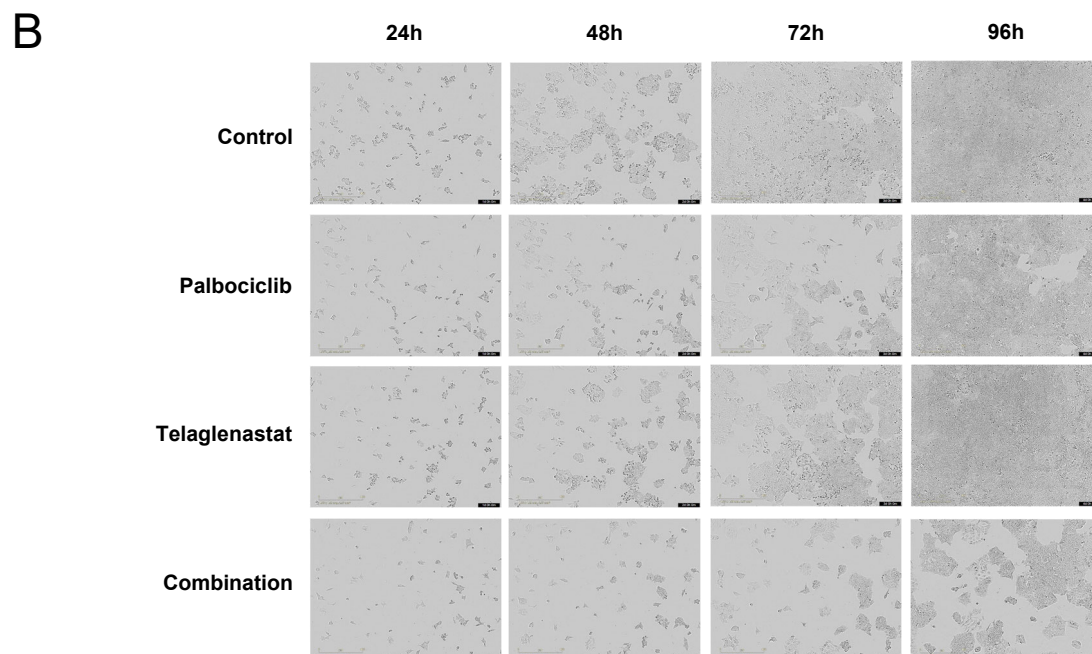
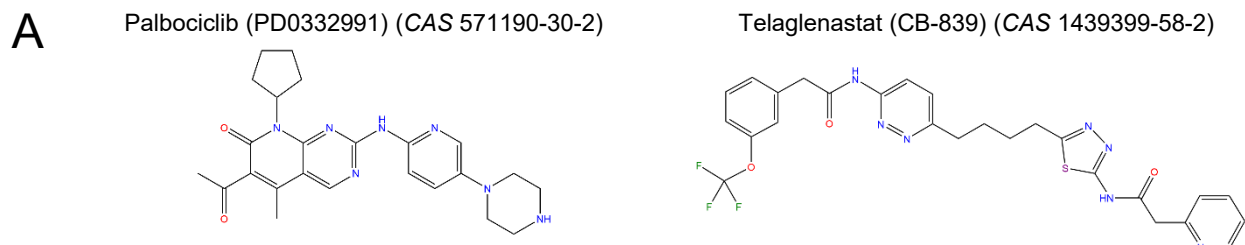


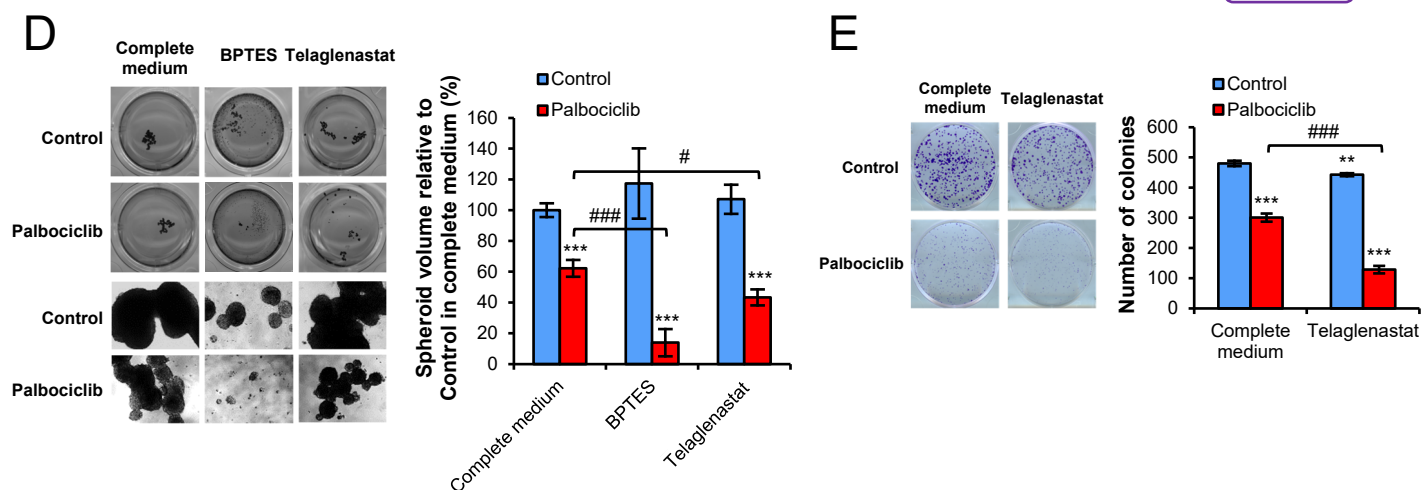
Supplementary Figure 1



C Combination Index (CI) equation of Chou and Talalay and CompuSyn software

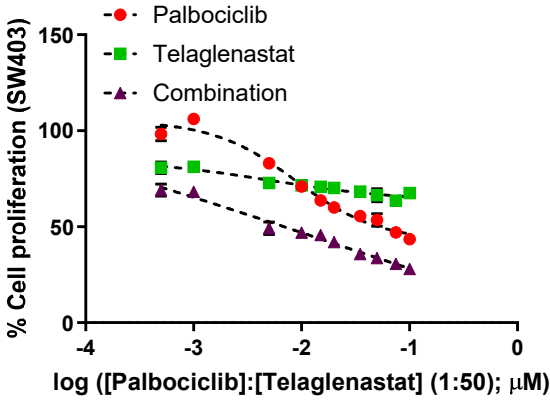
CI value	Agonistic effect	[Palbociclib] μM	[Telaglenastat] μM	Viability	SD	CI Value
<0.10	Very strong synergism	0.01	0.001	63.3	5.1	0.030
0.10–0.30	Strong synergism	0.05	0.003	36.5	2.1	0.034
0.30–0.70	Synergism	0.1	0.005	28.8	4.5	0.042
0.70–0.90	Moderate to slight synergism	0.25	0.01	22.0	2.4	0.065
0.90–1.10	Nearly additive	0.5	0.05	21.0	0.7	0.120
1.10–1.45	Slight to moderate antagonism	0.75	0.1	17.8	1.3	0.137
1.45–3.30	Antagonism	1	0.5	18.7	3.7	0.199
>3.30	Strong to very strong antagonism	1.5	1.0	15.7	1.0	0.224
		2	1.5	13.5	1.1	0.235
		3	2.0	11.9	0.2	0.290

CI < 0.3

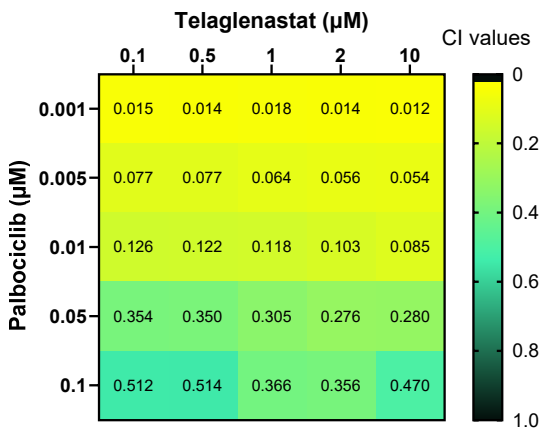
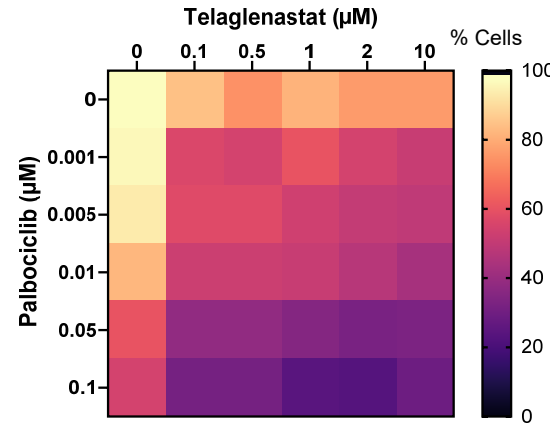


Supplementary Figure 1

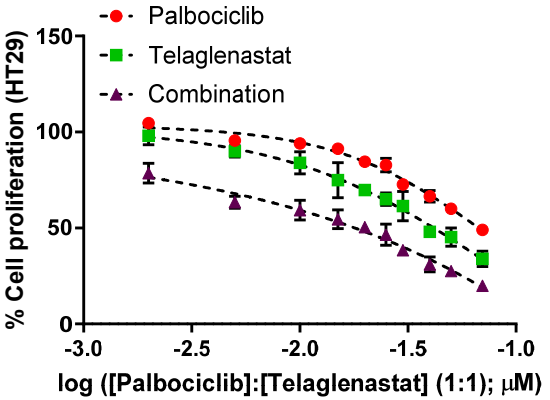
F



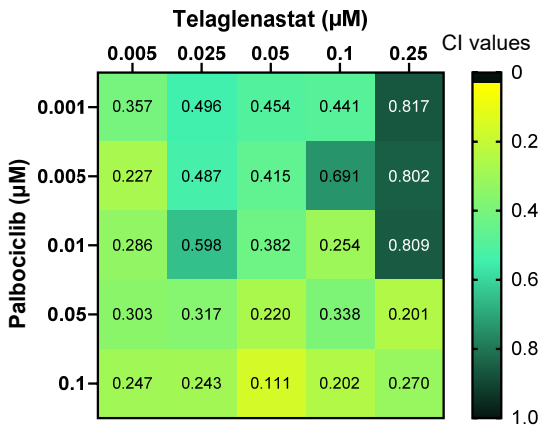
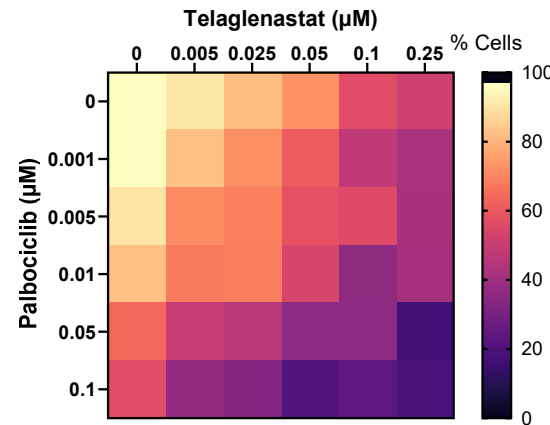
[Palbociclib] μM	[Telaglenastat] μM	Viability	SD	CI Value
0.0005	0.025	69.1	3.2	0.055
0.001	0.05	68.2	2.2	0.098
0.005	0.25	49.2	3.3	0.086
0.01	0.5	46.9	2.5	0.145
0.015	0.75	45.7	1.8	0.201
0.02	1	42.1	2.7	0.205
0.035	1.75	35.8	1.4	0.223
0.05	2.5	33.7	1.6	0.269
0.075	3.75	30.7	1.7	0.315
0.1	5	28.1	0.8	0.336



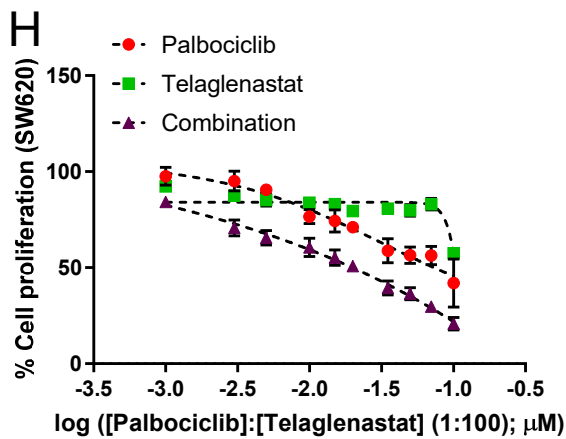
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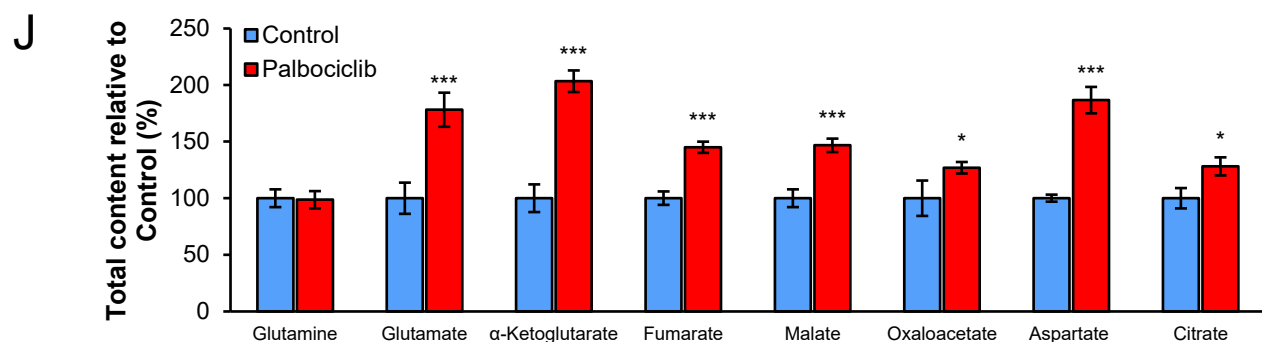
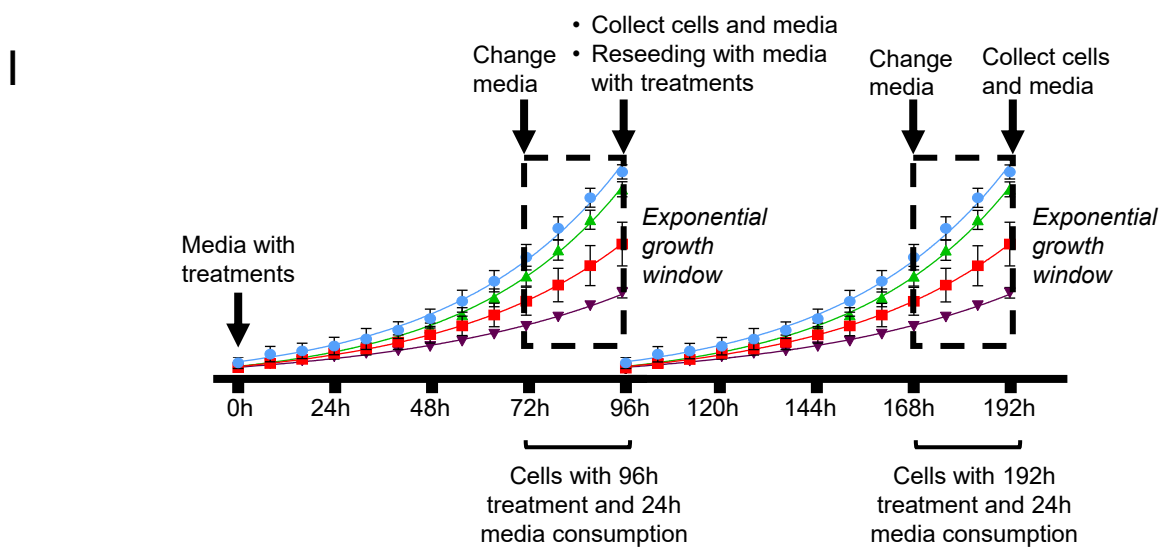
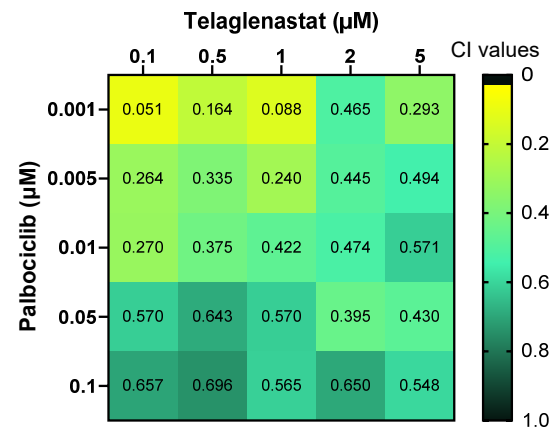
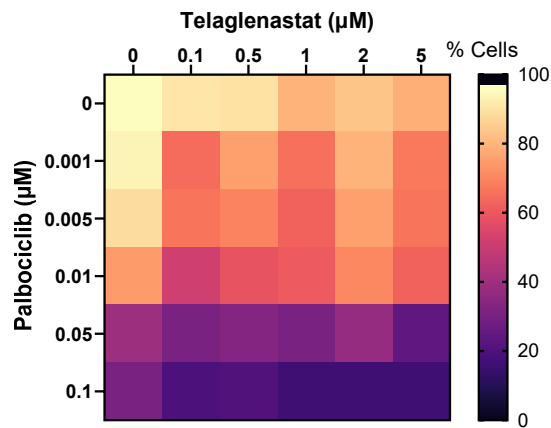
[Palbociclib] μM	[Telaglenastat] μM	Viability	SD	CI Value
0.002	0.002	78.5	5.2	0.230
0.005	0.005	63.4	3.1	0.291
0.01	0.01	59.3	5.1	0.496
0.015	0.015	54.6	4.9	0.622
0.02	0.02	50.4	1.7	0.711
0.025	0.025	46.6	5.5	0.772
0.03	0.03	38.4	2.9	0.680
0.04	0.04	31.0	3.9	0.670
0.05	0.05	27.6	1.9	0.720
0.07	0.07	19.9	2.6	0.682



Supplementary Figure 1

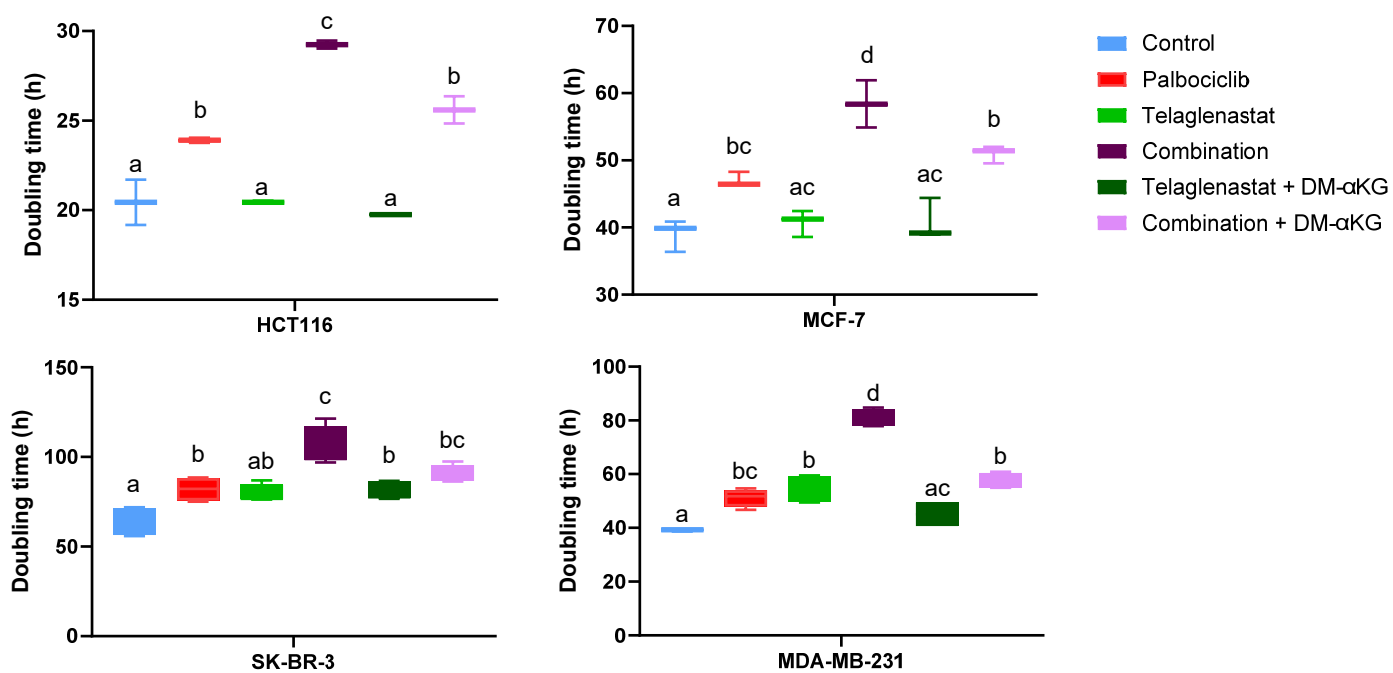


[Palbociclib] μM	[Telaglenastat] μM	Viability	SD	CI Value
0.001	0.1	84.2	1.6	0.210
0.003	0.3	70.7	4.2	0.154
0.005	0.5	65.6	3.8	0.184
0.01	1	60.6	4.8	0.277
0.015	1.5	55.2	4.0	0.315
0.02	2	50.8	2.3	0.338
0.035	3.5	39.4	3.6	0.344
0.05	5	36.4	3.1	0.422
0.07	7	29.7	2.4	0.417
0.1	10	20.8	3.2	0.345

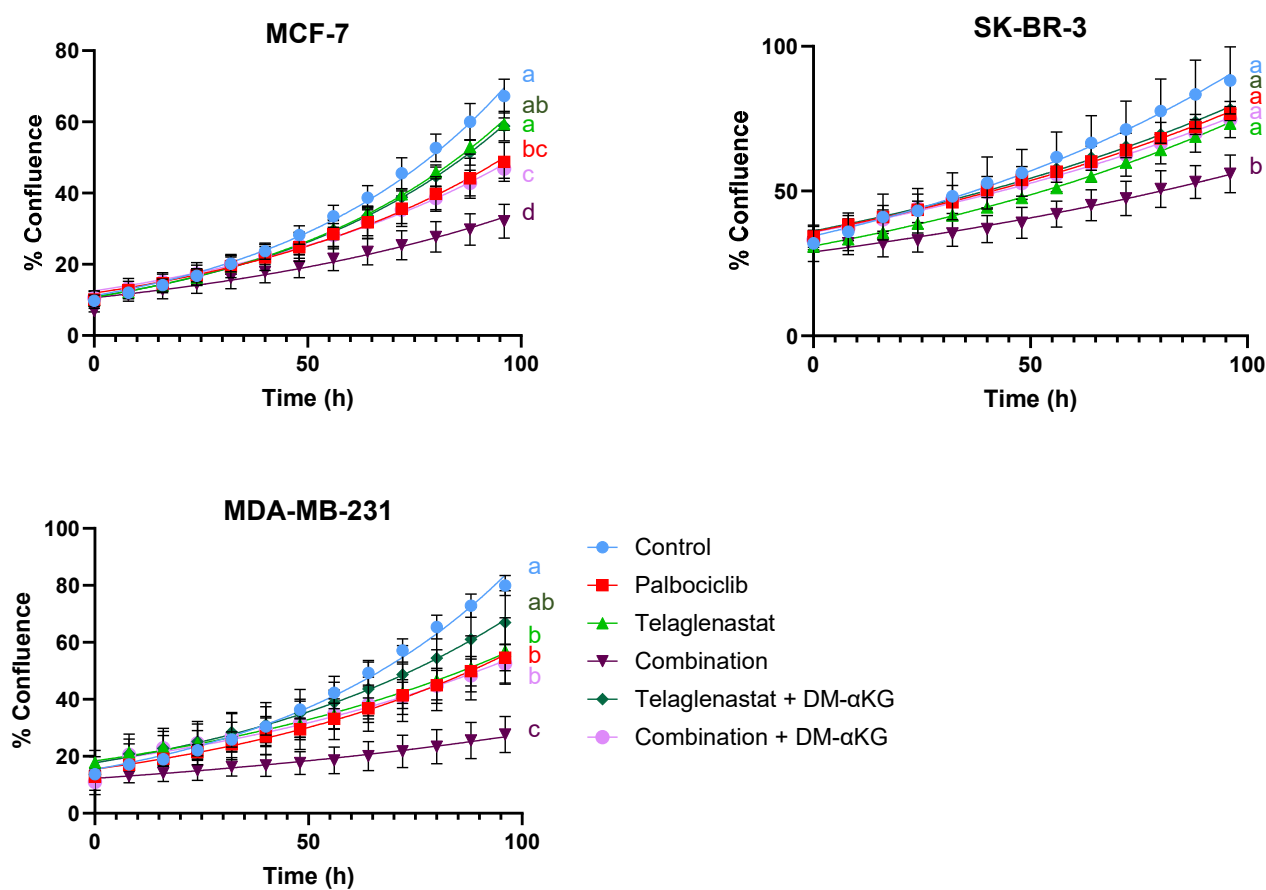


Supplementary Figure 1

K

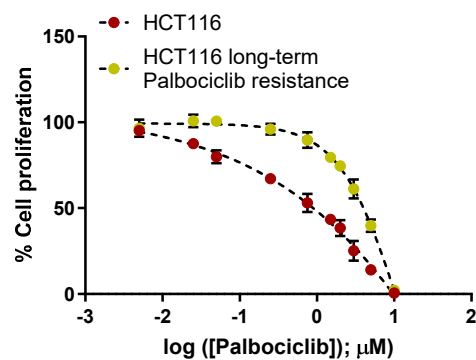


L

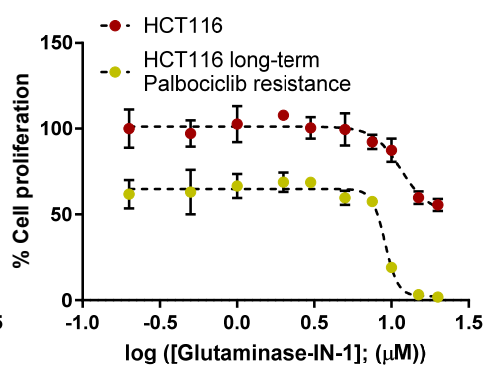
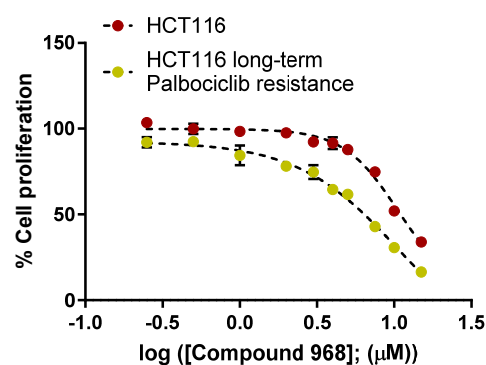
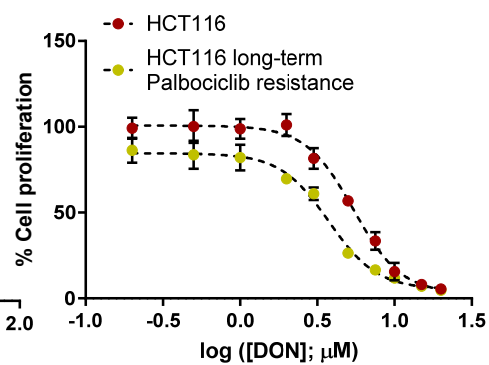
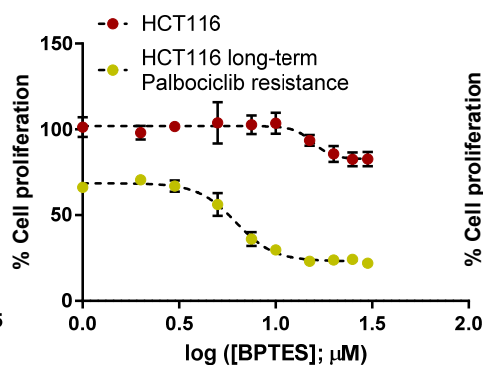
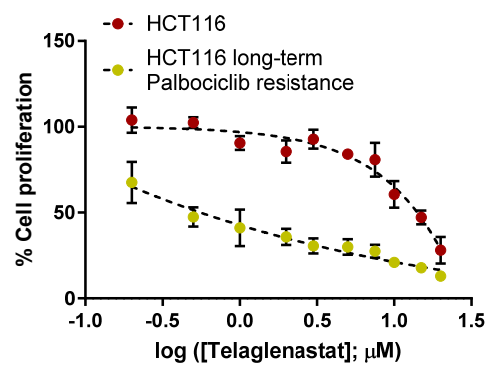


Supplementary Figure 1

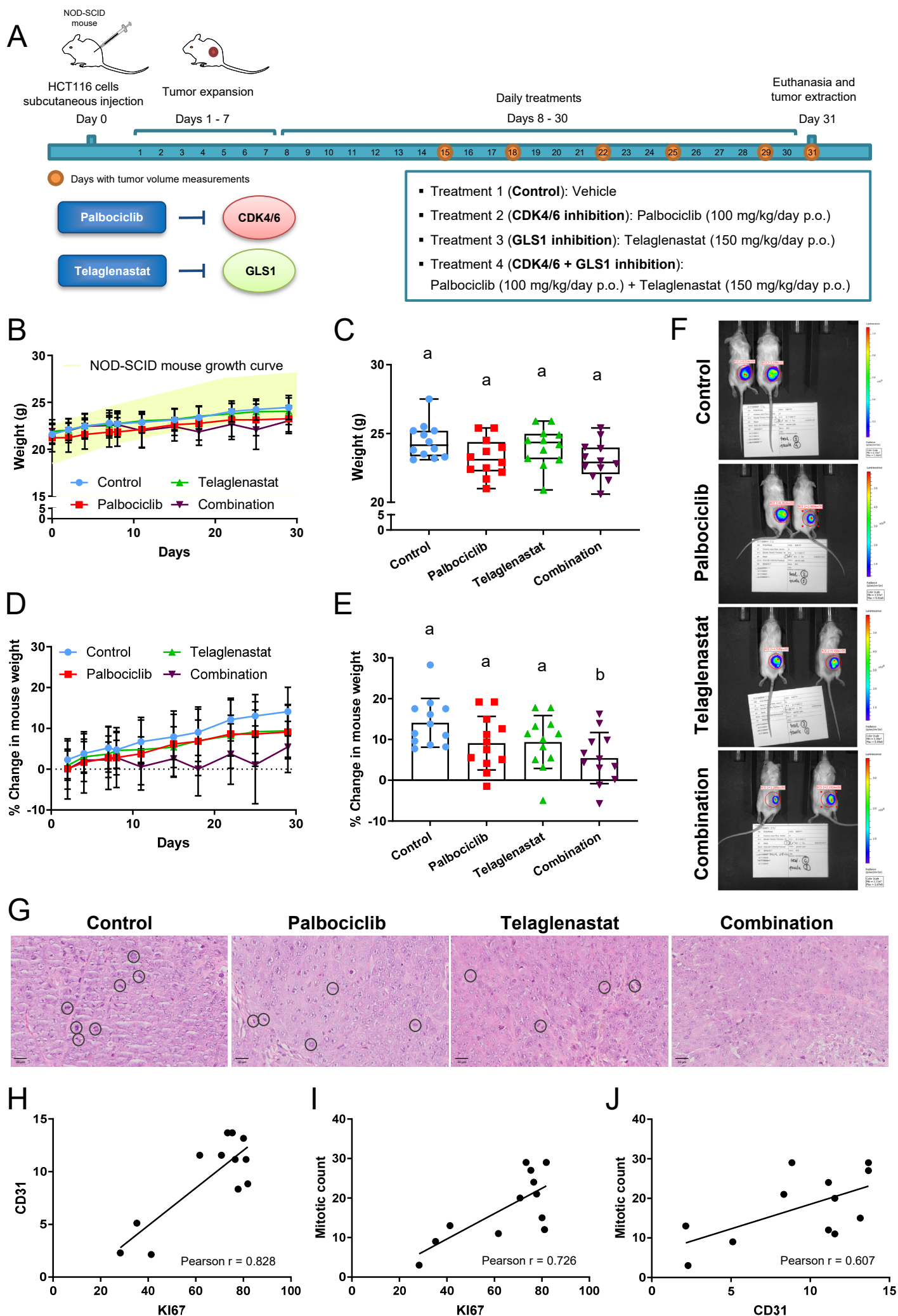
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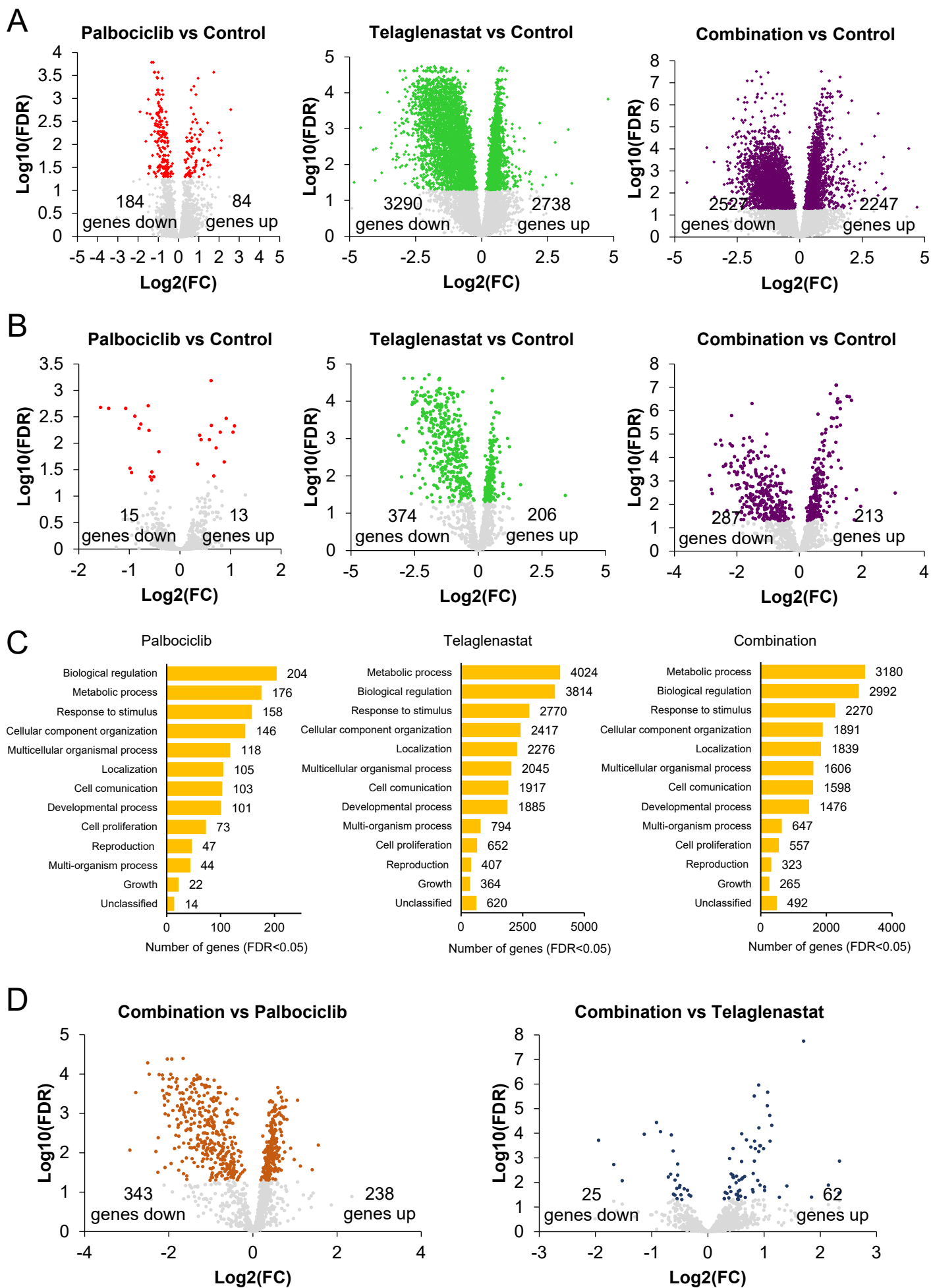
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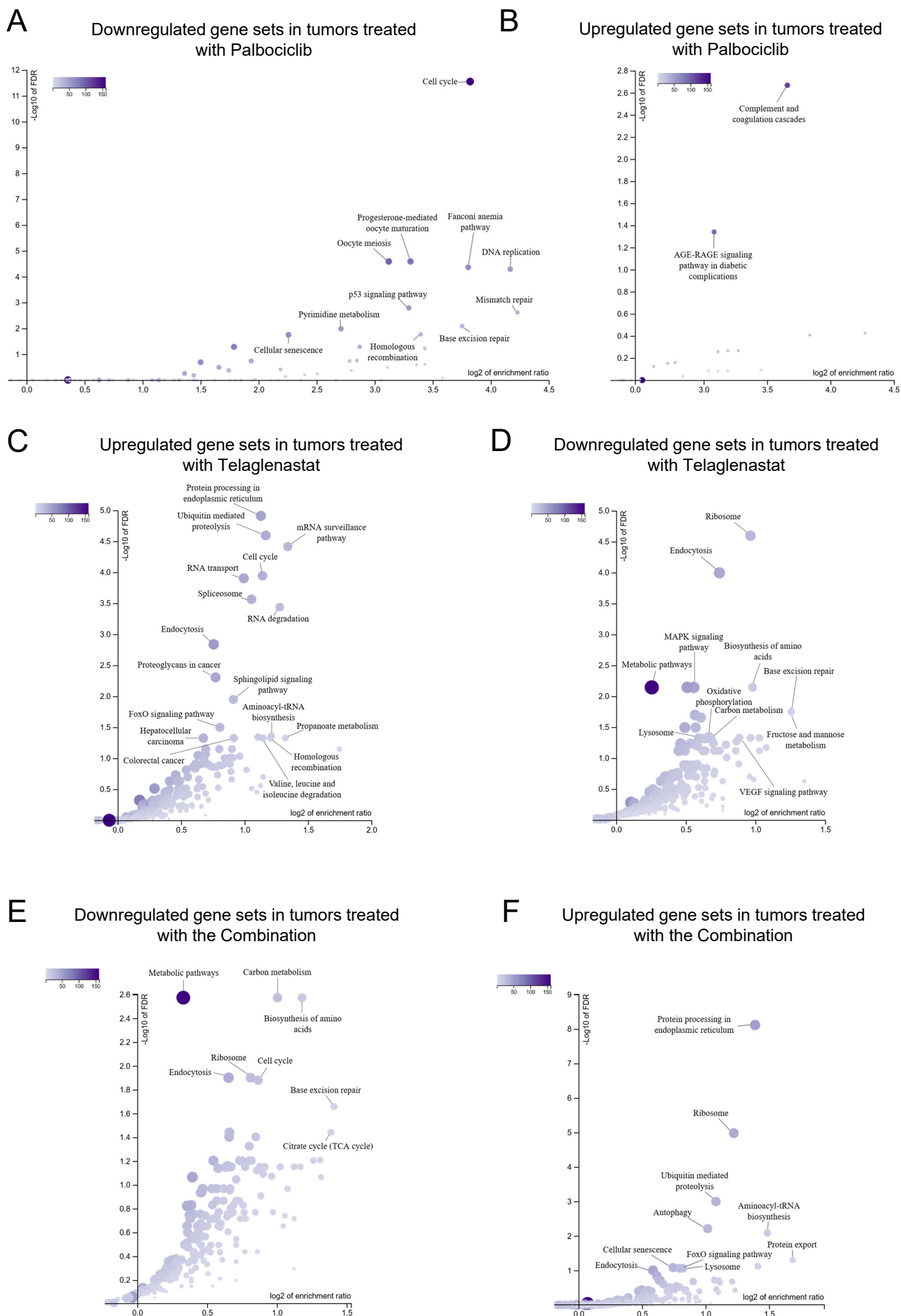
Supplementary Figure 2



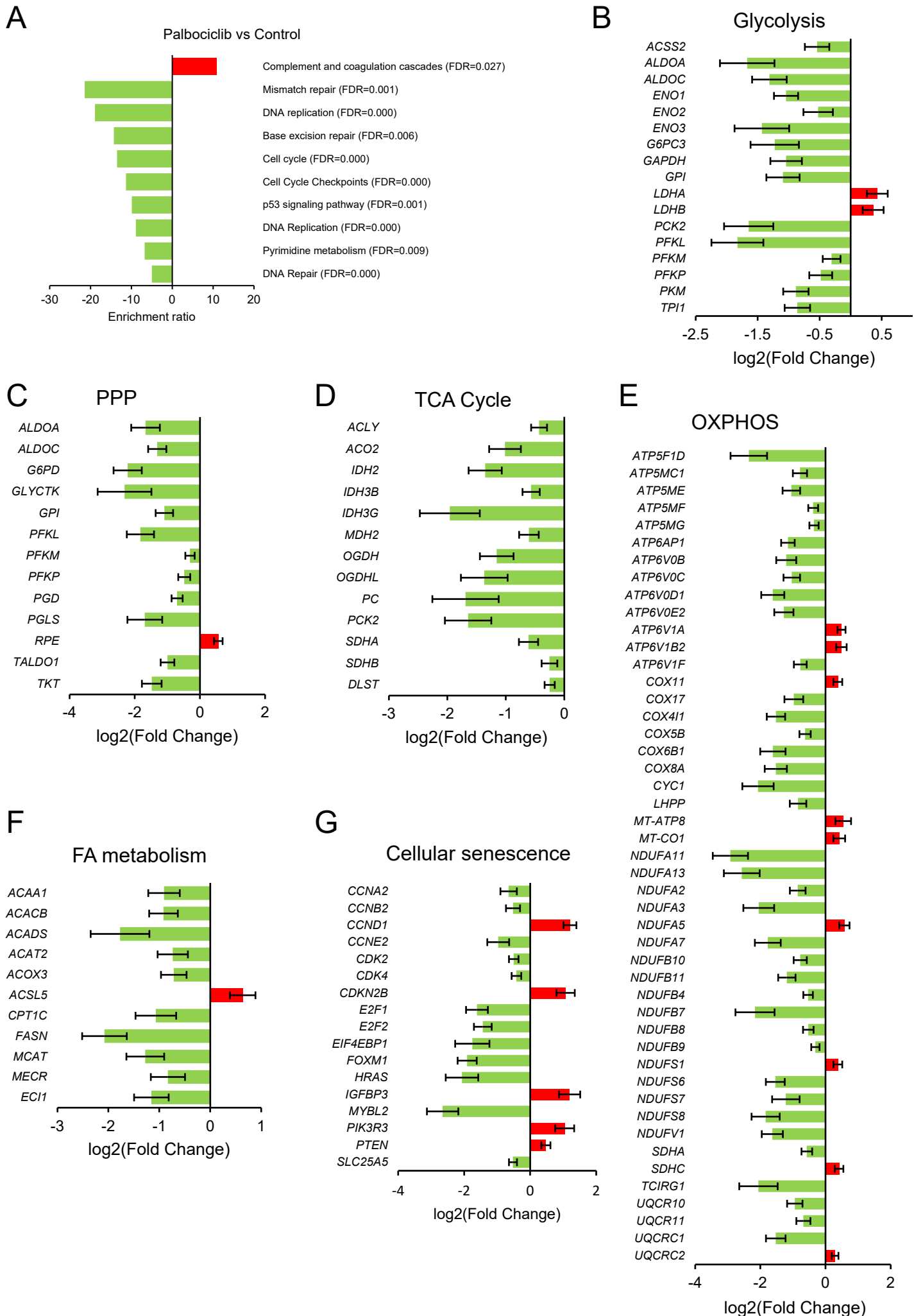
Supplementary Figure 3



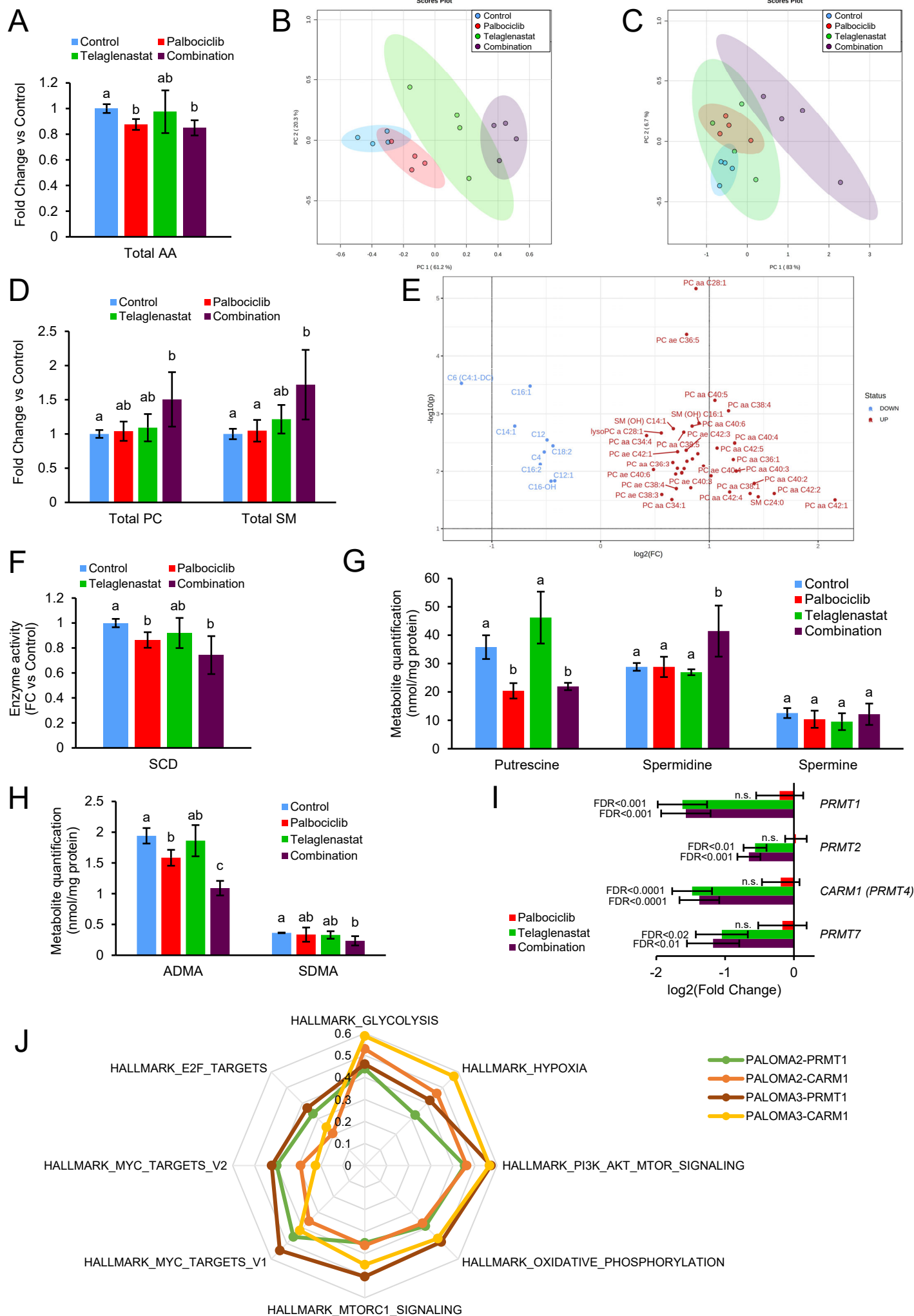
Supplementary Figure 4



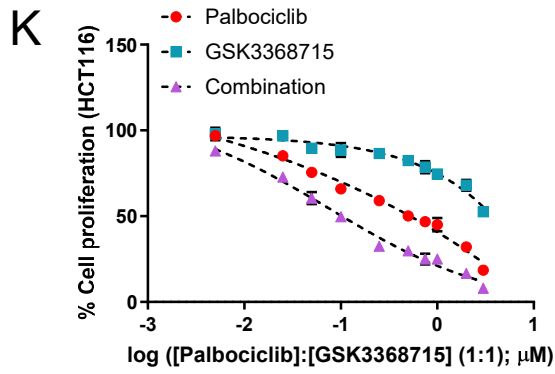
Supplementary Figure 5



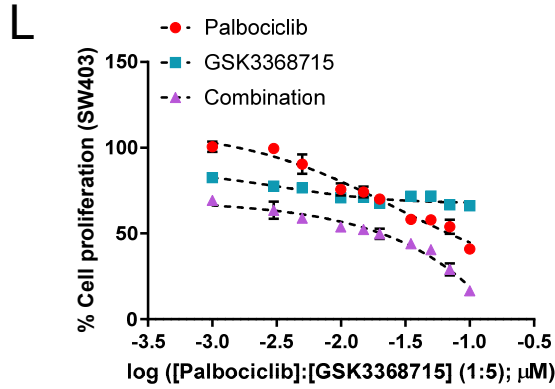
Supplementary Figure 6



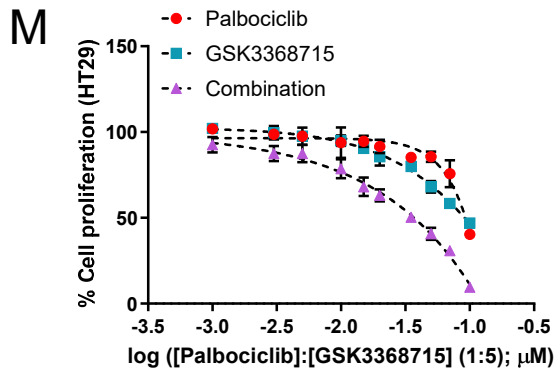
Supplementary Figure 6



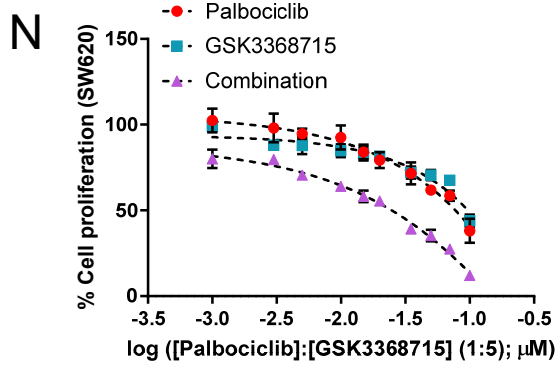
[Palbociclib] μM	[GSK3368715] μM	Viability	SD	CI Value
0.005	0.005	88.1	2.0	0.244
0.025	0.025	72.8	1.6	0.256
0.05	0.05	60.6	3.6	0.219
0.1	0.1	49.7	1.9	0.223
0.25	0.25	32.6	1.0	0.188
0.5	0.5	29.8	0.7	0.308
0.75	0.75	25.0	3.2	0.320
1	1	25.1	1.1	0.430
2	2	16.7	1.2	0.395
3	3	8.1	0.8	0.169



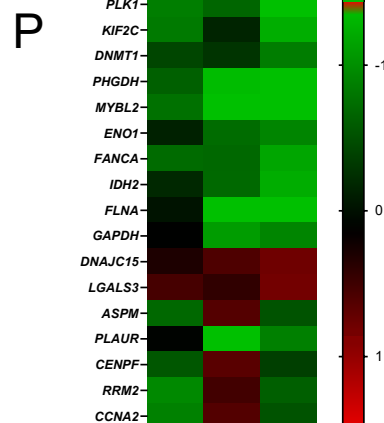
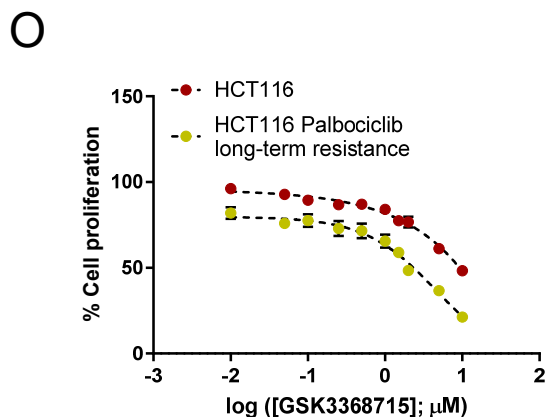
[Palbociclib] μM	[GSK3368715] μM	Viability	SD	CI Value
0.001	0.005	69.3	2.8	0.092
0.003	0.015	63.6	5.0	0.139
0.005	0.025	58.9	1.9	0.148
0.01	0.05	53.8	1.3	0.193
0.015	0.075	52.3	2.3	0.257
0.02	0.1	49.8	3.0	0.282
0.035	0.175	44.0	2.4	0.315
0.05	0.25	40.6	2.7	0.344
0.07	0.35	29.0	3.5	0.182
0.1	0.5	16.5	2.2	0.066



[Palbociclib] μM	[GSK3368715] μM	Viability	SD	CI Value
0.001	0.005	92.6	4.6	0.124
0.003	0.015	87.4	4.4	0.228
0.005	0.025	87.4	5.0	0.382
0.01	0.05	78.5	5.6	0.455
0.015	0.075	68.1	5.4	0.446
0.02	0.1	63.0	3.5	0.499
0.035	0.175	50.3	2.4	0.586
0.05	0.25	40.7	3.5	0.627
0.07	0.35	30.8	2.7	0.637
0.1	0.5	9.5	0.6	0.321



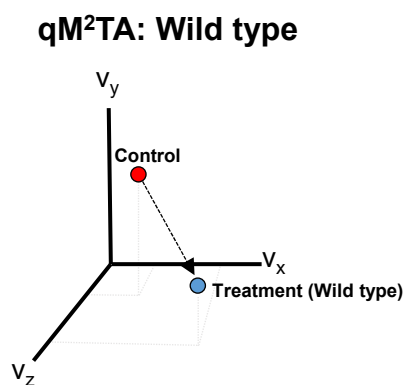
[Palbociclib] μM	[GSK3368715] μM	Viability	SD	CI Value
0.001	0.005	80.0	5.4	0.110
0.003	0.015	79.7	2.8	0.321
0.005	0.025	70.6	2.2	0.273
0.01	0.05	64.1	2.4	0.370
0.015	0.075	58.2	3.4	0.408
0.02	0.1	55.4	1.7	0.473
0.035	0.175	39.2	1.1	0.387
0.05	0.25	35.3	3.4	0.460
0.07	0.35	27.4	1.2	0.434
0.1	0.5	12.0	1.6	0.223



Supplementary Figure 7

A

Characterization of the metabolic adaptation to drug-induced stress

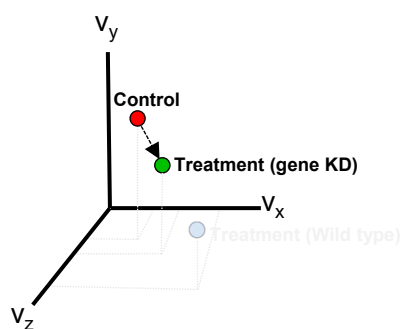


B

Identification of potential targets

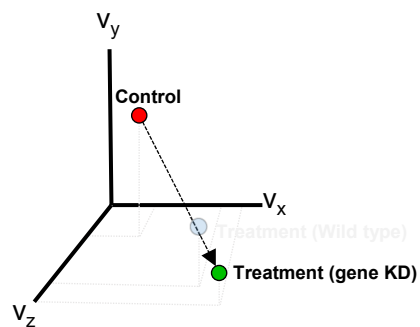
Good target

qM²TA: Gene KD

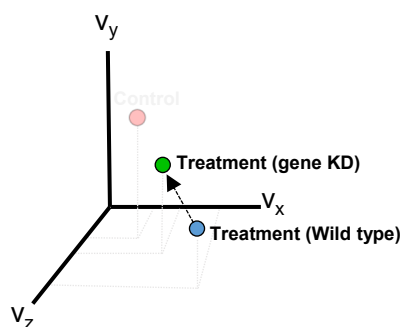


Bad target

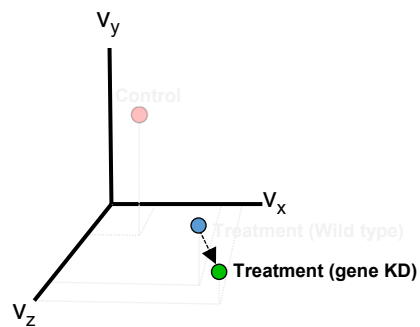
qM²TA: Gene KD



MOMA: Gene KD



MOMA: Gene KD



Supplementary Figure 8

