

# **Lysosomes in Hematopoietic Stem Cell Maintenance and as a Therapeutic Target in Blood Cancer**

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**Table S1. Examples of drugs that destabilize lysosomes in cancer and in other diseases.**

S.no	Compound	Type	Disease	Action/Comments	Refs
1	Verapamil	Calcium channel blocker	Rhabdomyosarcoma, Lung cancer, Pancreatic cancer & Hepatocellular carcinoma	Ca <sup>2+</sup> channel blocker	[1]
2	Mefloquine	Antimalarial drug	AML, CLL, Hepatocellular carcinoma, Prostate cancer & Breast cancer	Induces LMP & inhibits autophagy	[1]
3	Chloroquine	Lysosomotropic agent	Glioblastoma, Breast cancer, Bladder cancer, Lung cancer, Sarcomas & Carcinomas	Enhances lysosomal pH, and suppress lysosome-autophagosome fusion	[1]
4	Hydroxychloroquine	Lysosomotropic agent	Sarcomas & Carcinomas	Inhibits autophagy by impairing lysosomal fusion with the autophagosome	[2]
5	L-leucyl-L-leucine methyl ester (LLeMe)	Lysosomotropic agent	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Enhances lysosomal endocytosis	[3]
6	Cationic amphiphilic drugs (CADs)		Lung cancer, Breast cancer & Prostate cancer	Destabilize lysosomal membrane by inhibiting the function of lysosomal lipases	[1]
7	Hsp70 inhibitors	Inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Inhibits lysosomal membrane permeabilization	[1]
8	DP44mT (di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone)	Iron chelator	Cervical cancer, Breast cancer, Colorectal cancer, Osteosarcoma, Melanoma & AML	Inhibits autophagy	[1]
9	Bufexamac	HDAC10 inhibitor	Neuroblastoma	Inhibits lysosomal enzymes	[1]
10	VER-155008	HSP70 inhibitor	Colon cancer	Enhances lysosomal membrane permeabilization	[2]

11	TAS-116	HSP90 inhibitor	Adult T-cell leukemia/lymphoma	Enhances cathepsin B secretion from damaged lysosomes	[4]
12	NVP-AUY922	HSP90 inhibitor	Adult T-cell leukemia/lymphoma & CLL	Enhances cathepsin B secretion from damaged lysosomes	[5]
13	Obatoclox mesylate	Bcl-2 Inhibitor	Thyroid cancer	Inhibits lysosomal fusion with autophagic vacuoles	[6-8]
14	Mixed-charge nanoparticles	pH dependent aggregator	Breast cancer, Lung cancer & Melanoma	Crystallize within cancer lysosomes, induces lysosomal dysfunction and cell death	[2]
15	Omeprazole	V-ATPase inhibitor	AML	Inhibits lysosomal acidification and lysosomal fusion	[1]
16	Bafilomycin A1	V-ATPase inhibitor	B-cell acute leukemia	Inhibits lysosomal acidification and lysosomal fusion	[1]
17	Saliphenylhalamide	V-ATPase inhibitor	Breast cancer and Lung cancer	Impaired acidification of lysosomes	[2]
18	Concomycin A	V-ATPase inhibitor	Prostate cancer, Breast cancer & Hepatocellular carcinoma	Inhibits vacuolar pH neutralization, vacuolar trafficking, and vacuolar degradation	[9]
19	BRD1240	V-ATPase Inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Inhibits secretion of lysosomal enzymes	[10]
20	SB 242784	V-ATPases inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Inhibits secretion of lysosomal enzymes	[11-13]
21	Aliphenylhalamide	V-ATPases Inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Inhibits secretion of lysosomal enzymes	[11-13]
22	FR167356	V-ATPases inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Enhances lysosomal acidification	[12]

23	Salicylhalamide A	V-ATPases inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Enhances lysosomal acidification	[11]
24	Apilimod	PIKfyve inhibitor	B-cell malignancies & Melanoma	Disruption of lysosomal homeostasis by enlargement of lysosomes, impairment of trafficking, and prevention of autophagic cargo degradation	[14]
25	YM-201636	PIKfyve kinase inhibitor	B-cell malignancies	Dysregulated autophagy-induced cell death in neuronal cells	[15]
26	P140 peptide	CMA inhibitor	Lupus	Downregulated lysosomal degradation	[16]
27	Humanin	CMA inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Endogenous activator of chaperone-mediated autophagy	[17,18]
28	ML-SA1	TRPML1 agonist	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Enhances lysosomal exocytosis, induces secretion of lysosomal acid phosphatases, and increase LAMP1 expression	[19]
29	SF-22	TRPML1 agonist	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Enhances lysosomal exocytosis by increasing lysosomal Ca <sup>2+</sup> levels	[20]
30	MK6-83	TRPML1 agonist	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Enhances lysosomal exocytosis by increasing lysosomal Ca <sup>2+</sup> levels	[20]
31	Pepstatin A	Cathepsin D inhibitor	Carcinoma, Sarcoma, Melanoma, Lymphoma, and Leukemia	Suppress acidity of the lysosomes and therefore the enzymatic activities	[21]
40	NH <sub>4</sub> Cl	Phagosome-lysosome fusion inhibitor		Inhibits lysosomal acidification	[22]

41	Monensin	Lysosomotropic Agent		Inhibits lysosomal acidification	[23]
42	Miglustat	Glucosylceramide synthase Inhibitor	Gaucher disease	Used in various lysosomal storage disorder	[24]
43	Eliglustat	Glucosylceramide synthase Inhibitor	Gaucher disease	Used in various lysosomal storage disorder	[25]
44	Lucerastat	Glucosylceramide synthase Inhibitor	Fabry disease	Reduced LysoTracker Red staining of acidic compartment	[26,27]
45	Ibiglustat	Glucosylceramide synthase Inhibitor	Gaucher disease	Inhibits accumulation of a globotriaosylceramide which enhances breakdown of fatty acids in the lysosomes.	[28]
46	Genistein	Kinase inhibitor	Lysosomal storage diseases	Modulates lysosomal metabolism and Transcription Factor EB (TFEB) activation	[29,30]
47	Diparcil (IVA336)	Glycosaminoglycans Inhibitor	Mucopolysaccharidosis (MPS)	Decrease the lysosomal accumulation of chondroitin sulfate (CS) and dermatan sulfate (DS) in patients	[31,32]
48	Migalastat	Assists $\alpha$ -galactosidase A conformation	Fabry disease	Oral chaperone therapy for Fabry disease by increasing catalytic enzyme activity	[33]
49	Afegostat (isofagomine)	$\beta$ -glucosidase Inhibitor		Enhances pH-dependent lysosomal activity	[34]
50	Pyrimethamine	$\beta$ -glucosidase Inhibitor	Sandhoff and Tay–Sachs diseases	Induces lysosomal modification and release of cathepsin B	[35]
52	Ambroxol	$\beta$ -glucosidase Inhibitor	Gaucher disease	Modulate mitochondria, lysosomal biogenesis	[35]

53	<i>N</i> -Octyl- $\beta$ -valienamine	$\beta$ -Gucocerebrosidase Inhibitor	Gaucher disease	Epimer of <i>N</i> -octyl-4-epi- $\beta$ -valienamine for Gaucher disease	[36]
54	<i>N</i> -Acetylcysteine	$\beta$ -glucosidase Inhibitor	Pompe disease	Allosteric chaperone active in Pompe disease	[37]
55	5-(4-(4-Acetylphenyl)piperazin-1-ylsulfonyl)-6-chloroindolin-2-one	$\beta$ -glucosidase Inhibitor	Pompe disease	High chaperone activity against acid $\alpha$ -glucosidase	[38]
56	Chaperone 1-Deoxynojirimycin	$\beta$ -glucosidase Inhibitor	Pompe disease	Enhances lysosomal trafficking	[39]
57	$\alpha$ -Lobeline and 3,4,7-trihydroxyisoflavone	$\beta$ -Gucocerebrosidase Inhibitor	Krabbe disease	Effective in fibroblast cells from patients with Krabbe disease	[40]
58	<i>N</i> -Octyl-4-epi- $\beta$ -valienamine	$\beta$ -glucosidase Inhibitor	Lysosomal storage disorders	Enhanced $\beta$ -galactosidase activity, reduced substrate storage	[36]
59	5 <i>N</i> ,6 <i>S</i> -( <i>N'</i> -butyliminomethylidene)-6-thio-1-deoxygalactonojirimycin	$\beta$ -glucosidase Inhibitor	Neuronopathic GM1 gangliosidosis and non-neuronopathic Morquio B disease	Enhanced $\beta$ -galactosidase activity, reduced substrate storage	[41]
60	NCGC607	$\beta$ -Gucocerebrosidase Inhibitor	Gaucher Disease and Parkinsonism	Reduces lysosomal substrate storage and $\alpha$ -synuclein levels	[42]
61	Rapamycin/sirolimus	mTOR Inhibitor	Systemic lupus erythematosus, Rheumatoid arthritis and Various cancer Cell types	Used in the treatment of many diseases, including Systemic lupus erythematosus and Rheumatoid arthritis	[43,44]
62	CA030, CA-074 and their analogues	Cathepsin B inhibitor	Osteoarthritis and Melanoma metastases	Increased levels of cathepsin B. Promising therapeutic	[45,46]

				target for melanoma metastases	
63	Pepstatin A	Cathepsin D inhibitor	Renal fibrosis	Reduction of renal fibrosis in mouse models of CKD256	[47]
64	CLIK-148, CLIK-181 and CLIK-195	Cathepsin L inhibitor	Autoimmune diabetes	Inhibits cathepsin L levels	[48-50]
65	LHVS and CLIK-60	Cathepsin S inhibitor	Systemic lupus erythematosus	Inhibits cathepsin S levels	[51-53]
66	RO5461111/Roche	Cathepsin S inhibitor	Sjogrens syndrome and Systemic lupus erythematosus	Inhibits cathepsin S via inhibiting autoantigen presentation	[51,54]
67	CLIK-164 and SB-357114	Cathepsin K inhibitor	Osteoarthritis	Inhibits cathepsin K levels reduces collagen degradation	[55,56]
68	L-006235	Cathepsin K inhibitor	Osteoarthritis	Inhibits cathepsin K levels	[51]
69	PADK, SD1002 and SD1003	Cathepsin B and L inhibitor	Alzheimer disease	Inhibits levels of Cathepsin B and L	[57]
70	Lonafarnib	Lysosomal activator	Neurodegenerative disease	Inhibits farnesyl transferase and reduces tauopathy by activating lysosomal degradation	[58]

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