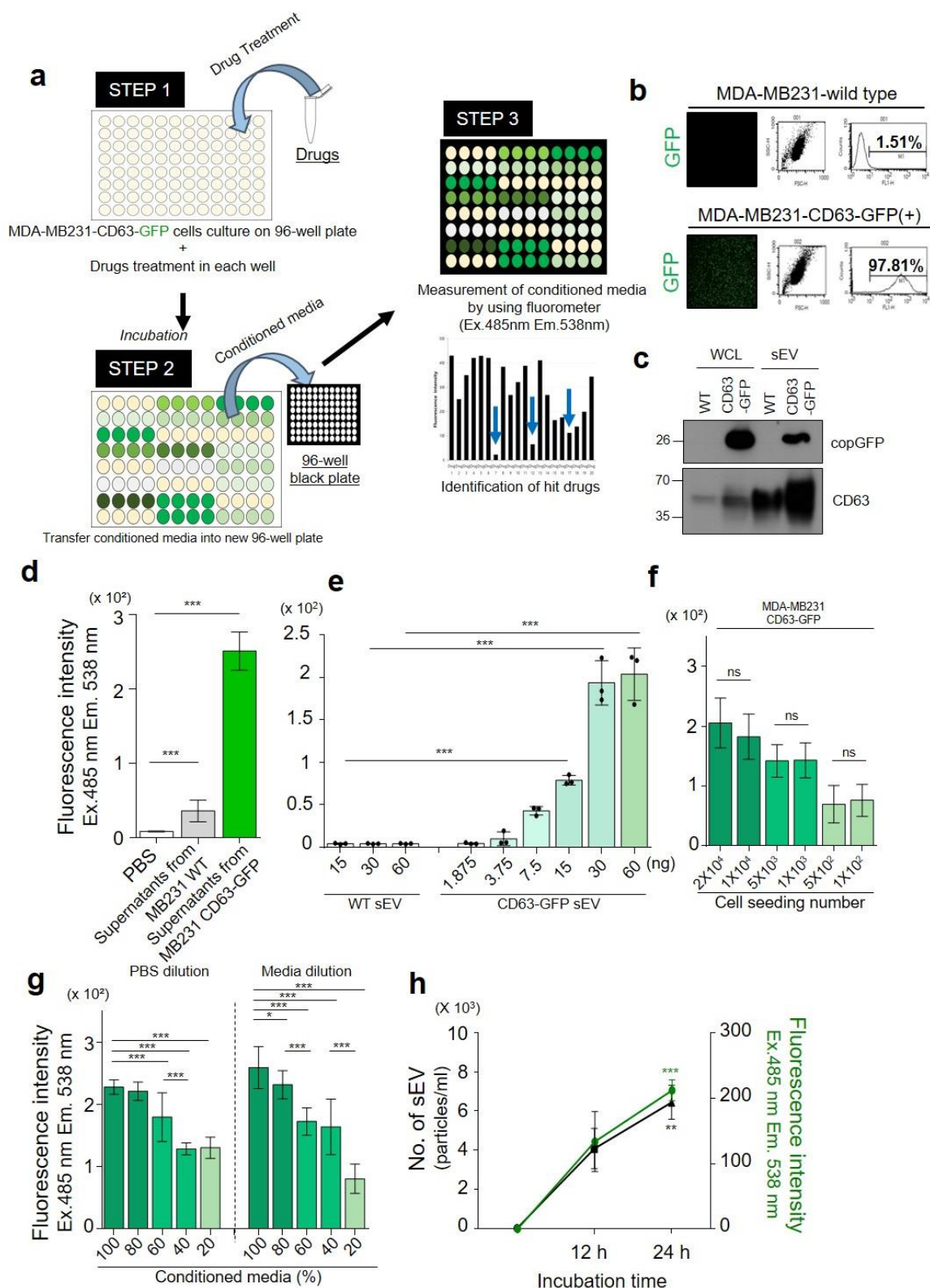


Supplementary Information

Sulfisoxazole inhibits the secretion of small extracellular vesicles by targeting the endothelin receptor A

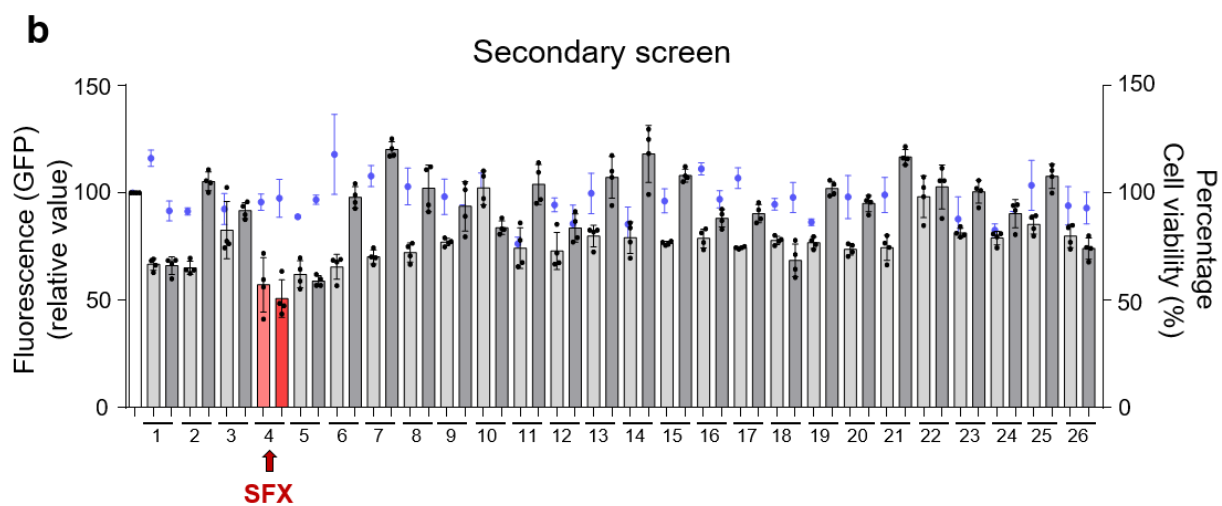
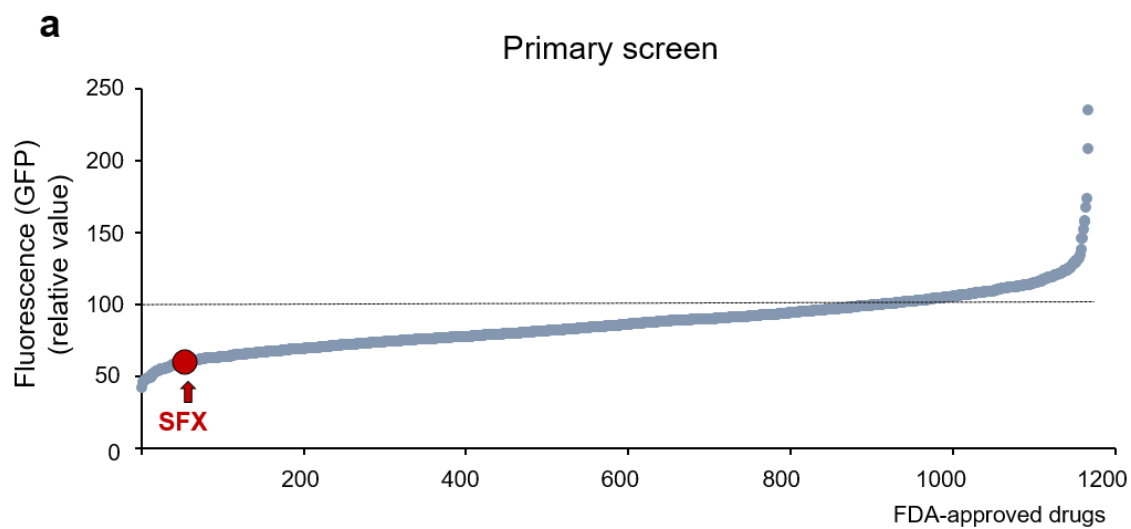
Im et al.

Supplementary Figures



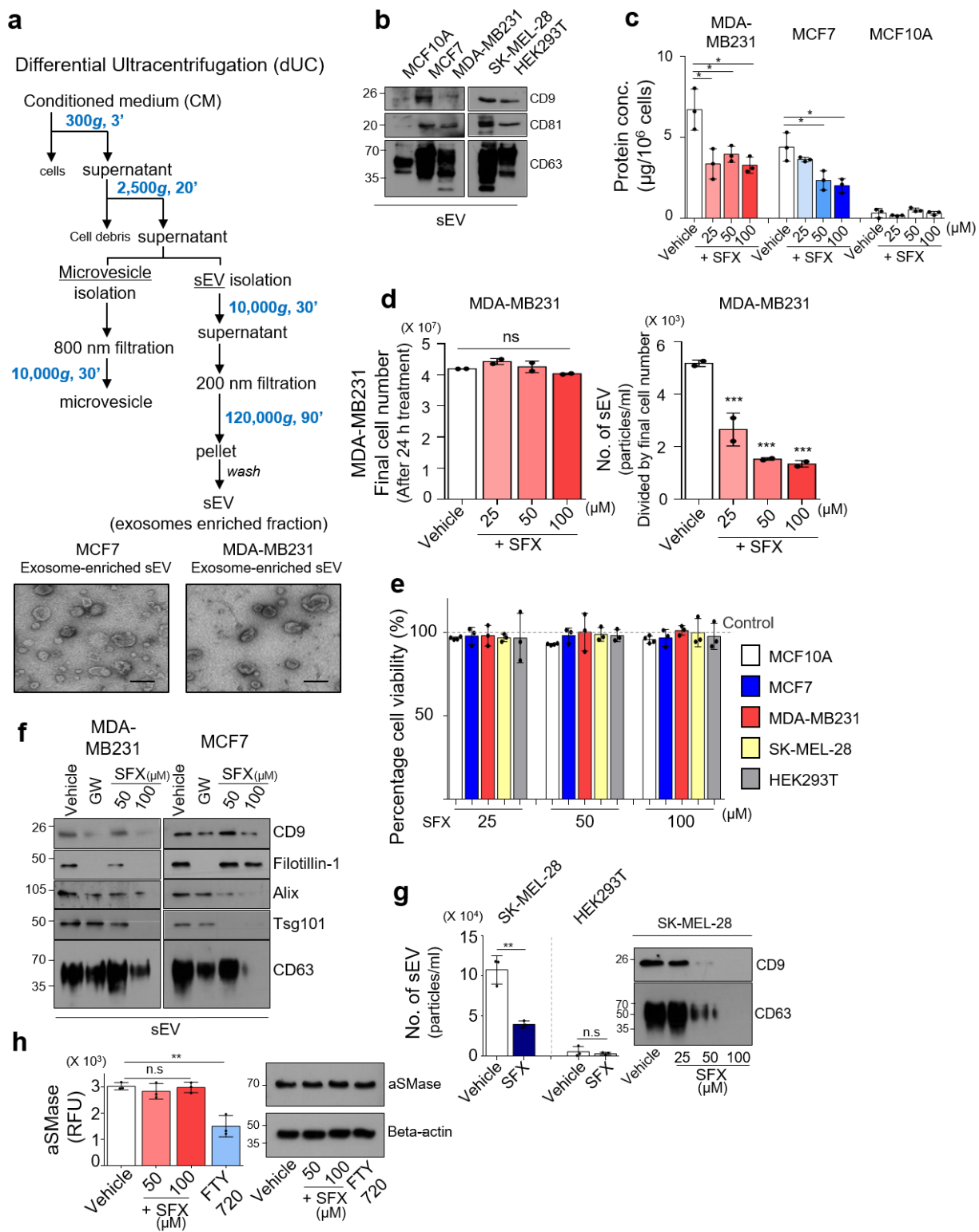
Supplementary Figure 1. High-throughput screening assay to identify an inhibitor of sEV secretion.

(a) Schematic illustration of the high-throughput screening assay system. **(b)** Flow cytometry analysis of WT and CD63-GFP-expressing MDA-MB231 cells (MDA-MB231-CD63-GFP(+)) cells. **(c)** Immunoblot of copGFP and CD63 in whole cell lysates and sEV from wild type and MDA-MB231-CD63-GFP(+) cells. **(d)** Measurements of fluorescence intensity in supernatants from wild-type or MDA-MB231-CD63-GFP(+) cells using a fluorometer. (Ex. 480 nm; Em. 538 nm) ($n=15$). **(e)** Measurement of fluorescence intensity from WT and CD63-GFP. Different amounts of sEV (15 to 60 ng) were added into the medium (phenol-negative DMEM). **(f)** Measurement of fluorescence intensity in the supernatant from MDA-MB231-CD63-GFP(+) cells ($n=24$). **(g)** Measurement of fluorescence intensity in the supernatant from MDA-MB231-CD63-GFP(+) cells. Supernatants were diluted in different volumes of PBS or medium to indicate relative percentage ($n=16$). **(h)** Comparison of the results derived from fluorescence with those from NTA in MDA-MB231-CD63-GFP (+) cells. MDA-MB231-CD63-GFP (+) cells were cultured for indicated times. The sEV and supernatants were prepared for counting sEV and calculating fluorescence, respectively, as described in the Method Section. Green, GFP intensity. Black, the number of sEV. Experiments were performed with 95% confluent cells. Significance was determined using an unpaired two-tailed Student's *t* test. *** $p<0.001$, ** $p<0.005$ and * $p<0.05$. Error Bar, S.D. Source data (b, d-h) are provided as a Source Data file.



Supplementary Figure 2. High-throughput screening assay to identify a sEV inhibitor, SFX.

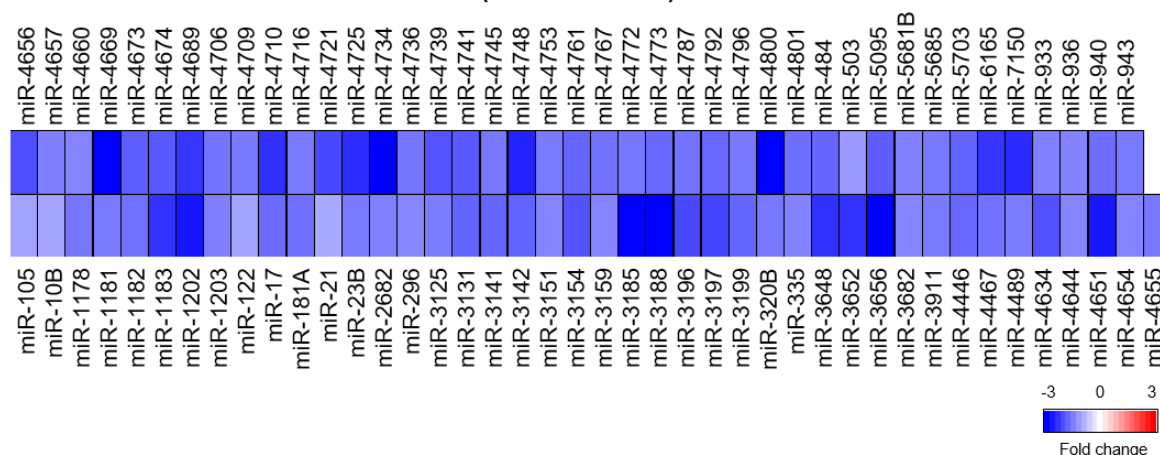
(a) Measurement of GFP fluorescence intensity in the supernatants from MDA-MB231-CD63-GFP (+) cells treated with 1,163 FDA-approved drugs. Drug concentrations were 30 μ M for the primary screening. **(b)** For the secondary screening, MDA-MB231 CD63-GFP (+) cells were treated with 50 or 100 μ M of 26 drugs. Blue dot, percentage cell viability. Bar, Fluorescence (GFP) intensity (relative value). ($n=3$) The secondary screening was performed in triplicates. Experiments were performed with 95% confluent cells. Source data (a-b) are provided as a Source Data file.



Supplementary Figure 3. SFX-mediated blockade of the sEV biogenesis and secretion pathway.

(a) Illustration of the differential ultracentrifugation methods used to isolate microvesicles and small extracellular vesicles (sEV). Bottom, Images of exosome-enriched sEV isolated from MCF7 or MDA-MB231 cells analyzed by TEM. Scale bar, 100 nm. **(b)** Immunoblot of CD9, CD81 and CD63 proteins in sEV from MCF10A, MCF7, MDA-MB231, SK-MEL-28, and HEK293T. **(c)** Measurements of the sEV protein from MDA-MB231, MCF7, and MCF10A cells. ($n=3$) **(d)** Measurement of final cell number after SFX treatment (left) and the calculated number of sEV (right) ($n=2$). **(e)** Measurement of cell viability of the indicated normal and cancer cells. Normal cell lines; MCF10A and HEK293T. Cancer cell lines; MDA-MB231, MCF7 and SK-MEL-28. Broken line, control value. ($n=3$) **(f)** Immunoblot of various sEV proteins. sEV were prepared from the equal numbers of cells. GW4869 was used as a positive control. **(g)** Left, The number of sEV secreted from SK-MEL-28 and HEK293T cells for 24 h in the presence of 100 μ M SFX. Right, Immunoblot of CD9 and CD63 proteins in sEV secreted from SK-MEL-28 after treatment with the different concentrations of SFX. ($n=3$) **(h)** Immunoblot (Right) and activity (Left) of acidic sphingomyelinase (aSMase) in MDA-MB231 cells. FTY720, a known aSMase inhibitor, was used as positive control. ($n=3$) Experiments were performed with 95% confluent cells. Significance was determined using an unpaired two-tailed Student's *t* test. $**p<0.005$. n.s, Not significant. Error Bar, S.D. Source data (c-e, g-h) are provided as a Source Data file.

Down regulated sEV miRNA
MDA-MB231
(SFX vs Vehicle)

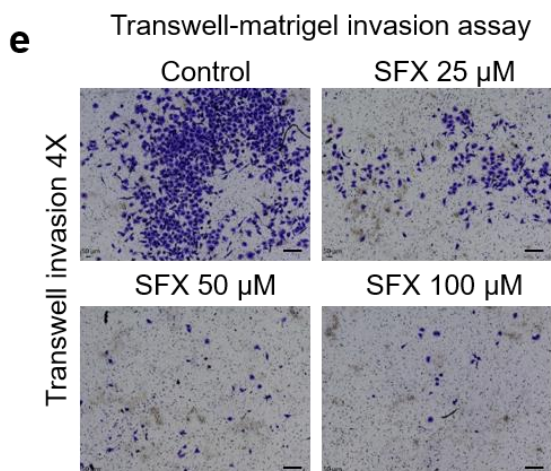
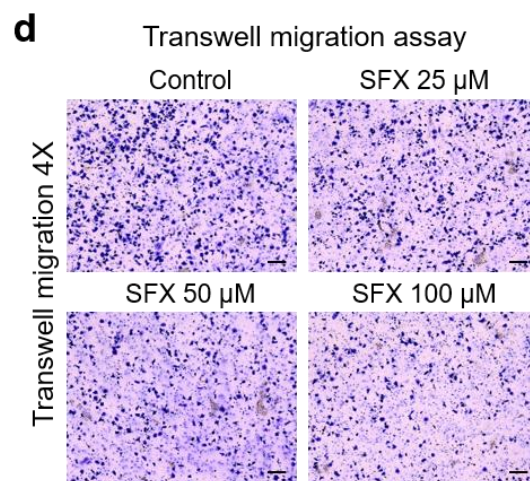
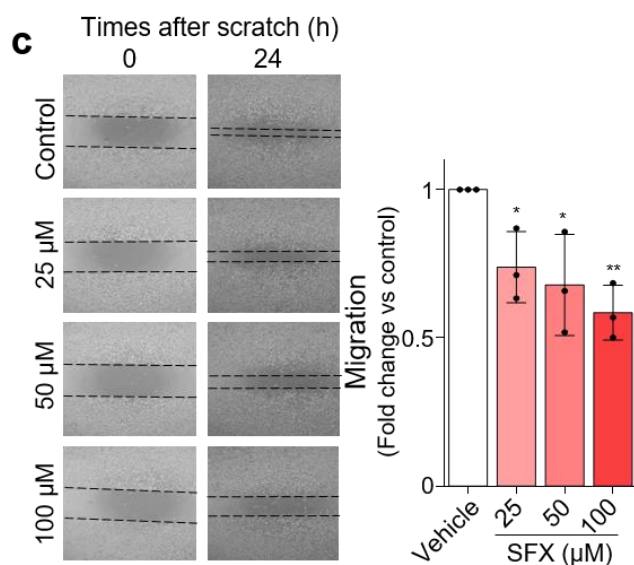
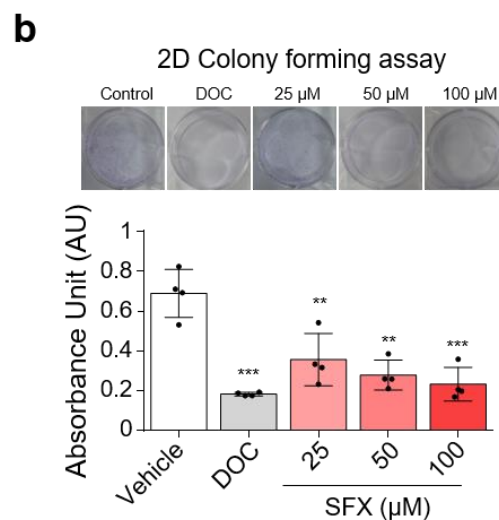
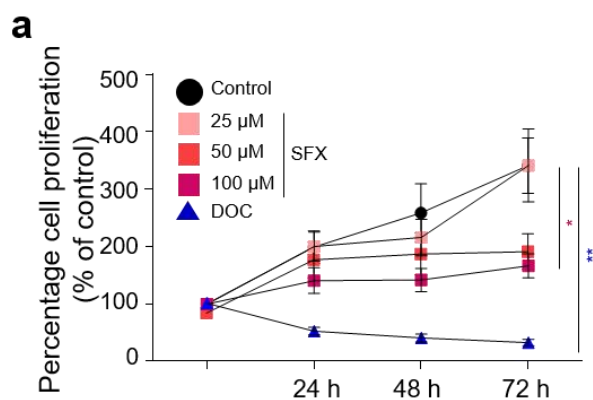


Down-regulated sEV protein
MDA-MB231
(SFX vs Vehicle)

Accession	Gene name	Protein name	SFX/Control Ratio
O00560	SDCB1	Syntenin-1	0.1
Q13733	AT1A4	Sodium/potassium-transporting ATPase subunit alpha-4	0.1
Q02241	KIF23	Kinesin-like protein KIF23	0.1
P55268	LAMB2	Laminin subunit beta-2	0.11
O43854	EDIL3	EGF-like repeat and discoidin I-like domain-containing protein 3	0.12
P04899	GNAI2	Guanine nucleotide-binding protein G(i) subunit alpha-2	0.12
P39060	COIA1	Collagen alpha-1(XVIII) chain	0.12
P0DMV8	HS71A	Heat shock 70 kDa protein 1A	0.12
P0DMV9	HS71B	Heat shock 70 kDa protein 1B	0.12
P98088	MUC5A	Mucin-5AC	0.13
P29317	EPHA2	Ephrin type-A receptor 2	0.13
P98160	PGBM	Basement membrane-specific heparan sulfate proteoglycan core protein	0.13
P60033	CD81	CD81 antigen	0.13
Q15286	RAB35	Ras-related protein Rab-35	0.13
P26006	ITA3	Integrin alpha-3	0.14
P23229	ITA6	Integrin alpha-6	0.17
P16070	CD44	CD44 antigen	0.17
P07355	ANXA2	Annexin A2	0.19
P14618	KPYM	Pyruvate kinase PKM	0.19
P08238	HS90B	Heat shock protein HSP 90-beta	0.2
P00533	EGFR	Epidermal growth factor receptor	0.2
Q99715	COCA1	Collagen alpha-1(XII) chain	0.23
Q08431	MFGM	Lactadherin	0.23
Q08380	LG3BP	Galectin-3-binding protein	0.25
P35527	K1C9	Keratin type I cytoskeletal 9	0.34
P13645	K1C10	Keratin type I cytoskeletal 10	0.37
P13473	LAMP2	Lysosome-associated membrane glycoprotein 2	0.38
P07996	TSP1	Thrombospondin-1	0.52

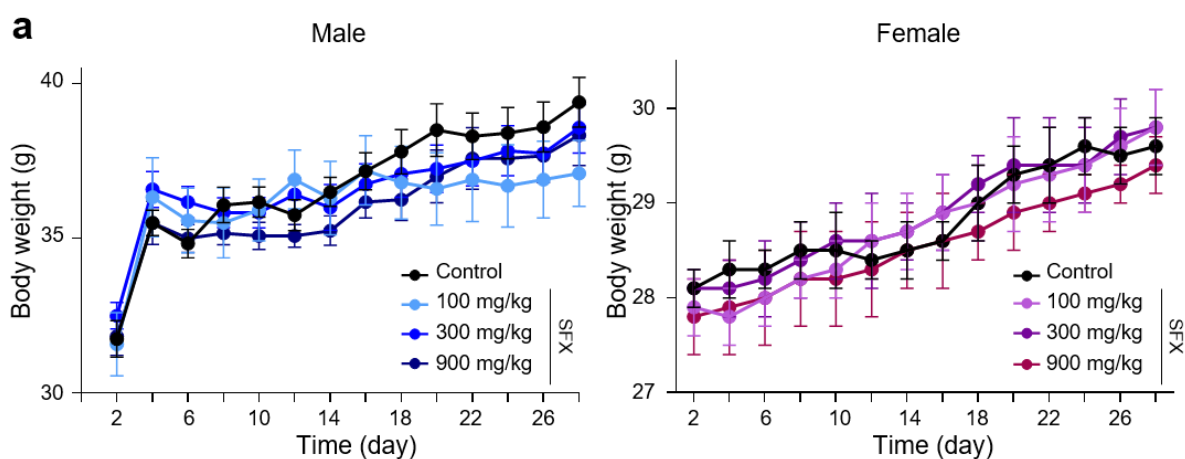
Supplementary Figure 4. SFX-mediated miRNA and protein cargo reduction.

(a) A heatmap of the selected sEV miRNA of SFX-treated MDA-MB231 cells, compared to untreated control cells. The heatmap represents the probe sets for miRNAs expressed at significantly lower levels after treatment with 100 μ M SFX, respectively. The GEO accession number of NCBI is GSE124320. **(b)** Selected sEV proteins of SFX-treated MDA-MB231 cells, compared to untreated control cells (false discovery rate, FDR < 5%). SFX/Control ratio was calculated and summarized. The accession number of ProteomeXchange Consortium is PXD012689.



Supplementary Figure 5. SFX-mediated suppression of cancer cell activities.

(a) Measurement of cancer cell proliferation. MDA-MB231 cells were treated with the indicated concentrations of SFX or 10 nM docetaxel (DOC) every 24 h for up to 3 days. After 24, 48 or 72 h, rates of cell proliferation were measured by MTT reduction method. DOC was used as a positive control. The population of starting cells for this experiment should be a low confluency of about 8%. **(b)** Analysis of the 2D colonic forming assay for SFX-treated MDA-MB231 cells. The population of starting cells was a low confluency of about 8%. **(c)** Analysis of a wound-healing assay in SFX-treated MDA-MB231 cells. Broken line, wound area. **(d)** Analysis of the transwell migration assay in SFX-treated MDA-MB231 cells. Migrated cells were stained using crystal violet solution and random fields were captured. Magnification, $\times 4$. Scale bar, 50 μm . **(e)** Analysis of a matrigel-coated transwell invasion assay in SFX-treated MDA-MB231 cells. Magnification, $\times 4$. Scale bar, 50 μm . All experiments were performed in triplicates. Experiments were performed with 95% confluent cells except for the proliferation and colony forming assays. Significance was determined using an unpaired two-tailed Student's t test. *** $p < 0.001$, ** $p < 0.005$ and * $p < 0.05$. Error Bar, S.D. Source data (a-c) are provided as a Source Data file.



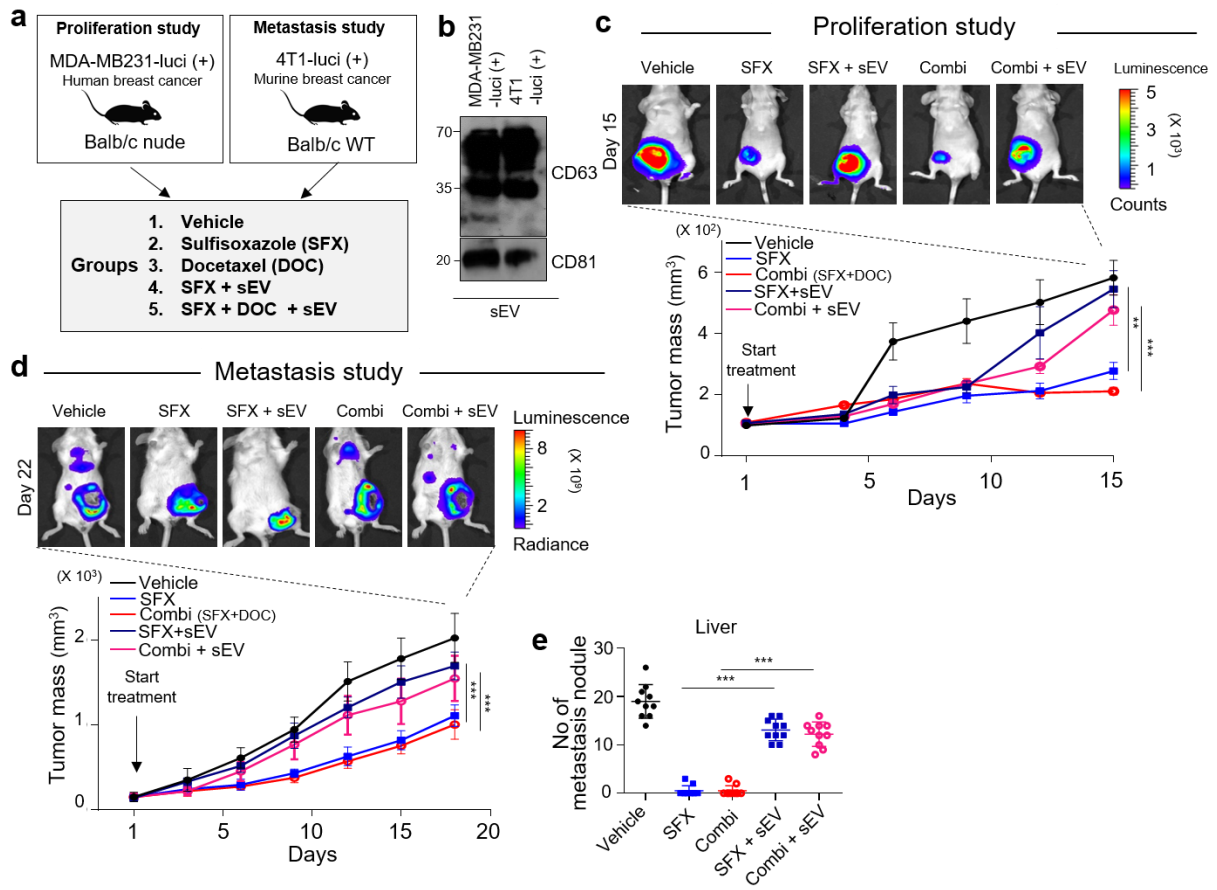
b Serum chemistry following a 28-repeated dose toxicity study of SFX in mice

parameter	male (mg/kg)				female (mg/kg)			
	control	100	300	900	control	100	300	900
AST (IU/L)	64.3 (10.4)	62.4 (9.5)	53.0 (10.1)	57.0 (16.9)	74.5 (21.4)	71.3 (28.7)	72.2 (23.6)	67.5 (15.5)
ALT (IU/L)	39.1 (18.4)	46.3 (19.9)	32.3 (17.3)	28.9 (9.2)	45.1 (11.6)	34.4 (16.7)	37.9 (28.2)	27.1 (5.7)
Glucose (mg/dl)	242.3 (30.0)	277.2 (51.1)	282.5 (50.2)	278.5 (31.9)	268.2 (60.7)	241.2 (18.7)	246.8 (27.0)	222.8 (19.7)
Tot_P (g/dl)	4.63 (0.31)	4.75 (0.41)	4.70 (0.32)	4.47 (0.21)	4.80 (0.19)	4.80 (0.38)	4.75 (0.27)	4.83 (0.12)
Albumin (g/dl)	1.50 (0.11)	1.52 (0.13)	1.52 (0.12)	0.45 (0.10)	1.65 (0.08)	1.58 (0.08)	1.63 (0.08)	1.65 (0.05)
Globulin (g/dl)	3.13 (0.23)	3.23 (0.33)	3.18 (0.21)	3.02 (0.12)	3.15 (0.14)	3.22 (0.40)	3.12 (0.20)	3.18 (0.10)
TG (mg/dl)	58.2 (21.1)	38.3 (15.6)	44.5 (14.9)	42.5 (18.6)	35.8 (21.2)	27.5 (12.1)	26.0 (16.4)	34.5 (7.6)
LDL (mg/dl)	5.83 (1.94)	6.00 (1.26)	7.83 (2.14)	8.00 (3.52)	6.17 (1.47)	8.83 (2.48)	7.17 (1.33)	7.33 (1.37)
BUN (mg/dl)	25.2 (4.0)	20.4 (1.7)	20.3 (1.6)	20.0 (1.8)	20.9 (2.9)	18.5 (2.8)	17.4 (1.5)	17.4 (3.6)
Scr (mg/dl)	0.38 (0.03)	0.38 (0.03)	0.36 (0.03)	0.34 (0.02)	0.39 (0.01)	0.38 (0.03)	0.36 (0.02)	0.33 (0.02)
Tot_B (mg/dl)	0.14 (0.06)	0.13 (0.04)	0.13 (0.02)	0.15 (0.04)	0.07 (0.01)	0.09 (0.02)	0.10 (0.02)	0.09 (0.02)

AST: aspartate transaminase, ALT: alanine transaminase, Tot_P: total protein, TG: triglyceride, LDL: low-density lipoprotein, BUN: blood urea nitrogen, Scr: serum creatinine, Tot_B: total bilirubin; data are mean (s.d.) (n=12).

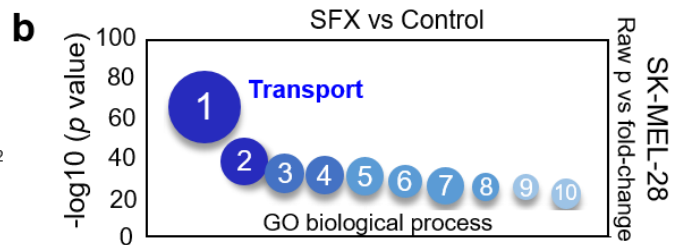
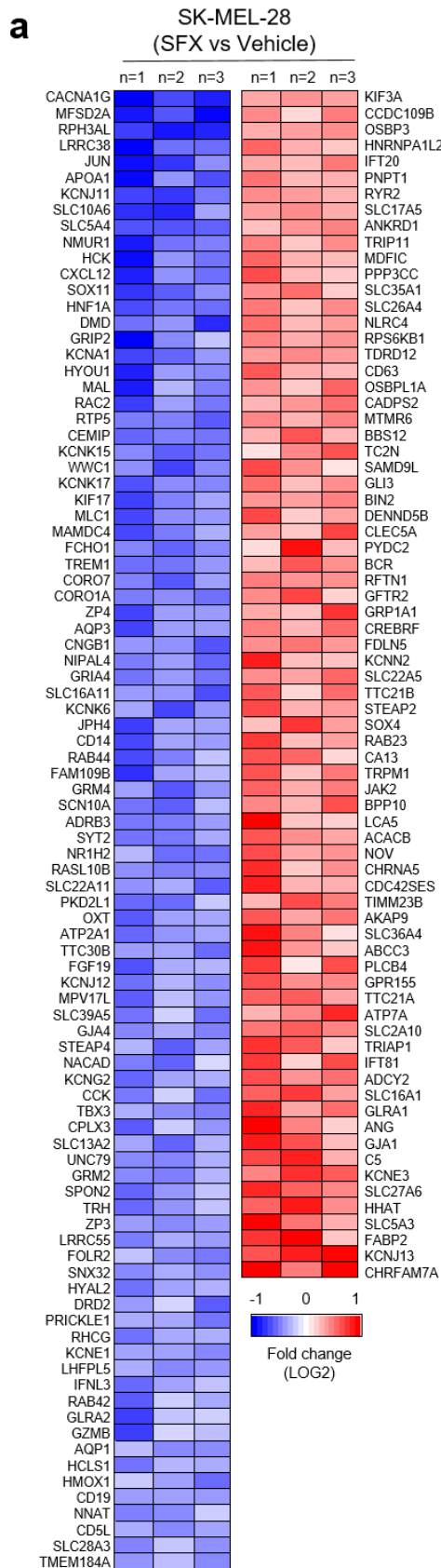
Supplementary Figure 6. No apparent sub-acute toxicities by SFX

(a) Body weight changes in male and female mice exposed to the different concentrations of SFX for 28 days ($n=12/\text{group}$). Body weight for each mouse was measured every 2 days. **(b)** Serum chemistry following a 28-repeated dose toxicity study of SFX in mice ($n=12/\text{group}$). Brace, S.D. of each parameter. Source data are provided as a Source Data file. Source data (a) is provided as a Source Data file.



Supplementary Figure 7. SFX suppresses breast cancer cell proliferation and metastasis via sEV modulation.

(a) Schematic illustration of the *in vivo* experimental designs with different treatments. **(b)** Immunoblot of CD63 and CD81 in sEV from MDA-MB231-luci (+) and 4T1-luci (+) cells. **(c)** Top, Representative image of cancer cells tracked with the IVIS imaging system following the injection of mice with luciferase-expressing MDA-MB231 cells. Bottom, Tumor mass volume of in BALB/c *nude* female mice inoculated with MDA-MB231-luci (+) cells and then treated with an indicated drug, vehicle and sEV ($n=8$ per group). **(d)** Top, *in vivo* images of 4T1 cancer cell-bearing mice using an IVIS imaging system. Bottom, Tumor mass volume of 4T1-luci (+) cells inoculated BALB/c *nude* female mice treated with an indicated drug, vehicle and sEV ($n=10$ per group). **(e)** Quantitative representation of liver nodules from mice bearing 4T1-luci (+) cells ($n=10$ per group). Significance was determined using an unpaired two-tailed Student's *t* test. *** $p<0.001$, ** $p<0.005$ and * $p<0.05$. Error Bar, S.D. Source data (c-e) are provided as a Source Data file.

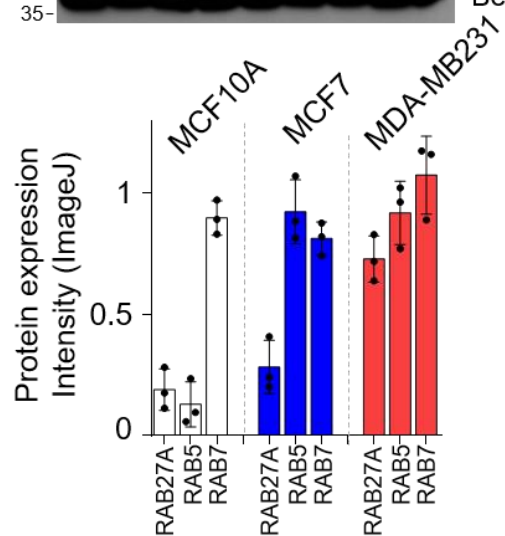
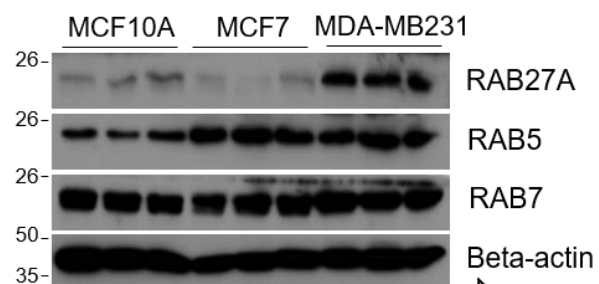
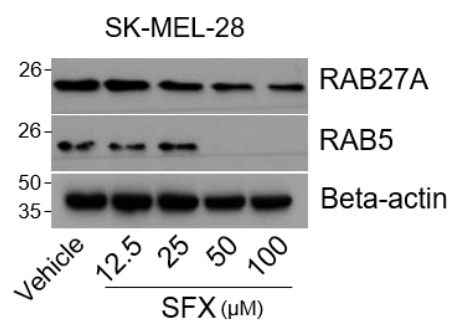
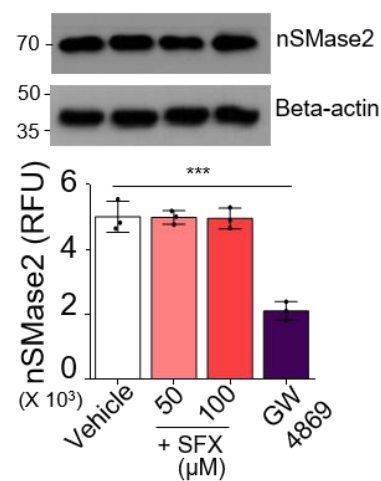
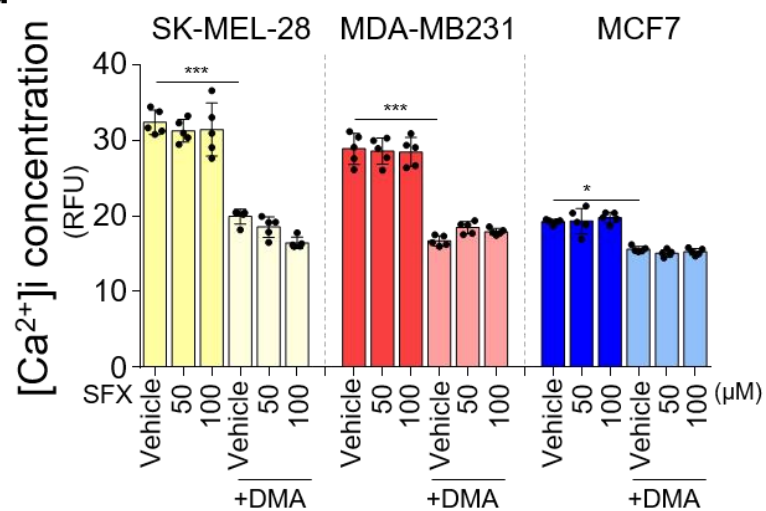


c

RANK	MDA-MB231	SK-MEL-28
	TERM	TERM
1	Transport	Transport
2	Small GTPase mediated signal transduction	Regulation of transport
3	Regulation of transport	Positive regulation of transport
4	Vesicle-mediated transport	Secretion
5	Secretion	Secretion by cell
6	Secretion by cell	Regulation of secretion
7	Endomembrane system organization	Vesicle-mediated transport
8	Endocytosis	Positive regulation of secretion
9	Positive regulation of transport	Positive regulation of secretion by cell
10	Regulation of secretion by cell	Endocytosis

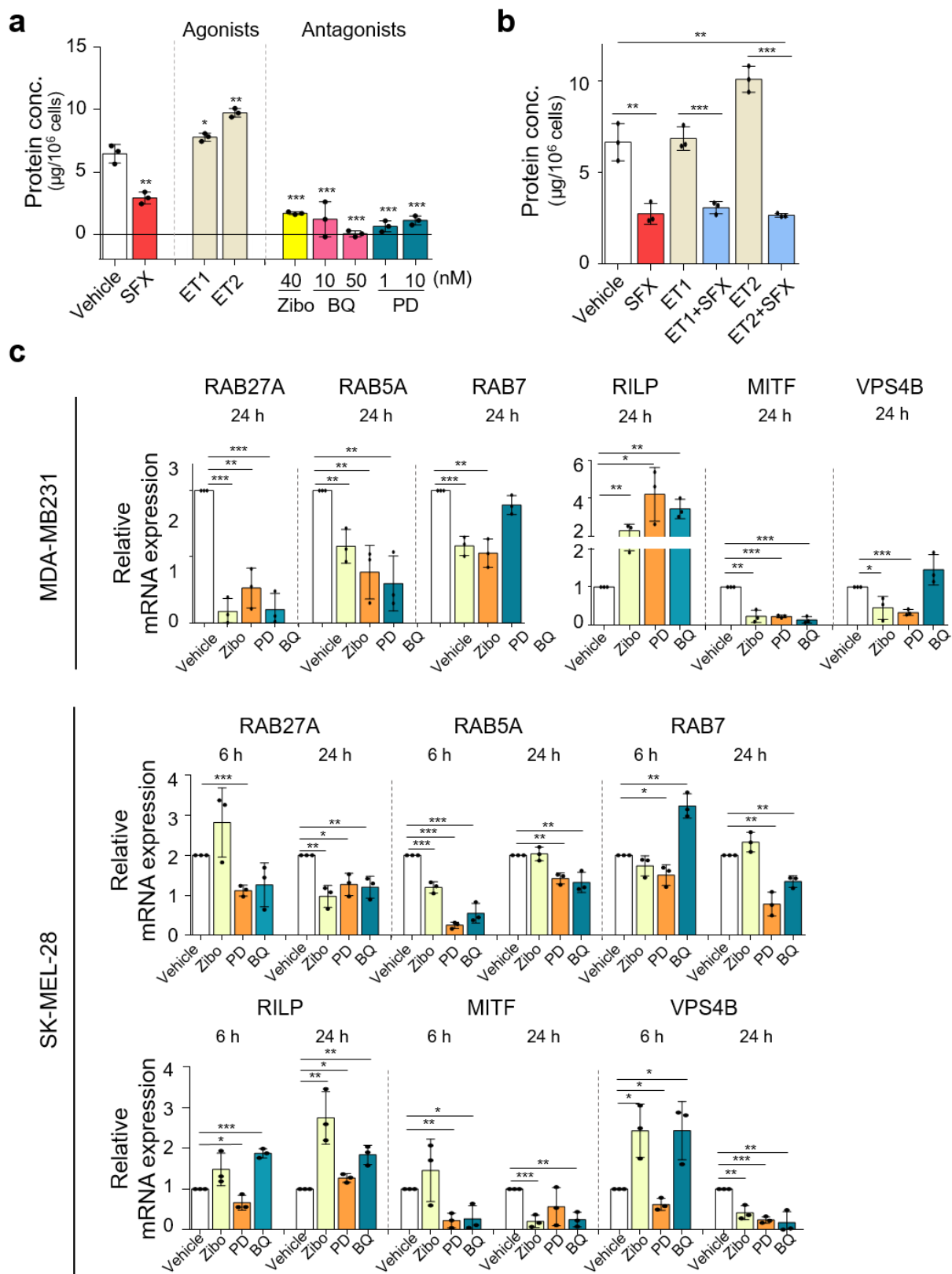
Supplementary Figure 8. SFX-mediated selective alteration of the genes involved in sEV secretion in SK-MEL-28 melanoma cells.

(a) A heatmap of the selected transcriptome of SFX-treated SK-MEL-28 cells, compared to untreated control cells. The heatmap represents the probe sets for transcripts expressed at significantly higher or lower levels after treatment with 100 μ M SFX, respectively ($FC = \pm 1.3$ p -value = 0.05). **(b)** The advanced bubble chart shows the enrichment of differentially expressed genes in the indicated signaling pathways. The x-axis label indicates the rank of GO biological processes, and the y-axis label represents p value. The sizes of the bubble represent the amounts of differentially expressed genes enriched in biological processes. **(c)** The rank of GO biological processes was summarized. Microarray was performed in triplicates. The GEO accession number of NCBI dataset is GSE117991.

a**b****c****d**

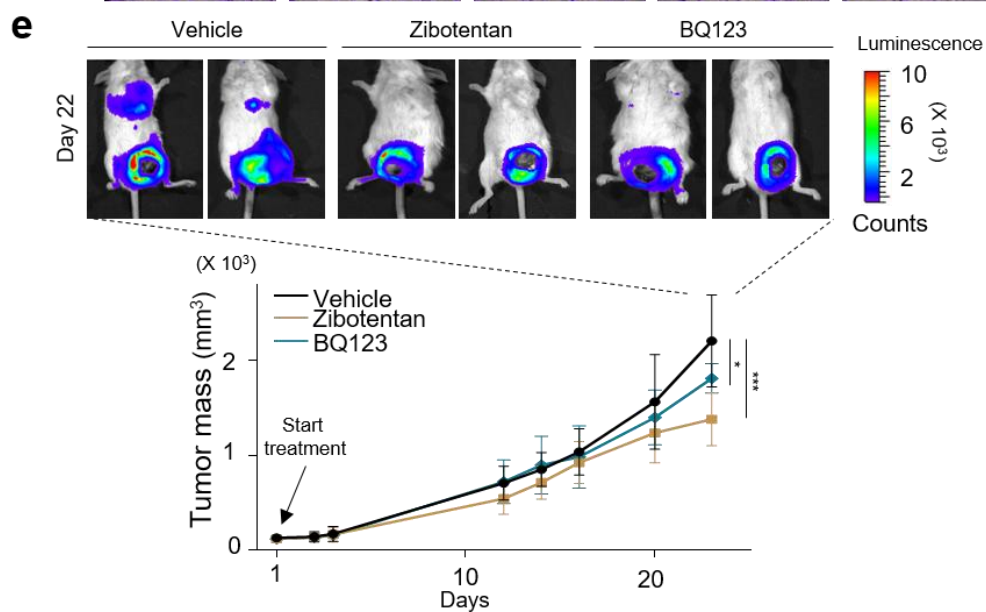
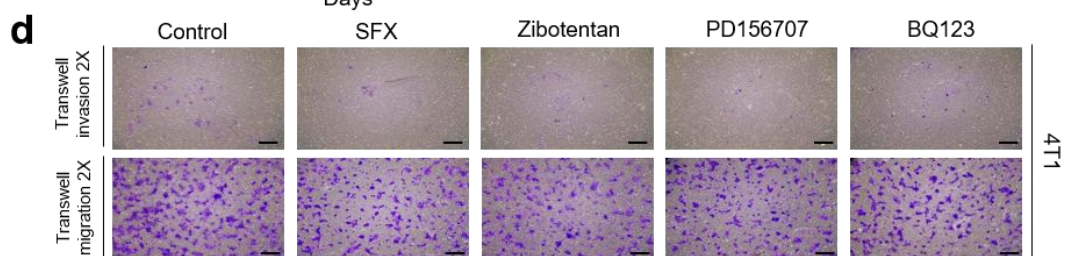
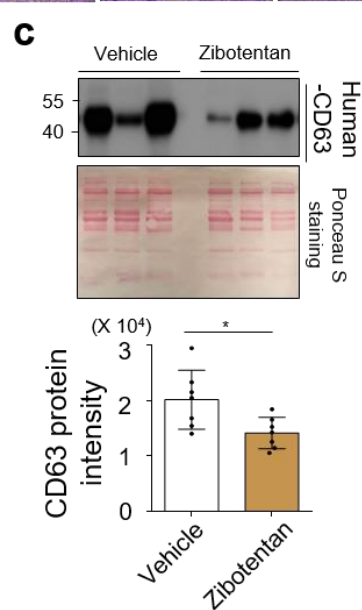
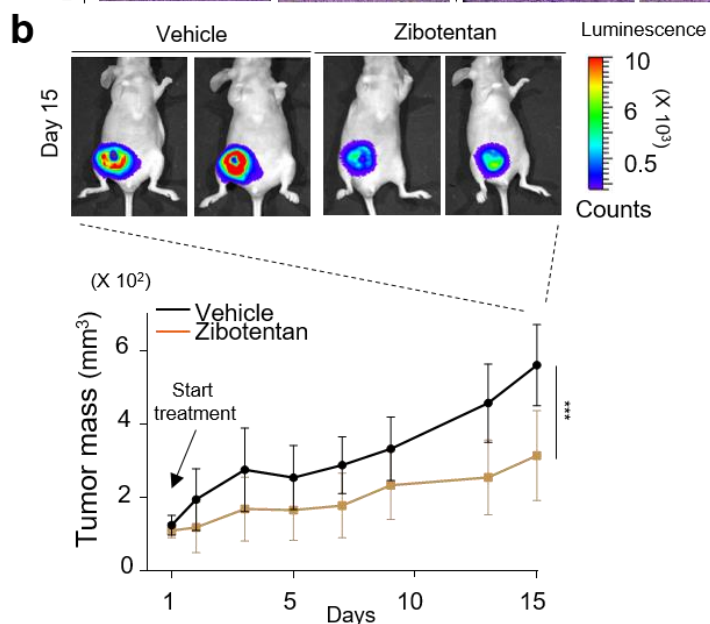
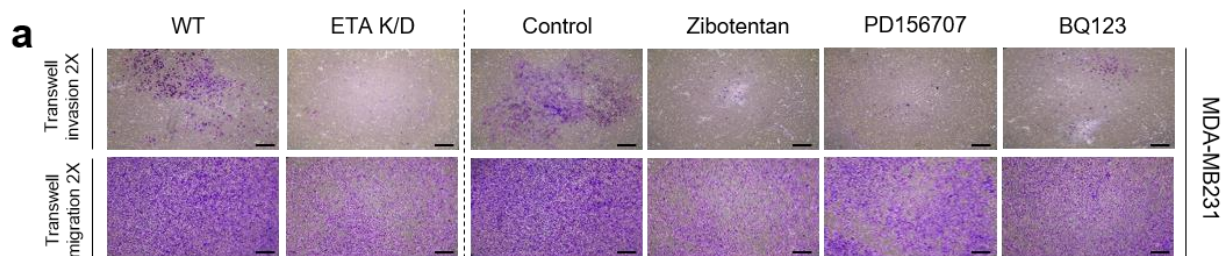
Supplementary Figure 9. SFX-mediated blockade of the sEV biogenesis/secretion pathway through the ESCRT-dependent pathway.

(a) Differential expression of the sEV biogenesis-related proteins in three breast cells. Basal expression levels of Rab27a, Rab5, and Rab7 in MCF10A, MCF7, and MDA-MB231 cells were measured by western blot analysis ($n=3$ per group). **(b)** Immunoblot of RAB27A and RAB5 in SK-MEL-28 melanoma cells treated with the indicated concentrations of SFX. **(c)** Immunoblot (top) and activity (bottom) of neutral sphingomyelinase-2 (nSMase2) in MDA-MB231 cells. GW4869, an inhibitor of nSMase2, was used as a positive control. **(d)** Measurement of intracellular calcium concentrations by Fluo-3AM method in SK-MEL-28, MCF7 and MDA-MB231 cells. Dimethyl amiloride (DMA) was used as a positive control. ($n=5$). All experiments were performed in triplicates. Experiment were performed using 95 % confluency of cells. Significance was determined using an unpaired two-tailed Student's t test. *** $p<0.001$ and * $p<0.05$. Error Bar, S.D. Source data (a-d) are provided as a Source Data file.



Supplementary Figure 10. ETA antagonists-mediated blockade of the mRNA expression levels of the proteins associated with sEV biogenesis and secretion.

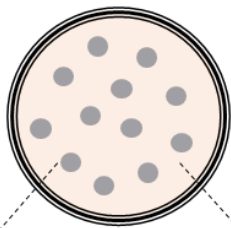
(a) Measurement of the amount of sEV proteins from ETA agonist- or antagonist-treated MDA-MB231 cells. **(b)** Measurement of the amounts of sEV proteins from MDA-MB231 cells treated with 10 nM ET1 or 10 nM ET2 in the presence of 100 μ M SFX. **(c)** Changes in the expression of RAB27A, RAB5A, RAB7, RILP, MITF, and VPS4B mRNA transcripts in MDA-MB231 and SK-MEL-28 cells by the indicated ETA antagonists. The levels of expressed genes were calculated by the delta-delta Ct ($\Delta\Delta$ Ct) method. Zibo, 40 nM Zibotentan. PD, 10 nM PD156707. BQ, 50 nM BQ123. All experiments were performed in triplicates. Experiment were performed using 95 % confluency of cells. Significance was determined using an unpaired two-tailed Student's t test. *** p <0.001, ** p <0.005 and * p <0.05. Error Bar, S.D. Source data (a-c) are provided as a Source Data file.



Supplementary Figure 11. ETA mediated suppression of cancer cell activities

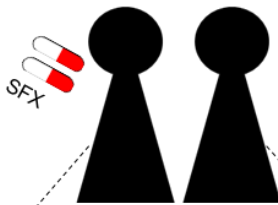
(a) Analysis of the transwell invasion (upper) and migration (bottom) assays in ETA antagonists-treated MDA-MB231 cells and MDA-MB231 ETA K/D cells. Invaded or migrated cells were stained using crystal violet solution and random fields were captured. Magnification, $\times 2$. Scale bar, 100 μm . **(b)** Top, Representative image of cancer cells tracked with the IVIS imaging system following the injection of mice with luciferase-expressing MDA-MB231 cells. Bottom, Tumor mass volume of in BALB/c *nude* female mice inoculated with MDA-MB231-luci (+) cells and then treated with an indicated drug or vehicle ($n=9$ per group). **(c)** Upper, Immunoblot of human CD63 in circulating cancer-cell derived sEV from MDA-MB231-luci (+)-bearing mice ($n=6$ per group) where similar amounts of protein/lane were verified by Ponceau S staining (Bottom). Bottom, Analysis of the relative protein intensity of CD63 measured using a densitometer system. **(d)** Analysis of the transwell invasion (upper) and migration (bottom) assays in ETA antagonists-treated 4T1 cells. Invaded or migrated cells were stained using crystal violet solution and random fields were captured. Magnification, $\times 2$. Scale bar, 100 μm . **(e)** Top, *in vivo* images of 4T1 cancer cell-bearing mice using an IVIS imaging system. Bottom, Tumor mass volume of 4T1-luci (+) cells inoculated BALB/c *nude* female mice treated with an indicated drug or vehicle ($n=9$ per group). Experiment were performed using 95 % confluency of cells. Significance was determined using an unpaired two-tailed Student's t test. *** $p<0.001$, ** $p<0.005$ and * $p<0.05$. Error Bar, S.D. Source data are provided as a Source Data file. Source data (b-c, e) are provided as a Source Data file.

MIC
(anti-bacterial effect)



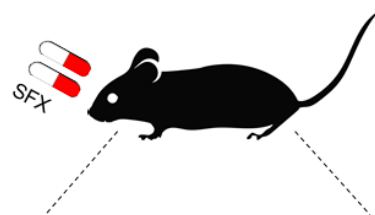
Strain	MIC	
<i>S.aureus</i>	32 µg/ml	≈ 120µM
<i>E.coli</i>	16 µg/ml	≈ 60µM

SFX
(antibiotic for human)



Maximum dosage for an antibiotic (human)
1~2 g orally every 6 h (4~8 g/ 24 h) ≈ 66.5~133 mg/kg

SFX
(for anti-cancer effect)



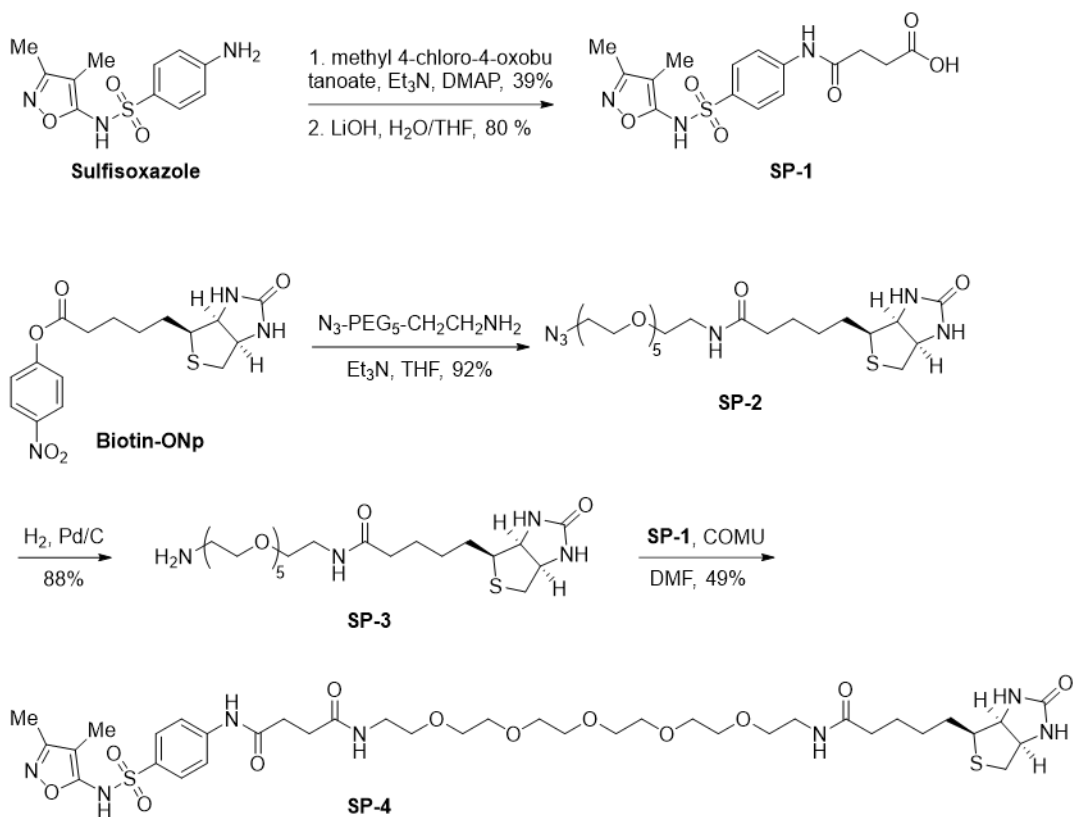
Dosage for anti-cancer effect (mouse)
200 mg/kg orally per day (0.2 g/ 24 h)
↓
Human Equivalent Dose (HED)* ≈ 16.22 mg/kg
↓
≈ 4.1~8.2 times lower than current dosage (133 mg/kg) for an antibiotic

Supplementary Figure 12. Clinical relevance of SFX dosages.

The unit ($\mu\text{g ml}^{-1}$) of MIC converted to the μM unit. The recommended dosage for an antibiotic in human usage is about 66.5 to 133 mg kg^{-1} . The dosage (200 mg kg^{-1}) for mouse study is converted to a human equivalent dose (approximately 16.22 mg kg^{-1}).

Supplementary Figure 13. Chemical structure of sulfisoxazole-based affinity probe

Synthesis of a sulfisoxazole-based affinity probe



Supplementary Figure 14. Full images of immunoblots.

Full uncropped images and signals detected by immunoblotting, with the regions used in the corresponding main display items indicated by red frames.

Figure 1g

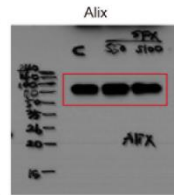
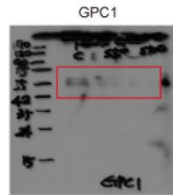
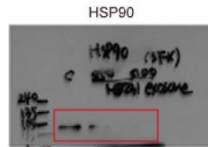
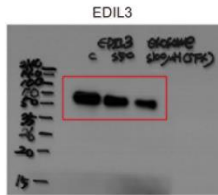


Figure 2f

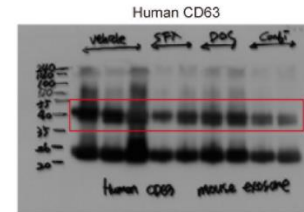


Figure 3d (upper)

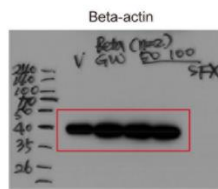
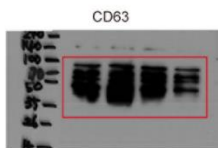
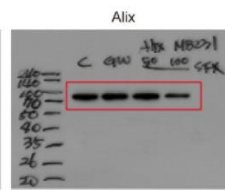
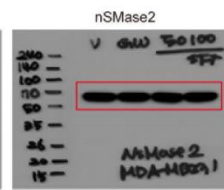
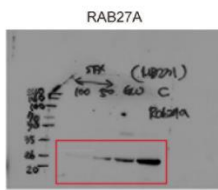


Figure 3d (bottom)

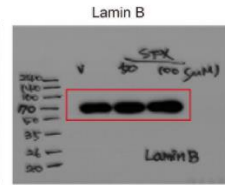
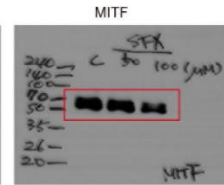
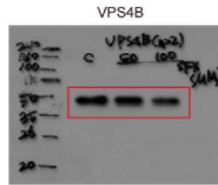


Figure 4d

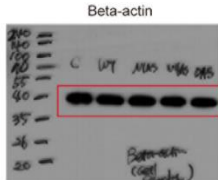
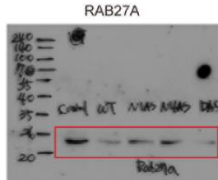


Figure 4f

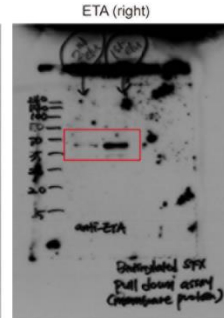
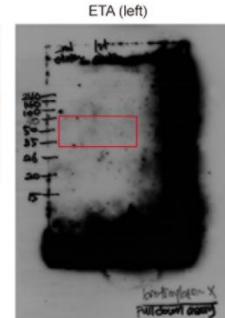


Figure 4g

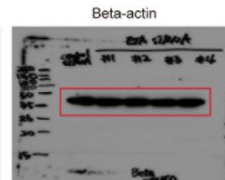
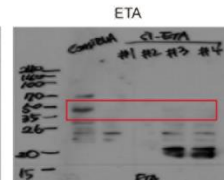
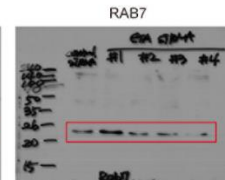
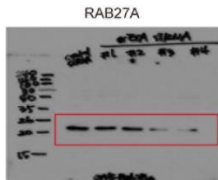


Figure 4h

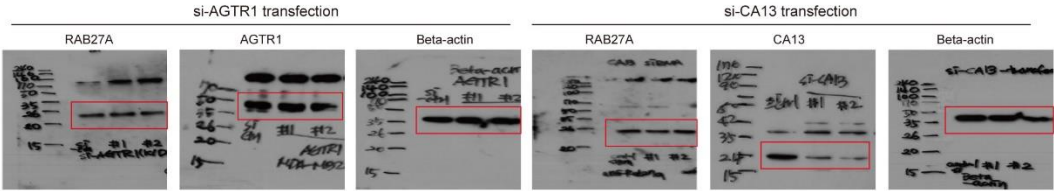


Figure 4j

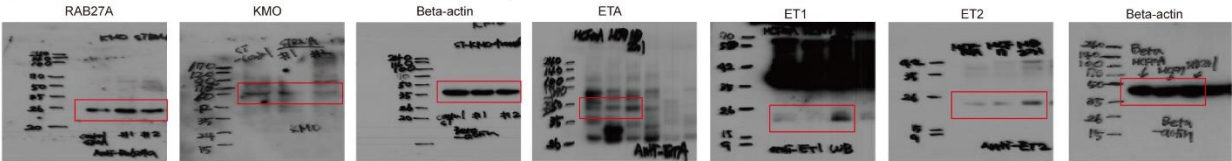


Figure 5b

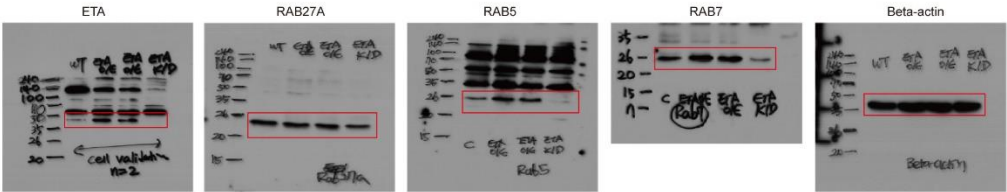


Figure 5b (cont.)

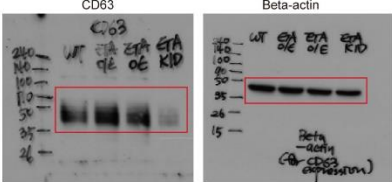


Figure 5g

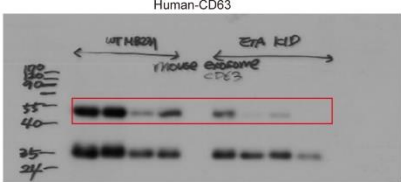


Figure 6b

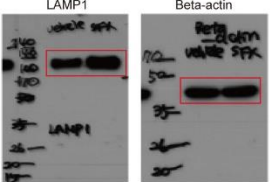
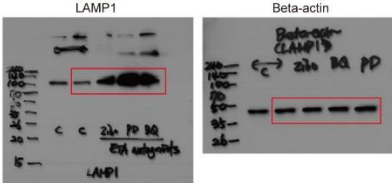
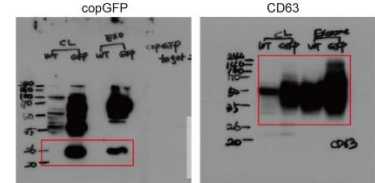


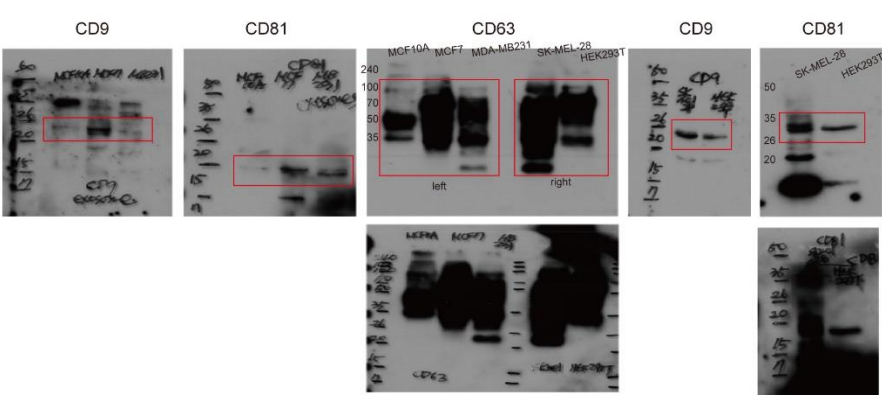
Figure 7c



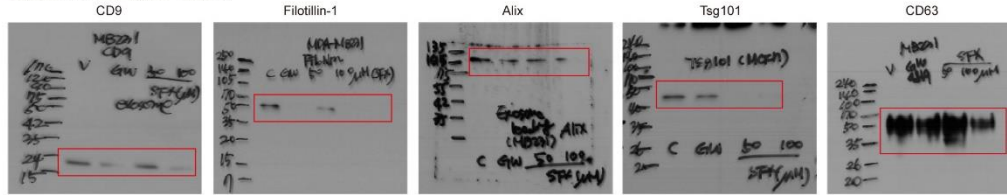
Supplementary figure 1c



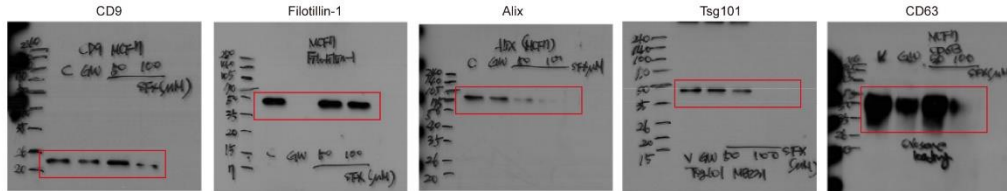
Supplementary figure 3b



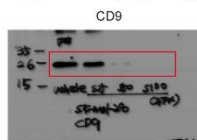
Supplementary figure 3f (left)



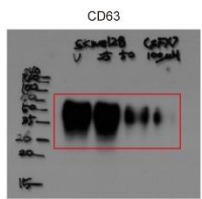
Supplementary figure 3f (right)



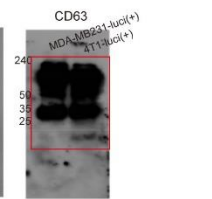
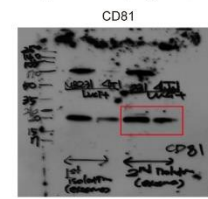
Supplementary figure 3g



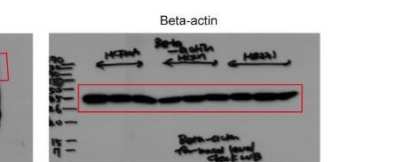
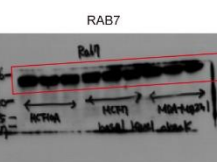
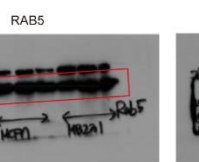
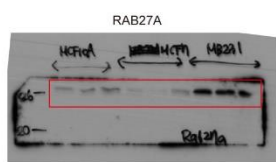
Supplementary figure 3h



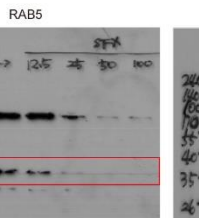
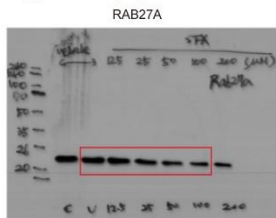
Supplementary figure 7b



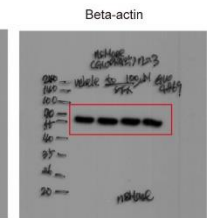
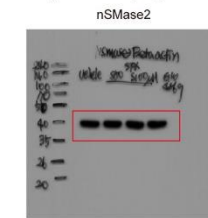
Supplementary figure 9a



Supplementary figure 9b



Supplementary figure 9c



Supplementary Table 1. List of primer sequences used for reverse-transcription-polymerase chain reaction (RT-PCR)

Primer sequences used for reverse-transcription-polymerase chain reaction (RT-PCR) (5' to 3')

Gene	Forward primer	Reverse primer
RAB27A	AGT TGA TGG AGC GAA CTG CT	CCC TAC ACC AGA GTC TCC CA
RAB5A	ACG GGC CAA ATA CGG GAA AT	TCA AAC TTT ACC CCA ATG GTA CT
RAB7	GAT GGT GGA TGA CAG GCT AGT	CGA GAG ACT GGA ACC GTT CCT
RILP	CAC CCC CGG AGT CCA AAA TA	CAC AGC CAG ACC CCT AAG TC
MITF	AAG GGC TTG CAG AAC ACC TTA	GCT GGT TTG GAC ATG GCA AG
VPS4B	GAA ATC GGA AGT GCC CGG AG	CCA TCA CTG TCA TTC CCC TTC TC
Beta-actin	TTC CTG GGC ATG GAG TCC TGT GG	CGC CTA GAA GCA TTT GCG GTG G

Supplementary Table 2. List of miRNA sequences used for miRNA expression analysis

miRNA sequence used for miRNA expression analysis

miRNA	miRBase Accession Number	Mature miRNA sequence	Assay ID
miR-21	MIMAT0000076	UAGCUUAUCAGACUGAUGUUGA	000397
miR-23b	MIMAT0000530	UAGCUUAUCAGACUGAUGUUGA	002126
miR-320b	MIMAT0005792	AAAAGCUGGGUUGAGAGGGCAA	002844
miR-182	MIMAT0000259	UUUGGCAAUGGUAGAACUCACACU	002334
miR-10b	MIMAT0004556	ACAGAUUCGAUUCUAGGGGAAU	002315
miR-105	MIMAT0004516	ACGGAUGUUUGAGCAUGUGCUA	002168
miR-122	MIMAT0000421	UGGAGUGUGACAAUGGUGUUUG	002245
miR-503	MIMAT0022925	GGGGUAUUGUUUCCGCUGCCAGG	001048
U6 snRNA		GTGCTCGCTTCGGCAGCACATATACTAAAATTGG AAVGATAVAGAGAAGATTAGCATGGCCCCTGCG CAAGGATGACACGCAAATTCGTGAAGCGTTCCA TATTTT	001973

Supplementary Table 3. List of siRNA sequences used for RNAi interference analysis

The siRNA sequence used for RNAi interference analysis

Target		Target sequence	Cat.#
ETA	#1	GUGAUAAUCCUGAGAGAU A	J-005485-05
	#2	GACAAGAACCGAUGUGAAU	J-005485-06
	#3	GCACUGGUUGGAUGUGUAA	J-005485-07
	#4	CCUCUGCGCUCUUAGUGUU	J-005485-08
AGTR1	#1	UGGAAGGCAUAAUACAUA	J-005428-07
	#2	CCUGUACGCUAGUGUGUUU	J-005428-08
KMO	#1	UGGAUUAACAUUCGAGGAA	J-009897-09
	#2	CGUUAUUAUAGCAUCGACAA	J-009897-10
CA13	#1	GGUAAACAAACUCGAUUCA	J-027325-09
	#2	CUGCCGUGUUGAUAGAAUA	J-027325-10