Synthetic Lethality Related Tumor Models

ONCO WuXi

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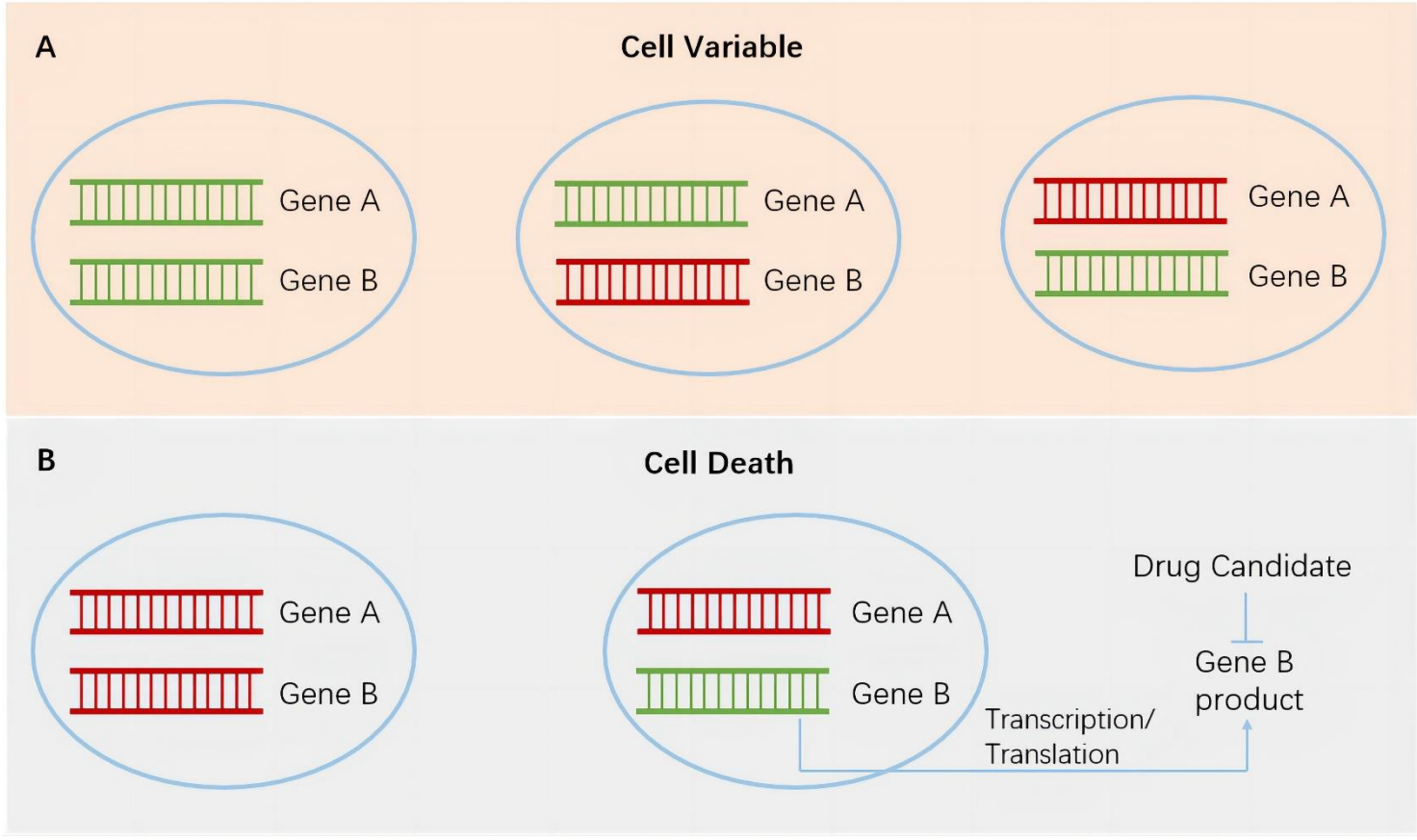
OncoWuXi Newsletter

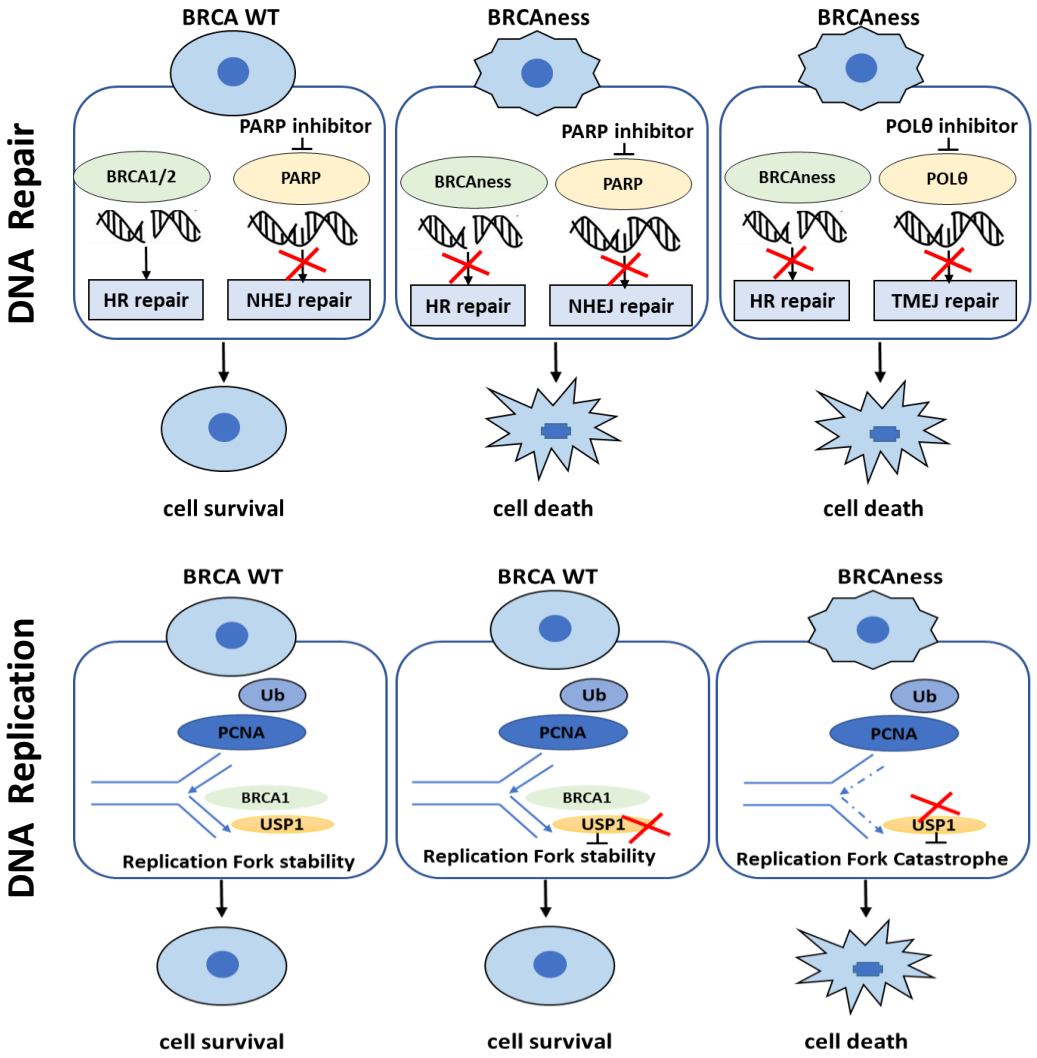
Synthetic lethality in cancer cells



Front. Oncol., 25 November 2024. https://doi.org/10.3389/fonc.2024.1460412

- Synthetic lethality refers to a phenomenon wherein simultaneous mutations in a pair of genes lead to the lethality of cells or organisms, whereas cells or organisms still survive when both genes remain wild type or when either gene is mutated.
- In each gene pair (genes A and B), using the highly variable gene A in tumor cells as a marker for tumor patient enrollment and targeting the protein product of gene B to develop specific antitumor drugs achieves specific and potent tumor cell killing without or rarely affecting normal cells.

BRCA deficiency related synthetic lethality approaches



- BRCA1, BRCA2 and other "BRCA-like" proteins play an important role in homologous recombination repair (HRR). When these proteins are impaired, the aberrant HRR pathway in BRCA1/2 mutant cells, coupled with PARP inhibitors-induced base excision repair impairment, results in genomic destabilization and cell death.
- HR and theta-mediated end-joining (TMEJ) pathways exhibit synthetic lethality. DNA polymerase theta (Polθ) is a key component of TMEJ, an essential backup pathway to repair resected double-strand breaks when the non-homologous end joining (NHEJ) and HR are impaired.
- USP1 exhibits DNA-mediated activation at the replication fork, protects the fork, and promotes survival in BRCA1-deficient cells. Inhibition of USP1 may be a useful treatment for a subset of PARP-inhibitor-resistant BRCA1-deficient tumors with acquired replication fork stabilization.

Murai, Junko, and Yves Pommier. Cancer research vol. 83,8 (2023): 1173-1174.

Bazan Russo, et al. Cancer gene therapy, 10.1038/s41417-024-00815-2. 9 Aug. 2024

Summary of BRCA deficiency related CDX models

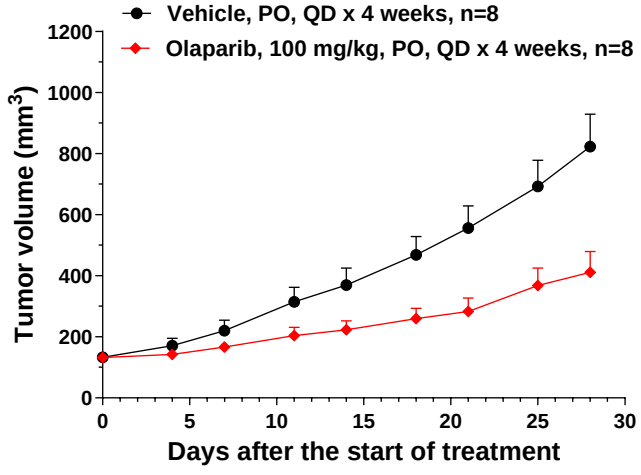
Cancer type	Model ID	Gene	Mutation	Model ID	Gene	Mutation
Adrenal	NCI-H295R	BRCA2	c.9349C>G:p.H3117D	-	-	-
Brain	LN18	BRCA2	c.2566A>T:p.N856Y	-	-	-
Breast	MDA-MB-436	BRCA1	c.5277+1G>A	BT474	BRCA2	c.9281C>A; p.S3094Ter
	MDA-MB-361	BRCA2	c.4970A>G:p.N1657S	HCC1569	BRCA2	c.3299A>C:p.N1100T; c.5583del:p.V1862Ter
Colorectal	LS180	BRCA1	c.2429A>C:p.N810T	LS180	BRCA2	c.9097del:p.T3033LfsTer29
	RKO	BRCA1	c.1303G>T:p.D435Y	RKO	BRCA2	c.5351del:p.N1784TfsTer7
	HCT116	BRCA2	c.8021dup:p.I2675DfsTer6	SW48	BRCA2	c.5073del:p.K1691NfsTer15
	DLD-1	BRCA2	c.3158T>C:p.L1053S; c.3599_3600del:p.C1200Ter; c.5351del:p.N1784TfsTer7	DLD-1 ($BRCA2^{-/-}$)	BRCA2	Knock out
Gastric	NUGC4	BRCA1	c.1367T>C:p.I456T	-	-	-
Lung	LU99	BRCA1	c.1029T>G:p.N343K	NCI-H2347	BRCA1	c.5090G>T:p.C1697F
Lymphoma	DoHH2	BRCA2	c.9235G>C:p.V3079L	-	-	-
Leukemia	MOLM-13	BRCA2	c.2456A>G:p.Q819R	MOLM-14	BRCA1	c.2456A>G:p.Q819R
Pancreatic	CAPAN1	BRCA2	c.5946del:p.S1982RfsTer22	-	-	-
Liver	JHH7	BRCA1	c.409C>A:p.L137I	-	-	-
Prostate	22Rv.1	BRCA2	c.9097dup:p.T3033NfsTer11	DU145	BRCA2	c.6851C>T:p.S2284L

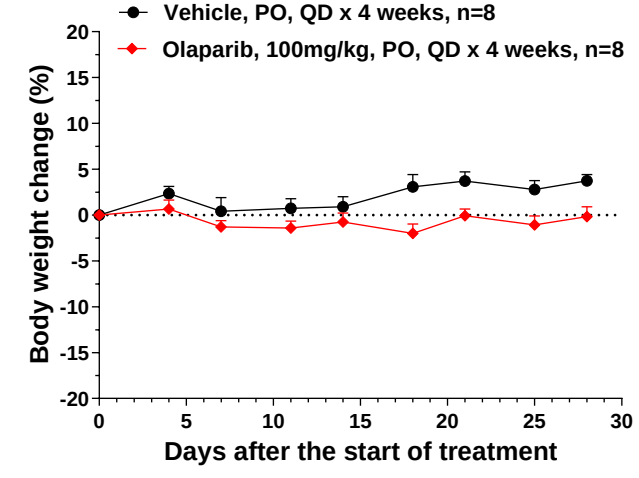
BRCA deficiency profile and PARP inhibitor evaluation in PDX models

Cancer type	Model ID	Gene	Mutation
Breast	BR-05-0014	BRCA2	c.1114A>C:p.N372H; c.7397T>C:p.V2466A
	BR-05-0022	BRCA2	c.7068_7069del:p.2356_2357del
	BR-05-0568	BRCA1	c.1630C>T:p.Q544X
Colorectal	CO-04-0003	BRCA2	c.6892G>T:p.E2298X
	CO-04-0028	BRCA1/2	BRCA1: c.3328_3330del:p.1110_1110del; BRCA2: c.1180G>T:p.E394X
	CO-04-0093	BRCA1	c.1961delA:p.K654fs
Gastric	ST-02-0386	BRCA1	c.3329delA:p.K1110fs
	ST-02-0328	BRCA2	c.1806delA:p.G602fs
Liver	LI-03-0014	BRCA2	c.10234A>G:p.I3412V
Lung	LU-01-0026	BRCA1	c.5503C>T:p.R1835X
	LU-01-0340	BRCA2	c.5066_5067insA:p.A1689fs
Pancreatic	PC-07-0003	BRCA2	c.2186T>C:p.I729T

Note: more BRCA deficiency-related models can be found in https://onco.wuxiapptec.com

Olaparib in BR-05-0568 breast cancer PDX model

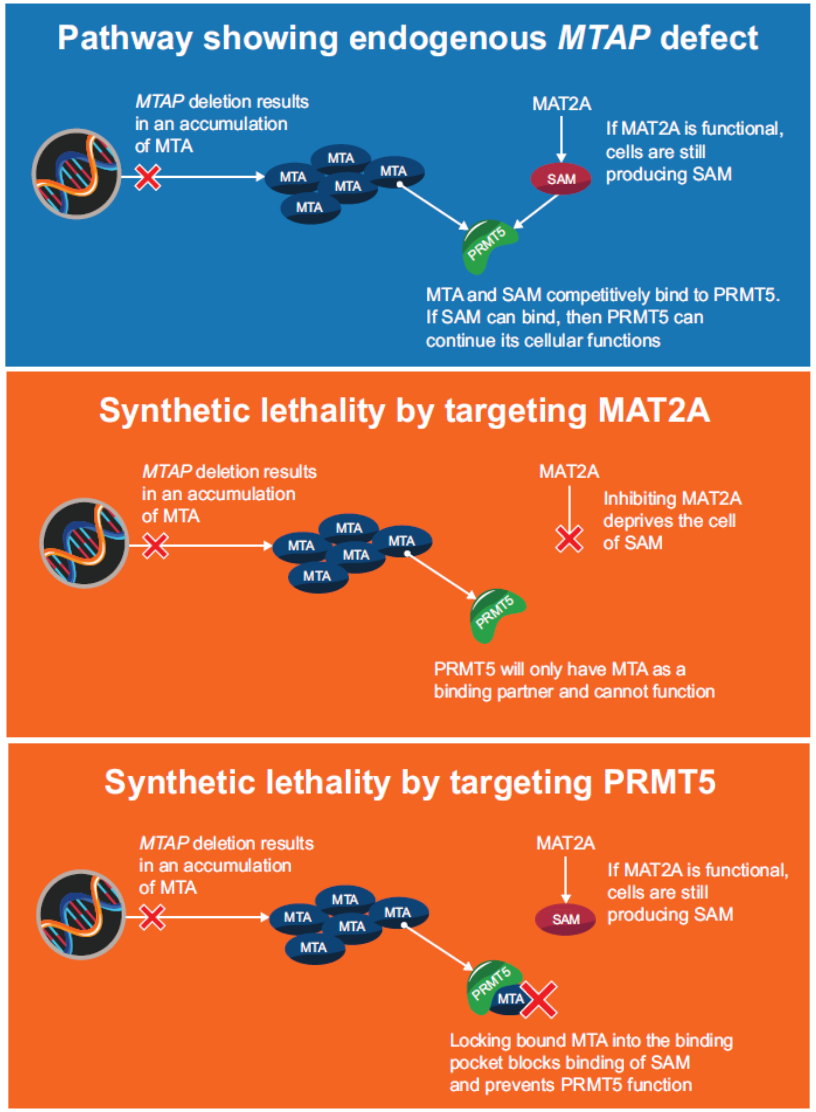




PRMT5 related synthetic lethality approaches

- PRMT5 (Protein arginine methyltransferase 5), as the major sDMA MTase, is emerging as the most promising target for a range of solid and blood cancers. Overexpression or dysregulation of PRMT5 has been observed in various cancer types, including breast, lung, ovarian, prostate, colorectal, gastric, liver, pancreatic, head and neck, bladder, lymphoma, melanoma and glioma, which in most cases is associated with poor patient survival, while genetic alterations are rare in PRMT5 genes.
- Inhibition of MAT2A in MTAP-deleted cancers is now developing as a new synthetic lethality approach. MTAP, locating adjacent to CDK2A, is collaterally co-deleted in about 15% of all the cancers. MTA accumulates intracellularly in the absence of MTAP, which subsequently inhibit PRMT5 activity. SAM, the substrate of MAT2A, is required for PRMT5 for its normal actions. Thus, inhibition of MAT2A leads to depletion of SAM, and further inhibition of PRMT5 results in synthetic lethality specifically in MTAP-deleted cells.

Hwang, J.W., Cho, Y. et al. Exp Mol Med ***53,*** *788–808 (2021).*
https://www.nature.com/articles/d42473-021-00591-9



Summary of PRMT5 related CDX models

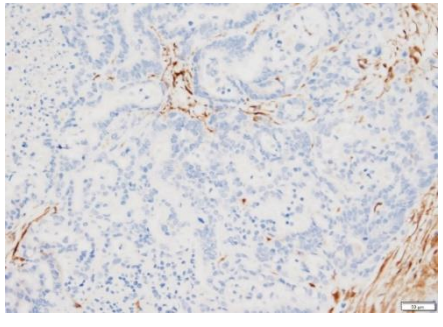
Cancer type	Model ID	PRMT5 RNAseq level	MTAP RNAseq level	Model ID	PRMT5 RNAseq level	MTAP RNAseq level
Bladder	RT112/84	65.22	0	SW780	100.54	0
	RT-4	64.78	0	UM-UC-3	119.41	0
Brain	Daoy	123.27	0	U118MG	74.27	0
Breast	MDA-MB-231	70.80	0	SUM149PT	70.48	0
Leukemia	HEL 92.1.7	81.22	0	Nalm-6	72.49	0
	K562	75.43	0	RS4;11	84.02	0
Gastric	MKN45	99.59	0	SNU-16	172.75	0
Lung	LU99	81.33	0	NCI-H1437	108.41	0
	NCI-H2126	69.16	0	NCI-H2170	120.68	0
	NCI-H2228	61.58	0	NCI-H2347	79.56	0
	NCI-H292	60.12	0	NCI-H3122	118.72	0
	NCI-H322	137.96	0	SW1573	63.94	0
Colorectal	HCT-116	83.27	56.56	HCT-116 ($MTAP^{-/-}$)	NA	NA
Pancreatic	BXPC3	57.38	0	KP4	100.41	0
	CAPAN1	95.24	0	MIAPACA2	59.39	0
Liver	SKHEP1	93.64	0	-	-	-
Melanoma	SK-MEL-5	57.64	0	-	-	-
Sarcoma	143B	141.45	0	SKNEP1	69.30	0
Thyroid	SW579	67.41	0	-	-	-

MTAP profile and PRMT5 inhibitor evaluation in PDX models

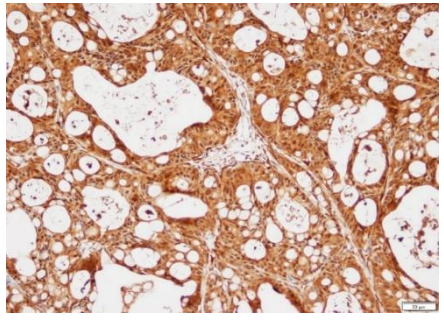
Cancer type	Model ID	Ratio of positive tumor cell	Cancer type	Model ID	Ratio of positive tumor cell
Pancreatic	PC-07-0010	0	Colorectal	CO-04-0124	100%
	PC-07-0016	0		CO-04-0722	0
	PC-07-0032	0	Lung	LU-01-1539	100%
	PC-07-0034	100%	Urothelial	UC-29-0001	0
	PC-07-0042	0		UC-29-0002	100%
	PC-07-0049	0		UC-29-0005	0
	PC-07-0052	0		UC-29-0006	0
	PC-07-0053	100%		UC-29-0008	100%
	PC-07-0071	0		UC-29-0010	0

Note: more PRMT5-related models can be found in https://onco.wuxiapptec.com

Representative images for IHC staining of MTAP

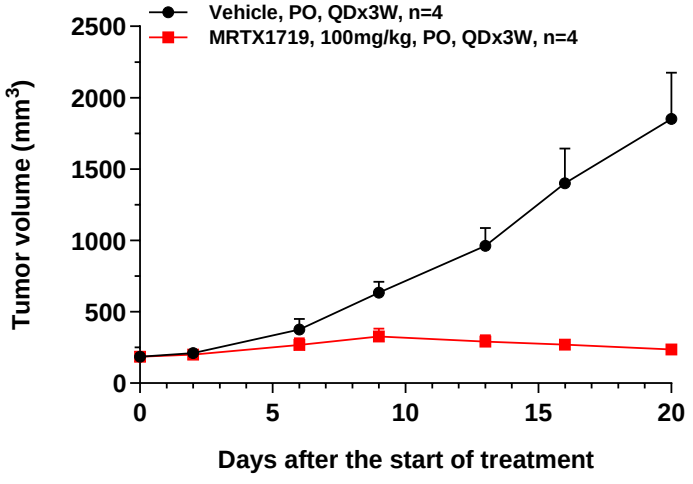


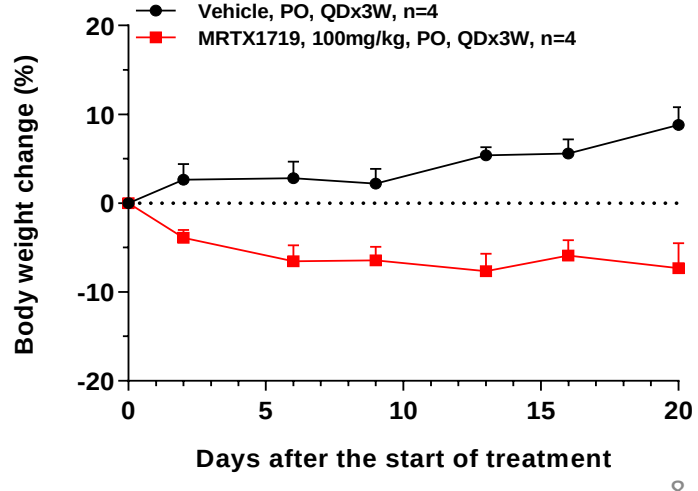
PC-07-0049



PC-07-0034

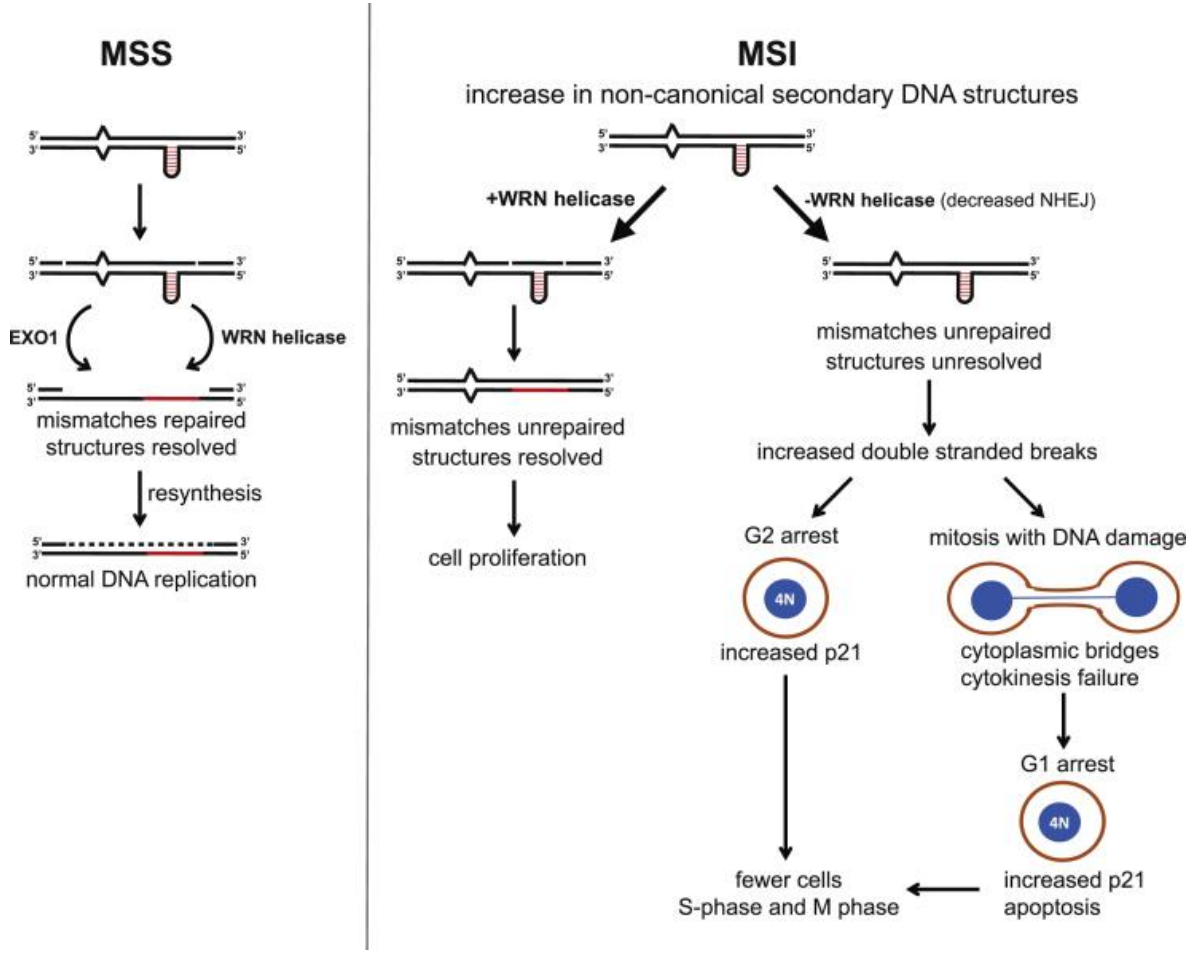
MRTX1719 in PC-07-0049 pancreatic cancer PDX model





WRN related synthetic lethality approaches

- Werner syndrome protein (WRN) is a human RecQ helicase involved in the maintenance of genome stability. Microsatellite instability (MSI), caused by defective mismatch repair (MMR), occurs frequently in colorectal, endometrial and gastric cancers.
- WRN was synthetic lethality with DNA mismatch repair proteins MLH1 & MSH2, loss of which is associated with high microsatellite instability (MSI-H). This suggests that WRN is broadly synthetic lethality with a defect in MMR or the downstream MSI phenotype.
- MSI-H cells exhibited increased double-stranded DNA breaks, altered cell cycles, and decreased viability in response to WRN knockdown, in contrast to microsatellite stable (MSS) lines, which tolerated depletion of WRN.



iSciense. 2019 Mar 29:13:488-497. doi: 10.1016/j.isci.2019.02.006.

Summary of WRN related MSI-H CDX models

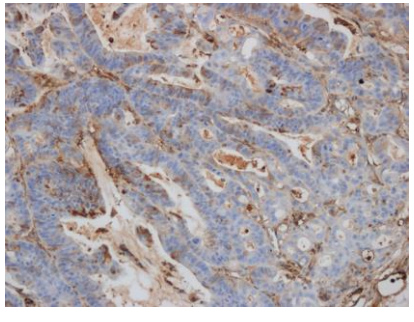
Cancer type	Model ID	MLH1 RNAseq level	MSH2 RNAseq level	MSH6 RNAseq level	PMS2 RNAseq level
Breast	HCC1569	62.04	9.56	129.99	19.50
Colorectal	HCT116	7.74	24.31	34.80	21.95
	HCT15	38.48	49.10	6.20	18.23
	LS441N	5.16	19.56	56.33	14.05
	RKO	0.11	35.42	56.96	6.37
	SW48	0.05	38.98	32.20	18.04
Gastric	NUGC3	0.04	28.77	102.22	13.17
	SNU-1	9.55	43.28	68.02	11.50
Leukemia	MOLT4	42.22	71.95	75.53	3.99
	RS411	35.14	53.76	298.56	6.60
Ovary	SK-OV-3	0.53	23.77	66.60	5.05
Prostate	DU145	18.76	33.62	52.32	12.45

MSI profile and WRN targeted inhibitor evaluation in PDX models

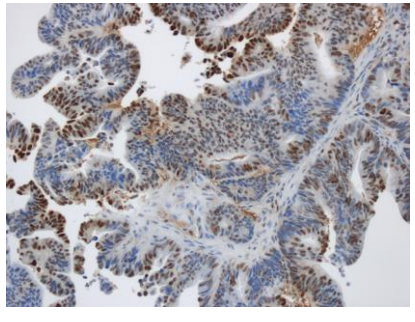
Cancer type	Model ID	MLH1	MSH2	MSH6	PMS2	Defective mismatch repair /MSI-H
Gastric	ST-02-0316	-	+	+	-	Yes
	ST-02-0322	-	+	+	-	Yes
Colorectal	CO-04-0093	+	-	-	+	Yes
	CO-04-0103	+	+	+	+	No
	CO-04-0114	-	+	+	-	Yes
	CO-04-0337	+	+	-	+	Yes

Note: more WRN-related models can be found in https://onco.wuxiapptec.com

Representative images for IHC staining of MLH1

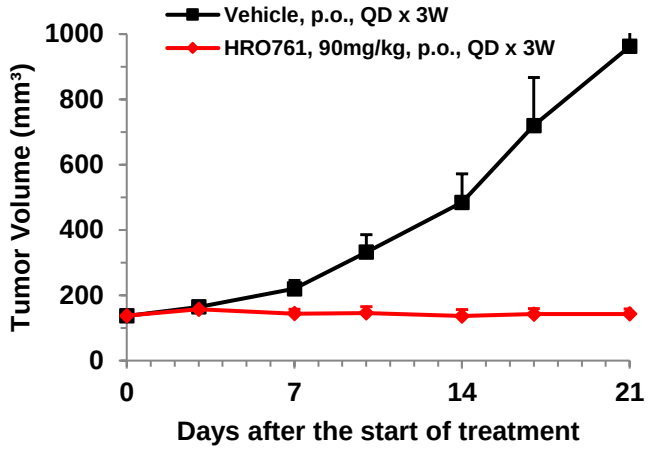


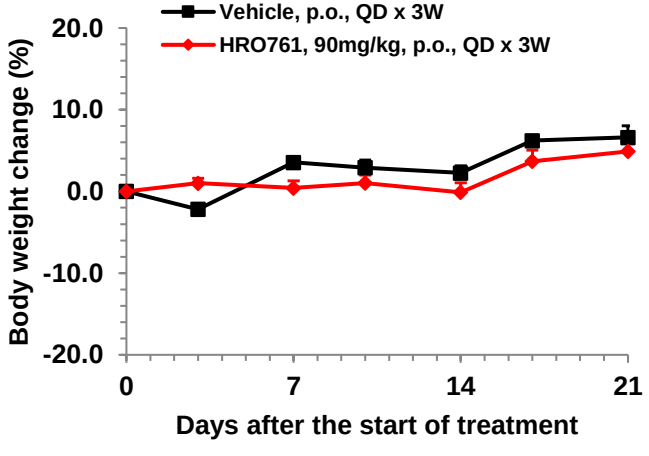
CO-04-0114



CO-04-0103

HRO761 in CO-04-0114 colorectal cancer PDX model





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