

Supplementary Table 1 Proteins in each group used in analyses

	Ubiquitin	Proteasome	Autophagy	Lysosome
Gene expression	ANAPC11, BIRC3, BIRC6, BRCA1, CBL, CBLB, CDC34, FANCL, HERC1, HERC3, HERC4, HUWE1, ITCH, MAP3K1, MDM2, MGRN1, MID1, NEDD4, NEDD4L, NHLRC1*, PML, PPIL2, RCHY1, SAE1, SIAH1, SIAH2, SMURF1, SMURF2, STUB1, SYVN1, TRAF6, TRIM32, TRIM37, TRIP12, UBA1, UBA2, UBA3, UBA6, UBA7, UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2E1, UBE2E2, UBE2E3, UBE2G1, UBE2G2, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L6, UBE2M, UBE2Q1, UBE2Q2, UBE2S, UBE2W, UBE2Z, UBE3A, UBE3B, UBE3C, UBE4A, UBE4B, UBR5, WWP1, WWP2, XIAP (70)	PSMA1, PSMA2, PSMA3, PSMA4, PSMA5, PSMA6, PSMA7, PSMB1, PSMB10, PSMB2, PSMB4, PSMB5, PSMB6, PSMB7, PSMB8, PSMB9, PSMC1, PSMC3, PSMC4, PSMC5, PSMC6, PSMD1, PSMD11, PSMD12, PSMD13, PSMD14, PSMD2, PSMD3, PSMD4, PSMD6, PSMD7, PSMD8, PSMD9, PSME1, PSME2, PSME3, PSME4, PSMF1 (38)	AMBRA1, ATG10, ATG101, ATG12, ATG13, ATG14, ATG16L1, ATG16L2, ATG2A, ATG2B, ATG3, ATG4A, ATG4B, ATG4C, ATG4D, ATG5, ATG7, ATG9A, BCL2, BCL2L1, BECN1, BNIP3, CAMKK2, CFLAR, DAPK1, EIF2AK3, EIF2S1, ERN1, GABARAP, HIF1A, LAMP1, LAMP2, MAPK1, MAPK3, MAPK8, MAPK9, MLST8, MTMR14, MTOR, PIK3C3, PIK3R4, PRKCD, PTEN, RAB1A, RAB33B, RAB7A, RAF1, RB1CC1, RHEB, RPS6KB1, RPTOR, SH3GLB1, SQSTM1, STK11, TBK1, TP53INP2, TSC1, TSC2, ULK1, ULK2, UVRAG, WIPI1, WIPI2, ZFYVE1 (64)	ABCA2, ABCB9, ACP2, AGA, AP1B1, AP1G1, AP1M1, AP1S1, AP3B1, AP3D1, AP3M1, AP3S1, AP4B1, AP4E1, AP4M1, AP4S1, ARSA, ARSB, ASAH1, ATP6V0A1, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V1H, CD164, CD68*, CLN5, CLTA, CLTB, CLTC, CTNS, CTSA, CTSB, CTSD, CTSF, CTSI, CTSL, CTSS, CTSZ, DNASE2, ENTPD4, FUCA1, GAA, GALC, GALNS, GBA, GGA1, GLA, GLB1, GM2A, GNPTAB, GNS, GUSB, HEXA, HEXB, HGSNAT, IDS, IDUA, IGF2R, LAPTM4A, LGMN, LIPA, M6PR, MAN2B1, MCOLN1, NAGA, NAGLU, NAGPA, NEU1, NPC1, NPC2, PPT1, PSAP, SCARB2, SGSH, SLC11A2, SLC17A5, SMPD1, SORT1, SUMF1, TPP1 (81)
	HERC4, HUWE1, ITCH, NEDD4L, PML, RCHY1, SAE1, STUB1, TRAF6, TRIM32, UBA1, UBA2, UBA3, UBA6, UBE2B, UBE2G1, UBE2G2, UBE2I, UBE2K, UBE2L6, UBE2M, UBE2Q1, UBE2Z, UBE3A, UBE3C, UBE4A, UBE4B, WWP1, XIAP (29)	PSMA1, PSMA2, PSMA3, PSMA4, PSMA5, PSMA6, PSMA7, PSMB1, PSMB10, PSMB2, PSMB4, PSMB5, PSMB6, PSMB7, PSMB8, PSMB9, PSMC1, PSMC3, PSMC4, PSMC5, PSMC6, PSMD1, PSMD11, PSMD12, PSMD13, PSMD14, PSMD2, PSMD3, PSMD4, PSMD6, PSMD7, PSMD8, PSMD9, PSME1, PSME2, PSME3, PSMF1 (37)	ATG14, ATG16L1, ATG2A, ATG2B, ATG3, ATG4B, ATG4C, ATG5, ATG7, ATG9A, BCL2L1, BECN1, EIF2S1, LAMP1, LAMP2, MAPK1, MAPK3, MAPK9, MLST8, MTOR, PIK3C3, PIK3R4, PRKCD, RAB1A, RAB33B, RAB7A, RHEB, RPTOR, SH3GLB1, SQSTM1, TBK1, WIPI2, ZFYVE1 (33)	ABCA2, ABCB9, ACP2, AGA, AP1B1, AP1G1, AP1M1, AP3B1, AP3D1, AP3M1, AP3S1, AP4E1, ARSA, ASAH1, ATP6V0A1, ATP6V0C, ATP6V0D1, ATP6V1H, CLTA, CLTB, CLTC, CTSA, CTSB, CTSD, CTSI, CTSZ, FUCA1, GAA, GALC, GBA, GGA1, GLB1, GM2A, GNS, GUSB, HEXA, HEXB, IGF2R, LIPA, M6PR, NAGA, NAGLU, NPC1, NPC2, PPT1, PSAP, SCARB2, SGSH, SLC11A2, SORT1, TPP1 (51)

*: missing value in Affimetrix Human data.

Supplementary Table 2 Drug effect on protein groups (mouse)

Affymetrix					mRNA-Seq				
Sum of fold change	Drug	Sample	GEO accession	Study and description	Sum of fold change	Drug	Sample	GEO accession	Study and description
Ubiquitin					Ubiquitin				
51.1	cocaine	Drd1a+ neurons	GSE13394	cocaine study 1 (chronic / acute)	83.2	isoprenaline / atenolol	heart ventricle	GSE82294	isoprenaline study 2 / atenolol study 1 (BTBR)
31.3		Drd2+ neurons		cocaine study 1 (chronic / acute)	76.2				isoprenaline study 2 / atenolol study 1 (LP/J)
37.7	phenobarbital	liver	GSE60684	phenobarbital study 5 (119d / 91d; CAR/PRX KO)	62.8				isoprenaline study 2 / atenolol study 1 (C57BL/6J)
36.1				phenobarbital study 5 (119d / 91d; C57BL/6)	59.2				isoprenaline study 2 / atenolol study 1 (SM/J)
32.6				phenobarbital study 5 (91d / 28d; C57BL/hCAR/hPXR)	57.7				isoprenaline study 2 / atenolol study 1 (FVB/NJ)
31.6				phenobarbital study 4 (57d / 14d)	55.7				isoprenaline study 2 / atenolol study 1
28.5				phenobarbital study 5 (91d / 7d; C57BL/hCAR/hPXR)	49.8				isoprenaline study 2 / atenolol study 1 (C57BLKS/J)
26.4				phenobarbital study 5 (119d / 1d; CAR/PRX KO)	47.9				isoprenaline study 2 / atenolol study 1 (C3H/HeJ)
25.2				phenobarbital study 5 (119d / 7d; CAR/PRX KO)	42.8				isoprenaline study 2 / atenolol study 1 (PL/J)
24.0				phenobarbital study 4 (57d / 7d)	38.8	paracetamol	hepatic monocyte	GSE122108	paracetamol study 1 (36h / 12h)
Proteasome					Proteasome				
30.9	interferon- α 1	cerebral cortex astrocyte		interferon- α 1 study 1 (12h / 4h; IRF9 KO)	54.6	isoprenaline / atenolol	heart ventricle	GSE82294	isoprenaline study 2 / atenolol study 1 (LP/J)
23.0				interferon- α 1 study 1 (12h / 4h; C57BL/6)	35.3				isoprenaline study 2 / atenolol study 1 (BTBR)
27.0	phenobarbital	liver	GSE60684	phenobarbital study 5 (14d / 7d; C57BL/hCAR/hPXR)	31.3				isoprenaline study 2 / atenolol study 1 (C57BL/6J)
20.3				phenobarbital study 1 (80 mg/kg/d; 14d / 3d)	17.3				isoprenaline study 2 / atenolol study 1 (C57BLKS/J)
17.1				phenobarbital study 5 (91d / 1d; C57BL/hCAR/hPXR)	46.3	aCD40	tumor-associated macrophages	GSE64741	melanoma study 9 (CSF1Ri+aCD40 / CSF1Ri)
16.9				phenobarbital study 5 (91d / 7d; C57BL/hCAR/hPXR)	43.4	CSF1Ri			melanoma study 9 (CSF1Ri+aCD40 / CD40)
14.7				phenobarbital study 4 (28d / 14d)	25.8	aCD40 / CSF1Ri			melanoma study 9 (aCD40 / CSF1Ri)
14.6				phenobarbital study 5 (28d / 1d; CAR/PRX KO)	15.2	aCD40	tumor infiltrating T-cells		melanoma study 9 (CSF1Ri+aCD40 / CSF1Ri)
13.1				phenobarbital study 5 (14d / 1d; C57BL/hCAR/hPXR)	39.2	paracetamol	hepatic monocyte	GSE122108	paracetamol study 1 (36h / 12h)
15.3	prazosin	liver	GSE44783	prazosin study 1 (14d / 3d)	39.0		Kupffer cell		paracetamol study 1 (36h / 12h)
Autophagy					Autophagy				
58.3	cocaine	Drd1a+ neurons	GSE13394	cocaine study 1 (chronic / acute; Drd1a+ neurons)	75.2	isoprenaline / atenolol	heart ventricle	GSE82294	isoprenaline study 2 / atenolol study 1 (BTBR)
44.9		Drd2+ neurons		cocaine study 1 (chronic / acute; Drd2+ neurons)	73.9				isoprenaline study 2 / atenolol study 1 (LP/J)
45.4	phenobarbital	liver	GSE60684	phenobarbital study 5 (119d / 1d; C57BL/hCAR/hPXR)	57.3				isoprenaline study 2 / atenolol study 1 (NOD)
39.4				phenobarbital study 5 (119d / 91d; C57BL/6)	51.0				isoprenaline study 2 / atenolol study 1 (C57BLKS/J)
36.1				phenobarbital study 5 (7d / 1d; CAR/PRX KO)	48.2				isoprenaline study 2 / atenolol study 1 (C57BL/6J)
35.5				phenobarbital study 4 (57d / 1d)	45.6				isoprenaline study 2 / atenolol study 1 (FVB/NJ)
34.1				phenobarbital study 5 (119d / 7d; C57BL/hCAR/hPXR)	38.3				isoprenaline study 2 / atenolol study 1 (C3H/HeJ)
31.7				phenobarbital study 5 (119d / 91d; CAR/PRX KO)	37.6				isoprenaline study 2 / atenolol study 1 (SM/J)
31.6				phenobarbital study 5 (91d / 28d; C57BL/hCAR/hPXR)	37.2				isoprenaline study 2 / atenolol study 1 (BALB/cByJ)
31.0				phenobarbital study 4 (28d / 1d)	34.7				isoprenaline study 2 / atenolol study 1 (PL/J)
Lysosome					Lysosome				
54.9	IL-33	mast cell	GSE39382	IL-3 + IL-33 study 1 / IL-3 study 1	108.9	isoprenaline / atenolol	heart ventricle	GSE82294	isoprenaline study 2 / atenolol study 1 (BTBR)
53.5	phenobarbital	liver	GSE60684	phenobarbital study 5 (7d / 1d; C57BL/hCAR/hPXR)	96.9				isoprenaline study 2 / atenolol study 1 (LP/J)
51.5				phenobarbital study 5 (14d / 1d; C57BL/hCAR/hPXR)	93.1				isoprenaline study 2 / atenolol study 1 (C57BL/6J)
50.9				phenobarbital study 5 (7d / 1d; CAR/PRX KO)	85.4				isoprenaline study 2 / atenolol study 1 (NOD)
50.2				phenobarbital study 5 (91d / 1d; C57BL/hCAR/hPXR)	75.6				isoprenaline study 2 / atenolol study 1 (C57BLKS/J)
41.0				phenobarbital study 4 (7d / 1d)	71.2				isoprenaline study 2 / atenolol study 1 (BALB/cByJ)
40.9				phenobarbital study 4 (3d / 1d)	70.4				isoprenaline study 2 / atenolol study 1 (FVB/NJ)
38.1				phenobarbital study 5 (119d / 91d; CAR/PRX KO)	65.1				isoprenaline study 2 / atenolol study 1 (A/J)
37.8				phenobarbital study 5 (119d / 1d; CAR/PRX KO)	60.1				isoprenaline study 2 / atenolol study 1 (SM/J)
40.2	cocaine	Drd1a+ neurons	GSE13394	cocaine study 1 (chronic / acute; Drd1a+ neurons)	102.6	paracetamol	hepatic monocyte	GSE122108	paracetamol study 1 (36h / 12h)

aCD40: agonistic anti-CD40 antibody, aCD40: agonistic anti-CD40 antibody, CSF1Ri: CSF-1R inhibitor,