Luhmann UF, Neidhardt J, Kloeckener-Gruissem B, Schäfer NF, Glaus E, Feil S and Berger W. (2008) Vascular changes in the cerebellum of Norrin /Ndph knockout mice correlate with high expression of Norrin and Frizzled-4. *Eur J Neurosci* **27**: 2619-28 [PMID:18547247]
124. Lum L and Beachy PA. (2004) The Hedgehog response network: sensors, switches, and routers. *Science* **304**: 1755-9 [PMID:15205520]
125. Luo J, Chen J, Deng ZL, Luo X, Song WX, Sharff KA, Tang N, Haydon RC, Luu HH and He TC. (2007) Wnt signaling and human diseases: what are the therapeutic implications? *Lab Invest* **87**: 97-103 [PMID:17211410]
126. Lyons JP, Mueller UW, Ji H, Everett C, Fang X, Hsieh JC, Barth AM and McCrea PD. (2004) Wnt-4 activates the canonical beta-catenin-mediated Wnt pathway and binds Frizzled-6 CRD: functional implications of Wnt/beta-catenin activity in kidney epithelial cells. *Exp Cell Res* **298**: 369-87 [PMID:15265686]
127. Lyuksyutova AI, Lu CC, Milanesio N, King LA, Guo N, Wang Y, Nathans J, Tessier-Lavigne M and Zou Y. (2003) Anterior-posterior guidance of commissural axons by Wnt-frizzled signaling. *Science* **302**: 1984-8 [PMID:14671310]
128. Ma L and Wang HY. (2007) Mitogen-activated protein kinase p38 regulates the Wnt/cyclic GMP/Ca2+ non-canonical pathway. *J Biol Chem* **282**: 28980-90 [PMID:17684012]
129. Ma L and Wang HY. (2006) Suppression of cyclic GMP-dependent protein kinase is essential to the Wnt/cGMP/Ca2+ pathway. *J Biol Chem* **281**: 30990-1001 [PMID:16920709]
130. MacDonald BT and He X. (2012) Frizzled and LRP5/6 receptors for Wnt/β-catenin signaling. *Cold Spring Harb Perspect Biol* **4** [PMID:23209147]
131. MacDonald BT, Tamai K and He X. (2009) Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev Cell* **17**: 9-26 [PMID:19619488]
132. MacDonald ML, Goldberg YP, Macfarlane J, Samuels ME, Trese MT and Shastry BS. (2005) Genetic variants of frizzled-4 gene in familial exudative vitreoretinopathy and advanced retinopathy of prematurity. *Clin Genet* **67**: 363-6 [PMID:15733276]
133. Magdesian MH, Carvalho MM, Mendes FA, Saraiva LM, Juliano MA, Juliano L, Garcia-Abreu J and Ferreira ST. (2008) Amyloid-beta binds to the extracellular cysteine-rich domain of Frizzled and inhibits Wnt/beta-catenin signaling. *J Biol Chem* **283**: 9359-68 [PMID:18234671]
134. Malaterre J, Ramsay RG and Mantamadiotis T. (2007) Wnt-Frizzled signalling and the many paths to neural development and adult brain homeostasis. *Front Biosci* **12**: 492-506 [PMID:17127312]
135. Malik TH and Shivdasani RA. (2000) Structure and expression of a novel frizzled gene isolated from the developing mouse gut. *Biochem J* **349 Pt 3**: 829-34 [PMID:10903145]
136. Manning DR, Shen F and Riobo NA. (2015) Evaluating the Activity of Smoothened Toward G Proteins Using [^{35}S]Guanosine 5'-(3-O-thio)triphosphate ([^{35}S]GTPγS). *Methods Mol Biol* **1322**: 35-44 [PMID:26179037]
137. Mao J, Ligon KL, Rakhlin EY, Thayer SP, Bronson RT, Rowitch D and McMahon AP. (2006) A novel somatic mouse model to survey tumorigenic potential applied to the Hedgehog pathway. *Cancer Res* **66**: 10171-8 [PMID:17047082]
138. Masckauchán TN, Shawber CJ, Funahashi Y, Li CM and Kitajewski J. (2005) Wnt/beta-catenin signaling induces proliferation, survival and interleukin-8 in human endothelial cells. *Angiogenesis* **8**: 43-51 [PMID:16132617]
139. Masdeu C, Faure H, Coulombe J, Schoenfelder A, Mann A, Brabet I, Pin JP, Traiffort E and Ruat M. (2006) Identification and characterization of Hedgehog modulator properties after functional coupling of Smoothened to G15. *Biochem Biophys Res Commun* **349**: 471-9 [PMID:16945339]
140. Meloni AR, Fralish GB, Kelly P, Salahpour A, Chen JK, Wechsler-Reya RJ, Lefkowitz RJ and Caron MG. (2006) Smoothened signal transduction is promoted by G protein-coupled receptor kinase 2. *Mol Cell Biol* **26**: 7550-60 [PMID:16908539]
141. Merle P, de la Monte S, Kim M, Herrmann M, Tanaka S, Von Dem Bussche A, Kew MC, Trepo C and Wands JR. (2004) Functional consequences of frizzled-7 receptor overexpression in human hepatocellular carcinoma. *Gastroenterology* **127**: 1110-22 [PMID:15480989]
142. Miao Y, Ha A, de Lau W, Yuki K, Santos AJM, You C, Geurts MH, Puschhof J, Pleguezuelos-Manzano C and Peng WC *et al.*. (2020) Next-Generation Surrogate Wnts Support Organoid Growth and Deconvolute Frizzled Pleiotropy In Vivo. *Cell Stem Cell* **27**: 840-851.e6 [PMID:32818433]
143. Mikels AJ and Nusse R. (2006) Purified Wnt5a protein activates or inhibits beta-catenin-TCF signaling depending on receptor context. *PLoS Biol* **4**: e115 [PMID:16602827]
144. Miyakoshi T, Takei M, Kajiya H, Egashira N, Takekoshi S, Teramoto A and Osamura RY. (2008) Expression of Wnt4 in human pituitary adenomas regulates activation of the beta-catenin-independent pathway. *Endocr Pathol* **19**: 261-73 [PMID:19034702]
145. Montcouquiol M, Sans N, Huss D, Kach J, Dickman JD, Forge A, Rachel RA, Copeland NG, Jenkins NA and Bogani D *et al.*. (2006) Asymmetric localization of Vangl2 and Fz3 indicate novel

mechanisms for planar cell polarity in mammals. *J Neurosci* **26**: 5265-75 [PMID:16687519]
146. Moyes KW, Sip CG, Obenza W, Yang E, Horst C, Welikson RE, Hauschka SD, Folch A and Laflamme MA. (2013) Human embryonic stem cell-derived cardiomyocytes migrate in response to gradients of fibronectin and Wnt5a. *Stem Cells Dev* **22**: 2315-25 [PMID:23517131]
147. Munchhof MJ, Li Q, Shavnya A, Borzillo GV, Boyden TL, Jones CS, LaGreca SD, Martinez-Alsina L, Patel N and Pelletier K *et al.*. (2012) Discovery of PF-04449913, a Potent and Orally Bioavailable Inhibitor of Smoothened. *ACS Med Chem Lett* **3**: 106-11 [PMID:24900436]
148. Nagayama S, Fukukawa C, Katagiri T, Okamoto T, Aoyama T, Oyaizu N, Imamura M, Toguchida J and Nakamura Y. (2005) Therapeutic potential of antibodies against FZD 10, a cell-surface protein, for synovial sarcomas. *Oncogene* **24**: 6201-12 [PMID:16007199]
149. Naz G, Pasternack SM, Perrin C, Mattheisen M, Refke M, Khan S, Gul A, Simons M, Ahmad W and Betz RC. (2012) FZD6 encoding the Wnt receptor frizzled 6 is mutated in autosomal-recessive nail dysplasia. *Br J Dermatol* **166**: 1088-94 [PMID:22211385]
150. Neumann J, Schaale K, Farhat K, Endermann T, Ulmer AJ, Ehlers S and Reiling N. (2010) Frizzled1 is a marker of inflammatory macrophages, and its ligand Wnt3a is involved in reprogramming Mycobacterium tuberculosis-infected macrophages. *FASEB J* **24**: 4599-612 [PMID:20667980]
151. Nile AH, de Sousa E Melo F, Mukund S, Piskol R, Hansen S, Zhou L, Zhang Y, Fu Y, Gogol EB and Kömüves LG *et al.*. (2018) A selective peptide inhibitor of Frizzled 7 receptors disrupts intestinal stem cells. *Nat Chem Biol* **14**: 582-590 [PMID:29632413]
152. Nusse R. (2005) Wnt signaling in disease and in development. *Cell Res* **15**: 28-32 [PMID:15686623]
153. Nusse R. (2003) Wnts and Hedgehogs: lipid-modified proteins and similarities in signaling mechanisms at the cell surface. *Development* **130**: 5297-305 [PMID:14530294]
154. Ogden SK, Ascano Jr M, Stegman MA and Robbins DJ. (2004) Regulation of Hedgehog signaling: a complex story. *Biochem Pharmacol* **67**: 805-14 [PMID:15104233]
155. Ogden SK, Fei DL, Schilling NS, Ahmed YF, Hwa J and Robbins DJ. (2008) G protein Galphai functions immediately downstream of Smoothened in Hedgehog signalling. *Nature* **456**: 967-70 [PMID:18987629]
156. Ohashi T, Oguro Y, Tanaka T, Shiokawa Z, Tanaka Y, Shibata S, Sato Y, Yamakawa H, Hattori H and Yamamoto Y *et al.*. (2012) Discovery of the investigational drug TAK-441, a pyrrolo[3,2-c]pyridine derivative, as a highly potent and orally active hedgehog signaling inhibitor: modification of the core skeleton for improved solubility. *Bioorg Med Chem* **20**: 5507-17 [PMID:22898254]
157. Pan W, Choi SC, Wang H, Qin Y, Volpicelli-Daley L, Swan L, Lucast L, Khoo C, Zhang X and Li L *et al.*. (2008) Wnt3a-mediated formation of phosphatidylinositol 4,5-bisphosphate regulates LRP6 phosphorylation. *Science* **321**: 1350-3 [PMID:18772438]
158. Papadopoulou S and Edlund H. (2005) Attenuated Wnt signaling perturbs pancreatic growth but not pancreatic function. *Diabetes* **54**: 2844-51 [PMID:16186384]
159. Petersen J, Wright SC, Rodríguez D, Matricon P, Lahav N, Vromen A, Friedler A, Strömqvist J, Wennmalm S and Carlsson J *et al.*. (2017) Agonist-induced dimer dissociation as a macromolecular step in G protein-coupled receptor signaling. *Nat Commun* **8**: 226 [PMID:28790300]
160. Planutis K, Planutiene M, Moyer MP, Nguyen AV, Pérez CA and Holcombe RF. (2007) Regulation of norrin receptor frizzled-4 by Wnt2 in colon-derived cells. *BMC Cell Biol* **8**: 12 [PMID:17386109]
161. Povelones M and Nusse R. (2005) The role of the cysteine-rich domain of Frizzled in Wingless-Armadillo signaling. *EMBO J* **24**: 3493-503 [PMID:16163385]
162. Qi X, Friedberg L, De Bose-Boyd R, Long T and Li X. (2020) Sterols in an intramolecular channel of Smoothened mediate Hedgehog signaling. *Nat Chem Biol* **16**: 1368-1375 [PMID:32929279]
163. Qi X, Liu H, Thompson B, McDonald J, Zhang C and Li X. (2019) Cryo-EM structure of oxysterol-bound human Smoothened coupled to a heterotrimeric G_i. *Nature* **571**: 279-283 [PMID:31168089]
164. Qian Y, Ma Z, Xu Z, Duan Y, Xiong Y, Xia R, Zhu X, Zhang Z, Tian X and Yin H *et al.*. (2024) Structural basis of Frizzled 4 in recognition of Dishevelled 2 unveils mechanism of WNT signaling activation. *Nat Commun* **15**: 7644 [PMID:39223191]
165. Qin M, Hayashi H, Oshima K, Tahira T, Hayashi K and Kondo H. (2005) Complexity of the genotype-phenotype correlation in familial exudative vitreoretinopathy with mutations in the LRP5 and/or FZD4 genes. *Hum Mutat* **26**: 104-12 [PMID:15981244]
166. Ramírez VT, Ramos-Fernández E, Henríquez JP, Lorenzo A and Inestrosa NC. (2016) Wnt-5a/Frizzled9 Receptor Signaling through the Gαo-Gβγ Complex Regulates Dendritic Spine Formation. *J Biol Chem* **291**: 19092-107 [PMID:27402827]
167. Ranchod TM, Ho LY, Drenser KA, Capone Jr A and Trese MT. (2011) Clinical presentation of familial exudative vitreoretinopathy. *Ophthalmology* **118**: 2070-5 [PMID:21868098]
168. Ranheim EA, Kwan HC, Reya T, Wang YK, Weissman IL and Francke U. (2005) Frizzled 9 knock-

out mice have abnormal B-cell development. *Blood* **105**: 2487-94 [PMID:15572594]
169. Rawal N, Castelo-Branco G, Sousa KM, Kele J, Kobayashi K, Okano H and Arenas E. (2006) Dynamic temporal and cell type-specific expression of Wnt signaling components in the developing midbrain. *Exp Cell Res* **312**: 1626-36 [PMID:16510140]
170. Raza SI, Muhammad N, Khan S and Ahmad W. (2013) A novel missense mutation in the gene FZD6 underlies autosomal recessive nail dysplasia. *Br J Dermatol* **168**: 422-5 [PMID:22861124]
171. Regard JB, Sato IT and Coughlin SR. (2008) Anatomical profiling of G protein-coupled receptor expression. *Cell* **135**: 561-71 [PMID:18984166]
172. Riccio G, Bottone S, La Regina G, Badolati N, Passacantilli S, Rossi GB, Accardo A, Dentice M, Silvestri R and Novellino E *et al.*. (2018) A Negative Allosteric Modulator of WNT Receptor Frizzled 4 Switches into an Allosteric Agonist. *Biochemistry* **57**: 839-851 [PMID:29293331]
173. Riobo NA and Manning DR. (2007) Pathways of signal transduction employed by vertebrate Hedgehogs. *Biochem J* **403**: 369-379 [PMID:17419683]
174. Riobo NA, Saucy B, Dilizio C and Manning DR. (2006) Activation of heterotrimeric G proteins by Smoothened. *Proc Natl Acad Sci USA* **103**: 12607-12 [PMID:16885213]
175. Robitaille J, MacDonald ML, Kaykas A, Sheldahl LC, Zeisler J, Dubé MP, Zhang LH, Singaraja RR, Guernsey DL, Zheng B, Siebert LF, Hoskin-Mott A, Trese MT, Pimstone SN, Shastry BS, Moon RT, Hayden MR, Goldberg YP and Samuels ME. (2002) Mutant frizzled-4 disrupts retinal angiogenesis in familial exudative vitreoretinopathy. *Nat Genet* **32**: 326-330 [PMID:12172548]
176. Sagara N, Toda G, Hirai M, Terada M and Katoh M. (1998) Molecular cloning, differential expression, and chromosomal localization of human frizzled-1, frizzled-2, and frizzled-7. *Biochem Biophys Res Commun* **252**: 117-22 [PMID:9813155]
177. Sahores M, Gibb A and Salinas PC. (2010) Frizzled-5, a receptor for the synaptic organizer Wnt7a, regulates activity-mediated synaptogenesis. *Development* **137**: 2215-25 [PMID:20530549]
178. Saitoh T, Hirai M and Katoh M. (2001) Molecular cloning and characterization of human Frizzled-5 gene on chromosome 2q33.3-q34 region. *Int J Oncol* **19**: 105-10 [PMID:11408929]
179. Saitoh T, Hirai M and Katoh M. (2001) Molecular cloning and characterization of human Frizzled-8 gene on chromosome 10p11.2. *Int J Oncol* **18**: 991-6 [PMID:11295046]
180. Sala CF, Formenti E, Terstappen GC and Caricasole A. (2000) Identification, gene structure, and expression of human frizzled-3 (FZD3). *Biochem Biophys Res Commun* **273**: 27-34 [PMID:10873558]
181. Salsano E, Paterra R, Figus M, Menghi F, Maderna E, Pollo B, Solero CL, Massimi L and Finocchiaro G. (2012) Expression profile of frizzled receptors in human medulloblastomas. *J Neurooncol* **106**: 271-80 [PMID:21850537]
182. Sammeta N, Yu TT, Bose SC and McClintock TS. (2007) Mouse olfactory sensory neurons express 10,000 genes. *J Comp Neurol* **502**: 1138-56 [PMID:17444493]
183. Schihada H, Kowalski-Jahn M, Turku A and Schulte G. (2021) Deconvolution of WNT-induced Frizzled conformational dynamics with fluorescent biosensors. *Biosens Bioelectron* **177**: 112948 [PMID:33486136]
184. Schulte G. (2010) International Union of Basic and Clinical Pharmacology. LXXX. The class Frizzled receptors. *Pharmacol Rev* **62**: 632-67 [PMID:21079039]
185. Schulte G. (2024) International Union of Basic and Clinical Pharmacology CXV: The Class F of G Protein-Coupled Receptors. *Pharmacol Rev* **76**: 1009-1037 [PMID:38955509]
186. Schulte G and Bryja V. (2007) The Frizzled family of unconventional G-protein-coupled receptors. *Trends Pharmacol Sci* **28**: 518-25 [PMID:17884187]
187. Schulte G, Bryja V, Rawal N, Castelo-Branco G, Sousa KM and Arenas E. (2005) Purified Wnt-5a increases differentiation of midbrain dopaminergic cells and dishevelled phosphorylation. *J Neurochem* **92**: 1550-3 [PMID:15748172]
188. Schulte G and Wright SC. (2018) Frizzleds as GPCRs - More Conventional Than We Thought! *Trends Pharmacol Sci* **39**: 828-842 [PMID:30049420]
189. Sen M, Lauterbach K, El-Gabalawy H, Firestein GS, Corr M and Carson DA. (2000) Expression and function of wingless and frizzled homologs in rheumatoid arthritis. *Proc Natl Acad Sci USA* **97**: 2791-6 [PMID:10688908]
190. Shastry BS. (2009) Persistent hyperplastic primary vitreous: congenital malformation of the eye. *Clin Experiment Ophthalmol* **37**: 884-90 [PMID:20092598]
191. Shen F, Cheng L, Douglas AE, Riobo NA and Manning DR. (2013) Smoothened is a fully competent activator of the heterotrimeric G protein G(i). *Mol Pharmacol* **83**: 691-7 [PMID:23292797]
192. Shen G, Ke J, Wang Z, Cheng Z, Gu X, Wei Y, Melcher K, Xu HE and Xu W. (2015) Structural basis of the Norrin-Frizzled 4 interaction. *Cell Res* **25**: 1078-81 [PMID:26227961]
193. Sinha S and Chen JK. (2006) Purmorphamine activates the Hedgehog pathway by targeting Smoothened. *Nat Chem Biol* **2**: 29-30 [PMID:16408088]
194. Slusarski DC, Corces VG and Moon RT. (1997) Interaction of Wnt and a Frizzled homologue triggers G-protein-linked phosphatidylinositol signalling. *Nature* **390**: 410-3 [PMID:9389482]

195. Slusher MM and Hutton WE. (1979) Familial exudative vitreoretinopathy. *Am J Ophthalmol* **87**: 152-6 [PMID:434067]
196. Sonnet M, Claus R, Becker N, Zucknick M, Petersen J, Lipka DB, Oakes CC, Andrulis M, Lier A and Milsom MD *et al.*. (2014) Early aberrant DNA methylation events in a mouse model of acute myeloid leukemia. *Genome Med* **6**: 34 [PMID:24944583]
197. Steinhart Z, Pavlovic Z, Chandrashekhar M, Hart T, Wang X, Zhang X, Robitaille M, Brown KR, Jaksani S and Overmeer R *et al.*. (2017) Genome-wide CRISPR screens reveal a Wnt-FZD5 signaling circuit as a druggable vulnerability of RNF43-mutant pancreatic tumors. *Nat Med* **23**: 60-68 [PMID:27869803]
198. Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, Thomas NS, Abeysinghe S, Krawczak M and Cooper DN. (2003) Human Gene Mutation Database (HGMD): 2003 update. *Hum Mutat* **21**: 577-81 [PMID:12754702]
199. Stone DM, Hynes M, Armanini M, Swanson TA, Gu Q, Johnson RL, Scott MP, Pennica D, Goddard A and Phillips H *et al.*. (1996) The tumour-suppressor gene patched encodes a candidate receptor for Sonic hedgehog. *Nature* **384**: 129-34 [PMID:8906787]
200. Stuebner S, Faus-Kessler T, Fischer T, Wurst W and Prakash N. (2010) Fzd3 and Fzd6 deficiency results in a severe midbrain morphogenesis defect. *Dev Dyn* **239**: 246-60 [PMID:19842188]
201. Su AI, Wiltshire T, Batalov S, Lapp H, Ching KA, Block D, Zhang J, Soden R, Hayakawa M and Kreiman G *et al.*. (2004) A gene atlas of the mouse and human protein-encoding transcriptomes. *Proc Natl Acad Sci USA* **101**: 6062-7 [PMID:15075390]
202. Sugimura R, He XC, Venkatraman A, Arai F, Box A, Semerad C, Haug JS, Peng L, Zhong XB and Suda T *et al.*. (2012) Noncanonical Wnt signaling maintains hematopoietic stem cells in the niche. *Cell* **150**: 351-65 [PMID:22817897]
203. Summerhurst K, Stark M, Sharpe J, Davidson D and Murphy P. (2008) 3D representation of Wnt and Frizzled gene expression patterns in the mouse embryo at embryonic day 11.5 (Ts19). *Gene Expr Patterns* **8**: 331-48 [PMID:18364260]
204. Taipale J, Chen JK, Cooper MK, Wang B, Mann RK, Milenkovic L, Scott MP and Beachy PA. (2000) Effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine. *Nature* **406**: 1005-9 [PMID:10984056]
205. Tanaka S, Akiyoshi T, Mori M, Wands JR and Sugimachi K. (1998) A novel frizzled gene identified in human esophageal carcinoma mediates APC/beta-catenin signals. *Proc Natl Acad Sci USA* **95**: 10164-9 [PMID:9707618]
206. Tauriello DV, Jordens I, Kirchner K, Slootstra JW, Kruitwagen T, Bouwman BA, Noutsou M, Rüdiger SG, Schwamborn K and Schambony A *et al.*. (2012) Wnt/β-catenin signaling requires interaction of the Dishevelled DEP domain and C terminus with a discontinuous motif in Frizzled. *Proc Natl Acad Sci USA* **109**: E812-20 [PMID:22411803]
207. Teglund S and Toftgård R. (2010) Hedgehog beyond medulloblastoma and basal cell carcinoma. *Biochim Biophys Acta* **1805**: 181-208 [PMID:20085802]
208. Terasaki H, Saitoh T, Shiokawa K and Katoh M. (2002) Frizzled-10, up-regulated in primary colorectal cancer, is a positive regulator of the WNT - beta-catenin - TCF signaling pathway. *Int J Mol Med* **9**: 107-12 [PMID:11786918]
209. Thomsen HK, Jacobsen M, Gerstoft J and Malchow-Møller A. (1985) The histomorphology of Kaposi sarcoma in three homosexual men. *Acta Pathol Microbiol Immunol Scand A* **93**: 17-23 [PMID:3969828]
210. Tickenbrock L, Schwäble J, Wiedehage M, Steffen B, Sargin B, Choudhary C, Brandts C, Berdel WE, Müller-Tidow C and Serve H. (2005) Flt3 tandem duplication mutations cooperate with Wnt signaling in leukemic signal transduction. *Blood* **105**: 3699-706 [PMID:15650056]
211. Toftgård R. (2000) Hedgehog signalling in cancer. *Cell Mol Life Sci* **57**: 1720-1731 [PMID:11130178]
212. Tokuhara M, Hirai M, Atomi Y, Terada M and Katoh M. (1998) Molecular cloning of human Frizzled-6. *Biochem Biophys Res Commun* **243**: 622-7 [PMID:9480858]
213. Traiffort E, Charytoniuk DA, Faure H and Ruat M. (1998) Regional distribution of Sonic Hedgehog, patched, and smoothened mRNA in the adult rat brain. *J Neurochem* **70**: 1327-30 [PMID:9489757]
214. Tremblay MR, Lescarbeau A, Grogan MJ, Tan E, Lin G, Austad BC, Yu LC, Behnke ML, Nair SJ and Hagel M *et al.*. (2009) Discovery of a potent and orally active hedgehog pathway antagonist (IPI-926). *J Med Chem* **52**: 4400-18 [PMID:19522463]
215. Tsutsumi N, Mukherjee S, Waghray D, Janda CY, Jude KM, Miao Y, Burg JS, Aduri NG, Kossiakoff AA and Gati C *et al.*. (2020) Structure of human Frizzled5 by fiducial-assisted cryo-EM supports a heterodimeric mechanism of canonical Wnt signaling. *Elife* **9** [PMID:32762848]
216. Turner MW, Cruz R, Mattos J, Baughman N, Elwell J, Fothergill J, Nielsen A, Brookhouse J, Bartlett A and Malek P *et al.*. (2016) Cyclopamine bioactivity by extraction method from Veratrum californicum. *Bioorg Med Chem* **24**: 3752-7 [PMID:27338657]
217. Tycko B, Li CM and Buttyan R. (2007) The Wnt/beta-catenin pathway in Wilms tumors and

prostate cancers. *Curr Mol Med* **7**: 479-89 [PMID:17691963]
218. Ueno K, Hirata H, Hinoda Y and Dahiya R. (2013) Frizzled homolog proteins, microRNAs and Wnt signaling in cancer. *Int J Cancer* **132**: 1731-40 [PMID:22833265]
219. Ueno K, Hiura M, Suehiro Y, Hazama S, Hirata H, Oka M, Imai K, Dahiya R and Hinoda Y. (2008) Frizzled-7 as a potential therapeutic target in colorectal cancer. *Neoplasia* **10**: 697-705 [PMID:18592008]
220. Uhlen M, Oksvold P, Fagerberg L, Lundberg E, Jonasson K, Forsberg M, Zwahlen M, Kampf C, Wester K and Hober S *et al.*. (2010) Towards a knowledge-based Human Protein Atlas. *Nat Biotechnol* **28**: 1248-50 [PMID:21139605]
221. Uitterdijk A, Hermans KC, de Wijs-Meijler DP, Daskalopoulos EP, Reiss IK, Duncker DJ, Matthijs Blankesteijn W and Merkus D. (2016) UM206, a selective Frizzled antagonist, attenuates adverse remodeling after myocardial infarction in swine. *Lab Invest* **96**: 168-76 [PMID:26658451]
222. van Amerongen R and Berns A. (2006) Knockout mouse models to study Wnt signal transduction. *Trends Genet* **22**: 678-89 [PMID:17045694]
223. van Amerongen R and Nusse R. (2009) Towards an integrated view of Wnt signaling in development. *Development* **136**: 3205-14 [PMID:19736321]
224. van Es JH, Jay P, Gregorieff A, van Gijn ME, Jonkheer S, Hatzis P, Thiele A, van den Born M, Begthel H and Brabletz T *et al.*. (2005) Wnt signalling induces maturation of Paneth cells in intestinal crypts. *Nat Cell Biol* **7**: 381-6 [PMID:15778706]
225. van Gijn ME, Blankesteijn WM, Smits JF, Hierck B and Gittenberger-de Groot AC. (2001) Frizzled 2 is transiently expressed in neural crest-containing areas during development of the heart and great arteries in the mouse. *Anat Embryol* **203**: 185-92 [PMID:11303904]
226. van Helden YG, Godschalk RW, Heil SG, Bunschoten A, Hessel S, Amengual J, Bonet ML, von Lintig J, van Schooten FJ and Keijer J. (2010) Downregulation of Fzd6 and Cthrc1 and upregulation of olfactory receptors and protocadherins by dietary beta-carotene in lungs of Bcmo1-/- mice. *Carcinogenesis* **31**: 1329-37 [PMID:20472610]
227. Varecza Z, Kvell K, Talabér G, Miskei G, Csongei V, Bartis D, Anderson G, Jenkinson EJ and Pongracz JE. (2011) Multiple suppression pathways of canonical Wnt signalling control thymic epithelial senescence. *Mech Ageing Dev* **132**: 249-56 [PMID:21549744]
228. von Maltzahn J, Bentzinger CF and Rudnicki MA. (2012) Wnt7a-Fzd7 signalling directly activates the Akt/mTOR anabolic growth pathway in skeletal muscle. *Nat Cell Biol* **14**: 186-91 [PMID:22179044]
229. Voss JH, Koszegi Z, Yan Y, Shorter E, Grätz L, Lanner JT, Calebiro D and Schulte G. (2025) WNT-induced association of Frizzled and LRP6 is not sufficient for the initiation of WNT/β-catenin signaling. *Nat Commun* **16**: 4848 [PMID:40413190]
230. Wang C, Wu H, Evron T, Vardy E, Han GW, Huang XP, Hufeisen SJ, Mangano TJ, Urban DJ and Katritch V *et al.*. (2014) Structural basis for Smoothened receptor modulation and chemoresistance to anticancer drugs. *Nat Commun* **5**: 4355 [PMID:25008467]
231. Wang C, Wu H, Katritch V, Han GW, Huang XP, Liu W, Siu FY, Roth BL, Cherezov V and Stevens RC. (2013) Structure of the human smoothened receptor bound to an antitumour agent. *Nature* **497**: 338-43 [PMID:23636324]
232. Wang HQ, Xu ML, Ma J, Zhang Y and Xie CH. (2012) Frizzled-8 as a putative therapeutic target in human lung cancer. *Biochem Biophys Res Commun* **417**: 62-6 [PMID:22138402]
233. Wang J, Mook Jr RA, Lu J, Gooden DM, Ribeiro A, Guo A, Barak LS, Lyerly HK and Chen W. (2012) Identification of a novel Smoothened antagonist that potently suppresses Hedgehog signaling. *Bioorg Med Chem* **20**: 6751-7 [PMID:23063522]
234. Wang Y, Guo N and Nathans J. (2006) The role of Frizzled3 and Frizzled6 in neural tube closure and in the planar polarity of inner-ear sensory hair cells. *J Neurosci* **26**: 2147-56 [PMID:16495441]
235. Wang Y, Huso D, Cahill H, Ryugo D and Nathans J. (2001) Progressive cerebellar, auditory, and esophageal dysfunction caused by targeted disruption of the frizzled-4 gene. *J Neurosci* **21**: 4761-71 [PMID:11425903]
236. Wang Y, Macke JP, Abella BS, Andreasson K, Worley P, Gilbert DJ, Copeland NG, Jenkins NA and Nathans J. (1996) A large family of putative transmembrane receptors homologous to the product of the Drosophila tissue polarity gene frizzled. *J Biol Chem* **271**: 4468-76 [PMID:8626800]
237. Wang Y, Thekdi N, Smallwood PM, Macke JP and Nathans J. (2002) Frizzled-3 is required for the development of major fiber tracts in the rostral CNS. *J Neurosci* **22**: 8563-73 [PMID:12351730]
238. Wang YK, Samos CH, Peoples R, Pérez-Jurado LA, Nusse R and Francke U. (1997) A novel human homologue of the Drosophila frizzled wnt receptor gene binds wingless protein and is in the Williams syndrome deletion at 7q11.23. *Hum Mol Genet* **6**: 465-72 [PMID:9147651]
239. Wang YK, Spörle R, Paperna T, Schughart K and Francke U. (1999) Characterization and expression pattern of the frizzled gene Fzd9, the mouse homolog of FZD9 which is deleted in Williams-Beuren syndrome. *Genomics* **57**: 235-48 [PMID:10198163]

240. Wang Z, Shu W, Lu MM and Morrisey EE. (2005) Wnt7b activates canonical signaling in epithelial and vascular smooth muscle cells through interactions with Fzd1, Fzd10, and LRP5. *Mol Cell Biol* **25**: 5022-30 [PMID:15923619]
241. Wei J and Hemmings GP. (2004) Lack of a genetic association between the frizzled-3 gene and schizophrenia in a British population. *Neurosci Lett* **366**: 336-8 [PMID:15288446]
242. Weierstall U, James D, Wang C, White TA, Wang D, Liu W, Spence JC, Bruce Doak R, Nelson G and Fromme P *et al*.. (2014) Lipidic cubic phase injector facilitates membrane protein serial femtosecond crystallography. *Nat Commun* **5**: 3309 [PMID:24525480]
243. Willert K, Brown JD, Danenberg E, Duncan AW, Weissman IL, Reya T, Yates 3rd JR and Nusse R. (2003) Wnt proteins are lipid-modified and can act as stem cell growth factors. *Nature* **423**: 448-52 [PMID:12717451]
244. Willert K and Nusse R. (2012) Wnt proteins. *Cold Spring Harb Perspect Biol* **4**: a007864 [PMID:22952392]
245. Willert KH. (2008) Isolation and application of bioactive Wnt proteins. *Methods Mol Biol* **468**: 17-29 [PMID:19099243]
246. Winn RA, Marek L, Han SY, Rodriguez K, Rodriguez N, Hammond M, Van Scoyk M, Acosta H, Mirus J and Barry N *et al*.. (2005) Restoration of Wnt-7a expression reverses non-small cell lung cancer cellular transformation through frizzled-9-mediated growth inhibition and promotion of cell differentiation. *J Biol Chem* **280**: 19625-34 [PMID:15705594]
247. Witze ES, Litman ES, Argast GM, Moon RT and Ahn NG. (2008) Wnt5a control of cell polarity and directional movement by polarized redistribution of adhesion receptors. *Science* **320**: 365-9 [PMID:18420933]
248. Wright SC, Cañizal MCA, Benkel T, Simon K, Le Gouill C, Matricon P, Namkung Y, Lukasheva V, König GM and Laporte SA *et al*.. (2018) FZD_5 is a $G\alpha_q$-coupled receptor that exhibits the functional hallmarks of prototypical GPCRs. *Sci Signal* **11** [PMID:30514810]
249. Wright SC, Kozielewicz P, Kowalski-Jahn M, Petersen J, Bowin CF, Slodkowicz G, Marti-Solano M, Rodríguez D, Hot B and Okashah N *et al*.. (2019) A conserved molecular switch in Class F receptors regulates receptor activation and pathway selection. *Nat Commun* **10**: 667 [PMID:30737406]
250. Wu QL, Zierold C and Ranheim EA. (2009) Dysregulation of Frizzled 6 is a critical component of B-cell leukemogenesis in a mouse model of chronic lymphocytic leukemia. *Blood* **113**: 3031-9 [PMID:19179304]
251. Xie J, Murone M, Luoh SM, Ryan A, Gu Q, Zhang C, Bonifas JM, Lam CW, Hynes M and Goddard A *et al*.. (1998) Activating Smoothened mutations in sporadic basal-cell carcinoma. *Nature* **391**: 90-2 [PMID:9422511]
252. Xu L, Chen B, Schihada H, Wright SC, Turku A, Wu Y, Han GW, Kowalski-Jahn M, Kozielewicz P and Bowin CF *et al*.. (2021) Cryo-EM structure of constitutively active human Frizzled 7 in complex with heterotrimeric G_s. *Cell Res* **31**: 1311-1314 [PMID:34239071]
253. Xu L, Tan L, Goldring MB, Olsen BR and Li Y. (2001) Expression of frizzled genes in mouse costochondral chondrocytes. *Matrix Biol* **20**: 147-51 [PMID:11334716]
254. Xu Q, Wang Y, Dabdoub A, Smallwood PM, Williams J, Woods C, Kelley MW, Jiang L, Tasman W and Zhang K *et al*.. (2004) Vascular development in the retina and inner ear: control by Norrin and Frizzled-4, a high-affinity ligand-receptor pair. *Cell* **116**: 883-95 [PMID:15035989]
255. Yamada M, Iwabuchi T, Takahashi K, Kurahashi C, Ohata H, Honda K, Higuchi T and Yamada M. (2005) Identification and expression of frizzled-3 protein in rat frontal cortex after antidepressant and electroconvulsive treatment. *J Pharmacol Sci* **99**: 239-46 [PMID:16258230]
256. Yanfeng WA, Tan C, Fagan RJ and Klein PS. (2006) Phosphorylation of frizzled-3. *J Biol Chem* **281**: 11603-9 [PMID:16513654]
257. Yang J, Si T, Ling Y, Ruan Y, Han Y, Wang X, Zhang H, Kong Q, Li X and Liu C *et al*.. (2003) Association study of the human FZD3 locus with schizophrenia. *Biol Psychiatry* **54**: 1298-301 [PMID:14643098]
258. Yang L, Wu X, Wang Y, Zhang K, Wu J, Yuan YC, Deng X, Chen L, Kim CC and Lau S *et al*.. (2011) FZD7 has a critical role in cell proliferation in triple negative breast cancer. *Oncogene* **30**: 4437-46 [PMID:21532620]
259. Yang S, Wu Y, Xu TH, de Waal PW, He Y, Pu M, Chen Y, DeBruine ZJ, Zhang B and Zaidi SA *et al*.. (2018) Crystal structure of the Frizzled 4 receptor in a ligand-free state. *Nature* **560**: 666-670 [PMID:30135577]
260. Ye X, Wang Y, Cahill H, Yu M, Badea TC, Smallwood PM, Peachey NS and Nathans J. (2009) Norrin, frizzled-4, and Lrp5 signaling in endothelial cells controls a genetic program for retinal vascularization. *Cell* **139**: 285-98 [PMID:19837032]
261. Ye X, Wang Y, Rattner A and Nathans J. (2011) Genetic mosaic analysis reveals a major role for frizzled 4 and frizzled 8 in controlling ureteric growth in the developing kidney. *Development* **138**: 1161-72 [PMID:21343368]
262. Yoshida S, Arita R, Yoshida A, Tada H, Emori A, Noda Y, Nakao S, Fujisawa K and Ishibashi T. (2004) Novel mutation in FZD4 gene in a Japanese pedigree with familial exudative

vitreoretinopathy. *Am J Ophthalmol* **138**: 670-1 [PMID:15488808]
263. You J, Nguyen AV, Albers CG, Lin F and Holcombe RF. (2008) Wnt pathway-related gene expression in inflammatory bowel disease. *Dig Dis Sci* **53**: 1013-9 [PMID:17939044]
264. Yu H, Smallwood PM, Wang Y, Vidaltamayo R, Reed R and Nathans J. (2010) Frizzled 1 and frizzled 2 genes function in palate, ventricular septum and neural tube closure: general implications for tissue fusion processes. *Development* **137**: 3707-17 [PMID:20940229]
265. Yu H, Ye X, Guo N and Nathans J. (2012) Frizzled 2 and frizzled 7 function redundantly in convergent extension and closure of the ventricular septum and palate: evidence for a network of interacting genes. *Development* **139**: 4383-94 [PMID:23095888]
266. Zerlin M, Julius MA and Kitajewski J. (2008) Wnt/Frizzled signaling in angiogenesis. *Angiogenesis* **11**: 63-9 [PMID:18253847]
267. Zhang K, Wu H, Hoppe N, Manglik A and Cheng Y. (2022) Fusion protein strategies for cryo-EM study of G protein-coupled receptors. *Nat Commun* **13**: 4366 [PMID:35902590]
268. Zhang W, Lu W, Ananthan S, Suto MJ and Li Y. (2017) Discovery of novel frizzled-7 inhibitors by targeting the receptor's transmembrane domain. *Oncotarget* **8**: 91459-91470 [PMID:29207657]
269. Zhang X, Zhao F, Wu Y, Yang J, Han GW, Zhao S, Ishchenko A, Ye L, Lin X and Ding K *et al*.. (2017) Crystal structure of a multi-domain human smoothened receptor in complex with a super stabilizing ligand. *Nat Commun* **8**: 15383 [PMID:28513578]
270. Zhang XM, Ramalho-Santos M and McMahon AP. (2001) Smoothened mutants reveal redundant roles for Shh and Ihh signaling including regulation of L/R asymmetry by the mouse node. *Cell* **105**: 781-92 [PMID:11440720]
271. Zhang Y, Yu X, Yuan Y, Ling Y, Ruan Y, Si T, Lu T, Wu S, Gong X and Zhu Z *et al*.. (2004) Positive association of the human frizzled 3 (FZD3) gene haplotype with schizophrenia in Chinese Han population. *Am J Med Genet B Neuropsychiatr Genet* **129B**: 16-9 [PMID:15274031]
272. Zhang Z, Lin X, Wei L, Wu Y, Xu L, Wu L, Wei X, Zhao S, Zhu X and Xu F. (2024) A framework for Frizzled-G protein coupling and implications to the PCP signaling pathways. *Cell Discov* **10**: 3 [PMID:38182578]
273. Zhao C, Avilés C, Abel RA, Almli CR, McQuillen P and Pleasure SJ. (2005) Hippocampal and visuospatial learning defects in mice with a deletion of frizzled 9, a gene in the Williams syndrome deletion interval. *Development* **132**: 2917-27 [PMID:15930120]
274. Zhao C and Pleasure SJ. (2005) Frizzled9 protein is regionally expressed in the developing medial cortical wall and the cells derived from this region. *Brain Res Dev Brain Res* **157**: 93-7 [PMID:15939089]
275. Zhao Y, Ren J, Hillier J, Lu W and Jones EY. (2020) Antiepileptic Drug Carbamazepine Binds to a Novel Pocket on the Wnt Receptor Frizzled-8. *J Med Chem* **63**: 3252-3260 [PMID:32049522]
276. Zhao Z, Lee CC, Baldini A and Caskey CT. (1995) A human homologue of the Drosophila polarity gene frizzled has been identified and mapped to 17q21.1. *Genomics* **27**: 370-3 [PMID:7558010]