Supplementary Material: Targeting Notch to Maximize Chemotherapeutic Benefits: Rationale, Advanced Strategies, and Future Perspectives

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Table S1. Principal Notch-inhibiting strategies.

Drug class	Drug Name	Molecular target	Notes on Notch inhibition	References
GSI	RO4929097/R4733	GS	Inhibition of Notch receptors at different concentration. Increased Notch3 cleavage at lower dosages.	[1]
GSI	LY3039478/ JSMD194	GS		
GSI	Nirogacestat/PF-3084014	GS	Higher inhibition of Notch2 than other Notch receptors. Increased Notch3 cleavage at low concentrations	[1]
GSI	AL101/BMS-906024	GS	Equal inhibition of all Notch receptors. Potentiation of Notch3 cleavage at low concentration.	[1]
GSI	AL102/BMS-986115	GS		
GSI	Avagacestat/ BMS-708163	N terminal fragment of PS1. No preferences for PS subtype.	Poor Notch-sparing activity	[2,3]
GSI	MRK-003	GS		
GSI	MRK-560	Higher affinity to GS complex containing PS1 rather than PS2		[4]
GSI	GSI-I	GS		
GSI	DAPT/GSI-IX	Catalytic pocket of PS1.	Potent Notch1 inhibition. Potentiation of Notch3 and Notch4 cleavage at lower concentrations	[1,5]
GSI	GSI-34	GS		
GSI	MK-0752	GS	Equivalent inhibition of Notch1, 2, and 4 cleavage. Increased Notch3 cleavage at low concentration	[1]
GSI	Compound E/GSI-XXI	GS		
GSI	Semagacestat/LY-450139	Catalytic pocket of PS1. No preferences for PS subtype	Potent Notch1 inhibition. Potentiation of Notch3 and Notch4 cleavage at lower concentrations	[1,2,6]
mAb	Tarextumab (OMP-59R5)	Notch2 and Notch3 receptors	Selective Notch2 and Notch3 inhibition at low doses Minimal binding to Notch1 and no binding to Notch4	[7,8]

mAb	Brontictuzumab (OMP-52M51)	Notch receptor negative regulation region (NRR)	Inhibition of activation of Notch1 bearing mutations in HD/PEST and HD/TAD domains	[9,10]
mAb	602.101	EGF-like repeats of Notch1	Inhibits binding of Notch ligands, specific for Notch1	[11]
mAb	Demcizumab (OMP-21M18)	DLL4	Prevents Notch activation by targeting DLL4 ligand	[12]
mAb	Enoticumab (REGN1035)	DLL4	Prevents Notch activation by targeting DLL4 ligand	[13]
mAb	MEDI0639	DLL4	Prevents Notch activation by targeting DLL4 ligand	[14]
Bispecific Ab	HD105	DLL4 and VEGF	Inhibits VEGF/VEGFR2 and DLL4/Notch interaction weaker than single monoclonal antibodies	[15]
Bispecific Ab	HB32	DLL4 and VEGF	Strong inhibition of VEGF and DLL4 simultaneously	[16]
Bispecific Ab	Navixizumab (OMP-305B83)	DLL4 and VEGF	Simultaneous VEGF and DLL4 inhibition	[17]
Bispecific Ab	ABT-165	DLL4 and VEGF	Simultaneous inhibition of VEGF and DLL4 and stronger anti-cancer activity if compared with single Abs	[18]
Bispecific T-cell engager (BiTE)	AMG757 and AMG119	Anti-DLL3 BiTE molecule and CD3 of T-cells	High specificity for DLL3 and capacity to engage human T cells and to initiate the cytotoxic response against tumor cells	[19]
Antibody-drug conjugate	Rovalpituzumab Tesirine	Anti-DLL3 antibody drug conjugate with the DNA-crosslinking agent pyrrolobenzodiazepine and a protease-cleavable linker	Anti-cancer activity in DLL3-expressing cancers	[20,21]
Immunoconjugates	PF-06650808	Anti-Notch3 antibody conjugated to the cytostatic agent auristatin	Selective for Notch3 at low doses	[22]
mAb	15D11	Jagged1	Jagged1 inhibition with minimal toxicity and excellent therapeutic efficacy against bone metastatis	[23]
Hydrocarbon-stapled peptide	SAHM1	MAML1	Prevents assembly of the Notch transcriptional activation complex by inhibiting MAML1 binding	[24]
Synthetic organic compound	IMR-1	MAML1	Prevents assembly of the Notch transcriptional activation complex by inhibiting MAML1 binding	[25]
RBP-jκ Inhibitor-1	RIN1	RBP-jκ	Inhibits transcriptional activation of Notch downstream genes, blocking the association of RBP-jκ with SHARP and NIC	[26]
Pan-Notch inhibitor	CB-103	BTD domain of RBPJ	Inhibits Notch-mediated transcription by interfering with assembly of the NTC	[27,28]

Notch1-selective small-molecule inhibitor	NADI-351	Notch1 transcriptional active complex	Inhibits Notch1-driven transcription by disruption of the NTC	[29]
HES1 inhibitor	JI051	HES1-PHB2 interaction	Inhibition of HES1-mediated transcriptional repression via the PHB2 chaperone	[30]
Natural SERCA inhibitor	Thapsigargin	SERCA pump	Prevents Notch1 receptor maturation through accumulation of unprocessed Notch1 in the ER/Golgi compartment	[31]
Natural SERCA inhibitor	Casearin J	SERCA pump	Inhibition of Notch1 receptor maturation and exocytosis in T-ALL cells carrying *Notch1* HD domain mutations	[32]
Calcium channel blocker	Bepridil	Ca^{2+} channel	Inhibits Notch1 translation, trafficking and/or maturation by reducing ER Ca^{2+} concentration	[33]
Demethylating agent	5-aza-2'deoxycitidine (DAC)	DNA methylation	Reactivation of Notch singling by increasing DLL1 expression in DGC and Notch receptors and targets expression in B-ALL; Inhibition of Notch signaling by enhancing expression of miR-34 in colangiocarcinoma, miR-139-5p in CRC, miR-199 in ovarian cancer	[34–39]
Immunomodulat or	Lenalidomide		Inhibition of *Notch2* expression in gastric cancer by enhancing DNA methylation	[40]
Natural compound	Resveratrol		Inhibits *MAML2* by increasing DNA methylation in breast cancer, functional modulation of Notch signaling in several other contexts	[41,42]
HDAC inhibitor	Valproic Acid (VPA)	HDAC4	Reactivation of Notch signaling in NET by increasing H4ac	[43,44]
LSD1 inhibitor	ORY-1001	LSD1	Reactivation of Notch1 in SCLC by indirectly increasing H3K27ac	[45]
JMJD3 inhibitor	GSK-J4	JMJD3	Indirect inhibition of Notch signaling in T-ALL and inhibition of Notch2 expression in CRC by increasing H3K27me3	[46–48]
P300/CBP inhibitor	A485	P300	Indirect inhibition of Notch signaling in T-ALL by reducing H3K27ac	[47]
EZH2 inhibitor	DZNep	EZH2	Suppression of Notch signaling by increasing miR-21-5p and miR-26a-1-5p	[49]
EZH2 inhibitor	GSK343	EZH2	Inhibits Notch signaling by up-regulating miR-21-5p and miR-26a-1-5p	[49]
Nucleic-acid	miR-34 mimic		Targeting Notch1 and/or Jagged1 in breast cancer and CRC	[50–53]
EZH2 inhibitor	GSK-126	EZH2	Inhibition of *Notch1* by increasing miR-34 in cholangiocarcinoma	[35]
Natural compound	delta-tocotrienol		Inhibition of *Notch1* by up-regulating miR-34 in NSCL	[54]
Nucleic-acid	miR-449a mimic		Inhibits Notch in ovarian cancer	[55]
Nucleic-acid	miR-129-5p		Inhibits Notch ligands DLK1 in NLSC	[56]

Pan-HDAC inhibitor	Trichostatin A	HDACs	Inhibition of Notch3 in T-ALL through its hyper-acetylation and consequent proteasomal degradation	[57]
HDAC Inhibitor	Tubacin	HDAC6	Inhibition of Notch3 protein expression and activity in T-ALL	[58]
Pan-HDAC Inhibitor	SAHA/Vorinostat	HDACs	Inhibition of Notch3 expression through its acetylation and consequent proteasomal degradation in urothelial cancer	[59]
HDAC Inhibitor	Apicidin	HDAC1 and HDAC3	Reduction of N1IC protein levels and activity in Notch-dependent leukemic cell lines	[60]
Antioxidant	N-acetylcysteine		Indirect inhibition of Notch2 expression in GBM	[61]
GSK-3β inhibitor	Lithium chloride (LiCl)	GSK-3β	Different effects on Notch stability and activity	[62,63]
EGFR Tyrosine kinase receptor inhibitor	Erlotinib	EGFR kinase	Increase of Notch3 signaling in EGFR-mutated lung cancer cells	[64]
Natural compound	Xanthohumol		Anti-cancer activity through Notch signaling inhibition	[65–69]
Natural compound	Butein		Inhibition of Notch signaling in T-ALL cell lines	[70]
Semisynthetic compound	Chalcone 8		Inhibition of Notch signaling in T-ALL cell lines	[70]
Natural compound	Juglone		Inhibition of Notch3-dependent T-ALL growth through Notch3 signaling downregulation	[71]
Natural compound	Quercetin		Anti-cancer activity through Notch1 signaling inhibition in HCC; Inhibition of Notch signaling in colon cancer	[72,73]
Natural compound	Luteolin		Inhibits Notch1 signaling by regulating miRNAs in breast cancer	[74]
Natural compound	Honokiol	γ-secretase complex	Inhibits Notch2 in melanoma cells and Notch1 in colon cancer by affecting Notch cleavage;	[75,76]
Natural compound	Curcumin		Anti-cancer activity by downregulation of Notch1 signaling in prostate cancer, in osteosarcoma and in oral SCC; Indirect downregulation of Notch1 signaling through EZH2 inhibition in NSCLC	[77–80]
Natural compound	Withaferin A		Inhibition of Notch signaling in colon cancer; Inhibition of Notch3 and Notch1 signaling in ovarian cancer	[81,82]
Natural compound	Cucurbitacin B	ankyrin domain of Notch1	Inhibits Notch1 signaling in colon cancer, by hindering its interaction with important co-factors	[83]
Natural compound	Diallyl trisulfide		Inhibition of Notch signaling in breast cancer	[84]

Natural molecule	ITE	AhR receptor	Reduction of tumor aggressiveness by downregulation of Jagged1-Notch1 activation in TNBC	[85,86]
Natural compound	N-methylhemeanthidine chloride (NMHC)	Hydrophobic pocket of Notch1 NRR	Reactivation of Notch1 signaling by facilitating its proteolytic cleavage and release of the active intracellular domain in AML	[87]
Natural compound	Chrysin		Anti-cancer activity through Notch1 signaling activation in ATC	[88]

Table S2. Clinical trials with GSI as a monotherapy registered at clinicaltrials.gov (accessed on 15 July 2021).

Agent	CT identifier	Phase/type	Cancer type	Results (as of 15 July 2021)
RO4929097/R4733	NCT01232829	II	Metastatic pancreatic cancer	Yes, published at clinicaltrials.gov (accessed on 14 July 2021)
	NCT01120275	II	Stage IV melanoma	Yes, [89]
	NCT01151449	II	Advanced breast cancer	Yes, published at clinicaltrials.gov (accessed on 14 July 2021)
	NCT01122901	II	Recurrent/progressive glioblastoma	Yes, published at clinicaltrials.gov (accessed on 14 July 2021)
	NCT01217411	I/II	Breast cancer brain metastases	Yes, published at clinicaltrials.gov (accessed on 14 July 2021)
	NCT01269411	I	Recurrent malignant glioma	Yes, published at clinicaltrials.gov (accessed on 15 July 2021)
	NCT01088763	I/II	Refractory solid tumors, CNS tumors, lymphoma, or T-cell leukemia	No
	NCT01096355	I	Metastatic or unresectable solid malignancies	No
	NCT01193868	II	NSCLC	Yes, published at clinicaltrials.gov (accessed on 15 July 2021)

	NCT01175343	II	Recurrent and/or metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	Yes, published at clinicaltrials.gov (accessed on 15 July 2021)
	NCT01141569	II	Advanced renal cell carcinoma after the failure of VEGFR therapy	Yes, published at clinicaltrials.gov (accessed on 15 July 2021)
	NCT01116687	II	Metastatic colorectal cancer	Yes, [90]
	NCT01251172	II	Multiple myeloma	No
	NCT01216787	II	Resectable melanoma	No
	NCT01070927	II	Recurrent/refractory NSCLC	No
	NCT01218620	I	Advanced solid tumors	No
	NCT00532090	I	Advanced solid tumors	No
Nirogacestat/PF-03084014	NCT02137564	II	AIDS-associated Kaposi sarcoma	No
	NCT02462707	I	Advanced solid tumors	No
	NCT02338531	II	Triple negative breast cancer	No
	NCT04195399	II	Inoperable desmoid tumors	No
	NCT03785964	III	Desmoid tumor/aggressive fibromatosis	No
	NCT02299635	II	Breast cancer	Yes, published at clinicaltrials.gov (accessed on 15 July 2021)
	NCT01981551	II	Desmoid tumors/aggressive fibromatosis	Yes, [91]
	NCT02955446	I	Desmoid tumor	No
	NCT00878189	I	Advanced cancer and leukemia	Yes, [92]
AL102/BMS-986115	NCT01986218	I	Advanced solid tumors	Yes, [93]
	NCT04871282	II/III	Progressing desmoid tumors	No
LY3039478/JSMD194	NCT02836600	I	Advanced solid tumors	Yes, [94]
	NCT02906618	I	Healthy	No
	NCT02917733	I	Healthy	No
	NCT02659865	I	Healthy	No
AL101/BMS-906024	NCT03691207	II	Adenoid cystic carcinoma	No
	NCT01292655	I	Advanced/metastatic solid tumors	Yes, [95]
	NCT04461600	II	Breast cancer	No
	NCT04111666	I	Healthy	No
MK-0752	NCT00106145	I	Advanced breast cancer	No
	NCT00100152	I	T-ALL (relapsed/refractory)	No
	NCT00572182	I	CNS (relapsed/refractory)	No
	NCT00803894	I	Healthy	No

Table S3. Clinical trials with monoclonal antibodies against Notch receptors and ligands as a monotherapy registered at clinicaltrials.gov (accessed on 19 July 2021).

Agent	**CT identifier**	**Phase/type**	**Cancer type**	**Results (as of 19 July 2021)**
Tarextumab (OMP-59R5)	NCT01277146	I	Solid tumors	Yes [7]
Brontictuzumab (OMP-52M51)	NCT02662608	n/a	Adenoid cystic carcinoma	Yes, published at clinicaltrials.gov (accessed on 19 July 2021)
	NCT01703572	I	Lymphoid malignancies	No
	NCT01778439	I	Solid tumors	Yes [9]
PF-06650808	NCT02129205	I	Advanced solid tumors	Yes, [22]
Demcizumab (OMP-21M18)	NCT00744562	I	Solid tumors	No
MEDI0639	NCT01577745	I	Solid tumors	Yes, published at clinicaltrials.gov (accessed on 19 July 2021)
Navixizumab (OMP-305B83)	NCT02298387	I	Solid tumors	Yes, [17]
AMG757	NCT04702737	I	Neuroendocrine prostate cancer	No
Rovalpituzumab tesirine (Rova-T)	NCT03543358	II	Cancer	Yes, published at clinicaltrials.gov (accessed on 19 July 2021)
	NCT02674568	II	Relapsed or refractory DLL3-expressing SCLC	Yes, [96]
	NCT03086239	I	Advanced, recurrent SCLC	Yes, [20]
	NCT01901653	I/II	Recurrent SCLC	Yes, [21]
	NCT03503890	N/A	SCLC	No
	NCT02874664	I	SCLC	No
	NCT03334487	III	Relapsed or refractory SCLC	No
	NCT02709889	I/II	Advanced solid tumors	Yes, [97]
AMG119	NCT03392064	I	Relapsed/refractory SCLC	No

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