Supplemental Experimental Procedures

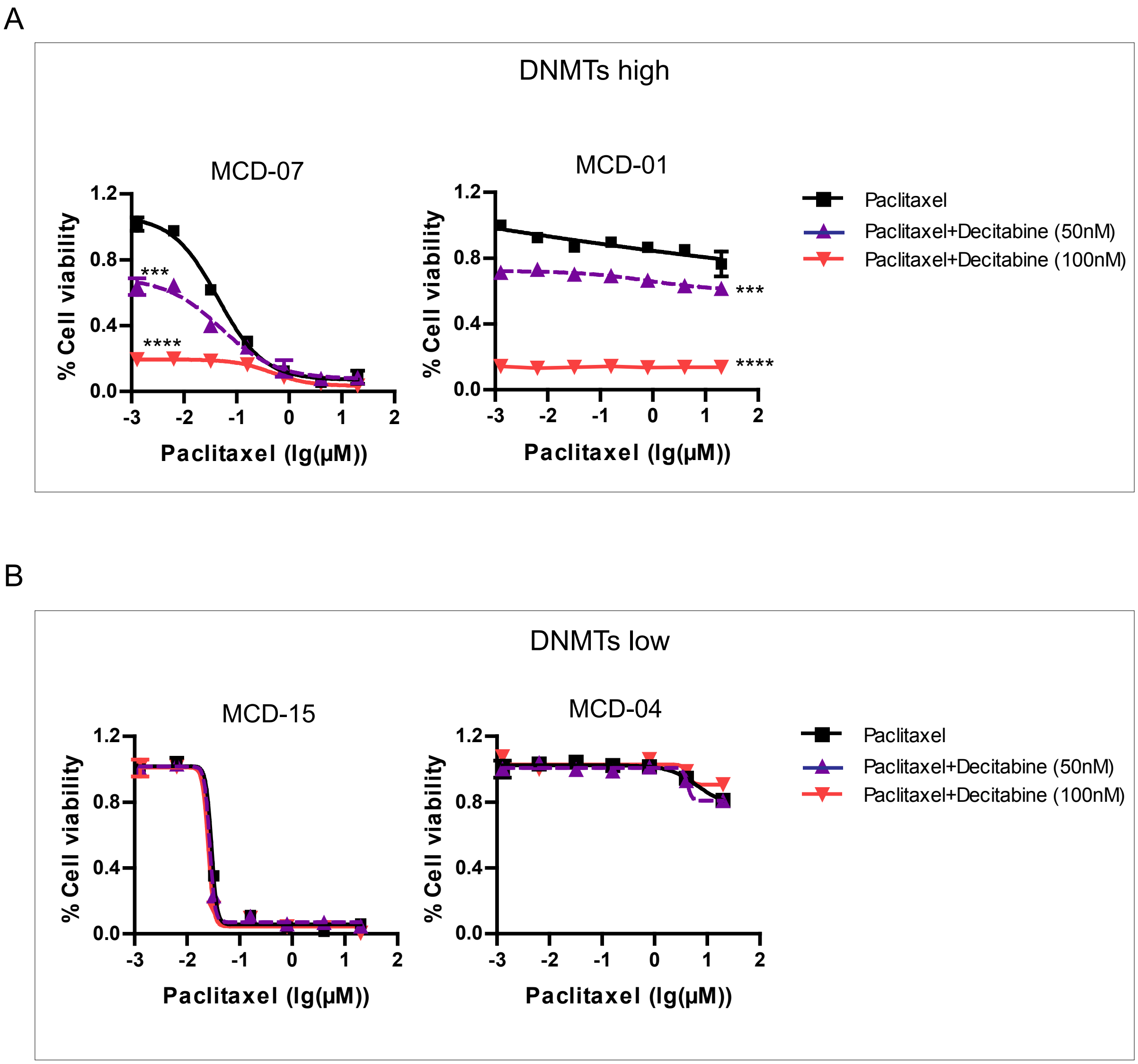
Evaluation of Paclitaxel and Decitabine Combination treatment in PDXs Spheroids

Tumor spheroids were cultured with full MEF medium with 5 µM ROCK inhibitor for 3-5 days followed by pretreating with full medium containing 50 nM or 100 nM deciatbine for four days. Addition of different concentrations of paclitaxel together with 50 nM or 100 nM decitabine was then added and treated for additional 3 days. Each treatment was performed in triplicate. Fresh decitabine was added daily. Cell viability was performed using the CellTiter-Glo 3D Cell Viability Assay Kit (Promega) according to the procedure provided by the manufacture. The luminescent signal was measured using a Safire2 plate reader. Percent viability was corrected back to vehicle.

Supplemental Figure Legends

Supplemental Figure S1. **Organoid treatment response to therapy.** Cell viability of organoids that expressing either high DNMTs (A) or low DNMTs (B)**,**in response to different concentration of paclitaxel alone or in combination with 50 nM or 100 nM decitabine. Data represents mean ± SEM (n=3). ***P < 0.001, and ****P < 0.0001 by 2-way ANOVA.

Supplemental Figure S1



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Supplemental Table S1. Patient Tumor Information and Decitabine Drug Response in both PDX organoids and in mice

Patient Tumor Information				Decitabine Response		
ID	**Clinical subtype**	**Tumor Origin**	**Clinical Chemotherapy Response**	**Organoid Decitabine Response**	**Xenograft Decitabine Response**	**Concordance**
MCD-01	TN	PostChemo	Resistant	Yes	Yes	Y
MCD-02	TN	Baseline	Sensitive	No	No	Y
MCD-03	TN	Baseline	Resistant	Yes	Yes	Y
MCD-04	TN	Baseline	Resistant	No	No	Y
MCD-05	TN	Baseline	Resistant	No	No	Y
MCD-06	TN	Baseline	Resistant	No		
MCD-07	TN	Baseline	Sensitive	Yes		
MCD-08	TN	Baseline	Sensitive	Yes		
MCD-09	TN	Baseline	Sensitive	No		
MCD-10	TN	Baseline	Sensitive	Yes		
MCD-11	TN	Baseline	Sensitive	Yes	Yes	Y
MCD-12	TN	Baseline	Resistant	Yes		
MCD-13	TN	Baseline	Sensitive	Moderate		
MCD-14	TN	Baseline	Sensitive	Moderate		
MCD-15	TN	Baseline	Sensitive	No		

Supplemental Table S2: Methylation level at the 9 diffetent CpGs at traf6 gene promoter

		Methylation level (%)		
		Pos. 1	Pos. 2	Pos. 3
TRAF6_a1	AU565	0.8	1.6	0.0
TRAF6_a1	AU565	1.2	1.3	0.0
TRAF6_a1	BT549	14.4	2.2	3.2
TRAF6_a1	BT549	13.2	2.1	3.1
TRAF6_a1	CAMA-1	0.9	1.4	0.0
TRAF6_a1	CAMA-1	1.2	1.1	1.6
TRAF6_a1	BT747	1.1	1.4	0.0
TRAF6_a1	BT747	0.7	1.2	1.4
TRAF6_a1	Hs 578T	0.7	1.2	0.0
TRAF6_a1	Hs 578T	1.3	1.1	1.7
TRAF6_a1	MDA231	1.5	1.3	1.1
TRAF6_a1	MDA231	1.3	1.2	2.3
TRAF6_a1	MDA361	1.6	1.4	0.0
TRAF6_a1	MDA361	1.7	0.9	1.4
TRAF6_a1	MDA468	1.2	1.3	1.0
TRAF6_a1	MDA468	1.0	1.5	2.0
TRAF6_a1	MCF7	0.7	1.0	0.0
TRAF6_a1	MCF7	1.3	1.0	1.6
TRAF6_a1	ZR75-1	1.0	1.2	0.0
TRAF6_a1	ZR75-1	1.3	0.8	1.7
TRAF6_a1	Ctr DNA	85.4	87.6	87.4

		Pos. 1	Pos. 2	Pos. 3	Pos. 4	Pos. 5	Pos. 6	Pos. 7
TRAF6_a2	AU565	2.4	0.9	1.8	2.3	1.6	1.2	1.5
TRAF6_a2	AU565	2.3	0.8	1.9	2.4	1.9	1.4	2.0
TRAF6_a2	BT549	2.4	0.9	1.9	2.1	1.8	1.1	1.1
TRAF6_a2	BT549	2.6	0.9	1.9	2.0	2.6	1.8	2.7
TRAF6_a2	CAMA-1	2.5	1.0	1.9	2.3	2.1	1.4	1.8
TRAF6_a2	CAMA-1	2.5	0.7	1.8	1.8	2.4	1.8	2.7
TRAF6_a2	BT747	2.5	1.2	2.2	2.6	2.0	2.1	2.0
TRAF6_a2	BT747	2.6	1.1	4.4	2.7	3.2	1.9	3.5
TRAF6_a2	Hs 578T	2.3	1.1	1.6	1.9	1.5	0.9	1.3
TRAF6_a2	Hs 578T	2.3	1.1	4.6	1.7	2.7	Failed	Failed
TRAF6_a2	MDA231	2.5	1.1	1.8	3.2	2.0	1.2	2.0
TRAF6_a2	MDA231	3.5	1.2	2.1	3.9	4.3	2.2	3.7

TRAF6_a2	MDA361	2.7	0.7	3.1	1.4	1.8	0.9	1.6
TRAF6_a2	MDA361	2.4	8.9	1.8	2.2	2.2	1.6	2.9
TRAF6_a2	MDA468	2.4	0.8	1.8	1.6	1.6	1.4	1.8
TRAF6_a2	MDA468	2.5	1.0	1.7	1.8	2.7	3.9	2.8
TRAF6_a2	MCF7	2.0	1.1	1.5	1.7	1.4	0.9	1.6
TRAF6_a2	MCF7	2.4	0.9	1.6	1.4	2.4	1.8	3.0
TRAF6_a2	ZR75-1	2.3	3.2	1.9	2.2	1.4	1.0	1.3
TRAF6_a2	ZR75-1	2.6	1.0	1.9	1.9	2.9	1.9	Failed
TRAF6_a2	Ctr DNA	75.1	82.0	75.9	69.3	78.3	44.2	60.6

		Pos. 1	Pos. 2	Pos. 3	Pos. 4	Pos. 5	Pos. 6	Pos. 7	Pos. 8	Pos. 9
TRAF6_a4	AU565	0.8	0.9	0.8	0.5	1.8	1.6	1.3	0.7	0.5
TRAF6_a4	AU565	0.6	1.1	0.9	0.0	1.8	1.7	1.9	0.6	0.6
TRAF6_a4	BT549	0.5	1.0	0.6	0.5	1.7	2.2	1.8	0.6	0.7
TRAF6_a4	BT549	0.7	0.8	0.5	0.5	2.0	1.6	1.7	0.8	0.0
TRAF6_a4	CAMA-1	1.1	0.6	0.7	0.7	2.0	3.8	1.2	1.0	0.0
TRAF6_a4	CAMA-1	0.7	1.1	0.7	0.0	1.7	1.6	1.4	0.0	0.0
TRAF6_a4	BT747	0.8	1.0	0.7	0.5	2.0	2.0	1.2	0.7	0.6
TRAF6_a4	BT747	0.6	0.6	0.8	0.0	1.6	1.4	1.1	0.7	0.0
TRAF6_a4	Hs 578T	1.0	0.6	0.8	0.6	2.1	1.3	1.1	2.2	0.0
TRAF6_a4	Hs 578T	0.8	0.9	0.8	0.5	1.9	1.6	1.2	0.0	0.7
TRAF6_a4	MDA231	0.8	1.2	Failed	0.0	2.0	2.3	1.5	0.7	2.2
TRAF6_a4	MDA231	0.9	0.7	0.8	0.5	2.0	1.2	1.3	0.0	1.7
TRAF6_a4	MDA361	1.0	0.7	0.6	0.0	2.1	1.5	0.8	0.0	0.0
TRAF6_a4	MDA361	1.2	1.4	0.7	0.6	1.9	1.9	1.3	0.9	0.8
TRAF6_a4	MDA468	0.7	0.8	0.6	0.4	1.9	1.6	1.4	0.7	0.5
TRAF6_a4	MDA468	0.9	0.8	0.5	0.5	1.7	0.4	1.4	0.6	0.0
TRAF6_a4	MCF7	0.6	0.7	0.5	0.0	1.8	1.3	0.9	0.0	0.0
TRAF6_a4	MCF7	0.6	0.9	0.5	0.4	1.4	0.6	1.2	0.5	0.6
TRAF6_a4	ZR75-1	0.7	1.2	0.6	0.6	2.1	1.5	1.4	0.0	0.5
TRAF6_a4	ZR75-1	0.7	0.9	0.5	0.0	0.5	1.1	1.6	0.0	0.0
TRAF6_a4	Ctr DNA	85.1	81.4	82.9	83.7	80.5	80.6	85.5	79.5	74.9

* Note: Ctr DNA was treated with methylase, and represented the high methylaiton levels for these CpG sites. Each sample was in duplicates.