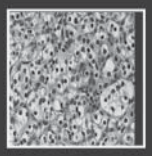
Pomegranates, Polyphenols, and Kidney Cancer



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June 25, 2009

Agents with Cancer Chemopreventive Potential

Anti-androgens
[5AR-1/2, AR]
(Finasteride, Dutasteride, DIM, SARMs)

Antioxidant Modulators
[ROS, GSH/GST-P1,iNOS]
(Selenium, Vitamin E, Lycopene, Polyphenols, Resveratrol, Sulforaphanes)

Arachidonic Acid Modulators
[NFkB, COX (PGE2), LOX (HETE), PPARs] **(ASA/NSAIDS, Celecoxib, Rofecoxib, R-flurbigrofen, NO-ASA, Vit E, Zileuton)**

Phytoestrogens
[ER-beta, 5AR, AR, RTK]
(Genistein, Daidzein/Equol, Resveratrol)

Anti-estrogens
[ER-alpha/beta, Aromatase, TGFalpha]
(Toremifene, Raloxifene, Arimidex, I3C/DIM)

Differentiation Agents
[VDR, RXR, HDAC, DNMT]
(Vit D Analogs, Targretin, SAHA, valproic acid)

Anti-proliferation/Cell Cycle Agents
[ODC, RXR/RAR, p21,p27]
(DFMO, Panretin, Vitamin D)

Signal Transduction Modulators (Kinases)
[EGFR **(Tarceva)**, PDGFR **(STI-571)**, VEGFR/PDGFR **(SU-11248)**, PI3K/AKT/mTOR **(Celecoxib, Rapamycin)**, NFkB **(polyphenols)**

Ras/Farnesyl/Geranyl Transferase Modulators
(Statins, SCH 66336, L-778,123,Perillyl Alcohol)

Anti-angiogenesis Modulators
(Thalidomide analogs, Avastin, Celecoxib)

PPAR (gamma/delta) Modulators
(Glitazones, DHEA Analogs, Retinoids, NSAIDs, 15d-PGJ2)

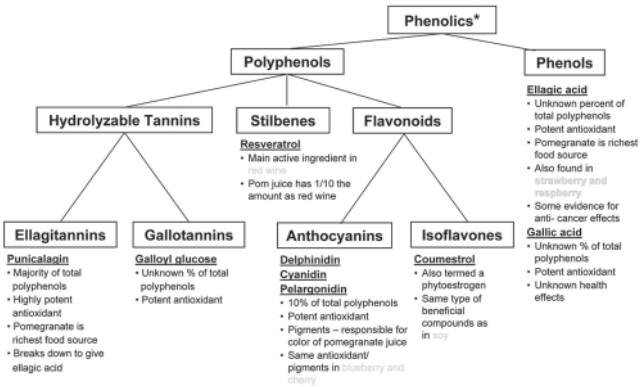
IGF-1/IGFBP-3 Modulators
(Soy, Retinoids,Tamoxifen, Lycopene, Vit D)

Novel Growth Factor Modulators
[ET-1, IL-6, NGF]
(Atrasentan, Celecoxib, Bowman-Birk Inhibitor)

Telomerase Modulators
Antiandrogens, SERMs, Polyphenols, Vit D, NGF

Gene-based vaccines
(P53, Rb, E1A/PSA, PSMA, PSA/B7/GMCSF)

Phenolics in Pomegranate Juice



*Phenolics include **phenols**, which have one phenol unit in their structure, and **polyphenols**, which have >1 phenol unit in their structure. For simplicity, we call all the compounds Polyphenols.*

Pomegranates and Prostate Cancer Pre-Clinical Data Summary: 2001

In vitro studies show:

- 59-75% growth inhibition of PC3
- Delayed progression into S phase
- Induction of apoptosis

In vivo studies in SCID mice show:

- 52% growth inhibition of LAPC-9 tumors
- 70% reduction in PSA
- Prolonged survival

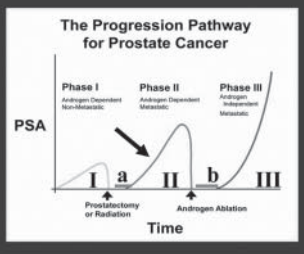
Phase II Study for Men with Rising PSA After RRP or XRT: 2002

- Men with Recurrent Prostate Cancer
- Rising PSA after RRP or XRT
- Low risk: PSA < 5, Gleason < 8
- No evidence of metastatic disease
- No previous hormone therapy
- Baseline PSA DT

Pantuck et al
Clinical Cancer Research, 2006

Treatment

8 oz. Pomegranate juice daily providing 1.5 mmol polyphenols



Updated Results: PSA Doubling Time Year 5

	PSADT Before Baseline	PSADT After Baseline	Change
Mean ± SD	15.0 months	58 months	43.0 months
		Non-Active 51 months Active 69 months	P=0.0001

ASCO, 2008

2009 Pomegranate Research Portfolio

- POM Phase II Continuation Study
- POM Phase III Multi-Center Study
- Neoadjuvant POM Pill Study

- POM and NFκB Pathway
- POM and IGF Axis

- POM and Kidney Cancer

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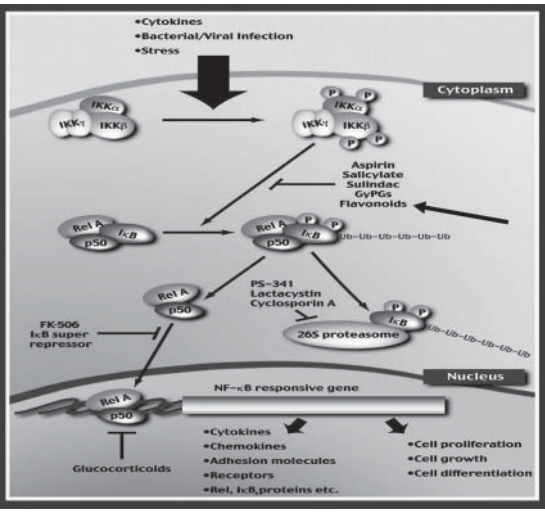

POMX inhibits constitutive and TNFα-induced NF-κB activity

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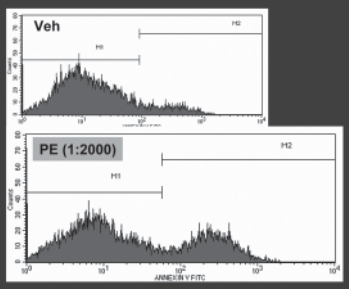
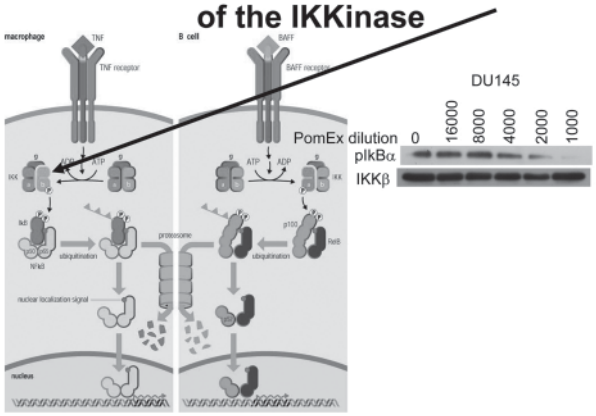
Cell growth inhibition is attributable to stimulation of apoptosis (Annexin V)



Dilution	Apoptosis (%)
Veh	11.1
1:4000	20.6
1:2000	31.4
1:1000	60.7
1:500	67.4

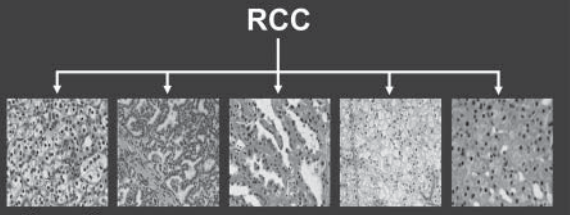
Pom is Inhibiting NFkB at the activation of the IKKinase



Something New for 2009

Pom and Kidney Cancer

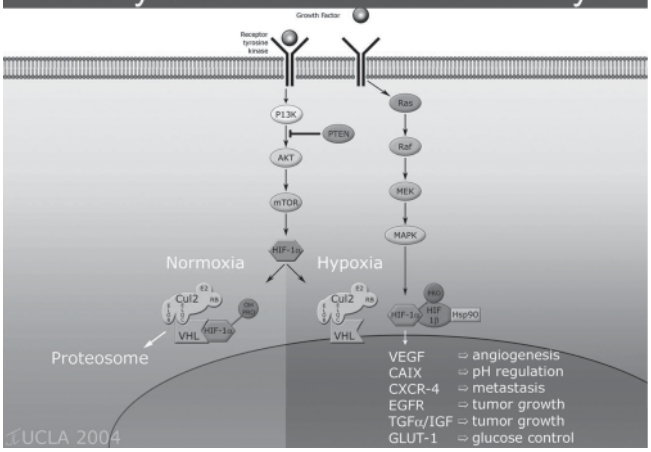
Kidney Cancer: A Family Of Tumors



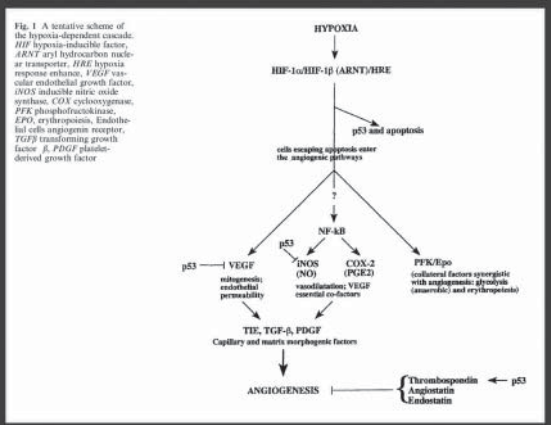
Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Incidence (%)	*75%*	*5%*	*10%*	*5%*	*5%*
Associated mutations	*VHL*	*c-Met*	*FH*	*BHD*	*BHD*

BHD=Birt-Hogg-Dubé; FH=fumarate hydratase; VHL=von Hippel-Lindau.
Modified from Linehan WM et al. *J Urol.* 2003;170:2163-2172.

Kidney Cancer Molecular Pathways



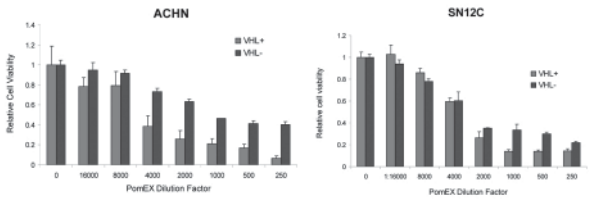
VHL, HIF and NFkB



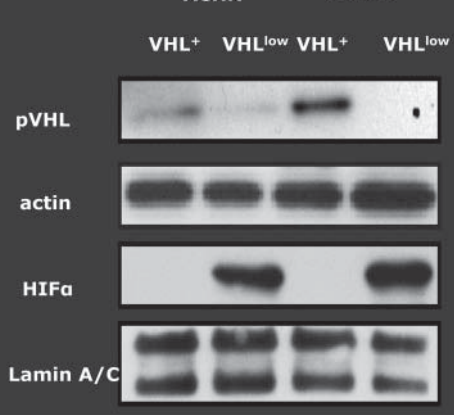
Pom Inhibits:

VEGFr/PDGFr	←	Sutent, Nexavar
HIF		
AKT	←	Toracel
C-MET/HGF	←	XL880, AMG101
NFkB	←	Velcade

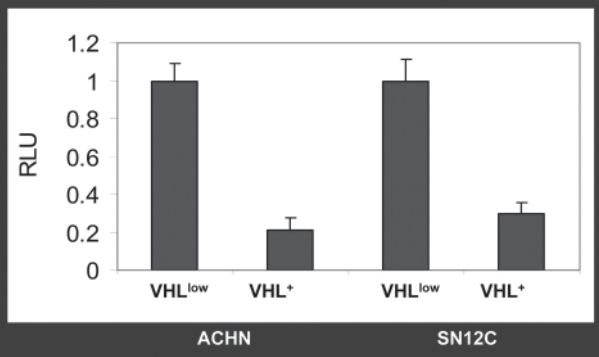
Both VHL+ and VHL- RCC Cells Sensitive to Killing Effects of POM-X



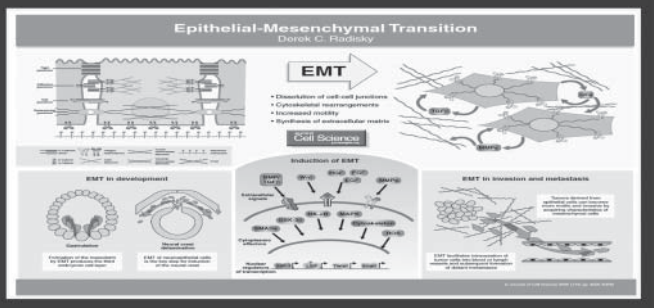
Isogenic VHL + and VHL – cell lines



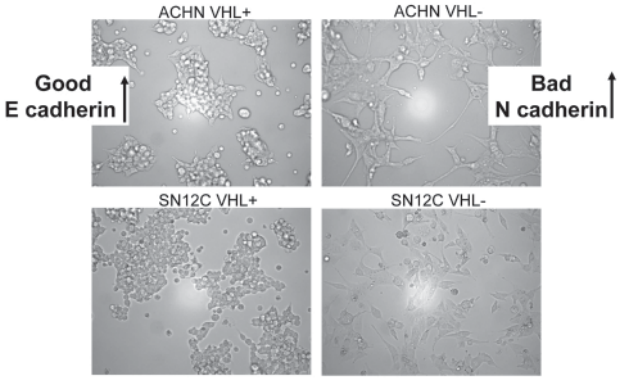
High NF-κB Activity in RCC cells lacking VHL



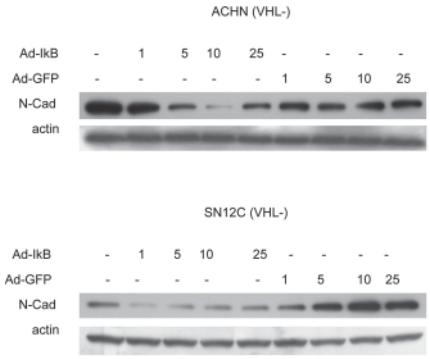
VHL, NFkB and EMT



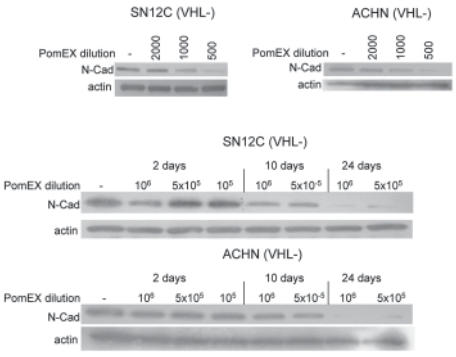
VHL Status and Epithelial and Mesenchymal Phenotype of Kidney Cancer Cell Lines



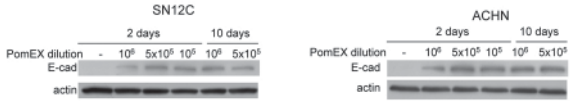
Inhibiting NFkB with a repressor in kidney cancer cells decreases N-Cadherin levels



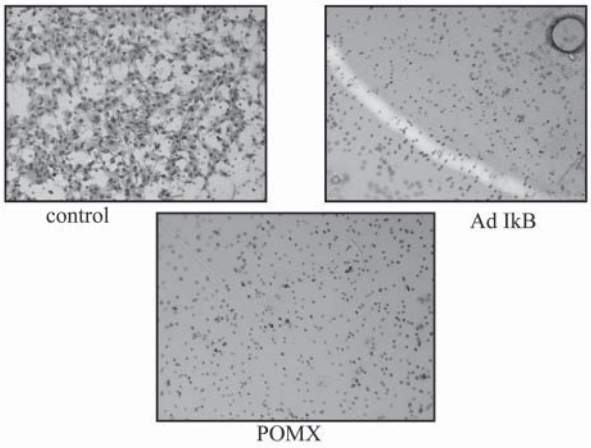
….So does chronic low dose administration of Pom-X



….and it increases levels of E-Cadherin



POM inhibits invasion of kidney cancer cells



Plans for 2009-2010

Complete current clinical trials

Further evaluation of POM for kidney cancer

?Clinical trials in RCC?

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