

## Notch receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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### Abstract

The canonical Notch signalling pathway has four type I transmembrane Notch receptors (Notch1-4) and five ligands (DLL1, 2 and 3, and Jagged 1-2). Each member of this highly conserved receptor family plays a unique role in cell-fate determination during embryogenesis, differentiation, tissue patterning, proliferation and cell death [2]. As the Notch ligands are also membrane bound, cells have to be in close proximity for receptor-ligand interactions to occur. Cleavage of the intracellular domain (ICD) of activated Notch receptors by  $\gamma$ -secretase is required for downstream signalling and Notch-induced transcriptional modulation [15, 3, 11, 22]. This is why  $\gamma$ -secretase inhibitors can be used to downregulate Notch signalling and explains their anti-cancer action. One such small molecule is [RO4929097](#) [8], although development of this compound has been terminated following an unsuccessful Phase II single agent clinical trial in metastatic colorectal cancer [19].

Aberrant Notch signalling is implicated in a number of human cancers [2, 20, 6, 16], with [demcizumab](#) and [tarextumab](#) identified as antibody inhibitors of ligand:receptor binding [13].

### Contents

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### Database links

## Notch receptors

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=914>

### Targets

[notch receptor 1](#)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2861>

[notch receptor 2](#)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2859>

[notch receptor 3](#)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2860>

[notch receptor 4](#)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2862>

## References

1. Agrawal N, Frederick MJ, Pickering CR, Bettgowda C, Chang K, Li RJ, Fakhry C, Xie TX, Zhang J and Wang J *et al.*. (2011) Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science* **333**: 1154-7 [PMID:21798897]
2. Al-Hussaini H, Subramanyam D, Reedijk M and Sridhar SS. (2011) Notch signaling pathway as a therapeutic target in breast cancer. *Mol. Cancer Ther.* **10**: 9-15 [PMID:20971825]
3. De Strooper B, Annaert W, Cupers P, Saftig P, Craessaerts K, Mumm JS, Schroeter EH, Schrijvers V, Wolfe MS and Ray WJ *et al.*. (1999) A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain. *Nature* **398**: 518-22 [PMID:10206645]
4. Garg V, Muth AN, Ransom JF, Schluterman MK, Barnes R, King IN, Grossfeld PD and Srivastava D. (2005) Mutations in NOTCH1 cause aortic valve disease. *Nature* **437**: 270-4 [PMID:16025100]
5. Gurney AL, Hoey TC, van der Horst ETH, Sato AK, Liu YC, Bruhns MF and Lewicki JA.. (2012) Antibodies to notch receptors. Patent number: US8226943 B2.
6. Lefort K, Mandinova A, Ostano P, Kolev V, Calpini V, Kolfschoten I, Devgan V, Lieb J, Raffoul W and Hohl D *et al.*. (2007) Notch1 is a p53 target gene involved in human keratinocyte tumor suppression through negative regulation of ROCK1/2 and MRCKalpha kinases. *Genes Dev.* **21**: 562-77 [PMID:17344417]
7. Lehmann BD, Pietenpol JA and Tan AR. (2015) Triple-negative breast cancer: molecular subtypes and new targets for therapy. *Am Soc Clin Oncol Educ Book* **35**: e31-9 [PMID:25993190]
8. Luistro L, He W, Smith M, Packman K, Vilenchik M, Carvajal D, Roberts J, Cai J, Berkofsky-Fessler W and Hilton H *et al.*. (2009) Preclinical profile of a potent gamma-secretase inhibitor targeting notch signaling with in vivo efficacy and pharmacodynamic properties. *Cancer Res.* **69**: 7672-80 [PMID:19773430]
9. McBride KL, Riley MF, Zender GA, Fitzgerald-Butt SM, Towbin JA, Belmont JW and Cole SE. (2008) NOTCH1 mutations in individuals with left ventricular outflow tract malformations reduce ligand-induced signaling. *Hum. Mol. Genet.* **17**: 2886-93 [PMID:18593716]
10. Nagamatsu I, Onishi H, Matsushita S, Kubo M, Kai M, Imaizumi A, Nakano K, Hattori M, Oda Y and Tanaka M *et al.*. (2014) NOTCH4 is a potential therapeutic target for triple-negative breast cancer. *Anticancer Res.* **34**: 69-80 [PMID:24403446]
11. Nam Y, Sliz P, Song L, Aster JC and Blacklow SC. (2006) Structural basis for cooperativity in recruitment of MAML coactivators to Notch transcription complexes. *Cell* **124**: 973-83 [PMID:16530044]
12. Ntziachristos P, Lim JS, Sage J and Aifantis I. (2014) From fly wings to targeted cancer therapies: a centennial for notch signaling. *Cancer Cell* **25**: 318-34 [PMID:24651013]
13. Previs RA, Coleman RL, Harris AL and Sood AK. (2015) Molecular pathways: translational and therapeutic implications of the Notch signaling pathway in cancer. *Clin. Cancer Res.* **21**: 955-61 [PMID:25388163]
14. Puente XS, Pinyol M, Quesada V, Conde L, Ordóñez GR, Villamor N, Escaramis G, Jares P, Beà S and González-Díaz M *et al.*. (2011) Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. *Nature* **475**: 101-5 [PMID:21642962]
15. Schroeter EH, Kisslinger JA and Kopan R. (1998) Notch-1 signalling requires ligand-induced proteolytic release of intracellular domain. *Nature* **393**: 382-6 [PMID:9620803]

16. Sjölund J, Johansson M, Manna S, Norin C, Pietras A, Beckman S, Nilsson E, Ljungberg B and Axelson H. (2008) Suppression of renal cell carcinoma growth by inhibition of Notch signaling in vitro and in vivo. *J. Clin. Invest.* **118**: 217-28 [PMID:18079963]
17. Stittrich AB, Lehman A, Bodian DL, Ashworth J, Zong Z, Li H, Lam P, Khromykh A, Iyer RK and Vockley JG *et al.*. (2014) Mutations in NOTCH1 cause Adams-Oliver syndrome. *Am. J. Hum. Genet.* **95**: 275-84 [PMID:25132448]
18. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, Kryukov GV, Lawrence MS, Sougnez C and McKenna A *et al.*. (2011) The mutational landscape of head and neck squamous cell carcinoma. *Science* **333**: 1157-60 [PMID:21798893]
19. Strosberg JR, Yeatman T, Weber J, Coppola D, Schell MJ, Han G, Almhanna K, Kim R, Valone T and Jump H *et al.*. (2012) A phase II study of RO4929097 in metastatic colorectal cancer. *Eur. J. Cancer* **48**: 997-1003 [PMID:22445247]
20. Vilimas T, Mascarenhas J, Palomero T, Mandal M, Buonamici S, Meng F, Thompson B, Spaulding C, Macaroun S and Alegre ML *et al.*. (2007) Targeting the NF-kappaB signaling pathway in Notch1-induced T-cell leukemia. *Nat. Med.* **13**: 70-7 [PMID:17173050]
21. Weng AP, Ferrando AA, Lee W, Morris 4th JP, Silverman LB, Sanchez-Irizarry C, Blacklow SC, Look AT and Aster JC. (2004) Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science* **306**: 269-71 [PMID:15472075]
22. Wilson JJ and Kovall RA. (2006) Crystal structure of the CSL-Notch-Mastermind ternary complex bound to DNA. *Cell* **124**: 985-96 [PMID:16530045]