Supplemental Data

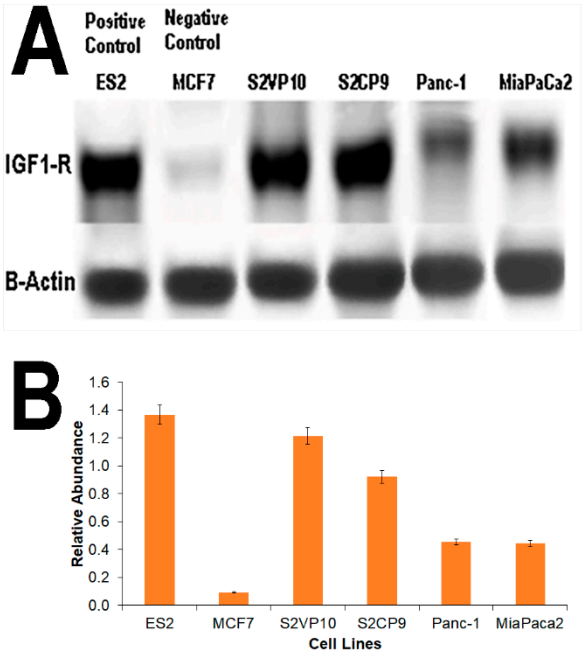


Figure S1: Western blot shows relative levels of Insulin like growth factor 1-receptor (IGF1-R) in pancreatic cancer cell lines. (**A**) Western blot was quantified (**B**) for IGF1-R and B-actin (control). Positive control was ES2 and negative (low expressing) control was MCF7.

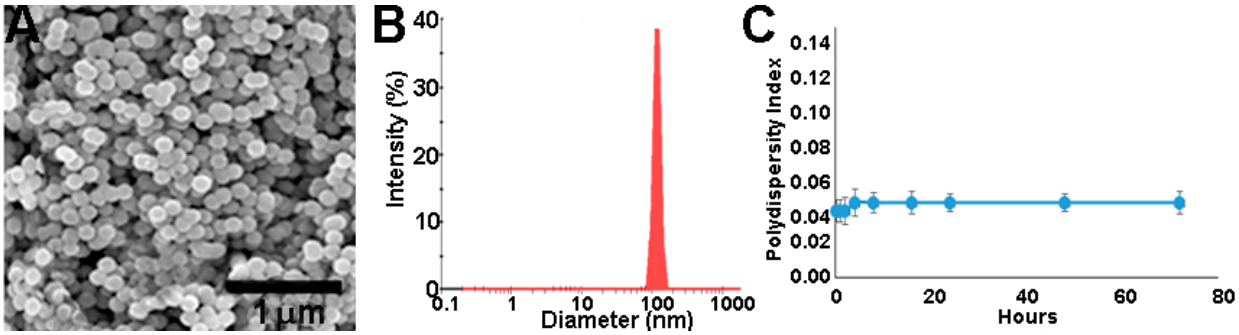


Figure S2: Characterization of Liposomes. (**A**) The synthesized liposomes were characterized by Scanning Electron Microscopy (SEM) (**B**) Dynamic Light Scattering (DLS), and (**C**) polydispersity index was measured. SEM analysis determined the average liposome particle diameter 111 nm± 6.1nm. The further characterization by DLS determined the average diameter 129nm ± 6.4nm with the uniform (0.04–0.05) polydispersion index (PDI) values.

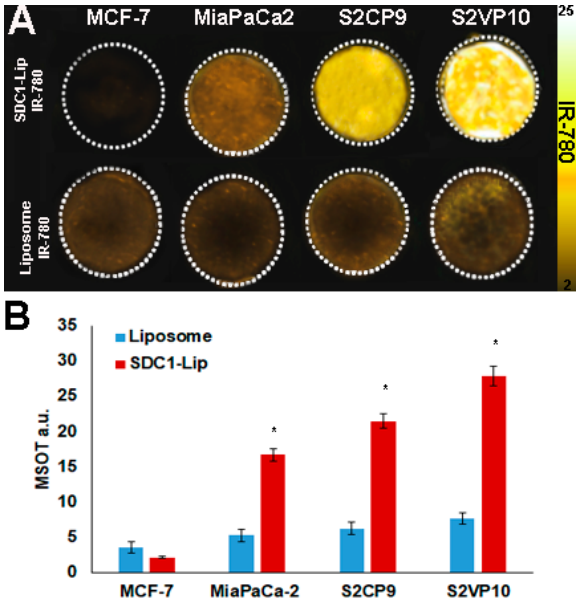


Figure S3: Tissue mimicking phantoms indicate relative level of SDC1-Lip uptake in IGF1-R low (MCF7) and pancreatic cells. Cells were plated in 6-well plates, treated with SDC1-Lip or untargeted liposome containing IR-780 dye as in flow cytometry. (**A**) Cell pellets were visualized using MSOT in tissue mimicking phantoms and quantified in (**B**) These results confirm the flow cytometry results indicating statistically significant increases SDC1-Lip in IGF-1R positive cells $p < 0.05$*.

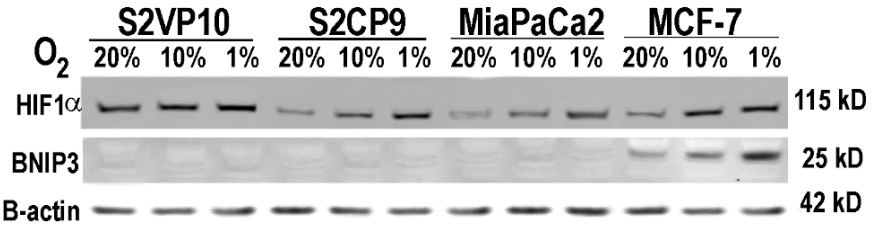
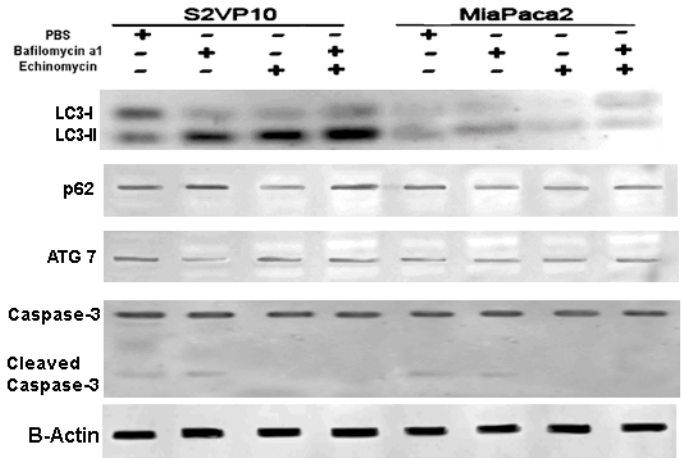


Figure S4: Evaluation of HIF1-α and BNIP3 expression in pancreatic cancer cell lines in normoxia and hypoxia. While S2VP10 exhibited chronic expression of HIF1-α in normoxia and hypoxia, both S2CP9 and MiaPaCa2 cell lines expressed HIF1-α with decreasing O_2. None of the pancreatic cancer cell lines tested expressed BNIP3 under normoxia or hypoxia conditions. MCF-7 (control) increased expression of both HIF1-α and BNIP3 with decreasing O_2 levels.



Supplemental Figure 5: Evaluation of Bafilomycin a1 combined with Echinomycin in pancreatic cancer cells. Similarly to the experiments and western blots in **Figure 3**, S2VP10 and MiaPaCa2 cells were treated with 5 nM Bafilomycin a1, 1 nM Echinomycin, or combination. Western blots demonstrate increased autophagy as demonstrated by increased LC3-II in both Bafilomycin a1 control

samples as well as Echinomycin treated samples and combination. The combination of the lysosomal inhibitor Bafilomycin A1 with Echinomycin further increased LC3 lipidation levels upon combination treatment with compared with either agent alone, indicating that the enhanced LC3 lipidation was due to induced autophagosome biogenesis, and not a block in autophagosome clearance. Furthermore, this increase in LC3-II without increase in cleaved caspase-3 supports the mechanism of cell death as autophagy without apoptosis.

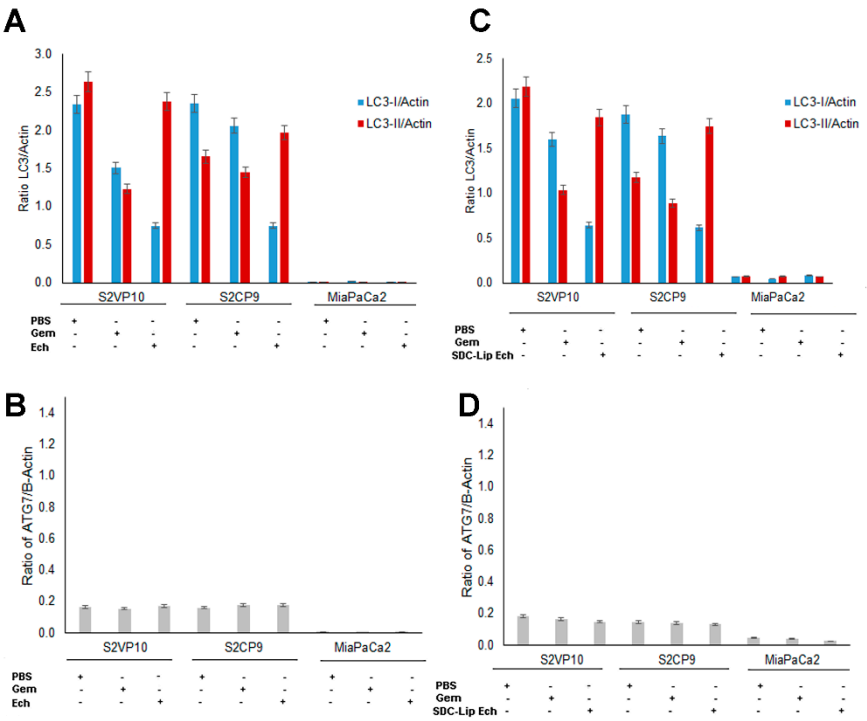


Figure S6: Dosimetry of western blots containing CL3-I, -II, and ATG 7 data from Figure 3. (A) Western blot dosimetry of LC3-I and LC3-II (B) ATG7 from cells treated with Echinomycin or Gemzar. (C) Western blot dosimetry of LC3-I and LC3-II (D) ATG7 from cells treated with SDC-Lip Echinomycin or Gemzar.

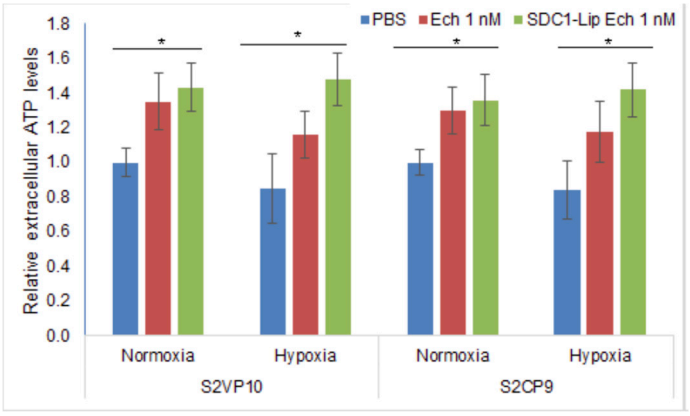


Figure S7: Assessment of extracellular ATP levels of S2VP10 and S2CP9 under normoxia and hypoxia following Echinomycin or SDC1-Echinomycin treatment. Cells were treated with 1nM of either free drug or the targeted liposomal drug formulation. After 24 h, the cell culture media (with any floating cells removed via centrifugation) was removed and ATP was measured using the ATPlite assay without including the cell lysate. The results of the assay were normalized to PBS normoxia treatment. The ATPlite assay demonstrated increased extracellular ATP levels in response to Echinomycin treatment in normoxia and hypoxia in S2VP10 and S2CP9. Statistical analysis was conducted via ANOVA with significance $p < 0.05$ indicated by a *.

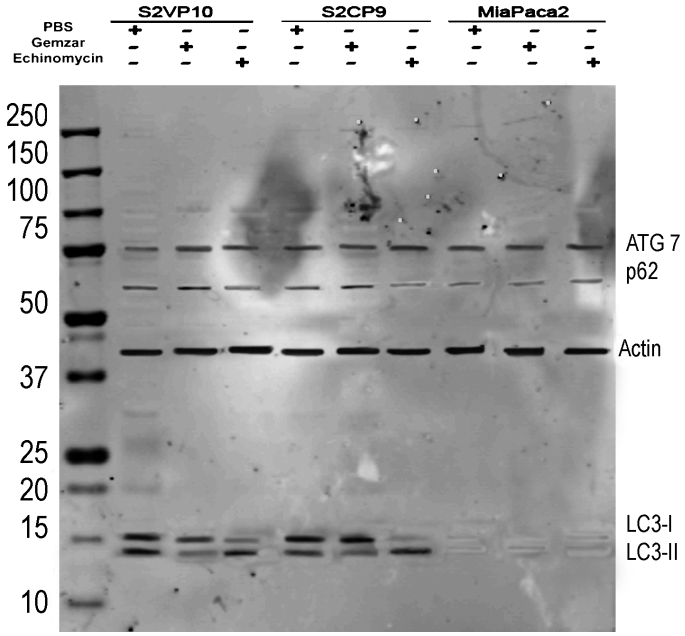
Western blot data

Figure 3A western blots

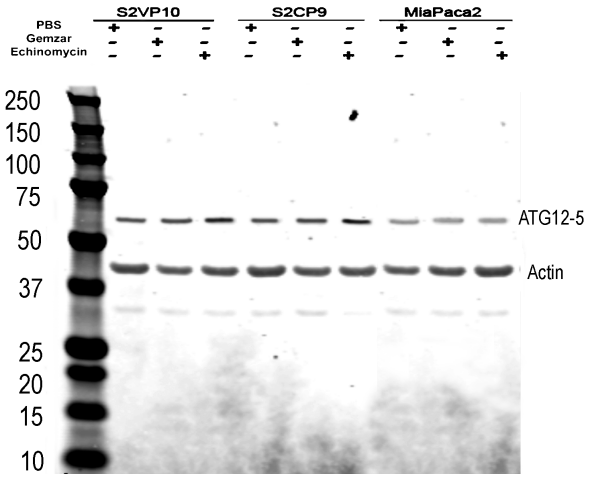
Dosimetry

	S2VP10			S2CP9			MiaPaCa2		
PBS	+	-	-	+	-	-	+	-	-
Gem	-	+	-	-	+	-	-	+	-
ECH	-	-	+	-	-	+	-	-	+
LC3-I	78.538	53.838	25.268	87.638	71.432	25.798	0.038	0.755	0.19
LC3-II	88.602	43.888	79.976	61.606	50.21	68.239	0.365	0.323	0.269
ATG7	5.492	5.504	5.79	5.965	6.171	6.174	0.087	0.033	0.127
ATG12	6.676	8.762	30.647	6.359	5.895	25.617	0.533	1.177	0.264
p62	44.807	47.992	35.653	43.3	45.845	32.304	23.284	21.826	22.274
Caspase 3	11.872	4.099	14.388	3.494	6.525	12.726	5.961	1.375	4.79
Cleaved Casp3	0.999	7.605	0.214	0.208	8.389	0.35	1.288	10.5	1.23
Caspase 9	38.202	11.245	49.694	28.765	12.515	16.967	36.99	14.947	40.367
Cleaved Casp9	0.169	5.912	0.267	1.082	14.464	0.695	1.196	27.395	1.354

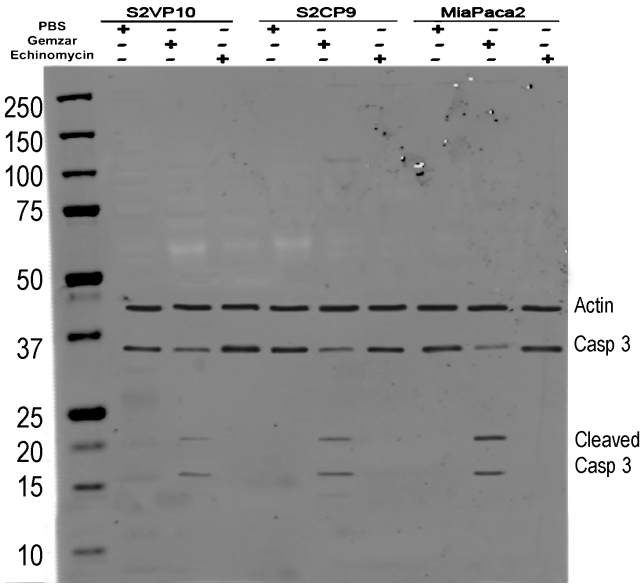
Whole blots forLC3-I/II, ATG7, p62



ATG 12-5



Caspase 3



Caspase 9

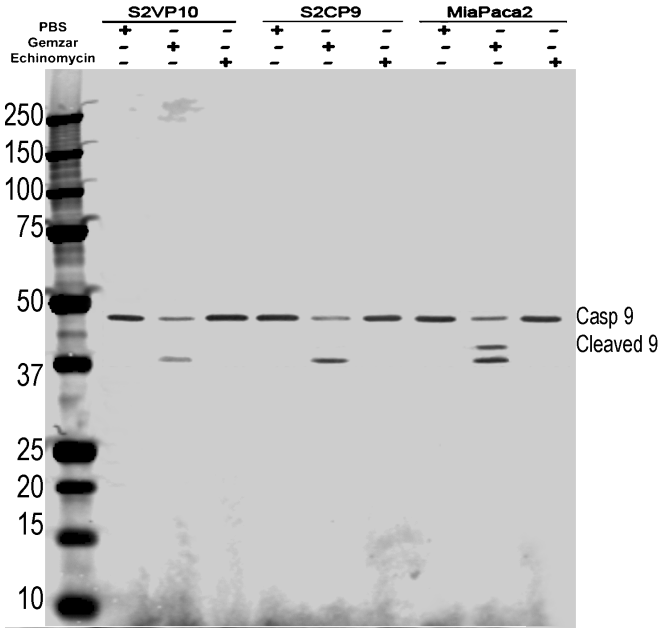
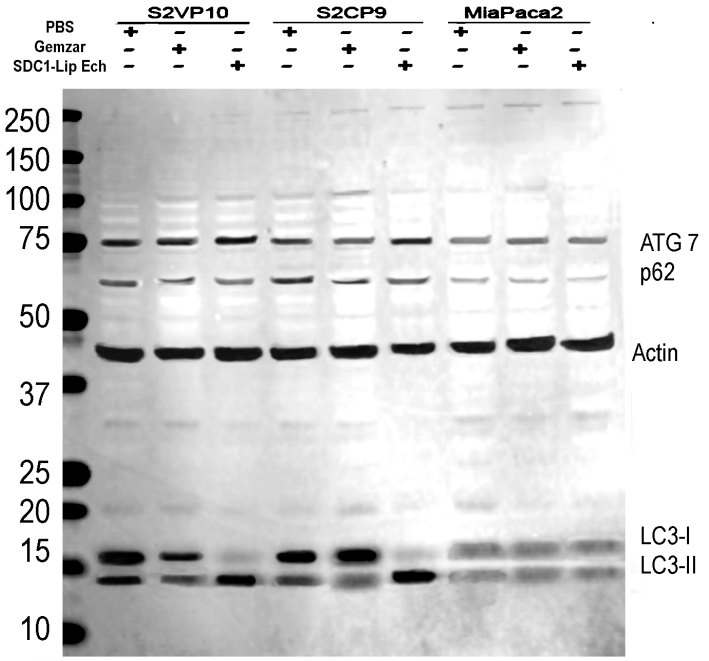


Figure 3B Western Blots

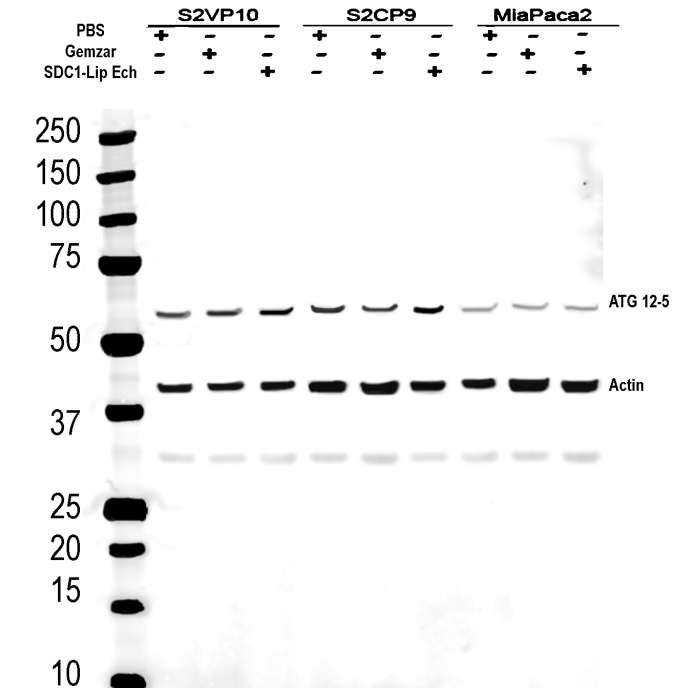
Dosimetry

	S2VP10			S2CP9			MiaPaCa2		
PBS	+	-	-	+	-	-	+	-	-
Gem	-	+	-	-	+	-	-	+	-
SDC1-lip-ECH	-	-	+	-	-	+	-	-	+
LC3-I	86.963	66.363	27.654	81.318	73.679	26.061	2.975	1.791	3.447
LC3-II	92.479	43.030	79.289	50.995	39.982	74.087	3.240	3.059	2.913
ATG7	7.773	6.857	6.289	6.285	6.231	5.576	1.998	1.642	1.088
ATG12	16.006	16.731	21.576	8.045	10.106	12.794	0.215	4.508	3.501
p62	42.081	45.091	28.979	43.081	45.081	29.634	19.663	20.724	20.071
Caspase 3	4.825	2.823	13.603	9.692	2.006	10.106	12.624	2.087	15.04
Cleaved Casp 3	0.156	5.905	0.289	0.687	5.728	0.343	3.281	16.165	0.010
Caspase 9	25.89	24.55	34.841	44.495	10.798	44.425	39.078	15.655	38.017
Cleaved Casp 9	0.151	13.911	1.373	4.714	20.254	5.367	2.572	38.195	3.095

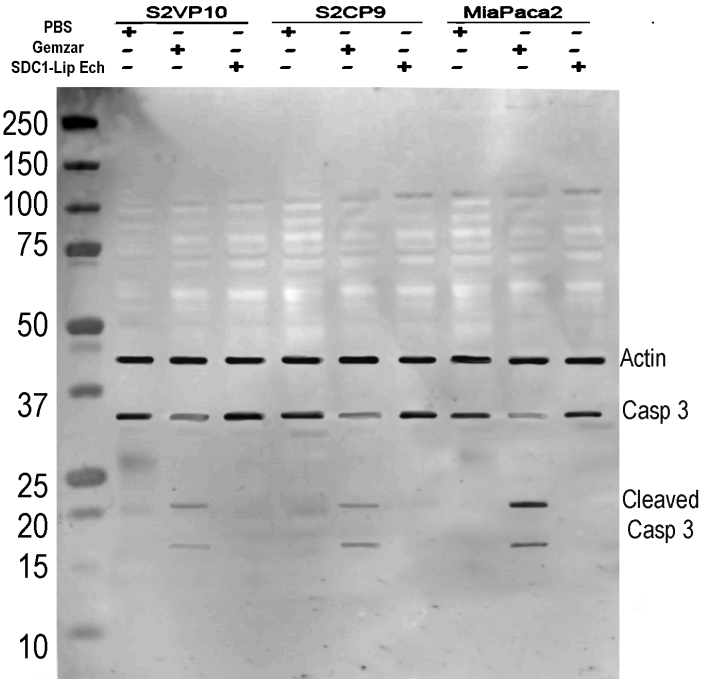
Whole blots forLC3-I/II, ATG7, p62



ATG 12-5



Caspase 3



Caspase 9

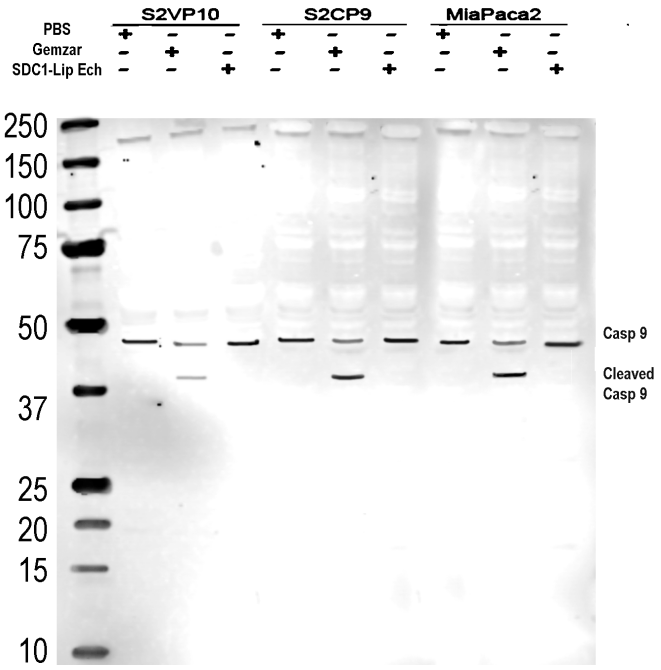


Figure 6 Whole Western Blots (2).

Fig 6	S2VP10				S2CP9			
	Cont	**Gem**	**Ech**	**SDC1-Lip Ech**	**Cont**	**Gem**	**Ech**	**SDC1-Lip Ech**
LC3-I	154.791	123.238	10.125	16.332	142.228	174.461	28.523	24.045
LC3-II	180.152	156.716	160.974	165.821	125.821	70.089	79.101	127.378
Caspase 3	100.684	59.132	117.859	150.451	122.202	81.679	153.423	178.291
Cleaved Casp 3	64.645	101.065	5.112	1.953	27.700	143.982	6.919	6.512

Figure 6 autophagy blot

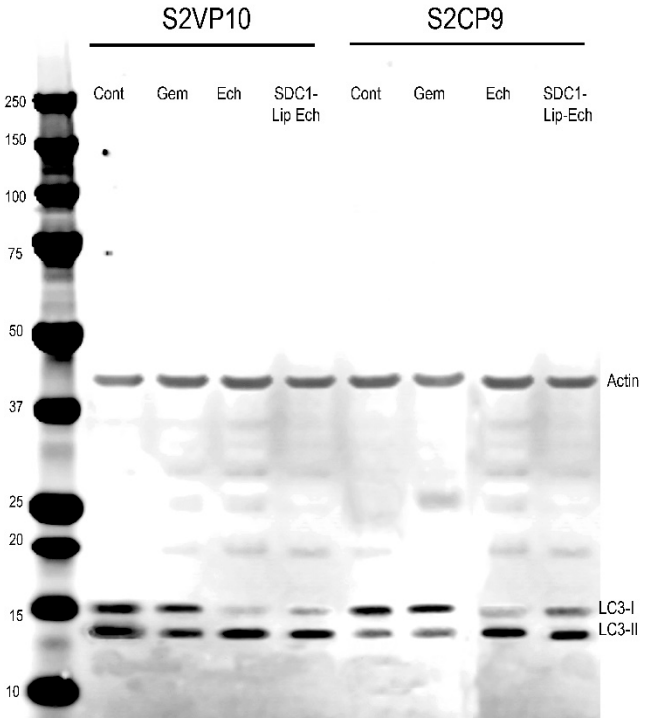
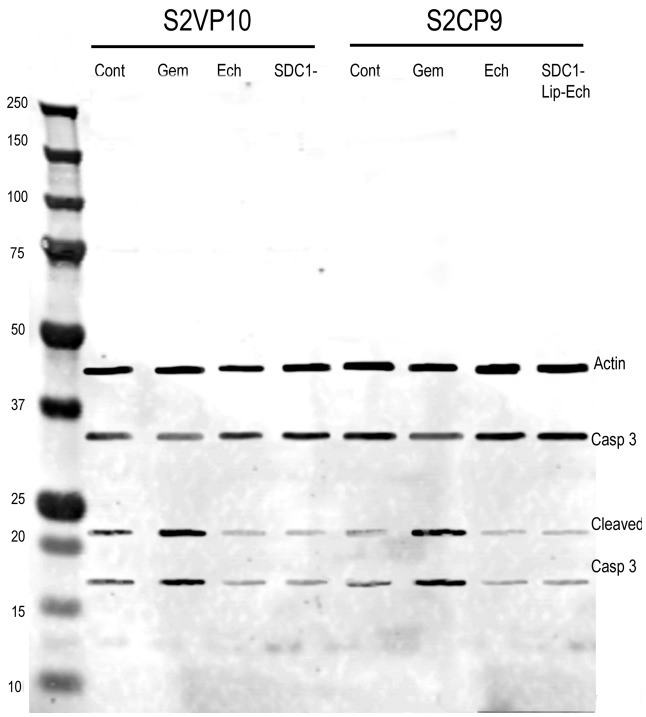
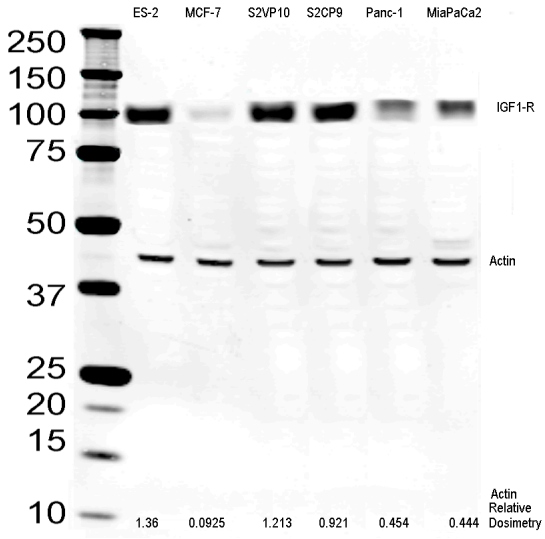


Figure 6 apoptosis blot



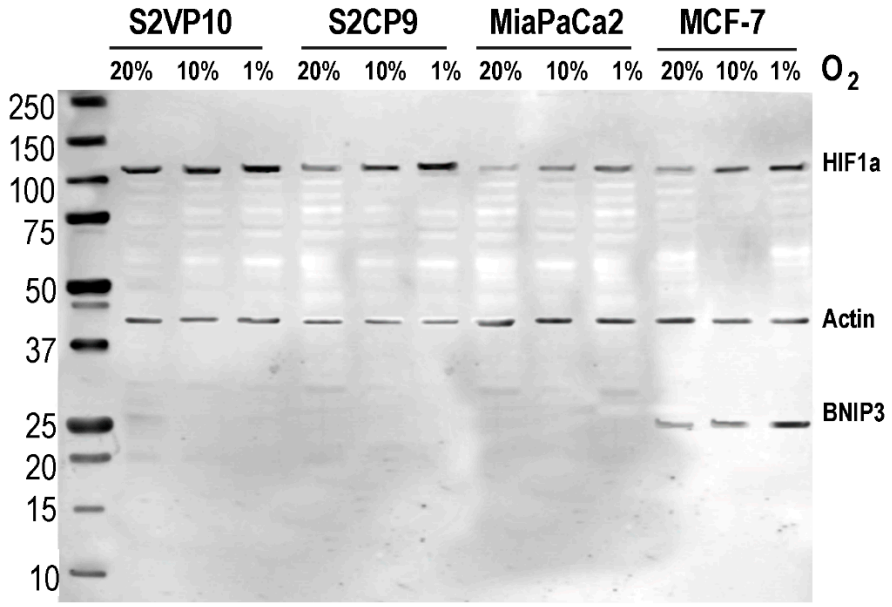
Supplemental Figure 1

Whole Western Blot



Supplemental Figure 4

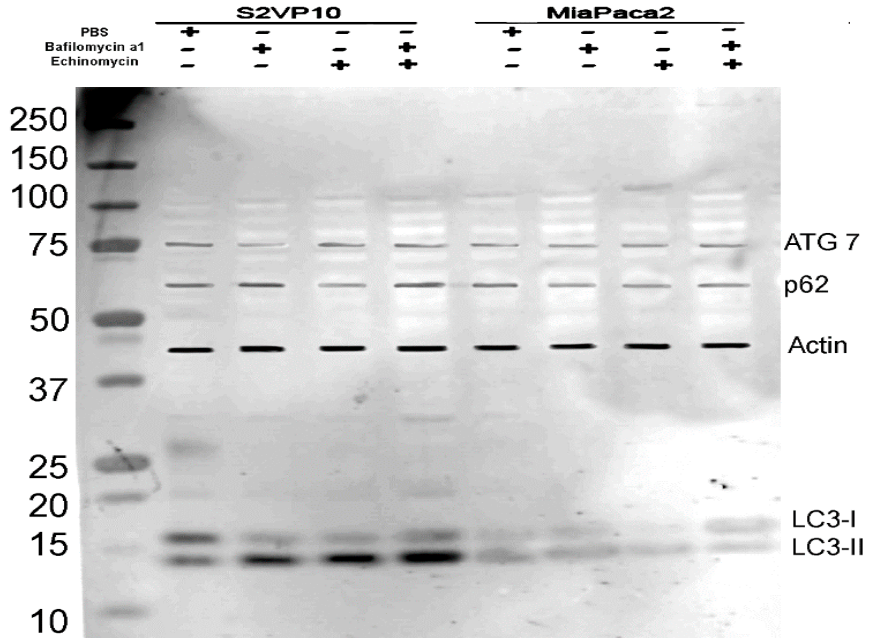
	S2VP10			S2CP9			MiaPaCa2			MCF-7		
O2	20%	10%	1%	20%	10%	1%	20%	10%	1%	20%	10%	1%
HIF1a	136.127	124.062	133.746	69.143	98.639	120.073	50.315	69.769	61.62	29.106	69.386	93.311
BNIP3	1.334	1.297	1.366	0.978	1.674	1.646	1.257	1.431	1.327	34.479	43.363	58.899

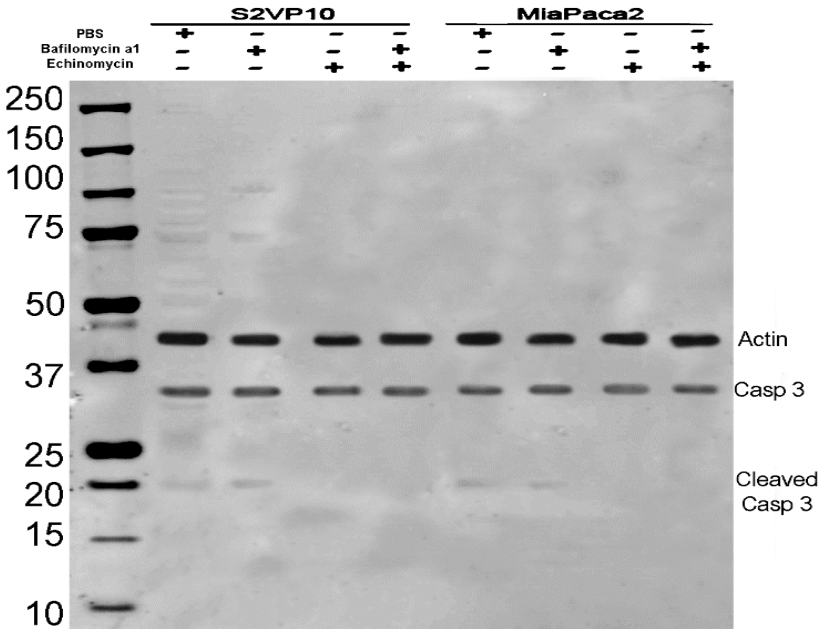


Supplemental Figure 5: 2 blots

Whole western blots Autophagy and Caspase 3

	S2VP10				MiaPaCa2			
PBS	+	-	-	-	+	-	-	-
Baf a1	-	+	-	+	-	+	-	+
ECH	-	-	+	+	-	-	+	+
LC3-I	108.358	64.55	43.451	34.638	52.59	49.753	37.225	55.693
LC3-II	104.551	145.187	170.698	183.809	50.115	52.031	42.713	50.816
ATG7	10.293	5.228	12.815	13.366	13.13	12.685	12.242	12.374
p62	48.676	59.363	31.553	68.975	49.909	37.39	26.617	39.997
Casp 3	25.954	22.807	21.219	17.992	18.712	12.399	13.727	16.909
Cleaved Casp 3	1.2056	1.4351	0.102	0.619	1.405	1.384	0.13	0.997




S2VP10
MiaPaca2
PBS
Bafilomycin a1
Echinomycin
250
150
100
75
50
37
25
20
15
10
Actin
Casp 3
Cleaved
Casp 3