“Modulating Tumor Microenvironment Responses to Genotoxic Cancer Therapy”

Pete Nelson, MD

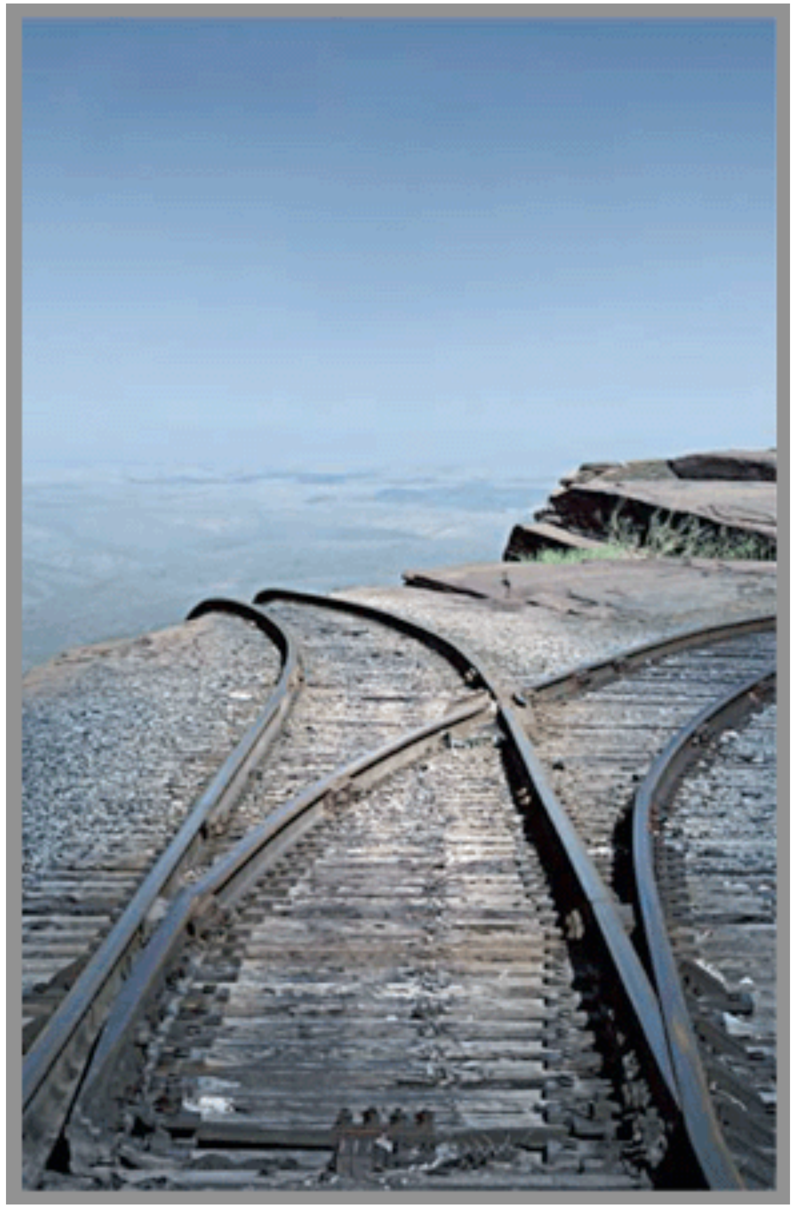
SITC, 2013

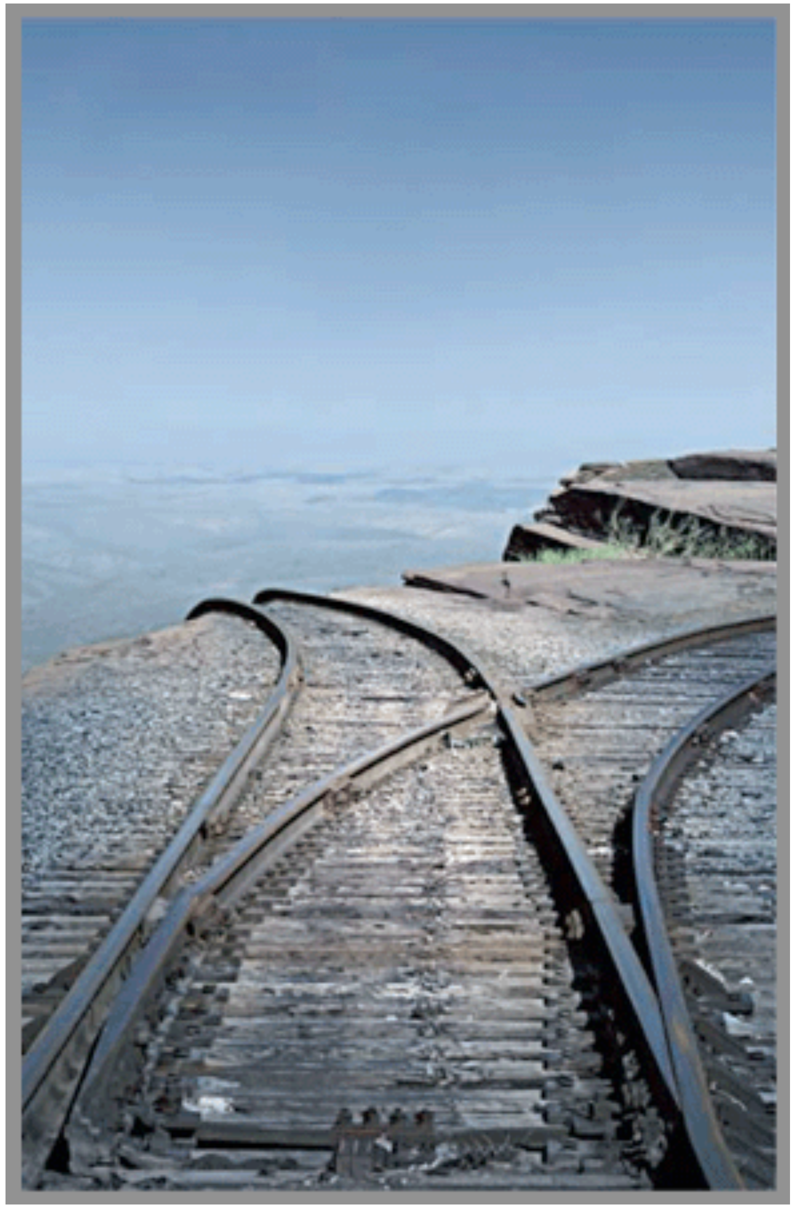
FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

This is a discussion about
Real Estate….(location, location, location)

CONTEXT

Context….

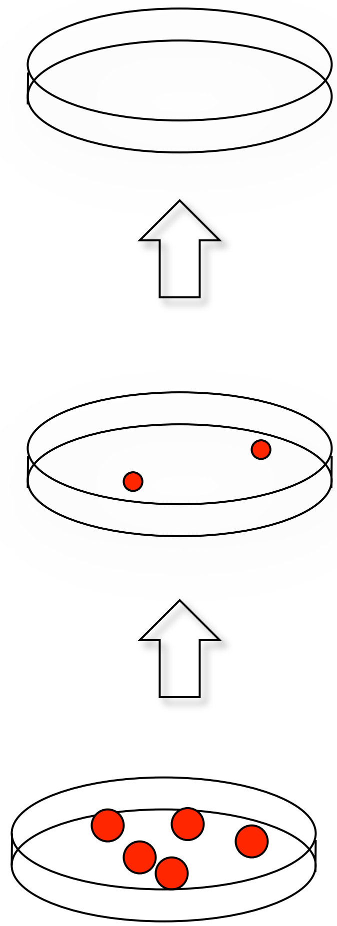




Same Train....

Different Destinations....

Same Train....

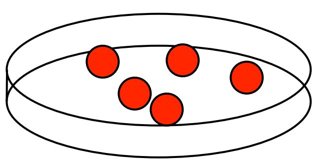


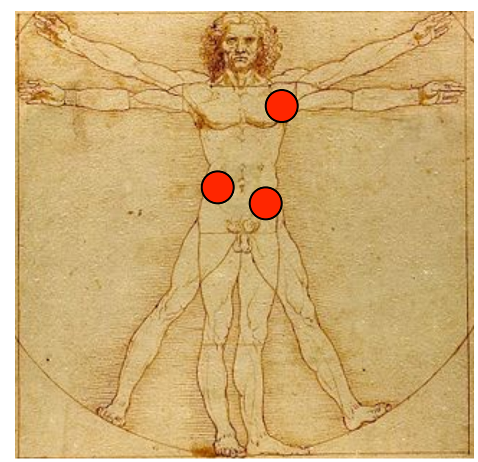
Treatment

(chemotherapy...)

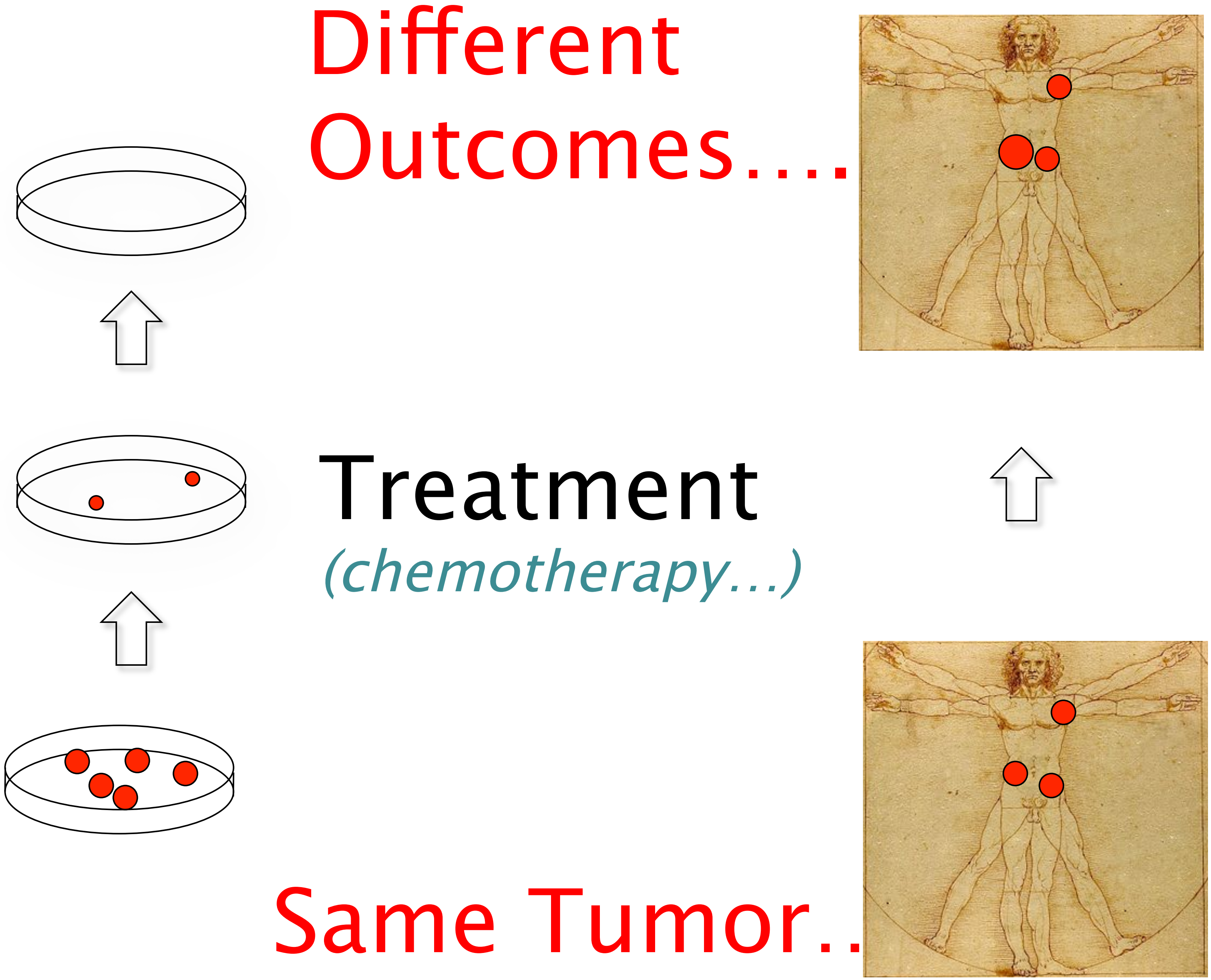
Treatment

(chemotherapy…)

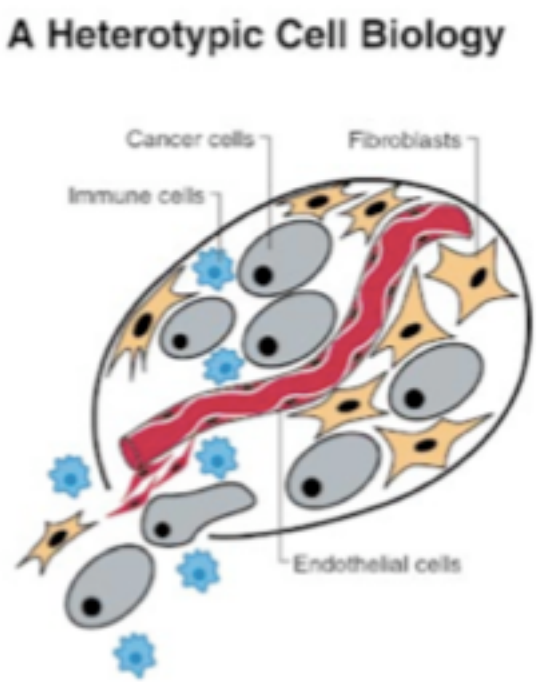




'Same' Tumor..


Different Outcomes....
Treatment
(chemotherapy...)
Same Tumor..

Context of a malignancy *in vivo*: the Tumor Microenvironment (TME)



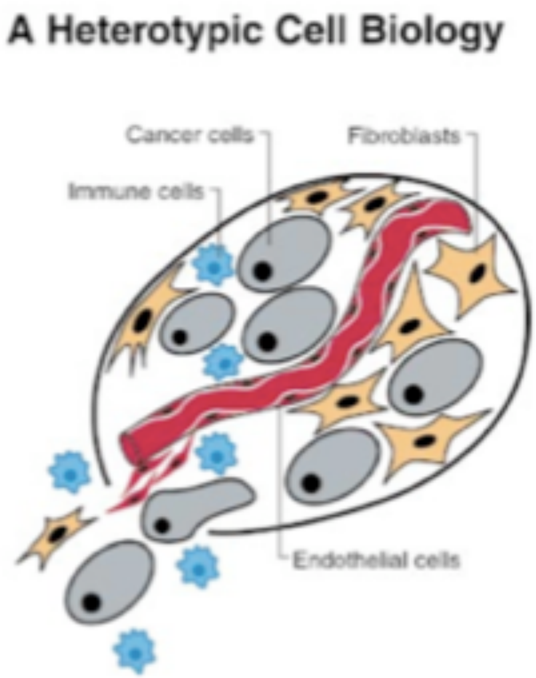
Resident Cellular Components

- ✓Fibroblasts
- ✓Smooth Muscle
- ✓Neuroendocrine Cells
- ✓Endothelium
- ✓Nerves

Structural Components

- ✓Matrix

Context of a malignancy *in vivo*: the Tumor Microenvironment (TME)



Resident Cellular Components
- ✓Fibroblasts
- ✓Smooth Muscle
- ✓Neuroendocrine Cells
- ✓Endothelium
- ✓Nerves

Structural Components
- ✓Matrix

Infiltrating (non-resident) Cells
- ✓Inflammatory
- ✓Bone-marrow derived (MSC)

Molecular Components
- ✓Growth Factors/Cytokines
- ✓Nutrients
- ✓Hormones

This is a discussion about
Real Estate….

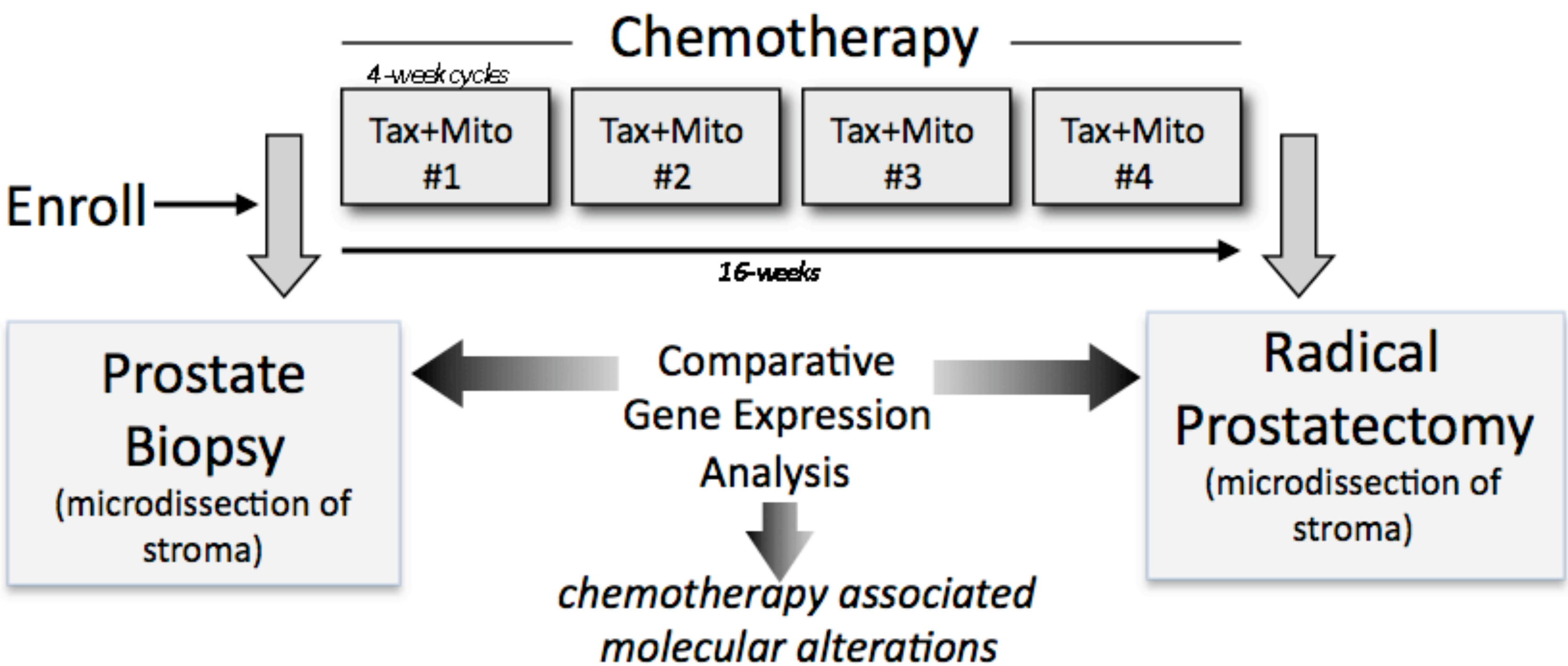
CONTEXT

4th Dimension…<u>time</u>

the real estate…the landscape…changes..

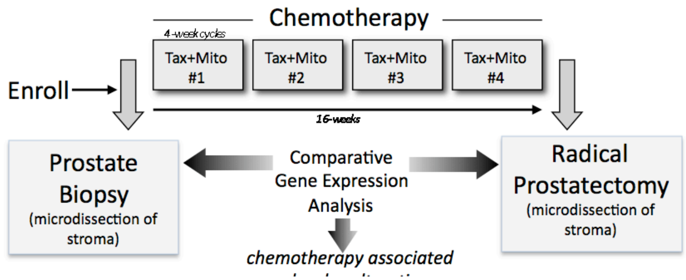
Neoadjuvant Chemotherapy Trial for High-Risk Prostate Adenocarcinoma

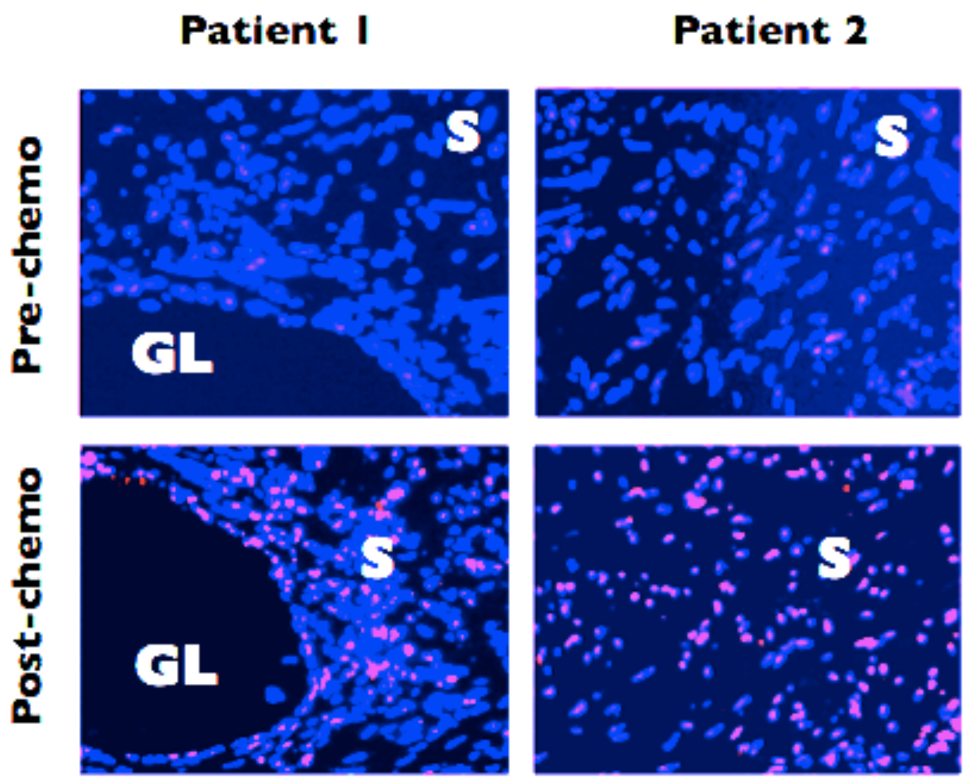
Mitoxantrone---Docetaxel



54 Patients: No Complete Responses

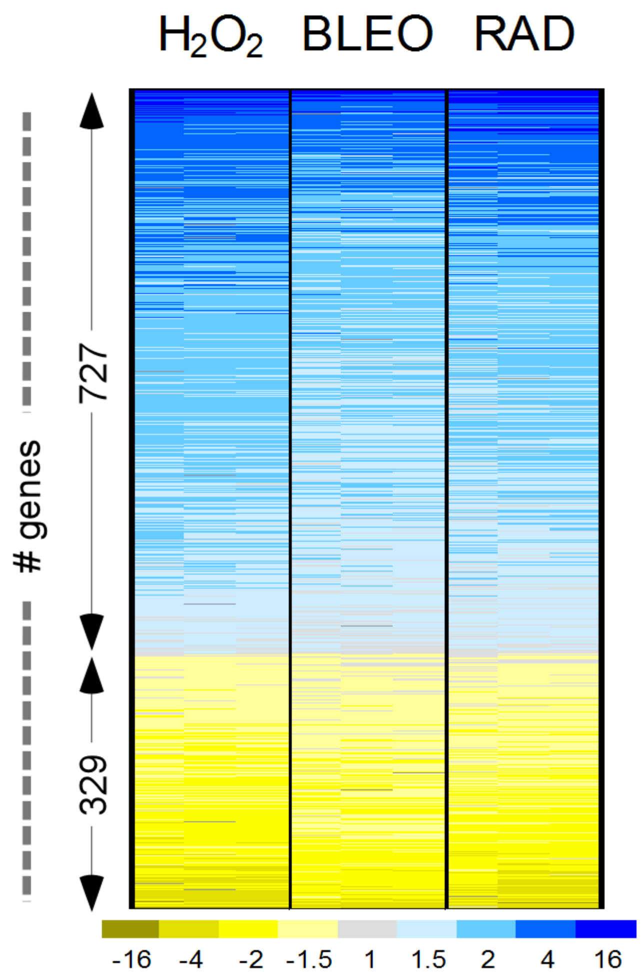
Neoadjuvant Chemotherapy Trial for High-Risk Prostate Adenocarcinoma





H2AX DNA Damage Foci

DNA Damage-associated Gene Expression



Gene expression in primary prostate fibroblasts

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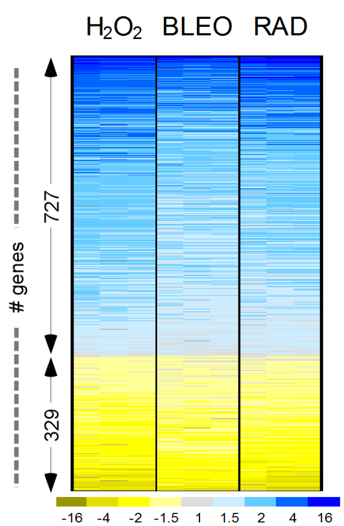
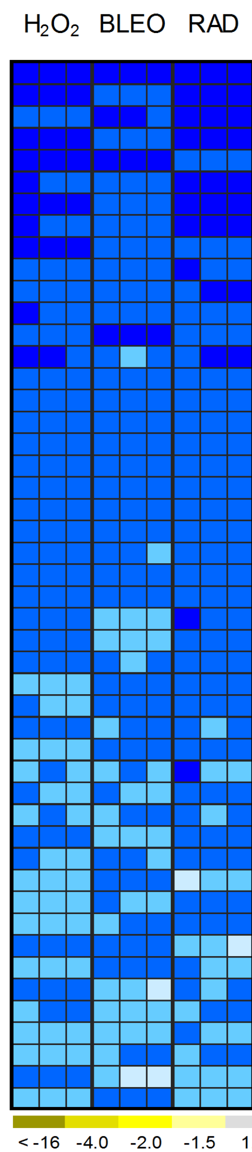
DNA Damage-associated Secretory Program: DDSP

A



Extracellular/
Secreted
≥ 3.5 fold

B

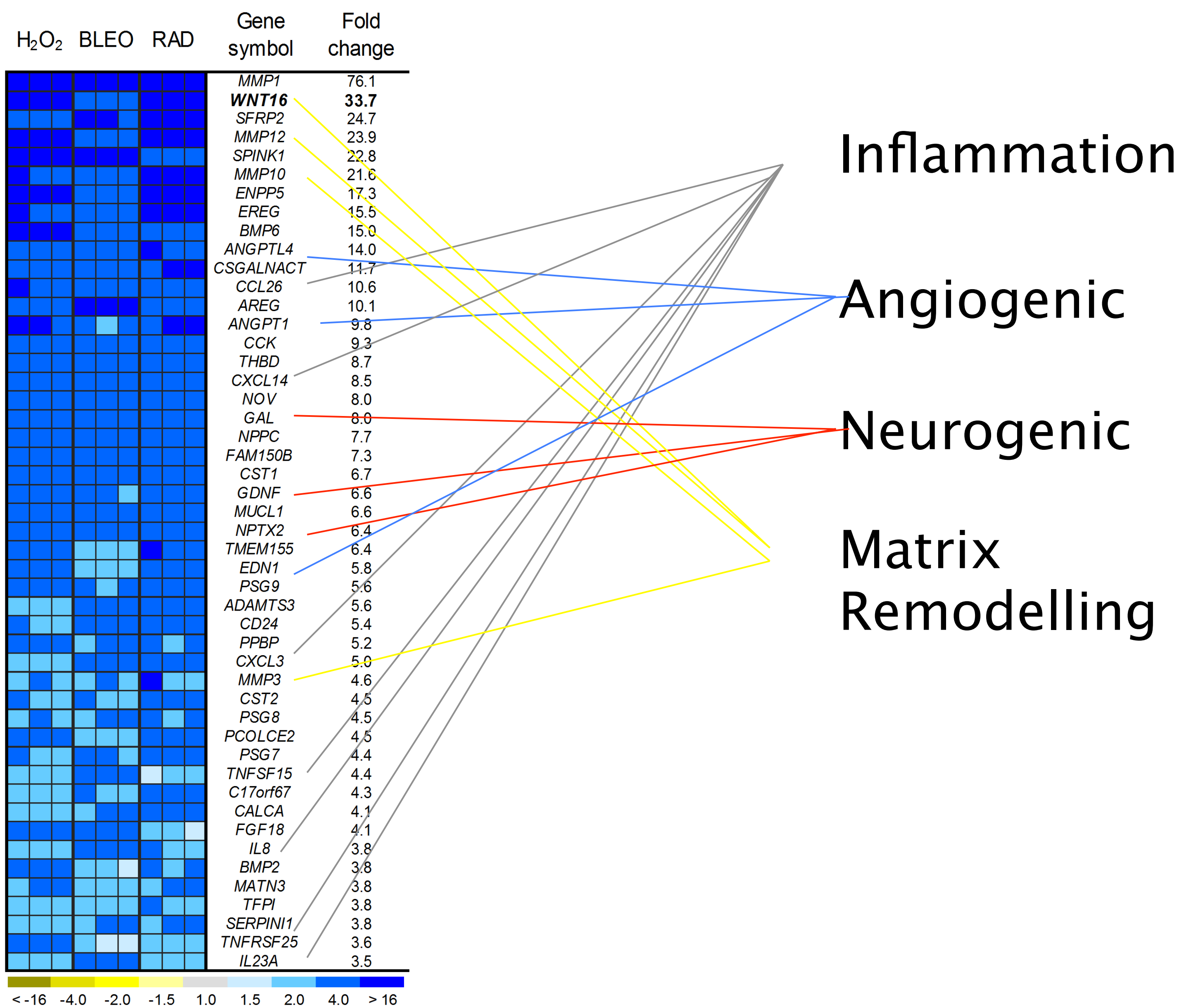


Gene symbol	Fold change
MMP1	76.1
WNT16	**33.7**
SFRP2	24.7
MMP12	23.9
SPINK1	22.8
MMP10	21.6
ENPP5	17.3
EREG	15.5
BMP6	15.0
ANGPTL4	14.0
CSGALNACT	11.7
CCL26	10.6
AREG	10.1
ANGPT1	9.8
CCK	9.3
THBD	8.7
CXCL14	8.5
NOV	8.0
GAL	8.0
NPPC	7.7
FAM150B	7.3
CST1	6.7
GDNF	6.6
MUCL1	6.6
NPTX2	6.4
TMEM155	6.4
EDN1	5.8
PSG9	5.6
ADAMTS3	5.6
CD24	5.4
PPBP	5.2
CXCL3	5.0
MMP3	4.6
CST2	4.5
PSG8	4.5
PCOLCE2	4.5
PSG7	4.4
TNFSF15	4.4
C17orf67	4.3
CALCA	4.1
FGF18	4.1
IL8	3.8
BMP2	3.8
MATN3	3.8
TFPI	3.8
SERPINI1	3.8
TNFRSF25	3.6
IL23A	3.5

Secreted proteins with potential for paracrine activity

Sun et al 2012 Nat Med Aug 5

DNA Damage-associated Secretory Program: DDSP



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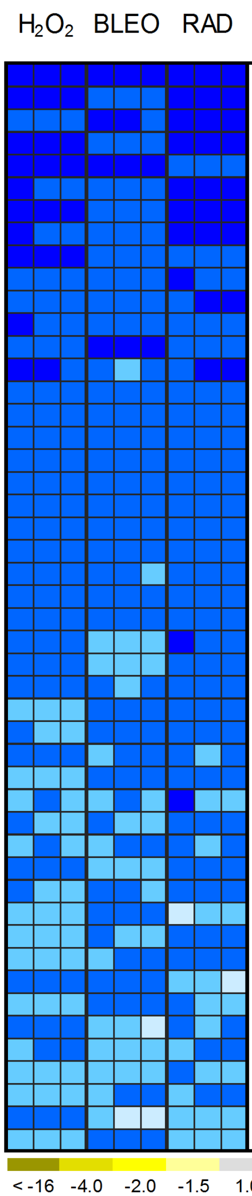

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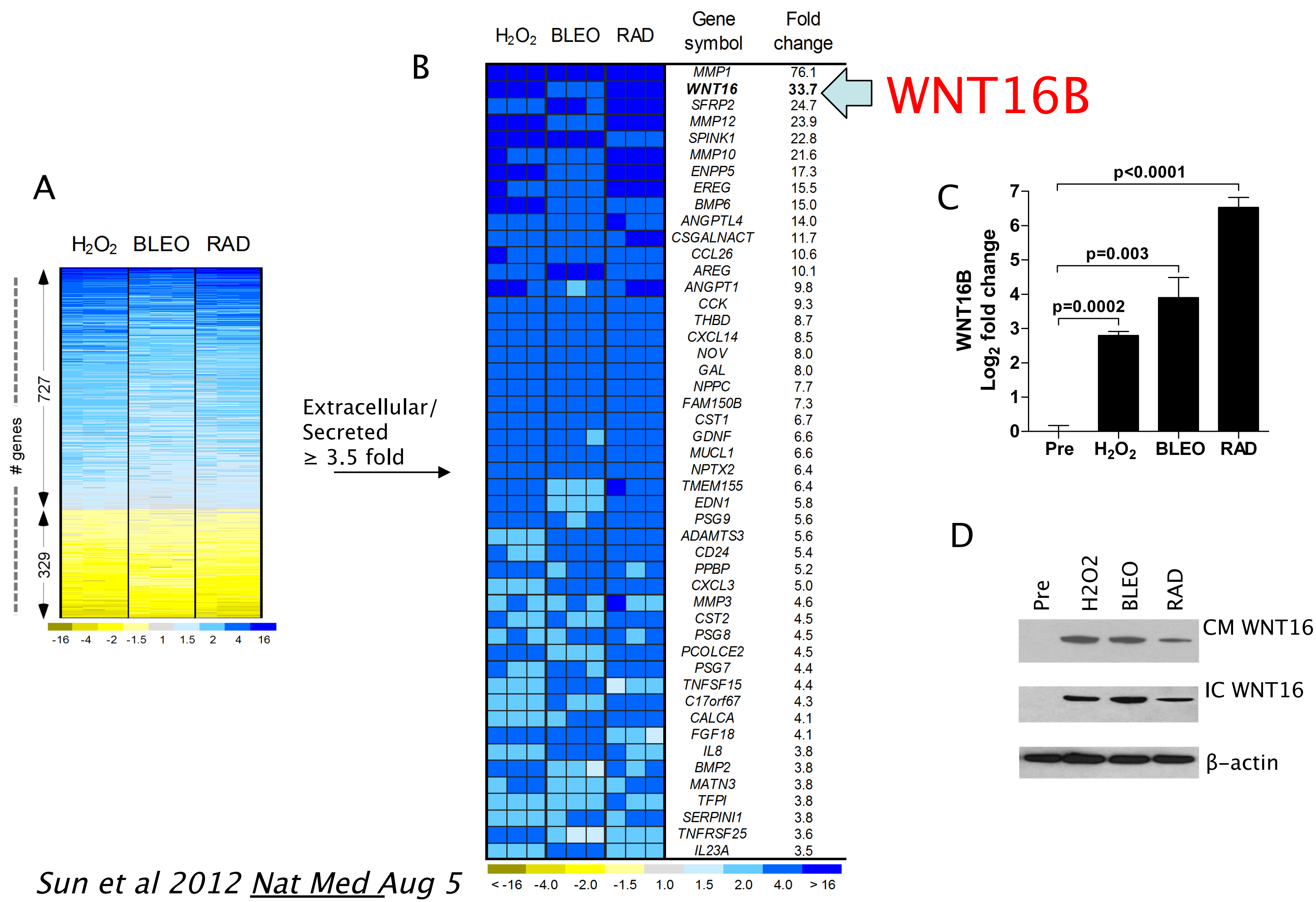
TMEM155	6.4
EDN1	5.8
PSG9	5.6
ADAMTS3	5.6
CD24	5.4
PPBP	5.2
CXCL3	5.0
MMP3	4.6
CST2	4.5
PSG8	4.5
PCOLCE2	4.5
PSG7	4.4
TNFSF15	4.4
C17orf67	4.3
CALCA	4.1
FGF18	4.1
IL8	3.8
BMP2	3.8
MATN3	3.8
TFPI	3.8
SERPINI1	3.8
TNFRSF25	3.6
IL23A	3.5

Immune Modulation

IL6
IL8
CCL8
CCL11
CCL13
CXCL1
CXCL2
CXCL3
CX3CL1
IL6ST
IL33

DNA Damage-associated Secretory Program: DDSP



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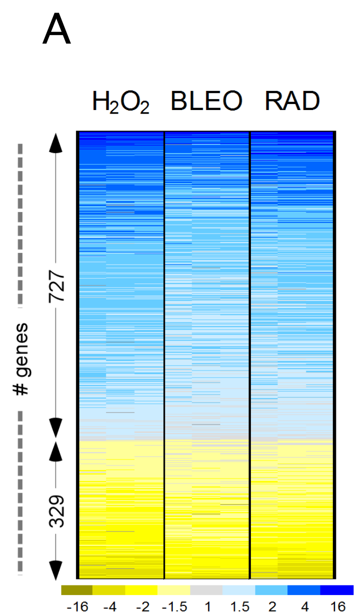
DNA Damage-associated Secretory Program: DDSP



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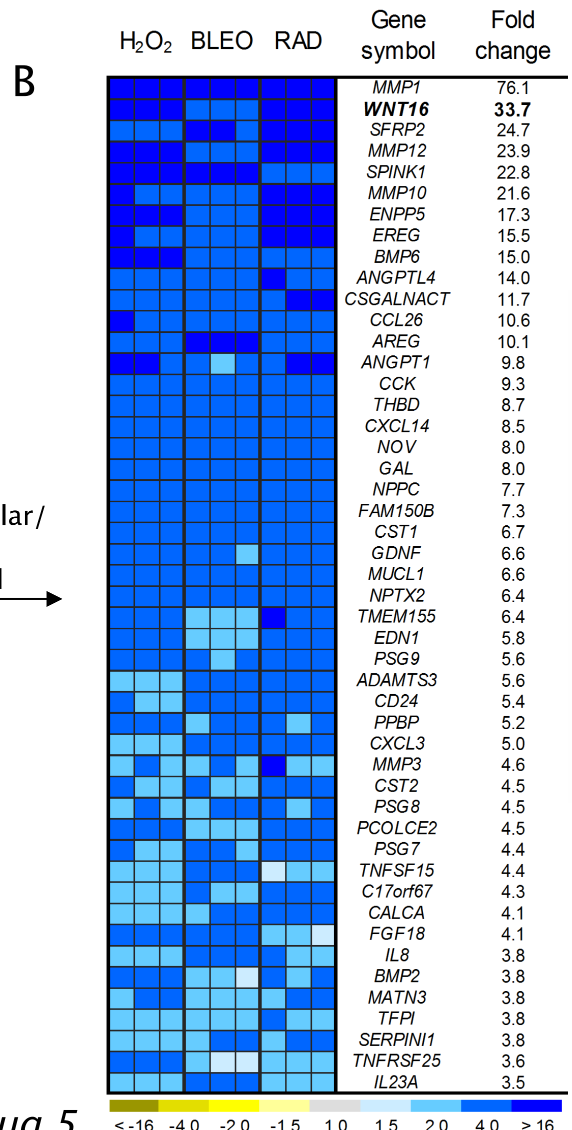
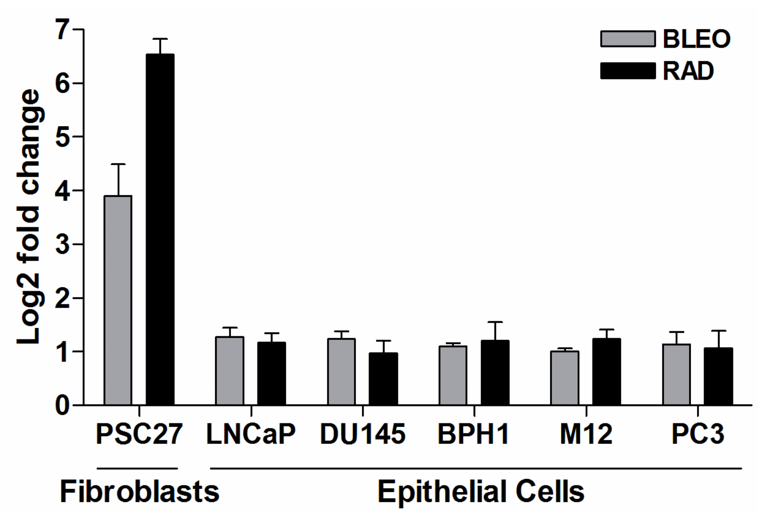


WNT16B



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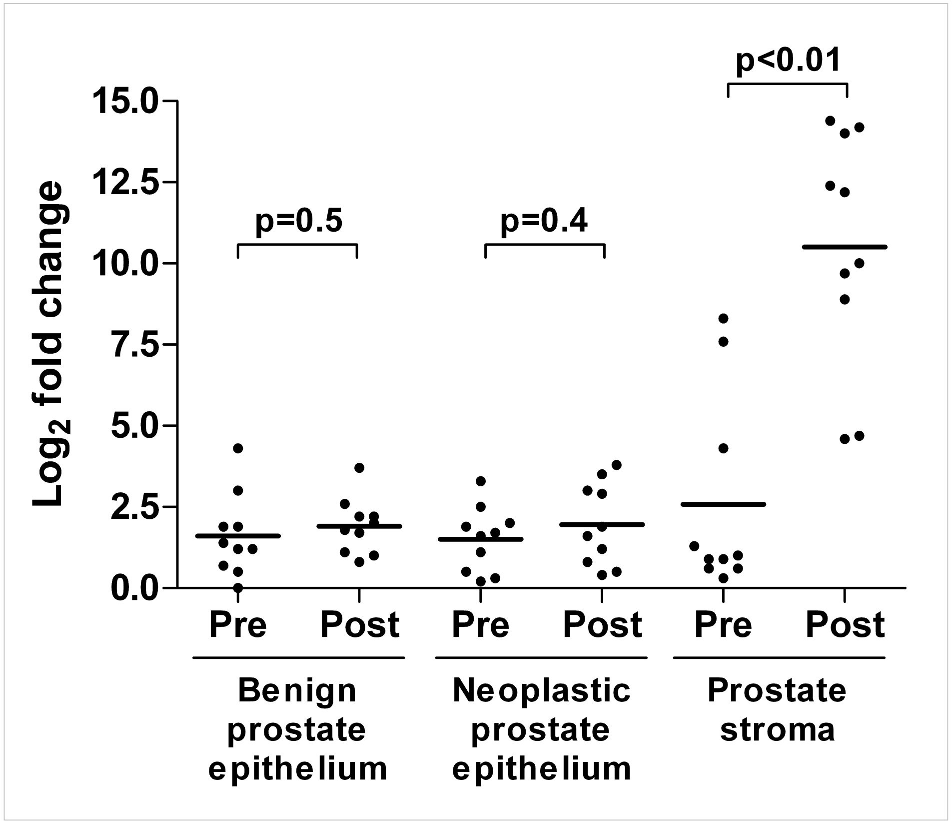
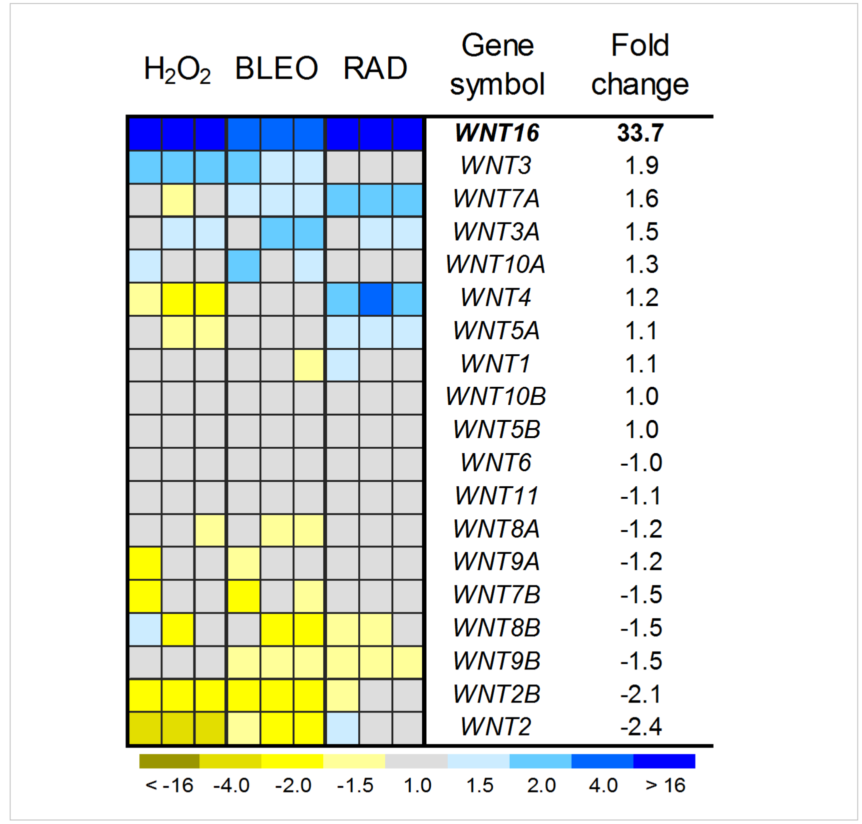
Cell Type- and WNT Type-Specific Damage Response
In Vivo





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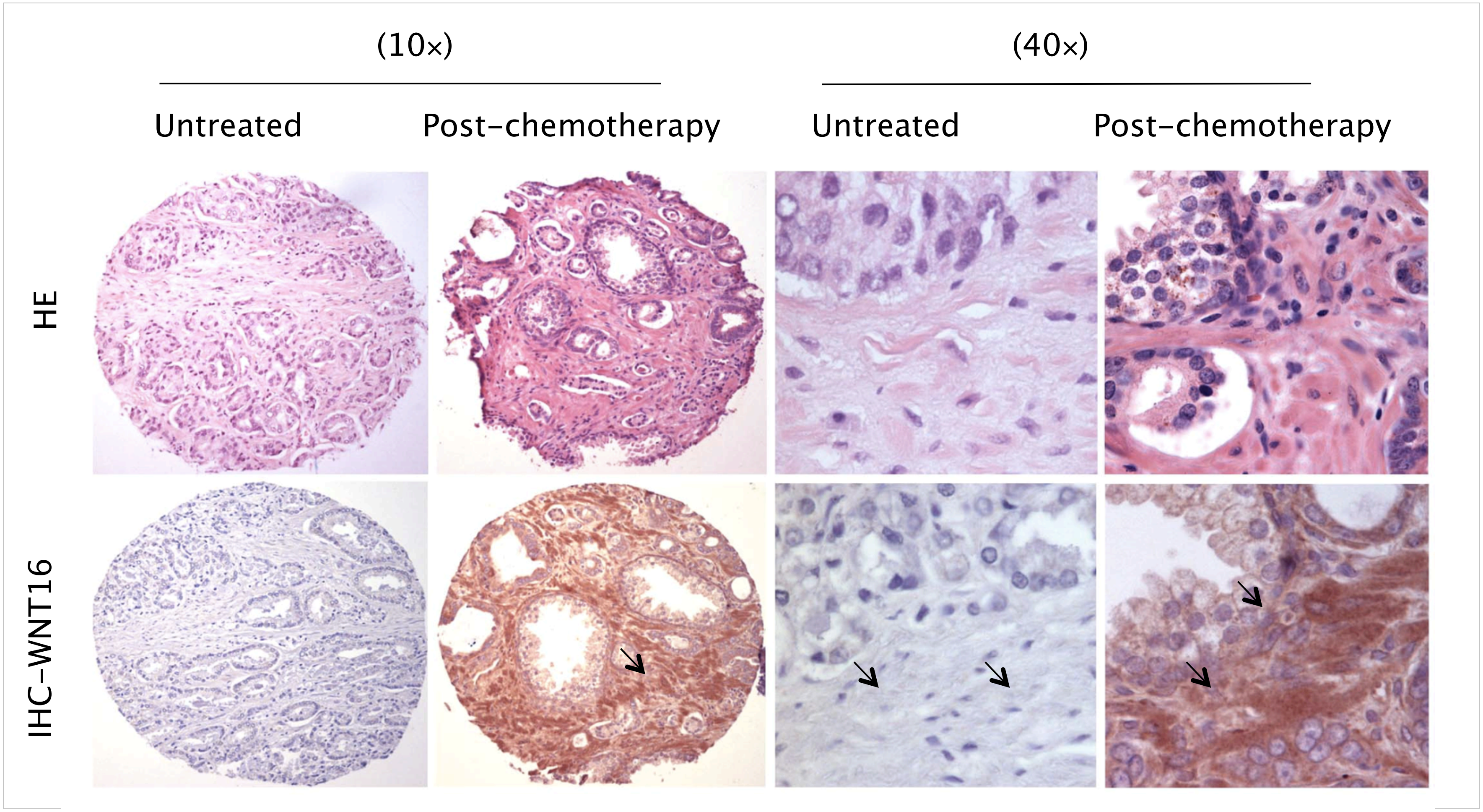
WNT16B Is Altered in the TME by Chemotherapy



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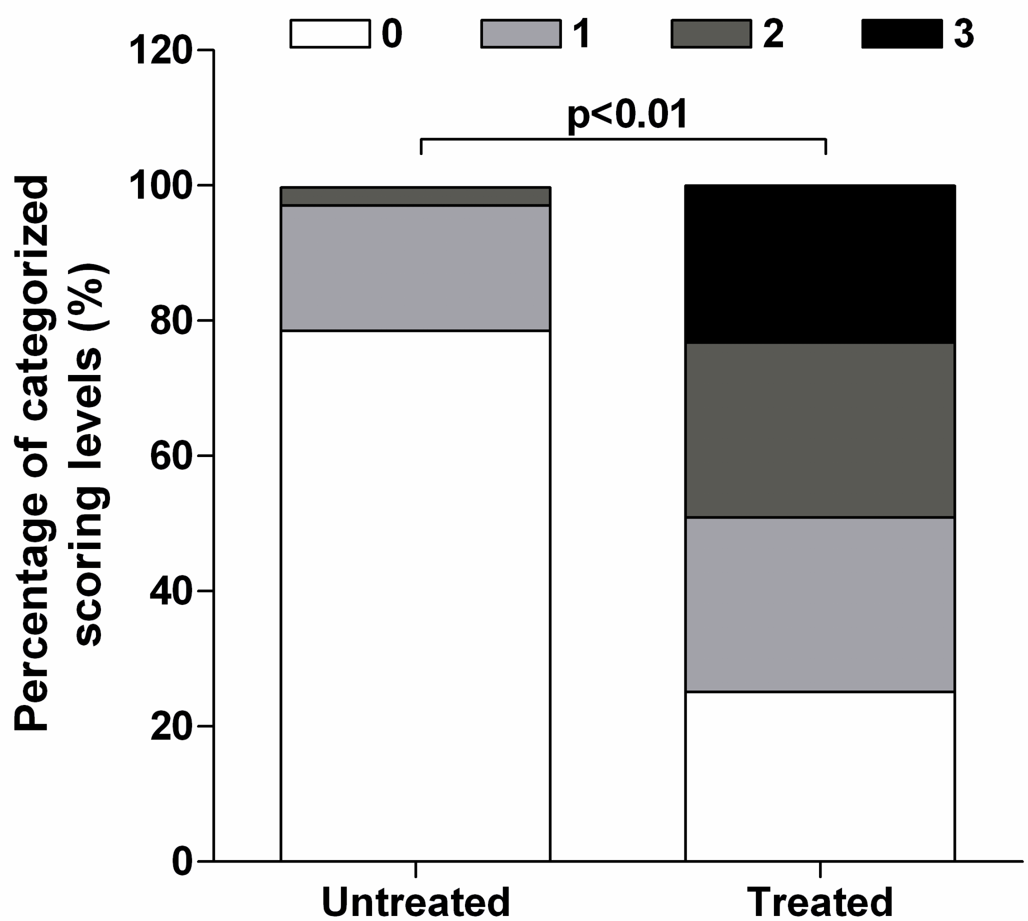

Cores=186
Patients=30

Cores=267
Patients=50

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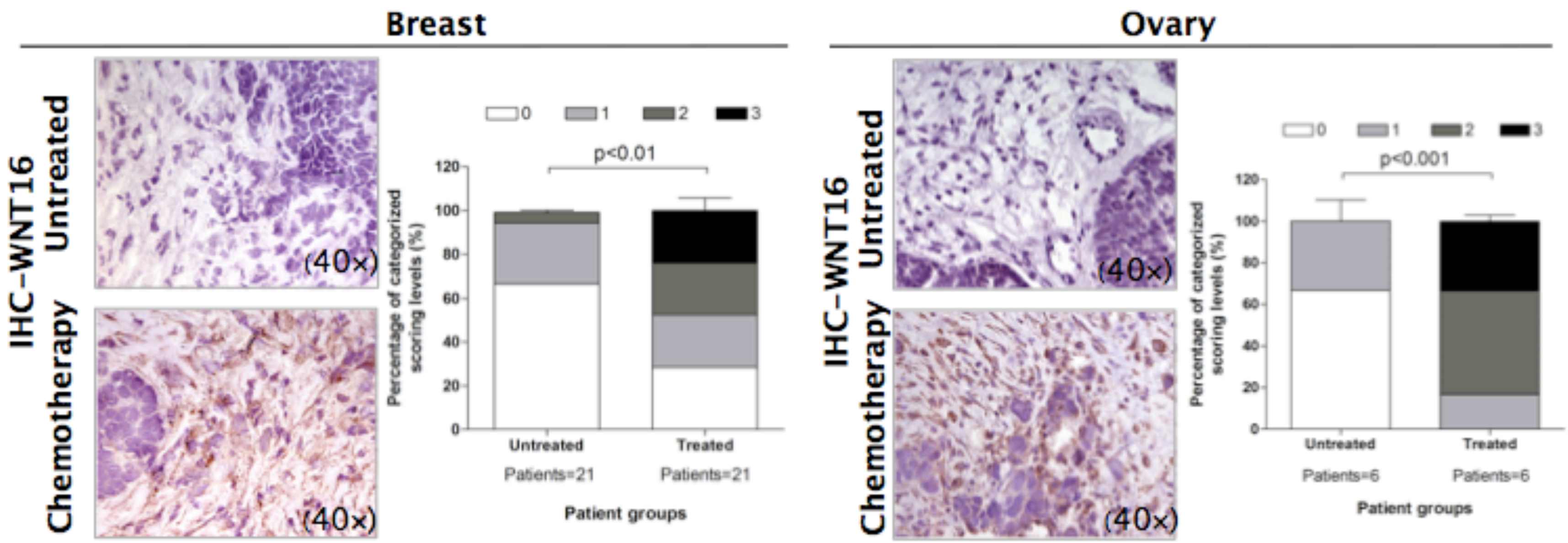
WNT16B Is Altered in the TME by Chemotherapy in Breast and Ovarian Tumors



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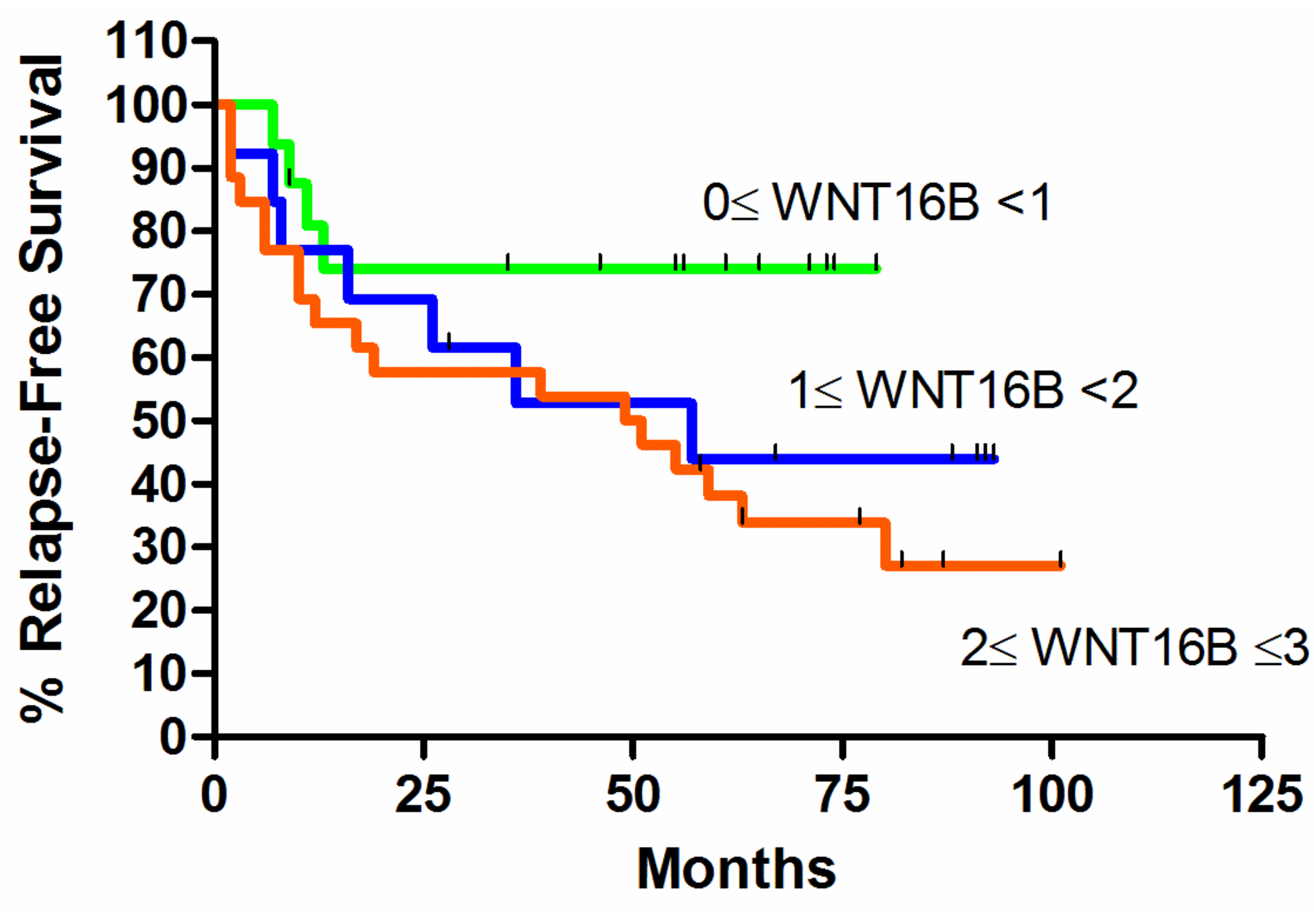
WNT16B and Outcomes following Neoadjuvant Chemotherapy and RRP



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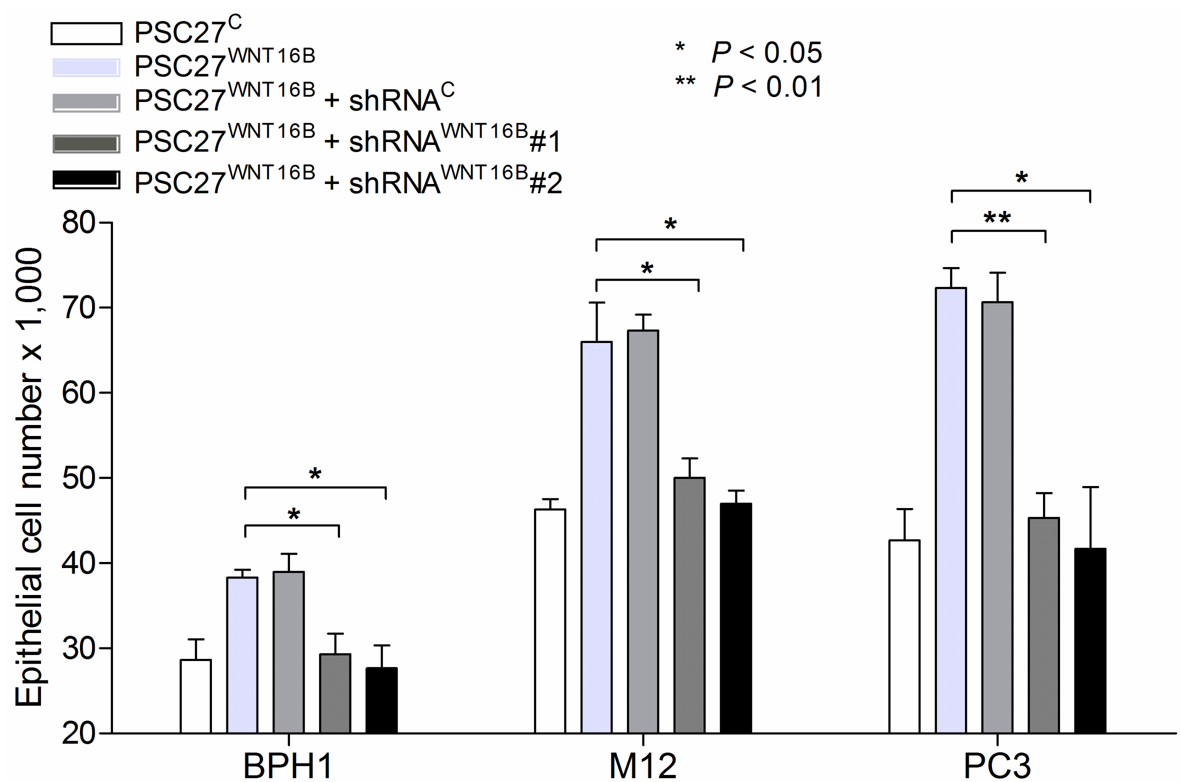
Fibroblast-Derived WNT16B Promotes Epithelial Cell Proliferation



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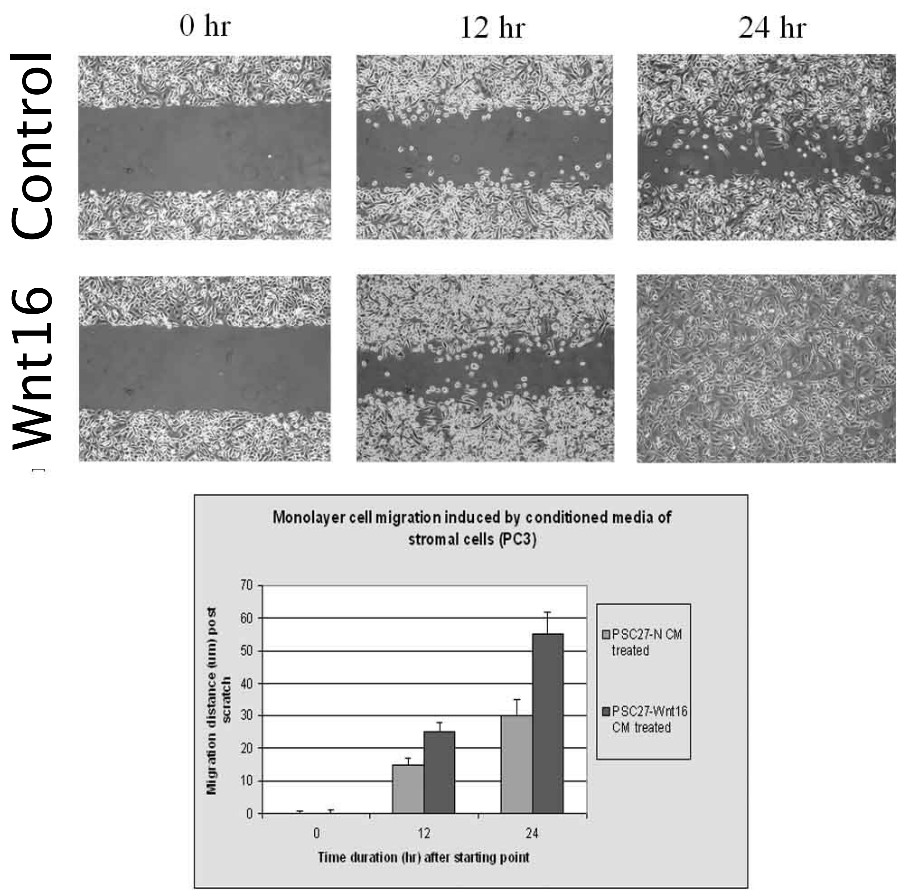
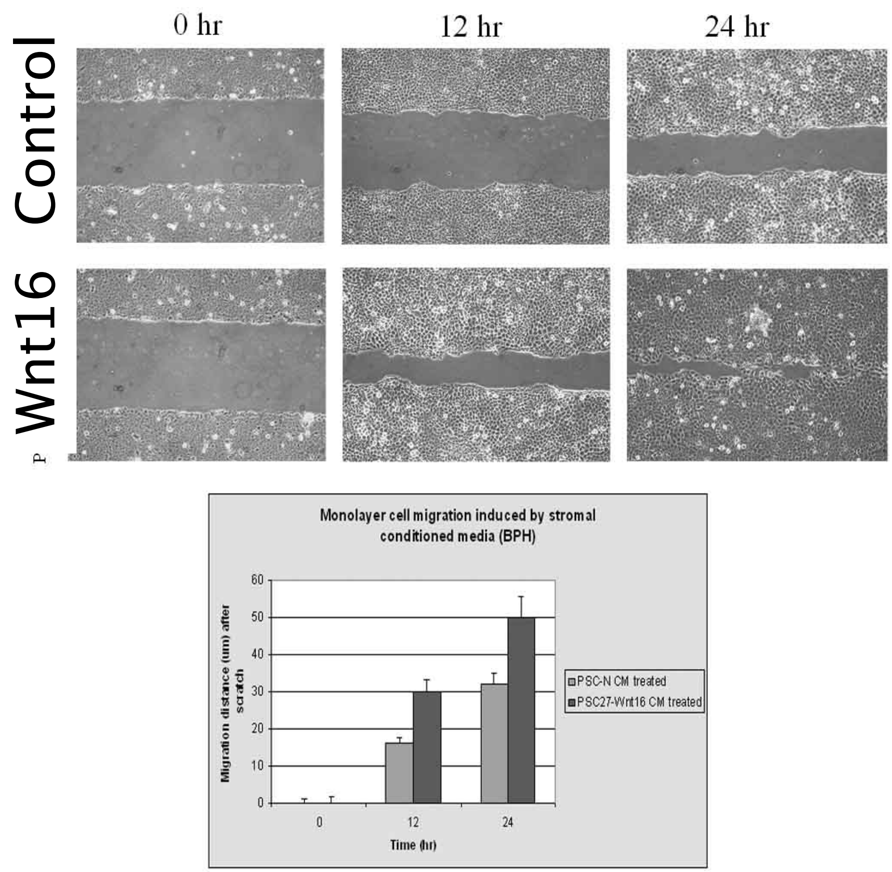
Fibroblast-Derived WNT16B Promotes Epithelial Cell Migration Through Paracrine Effects

PC3



BPH 1



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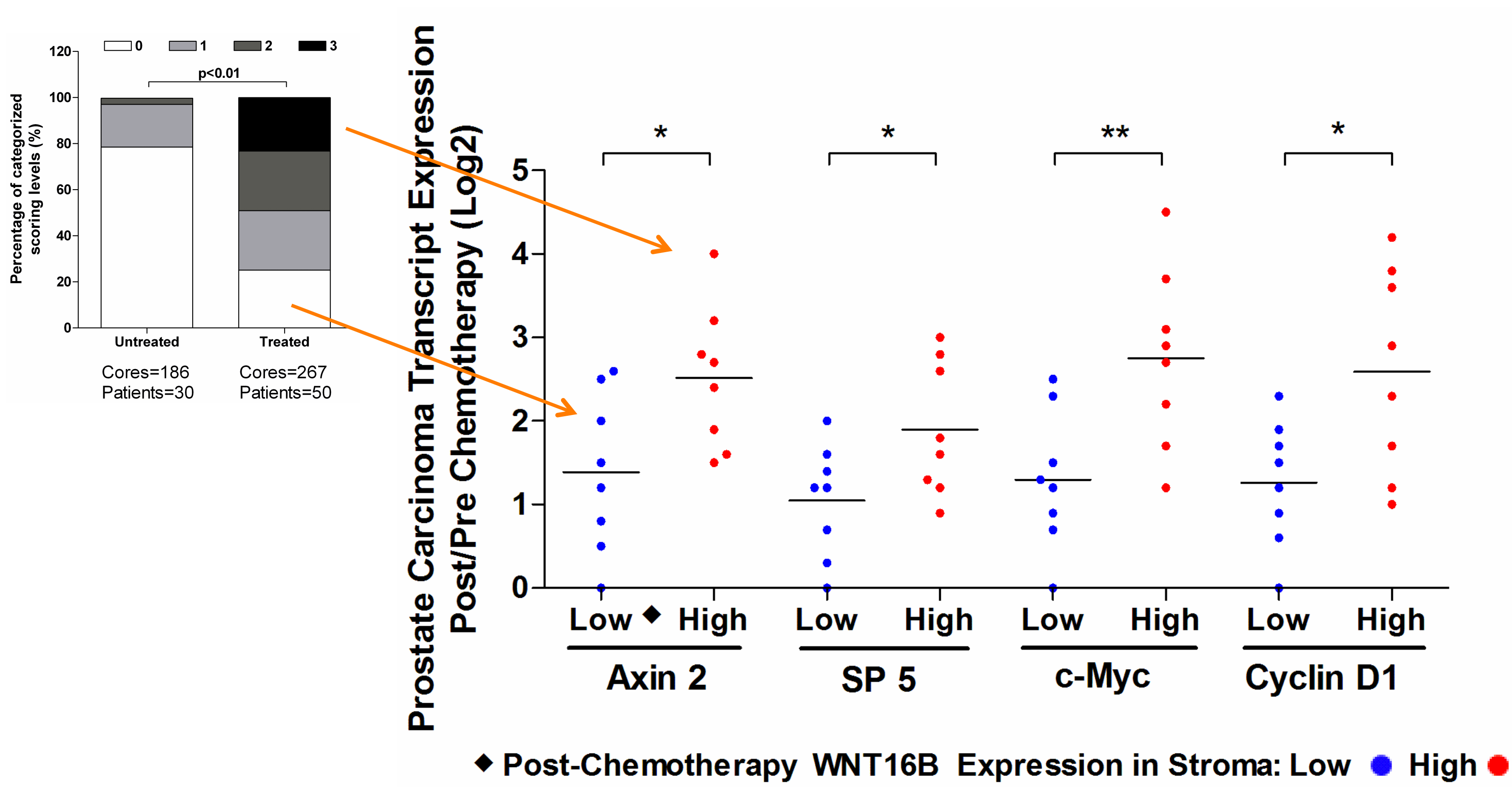
β-Catenin Target Genes Associate with WNT16B Expression After Chemotherapy



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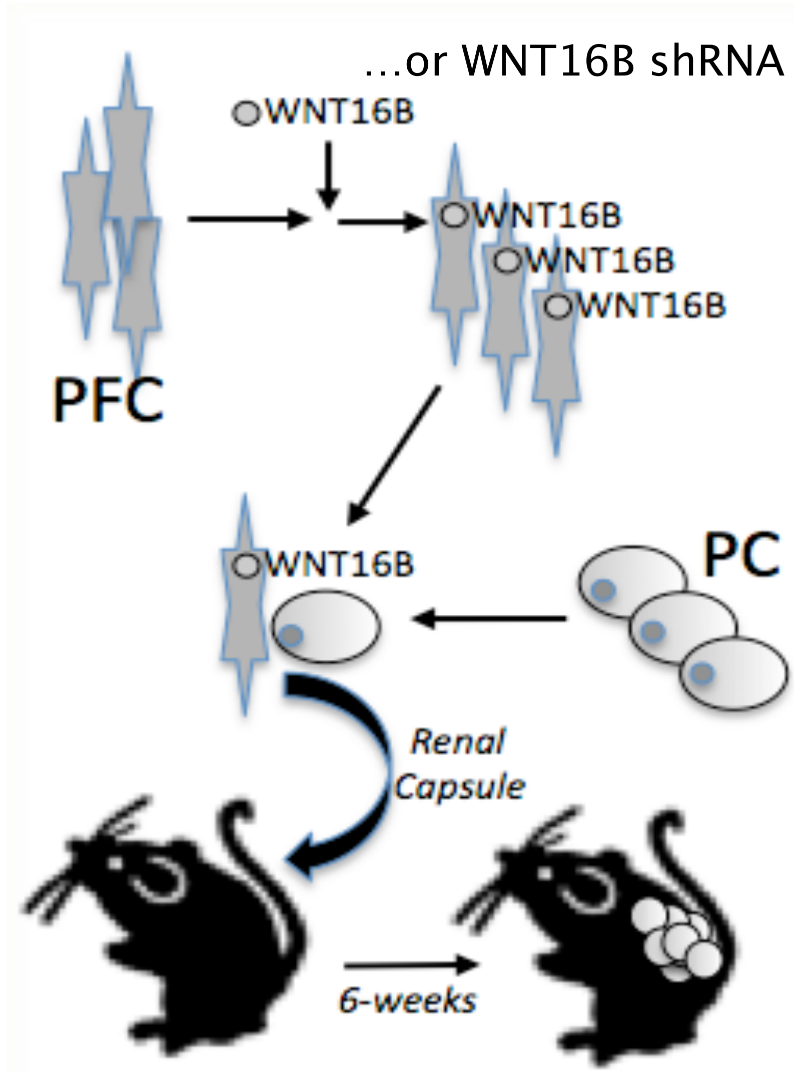
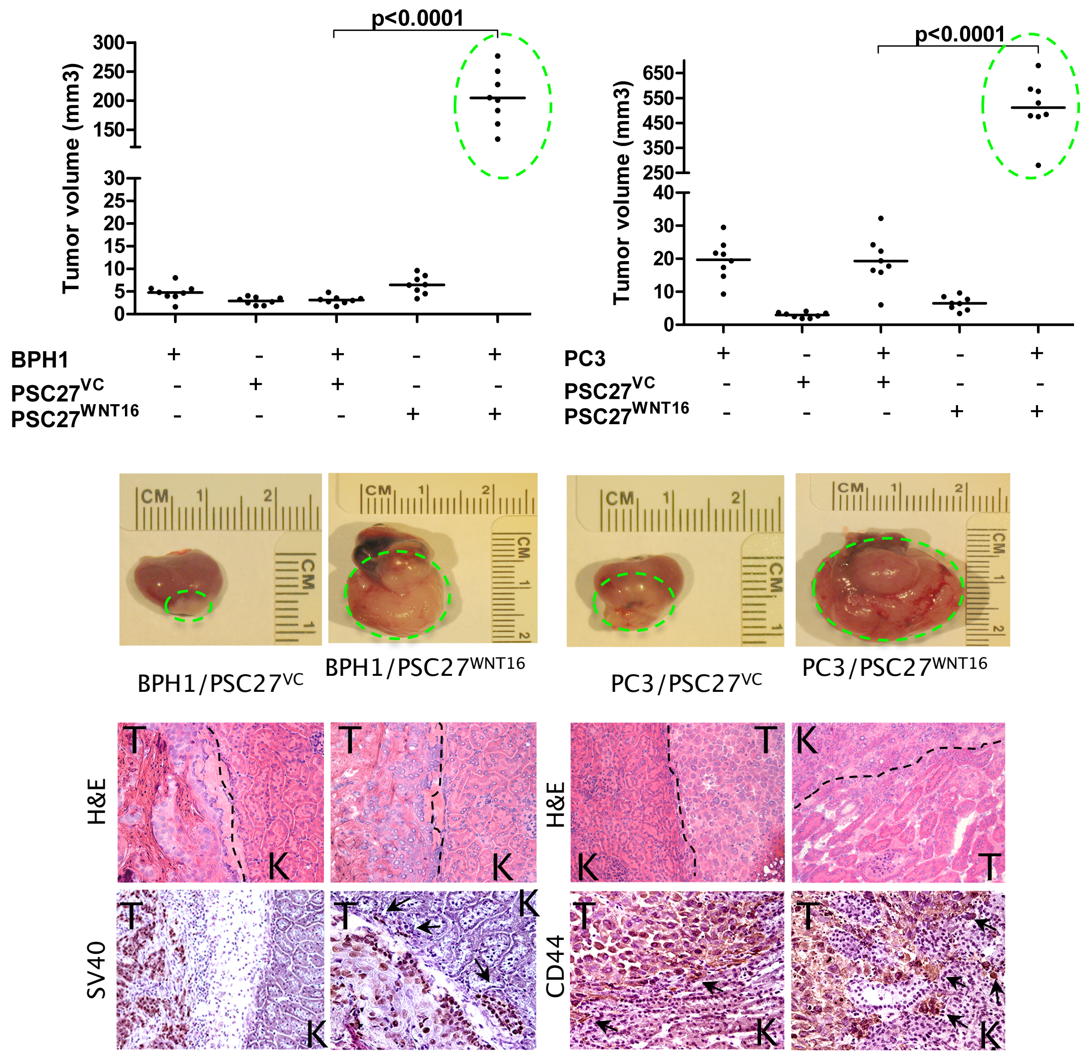
Fibroblast WNT16B Promotes Tumor Growth



Stromal WNT16B Promotes Tumor Growth



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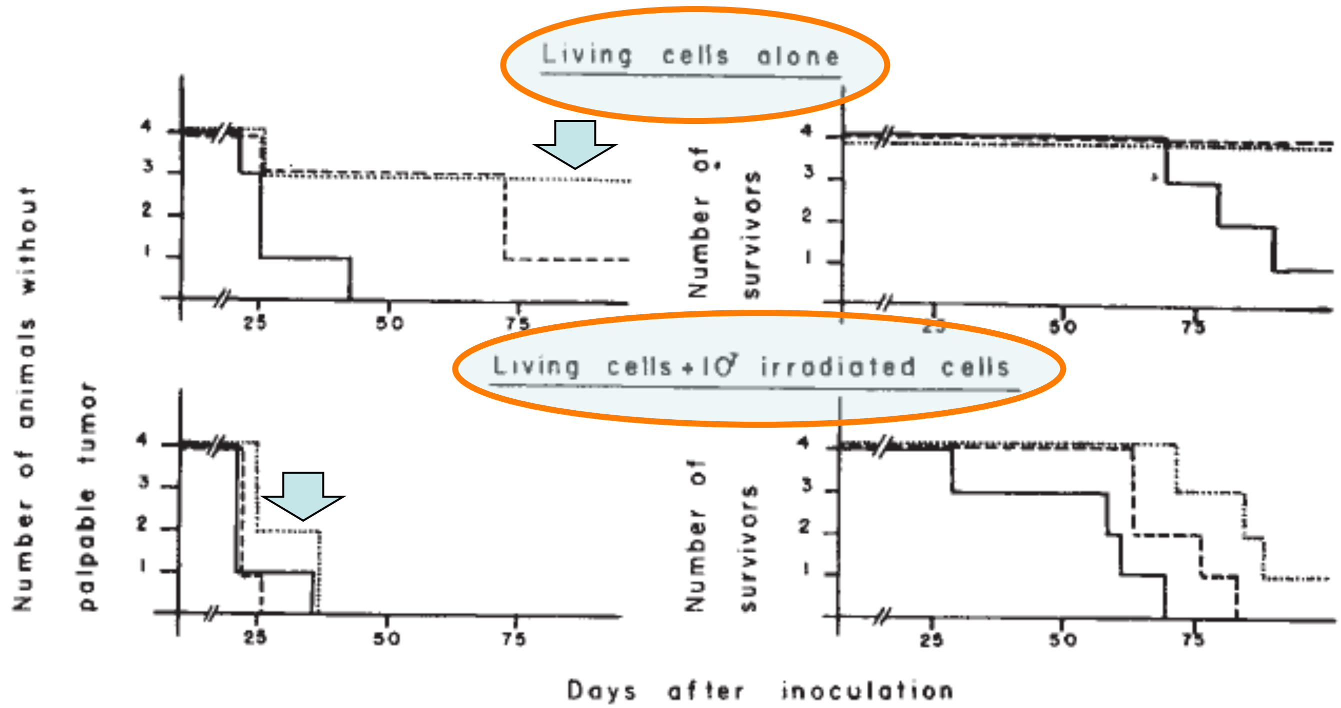
Effect of Tumour Cells killed by X-rays upon the Growth of Admixed Viable Cells

TUMOURS irradiated with sublethal X-ray doses can be schematically considered as containing two kinds of tumour cells, differing in their prospective

Laszlo Revesz

1950's

1392 NATURE Dec



——, 5×10^3 living cells; – – – –, 5×10^2 living cells; . . . . . ., 5×10 living cells

Fig. 2. Effect of cells lethally damaged by X-rays on the growth of viable cells admixed in various numbers. A spontaneous mammary carcinoma of the *C3H* strain was used. The curves on the left show the appearance of palpable tumours; those on the right denote survival time. Note higher incidence of tumours, reduced latency-period and decrease of survival-time in animals receiving the mixture

Br. J. Cancer (1977) **36**, 94

REACTIONS OF THE TUMOUR BED TO LETHALLY IRRADIATED TUMOUR CELLS, AND THE RÉVÉSZ EFFECT

H. A. S. van den BRENK, M. C. CROWE and M. G. STONE

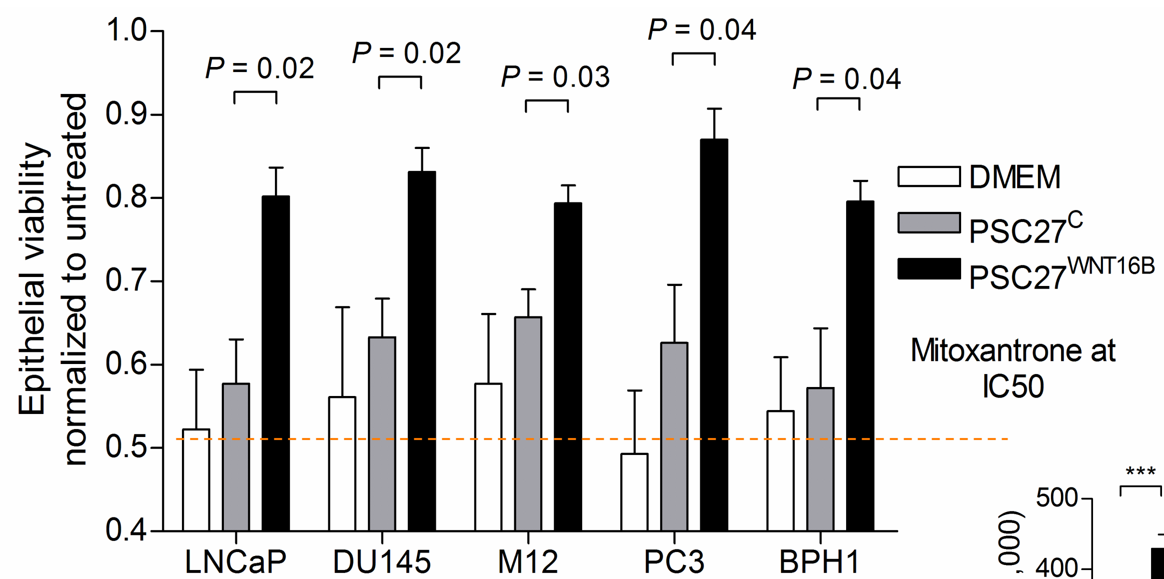
From the Richard Dimbleby Department of Cancer Research, St. Thomas's Hospital Medical School, London SE1 7EH

In experimental animals the growth of transplanted allogeneic and syngeneic tumours can be markedly enhanced by adding lethally irradiated (LI) tumour cells in excess to the implanted inoculum of intact, viable (V) tumour cells. This phenomenon was discovered by Révész (1956) who showed that it depended primarily on the metabolic activities of LI cells, and their production of diffusible metabolites *in situ* which conditioned the cellular micro-environment of V cells, and established a "milieu propitieux" for their growth. Subsequent studies of the

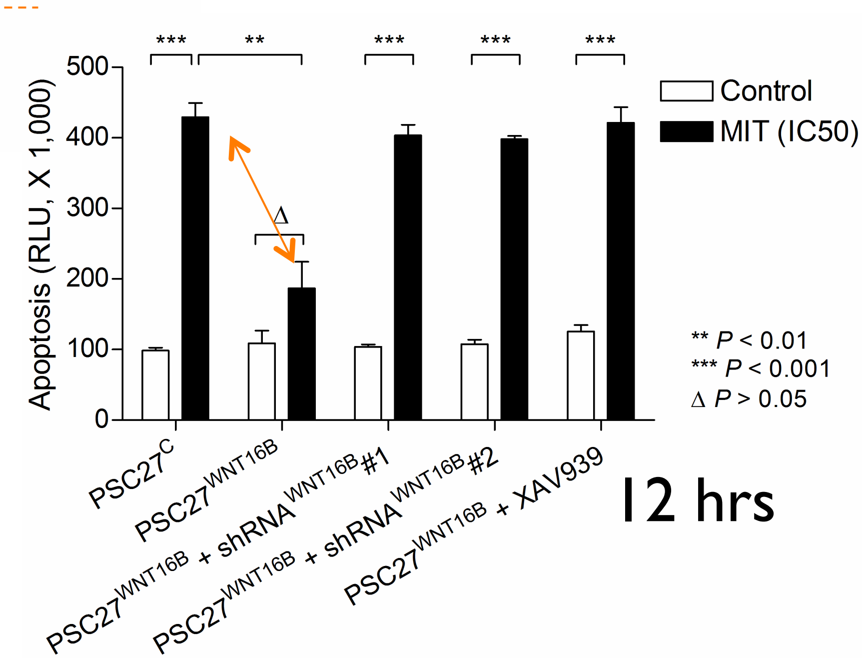
Revesz Effect + Corollaries

- ✓ Lethally-irradiated tumor cells reduced the number of non-irradiated tumor cells required to initiate a tumor…
- ✓ Lethally-irradiated tumor cells reduced the latency period of tumor growth…
- ✓ Irradiating the tumor bed (microenvironment conferred the same effects, and enhanced metastasis…
- ✓ Irradiated benign cells, co-implanted with tumor cells, conferred this effect

Prostate Cancer Cell Chemo-resistance is Enhanced by Paracrine-Acting WNT16B



72 hrs



12 hrs

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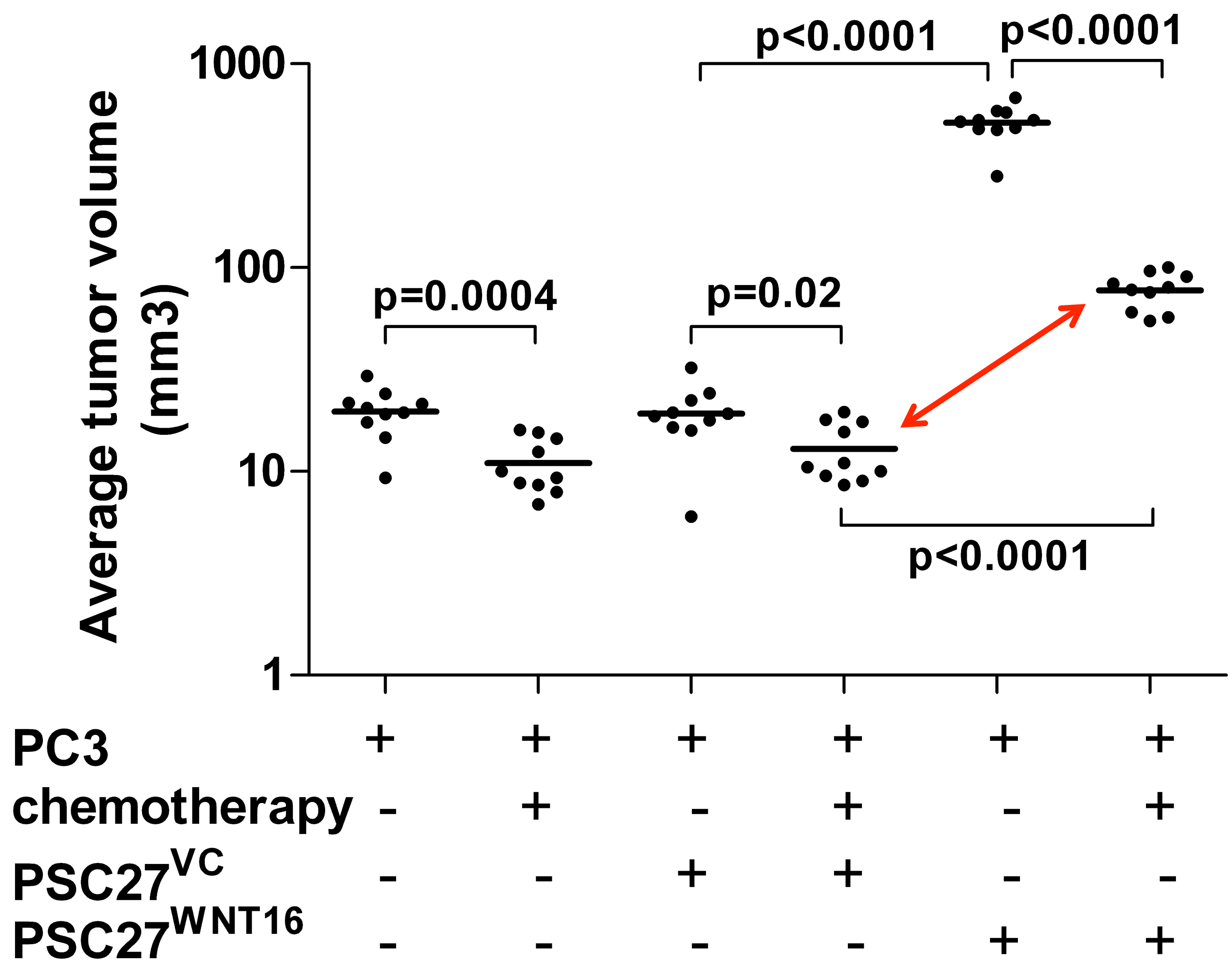
Prostate Cancer Chemo-resistance Enhanced by Paracrine-Acting WNT16B *In Vivo*



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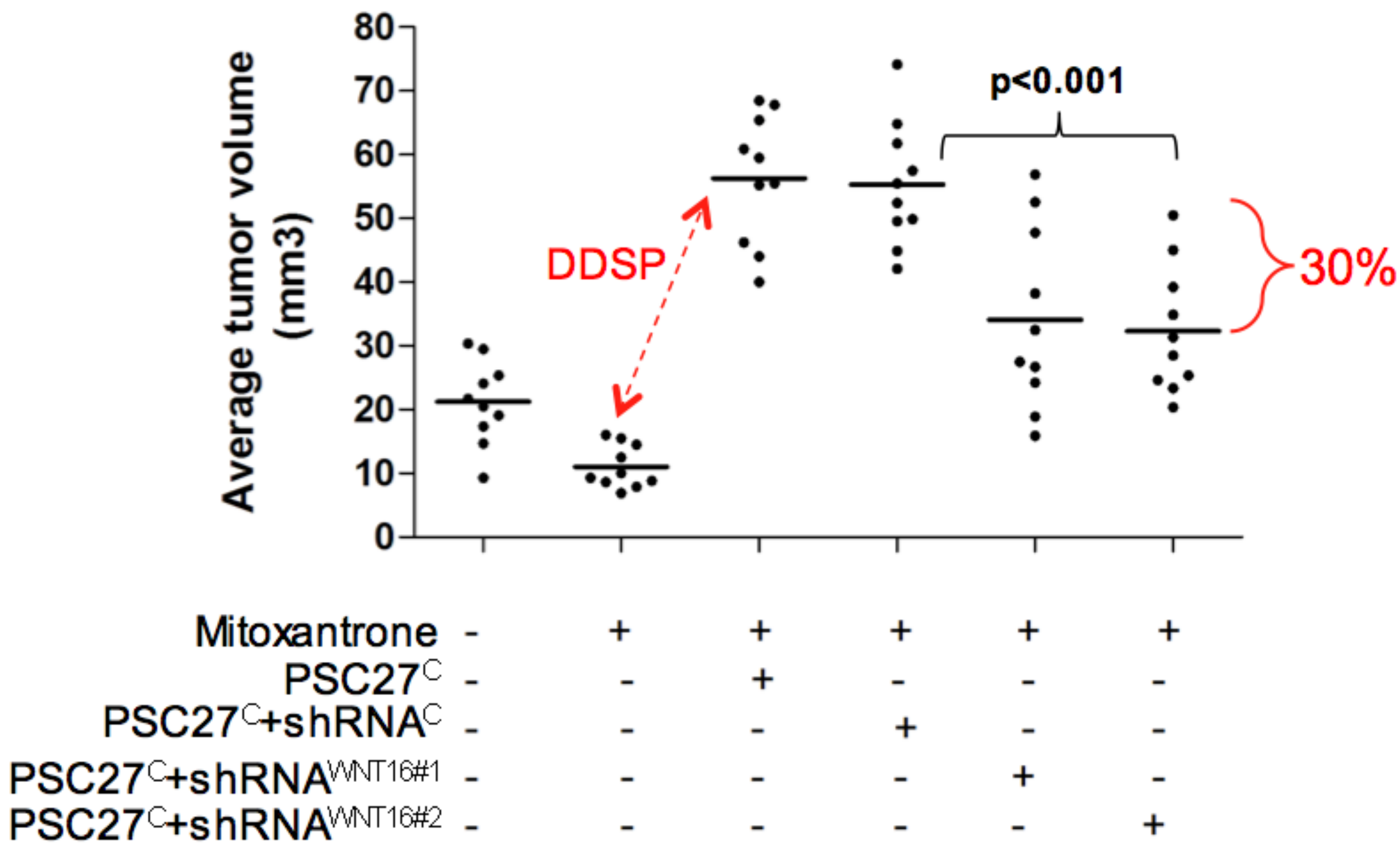
Suppression of the WNT16B contribution to the full DDSP attenuates the chemoprotective effect of the DDSP *In Vivo*



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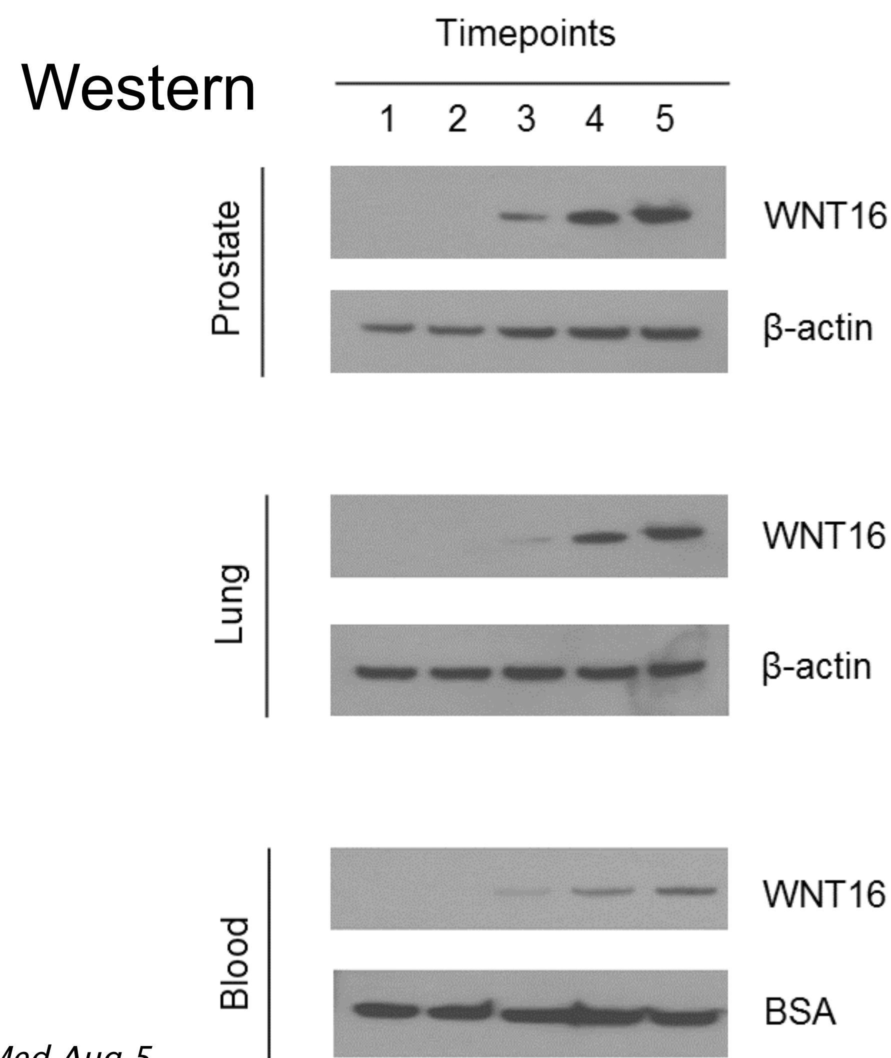
Enhanced Wnt16B expression in multiple organs of chemotherapy-treated mice



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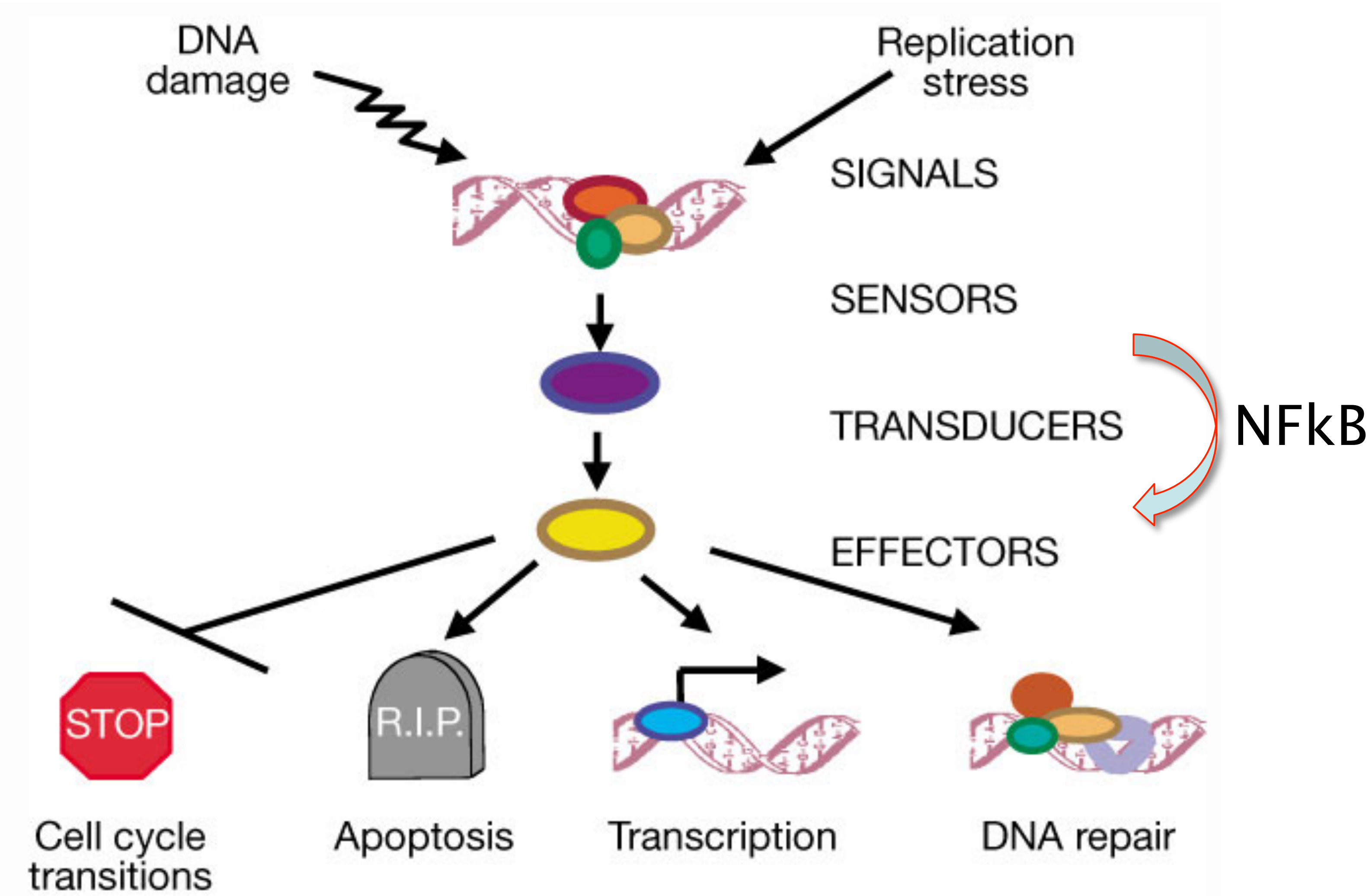
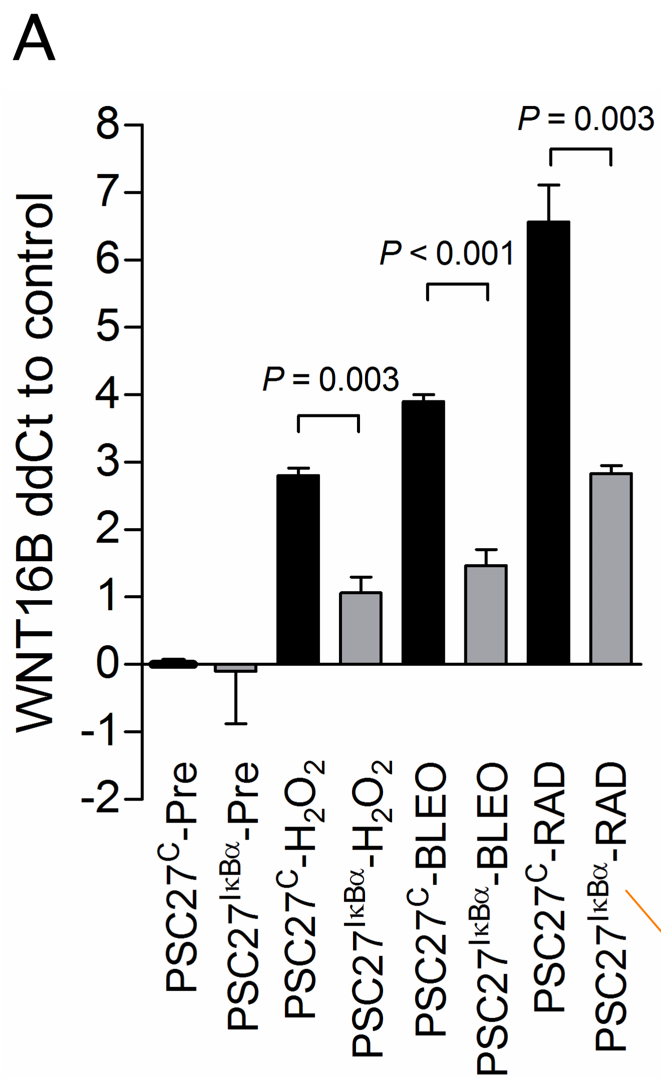
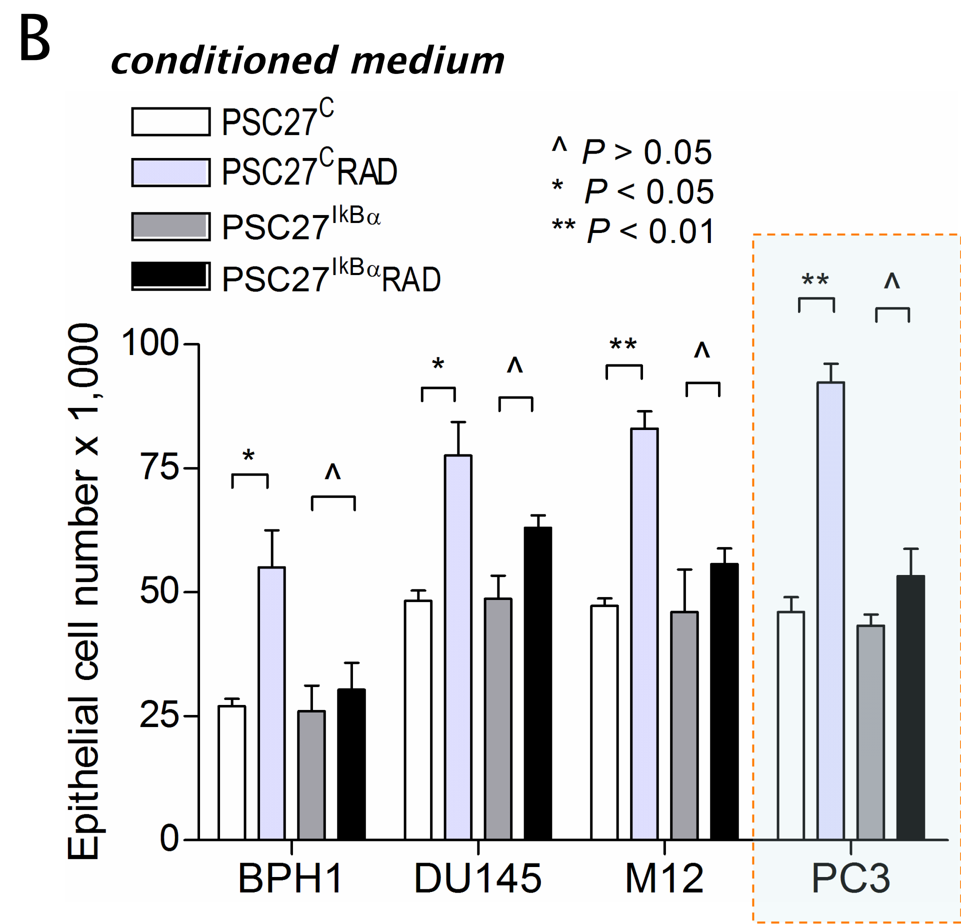
DDSP: Transduction of Damage to Effector Proteins



DNA Damage Induction of WNT16B Occurs Via NFkB





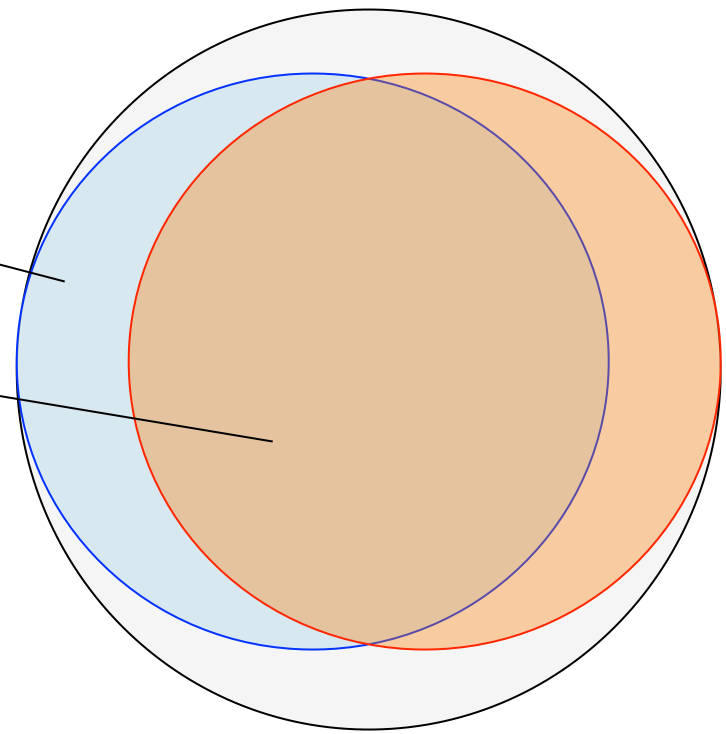
IκBα construct represses NFκB signaling…..

DDSP: Master Regulators?

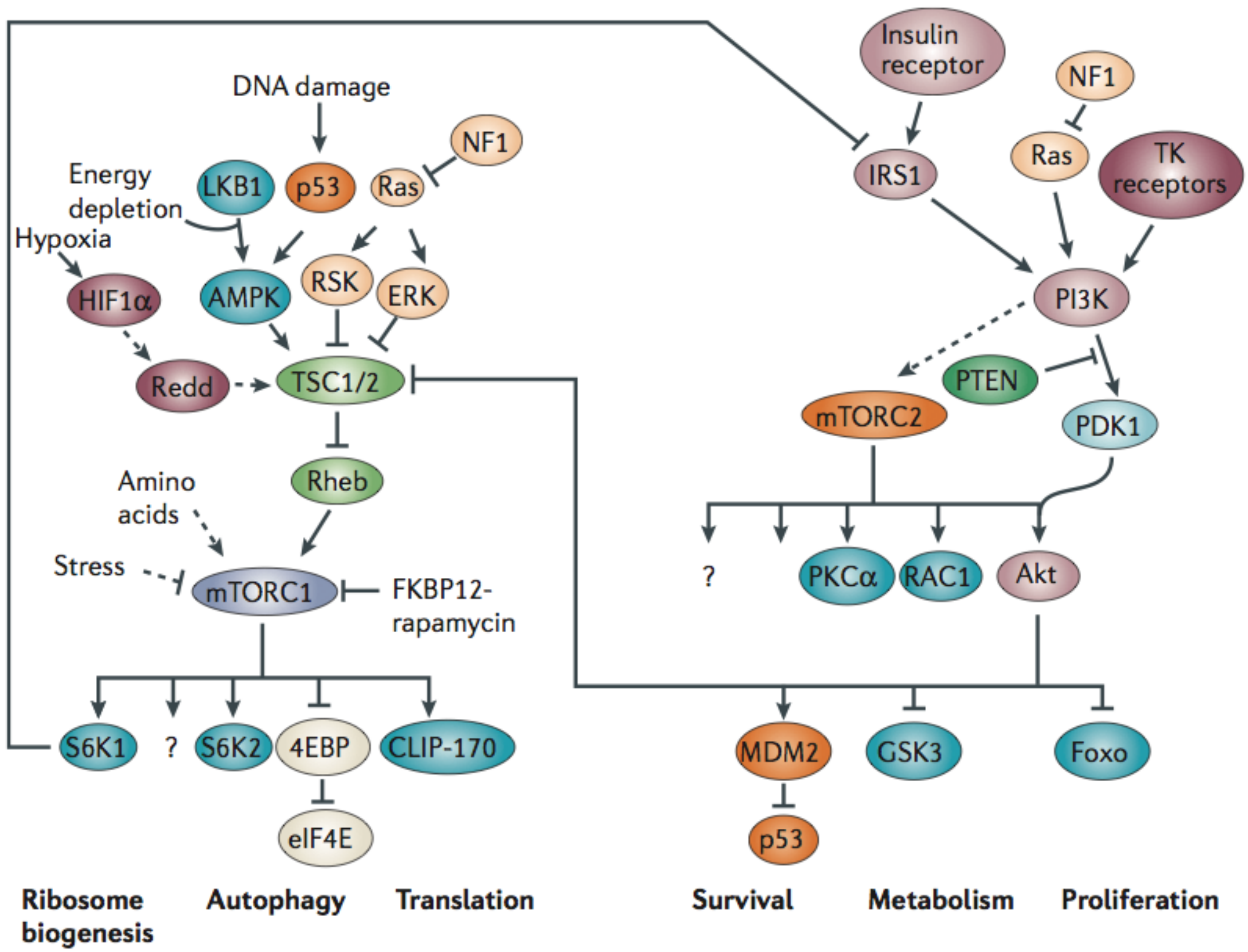
Focus on pathways that are verified or likely regulators of the DNA damage secretory response.

The target molecules will include the DDR proteins:

- ✓ ATM
- ✓ CHK2
- ✓ p38MAPK
- ✓ NFκB
- ✓ mTOR
- ✓ IL-1α
- ✓ HSP27?

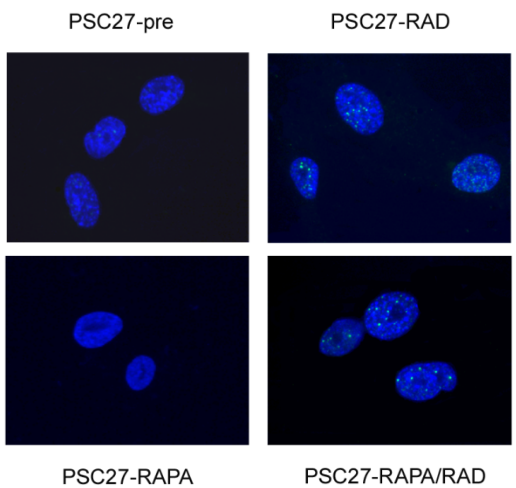


DDSP: Master Regulators?--mTOR

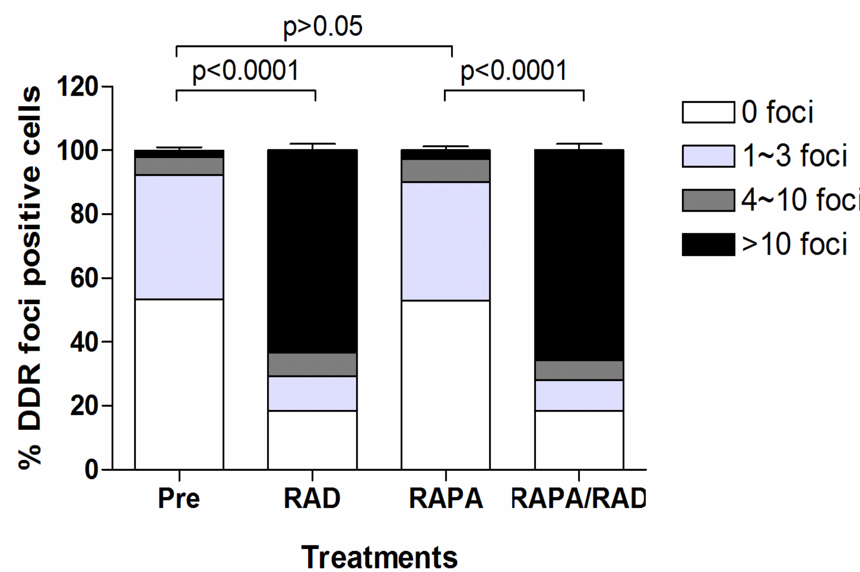


mTOR blockade with Rapamycin does not augment or inhibit DNA damage

IF staining for DNA double strand breaks



IF staining for DNA double strand breaks: Quantitation



Sun et al unpublished

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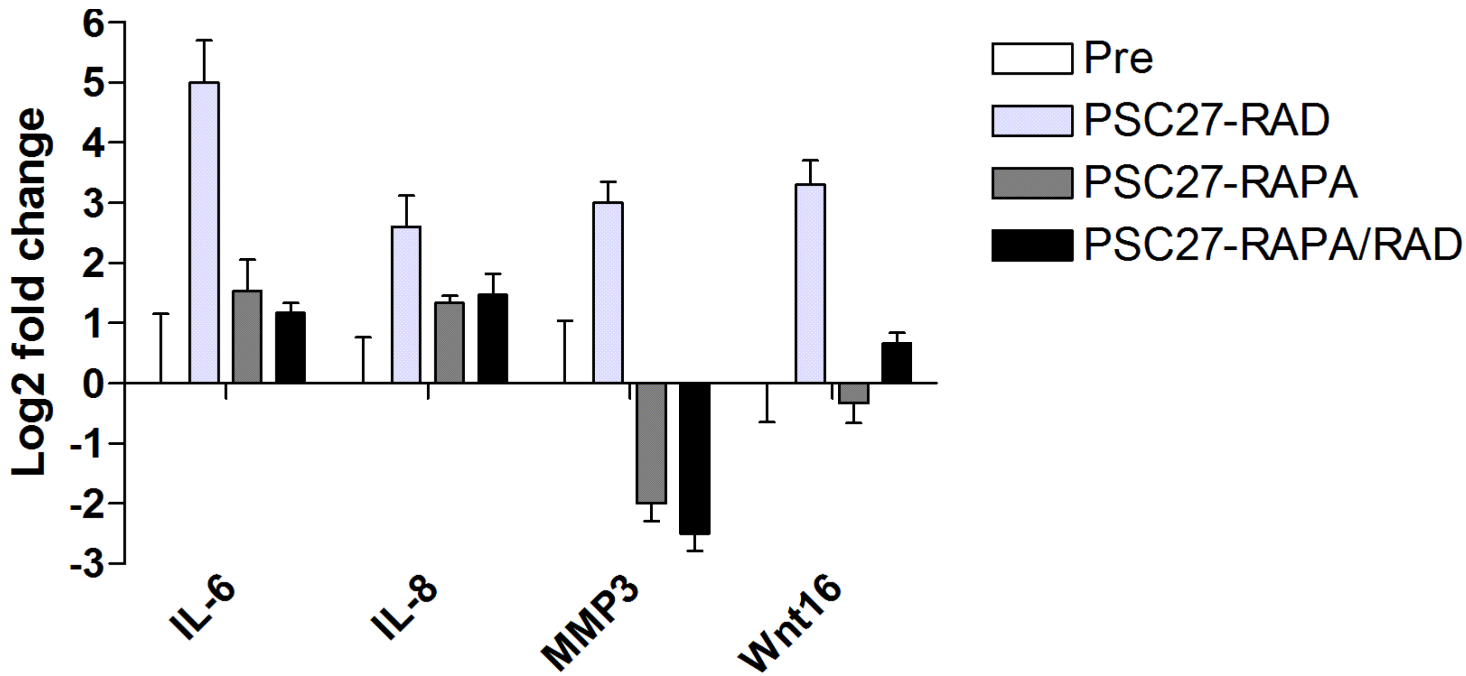
mTOR Blockade Largely Suppresses Key Effectors of the DNA Damage Secretory Program



DDSP Components

Sun et al unpublished

mTOR is an upstream regulator of the DDSP

control *XRT* *XRT+Rapamycin*

Probe ID	Entrez GeneID	Gene Symbol	Gene Name	C	XRT	X+R	C vs. XRT Fold	C vs. X+R Fold
A_32_P133072	10418	SPON1	spondin 1, extracellular matrix protein				76.7	-3.2
A_23_P7144	2919	CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)				54.0	10.6
A_24_P355246	5125	PCSK5	proprotein convertase subtilisin/kexin type 5				53.5	-2.9
A_23_P37727	6376	CX3CL1	chemokine (C-X3-C motif) ligand 1				49.2	1.7
A_23_P148088	2266	FGG	fibrinogen gamma chain				32.1	-2.3
A_23_P207456	6355	CCL8	chemokine (C-C motif) ligand 8				31.0	-2.0
A_23_P154605	55959	SULF2	sulfatase 2				26.8	-1.5
A_32_P223777	3572	IL6ST	interleukin 6 signal transducer (gp130, oncostatin M receptor)				24.7	9.3
A_23_P91390	7056	THBD	thrombomodulin				23.9	1.2
A_23_P11787	54361	WNT4	wingless-type MMTV integration site family, member 4				21.2	-6.0
A_32_P87013	3576	IL8	interleukin 8				20.3	5.9
A_23_P300033	5156	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide				19.2	2.5
A_23_P134601	51384	WNT16	wingless-type MMTV integration site family, member 16				17.4	-6.6
A_23_P136777	347	APOD	apolipoprotein D				16.4	1.1
A_23_P169819	2042	EPHA3	EPH receptor A3				16.3	5.7
A_23_P156087	2690	GHR	growth hormone receptor				16.0	1.7
A_23_P303671	1842	ECM2	extracellular matrix protein 2, female organ and adipocyte specific				15.8	-2.0
A_23_P317591	10371	SEMA3A	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A				15.6	4.5
A_23_P340698	4321	MMP12	matrix metallopeptidase 12 (macrophage elastase)				15.3	-2.5
A_24_P46130	55	ACPP	acid phosphatase, prostate				14.8	-1.5
A_23_P204630	59277	NTN4	netrin 4				14.2	-1.2
A_23_P166109	23767	FLRT3	fibronectin leucine rich transmembrane protein 3				13.6	2.9
A_24_P133253	4254	KITLG	KIT ligand				13.4	3.9
A_23_P148249	79875	THSD4	thrombospondin, type I, domain containing 4				13.2	2.8
A_24_P183150	2921	CXCL3	chemokine (C-X-C motif) ligand 3				13.0	2.3
A_23_P351667	8745	ADAM23	ADAM metallopeptidase domain 23				12.7	-1.1
A_32_P60065	2151	F2RL2	coagulation factor II (thrombin) receptor-like 2				12.7	3.0
A_23_P82929	4856	NOV	nephroblastoma overexpressed gene				12.6	1.7
A_23_P156880	5167	ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1				12.3	3.9
A_23_P219161	10439	OLFM1	olfactomedin 1				12.0	5.8
A_24_P935839	2898	GRIK2	glutamate receptor, ionotropic, kainate 2				11.7	2.7
A_23_P13094	4319	MMP10	matrix metallopeptidase 10 (stromelysin 2)				11.4	-4.5
A_24_P125335	6357	CCL13	chemokine (C-C motif) ligand 13				10.6	-1.2
A_23_P59807	7472	WNT2	wingless-type MMTV integration site family member 2				10.2	-14.4
A_23_P167920	28514	DLL1	delta-like 1 (Drosophila)				10.2	-3.3
A_23_P66635	6356	CCL11	chemokine (C-C motif) ligand 11				9.9	-4.3
A_23_P83028	8434	RECK	reversion-inducing-cysteine-rich protein with kazal motifs				9.8	4.0
A_23_P23705	54558	SPATA6	spermatogenesis associated 6				9.7	1.9
A_24_P110558	492311	C5orf53	chromosome 5 open reading frame 53				9.7	4.8
A_23_P115261	183	AGT	angiotensinogen (serpin peptidase inhibitor, clade A, member 8)				9.7	-1.8
A_23_P217737	538	ATP7A	ATPase, Cu++ transporting, alpha polypeptide				9.3	4.0
A_23_P31945	90865	IL33	interleukin 33				9.3	2.0
A_23_P425681	885	CCK	cholecystokinin				9.2	4.4
A_23_P121064	5806	PTX3	pentraxin 3, long				9.1	-1.0
A_23_P73114	5627	PROS1	protein S (alpha)				8.8	1.7
A_23_P253221	50649	ARHGEF4	Rho guanine nucleotide exchange factor (GEF) 4				8.6	3.1
A_23_P64617	8322	FZD4	frizzled homolog 4 (Drosophila)				8.6	1.1
A_23_P423331	84628	NTNG2	netrin G2				8.5	-1.1
A_23_P213745	9547	CXCL14	chemokine (C-X-C motif) ligand 14				7.8	1.3
A_23_P213562	2149	F2R	coagulation factor II (thrombin) receptor				7.8	3.6
A_23_P342275	9510	ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1				7.7	1.2
A_23_P119943	3485	IGFBP2	insulin-like growth factor binding protein 2, 36kDa				7.7	-8.3
A_24_P220485	169611	OLFML2A	olfactomedin-like 2A				7.2	-2.9
A_23_P124084	4016	LOXL1	lysyl oxidase-like 1				6.9	4.0
A_24_P295010	5272	SERPINB9	serpin peptidase inhibitor, clade B (ovalbumin), member 9				6.8	1.6
A_23_P57709	26577	PCOLCE2	procollagen C-endopeptidase enhancer 2				6.8	-2.5
A_23_P114740	3075	CFH	complement factor H				6.7	-1.9
A_23_P315364	2920	CXCL2	chemokine (C-X-C motif) ligand 2				6.6	1.3
A_23_P301304	2260	FGFR1	fibroblast growth factor receptor 1				6.6	3.9

Rapamycin blocks major components of the DDSP

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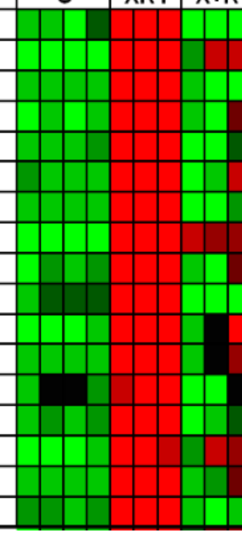
Red=induced by DNA damage…

DDSP: Master Regulators?--mTOR

Probe ID	Entrez GeneID	Gene Symbol	Gene Name	C	XRT	X+R	C vs. XRT Fold	C vs. X+R Fold
A_32_P133072	10418	SPON1	spondin 1, extracellular matrix protein				76.7	-3.2
A_23_P7144	2919	CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)				54.0	10.6
A_24_P355246	5125	PCSK5	proprotein convertase subtilisin/kexin type 5				53.5	-2.9
A_23_P37727	6376	CX3CL1	chemokine (C-X3-C motif) ligand 1				49.2	1.7
A_23_P148088	2266	FGG	fibrinogen gamma chain				32.1	-2.3
A_23_P207456	6355	CCL8	chemokine (C-C motif) ligand 8				31.0	-2.0
A_23_P154605	55959	SULF2	sulfatase 2				26.8	-1.5
A_32_P223777	3572	IL6ST	interleukin 6 signal transducer (gp130, oncostatin M receptor)				24.7	9.3
A_23_P91390	7056	THBD	thrombomodulin				23.9	1.2
A_23_P11787	54361	WNT4	wingless-type MMTV integration site family, member 4				21.2	-6.0
A_32_P87013	3576	IL8	interleukin 8				20.3	5.9
A_23_P300033	5156	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide				19.2	2.5
A_23_P134601	51384	WNT16	wingless-type MMTV integration site family, member 16				17.4	-6.6
A_23_P136777	347	APOD	apolipoprotein D				16.4	1.1
A_23_P169819	2042	EPHA3	EPH receptor A3				16.3	5.7
A_23_P156087	2690	GHR	growth hormone receptor				16.0	1.7
A_23_P303671	1842	ECM2	extracellular matrix protein 2, female organ and adipocyte specific				15.8	-2.0



Rapamycin

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DDSP: Master Regulators?--mTOR

Probe ID	Entrez GeneID	Gene Symbol	Gene Name	C	XRT	X+R	C vs. XRT Fold	C vs. X+R Fold
A_32_P225659	257313	UTS2D	urotensin 2 domain containing				71.9	56.4
A_23_P363034	116236	ABHD15	abhydrolase domain containing 15				28.5	23.2
A_23_P359630	5343	PLGLB1	plasminogen-like B1				23.1	37.0
A_23_P429950	3730	KAL1	Kallmann syndrome 1 sequence				22.7	15.2
A_23_P4161	22901	ARSG	arylsulfatase G				16.8	16.9
A_24_P937405	11098	PRSS23	protease, serine, 23				16.7	8.9
A_24_P205994	255324	EPGN	epithelial mitogen homolog (mouse)				13.1	15.9
A_24_P413941	205327	C2orf69	chromosome 2 open reading frame 69				10.7	8.0
A_23_P214079	6690	SPINK1	serine peptidase inhibitor, Kazal type 1				10.6	9.3
A_23_P218918	2247	FGF2	fibroblast growth factor 2 (basic)				10.3	15.4
A_23_P218858	25890	ABI3BP	ABI family, member 3 (NESH) binding protein				8.6	12.9
A_23_P215634	3486	IGFBP3	insulin-like growth factor binding protein 3				8.1	7.0
A_24_P325992	3977	LIFR	leukemia inhibitory factor receptor alpha				8.0	5.8
A_24_P787897	64131	XYLT1	xylosyltransferase I				7.9	11.1
A_23_P23611	278	AMY1C	amylase, alpha 1C (salivary)				7.5	5.4
A_23_P258136	25878	MXRA5	matrix-remodelling associated 5				7.3	5.2
A_23_P24129	22943	DKK1	dickkopf homolog 1 (Xenopus laevis)				7.3	5.9

Rapamycin

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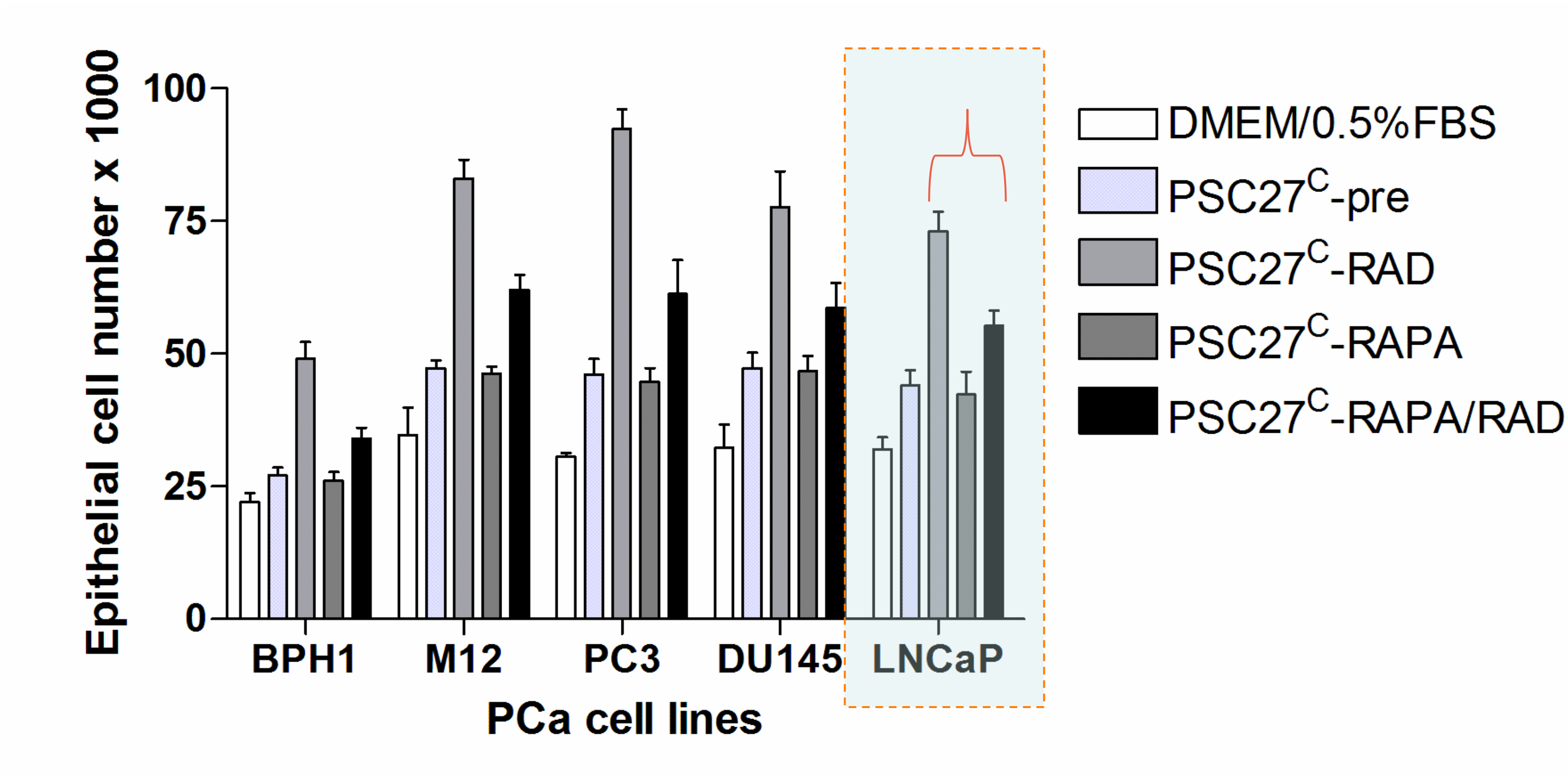
DDSP: Master Regulators?--mTOR

Probe ID	Entrez GeneID	Gene Symbol	Gene Name	C	XRT	X+R	C vs. XRT Fold	C vs. X+R Fold
A_24_P784765	966	CD59	CD59 molecule, complement regulatory protein				15.5	33.7
A_24_P181254	10562	OLFM4	olfactomedin 4				15.0	220.4
A_23_P214821	1906	EDN1	endothelin 1				13.1	61.8
A_23_P126836	7292	TNFSF4	tumor necrosis factor (ligand) superfamily, member 4				11.1	84.6
A_23_P94754	9966	TNFSF15	tumor necrosis factor (ligand) superfamily, member 15				11.0	36.5
A_24_P535256	3624	INHBA	inhibin, beta A				8.9	18.4
A_24_P158946	121512	FGD4	FYVE, RhoGEF and PH domain containing 4				6.9	22.7
A_32_P313405	284217	LAMA1	laminin, alpha 1				5.9	10.9
A_24_P234116	54964	C1orf56	chromosome 1 open reading frame 56				5.7	8.9
A_23_P130158	7473	WNT3	wingless-type MMTV integration site family, member 3				5.5	14.3
A_23_P404494	3575	IL7R	interleukin 7 receptor				5.2	8.2
A_24_P290585	55075	UACA	uveal autoantigen with coiled-coil domains and ankyrin repeats				4.3	9.4
A_24_P111106	2246	FGF1	fibroblast growth factor 1 (acidic)				3.3	5.9
A_32_P5040	388677	NOTCH2NL	notch 2 N-terminal like				3.3	5.6
A_32_P171043	147372	CCBE1	collagen and calcium binding EGF domains 1				3.2	5.7
A_32_P148345	302	ANXA2	annexin A2				3.1	4.8
A_23_P1331	1305	COL13A1	collagen, type XIII, alpha 1				3.1	8.9

Rapamycin

Sun et al unpublished

Enhanced epithelial cell proliferation induced by DNA damage to fibroblasts (PSC27-RAD) is attenuated by treatment of fibroblasts with Rapamycin (RAPA/RAD)



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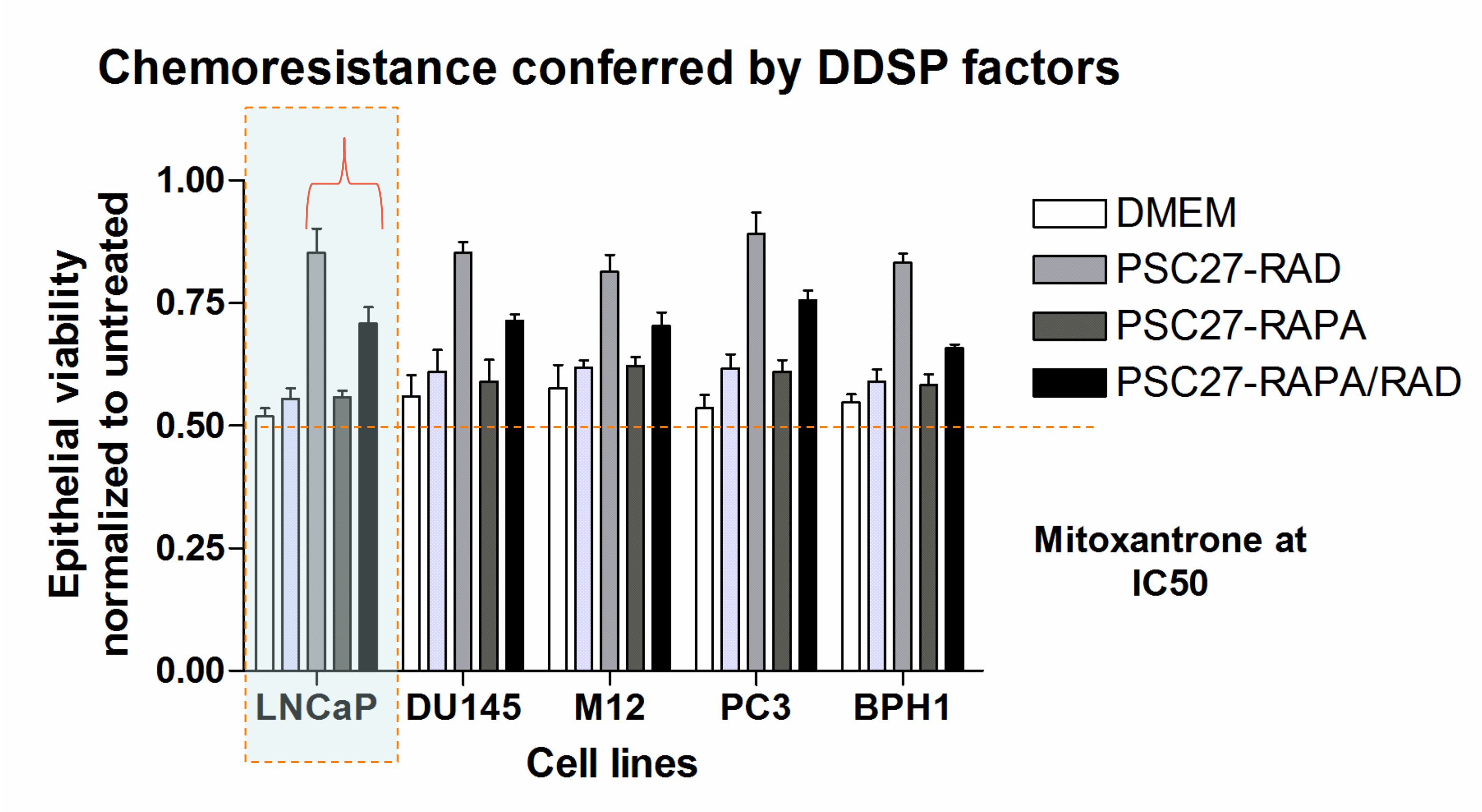
Resistance to chemotherapy conferred by the DDSP from prostate fibroblasts (PSC27-RAD) is attenuated by pre-treatment of fibroblasts with Rapamycin (RAPA/RAD)



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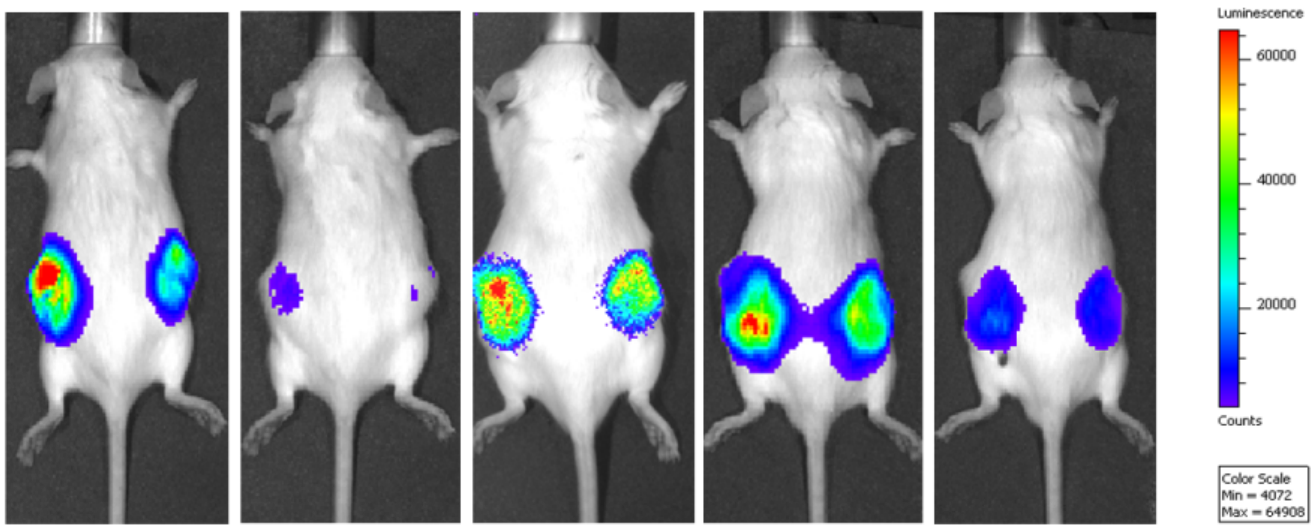
Prostate Cancer Xenografts: Tumor Epithelium +/- Prostate Fibroblasts (PSC27)

1. Fibroblasts induce prostate cancer resistance to systemic chemotherapy

2. Inhibition of the fibroblast DDSP with rapamycin attenuates prostate cancer chemotherapy resistance



PC3	+	+	+	+	+
PSC27	–	–	+	+	+
Chemo	–	+	–	+	+
RAPA	–	–	–	–	+

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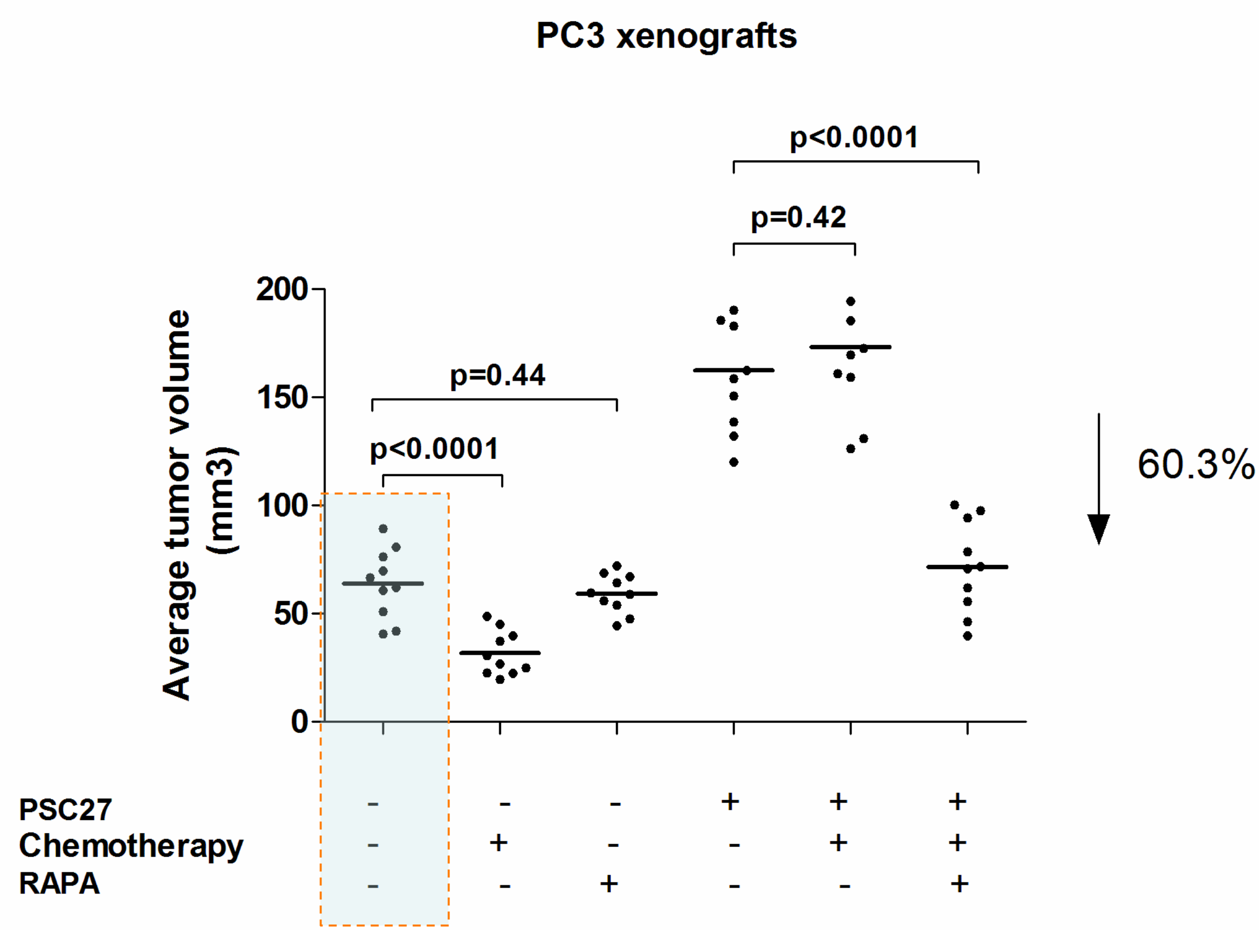
Diminished chemoresistance of prostate tumor xenografts by rapamycin administration



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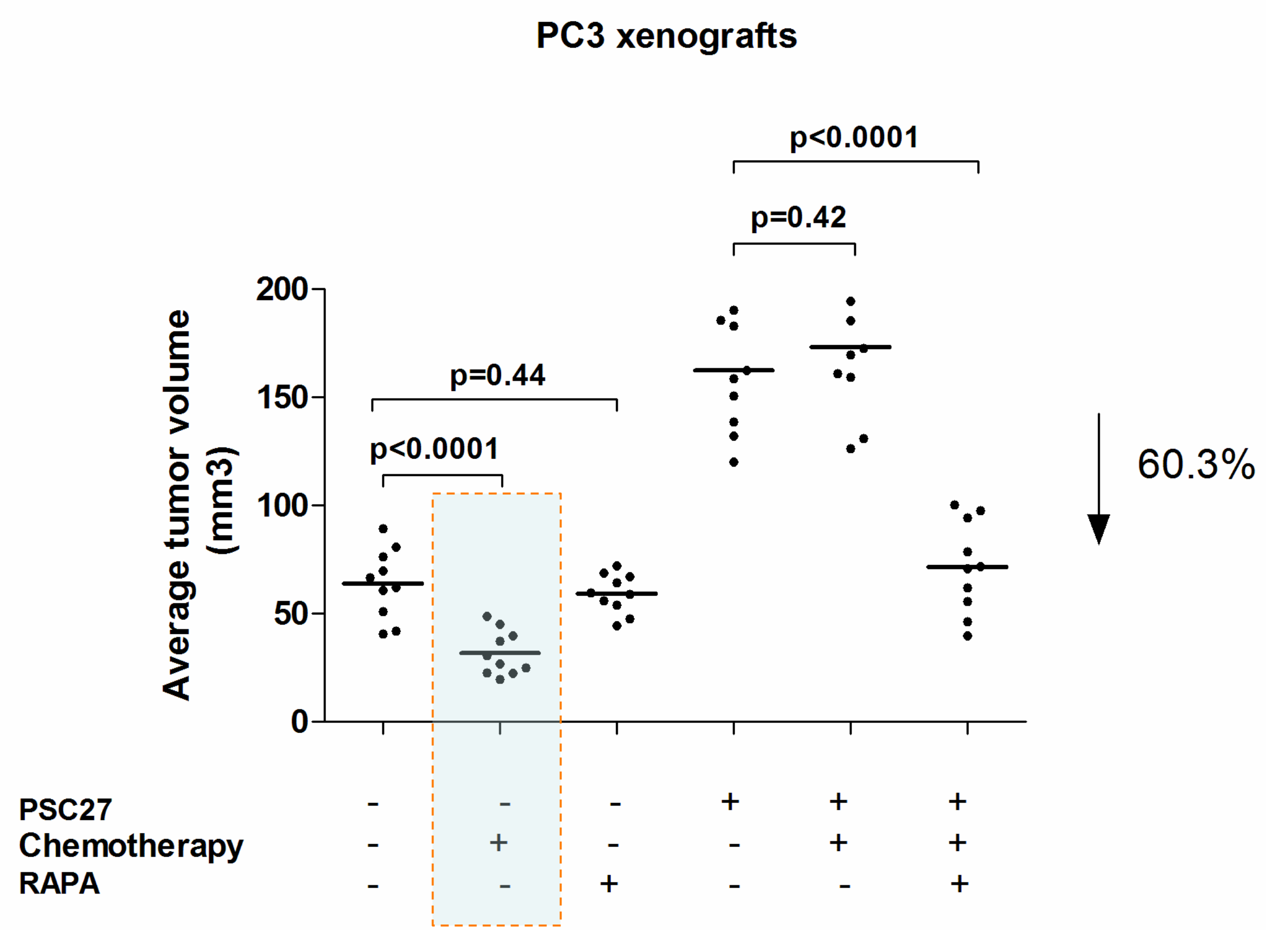
Tumor cells alone

Diminished chemoresistance of prostate tumor xenografts by rapamycin administration



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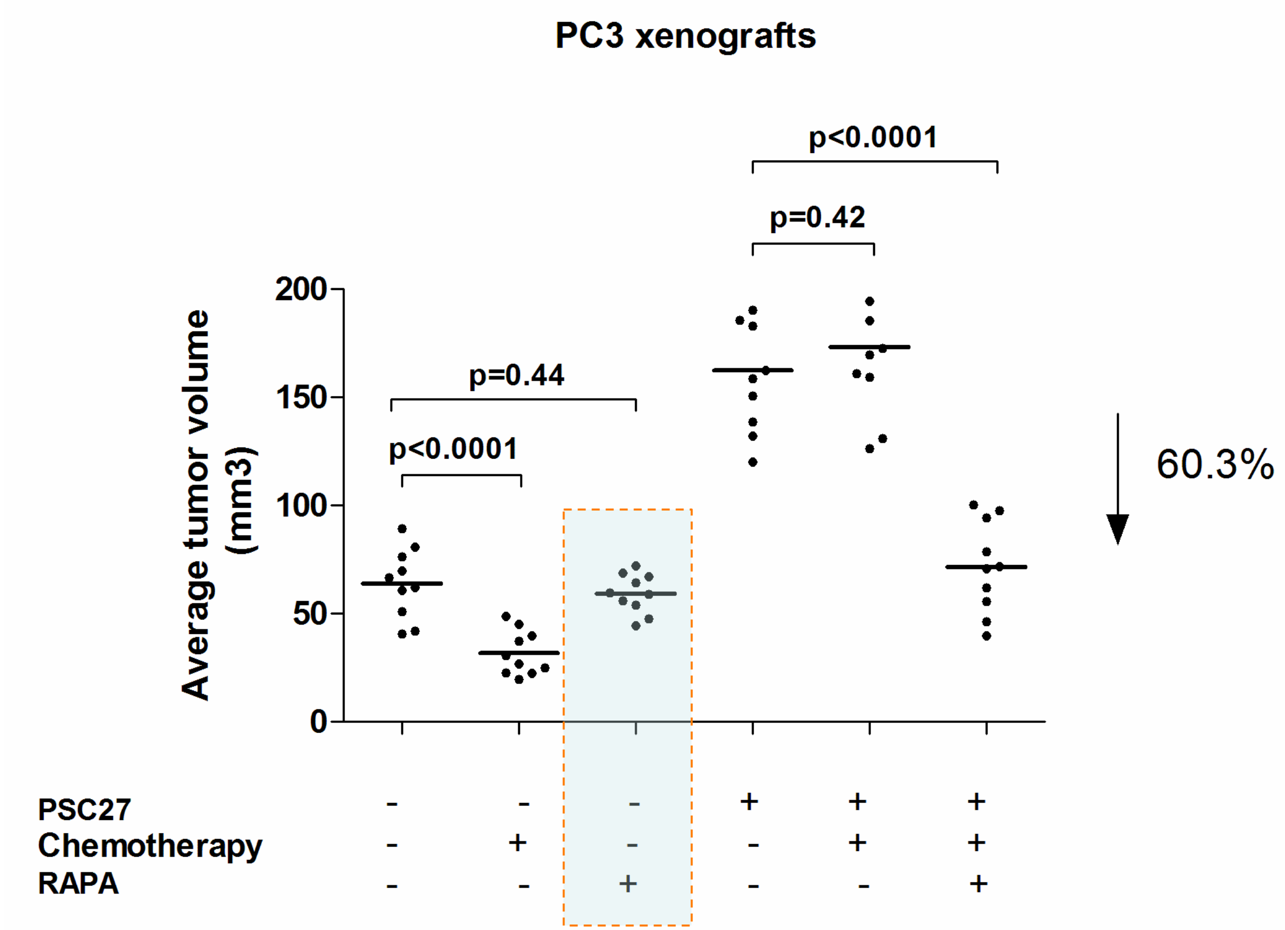
Tumor cells + chemotherapy

Diminished chemoresistance of prostate tumor xenografts by rapamycin administration



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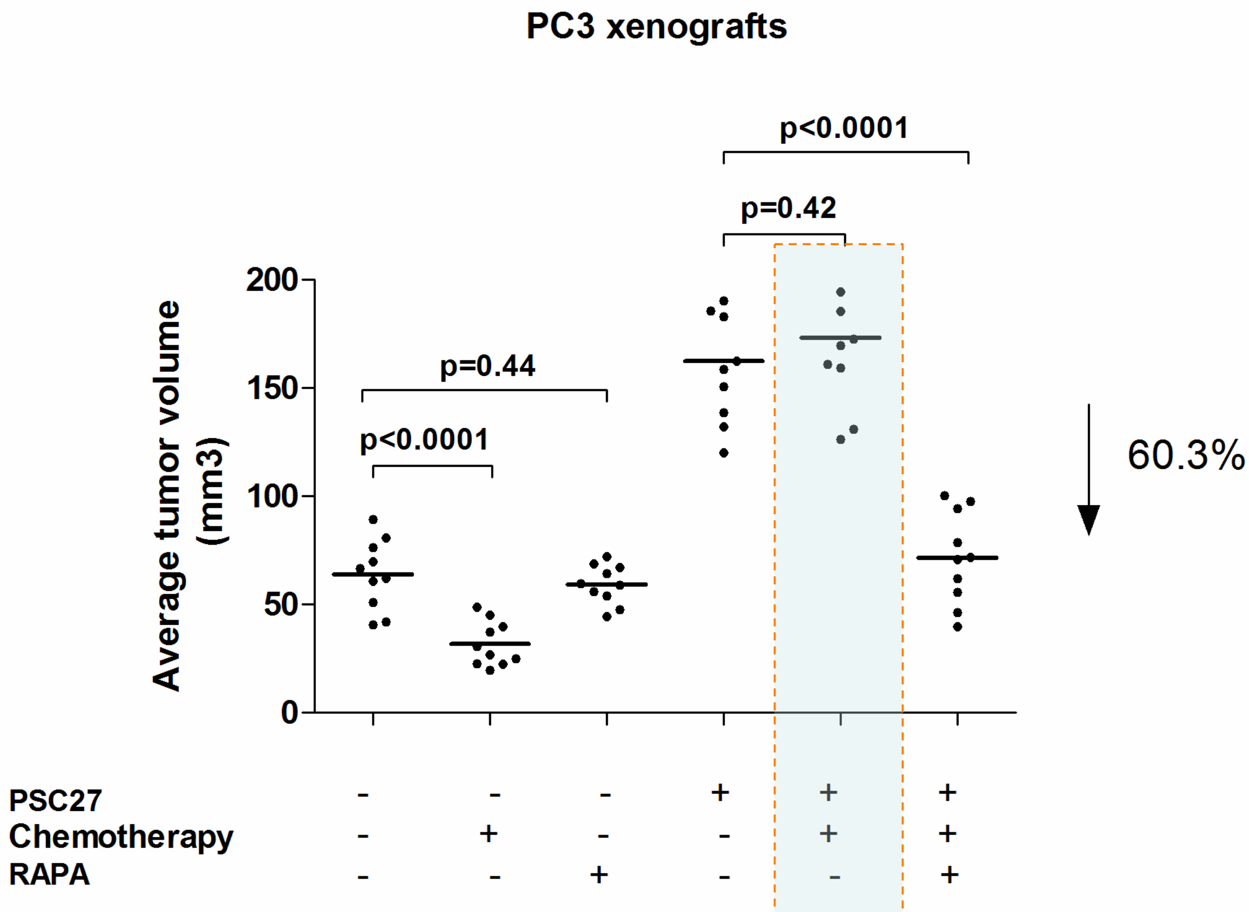
No RAPA Effect

Diminished chemoresistance of prostate tumor xenografts by rapamycin administration



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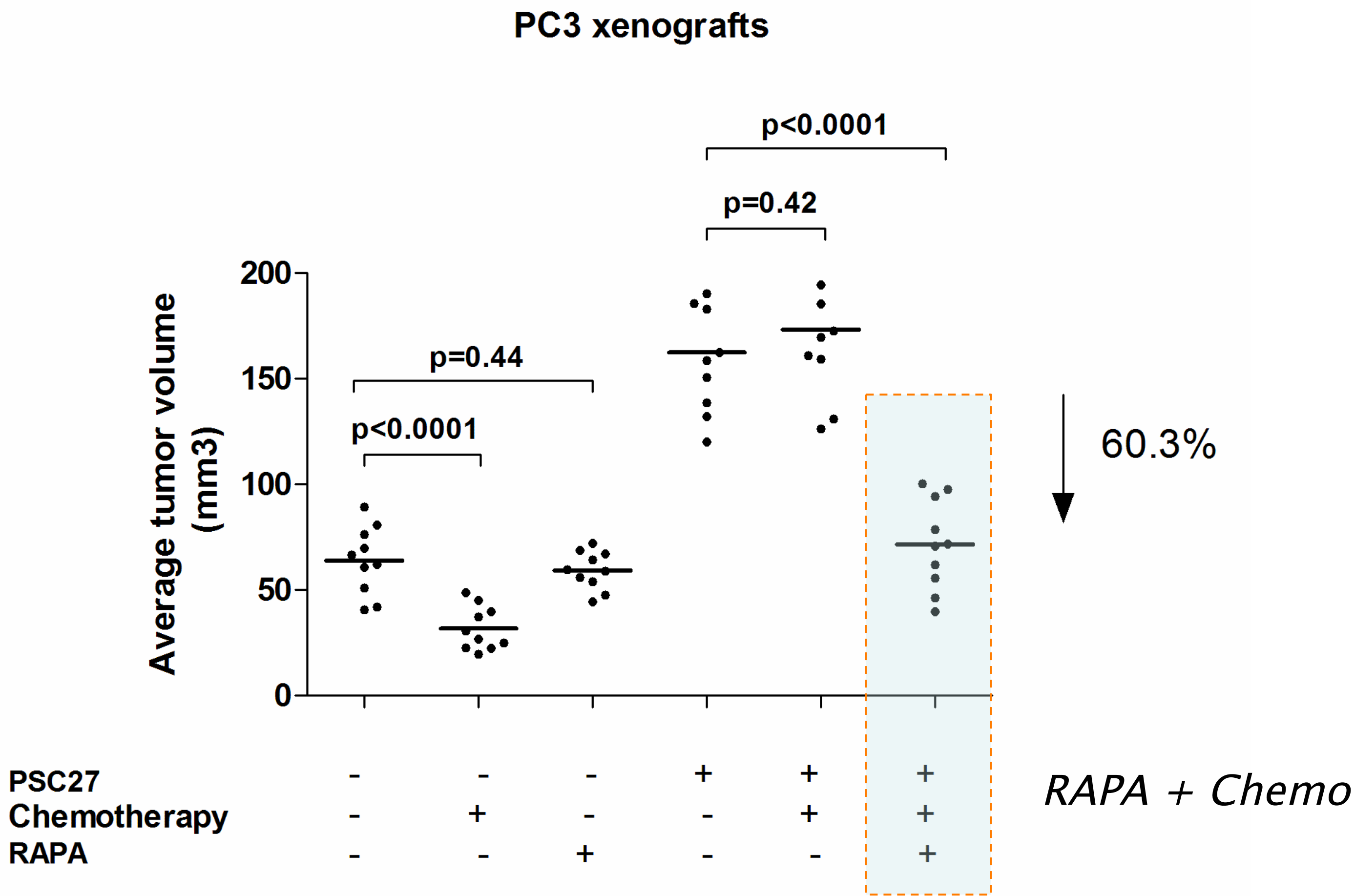
Tumor cells+Fibroblasts+Chemo

Diminished chemoresistance of prostate tumor xenografts by rapamycin administration



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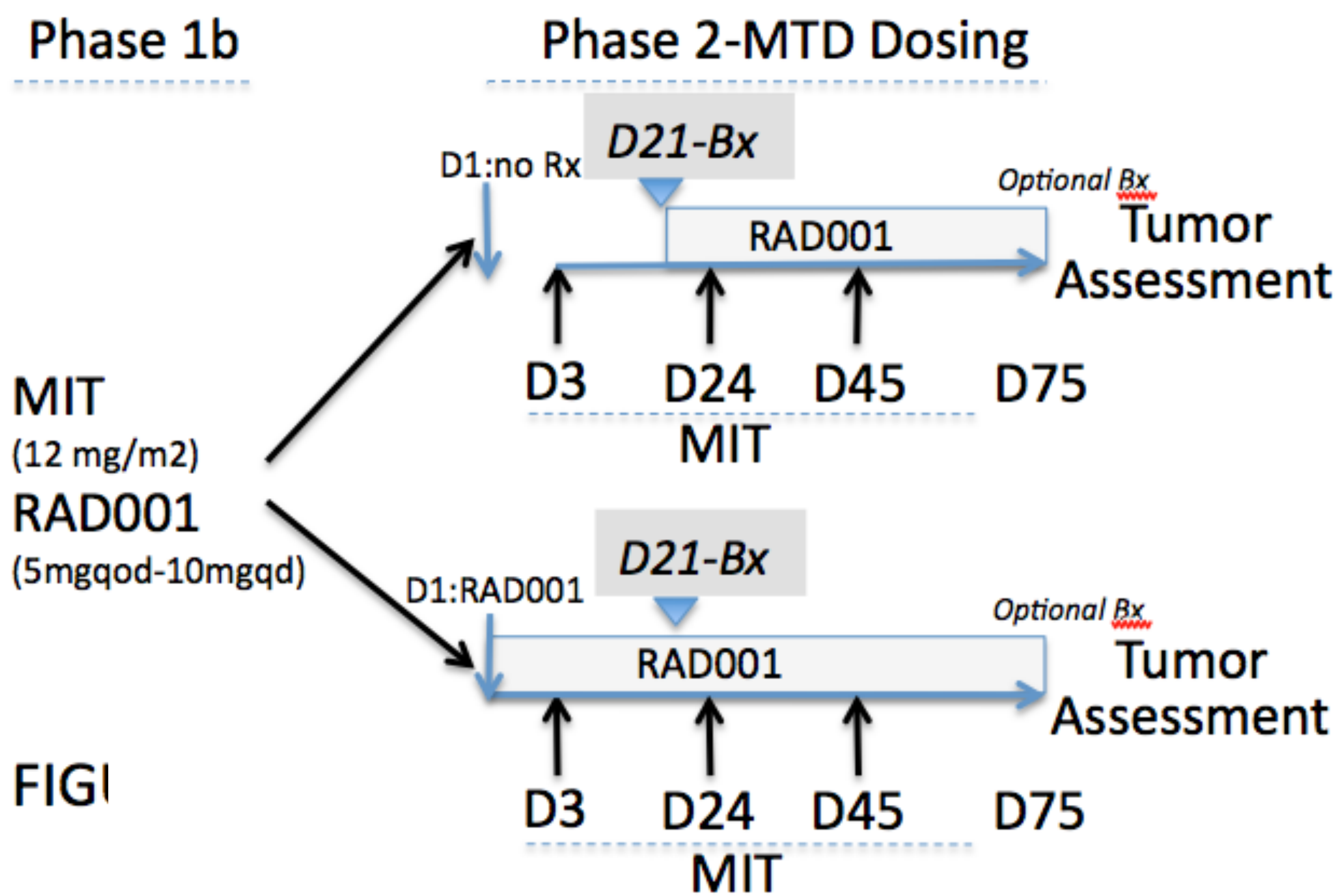
Clinical Trial: Co-Targeting Microenvironment Damage Response Signals



SUMMARY

- DNA Damage results in a reproducible and expansive gene expression program that includes paracrine mediators of epithelial growth (e.g. AREG, HGF, WNT16B…).

- The fibroblast DDSP includes a spectrum of secreted cytokines and chemokines that modulate immune cell function (e.g. IL6, IL8, CXCL2… WNT16B?).

- The DDSP may contribute to therapy resistance through multiple mechanisms:
  - ✓EMT
  - ✓Resistance to apoptosis
  - ✓Angiogenesis
  - ✓Enhanced tumor cell proliferation/tumor repopulation
  - ✓Modulation of tumor immunity

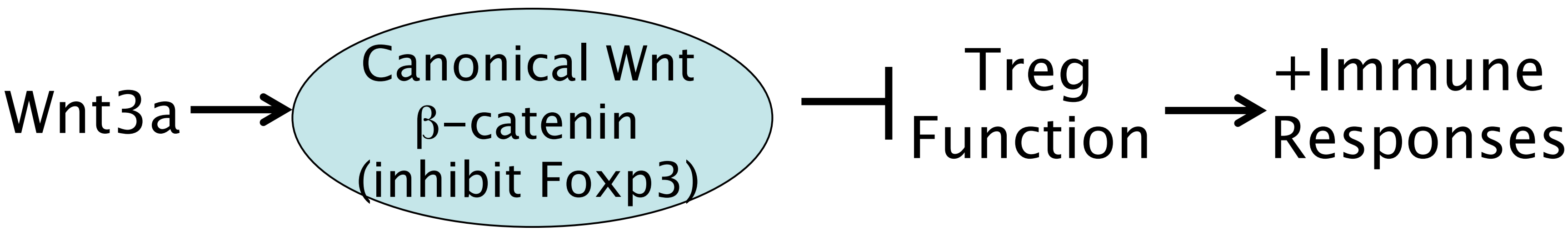
Complexities in Modulating Microenvironments…

Cell PRESS

Immunity
Article

Canonical Wnt Signaling Negatively Modulates Regulatory T Cell Function

Jorg van Loosdregt,[1,2,3] Veerle Fleskens,[1,3] Machteld M. Tiemessen,[8] Michal Mokry,[4] Ruben van Boxtel,[3] Jenny Meerding,[2,5] Cornelieke E.G.M. Pals,[1,3] Dorota Kurek,[9] Miranda R.M. Baert,[8] Eveline M. Delemarre,[2,5] Andrea Gröne,[10] Marianne J.A. Groot Koerkamp,[6] Alice J.A.M. Sijts,[11] Edward E.S. Nieuwenhuis,[4] Madelon M. Maurice,[3] Johan H. van Es,[7] Derk ten Berge,[9] Frank C. Holstege,[6] Frank J.T. Staal,[8] Dietmar M.W. Zaiss,[11] Berent J. Prakken,[2,5] and Paul J. Coffer[1,2,3,*]



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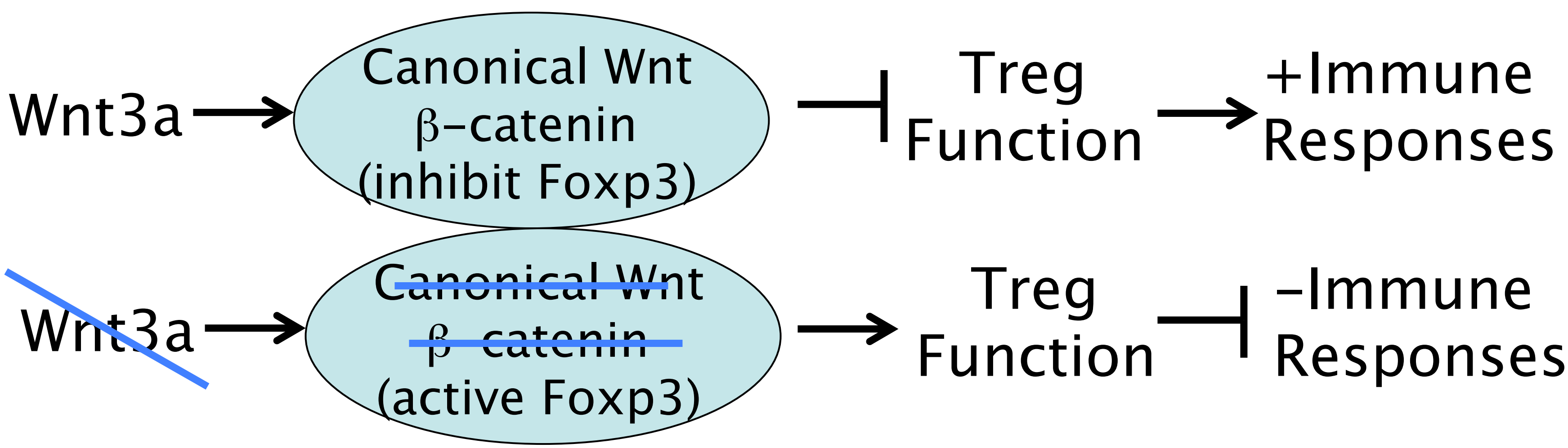

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Complexities in Modulating Microenvironments…

Cell PRESS

Immunity
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Wnt3a → Canonical Wnt β-catenin (inhibit Foxp3) ⊣ Treg Function → +Immune Responses

~~Wnt3a~~ → ~~Canonical Wnt~~ ~~β-catenin~~ (active Foxp3) → Treg Function ⊣ −Immune Responses

WNT16b → ??

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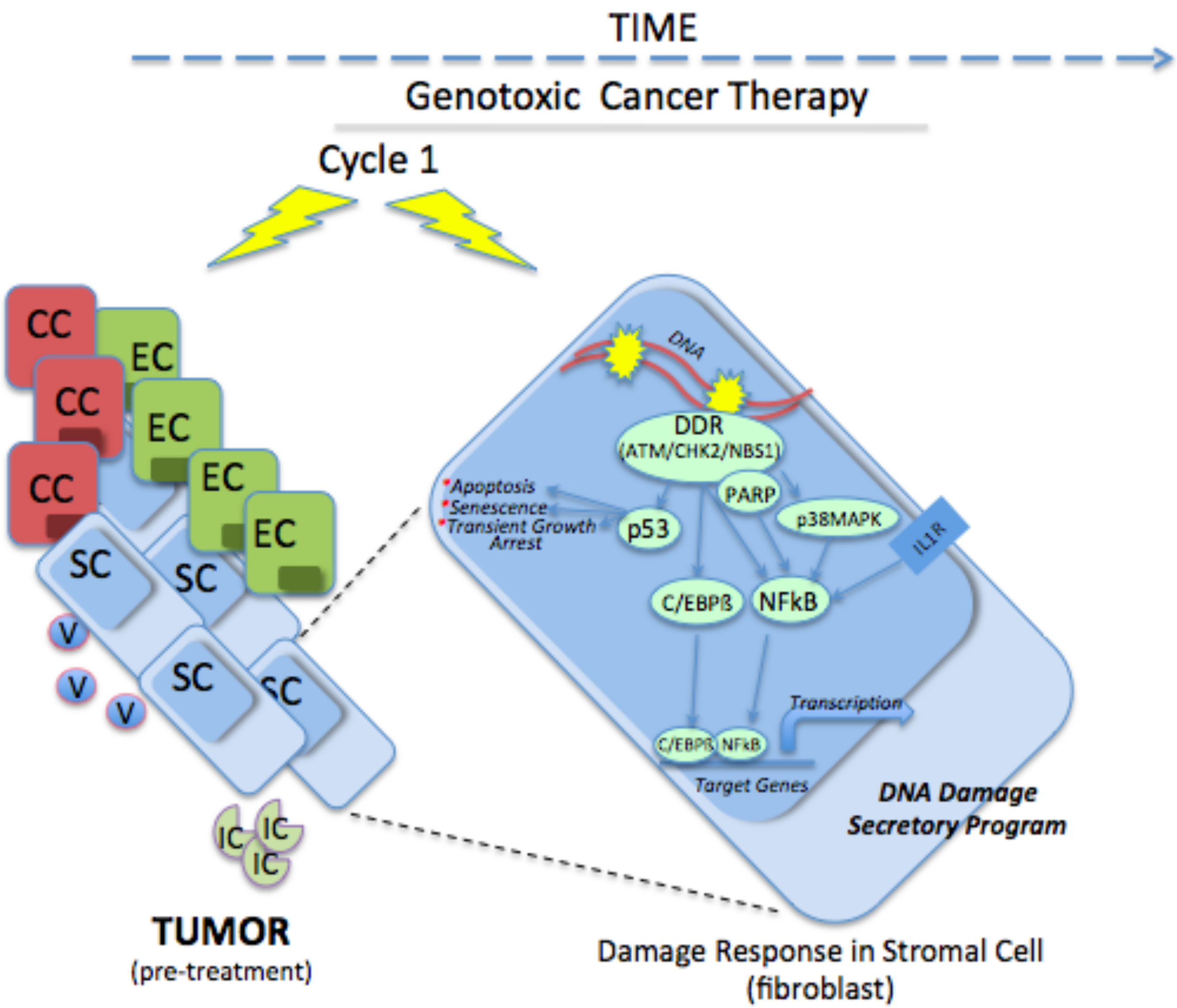
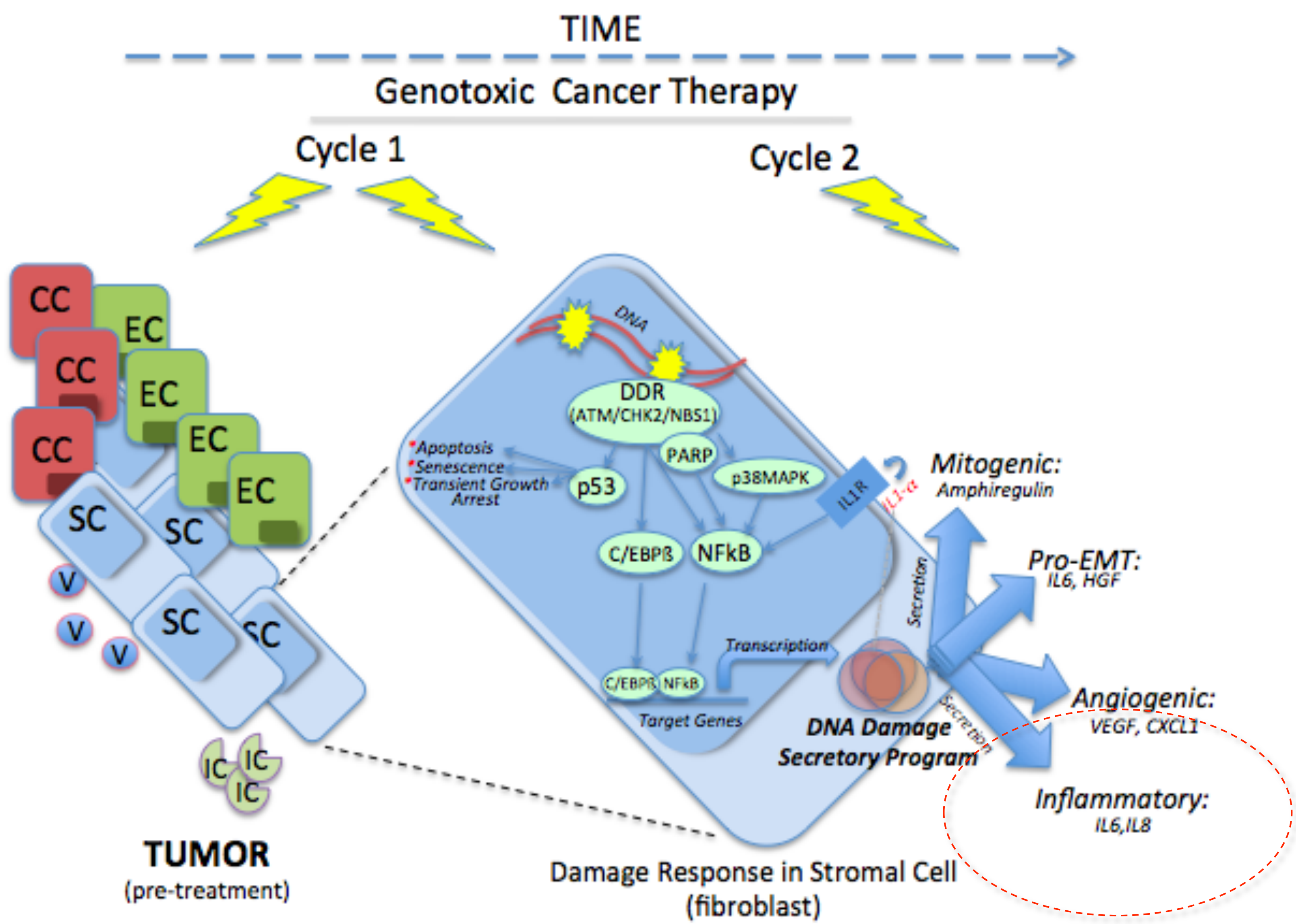
Effects of Cytotoxic Cancer Therapeutics on Benign Cells Comprising the Tumor Microenvironment



Sun and Nelson *Clin Cancer Res*. 2012 Aug 1;18(15):4019-25.



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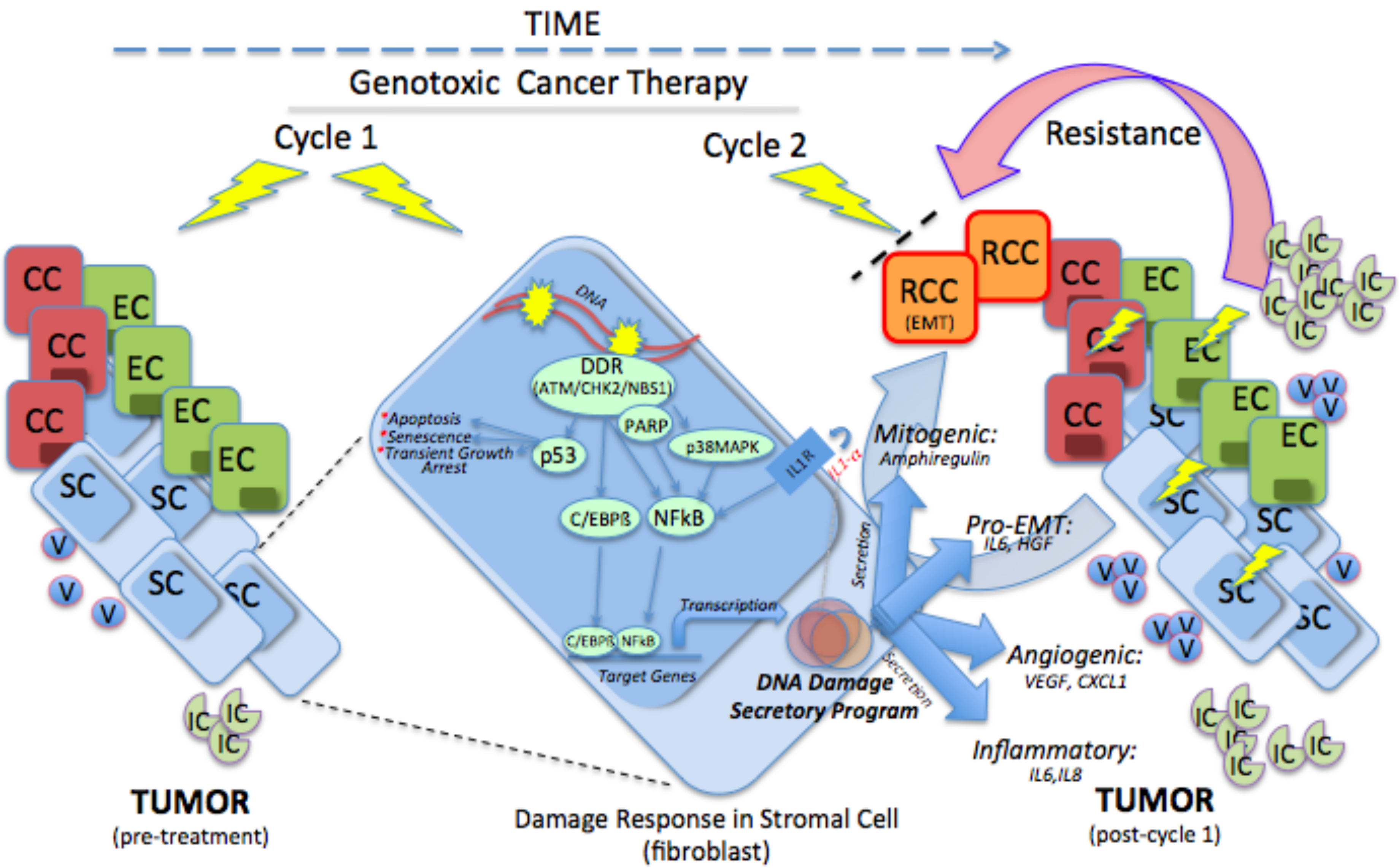

Sun and Nelson *Clin Cancer Res*. 2012 Aug 1;18(15):4019–25.

Key Questions/Directions

✓What are the key initiators and effectors of the DNA Damage program?

✓Is the DNA damage program (and DDSP) the same in every tissue? Every cell?

✓What contributes to the inter-individual variation in the microenvironment DDSP ?

✓Does the therapy-induced DNA Damage/stress program contribute substantially to treatment resistance? Can it be modified to enhance responses?

✓What is the *composite* effect of the DDSP on tumor cells versus immune responses

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Tom Beer–OHSU

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Larry True
Bob Vessella
May Reed
Steve Plymate

NCI TMEN; NCI PNW Prostate SPORE; PCF; DOD