Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
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Title page

Notch 1 in cancer therapy: possible clinical implications and challenges

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Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
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Running Title Page

Running tittle: Notch 1 in the clinical management of cancer

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Number of manuscript pages: 44 pages (with tables, figures, and references)
Number of figures: 2
Number of tables: 2
Word count of abstract: 234
Word count of introduction: 472
Word count of discussion: 5726
Number of references: 164

Abbreviation list

ABCC1: ATP binding cassette subfamily c member 1

ASPH: aspartate β-hydroxylase

BRAF: rapidly accelerated fibrosarcoma

CADASIL: cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy syndrome

CD44: cluster of differentiation 44

CK2: casein kinase 2

DAPT: N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester

DCIS: ductal carcinoma in situ

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Dll: delta-like

DLS ligands: delta/serrate ligands

EGF: endothelial growth factor

EMT: epithelial-to-mesenchymal transition

ErbB4: Erb-B2 receptor tyrosine kinase 4

ERK: extracellular signal-regulated kinase

FFPE: formalin-fixed paraffin-embedded

GSI: gamma-secretase inhibitor

Hey-1: hairy/enhancer-of-split related with YRPW motif protein 1

JAG 1: Jagged 1

JNK: C-Jun N-terminal kinase

LAG-2: lin-12 and glp-1 phenotype

lncRNA: long noncoding RNA

mAb: monoclonal antibodies

MAPK: mitogen-activated protein kinase

MCF-7: Michigan cancer foundation-7

MDA-MB-231: M.D. Anderson and MB stands

miRNA: micro-RNA

NICD: notch intracellular domain

PEST domain: proline (P), glutamic acid (E), serine (S), and threonine (T) rich domain

POFUT 1: protein o-fucosyltransferase-1

PPI: protein-protein interaction

PTEN**:** phosphatase and tensin homolog

Ras: rat sarcoma

SERCAs: Sarco/endoplasmic reticulum calcium ATPases

shRNA: short hairpin RNA

siRNA: short interference RNA

T-ALL: t-cell acute lymphoblastic leukemia

TNBC: triple negative breast cancer

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Abstract

The Notch family consists of four highly conserved transmembrane receptors, the release of the active intracellular domain requires the enzymatic activity of gamma secretase. Notch is involved in embryonic development and in many physiological processes of normal cells where it regulates growth, apoptosis and differentiation. Notch 1, a member of the Notch family, is implicated in many types of cancer, including breast cancer (especially triple negative breast cancer), leukemias, brain tumors, and many others. Notch 1 is tightly connected to many signaling pathways that are therapeutically involved in tumorigenesis. Together, they impact apoptosis, proliferation, chemosensitivity, immune-response and the population of cancer stem cells. Notch 1 inhibition can be achieved through various and diverse methods, among the most common are the gamma secretase inhibitors which produce a pan-Notch inhibition, or the use of Notch 1 siRNA or Notch 1 monoclonal antibodies (mAb) which produce a more specific blockade. Downregulation of Notch 1 can be used alone or in combination with chemotherapy where a synergistic effect and a decrease in chemoresistance can be achieved. Targeting Notch1 in cancers that harbor high expression levels of Notch 1 offers an addition to therapeutic strategies recruited for managing cancer. Considering available evidence, Notch 1 offers a legitimate target that might be incorporated in future strategies for combating cancer. In this review, the possible clinical applications of Notch 1 inhibition and the obstacles that hinder its clinical application are discussed.

Keywords: Notch 1, cancer, cancer stem cells (CSC), Notch signaling pathway, gamma-secretase inhibitor

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Significance Statement

Notch 1 plays an important role in different types of cancer. Numerous approaches of Notch 1 inhibition possess potential benefits in the management of various clinical aspects of cancer. The application of different Notch 1 inhibition modalities faces many challenges.

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1. Introduction

Notch proteins are transmembrane receptors that were first identified in Drosophila melanogaster, they exert an important role in the transfer of cell-to-cell signals and in the regulation of embryonic development. They determine the fate of cells by regulating their differentiation, apoptosis, and proliferation. The Notch receptor, after post-translational modifications, consists of an extracellular part (with multiple tandem epidermal growth factor EGF-like repeats) that binds to ligands expressed on an adjacent cell, a transmembrane region, and an intracellular part that transports the signal (Bianchi et al., 2006). When the extracellular domain binds to any of the DLS ligands (Delta/Serrate/ or LAG-2) it forms a complex that is internalized into the cytoplasm by endocytosis and mediates a metalloprotease cleavage of the extracellular domain. Notch Intracellular Domain (NICD) is released by γ-secretase cleavage of the fragment that is bound to the membrane which, in turn, is translocated to the nucleus and binds to the transcription complex that removes the repression of Notch targets, the Hes and Hey proteins, Figure 1. Cis-inhibitory complexes that limit the Notch activity is formed when the Notch receptor and ligands that are expressed on the same cell surface interact (Chillakuri et al., 2012).

There are four Notch receptors and five transmembrane Notch ligands that belong to Delta/Delta-like (Dll-1, -3 and -4) and Serrate/Jagged (J-1 and -2) ligand families (Lindsell et al., 1996). Although the Notch receptors share ligands and structural similarities, they have different functions. In humans, Notch 1 and 4 are crucial for T-cell development (Hozumi et al., 2008; Radtke et al., 1999), Notch 3 mutations cause cerebral autosomal-dominant arteriopathy with

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subcortical infarcts and leukoencephalopathy (CADASIL) syndrome (Joutel 2011), Notch 4 on the other hand doesn't seem to be an important player but it overlaps with Notch1 (Krebs et al., 2000).

The Notch pathway is an important key player in malignancies, abnormalities in Notch signaling are involved in many hallmarks of cancer (Aster et al., 2017). The role of Notch signaling pathway in cancer is context dependent and varies from being oncogenic to tumor suppressive (Li et al., 2010).

Although most of the members of the Notch receptor family are generally involved in many cancers, targeting individual Notch receptors offers many advantages including reduced toxicity and enhanced effects on specific receptors that are involved in certain types of cancer (Wu et al., 2010). Notch 1 activating mutations were identified as an oncogene in many cancers including triple negative breast cancer (Stoeck et al., 2014), T-cell acute lymphoblastic leukemia (T-ALL) (Ferrando 2009; Pear et al., 1996). Conversely, blockade of Notch 1 in the skin of mice resulted in the formation of skin tumors which may be mediated through an increase in beta-catenin signaling (Nicolas et al., 2003). The disparities in the role of Notch signaling suggest an effect that is dependent on tissue type, development stage, and co-involved signaling pathways.

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2. Tumorigenesis

The role of Notch 1 in the tumorigenesis of many types of cancer was explored extensively.

2.1 Prostate cancer

The oncogenic effect of Notch1 was confirmed in prostate cancer when Notch 1 expression was discovered in cultured prostate cancer cells that originated from primary tumors, lymph node metastasis, brain metastasis, and bone metastasis (Leong et al., 2008). EMT markers were investigated in metastatic prostate cancer, data analysis obtained from primary and bone metastasis FFPE samples showed that metastatic samples had significantly higher frequency of Notch 1 positive cells, and Notch-1 expression was also higher in bone metastatic prostate cancer tissue samples compared to those of the primary prostate cancer ($p = 0.057$) (Sethi et al., 2010).

The relationship between Notch 1 and prostate cancer was further complicated by the finding that dysregulation of this signaling pathway also occurs in prostate cancer. Analysis of data from the Gene Logic database revealed that the expression of Notch 1 and the downstream target gene, Hey-1, were downregulated in prostate adenocarcinoma samples when compared to normal prostate samples in normal people or adjacent to prostate cancer cells. The expression of many genes was changed as a result of Notch 1 ablation, these were important for proliferation, cell cycle, DNA repair, DNA replication, cell growth, cancer, and many other functions (Wang et al., 2006). Additionally, Whelan et al demonstrated that in prostate cancer, diminished Notch 1 signaling was correlated with adenocarcinoma through dysregulation of PTEN (Whelan et al., 2009). Despite the previous conflicting data that does not confirm whether Notch 1 is a tumor

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suppressor or an oncogene in prostate cancer, O'Brien et al suggested that Notch inhibition at the localized prostate stage could prevent progression of cancer (O'Brien et al., 2017).

2.2 T-cell acute lymphoblastic leukemia

The role of Notch 1 in T-cell acute lymphoblastic leukemia is more well defined and was well established by Weng et al (Weng et al., 2004). In their analysis of human T-ALLs, more than 50% had activating mutations in the Notch 1 gene. The study proposed Notch 1 as a possible therapeutic target, especially for patients who are refractory. One of the Notch1 target genes was c-myc, where increased expression of intracellular Notch1 was associated with increased c-myc mRNA levels in primary mouse T-cell tumors. Additionally, inhibition of Notch1 (with gamma secretase inhibitor, GSI) caused a reduction in c-myc mRNA levels and inhibited leukemic cell growth (Sharma et al., 2006). Another Notch 1 target was mTOR, which was deactivated by the gamma-secretase inhibitor DAPT, a well-known inhibitor of Notch. This effect was rescued by increased expression of the intracellular domain of Notch and expression of c-myc, which suggests that myc is an intermediate between Notch 1 and mTOR (Chan et al., 2007). Cell cycle is also influenced by Notch 1, it enhances the progression of T cells through the G1/S phase of the cell cycle by increasing the expression of cyclin D3, and CDK4. Notch-dependent human T-ALL cell lines treated with a gamma secretase inhibitor (LY-411,575) were rescued from cell cycle arrest by increased expression of cyclin D3 (Joshi et al., 2009). Notch 1 may also increase cell cycle progression by reducing the levels of protein p 27 Kip1 through promotion of its degradation by E3 ubiquitin ligase SKP2 in T-ALL cells (Dohda et al., 2007).

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2.3 Breast cancer

In breast cancer, when sections of primary breast tumors from the lumino-basal subtype patients and xenografted tumors were analyzed, the Notch1 transcripts were elevated in basal-like/claudin-low, ESR1− tumors. This high level of Notch 1 activity was suppressed by a gamma-secretase inhibitor (GSI). Several GSIs were examined: DAPT, N-[N-(3,5-Difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester; compound E [(2S)-2-[(3,5-Difluorophenyl)acetyl]amino-N-[(3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]propanamide] ; XIX, (2S,3R)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-4-hydroxy-N-((3S)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyramide. In addition, treatment with GSIs or Notch 1 downregulation by shRNA maintained an ER+ luminal phenotype in breast cell lines even in the absence of estrogen (Haughian et al., 2012).

In mouse models, continuous Notch1 activation in the mammary epithelium induced neoplasms, and was correlated with increased levels of cyclin D1, a possible target of Notch signals in the mammary epithelium (Kiaris et al., 2004).

Notch 1 was especially implicated in triple negative breast cancer (TNBC). In 200 human breast cancer samples, higher expression of mRNA levels of Notch 1 was statistically significant in TNBC but insignificant in ER – samples. By applying a predictive model for TNBC, a one-unit increase in the log of Notch-1 led to an increase in the likelihood of having TNBC by 6.4 folds (95% CI: 2.04-20.11) (Yuan et al., 2015). Notch 1 was also correlated with Ras/MAPK pathways, and hyperactivation of Notch1 and Ras/MAPK were coordinated (Mittal et al., 2014). Signaling pathways upstream of Notch 1 were also revealed, C-Jun N-terminal kinase (JNK), a member of the MAPK family, promoted cancer stem cells tumorigenesis in TNBC through an upregulation of Notch1 at both transcription and protein levels (Xie et al., 2016).

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One meta-analysis examined 3867 patients and revealed that Notch 1 in breast cancer tissues compared to normal ones was significantly over-expressed. Furthermore, patients with higher Notch 1 expression were more likely to progress from ductal carcinoma in situ to invasive cancer with an odds ratio of 3.75 (95% CI, 1.8-7.78) (Yuan et al., 2015). The involvement of Notch 1 in EMT was examined in breast cancer cell lines, abnormal expression of Notch1 intracellular domain led to an decrease in E-CADHERIN levels and promoted invasiveness in MCF-7 cells, while Notch 1 inhibition using DAPT (RO4929097) in MDA-MB-231 caused an increase in E-CADHERIN levels and reduced invasiveness (Bolos et al., 2013).

2.4 Glioblastoma

In Glioblastomas (GBMs), a recent study evaluated Notch 1 expression profiles using four cohorts of gliomas. Results from this study showed that Notch 1 was overexpressed in GBM patients compared to normal controls, and there was positive correlation between Notch 1 and RELA (NF-κB(p65)) levels. In addition, they were both colocalized in the same GBM tissue cells (Hai et al., 2018).

When 69 glioma tissue specimens were compared to 8 normal specimens, Notch 1 level was over expressed in 71% of glioma specimens compared to 13 % of 8 normal specimens, ($P < 0.05$) (Han et al., 2017).

2.5 Head and neck squamous cell carcinoma

Notch 1 blockade was associated with a reduction in immunosuppression in this type of carcinoma. Genetically modified head and neck squamous cell carcinoma mice models that exhibited increased activity of Notch 1, were exposed to a γ-secretase inhibitor (DAPT). This led

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to enhanced tumour immunity mediated by a decrease in the immune checkpoint molecules, myeloid-derived suppressor cells, and tumour-associated macrophages (Mao et al., 2018).

Weiland et al investigated the role of Notch1 active intracellular domain protein (N1-ICD) located in vascular endothelial cells (ECs) in metastasis. The expression of N1-ICD was elevated in several types of cancer including lung adenocarcinoma, serous ovarian carcinoma, colorectal carcinoma, breast carcinoma, and melanoma. When compared with clinical data, an association between the levels of N1-ICD and metastasis was demonstrated. For example, patients with positive sentinel lymph nodes had higher rates of positive N1-ICD. Similarly, melanoma patients with positive N1-ICD expression had higher rates of metastasis (Wieland et al., 2017).

3. Notch 1 and cancer stem cells

Notch, Hedgehog, Wnt, and JAK/STAT are signaling pathways that are important for the survival of cancer stem cells (CSCs) (Matsui 2016). Many studies provided proof that the antitumor and chemo-sensitization effect of Notch 1 downregulation and pharmacological inhibition was mainly a consequence of a reduction in the cancer stem cell population.

3.1 Breast Cancer

In triple negative breast cancer (TNBC) cell lines, the use of Notch1 monoclonal antibodies (mAbs) has been shown to significantly reduce the cancer stem cell (CD44+/CD24-/low) population (Qiu et al., 2013). When cancer stem cells with stemness markers were isolated from renal cell carcinoma cell line, Notch 1, among other Notch receptors, was overexpressed in these stem cells. Notch1/2 inhibition with a gamma secretase inhibitor (MRK-003) increased sensitivity to cisplatin and sorafenib and reduced stemness markers. Xenografts from these treated cancer stem cells manifested enhanced apoptosis and decreased proliferation (Xiao et al.,

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2017). In HER2+ breast cancer, Notch 1 plays an important role in the development of trastuzumab resistance by enhancing stem cell survival. The enrichment of the stem cell population by Notch 1 and, consequently, poor survival rates were mediated via inhibition of PTEN (Baker et al., 2018).

3.2 Colorectal cancer

In colon tumor cell line HCT-116, the transduction of intracellular domain of Notch 1 (ICN1) produced an increase in the CD44, a cell-surface glycoprotein that is overexpressed in cancer stem cells. Inhibition of the Notch 1 signaling pathway by using pan-Notch inhibitor DAPT led to a 41% decrease in CD44 ($P < 0.001$). Previous results indicate the correlation of stemness and Notch 1 expression in colon cancer (Fender et al., 2015).

3.3 Ovarian cancer

Galectin-3 is an extracellular protein that functions as a cross-linker. Galectin-3 protein was correlated with increased stemness of ovarian cancer cells that is reflected clinically as poor survival and relapse in ovarian cancer patients (Kim et al., 2011). Overexpression of Galectin-3 in human ovarian cancer cell line, A2780, caused increased activity of Notch signaling. Furthermore, a reduction in the expression of this protein decreased NICD1 levels and its target genes, Hes1 and Hey1 (Kang et al., 2016).

3.4 Glioblastoma

Protein Kinase C iota (PRKCI) gene, a member of the atypical Protein Kinase C (PKC) family, in glioblastoma (GBM) stem-like cell (GSC) is spatially close to Notch 1 gene. Silencing PRKCI gene with shRNAs was correlated with downregulation of the Notch pathway genes (including

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Notch 1) in vitro, and reduced tumor growth in vivo. Targeting PRKCI using shRNAs also led to reduced proliferation in GSC lines, NCH421k, NCH644 and NCH44 (Phillips et al., 2016).

A recent review (2018) of the trials targeting cancer stem cells through the Notch signaling pathway was conducted by Venkatesh et al. The assembled evidence in this review suggested that Notch inhibition represents a promising opportunity to manage cancer through its strongest, most resistance component, cancer stem cells (Venkatesh et al., 2018).

4. Notch 1 as a prognostic tool

Extensive efforts were made in recent years to explore the prognostic value of Notch 1 in different types of cancer.

4.1 Breast cancer

When correlated with patient follow-up data, high levels of Notch 1 expression in breast cancer tissues were associated with lower 5-year survival rates compared to tissues with low levels of Notch 1 (49% versus 64%). Additionally, tumors that expressed high levels of Notch 1 either expressed high or low levels of JAG1. Those with high expression levels of both Notch 1 and JAG1 have reduced overall survival compared to other tumors (Reedijk et al., 2005). Further evidence for the prognostic value of Notch 1 was provided by a meta-analysis that examined the microarray data of 4,463 patients from 17 studies. Increased levels of Notch 1 were correlated with a decrease in recurrence-free survival regardless of other prognostic factors or type of breast cancer (Abravanel et al., 2015). In another study that used antibodies for active Notch1 intracellular domain (NICD) and pErk1/2 specific antibodies to detect Ras/MAPK activity in grade III ductal carcinoma breast cancer patients, 61.7% of patients exhibited a high Notch 1 and high pErk phenotype. Interestingly, 89% patients (71 out of 80) of the high pErk samples had

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high Notch 1 levels and more than two thirds of the TNBC cases belonged to this phenotype (Mittal et al., 2014). Another study that investigated the prognostic value of Notch 1 examined paraffin-embedded ductal carcinoma in situ (DCIS) tissues. Results from the study revealed that increased levels of Notch 1 intracellular domain (NICD) was correlated with recurrence at 5 years ($P = 0.012$).

4.2 Gallbladder cancer

The clinicopathological importance of Notch 1 was also investigated in gallbladder cancer. This rare and aggressive cancer includes three subtypes: adenocarcinoma (AC), which is the most common subtype, squamous cell carcinoma (SC) and adenosquamous carcinoma (ASC). Notch 1 expression was significantly associated with low surgical curability, invasion, and metastasis in all subtypes. Additionally, when compared to patients with negative Notch 1/ Notch 3 expression, those with positive Notch 1/Notch 3 expression had statistically significant shorter survival times ($p < 0.05$ in all subtypes). Authors concluded that Notch1 expression was one of the factors the independently predicted poor prognosis in squamous cell/adeno-squamous carcinomas and adenocarcinomas patients (Liu et al., 2016).

4.3 Glioblastoma

Notch 1 expression was negatively correlated with overall survival in glioblastoma patients, those with low Notch1 expression had an overall survival of 26 months compared to 15 months in patients with high Notch 1 expression ($P = 0.002$). Furthermore, Notch 1 expression independently predicted overall survival (Han et al., 2017).

In addition, analysis of survival data from numerous databases revealed that high expression levels of Jagged1 (ligand for Notch 1 receptor) was positively correlated with poor survival, $P <$

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0.0001. Higher expression levels of Notch 1 ligand were associated with higher levels of NF-κB(p65) (Hai et al., 2018).

4.4 T-cell acute lymphoblastic leukemia

In a study of South Indian T-cell acute lymphoblastic leukemia pediatric patients, decreased degradation of Notch 1 was associated with better clinical outcome. The degradation of Notch 1 was controlled by the E3 ubiquitin ligase FBXW7 and the PEST domain in Notch 1. Consequently, mutations in NOTCH1/FBXW7 led to increased stability of the Notch1. In these pediatric patients, NOTCH1/FBXW7 activating mutations were associated with increased levels of Notch 1 protein. When compared with NOTCH1/FBXW7 nonmutated patients, two thirds (65%) of NOTCH1/FBXW7-mutated T-ALL patients responded better to prednisolone and had a more favorable clinical outcome (Natarajan et al., 2015).

4.5 Adrenocortical tumors

Aberrations in the Notch pathway is the most frequent abnormality in adrenocortical tumors (ACTs). When fresh frozen samples of adrenocortical carcinomas (ACC) were analyzed, there was an over-expression of the Jagged1(Notch1 ligand) and the HEY2 (downstream target of Notch1) compared to normal adrenal glands or benign adrenocortical lesions. Over expression of the Jagged 1 and HEY 2 were at both the mRNA and protein level. However, in terms of clinical outcome measured as overall survival (OS), the impact of Jagged1 and HEY2 was not the same. High levels of HEY2 expression were associated with poor prognosis (median overall survival: 50 vs 100 months, $P = 0.13$, HR=1.68, 95%CI = 0.86-3.37), while high Jagged1 protein levels were associated with favorable impact on survival but only in patients who did not receive treatment (median overall survival: 108 vs 50 months, $P < 0.05$, HR = 0.47, 95%CI = 0.24-0.94).

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Moreover, the positive effect of Jagged1 was especially evident in cancers associated with low nuclear β-catenin expression (Ronchi et al., 2015).

4.6 Lung cancer

In non-small cell lung cancer (NSCLC) patients, Notch 1 levels also had clinical predictive value. A recent meta-analysis that assessed 19 studies and involved 3663 non-small cell lung cancer (NSCLC) patients revealed that Notch1 and Notch3 overexpression was associated with poor overall survival (Notch1: HR, 1.29; 95% CI, 1.06-1.57) (Yuan et al., 2015).

4.7 Other types of cancer

Notch 1 was also explored for its prognostic value in many other types of cancer. In hepatocellular carcinoma, overexpression was associated with poor survival and a more aggressive disease (Wu et al., 2015), in colorectal cancer (CRC), where the extent of expression of Notch1and Jagged1 was correlated with histological grading and lymph node metastasis of CRC (Zheng et al., 2015), and in acute myeloid leukemia where high gene expression levels of Notch1 and Jagged1 independently predicted poor prognosis in terms of overall survival and relapse-free survival (Xu et al., 2011).

5. Resistance to therapy

Chemotherapy, hormone therapy, and radiation remain the main modalities of clinical management in cancer. Yet, successful management of these therapeutic strategies is limited by resistance. Many in vitro studies confirmed the association of resistance with Notch 1 overexpression in many types of cancer.

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5.1 Breast cancer

Further evidence concerning the effect of Notch 1 inhibition on chemosensitivity was shown in TNBC cell line MDA-MB-231. The cytotoxic effect of paclitaxel was enhanced after its combination with Notch1-siRNA, this was achieved by altering the expression of paclitaxel targets, through increased expression of Caspase-3 and Caspase-9 and reduced expression of Bcl-2 (Zhou et al., 2017). Another study used a similar approach and was conducted by Zang et al, revealed that Notch1-siRNA caused downregulation of Notch 1 and improved chemosensitivity to doxorubicin and docetaxel (Zang et al., 2010). Notch1 monoclonal antibodies (mAb) were also used in triple negative breast cancer xenografts to investigate its effect when combined with docetaxel. Notch 1 blockade improved the cytotoxic effects of docetaxel through targeting cancer stem cell population (Qiu et al., 2013).

Notch-1 inhibition by either siRNA or a gamma secretase inhibitor (LY411,575 and MRK-003) improved sensitivity to trastuzumab in trastuzumab-resistant cells (Osipo et al., 2008; Pandya et al., 2011). When ABCC1-expressing MDR MCF7/VP cells were compared to MCF7/ wild type cells, higher levels of intracellular Notch 1, cleaved form of the Notch 1, were detected. Furthermore, the use of either a γ-secretase inhibitor (DAPT) or shRNA resulted in a reduction in intracellular Notch 1, which was followed by a decrease in ABCC1 (Cho et al., 2011). In MDA-MB-231 and MCF-7 human breast cancer cell lines, treatment of cells with a combination of Notch-1 siRNA and numerous doses of doxorubicin/docetaxel led to increased chemosensitivity (Zang et al., 2010).

Chemoresistance of breast related bone metastasis was also examined. The effect of a monoclonal antibody against Jagged1 (ligand for Notch 1 receptor), clone 15D11, was studied in bone metastasis. Mice treated with paclitaxel alone developed resistance to chemotherapy, while

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those that received paclitaxel and Jagged1 antibodies exhibited a significant reduction of bone metastasis and no development of resistance (Zheng et al., 2017).

5.2 Chronic lymphocytic leukemia (CLL)

In cells isolated from CLL patients, the presence of Notch 1 activating mutations prompted resistance to fludarabine, this effect was reversed using Notch 1 blockade induced by a gamma secretase inhibitor (GSI-IX) (Arruga et al., 2014).

5.3 Lung cancer

In p 53 competent lung cancer cell lines, induction of Notch1 prevented cell death after exposure to Adriamycin. It was proposed that this was mediated through inhibition of the functions of p53 (Mungamuri et al., 2006). Notch1 downregulation using siRNA in small cell lung carcinoma (SCLC) cell lines, H69AR and SBC-3, resulted in increased chemosensitivity mediated through a reduction in cell adhesion-mediated drug resistance (CAM-DR) (Hassan et al., 2016).

In non-small lung carcinoma (NSCLC), the combination of gamma secretase inhibitor (BMS-906024) with paclitaxel and cisplatin increased sensitivity to these chemotherapies and resulted in improved antitumor effect in both cell lines and NSCLC patient-derived xenografts (PDXs). Interestingly, samples without KRAS and BRAF mutations exhibited a higher synergistic effect with paclitaxel compared to samples with KRAS or BRAF activating mutations. However, samples with high Notch 1/ Notch 3 expression were not correlated with increased synergy. This suggests that the effect of gamma secretase inhibitors in a certain subgroup of NSCLC samples is not through Notch inhibition (Morgan et al., 2017).

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5.4 Radiotherapy

Notch 1 is also involved in radiotherapy resistance. The response of cancer-initiating cells (CD24(-/low)/CD44+) and activation of Notch 1 signaling pathway to radiation was explored. Cells treated with ionizing radiation had enhanced activation of Notch 1 signaling pathway (Phillips et al., 2006). In glioblastoma cell lines (U87MG and U251), down regulation of Notch 1 using CRISPR/Cas9 improved sensitivity to radiation through enhancing apoptosis and significantly reduced tumor growth in mouse xenografts, $P < 0.05$ (Han et al., 2017).

The treatment schedule, whether Notch 1 inhibition is administrated before or after chemotherapy/radiation, is an important factor in determining the effect of this addition. The schedule of administration of Notch 1 inhibitors is important to achieve an equilibrium between pro- and anti-angiogenic effects. This equilibrium will partially normalize the vasculature before treatment with chemotherapy/ radiation and enhance tumor oxygenation and blood supply which will result in improved antitumor effects. The timing of Notch 1 treatment is also crucial to counteract the increased levels of Notch 1 after chemotherapy/radiation treatment that is correlated with resistance (Yahyanejad et al., 2016).

6. Targeting Notch 1 in cancer

Anti- cancer effects using Notch 1 inhibition can be achieved by numerous strategies, Figure 2.

These include: Notch 1 monoclonal antibodies, Notch 1 decoy, Notch 1 siRNA, Notch 1 miRNA, natural products, anti-DLL4 antibodies, alpha secretase inhibitors, gamma secretase inhibitors, Sarco/endoplasmic reticulum calcium ATPases (SERCAs) inhibitors (SERCAs are pumps that are important for Notch 1 trafficking), Protein O-fucosyltransferase-1 knockdown (POFUT1- transfers fucose to epidermal growth factor-like repeats in Notch receptor), and pan –

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Notch inhibition that is mediated through protein-protein interaction (PPI) inhibitors that targets the Notch transcription complex in the nucleus (Sorrentino et al., 2019). These Notch 1 inhibition approaches can be further developed and may provide promising therapeutic agents, Table 1.

The most studied mode of deactivation of Notch signaling pathway is inhibition that is mediated through the gamma secretase enzyme. The γ-Secretase inhibitors (GSIs) are functionally different with variable cleavage effects on the Notch precursors. Hence, they do not possess equivalent biological effects (Ran et al., 2017).

Several clinical trials are being conducted to explore the potential impact of secretase inhibitors in cancer therapy as single agents (De Jesus-Acosta et al., 2014; Deangelo et al., 2006; Hughes et al., 2015; Krop et al., 2012; Pant et al., 2016; Papayannidis et al., 2015; Strosberg et al., 2012; Tolcher et al., 2012), or in combination with other drugs. An oral GSI combined with docetaxel was assessed for safety and efficacy in a phase Ib, open-label, multicenter study in patients with advanced triple-negative breast cancer. Results have shown that the pharmacokinetics of docetaxel was not changed by co-administration of GSI (PF-03084014) and demonstrated an acceptable safety profile (Locatelli et al., 2017). In another study, the impact of docetaxel combination of increasing doses of docetaxel with gamma secretase inhibitor (MK-0752) was studied in both xenograft model and, clinically, in advanced breast cancer. Results showed that the combination was effective in reducing cancer stem cells and with acceptable safety profile in patients (Schott et al., 2013). The pharmacodynamic and pharmacokinetic properties of the gamma secretase inhibitor, MK-0752, was also explored in refractory or recurrent CNS malignancies in children. The study estimated the maximum-tolerated dose, investigated the dose-limiting toxicities, and revealed that this gamma secretase inhibitor was tolerated in

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children (Fouladi et al., 2011). PF-03084014, a gamma secretase inhibitor, was tested in phase 1 trial in various types of cancer such as desmoid cancers and advanced solid malignancies to determine safety, tolerability, and the dose needed for phase 2 clinical studies. Results showed that the gamma secretase inhibitor had an acceptable safety profile (Hughes et al., 2015; Messersmith et al., 2015). LY900009, another gamma secretase inhibitor, was also studied in a phase 1 trial to determine safety and dose needed in advanced cancers to reduce tumor progression (Pant et al., 2016).

In advanced solid cancers, gamma secretase inhibitors were also combined with other anticancer medications in phase 1 trials to investigate toxicities and tolerability in patients. RO4929097, an oral gamma secretase inhibitor was combined with temsirolimus (Diaz-Padilla et al., 2013), and with gemcitabine (Richter et al., 2014).

Despite the promising role that gamma secretase inhibitors may hold, their use in the clinical management of cancer faces many challenges. A major obstacle to their clinical use seems to be their gastrointestinal adverse effects (Imbimbo 2008). These adverse effects are a consequence of simultaneous inhibition of both notch1 and Notch 2 and blockade of either one individually ameliorates the gastrointestinal toxicity (Wu et al., 2010). This suggests that alternative approaches would be more appropriate such as: targeting Notch receptors independently, using combination therapies that utilize lower doses, or targeting only cells with mutant Notch while sparing the wild type cells. Other strategies that manipulate dosing regimens were also investigated to reduce or avoid gastrointestinal toxicity of gamma secretase inhibitors. One strategy was to use a combination of Notch 1 inhibition with glucocorticoids, this regimen reduced intestinal toxicity and improved the response of the glucocorticoid resistant T-ALL

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(Real et al., 2009). The study tested two gamma secretase inhibitors: compound E ([(2S)-2-{[(3,5-difluorophenyl)-acetylamino}-N-[(3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl] propanamide) and DBZ ((2S)-2-[2-(3,5-difluorophenyl)-acetylamino]-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,-d]azepin-7-yl)-propionamide. Another approach was to employ intermittent dosing schedules, dosage regimens using the gamma secretase inhibitor, RO4929097, with frequent drug holidays were shown to be well tolerated and effective (Tolcher et al., 2012).

Another important aspect of utilizing the gamma secretase inhibitors or any other pharmacologic Notch 1 inhibition is the issue of resistance to Notch 1 inhibition. The detection of Notch 1 resistance dictates the need to understand the mechanisms and signaling pathways that are involved. Furthermore, it is crucial to tease out the subgroup of patients that possess this resistance and develop methods and approaches to overcome it and improve response to Notch 1 inhibition. In T-cell acute lymphoblastic leukemia mouse models, resistance to Notch1 inhibition was induced by loss of function mutations of PTEN (Mendes et al., 2016). Similar results were discovered in Drosophila melanogaster, where loss of PTEN function was associated with resistance to Notch 1 inhibition (Palomero et al., 2007) produced by the gamma secretase inhibitor, Compound E (Seiffert et al., 2000). In T cell acute lymphoblastic leukemia (T-ALL), PTEN downregulation was not a result of PTEN gene mutations and subsequent decrease in protein level, but rather a decrease in PTEN lipid phosphatase activity. This diminished posttranslational activity is caused by hyperactivity of casein kinase 2 (CK2) and high levels of reactive oxygen species (Silva et al., 2008). Based on the previous findings, targeting both, the

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casein kinase 2 (CK2) and Notch inhibition, through a combination of CK2 inhibitors and gamma secretase inhibitors in vitro resulted in improved anti-tumor effect and reduced proliferation (Silva et al., 2010).

Resistance to gamma secretase inhibitors can also be mediated through epigenetic mechanism, where the withdrawal of the gamma secretase inhibitor (Compound E) can lead to the reversal of resistance (Knoechel et al., 2014).

Another challenge that faces the clinical use of gamma secretase inhibitors is that the secretase enzyme catalyzes many substrates, such as CD44, Notch receptors (all four receptors), many Notch ligands, ErbB4, E-cadherin and many others (Haapasalo et al., 2011; Nickoloff et al., 2003). An inhibitor of gamma secretase may affect the previously mentioned substrates and might also inhibit other proteases involved in cell function (Shih Ie et al., 2007).

Another interesting approach to inhibit Notch 1 in pancreatic cancer is through targeting Aspartate β-hydroxylase (ASPH) that catalyzes the hydroxylation of EGF-like repeats in Notch receptors and ligands. Treatment of pancreatic cancer cell lines with MO-I-1100, an inhibitor of B-hydroxylase, led to reduced cell growth that is mediated through downregulation of Notch signaling pathways (including Notch 1) (Dong et al., 2015).

Pan Notch inhibition can also be achieved through small molecules that inhibit protein-protein interaction (PPI) and impair the Notch transcription complex in the nucleus. Recently, a phase 1-2A study was launched to examine the pharmacokinetics and optimum dose and dosing schedule of CB-103 (PPI inhibitor) in patients with advanced solid tumors and blood malignancies (Perez Garcia et al., 2018).

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Dll4 blockade is another approach by which Notch 1 inhibition can be achieved, Dll4 is one of the five Notch membrane-bound ligands [Jagged1, Jagged2, Delta-like (Dll)-1, Dll3, and Dll4]. Dll4 protein binds to Notch 1 receptor and initiates the Notch 1 signaling reactions, blockade of DLL4/Notch 1 signaling pathway allows for a more specific inhibition that targets angiogenesis rather than a more general approach such as using gamma-secretase inhibitors.

Dll4 protein is specific to the endothelium especially arterial vessels and plays a vital role in the development of blood vessels during embryonic stage and growth of new blood vessels (angiogenesis) throughout life. Additionally, it is highly expressed throughout tumor angiogenesis and induced by hypoxia (Mailhos et al., 2001).

Selective blockade of Dll4 exhibited anti-tumor effects, this inhibition was achieved by selective Dll4 antibodies. The treatment of MDA-MB-435, HM7, Colo205 and Calu6, well established xenograft tumor models caused a reduction in the tumor growth rate compared to the control (Ridgway et al., 2006). Another method for Dll4 blockade was to use a soluble Dll4 fusion protein that binds to receptors but does not produce a signal. The inhibition of Dll4/Notch resulted in disturbance of the balance that is needed to produce healthy productive vessels, which in turn led to non-efficient angiogenesis that inhibited tumor growth (Noguera-Troise et al., 2006). Similar results were obtained using the same approach in colon cancer and Kaposi sarcoma xenografts (Scehnet et al., 2007).

Clinical trials were initiated to investigate the therapeutic advantages of anti-DLL4 antibodies, as a single agent (Casulo et al., 2016; Chiorean et al., 2015), (NCT01952249) and (NCT01577745), or in combination with gemcitabine with or without (+/-) Abraxane® (NCT01189929) (which was discontinued), in combination with FOLFIRI (NCT01189942), and in combination with carboplatin and pemetrexed (NCT01189968).

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Brontictuzumab is an anti-Notch 1 monoclonal antibody which binds to the extracellular domain of the receptor. The drug was assessed in a Phase I study to determine the safety, pharmacokinetics, and clinical benefit in patients with solid tumors. At the maximum tolerated dose (1.5 mg/kg every 3 weeks), the drug was well tolerated by the patients and accompanied by the usual gastrointestinal toxicity that is seen in Notch inhibition which was mainly manifested as diarrhea (Ferrarotto et al., 2018).

Alpha secretases are a family of metalloproteinases (also called ADAM - a disinterring and metalloproteinase) that cleave the Notch extracellular domain. This cleavage facilitates the release of intracellular domain by the gamma secretase enzyme, especially ADAM10 for Notch 1 signaling (Bozkulak et al., 2009). Although inhibitors of this family of enzymes are not as widely studied as the gamma secretase inhibitors, in glioblastoma (GBM), alpha secretase inhibitors decreased the growth of adherent GBM and GBM stem cell lines and prolonged survival in mouse models (Floyd et al., 2012).

Natural products were always a valuable source of possible anticancer therapy, many exert an anti-tumor effect through Notch 1 inhibition, these can be explored as single treatments or adjuvant therapy with other Notch 1 inhibitors for possible additive or synergistic effect, Table 2. Thapsigargin, which is obtained from the roots of Thapsia garganica, has been linked to an inhibition of SARCA channels which consequently led to aberrant Notch 1 trafficking and subsequent reduction in Notch 1 cell surface receptors. Phase 1 clinical trial was launched to assess the safety of Mipsagargin, a prodrug of thapsigargin, and establish the dose that is needed for phase 2 studies in patients with advanced solid tumors. Mipsagargin had acceptable pharmacokinetic properties and was well tolerated by patients (Mahalingam et al., 2016).

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Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are important members of the non-coding RNAs. Although they do not code for proteins, they serve as important regulators of gene expression. Mutations and aberrant expression of these non-coding RNAs were strongly associated with tumorigenesis and resistance of cancer (Hayes et al., 2015; Khurana et al., 2016).

In a study that examined the role of Notch 1 in cisplatin-resistant gastric cancer cell lines SGC7901/DDP and BGC823/DDP, results showed that Notch 1 was overexpressed in these resistant cells. Further examination of the expression of lncRNA, AK022798, suggested that the effect of Notch 1 on the evolution of these resistant cells might be mediated through this lncRNA. Moreover, the use of siRNA to downregulate lncRNA AK022798 expression, reduced the expression of drug resistance genes (Hang et al., 2015).

miRNAs consist of 19-24 nucleotides and can negatively or positively regulate different genes and signaling pathways (Chen et al., 2016). miRNAs can lead to increased or decreased levels of Notch 1 depending on the type of miRNA and cancer.

miR-223 is a non-coding RNA that was overexpressed in gemcitabine-resistant (GR) pancreatic cancer cells. miR-223 exerted an important role in the generation of the EMT phenotype through the downregulation of Fbw7 that led to increased stability of Notch1 (Ma et al., 2015).

In breast cancer, miR-34a inhibited proliferation, migration, and cancer stem cell population through downregulation of Notch 1. In addition, overexpression of miR-34a enhanced chemosensitivity towards paclitaxel (PTX) via negative regulation of Notch 1. In TNBC cell line MDA-MB-231, a negative correlation was established between miR-9 and Notch1 and increased expression of miR-9 abolished Notch1 intracellular domain.

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In breast cancer, when human tissue specimens were examined, miR-34a was downregulated in tumor tissues in comparison with the adjacent normal tissues. In addition, overexpression of miR-34a in MCF-7 cell line led to an inhibition of viability and invasion of cancer cells. These effects were induced through targeting Notch 1 (Rui et al., 2018). In TNBC cells, miR-34a was co-delivered with doxorubicin to MDA-MB-231 cells using nanoparticles. The use of the combination enhanced the anti-tumor effects of doxorubicin. In addition, recovery of normal levels of miR-34a in cancer cells led to reduced migration that was mediated through lowering the expression levels of Notch 1 (Deng et al., 2014).

In Glioblastoma, miRNAs that are specific to the Notch signaling pathway (including Notch 1) may reach up to 32 miRNAs. These include: miR-9, miR-34a, miR-92b, miR-124, miR-137, and miR-219-5p (Sun et al., 2012). In glioma cell lines, overexpression of miR-145 reduced Notch1 activation through decreased levels of Notch 1protein and its gene targets (Du et al., 2017). miR-34a was also involved in tumorigeneses of glioblastoma via Notch 1, overexpression of this miRNA in glioma cells reduced Notch 1 protein levels and inhibited tumor growth in xenografts (Li et al., 2009). In the glioblastoma cell line that represents p53-wild type (U87MG), mir-34a-5p negatively controlled the Notch-1/EGFR axis and led to inhibition of cell proliferation. This cross talk was achieved by activation of the M2 acetylcholine muscarinic receptors (Di Bariet al., 2018). Numerous miRNAs were studied and were successfully used to inhibit Notch 1 activity which makes them a promising therapeutic approach for numerous types of cancer.

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Conclusion

Signaling pathways in cancer are not equal, some are more important than others and constitute key nodes in the web of tumorigenesis. The Notch family is one of these important pathways and Notch 1 aberrant activity is detected in many cancers. In some cancers the role of Notch 1 is clear, but in others many future studies are needed to provide a more defined answer. The role of Notch 1 is as heterogenous as cancer, its role in terms of magnitude, crosstalk with other signaling pathways, and whether it behaves as a tumor suppressor or an oncogene depends on the type of cancer, stage, and mutations in other relevant genes. Yet, despite its multifaceted role, it remains a valuable and legitimate target that must be explored in the pursue of new and safer therapeutic modalities.

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Authorship Contributions

Wrote or contributed to the writing of the manuscript: Gharaibeh, Elmadany, Alwosaibai, Alshaer.

Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
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References

Abravanel DL, Belka GK, Pan TC, Pant DK, Collins MA, Sterner CJ and Chodosh LA (2015) Notch promotes recurrence of dormant tumor cells following HER2/neu-targeted therapy. J Clin Invest 125: 2484-96.

Agnusdei V, Minuzzo S, Frasson C, Grassi A, Axelrod F, Satyal S, Gurney A, Hoey T, Seganfreddo E, Basso G, Valtorta S, Moresco RM, Amadori A and Indraccolo S (2014) Therapeutic antibody targeting of Notch1 in T-acute lymphoblastic leukemia xenografts. Leukemia 28: 278-288.

Akbarzadeh M, Majidinia M, Fekri Aval S, Mahbub S and Zarghami N (2018) Molecular targeting of Notch signaling pathway by DAPT in human ovarian cancer: possible anti metastatic effects. Asian Pac J Cancer Prev 19: 3473-3477.

Ambrogio C, Gomez-Lopez G, Falcone M, Vidal A, Nadal E, Crosetto N, Blasco RB, Fernandez-Marcos PJ, Sanchez-Cespedes M, Ren X, Wang Z, Ding K, Hidalgo M, Serrano M, Villanueva A, Santamaria D and Barbacid M (2016) Combined inhibition of DDR1 and Notch signaling is a therapeutic strategy for KRAS-driven lung adenocarcinoma. Nat Med 22: 270-7.

Arruga F, Gizdic B, Serra S, Vaisitti T, Ciardullo C, Coscia M, Laurenti L, D'Arena G, Jaksic O, Inghirami G, Rossi D, Gaidano G and Deaglio S (2014) Functional impact of NOTCH1 mutations in chronic lymphocytic leukemia. Leukemia 28: 1060-70.

Aste-Amézaga M, Zhang N, Lineberger JE, Arnold BA, Toner TJ, Gu M, Huang L, Vitelli S, Vo KT, Haytko P, Zhao JZ, Baleydier F, L'Heureux S, Wang H, Gordon WR, Thoryk E, Andrawes MB, Tiyanont K, Stegmaier K, Roti G, Ross KN, Franlin LL, Wang H, Wang F, Chastain M, Bett AJ, Audoly LP, Aster JC, Blacklow SC and Huber HE (2010) Characterization of Notch1 antibodies that inhibit signaling of both normal and mutated Notch1 receptors. PLoS One 5: e9094.

Aster JC, Pear WS and Blacklow SC (2017) The Varied roles of Notch in cancer. Annu Rev Pathol 12: 245-275.

Baker A, Wyatt D, Bocchetta M, Li J, Filipovic A, Green A, Peiffer DS, Fuqua S, Miele L, Albain KS and Osipo C (2018) Notch-1-PTEN-ERK1/2 signaling axis promotes HER2+ breast cancer cell proliferation and stem cell survival. Oncogene 37: 4489-4504.

Baldoni S, Del Papa B, Dorillo E, Aureli P, De Falco F, Rompietti C, Sorcini D, Varasano E, Cecchini D, Zei T, Di Tommaso A, Rosati E, Alexe G, Roti G, Stegmaier K, Di Ianni M, Falzetti F and Sportoletti P (2018) Bepridil exhibits anti-leukemic activity associated with NOTCH1 pathway inhibition in chronic lymphocytic leukemia. Int J Cancer 143: 958-970.

Bettinsoli P, Ferrari-Toninelli G, Bonini SA, Prandelli C and Memo M (2017) Notch ligand Delta-like 1 as a novel molecular target in childhood neuroblastoma. BMC Cancer 17: 352.

Bianchi S, Dotti MT and Federico A (2006) Physiology and pathology of notch signalling system. J Cell Physiol 207: 300-308.

Bleeker NP, Cornea RL, Thomas DD and Xing C (2013) A novel SERCA inhibitor demonstrates synergy with classic SERCA inhibitors and targets multidrug-resistant AML. Mol Pharm 10: 4358-4366.

Bolos V, Mira E, Martinez-Poveda B, Luxan G, Canamero M, Martinez AC, Manes S and de la Pompa JL (2013) Notch activation stimulates migration of breast cancer cells and promotes tumor growth. Breast Cancer Res 15: R54.

Bozkulak EC and Weinmaster G (2009) Selective use of ADAM10 and ADAM17 in activation of Notch1 signaling. Mol Cell Biol 29: 5679-95.

Casulo C, Ruan J, Dang N, Gore L, Diefenbach C, Beaven A, Castro J, Porcu P, Faoro L, Dupont J, Kapoun A, Wang M, McGuire K and Flinn I (2016) Safety and preliminary efficacy results of a phase I first-in-human study of the novel Notch-1 targeting antibody brontictuzumab (omp-52m51) administered intravenously to patients with hematologic malignancies. Blood 128: 5108-5108.

Chan SM, Weng AP, Tibshirani R, Aster JC and Utz PJ (2007) Notch signals positively regulate activity of the mTOR pathway in T-cell acute lymphoblastic leukemia. Blood 110: 278-86.

Chen X, Fan S and Song E (2016) Noncoding RNAs: new players in cancers. Adv Exp Med Biol 927: 1-47.

Chen Y, Shu W, Chen W, Wu Q, Liu H and Cui G (2007) Curcumin, both histone deacetylase and p300/cbp-specific inhibitor, represses the activity of nuclear factor kappa b and Notch 1 in Raji cells. Basic Clin Pharmacol Toxicol 101: 427-433.

Chillakuri CR, Sheppard D, Lea SM and Handford PA (2012) Notch receptor-ligand binding and activation: insights from molecular studies. Semin Cell Dev Biol 23: 421-428.

Chiorean EG, LoRusso P, Strother RM, Diamond JR, Younger A, Messersmith WA, Adriaens L, Liu L, Kao RJ, DiCioccio AT, Kostic A, Leek R, Harris A and Jimeno A (2015) A phase I first-in-human study of enoticumab (Regn421), a fully human delta-like ligand 4 (Dll4) monoclonal antibody in patients with advanced solid tumors. Clin Cancer Res 21: 2695-2703.

Cho S, Lu M, He X, Ee PL, Bhat U, Schneider E, Miele L and Beck WT (2011) Notch1 regulates the expression of the multidrug resistance gene ABCC1/MRP1 in cultured cancer cells. Proc Natl Acad Sci 108: 20778-83.

Curry CL, Reed LL, Golde TE, Miele L, Nickoloff BJ and Foreman KE (2005) Gamma secretase inhibitor blocks Notch activation and induces apoptosis in Kaposi's sarcoma tumor cells. Oncogene 24: 6333-44.

Dai Y, Wilson G, Huang B, Peng M, Teng G, Zhang D, Zhang R, Ebert MP, Chen J, Wong BC, Chan KW, George J and Qiao L (2014) Silencing of Jagged1 inhibits cell growth and invasion in colorectal cancer. Cell Death Dis 5: e1170.

De Ford C, Heidersdorf B, Haun F, Murillo R, Friedrich T, Borner C and Merfort I (2016) The clerodane diterpene casearin J induces apoptosis of T-ALL cells through SERCA inhibition, oxidative stress, and interference with Notch1 signaling. Cell Death Dis 7: e2070-e2070.

De Jesus-Acosta A, Laheru D, Maitra A, Arcaroli J, Rudek MA, Dasari A, Blatchford PJ, Quackenbush K and Messersmith W (2014) A phase II study of the gamma secretase inhibitor RO4929097 in patients with previously treated metastatic pancreatic adenocarcinoma. Invest New Drugs 32: 739-745.

Deangelo DJ, Stone RM, Silverman LB, Stock W, Attar EC, Fearen I, Dallob A, Matthews C, Stone J, Freedman SJ and Aster J (2006) A phase I clinical trial of the notch inhibitor MK-0752 in patients with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) and other leukemias. J Clin Oncol 24: 6585-6585.

Deng X, Cao M, Zhang J, Hu K, Yin Z, Zhou Z, Xiao X, Yang Y, Sheng W, Wu Y and Zeng Y (2014) Hyaluronic acid-chitosan nanoparticles for co-delivery of MiR-34a and doxorubicin in therapy against triple negative breast cancer. Biomaterials 35: 4333-44.

Di Bari M, Bevilacqua V, De Jaco A, Laneve P, Piovesana R, Trobiani L, Talora C, Caffarelli E and Tata AM (2018) Mir-34a-5p mediates cross-talk between m2 muscarinic receptors and Notch-1/EGFR pathways in u87mg glioblastoma cells: implication in cell proliferation. Int J Mol Sci 19 (6):1631.

Diaz-Padilla I, Hirte H, Oza AM, Clarke BA, Cohen B, Reedjik M, Zhang T, Kamel-Reid S, Ivy SP, Hotte SJ, Razak AA, Chen EX, Brana I, Wizemann M, Wang L, Siu LL and Bedard PL (2013) A phase Ib combination study of RO4929097, a gamma-secretase inhibitor, and temsirolimus in patients with advanced solid tumors. Invest New Drugs 31: 1182-91.

Dohda T, Maljukova A, Liu L, Heyman M, Grander D, Brodin D, Sangfelt O and Lendahl U (2007) Notch signaling induces SKP2 expression and promotes reduction of p27Kip1 in T-cell acute lymphoblastic leukemia cell lines. Exp Cell Res 313: 3141-52.

Dong X, Lin Q, Aihara A, Li Y, Huang CK, Chung W, Tang Q, Chen X, Carlson R, Nadolny C, Gabriel G, Olsen M and Wands JR (2015) Aspartate beta-Hydroxylase expression promotes a malignant pancreatic cellular phenotype. Oncotarget 6: 1231-48.

Du Y, Li J, Xu T, Zhou D-D, Zhang L and Wang X (2017) MicroRNA-145 induces apoptosis of glioma cells by targeting BNIP3 and Notch signaling. Oncotarget 8: 61510-61527.

Fan X, Khaki L, Zhu TS, Soules ME, Talsma CE, Gul N, Koh C, Zhang J, Li Y-M, Maciaczyk J, Nikkhah G, Dimeco F, Piccirillo S, Vescovi AL and Eberhart CG (2010)

Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
This article has not been copyedited and formatted. The final version may differ from this version.

NOTCH pathway blockade depletes CD133-positive glioblastoma cells and inhibits growth of tumor neurospheres and xenografts. Stem cells 28: 5-16.

Fender AW, Nutter JM, Fitzgerald TL, Bertrand FE and Sigounas G (2015) Notch-1 promotes stemness and epithelial to mesenchymal transition in colorectal cancer. J Cell Biochem 116: 2517-27.

Ferrando AA (2009) The role of NOTCH1 signaling in T-ALL. Hematology Am Soc Hematol Educ Program 353-361.

Ferrarotto R, Eckhardt G, Patnaik A, LoRusso P, Faoro L, Heymach JV, Kapoun AM, Xu L and Munster P (2018) A phase I dose-escalation and dose-expansion study of brontictuzumab in subjects with selected solid tumors. Ann Oncol 29: 1561-1568.

Floyd DH, Kefas B, Seleverstov O, Mykhaylyk O, Dominguez C, Comeau L, Plank C and Purow B (2012) Alpha-secretase inhibition reduces human glioblastoma stem cell growth in vitro and in vivo by inhibiting Notch. Neuro Oncol 14: 1215-26.

Fouladi M, Stewart CF, Olson J, Wagner LM, Onar-Thomas A, Kocak M, Packer RJ, Goldman S, Gururangan S, Gajjar A, Demuth T, Kun LE, Boyett JM and Gilbertson RJ (2011) Phase I trial of MK-0752 in children with refractory CNS malignancies: a pediatric brain tumor consortium study. J Clin Oncol 29: 3529-3534.

Funahashi Y, Hernandez SL, Das I, Ahn A, Huang J, Vorontchikhina M, Sharma A, Kanamaru E, Borisenko V, Desilva DM, Suzuki A, Wang X, Shawber CJ, Kandel JJ, Yamashiro DJ and Kitajewski J (2008) A notch1 ectodomain construct inhibits endothelial notch signaling, tumor growth, and angiogenesis. Cancer Res 68: 4727-35.

Haapasalo A and Kovacs DM (2011) The many substrates of presenilin/γ-secretase. J Alzheimers Dis 25: 3-28.

Habets RA, de Bock CE, Serneels L, Lodewijckx I, Verbeke D, Nittner D, Narlawar R, Demeyer S, Dooley J, Liston A, Taghon T, Cools J and de Strooper B (2019) Safe targeting of T cell acute lymphoblastic leukemia by pathology-specific NOTCH inhibition. Sci Transl Med 11: (494):eaau6246.

Hai L, Liu P, Yu S, Yi L, Tao Z, Zhang C, Abeysekera IR, Li T, Tong L, Ma H, Liu B, Xie Y, Zhou X, Lin Y, Zhu M, Zhang K, Ren B, Ming H, Huang Y and Yang X (2018) Jagged1 is clinically prognostic and promotes invasion of glioma-initiating cells by activating NF-kappa B (p65) signaling. Cell Physiol Biochem 51: 2925-2937.

Hai L, Zhang C, Li T, Zhou X, Liu B, Li S, Zhu M, Lin Y, Yu S, Zhang K, Ren B, Ming H, Huang Y, Chen L, Zhao P, Zhou H, Jiang T and Yang X (2018) Notch1 is a prognostic factor that is distinctly activated in the classical and proneural subtype of glioblastoma and that promotes glioma cell survival via the NF-κB(p65) pathway. Cell Death Dis 9: 158.

Han N, Hu G, Shi L, Long G, Yang L, Xi Q, Guo Q, Wang J, Dong Z and Zhang M (2017) Notch1 ablation radiosensitizes glioblastoma cells. Oncotarget 8: 88059-88068.

Hang Q, Sun R, Jiang C and Li Y (2015) Notch 1 promotes cisplatin-resistant gastric cancer formation by upregulating lncRNA AK022798 expression. Anticancer Drugs 26: 632-40.

Hassan WA, Yoshida R, Kudoh S, Kameyama H, Hasegawa K, Niimori-Kita K and Ito T (2016) Notch1 controls cell chemoresistance in small cell lung carcinoma cells. Thorac Cancer 7: 123-128.

Haughian JM, Pinto MP, Harrell JC, Bliesner BS, Joensuu KM, Dye WW, Sartorius CA, Tan AC, Heikkila P, Perou CM and Horwitz KB (2012) Maintenance of hormone responsiveness in luminal breast cancers by suppression of Notch. Proc Natl Acad Sci 109: 2742-7.

Hayashi I, Takatori S, Urano Y, Miyake Y, Takagi J, Sakata-Yanagimoto M, Iwanari H, Osawa S, Morohashi Y, Li T, Wong PC, Chiba S, Kodama T, Hamakubo T, Tomita T and Iwatsubo T (2012) Neutralization of the γ-secretase activity by monoclonal antibody against extracellular domain of nicastrin. Oncogene 31: 787-798.

Hayes EL and Lewis-Wambi JS (2015) Mechanisms of endocrine resistance in breast cancer: an overview of the proposed roles of noncoding RNA. Breast Cancer Res 17: 40.

He Y and Zou L (2019) Notch-1 inhibition reduces proliferation and promotes osteogenic differentiation of bone marrow mesenchymal stem cells. Exp Ther Med 18: 1884-1890.

Hozumi K, Mailhos C, Negishi N, Hirano K, Yahata T, Ando K, Zuklys S, Hollander GA, Shima DT and Habu S (2008) Delta-like 4 is indispensable in thymic environment specific for T cell development. J Exp Med 205: 2507-13.

Hughes DP, Kummar S and Lazar AJ (2015) New, tolerable gamma-secretase inhibitor takes desmoid down a notch. Clin. Cancer. Res. 21: 7-9.

Imbimbo BP (2008) Therapeutic potential of gamma-secretase inhibitors and modulators. Curr Top Med Chem 8: 54-61.

Jiang L, Lin T, Xu C, Hu S, Pan Y and Jin R (2016) miR-124 interacts with the Notch1 signalling pathway and has therapeutic potential against gastric cancer. J Cell Mol Med 20: 313-322.

Joshi I, Minter LM, Telfer J, Demarest RM, Capobianco AJ, Aster JC, Sicinski P, Fauq A, Golde TE and Osborne BA (2009) Notch signaling mediates G1/S cell-cycle progression in T cells via cyclin D3 and its dependent kinases. Blood 113: 1689-98.

Joutel A (2011) Pathogenesis of CADASIL: transgenic and knock-out mice to probe function and dysfunction of the mutated gene, Notch3, in the cerebrovasculature. Bioessays 33: 73-80.

Kang HG, Kim DH, Kim SJ, Cho Y, Jung J, Jang W and Chun KH (2016) Galectin-3 supports stemness in ovarian cancer stem cells by activation of the Notch1 intracellular domain. Oncotarget 7: 68229-68241.

Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
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Khurana E, Fu Y, Chakravarty D, Demichelis F, Rubin MA and Gerstein M (2016) Role of non-coding sequence variants in cancer. Nat Rev Genet 17: 93-108.

Kiaris H, Politi K, Grimm LM, Szabolcs M, Fisher P, Efstratiadis A and Artavanis-Tsakonas S (2004) Modulation of notch signaling elicits signature tumors and inhibits hras1-induced oncogenesis in the mouse mammary epithelium. Am J Pathol 165: 695-705.

Kim MK, Sung CO, Do I-G, Jeon H-K, Song TJ, Park HS, Lee Y-Y, Kim B-G, Lee J-W and Bae D-S (2011) Overexpression of Galectin-3 and its clinical significance in ovarian carcinoma. Int J Clin Oncol 16: 352-358.

Knoechel B, Roderick JE, Williamson KE, Zhu J, Lohr JG, Cotton MJ, Gillespie SM, Fernandez D, Ku M, Wang H, Piccioni F, Silver SJ, Jain M, Pearson D, Kluk MJ, Ott CJ, Shultz LD, Brehm MA, Greiner DL, Gutierrez A, Stegmaier K, Kung AL, Root DE, Bradner JE, Aster JC, Kelliher MA and Bernstein BE (2014) An epigenetic mechanism of resistance to targeted therapy in T cell acute lymphoblastic leukemia. Nat Genet 46: 364-370.

Koduru S, Kumar R, Srinivasan S, Evers MB and Damodaran C (2010) Notch-1 inhibition by Withaferin-A: a therapeutic target against colon carcinogenesis. Mol Cancer Ther 9: 202-10.

Kondratyev M, Kreso A, Hallett RM, Girgis-Gabardo A, Barcelon ME, Ilieva D, Ware C, Majumder PK and Hassell JA (2012) Gamma-secretase inhibitors target tumor-initiating cells in a mouse model of ERBB2 breast cancer. Oncogene 31: 93-103.

Koprowski S, Sokolowski K, Kunnimalaiyaan S, Gamblin TC and Kunnimalaiyaan M (2015) Curcumin-mediated regulation of Notch1/hairy and enhancer of split-1/survivin: molecular targeting in cholangiocarcinoma. J Surg Res 198: 434-40.

Koyama D, Kikuchi J, Hiraoka N, Wada T, Kurosawa H, Chiba S and Furukawa Y (2014) Proteasome inhibitors exert cytotoxicity and increase chemosensitivity via transcriptional repression of Notch1 in T-cell acute lymphoblastic leukemia. Leukemia 28: 1216-1226.

Krebs LT, Xue Y, Norton CR, Shutter JR, Maguire M, Sundberg JP, Gallahan D, Closson V, Kitajewski J, Callahan R, Smith GH, Stark KL and Gridley T (2000) Notch signaling is essential for vascular morphogenesis in mice. Genes Dev 14: 1343-52.

Krop I, Demuth T, Guthrie T, Wen PY, Mason WP, Chinnaiyan P, Butowski N, Groves MD, Kesari S, Freedman SJ, Blackman S, Watters J, Loboda A, Podtelezhnikov A, Lunceford J, Chen C, Giannotti M, Hing J, Beckman R and Lorusso P (2012) Phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. J Clin Oncol 30: 2307-13.

Leong KG and Gao W-Q (2008) The Notch pathway in prostate development and cancer. Differentiation 76: 699-716.

Lewis HD, Leveridge M, Strack PR, Haldon CD, O'Neil J, Kim H, Madin A, Hannam JC, Look AT, Kohl N, Draetta G, Harrison T, Kerby JA, Shearman MS and Beher D (2007)

Apoptosis in T cell acute lymphoblastic leukemia cells after cell cycle arrest induced by pharmacological inhibition of notch signaling. Chem Biol 14: 209-19.

Li Y, Burns JA, Cheney CA, Zhang N, Vitelli S, Wang F, Bett A, Chastain M, Audoly LP and Zhang Z-Q (2010) Distinct expression profiles of Notch-1 protein in human solid tumors: Implications for development of targeted therapeutic monoclonal antibodies. Biologics 4: 163-171.

Li Y, Guessous F, Zhang Y, Dipierro C, Kefas B, Johnson E, Marcinkiewicz L, Jiang J, Yang Y, Schmittgen TD, Lopes B, Schiff D, Purow B and Abounader R (2009) MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. Cancer Res 69: 7569-76.

Li Y, Zhang J, Ma D, Zhang L, Si M, Yin H and Li J (2012) Curcumin inhibits proliferation and invasion of osteosarcoma cells through inactivation of Notch-1 signaling. FEBS J 279: 2247-59.

Liao W, Li G, You Y, Wan H, Wu Q, Wang C and Lv N (2018) Antitumor activity of Notch1 inhibition in human colorectal carcinoma cells. Oncol Rep 39: 1063-1071.

Lindsell CE, Boulter J, diSibio G, Gossler A and Weinmaster G (1996) Expression patterns of Jagged, Delta1, Notch1, Notch2, and Notch3 genes identify ligand-receptor pairs that may function in neural development. Mol Cell Neurosci 8: 14-27.

Liu L, Yang ZL, Wang C, Miao X, Liu Z, Li D, Zou Q, Li J, Liang L, Zeng G and Chen S (2016) The Expression of Notch 1 and Notch 3 in gallbladder cancer and their clinicopathological significance. Pathol Oncol Res 22: 483-92.

Locatelli MA, Aftimos P, Dees EC, LoRusso PM, Pegram MD, Awada A, Huang B, Cesari R, Jiang Y, Shaik MN, Kern KA and Curigliano G (2017) Phase I study of the gamma secretase inhibitor PF-03084014 in combination with docetaxel in patients with advanced triple-negative breast cancer. Oncotarget 8: 2320-2328.

Luistro L, He W, Smith M, Packman K, Vilenchik M, Carvajal D, Roberts J, Cai J, Berkofsky-Fessler W, Hilton H, Linn M, Flohr A, Jakob-Røtne R, Jacobsen H, Glenn K, Heimbrook D and Boylan JF (2009) Preclinical profile of a potent γ-secretase inhibitor targeting Notch signaling with in vivo efficacy and pharmacodynamic properties. Cancer Res 69: 7672-7680.

Ma J, Fang B, Zeng F, Ma C, Pang H, Cheng L, Shi Y, Wang H, Yin B, Xia J and Wang Z (2015) Down-regulation of miR-223 reverses epithelial-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. Oncotarget 6: 1740-9.

Mahalingam D, Wilding G, Denmeade S, Sarantopoulas J, Cosgrove D, Cetnar J, Azad N, Bruce J, Kurman M, Allgood VE and Carducci M (2016) Mipsagargin, a novel thapsigargin-based PSMA-activated prodrug: results of a first-in-man phase I clinical trial in patients with refractory, advanced or metastatic solid tumours. Br J Cancer 114: 986-994.

Mailhos C, Modlich U, Lewis J, Harris A, Bicknell R and Ish-Horowicz D (2001) Delta 4, an endothelial specific notch ligand expressed at sites of physiological and tumor angiogenesis. Differentiation 69: 135-144.

Mao L, Zhao ZL, Yu GT, Wu L, Deng WW, Li YC, Liu JF, Bu LL, Liu B, Kulkarni AB, Zhang WF, Zhang L and Sun ZJ (2018) gamma-Secretase inhibitor reduces immunosuppressive cells and enhances tumour immunity in head and neck squamous cell carcinoma. Int J Cancer 142: 999-1009.

Matsui WH (2016) Cancer stem cell signaling pathways. Medicine 95: S8-s19.

McMillan BJ, Zimmerman B, Egan ED, Lofgren M, Xu X, Hesser A and Blacklow SC (2017) Structure of human POFUT1, its requirement in ligand-independent oncogenic Notch signaling, and functional effects of Dowling-Degos mutations. Glycobiology 27: 777-786.

Mendes RD, Cante-Barrett K, Pieters R and Meijerink JP (2016) The relevance of PTEN-AKT in relation to NOTCH1-directed treatment strategies in T-cell acute lymphoblastic leukemia. Haematologica 101: 1010-7.

Messersmith WA, Shapiro GI, Cleary JM, Jimeno A, Dasari A, Huang B, Shaik MN, Cesari R, Zheng X, Reynolds JM, English PA, McLachlan KR, Kern KA and LoRusso PM (2015) A Phase I, dose-finding study in patients with advanced solid malignancies of the oral γ-secretase inhibitor PF-03084014. Clin Cancer Res 21: 60-67.

Mittal S, Sharma A, Balaji SA, Gowda MC, Dighe RR, Kumar RV and Rangarajan A (2014) Coordinate hyperactivation of Notch1 and Ras/MAPK pathways correlates with poor patient survival: novel therapeutic strategy for aggressive breast cancers. Mol Cancer Ther 13: 3198-3209.

Mizugaki H, Sakakibara-Konishi J, Ikezawa Y, Kikuchi J, Kikuchi E, Oizumi S, Dang TP and Nishimura M (2012) γ-Secretase inhibitor enhances antitumour effect of radiation in Notch-expressing lung cancer. Br J Cancer 106: 1953-9.

Moellering RE, Cornejo M, Davis TN, Del Bianco C, Aster JC, Blacklow SC, Kung AL, Gilliland DG, Verdine GL and Bradner JE (2009) Direct inhibition of the NOTCH transcription factor complex. Nature 462: 182-188.

Morgan KM, Fischer BS, Lee FY, Shah JJ, Bertino JR, Rosenfeld J, Singh A, Khiabanian H and Pine SR (2017) Gamma secretase inhibition by BMS-906024 enhances efficacy of paclitaxel in lung adenocarcinoma. Mol Cancer Ther 16: 2759-2769.

Mungamuri SK, Yang X, Thor AD and Somasundaram K (2006) Survival signaling by Notch1: mammalian target of rapamycin (mTOR)-dependent inhibition of p53. Cancer Res 66: 4715-24.

Nasrin A, Hassan M and Ye P (2018) Inhibition of Notch signaling pathway using gamma-secretase inhibitor delivered by a low dose of Triton-X100 in cultured oral cancer cells. Biochem. Biophys Res Commun 495: 2118-2124.

Natarajan V, Bandapalli OR, Rajkumar T, Sagar TG and Karunakaran N (2015) NOTCH1 and FBXW7 mutations favor better outcome in pediatric South Indian T-cell acute lymphoblastic leukemia. J Pediatr Hematol Oncol 37: e23-30.

Nickoloff BJ, Hendrix MJ, Pollock PM, Trent JM, Miele L and Qin JZ (2005) Notch and NOXA-related pathways in melanoma cells. J Investig Dermatol Symp Proc 10: 95-104.

Nickoloff BJ, Osborne BA and Miele L (2003) Notch signaling as a therapeutic target in cancer: a new approach to the development of cell fate modifying agents. Oncogene 22: 6598-608.

Nicolas M, Wolfer A, Raj K, Kummer JA, Mill P, van Noort M, Hui CC, Clevers H, Dotto GP and Radtke F (2003) Notch1 functions as a tumor suppressor in mouse skin. Nat Genet 33: 416-21.

Noguera-Troise I, Daly C, Papadopoulos NJ, Coetzee S, Boland P, Gale NW, Lin HC, Yancopoulos GD and Thurston G (2006) Blockade of Dll4 inhibits tumour growth by promoting non-productive angiogenesis. Nature 444: 1032-1037.

O'Brien R and Marignol L (2017) The Notch-1 receptor in prostate tumorigenesis. Cancer Treat Rev 56: 36-46.

Ono M, Takimoto R, Osuga T, Okagawa Y, Hirakawa M, Yoshida M, Arihara Y, Uemura N, Hayasaka N, Miura S, Matsuno T, Tamura F, Sato Y, Sato T, Iyama S, Miyanishi K, Takada K, Kobune M and Kato J (2016) Targeting Notch-1 positive acute leukemia cells by novel fucose-bound liposomes carrying daunorubicin. Oncotarget 7: 38586-38597.

Osipo C, Patel P, Rizzo P, Clementz AG, Hao L, Golde TE and Miele L (2008) ErbB-2 inhibition activates Notch-1 and sensitizes breast cancer cells to a gamma-secretase inhibitor. Oncogene 27: 5019-32.

Palomero T, Sulis ML, Cortina M, Real PJ, Barnes K, Ciofani M, Caparros E, Buteau J, Brown K, Perkins SL, Bhagat G, Agarwal AM, Basso G, Castillo M, Nagase S, Cordon-Cardo C, Parsons R, Zuniga-Pflucker JC, Dominguez M and Ferrando AA (2007) Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. Nat Med 13: 1203-10.

Pandya K, Meeke K, Clementz AG, Rogowski A, Roberts J, Miele L, Albain KS and Osipo C (2011) Targeting both Notch and ErbB-2 signalling pathways is required for prevention of ErbB-2-positive breast tumour recurrence. Br J Cancer 105: 796-806.

Pant S, Jones SF, Kurkjian CD, Infante JR, Moore KN, Burris HA, McMeekin DS, Benhadji KA, Patel BKR, Frenzel MJ, Kursar JD, Zamek-Gliszczynski MJ, Yuen ESM, Chan EM and Bendell JC (2016) A first-in-human phase I study of the oral Notch inhibitor, LY900009, in patients with advanced cancer. Eur J Cancer 56: 1-9.

Papayannidis C, DeAngelo DJ, Stock W, Huang B, Shaik MN, Cesari R, Zheng X, Reynolds JM, English PA, Ozeck M, Aster JC, Kuo F, Huang D, Lira PD, McLachlan KR, Kern KA,

Garcia-Manero G and Martinelli G (2015) A Phase 1 study of the novel gamma-secretase inhibitor PF-03084014 in patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. Blood Cancer J 5: e350-e350.

Paris D, Quadros A, Patel N, DelleDonne A, Humphrey J and Mullan M (2005) Inhibition of angiogenesis and tumor growth by beta and gamma-secretase inhibitors. Eur J Pharmacol 514: 1-15.

Pear WS, Aster JC, Scott ML, Hasserjian RP, Soffer B, Sklar J and Baltimore D (1996) Exclusive development of T cell neoplasms in mice transplanted with bone marrow expressing activated Notch alleles. J Exp Med 183: 2283-91.

Perez Garcia JM, Cortés J, Stathis A, Mous R, López-Miranda E, Azaro A, Genta S, Nuciforo P, Vivancos A, Ferrarotto R, Bertoni F, Rossi D, Spardy Burr N, Schönborn-Kellenberger O, Jorga K, Beni L, Lehal R, Bauer M, Weber D and Garralda E (2018) First-in-human phase 1-2A study of CB-103, an oral Protein-Protein Interaction Inhibitor targeting pan-NOTCH signalling in advanced solid tumors and blood malignancies. J Clin Oncol 36: TPS2619-TPS2619.

Phillips E, Lang V, Bohlen J, Bethke F, Puccio L, Tichy D, Herold-Mende C, Hielscher T, Lichter P and Goidts V (2016) Targeting atypical protein kinase C iota reduces viability in glioblastoma stem-like cells via a notch signaling mechanism. Int J Cancer 139: 1776-87.

Phillips TM, McBride WH and Pajonk F (2006) The response of CD24(-/low)/CD44+ breast cancer-initiating cells to radiation. J Natl Cancer Inst 98: 1777-85.

Ponnurangam S, Mammen JM, Ramalingam S, He Z, Zhang Y, Umar S, Subramaniam D and Anant S (2012) Honokiol in combination with radiation targets notch signaling to inhibit colon cancer stem cells. Mol Cancer Ther 11: 963-72.

Qin JZ, Stennett L, Bacon P, Bodner B, Hendrix MJ, Seftor RE, Seftor EA, Margaryan NV, Pollock PM, Curtis A, Trent JM, Bennett F, Miele L and Nickoloff BJ (2004) p53-independent NOXA induction overcomes apoptotic resistance of malignant melanomas. Mol Cancer Ther 3: 895-902.

Qiu M, Peng Q, Jiang I, Carroll C, Han G, Rymer I, Lippincott J, Zachwieja J, Gajiwala K, Kraynov E, Thibault S, Stone D, Gao Y, Sofia S, Gallo J, Li G, Yang J, Li K and Wei P (2013) Specific inhibition of Notch1 signaling enhances the antitumor efficacy of chemotherapy in triple negative breast cancer through reduction of cancer stem cells. Cancer Lett 328: 261-70.

Radtke F, Wilson A, Stark G, Bauer M, van Meerwijk J, MacDonald HR and Aguet M (1999) Deficient T cell fate specification in mice with an induced inactivation of Notch1. Immunity 10: 547-58.

Ran Y, Hossain F, Pannuti A, Lessard CB, Ladd GZ, Jung JI, Minter LM, Osborne BA, Miele L and Golde TE (2017) γ-Secretase inhibitors in cancer clinical trials are pharmacologically and functionally distinct. EMBO Mol Med 9: 950-966.

Rasul S, Balasubramanian R, Filipović A, Slade MJ, Yagüe E and Coombes RC (2009) Inhibition of gamma-secretase induces G2/M arrest and triggers apoptosis in breast cancer cells. Br J Cancer 100: 1879-1888.

Real PJ, Tosello V, Palomero T, Castillo M, Hernando E, de Stanchina E, Sulis ML, Barnes K, Sawai C, Homminga I, Meijerink J, Aifantis I, Basso G, Cordon-Cardo C, Ai W and Ferrando A (2009) Gamma-secretase inhibitors reverse glucocorticoid resistance in T cell acute lymphoblastic leukemia. Nat Med 15: 50-58.

Reedijk M, Odorcic S, Chang L, Zhang H, Miller N, McCready DR, Lockwood G and Egan SE (2005) High-level coexpression of JAG1 and NOTCH1 is observed in human breast cancer and is associated with poor overall survival. Cancer Res 65: 8530-7.

Richter S, Bedard PL, Chen EX, Clarke BA, Tran B, Hotte SJ, Stathis A, Hirte HW, Razak AR, Reedijk M, Chen Z, Cohen B, Zhang WJ, Wang L, Ivy SP, Moore MJ, Oza AM, Siu LL and McWhirter E (2014) A phase I study of the oral gamma secretase inhibitor R04929097 in combination with gemcitabine in patients with advanced solid tumors (PHL-078/CTEP 8575). Invest New Drugs 32: 243-9.

Ridgway J, Zhang G, Wu Y, Stawicki S, Liang W-C, Chanthery Y, Kowalski J, Watts RJ, Callahan C, Kasman I, Singh M, Chien M, Tan C, Hongo J-AS, de Sauvage F, Plowman G and Yan M (2006) Inhibition of Dll4 signalling inhibits tumour growth by deregulating angiogenesis. Nature 444: 1083-1087.

Ronchi CL, Sbiera S, Altieri B, Steinhauer S, Wild V, Bekteshi M, Kroiss M, Fassnacht M and Allolio B (2015) Notch1 pathway in adrenocortical carcinomas: correlations with clinical outcome. Endocr Relat Cancer 22: 531-43.

Roti G, Carlton A, Ross KN, Markstein M, Pajcini K, Su AH, Perrimon N, Pear WS, Kung AL, Blacklow SC, Aster JC and Stegmaier K (2013) Complementary genomic screens identify SERCA as a therapeutic target in NOTCH1 mutated cancer. Cancer Cell 23: 390-405.

Roti G, Qi J, Kitara S, Sanchez-Martin M, Saur Conway A, Varca AC, Su A, Wu L, Kung AL, Ferrando AA, Bradner JE and Stegmaier K (2018) Leukemia-specific delivery of mutant NOTCH1 targeted therapy. J Exp Med 215: 197-216.

Rui X, Zhao H, Xiao X, Wang L, Mo L and Yao Y (2018) MicroRNA-34a suppresses breast cancer cell proliferation and invasion by targeting Notch1. Exp Ther Med 16: 4387-4392.

Scehnet JS, Jiang W, Kumar SR, Krasnoperov V, Trindade A, Benedito R, Djokovic D, Borges C, Ley EJ, Duarte A and Gill PS (2007) Inhibition of Dll4-mediated signaling induces proliferation of immature vessels and results in poor tissue perfusion. Blood 109: 4753-4760.

Schott AF, Landis MD, Dontu G, Griffith KA, Layman RM, Krop I, Paskett LA, Wong H, Dobrolecki LE, Lewis MT, Froehlich AM, Paranilam J, Hayes DF, Wicha MS and Chang JC

(2013) Preclinical and clinical studies of gamma secretase inhibitors with docetaxel on human breast tumors. Clin Cancer Res 19: 1512-1524.

Seiffert D, Bradley JD, Rominger CM, Rominger DH, Yang F, Meredith JE, Jr., Wang Q, Roach AH, Thompson LA, Spitz SM, Higaki JN, Prakash SR, Combs AP, Copeland RA, Arneric SP, Hartig PR, Robertson DW, Cordell B, Stern AM, Olson RE and Zaczek R (2000) Presenilin-1 and -2 are molecular targets for gamma-secretase inhibitors. J Biol Chem 275: 34086-91.

Sethi S, Macoska J, Chen W and Sarkar FH (2010) Molecular signature of epithelial-mesenchymal transition (EMT) in human prostate cancer bone metastasis. Am J Transl Res 3: 90-99.

Shan W, Balog A, Quesnelle C, Gill P, Han WC, Norris D, Mandal S, Thiruvenkadam R, Gona KB, Thiyagarajan K, Kandula S, McGlinchey K, Menard K, Wen ML, Rose A, White R, Guarino V, Shen DR, Cvijic ME, Ranasinghe A, Dai J, Zhang Y, Wu DR, Mathur A, Rampulla R, Trainor G, Hunt JT, Vite GD, Westhouse R, Lee FY and Gavai AV (2015) BMS-871: a novel orally active pan-Notch inhibitor as an anticancer agent. Bioorg Med Chem Lett 25: 1905-9.

Shang H, Braggio D, Lee YJ, Al Sannaa GA, Creighton CJ, Bolshakov S, Lazar AJ, Lev D and Pollock RE (2015) Targeting the Notch pathway: A potential therapeutic approach for desmoid tumors. Cancer 121: 4088-96.

Sharma A, Gadkari RA, Ramakanth SV, Padmanabhan K, Madhumathi DS, Devi L, Appaji L, Aster JC, Rangarajan A and Dighe RR (2015) A novel monoclonal antibody against Notch1 targets leukemia-associated mutant Notch1 and depletes therapy resistant cancer stem cells in solid tumors. Sci Rep 5: 11012.

Sharma A, Paranjape AN, Rangarajan A and Dighe RR (2012) A monoclonal antibody against human Notch1 ligand-binding domain depletes subpopulation of putative breast cancer stem-like cells. Mol Cancer Ther 11: 77-86.

Sharma VM, Calvo JA, Draheim KM, Cunningham LA, Hermance N, Beverly L, Krishnamoorthy V, Bhasin M, Capobianco AJ and Kelliher MA (2006) Notch1 contributes to mouse T-cell leukemia by directly inducing the expression of c-myc. Mol Cell Biol 26: 8022-31.

Shih Ie M and Wang TL (2007) Notch signaling, gamma-secretase inhibitors, and cancer therapy. Cancer Res. 67: 1879-82.

Shiraishi T, Sakaitani M, Otsuguro S, Maenaka K, Suzuki T and Nakaya T (2019) Novel Notch signaling inhibitor NSI-1 suppresses nuclear translocation of the Notch intracellular domain. Int J Mol Med 44: 1574-1584.

Silkenstedt E, Arenas F, Colom-Sanmartí B, Xargay-Torrent S, Higashi M, Giró A, Rodriguez V, Fuentes P, Aulitzky WE, van der Kuip H, Beà S, Toribio ML, Campo E, López-Guerra M and Colomer D (2019) Notch1 signaling in NOTCH1-mutated mantle cell

lymphoma depends on Delta-Like ligand 4 and is a potential target for specific antibody therapy. J Exp Clin Cancer Res 38: 446-446.

Silva A, Jotta PY, Silveira AB, Ribeiro D, Brandalise SR, Yunes JA and Barata JT (2010) Regulation of PTEN by CK2 and Notch1 in primary T-cell acute lymphoblastic leukemia: rationale for combined use of CK2- and gamma-secretase inhibitors. Haematologica 95: 674-678.

Silva A, Yunes JA, Cardoso BA, Martins LR, Jotta PY, Abecasis M, Nowill AE, Leslie NR, Cardoso AA and Barata JT (2008) PTEN posttranslational inactivation and hyperactivation of the PI3K/Akt pathway sustain primary T cell leukemia viability. J Clin Invest 118: 3762-74.

So JY, Wahler J, Das Gupta S, Salerno DM, Maehr H, Uskokovic M and Suh N (2015) HES1-mediated inhibition of Notch1 signaling by a Gemini vitamin D analog leads to decreased CD44(+)/CD24(-/low) tumor-initiating subpopulation in basal-like breast cancer. J Steroid Biochem Mol Biol 148: 111-121.

Sorrentino C, Cuneo A and Roti G (2019) Therapeutic targeting of Notch signaling pathway in hematological malignancies. Mediterr J Hematol Infect Dis 11: e2019037-e2019037.

Stoeck A, Lejnine S, Truong A, Pan L, Wang H, Zang C, Yuan J, Ware C, MacLean J, Garrett-Engele PW, Kluk M, Laskey J, Haines BB, Moskaluk C, Zawel L, Fawell S, Gilliland G, Zhang T, Kremer BE, Knoechel B, Bernstein BE, Pear WS, Liu XS, Aster JC and Sathyanarayanan S (2014) Discovery of biomarkers predictive of GSI response in triple-negative breast cancer and adenoid cystic carcinoma. Cancer Discov 4: 1154-67.

Strosberg JR, Yeatman T, Weber J, Coppola D, Schell MJ, Han G, Almhanna K, Kim R, Valone T, Jump H and Sullivan D (2012) A phase II study of RO4929097 in metastatic colorectal cancer. Eur J Cancer 48: 997-1003.

Sun J, Gong X, Purow B and Zhao Z (2012) Uncovering MicroRNA and Transcription Factor Mediated Regulatory Networks in Glioblastoma. PLoS Comput. Biol. 8: e1002488.

Tanaka S, Nakada M, Yamada D, Nakano I, Todo T, Ino Y, Hoshii T, Tadokoro Y, Ohta K, Ali MA, Hayashi Y, Hamada J and Hirao A (2015) Strong therapeutic potential of gamma-secretase inhibitor MRK003 for CD44-high and CD133-low glioblastoma initiating cells. J Neurooncol 121: 239-50.

Tolcher AW, Messersmith WA, Mikulski SM, Papadopoulos KP, Kwak EL, Gibbon DG, Patnaik A, Falchook GS, Dasari A, Shapiro GI, Boylan JF, Xu Z-X, Wang K, Koehler A, Song J, Middleton SA, Deutsch J, Demario M, Kurzrock R and Wheler JJ (2012) Phase I study of RO4929097, a gamma secretase inhibitor of Notch signaling, in patients with refractory metastatic or locally advanced solid tumors. J Clin Oncol 30: 2348-2353.

Venkatesh V, Nataraj R, Thangaraj GS, Karthikeyan M, Gnanasekaran A, Kaginelli SB, Kuppanna G, Kallappa CG and Basalingappa KM (2018) Targeting Notch signalling pathway of cancer stem cells. Stem Cell Investig 5: 5.

Wang X-D, Leow CC, Zha J, Tang Z, Modrusan Z, Radtke F, Aguet M, de Sauvage FJ and Gao W-Q (2006) Notch signaling is required for normal prostatic epithelial cell proliferation and differentiation. Dev Biol 290: 66-80.

Wang Y, Hou H, Li M, Yang Y and Sun L (2016) Anticancer effect of eupatilin on glioma cells through inhibition of the Notch-1 signaling pathway. Mol Med Rep 13: 1141-6.

Weng AP, Ferrando AA, Lee W, Morris JPt, 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.

Whelan JT, Kellogg A, Shewchuk BM, Hewan-Lowe K and Bertrand FE (2009) Notch-1 signaling is lost in prostate adenocarcinoma and promotes PTEN gene expression. J Cell Biochem 107: 992-1001.

Wieland E, Rodriguez-Vita J, Liebler SS, Mogler C, Moll I, Herberich SE, Espinet E, Herpel E, Menuchin A, Chang-Claude J, Hoffmeister M, Gebhardt C, Brenner H, Trumpp A, Siebel CW, Hecker M, Utikal J, Sprinzak D and Fischer A (2017) Endothelial Notch1 activity facilitates metastasis. Cancer Cell 31: 355-367.

Wu T, Jiao M, Jing L, Wang MC, Sun HF, Li Q, Bai YY, Wei YC, Nan KJ and Guo H (2015) Prognostic value of Notch-1 expression in hepatocellular carcinoma: a meta-analysis. Onco Targets Ther 8: 3105-14.

Wu Y, Cain-Hom C, Choy L, Hagenbeek TJ, de Leon GP, Chen Y, Finkle D, Venook R, Wu X, Ridgway J, Schahin-Reed D, Dow GJ, Shelton A, Stawicki S, Watts RJ, Zhang J, Choy R, Howard P, Kadyk L, Yan M, Zha J, Callahan CA, Hymowitz SG and Siebel CW (2010) Therapeutic antibody targeting of individual Notch receptors. Nature 464: 1052-7.

Xiao W, Gao Z, Duan Y, Yuan W and Ke Y (2017) Notch signaling plays a crucial role in cancer stem-like cells maintaining stemness and mediating chemotaxis in renal cell carcinoma. J Exp Clin Cancer Res 36: 41.

Xie X, Kaoud TS, Edupuganti R, Zhang T, Kogawa T, Zhao Y, Chauhan GB, Giannoukos DN, Qi Y, Tripathy D, Wang J, Gray NS, Dalby KN, Bartholomeusz C and Ueno NT (2016) c-Jun N-terminal kinase promotes stem cell phenotype in triple-negative breast cancer through upregulation of Notch1 via activation of c-Jun. Oncogene 36: 2599.

Xu X, Zhao Y, Xu M, Dai Q, Meng W, Yang J and Qin R (2011) Activation of Notch signal pathway is associated with a poorer prognosis in acute myeloid leukemia. Med Oncol 28 Suppl 1: S483-9.

Yahyanejad S, Theys J and Vooijs M (2016) Targeting Notch to overcome radiation resistance. Oncotarget 7: 7610-7628.

Yu P, Petrus MN, Ju W, Zhang M, Conlon KC, Nakagawa M, Maeda M, Bamford RN and Waldmann TA (2015) Augmented efficacy with the combination of blockade of the Notch-1

pathway, bortezomib and romidepsin in a murine MT-1 adult T-cell leukemia model. Leukemia 29: 556-66.

Yuan X, Wu H, Xu H, Han N, Chu Q, Yu S, Chen Y and Wu K (2015) Meta-analysis reveals the correlation of Notch signaling with non-small cell lung cancer progression and prognosis. Sci Rep 5: 10338.

Yuan X, Zhang M, Wu H, Xu H, Han N, Chu Q, Yu S, Chen Y and Wu K (2015) Expression of Notch1 correlates with breast cancer progression and prognosis. PLoS One 10: e0131689-e0131689.

Zang S, Chen F, Dai J, Guo D, Tse W, Qu X, Ma D and Ji C (2010) RNAi-mediated knockdown of Notch-1 leads to cell growth inhibition and enhanced chemosensitivity in human breast cancer. Oncol Rep 23: 893-9.

Zhang Q, Yuan Y, Cui J, Xiao T and Jiang D (2016) Paeoniflorin inhibits proliferation and invasion of breast cancer cells through suppressing Notch-1 signaling pathway. Biomed Pharmacother 78: 197-203.

Zhen-Jun S, Yuan-Yuan Z, Ying-Ying F, Shao-Ju J, Jiao Y, Xiao-Wei Z, Jian C, Yao X and Li-Ming Z (2012) beta, beta-Dimethylacrylshikonin exerts antitumor activity via Notch-1 signaling pathway in vitro and in vivo. Biochem Pharmacol 84: 507-12.

Zheng CG, Chen R, Xie JB, Liu CB, Jin Z and Jin C (2015) Immunohistochemical expression of Notch1, Jagged1, NF-kappaB and MMP-9 in colorectal cancer patients and the relationship to clinicopathological parameters. Cancer Biomark 15: 889-97.

Zheng H, Bae Y, Kasimir-Bauer S, Tang R, Chen J, Ren G, Yuan M, Esposito M, Li W, Wei Y, Shen M, Zhang L, Tupitsyn N, Pantel K, King C, Sun J, Moriguchi J, Jun HT, Coxon A, Lee B and Kang Y (2017) Therapeutic antibody targeting tumor- and osteoblastic niche-derived Jagged1 sensitizes bone metastasis to chemotherapy. Cancer Cell 32: 731-747.e6.

Zhou YF, Sun Q, Zhang YJ, Wang GM, He B, Qi T, Zhou Y, Li XW, Li S and He L (2017) Targeted inhibition of Notch1 gene enhances the killing effects of paclitaxel on triple negative breast cancer cells. Asian Pac J Trop Med 10: 179-183.

Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
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Footnotes

Funding: This work was not funded by any party.

Finantial Disclosure: The authors have no financial disclosures to report.

Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
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Figure Legends

Figure 1. Notch signaling pathway. DLL: delta like canonical Notch ligand; EGF-like repeats: endothelial growth factor–like repeats; TACE :tumor necrosis factor-α-converting enzyme (also called ADAM 17); NNR: negative regulatory region; LNR: Lin-12 and Notch repeats; HD: heterodimerization domain; RBPJ: DNA binding factor - recombination signal binding protein for immunoglobulin kappa J region; MAML: coactivator of the Mastermind-like family; C0-A: Coactivator; Hes: hairy and enhancer of split; Hey: hairy/enhancer-of-split related with YRPW motif protein; NICD: notch intracellular domain; RAM: RBP-j associated molecule; ANK: ankyrin repeats; TAD: trans-activation domain; NLS: nuclear localization signal; PEST: proline (P), glutamic acid (E), serine (S), and threonine (T) domain that controls the ubiquitin- mediated degradation. Figure was created using BioRender.com.

Figure 2. Notch 1 inhibition modalities. NICD: notch intracellular domain; SERCA: Sarco/endoplasmic reticulum calcium ATPase; POFUT1: protein O-fucosyltransferase-1 knockdown; MAML: coactivator of the Mastermind-like family; C0-A: Coactivator; RBPJ: DNA binding factor - recombination signal binding protein for immunoglobulin kappa J region; ER: endoplasmic reticulum. Figure was created using BioRender.com.

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Tables

Table 1. Different modalities of Notch 1 inhibition with antitumor effects in different types of cancer.

Study	Type of cancer	Notch 1 inhibition	Tissue / cell line	Outcome measured	Results
Qin, et al. 2004	Melanoma	γ-secretase tripeptide inhibitor: z-Leu-Leu-Nle-CHO)	Melanoma cell lines Xelanoma xenografts	Investigate the effect on apoptosis	Enhanced apoptosis Up-regulation of BH3-only members (Bim and NOXA).
Curry, et al. 2005	Kaposi's sarcoma (KS)	γ-secretase inhibitors: tripeptide aldehyde inhibitor and a peptidomimetic inhibitor (LY-411,575)	KS cell line, SLK Nude mice injected with SLK cells intradermally	Investigate the effect on apoptosis	Enhanced apoptosis mediated through growth inhibition or tumor regression
Paris, et al. 2005	Human glioblastoma and human lung adenocarcinoma	γ -secretase inhibitor: LK-6	Human glioblastoma (U-87 MG) xenografts Human lung adenocarcinoma (A-549) cell lines xenografts	Assess the effect on tumor volume, vascularization, angiogenesis, and proliferation	Inhibition of brain tumor growth Reduction of vascularization Inhibition of tumor angiogenesis Inhibition of proliferation
Nickoloff, et al. 2005	Melanoma	γ-Secretase inhibitor: N-benzyloxycarbonyl-Leu-Leu-Nle-CHO	Melanoma cell lines	Examine the effect on apoptosis	Enhanced apoptosis Induced a pro-apoptotic BH3-only protein, NOXA
Noguera-Troise, et al. 2006	Lung carcinoma	Dll4 fusion protein	Human umbilical vein endothelial cells Lewis lung tumour mice model	Examine the effect of Dll4 inhibition on tumor growth	Reduced tumor growth
Lewis, et al. 2007	T cell acute lymphoblastic leukemia (T-ALL)	γ-Secretase Inhibitor: MRK-003	T cell acute lymphoblastic leukemia (T-ALL) cell line	Examine the effect on apoptosis and cell viability	Decreased cell viability Induction of apoptosis
Scehnet, et al. 2007	Colon cancer Kaposi sarcoma	Dll4 fusion protein	HT29 (human colon cancer cell line) KS-IMM (human Kaposi sarcoma cancer cell line)	Investigate the anti-tumor effects of Dll4 inhibition using fusion proteins	Inhibition of tumor growth
Ridgway, et al. 2007	Breast cancer Colon adenocarcinoma Lung adenocarcinoma	Dll4 antibodies	MDA-MB-435, HM7, Colo205 and Calu6 xenograft tumour models EL4 mouse lymphoma tumour model	Examine the anti-tumor effect of anti-Dll4 antibodies	Reduced rate of tumor growth
Funahashi, et al. 2008	Mouse mammary cells Human neuroblastoma cells	Notch1 decoy	Human umbilical vein ECs (HUVEC) Mouse mammary carcinoma Mm5MT and NGP human neuroblastoma cells and xenografts	Investigate the effect of the decoy on angiogenesis in vitro and in vivo	Inhibited angiogenesis in mouse skin No effect on tumorigenicity of cells in vitro Reduced xenograft growth in mice
Rasul, et al. 2009	Breast cancer	Gamma secretase inhibitors: DAPT Compound E ((2S)-2-{[(3,5-Difluorophenyl)acetyl]amin-N-[(3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]propanamide) Inhibitor 1 (GSI1: z-Leu-Leu-Nle-CHO)	ER-positive (MCF-7, T47D, and ZR-75-1) cell lines ER-negative (MDA-MB-231 and CAL-51) cell lines	Examine effect on Apoptosis	Enhanced apoptosis independent of ER status Downregulation of Bcl-2, Bax and Bcl-XL Proteasome inhibition Induction of cell cycle arrest at G2/M
Luistro, et al. 2009	Pulmonary adenocarcinoma Breast cancer Colorectal adenocarcinoma Pancreatic Carcinoma Metastatic site of pancreatic cancer Pulmonary anaplastic adenocarcinoma	γ secretase inhibitor: RO4929097	Human cancer cell lines and the xenograft models of A549, MDA-MB-468, LOVO, BxPC3, HCT-116, AsPC-1, MiaPaCa-2, and Calu-6	Examine the efficacy and Pharmacodynamic Properties	Down-regulation of angiogenic genes Tumor cell differentiation Antitumor activity Active following oral dosing No body weight loss or Notch-related toxicities
Moellering, et al. 2009	T-cell acute lymphoblastic leukaemia (T-ALL)	Notch 1 antibody	T-ALL cell lines: CUTLL1, SUPT1, HPB-ALL, TALL-1, DND-41 and KOPT-K1 Mouse model of T-ALL with dual NOTCH1 mutations identified in human T-ALL cells	Explore the effect on Cell proliferation	Activation of caspase 3 and 7 Induced apoptosis Significant decrease in disease burden and leukaemic infiltration in secondary recipient mice that received treatment
Real, et al. 2009	T cell acute lymphoblastic leukemia (T-ALL)	Gamma secretase inhibitors plus glucocorticoids γ secretase inhibitors: compound E ([(2S)-2-{[(3,5-difluorophenyl)-acetylamino}-N-[(3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl] propenamide and DBZ ((2S)-2-[2-(3,5-difluorophenyl)-acetylamino]-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,-d]azepin-7-yl)-propionamide	Patient derived xenografts	Investigate the effect of using a combination of GSIs and glucocorticoids on the intestinal toxicity and antitumor efficacy	Enhanced antileukemic effects of GSIs Reduction of intestinal toxicity Improved sensitivity in glucocorticoid-resistant T-ALL
Wu, et al. 2010	T-cell acute lymphoblastic leukaemia (T-ALL) Human colon cancer Anaplastic carcinoma Colon adenocarcinoma	Notch1 antibody	T-cell acute lymphoblastic leukaemia (T-ALL) cell line and xenograft models of , HPB-ALL Xenograft models of Calu-6 and HM7 cell lines Human colon cancer line, MT-3	Assess the function and intestinal toxicity of Notch1 and Notch 2 specific inhibitors	Dysregulation of tumour angiogenesis mediated through a decrease in tumour volume and growth inhibition
Aste-Amézaga, et al. 2010	Human colon carcinoma Human pancreatic cancer Human colon adenocarcinoma T-cell Acute Lymphoblastic Leukemia	Notch 1 EGF-repeat region antibody Notch 1 negative regulatory region (NRR) antibody	Cancer cell lines :LS-1034, BxPC3, Colo_205, and TALL-1, T-REX™-293 and Flp-In™ -3T3.	Investigate the inhibitory effect of Notch 1 antibodies (wild type)	no significant anti-proliferative effect on cell lines NRR antibodies inhibit activation of Notch1 receptors with T-ALL mutations

Molecular Pharmacology Fast Forward. Published on September 10, 2020 as DOI: 10.1124/molpharm.120.000006
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Fan, et al. 2010	Glioblastoma (GBM)	γ-secretase inhibitor: [11-endo]-N-(5,6,7,8,9,10-hexahydro-6,9-methanobenzo[a] [8]annulen-11-yl)-thiophene-2-sulfonamide,	GBM-derived neurosphere cultures	Estimate the frequency of Glioblastoma Cancer stem cells by measuring its markers	Depletion of stem-like cells
Pandya, et al. 2011	ErbB-2-positive breast tumour	γ-secretase inhibitors: LY 411 575 and MRK-003,	Orthotopic breast tumour xenografts from trastuzumab- or lapatinib-sensitive and trastuzumab-resistant BT474 cells	Assess the antitumor activity of GSIs	Reduction in tumour recurrence after trastuzumab treatment in sensitive tumors Partial reversal of trastuzumab resistance
Mizutaki, et al. 2012	Non-small-cell lung cancer (NSCLC)	γ-secretase inhibitors: γ-secretase inhibitor I (in vitro) and γ-secretase inhibitor XX (in vitro, in vivo)	NSCLC cell lines: H460, A549 and H1395 H460 and A549 xenografts in female nude mice	Evaluate the anti-tumour effect of γ-secretase inhibitors at 24 hours after radiation in Notch expressing lung cancer cell lines	Improved the cytotoxicity of radiation in lung cancer after the administration of GSIs both in vitro and in vivo that is mediated through the activation of apoptosis
Hayashi, et al. 2012	Pulmonary adenocarcinoma T-acute lymphoblastic leukemia	Anti γ-secretase monoclonal antibody (A5226A)	A549 and DND-41 cell lines DND-41 xenografts in immunodeficient mice	Investigate the anti-tumor effect of the gamma secretase antibody	Decreased proliferation in vivo
Kondratyev, et al. 2012	ErbB-2-positive breast tumour	γ secretase inhibitor: MRK-003	Mouse model of ERBB2 breast cancer Tumor-spheres established from mammary tumors from Neu (N202) transgenic strain	Investigate the effect of gamma-secretase inhibitors on cancer stem cells	Eradication of cancer stem cells in vivo and in vitro Enhanced apoptosis and differentiation
Sharma, et al. 2012	Breast cancer	Notch1 monoclonal antibody	MDA-MB-231 cell line	Study the potential effects of Notch 1 antibody	Reduction in CD44(Hi)/CD24(Low) subpopulation Reduced cancer stem cell population Decreased cell proliferation and apoptosis
Floyd, et al. 2012	Glioblastoma multiforme (GBM)	α secretase inhibitor compound INCB3619 (methyl(6S,7S)-7-[(hydroxyamino) carbonyl]-6-[(4-phenyl-3,6-dihydropyridin-1(2H)-yl) carbonyl]-5-azaspiro[2.5]octane-5-carboxylate) γ secretase inhibitor: DAPT	Adherent GBM cell lines U87MG, U251MG, T98G, U373MG, and A172 GBM stem cell lines 0308 and 0822 Human GBM stem cell mouse xenograft	Examine the effect of α secretase inhibitor in adherent GBM and GBM stem cell lines Study the effect of nanoparticles loaded with these inhibitors	Decreased growth of adherent GBM and GBM stem cell lines Nanoparticles loaded with α secretase inhibitor compared to those loaded with vehicle or gamma secretase inhibitor prolonged survival in mouse model This effect is mediated via a decrease in YKL-40 and LIF receptor
Bleeker, et al. 2013	Acute myeloid leukemia	Ethyl 2-amino-6-(3,5-dimethoxyphenyl)-4-(2-ethoxy-2-oxoethyl)-4H-chromene-3-carboxylate (CXL017) – an inhibitor of sarco/endoplasmic reticulum Ca(2+)-ATPase (SERCA) in combination with thapsigargin, cyclopiazonic acid, and 2,5-di-tert-butylhydroquinone.	(HL60) and multidrug-resistant (HL60/MX2) cell lines	Assess thew possible additive effects the compound with other SERCA inhibitors	Synergistic effect with every SERCA inhibitor Enhanced cytotoxicity for the resistant cell line
Agnusdei, et al. 2014	T-acute lymphoblastic leukemia (T-ALL)	Notch1 monoclonal antibody	Patient derived xenografts in NOD/SCID mice	Investigate anti-tumor effects of notch 1 antibodies	Enhanced T-ALL cell apoptosis Reduced proliferation Inhibition of Notch-target genes expression Ameliorated leukemia-initiating cell functions
Dai, et al. 2014	Colorectal cancer (CRC)	Jagged1-shRNA	Xenograft mouse model colorectal cancer cell lines, HCT15, HT29, DLD1 and HCT116 cells	Examine the effects of targeting Jagged1(a ligand to all four notch 1 receptors)	Decreased cell viability in vitro G0/G1 phase cell cycle arrest Decreased migration and invasiveness in vitro Decreased Cyclin D1, Cyclin E and c-Myc expression. Reduced cell proliferation, growth rate, and metastasis in vivo
Koyama, et al. 2014	T-cell acute lymphoblastic leukemia (T-ALL)	Bortezomib (proteasome inhibitor) Combination of bortezomib and dexamethasone, doxorubicin, vincristine, doxorubicin, mithramycin, dexamethasone, cytosine arabinoside and 4-hydroxycyclophospamide	Jurkat, CEM, MOLT4 and KOPT-K1, KMS12-BM, U266, RPMI8226 (MM), KOPM30 (B-ALL), HBL-2 (mantle cell lymphoma), NAMALWA (Burkitt lymphoma), HL-60 and K562 (acute myeloid leukemia) Murine xenografts	Investigate the mechanism of anti-cancer effects of bortezomib and its influence on Notch 1 signal	Reduced transcription of Notch1 and decreased levels of NICD Reduction in downstream Notch 1 targets: Hes1, GATA3, RUNX3 and nuclear factor-κB (NF-κB) Increased levels of Notch 1 ICD lead to resistance to bortezomib, dexamethasone, and cytosine arabinoside Combination of doxorubicin or dexamethasone and bortezomib improved the downregulation of bortezomib on Notch 1 Treatment with either dexamethasone or bortezomib reduced tumor growth,
Sharma, et al. 2015	Breast cancer Squamous carcinoma Human colon cancer Acute lymphoblastic leukemia (ALL)	Monoclonal antibody (MAb) for the Negative Regulatory Region of Notch1 (NRR)	HEK293, MCF-7, BT-474, MDA-MB-231, HCC-1806, HCT-116, Jurkat and CCRF-CEM cell lines MDA-MB-231, HCC-1806, BT-474 and HCT-116 xenografts in female nude mice	Investigate the antitumor effect of Notch 1 antibodies	Reduced proliferation Reduction in CD34/CD44 high population Enhanced sensitivity to Doxorubicin
So, et al. 2015	Breast cancer	1,25-dihydroxy-20R-21(3-hydroxy-3-deuteromethyl-4,4,4-trideuterobutyl)-23-yne-26,27-hexafluoro-cholecalciferol (BXL0124), Gemini vitamin D analog	MCF10DCIS cell line	Explore the effect of Gemini vitamin D on Notch 1 inhibition and cancer stem cell population	Reduction in Notch 1 receptors and ligands Reduction in the CD44(+)/CD24(-/low) cancer stem cell population

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Yu, et al. 2015	Adult T-cell leukemia (ATL)	Combination of γ-secretase inhibitor, bortezomib and romidepsin γ-secretase inhibitors: RO4929097 and compound E	Murine model of human ATL: MT-1 model	Explore the antitumor effects of a combination of γ-secretase inhibitor, bortezomib and romidepsin	Improved antitumor effect in terms of tumor size, tumor markers in the serum. Enhanced survival of the MT-1 tumor-bearing mice
Tanaka, et al. 2015	Glioblastoma initiating cells (GICs)	γ-secretase inhibitor: MRK003	Patient-derived GICs	Examine the effect of Notch 1 inhibition on cancer stem cells	Reduced viability and sphere-formation ability Enhanced apoptosis
Ambrogio, et al. 2015	(KRAS)-mutant lung adenocarcinoma	γ-secretase inhibitor: LY-411575	Kras mutated mice Data set of lung adenocarcinomas KRAS-mutant lung adenocarcinoma cell lines expressing variable DDR1 level Patient-derived xenograft (PDX) model using human KRAS-mutant adenocarcinomas (PDX1–3)	Explore the anti-tumor effect of combined inhibition of DDR1 and Notch signaling	Induced apoptosis Higher apoptotic response than cisplatin/paclitaxel, irrespective of Trp53 status
Shang, et al. 2015	Desmoid tumors (DTs)	γ-secretase inhibitor: PF-03084014	DT cell strains	Examine the antitumor effects of PF-03084014	Reduced cell invasion Induced growth inhibition Induced cell cycle arrest
Shan, et al. 2015	T-cell acute lymphoblastic leukaemia (T-ALL) Triple negative Breast Cancer	γ-secretase inhibitor: BMS-871	MDA-MB-157 triple negative breast cancer xenograft model TALL-1 tumor model	Examine the anticancer effects of BMS-871	Inhibition of tumor growth
Ono, et al. 2016	Acute myelogenous leukemia (AML)	L-fucose-bound liposomes loaded with daunorubicin	Patient derived Acute leukemia cells Cell lines: HL60, RPMI8226, KG1 and MOLT4 cells	Consequences of targeting Notch-1 positive AML cells by fucose-bound liposomes	Inhibition of tumor growth in mouse models Reduced proliferation of AML patient-derived leukemia cells
Jiang, et al. 2016	Gastric cancer (GC)	miR-124	GES-1 cell line and GC cell lines: SGC-7901, BGC-823, MGC-803, KATO-3 and AGS Gastric cancer	Investigate the connection between miRNAs and the Notch signaling pathway in gastric cancer	Inhibition of cell growth, migration and invasion Arrested cell cycle Regulated Notch 1 ligand (JAG1)
Tanaka, et al. 2015	Glioblastoma (GBM)	γ-secretase inhibitor: MRK003	Patient derived GICs	Examine the effectiveness of MRK003 on GBM initiating cells (GICs)	Reduced viability of GICs Reduced sphere formation Induced apoptosis
Bettinsoli, et al. 2017	Neuroblastoma	miRNA-34 siRNAs targeting the DLL1 gene	Neuroblastoma cell lines (DSMZ), SH-SY5Y, IMR-32, KELLY	Assess the anti-tumor effect of Delta-like 1 (DLL1) inhibition	Halted cell proliferation Initiated neuronal differentiation
Nasrin, et al. 2017	Oral squamous cell carcinoma	γ-secretase inhibitor: DAPT with Triton-X100 (0.001%)	Human oral squamous cell carcinoma (OSCC) cell line H413	Study the effect of using a cell permeabilization agent (Triton-X100) to deliver GSIs in cancer	Decrease in Notch1 gene expression Inhibition of cell growth
McMillan, et al. 2017	T cell acute lymphoblastic leukemia (T-ALL)	CRISPR-mediated knockout of POFUT1 (an enzyme that transfers fucose to epidermal growth factor-like repeats in Notch receptors)	U2OS and 293T cells	Investigate the effect of POFUT1 knockout on Notch 1 signaling	Suppression of normal and certain mutated Notch1 signaling
Han, et al. 2017	Glioblastoma (GBM)	Notch1 downregulation via CRISPR/Cas9	Glioblastoma cell lines: U87MG and U251 Mouse xenografts	Examine the effect of Notch 1 down regulation on sensitivity to radiation, the ability of glioblastoma cell lines to clone itself and grow, and the growth of xenografts	Reduced radio-resistance Enhanced apoptosis Reduced xenograft growth
Liao, et al. 2018	Colorectal cancer	Notch-1-siRNA γ-secretase inhibitor: DAPT	Colorectal cancer cell lines (COLO 205, HT29, SW480, SW1116 and LoVo) Colorectal carcinoma, colorectal adenoma and paracancerous tissues and normal colorectal tissues	Examine the role of Notch-1 in colorectal cancer	Reduced growth and proliferation of colorectal cancer cells Induced cell apoptosis.
Akbarzadeh, et al. 2018	Ovarian cancer	γ- secretase inhibitor: DAPT (N-[N-(3,5-difluorophenacetyl)-Lalanyl]- S-phenylglycine t-butyl ester)	OVCAR-3 cells	Investigate the effect on proliferation, metastasis, and activity of metalloproteinases 2 and 9	Decreased proliferation and metastasis Reduced activity of metalloproteinases 2 and 9
Baldoni, et al. 2018	Chronic lymphocytic leukemia (CLL).	Bepridil (calcium channel blocker)	Culture of primary cells from CLL patients	Investigate the anti-tumor effects of Bepridil	Reduction of leukemic cells infiltration Reduced apoptosis Reduced activation of Notch 1
Di Bari, et al. 2018	Glioblastoma (GBM)	mir-34a-5p	U87MG and U251MG cell lines	Examine the relationship between M2 receptors and Notch-1 and EGFR pathways	M2 activation negatively controlled Notch 1 through increased levels of mir-34a-5p in wild type cells M 2 activation led to inhibition of proliferation and induction of apoptosis
Habets, et al. 2019	T cell acute lymphoblastic leukemia (T-ALL)	Selective inhibitor of PSEN1 (catalytic center of secretase complexes): MRK-560	Psen1 (catalytic center of secretase complexes) knockout mouse Patient derived NOTCH1-driven leukemia mouse models HPB-ALL, DND-41, and Jurkat cell lines	Explore the anti-tumor effects	Decreased the evolvement of mutant NOTCH1-driven leukemia in mice in vivo Cell cycle arrest in T-ALL cell lines
He Y and Zou L. 2019	Osteosarcoma	Notch 1small interfering RNA (siRNA) γ-secretase inhibitor: DAPT	bone marrow mesenchymal stem cell (BMSC) cell line	Investigate the influence of Notch 1 inhibition on the differentiation and tumorigenesis of BMSC	Reduced proliferation Enhanced osteogenic differentiation of BMSCs.
Shiraishi, et al. 2019	Breast cancer Neuroblastoma	Notch signaling inhibitor-1 (NSI-1) that targets the intracellular domain (NICD)	Human breast adenocarcinoma cell lines (MCF7 and MDA-MB-231) Human neuroblastoma cell line (SH-SY5Y)	Investigate the effect of an inhibitor that targets Notch intracellular domain (NICD) of Notch	Reduced expression of HES1 Inhibited the translocation of NICD into the nucleus Reduced cell viability of MCF7 and MDA-231 cells
Silkenstedt, et al. 2019	Mantle cell lymphoma (MCL)	Notch1 monoclonal antibody: OMP-52M51	MCL mouse model NOTCH1-mutated Mino cells JeKo-1 cell line	Explore the effects of notch 1 antibodies	Reduction in Notch target genes in Notch1-mutated cells Suppression of lymphomagenesis and disease progression in Notch1-mutated cells

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Table 2. Natural products with antitumor effects mediated through Notch 1 inhibition.

Study	Type of cancer	Notch 1 inhibition	Tissue / cell line	Outcome measured	Results
Chen, et al. 2007	Raji cell line	Curcumin	Raji cell line	Explore the mechanisms by which curcumin affects Raji cells	Inhibition of proliferation Attenuation of Notch 1 and NF-κB signaling pathways
Koduru, et al. 2010	Colon cancer	Withaferin-A (WA) is a bioactive compound derived from *Withania somnifera*	Colon cancer cell lines: HCT-116, SW-480 and SW-620)	Examine the effect of WA on Notch 1 signal inhibition	Induction of apoptosis
Li, et al. 2012	Osteosarcoma	Curcumin Notch 1 small-interfering RNA	Osteosarcoma cell lines: U2OS, SaOS-2 and MG-63	Investigate the antitumor effect of curcumin in osteosarcoma cell lines	Suppression of Notch 1 expression and its downstream genes Cell cycle arrest at the G2/M phase Prevent proliferation and invasion of osteosarcoma cells
Zhen-Jun, et al. 2012	Gastric cancer	β,β-Dimethylacrylshikonin (DA), a component of Radix Lithospermum erythrorhizon	Human gastric cancer cell line SGC-7901 Murine gastric cancer cell line MFC	Examine effects of DA on cell growth in human gastric cancer cell line	Reduced activation of Notch-1 signaling pathway Inhibition of progression of gastric cancer cells
Ponnurangam, et al. 2012	Colon cancer	Honokiol in combination with ionizing radiation (IR)	Colon cancer cell lines and xenografts: HCT116 and SW480	Examine the effect of combination on sensitivity of cancer stem cells to IR	Inhibition of cancer growth Inhibition of notch 1 signaling pathway
Roti, et al. 2013	T-cell acute lymphoblastic leukemia (T-ALL)	Thapsigargicin (small-molecule SERCA inhibitor that is found in the roots of Thapsia garganica.	DND41 cell line	Investigate the effect of inhibition of calcium channels responsible for Notch 1 trafficking inhibitors	Decreased levels of Notch1 receptors in cell lines Aberrated Notch1 maturation in cultured cells Tumor growth suppression in T-ALL xenograft mode
Koprowski, et al. 2015	Cholangiocarcinoma (CCA)	Curcumin	Cholangiocarcinoma (CCA) cell lines: CCLP-1 and SG-231	Explore the antitumor effects of curcumin on Cholangiocarcinoma (CCA)	Decreased levels of Notch1, HES-1 Enhanced apoptosis Inhibition of growth
Wang, et al. 2016	Glioma	Eupatilin, a flavonoid in Artemisia asiatica Nakai (Asteraceae) Notch-1 small interfering RNA (siRNA)	Human glioma cell lines: LN229 and U87MG	Investigate the molecular mechanism and effects of Eupatilin	Inhibition of proliferation Decreased cell invasion and migration Enhanced apoptosis Suppression of Notch-1 expression
Zhang, et al. 2016	Breast cancer	Paeoniflorin (PF), an ingredient of Chinese peony	Human breast cancer cell lines: MDA-MB-231 and MCF-7	Examine the antitumor effects of Paeoniflorin (PF) in breast cancer	Reduced proliferation and invasion of breast cancer cells Reduced expression of Notch-1
De Ford, et al. 2016	T cell acute lymphoblastic leukemia (T-ALL)	Casearin J (tricyclic clerodane diterpene found in Casearia Sylvestris) - inhibitor of the SERCA pump	CCRF-CEM, CEM-ADR5000, and Jurkat cell lines CD3+ cells from human blood	Investigate the anti-tumor effects of the SERCA inhibitor	Induced cell death Inhibition of HD mutant Notch exocytosis Enhanced apoptosis
Roti, et al. 2018	T cell acute lymphoblastic leukemia (T-ALL)	Folate conjugated to an alcohol derivative of thapsigargin (inhibitor of mutant notch 1 receptor trafficking))	17 T-ALL cell lines	Examine the selective antitumor effects	Reduced T-ALL cell viability Selective effects on mutant cells compared to wild type Decreased ICN1 (intracellular domain of notch 1) levels in T-ALL cells,

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Figure 1

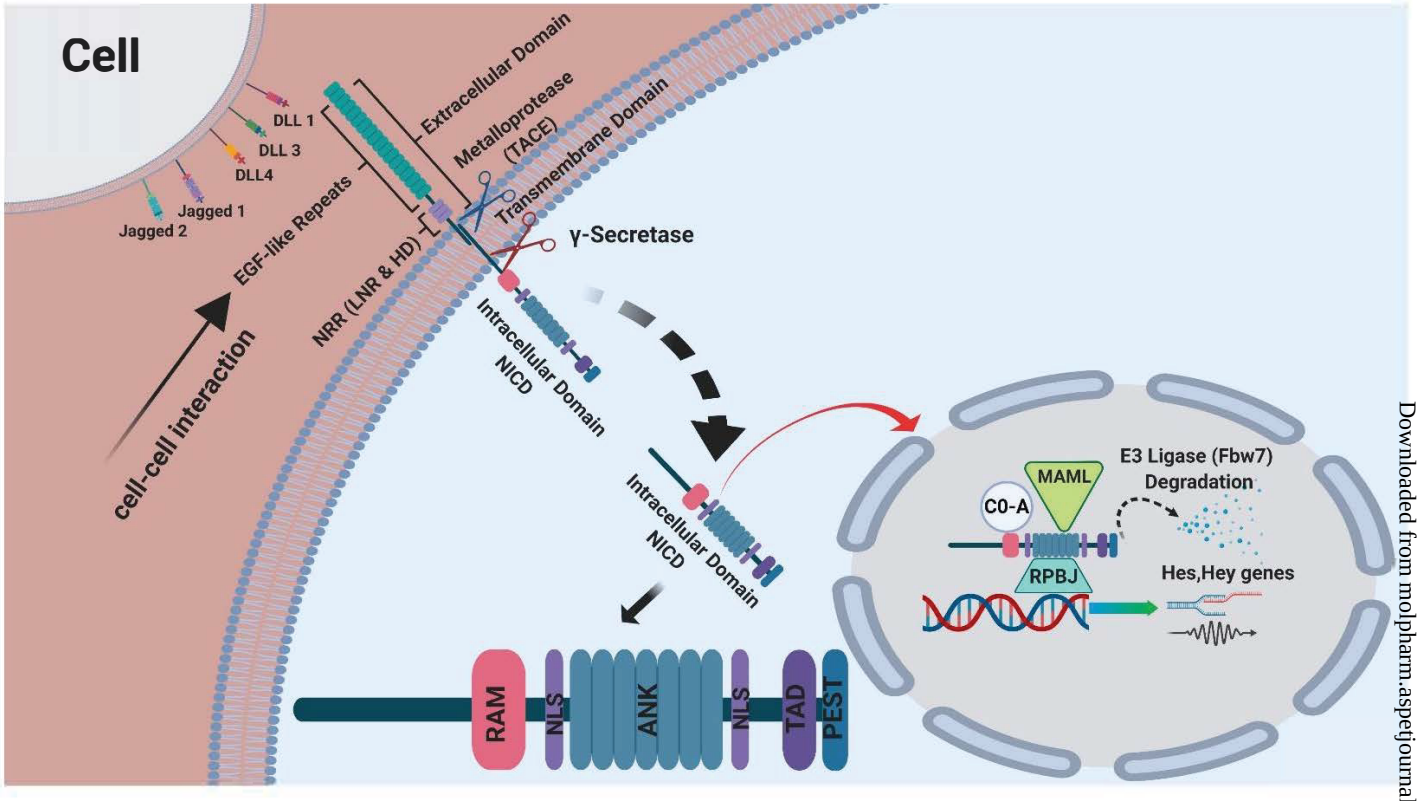

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Figure 2