METABOLIC SYNDROME & ANDROGEN DEPRIVATION

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Metabolic syndrome

- A constellation of metabolic abnormalities associated with increased risk of
  - CV disease RR = 2.35 (2.02-2.73)*
  - DM2 RR = 3.97 (1.35-11.6)**
  - CV-specific mortality RR = 2.40 (1.87 - 3.08)*
  - all-cause mortality RR: 1.58 (1.39 - 1.78)*
- Thought to result from dietary excess and sedentary lifestyle in a genetically susceptible individual
- Prevalence among adults is 34% in USA and 19% in Canada
- Controversies:
  - Optimal definition / cut-offs?
  - Prognostic implications?
  - Therapeutic implications?

Reaven, Banting lecture 1988
Lakka et al. JAMA 2002
*Mottillo et al. JACC 2010
**Meigs et al. J Clin Endo Metab 2006
Mozumdar et al. Diabetes care 2011
Riediger et al. CMAJ 2011

METABOLIC SYNDROME: WHY IS IT IMPORTANT?

- Increases risk of prostate cancer
- Increases aggressivity of PCA
- You induce it when you put a man on ADT
- Increases risk of death in your Pca patients
- May be a target for improving outcomes

Q#1: WHICH OF THE FOLLOWING IS NOT A COMPONENT OF THE CLASSIC METABOLIC SYNDROME ?

A) Hypertension

B) Obesity

C) High LDL Cholesterol

D) High triglycerides

E) Insulin resistance

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Criteria for Metabolic Syndrome

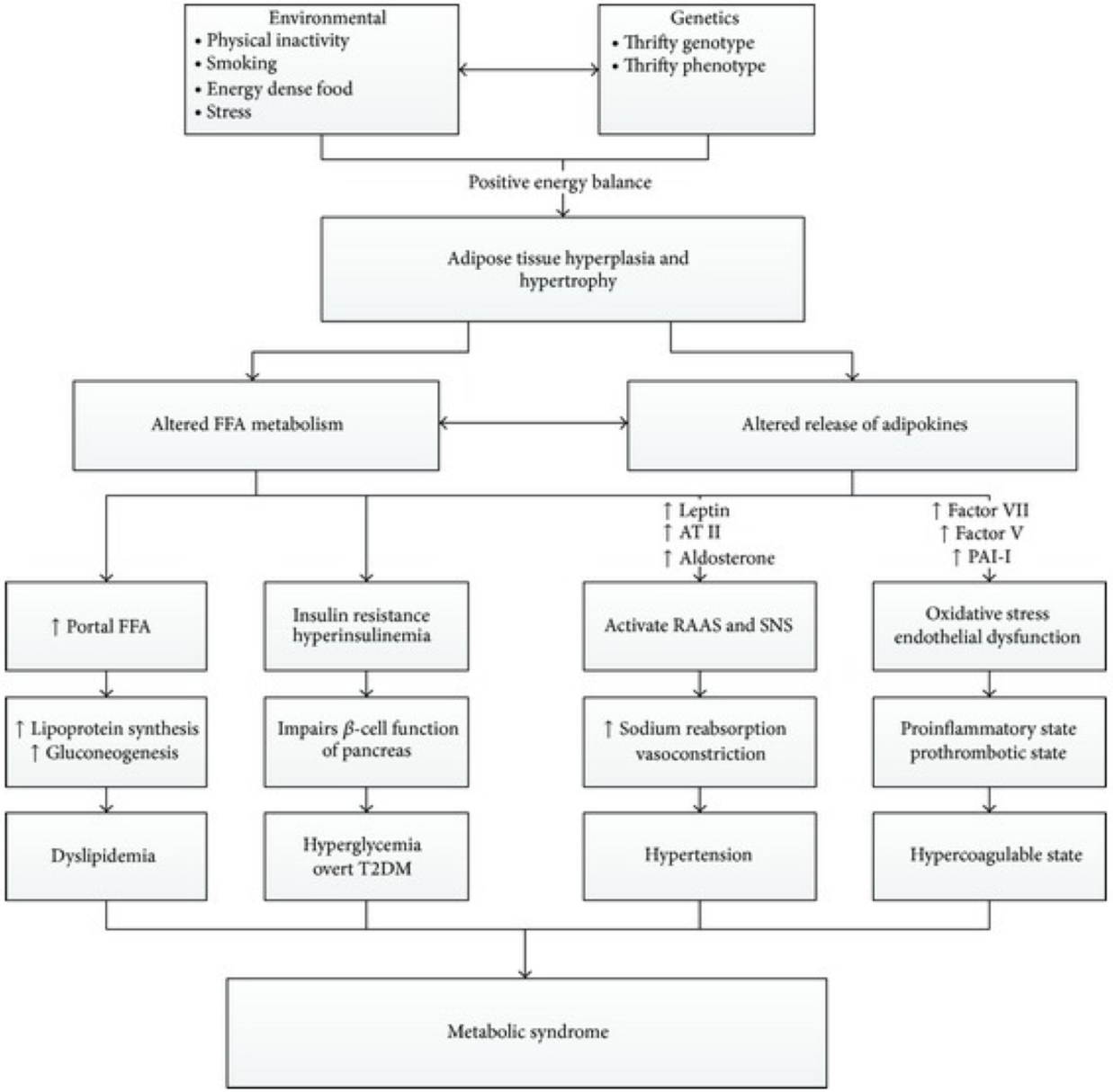
- Diagnosis of metabolic syndrome requires *any three* of the following:
  - Obesity, defined as body mass index ≥ 30 kg/m^2
  - Elevated serum triglycerides, defined as ≥ 150 mg/dL (1.7 mmol/L) on fasting lipid profile, or treatment for this abnormality
  - Reduced serum high-density lipoprotein-cholesterol, defined as < 40 mg/dL (1.03 mmol/L) in men on fasting lipid profile, or treatment for this abnormality
  - Elevated blood pressure, defined based on physician diagnosis of hypertension or use of antihypertensive medications
  - Elevated fasting glucose, defined as ≥ 100 mg/dL (5.6 mmol/L), or use of medication for hyperglycaemia, or physician-diagnosed type 2 diabetes mellitus

(adapted from the American Heart Association/National Heart, Lung, and Blood Institute and International Diabetes Federation interim consensus statement)

Metabolic syndrome: various definitions

Clinical Measure	WHO (1998)	ATP III (2001)	IDF (2005)	AHA/NHLBI (2005)	IDF & AHA/NHLBI Joint Interim (2009)
Insulin resistance	***Mandatory*** IGT, IFG, T2DM, or lowered insulin sensitivity* plus any 2 of the following	None, but any 3 of the following 5 features	None	None, but any 3 of the following 5 features	
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥102 cm in men or ≥88 cm in women†	***Mandatory*** Increased WC (population specific) plus any 2 of the following	WC ≥102 cm in men or ≥88 cm in women†	Ethnicity/pop- specific WC
Lipid - **High TG** - **Low HDL**	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women Or use of specific drug for this (nicotinic acid or fibrate)	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women Or use of specific drug for this (nicotinic acid or fibrate)
Blood pressure	≥140/90 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx	≥130/85 mm Hg or medical tx for HTN	≥130/85 mm Hg or medical tx for HTN
Glucose	***Mandatory*** IGT, IFG, or T2DM	>110 mg/dL (includes diabetes)‡	≥100 mg/dL (includes diabetes)	>100 mg/dL (includes diabetes)‡	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria				

Grundy et al. Circulation 2005



Batsis et al. Clin pharmacol ther 2007

Q#2:Which of the following Urology condition is not associated with MetS?

A) Urolithiasis

B) BPH/LUTS

C) Erectile Dysfunction

D) Overactive bladder

E) None of the above

UROLOGICAL CONSEQUENCES OF /METABOLIC SYNDROME

- Renal
  - CRF
  - Stones
  - Pyelonephritis/Inflammation
- Bladder
  - UTI
  - OAB
  - Cystopathy/Retention
- Prostate
  - Calcification
  - Prostatitis
  - BPH/LUTS
- Infertility
- Andropause
- Erectile Dysfunction
- Cancer ?
  - Literature inconsistent

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Prostate cancer epidemiology

- The most common non-cutaneous malignancy
- Accounts for largest number of new cancer diagnoses
  - 23,231 new cases, or 142.3 per 100,000 men in Canada (2007)

	Canada	US
Lifetime risk of PC	14.3% (1 in 7)	16.7% (1 in 6)
Lifetime risk of PC mortality	3.6% (1 in 28)	2.8% (1 in 36)
Risk of PC dx & die of something else	10.7%	13.9%

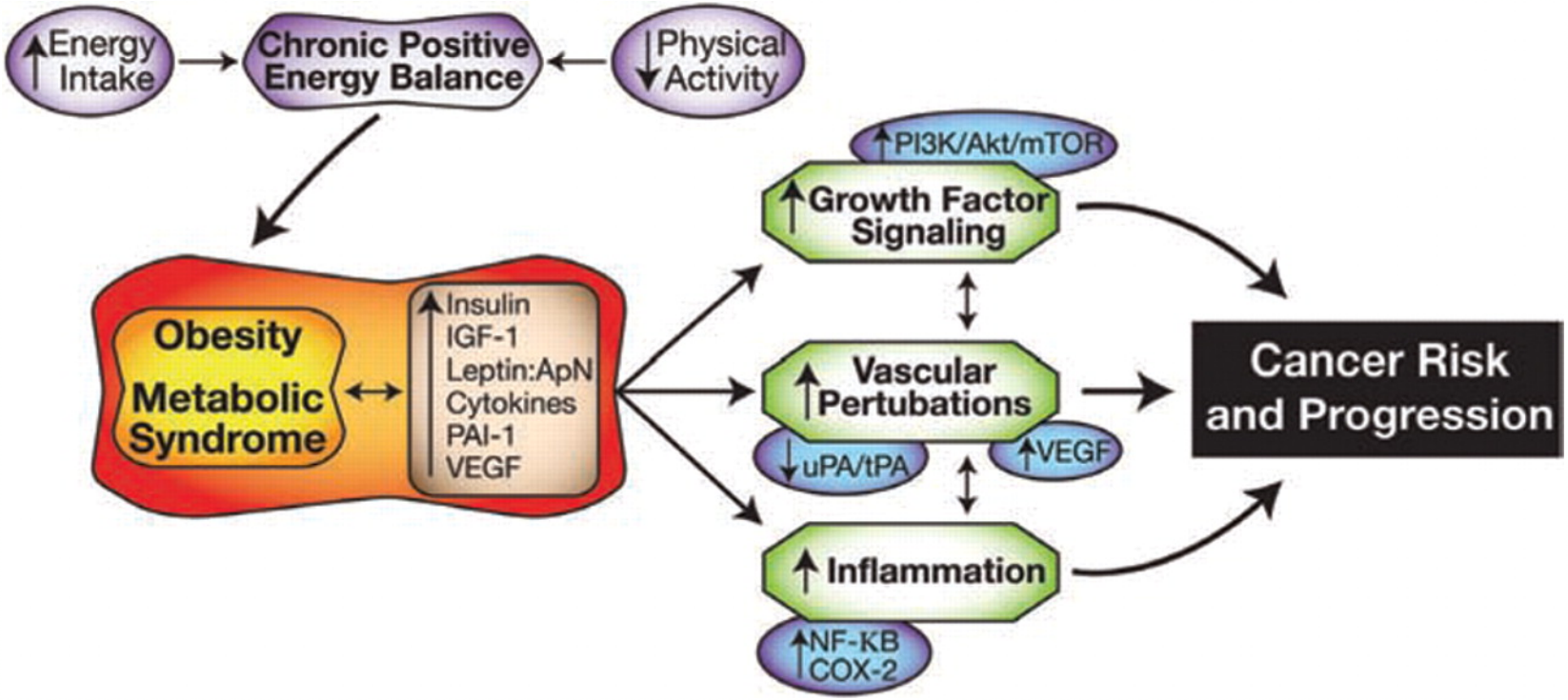
Statistics Canada, 2011

Canadian Cancer Society, 2012 Estimates

American Cancer Society, 2012 Estimates

Obesity, metabolic syndrome, and cancer: overview of mechanisms.

- Many of the resulting metabolic derangements & cytokine abnormalities are also implicated in carcinogenesis



Hursting S D , Hursting M J Arterioscler Thromb Vasc Biol 2012;32:1766-1770

American Heart Association
Learn and Live

Epidemiologic evidence between Met-S and PC

Table 2 – Relevant clinical studies of the relationship between metabolic syndrome and prostate cancer

Authors, yr	Study design	Country	Population	Cohort size	Exposure assessment: MetS criteria	No. of cases	Results/comments (outcome: PCa)	Level of evidence
Laukkanem et al., 2004 [49]	Longitudinal cohort study	Finland	Kuopio communities	1880 (white)	WHO	56	Risk increase (RR: 1.94; 95% CI, 1.06–3.53)	3b
Lund Haheim et al., 2006 [50]	Longitudinal cohort study	Norway	Oslo study	15 933 (white)	Upper quartile levels ATP-III criteria	507	Risk increase (RR: 1.56; 95% CI, 1.21–2.0)	2b
Martin et al., 2009 [51]	Longitudinal cohort study	Norway	HUNT 2	29 364 (white)	NCEP-ATP-III	687	No association (HR: 0.91; 95% CI, 0.877–1.09)	2b
Beebe-Dimmer et al., 2009 [52]	Case-control study	United States	GECAP	881 (56% white; 44% African American)	NCEP-ATP-III	637	Risk increase in African American population (OR: 1.71; 95% CI, 0.97–3.01)	3b
Tande et al., 2006 [53]	Longitudinal cohort study	United States	ARIC	6429 (49% white; 61% African American)	NCEP-ATP-III	385	Risk reduction (RR: 0.77; 95% CI, 0.51–1.05)	2b
De Nunzio et al., 2011 [54]	Cohort study	Italy	Prostate biopsy cohort study	195 (white)	NCEP-ATP-III	102	No association (OR: 0.97; 95% CI, 0.48–1.95); increased risk for Gleason score ≥7 in patients with PCa (OR: 3.82; 95% CI, 1.33–10.9)	3b
Wallner et al., 2011 [56]	Cohort study	United States	Olmsted County	2445 (white)	WHO	206	HR: 0.81; 95% CI, 0.2–3.3 (2 patients with PCa out of 28 patients with MetS)	3b

SD = standard deviation; MetS = metabolic syndrome; PCa = prostate nisation; RR = risk ratio; CI = confidence interval; NCEP-ATP-III = National Cholesterol Education Program Adult Treatment Panel III; HUNT 2 = Nord-Trondelang Health Study; GECAP Cancer Study; OR = odds ratio; ARIC = Atherosclerosis Risk in Communities.

Evidence favours an association between MetS and PC:

- Elevated risk: n=6 (one incr. risk for high grade disease only)
- No increase in incidence, incr. in PC-related mortality: n=1
- No association: n=2
- Lower risk: n=1

De Nunzio et al. Eur Urol 2012
Haggstrom et al. Cancer 2012

Metabolic Syndrome and Prostate Cancer

European Association of Urology

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Dissecting the Association Between Metabolic Syndrome and Prostate Cancer Risk: Analysis of a Large Clinical Cohort

Bimal Bhindi[a,*], *Jennifer Locke*[b], *Shabbir M.H. Alibhai*[c], *Girish S. Kulkarni*[a,d], *David S. Margel*[e], *Robert J. Hamilton*[a], *Antonio Finelli*[a], *John Trachtenberg*[a], *Alexandre R. Zlotta*[a], *Ants Toi*[f], *Karen M. Hersey*[a], *Andrew Evans*[g], *Theodorus H. van der Kwast*[g], *Neil E. Fleshner*[a]

Table 4 – Univariate and multivariable associations between number of metabolic risk factors and prostate cancer (PCa), clinically significant PCa, and intermediate- or high-grade PCa

	PCa diagnosis Row % (*n*/total)	No PCa Row % (*n*/total)	*p* value*	Age-adjusted OR (95% CI)**	*p* value	Multivariable OR (95% CI)**	*p* value
PCa overall							
Dichotomously defined							
MetS	64.4 (318/494)	35.6 (176/494)	<0.001	1.35 (1.10–1.67)	0.005	1.45 (1.16–1.82)	0.001
No. of metabolic risk factors							
0 components	54.2 (280/517)	45.8 (237/517)	<0.001	Ref	Ref	Ref	Ref
1 components	54.8 (371/677)	45.2 (306/677)		0.96 (0.76–1.22)	0.76	1.04 (0.81–1.34)	0.76
2 components	59.2 (324/547)	40.8 (223/547)		1.12 (0.88–1.44)	0.35	1.16 (0.89–1.51)	0.28
≥3 components (ie, MetS)	64.4 (318/494)	35.6 (176/494)		1.38 (1.07–1.79)	0.013	1.54 (1.17–2.04)	0.002
Clinically significant PCa							
Dichotomously defined							
No MetS	31.6 (551/1741)	68.4 (1190/1741)		Ref	Ref	Ref	Ref
No. of metabolic risk factors							
0 components	29.0 (150/517)	71.0 (367/517)	<0.001	Ref	Ref	Ref	Ref
1 components	30.0 (203/677)	70.0 (474/677)		0.98 (0.76–1.27)	0.90	1.06 (0.80–1.39)	0.70
2 components	36.2 (198/547)	63.8 (349/547)		1.27 (0.98–1.65)	0.071	1.33 (1.00–1.77)	0.048
Intermediate- or high-grade PCa							
Dichotomously defined							
MetS	35.0 (173/494)	65.0 (321/494)	0.002	1.33 (1.07–1.65)	0.011	1.38 (1.09–1.74)	0.007
No MetS	27.8 (484/1741)	72.2 (1257/1741)		Ref	Ref	Ref	Ref
No. of metabolic risk factors							
0 components	24.8 (128/517)	75.2 (389/517)	<0.001	Ref	Ref	Ref	Ref
1 components	26.3 (178/677)	73.7 (499/677)		1.01 (0.77–1.32)	0.95	1.06 (0.80–1.41)	0.67
2 components	32.5 (178/547)	67.5 (369/547)		1.33 (1.01–1.74)	0.041	1.36 (1.02–1.82)	0.038
≥3 components (ie, MetS)	35.0 (173/494)	65.0 (321/494)		1.46 (1.11–1.93)	0.007	1.56 (1.16–2.10)	0.003

CI = confidence interval; MetS = metabolic syndrome; OR = odds ratio; PCa = prostate cancer.

* Pearson chi-square test and Cochran-Armitage test for trend.

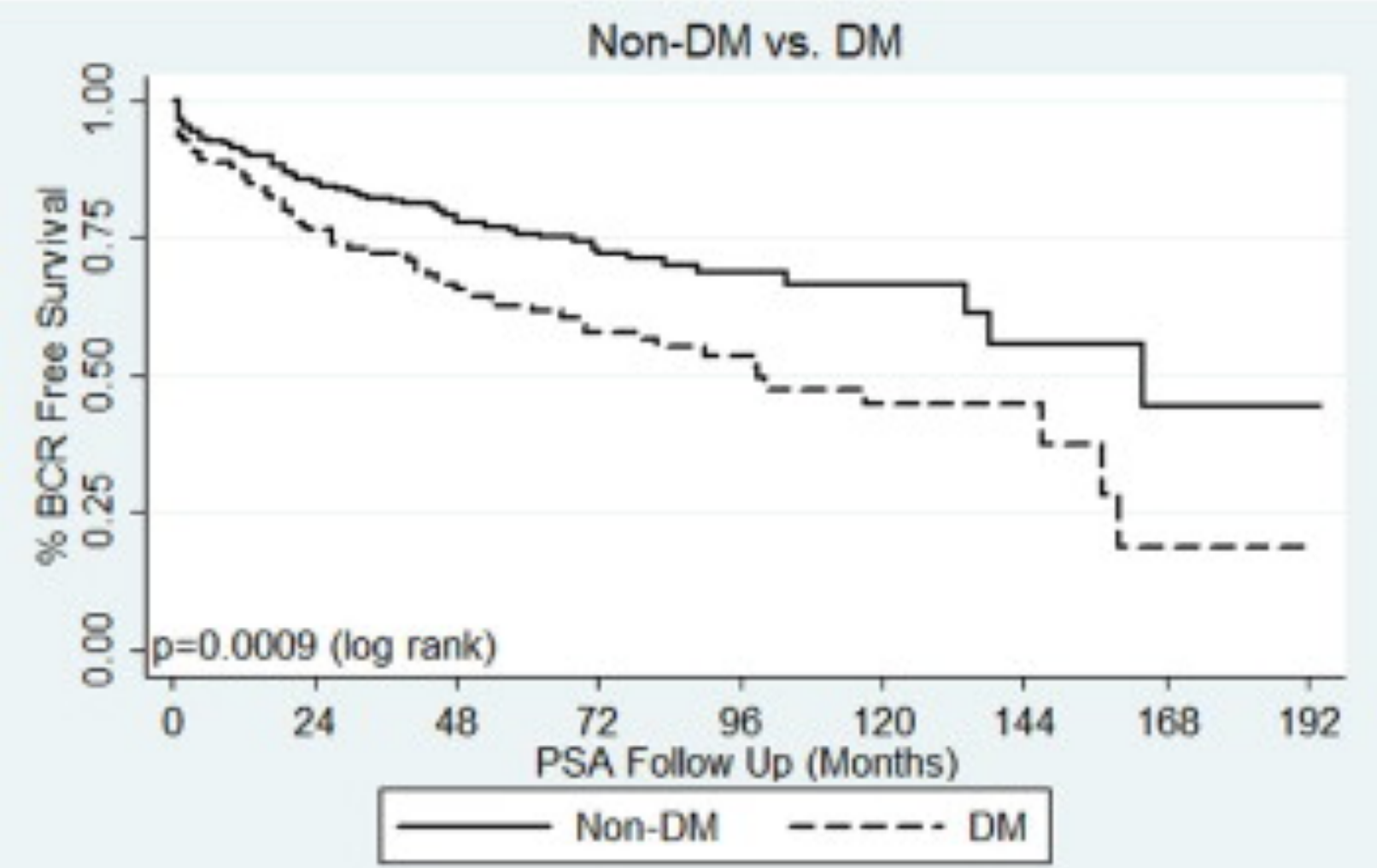
** Using multivariable logistic regression to adjust for the following clinical confounders: age, ethnicity, family history of PCa, prostate volume, history of previous prostate biopsy, and use of 5α-reductase inhibitors. Prostate volume was log-transformed to improve model fit.

ACTIVE SURVEILLANCE POPULATION

Bhindi Eur Urol 2014

- 585 men on AS
- Risk of progression after confirmatory biopsy increased
- Each 5 units of BMI increased risk of progression by 50%

The effect of Type II DM on biochemical failure



Patel et al. Clinical outcomes after radical prostatectomy in diabetic patients treated with metformin. Urology 2011; 76(5): 1240–1244

Metabolism and Prostate Cancer

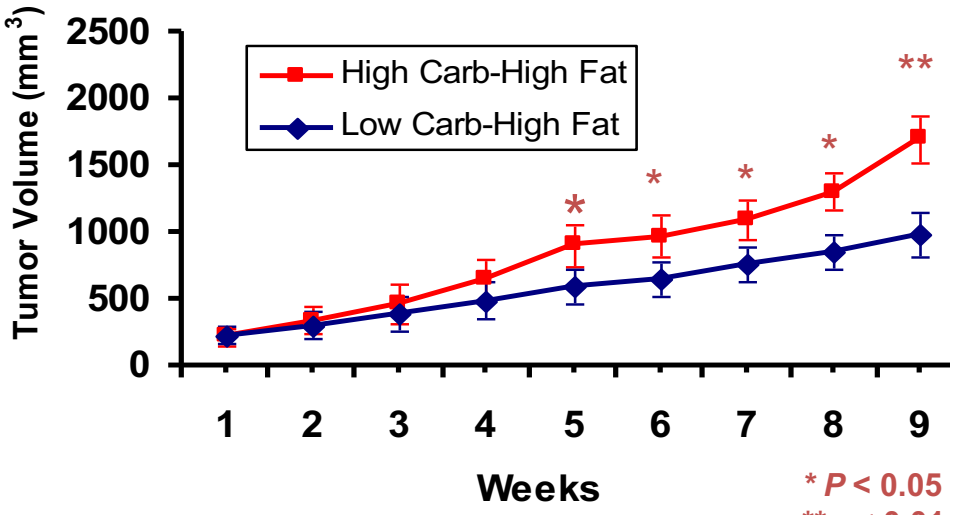
JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE

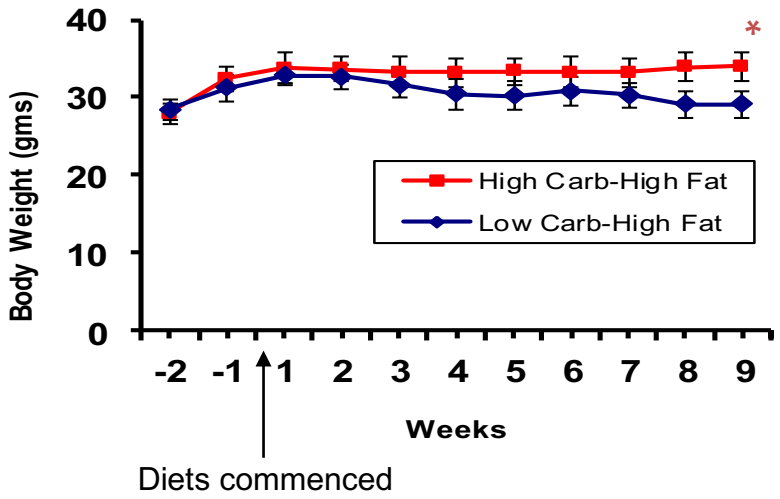
2007 Volume 99, Issue 23 Pp. 1793-1800

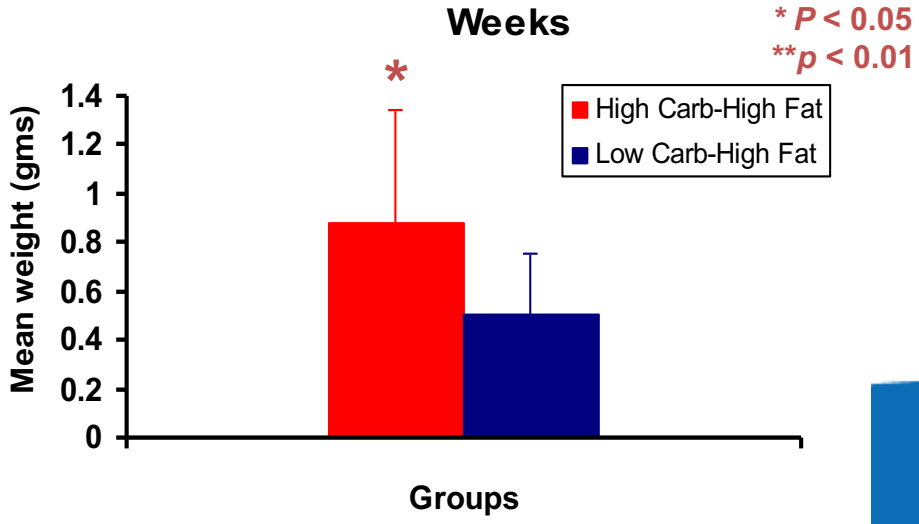
Association of Diet-Induced Hyperinsulinemia With Accelerated Growth of Prostate Cancer (LNCaP) Xenografts

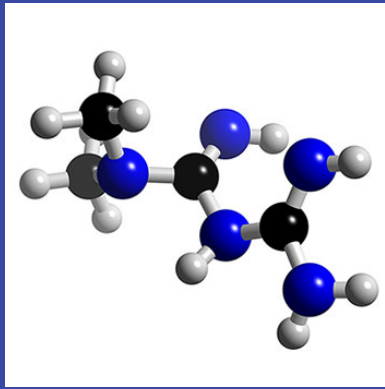
Vasundara Venkateswaran, Ahmed Q. Haddad, Neil E. Fleshner, Rong Fan, Linda M. Sugar, Rob Nam, Laurence H. Klotz, Michael Pollak

Increased tumour volume and wet weight in animals on high-carbohydrate diet









Metformin

(1,1-dimethylbiguanide hydrochloride)

- Biguanide oral hypoglycaemic agents
- Primary Tx for type II diabetes
- Recent studies- prevents cancer

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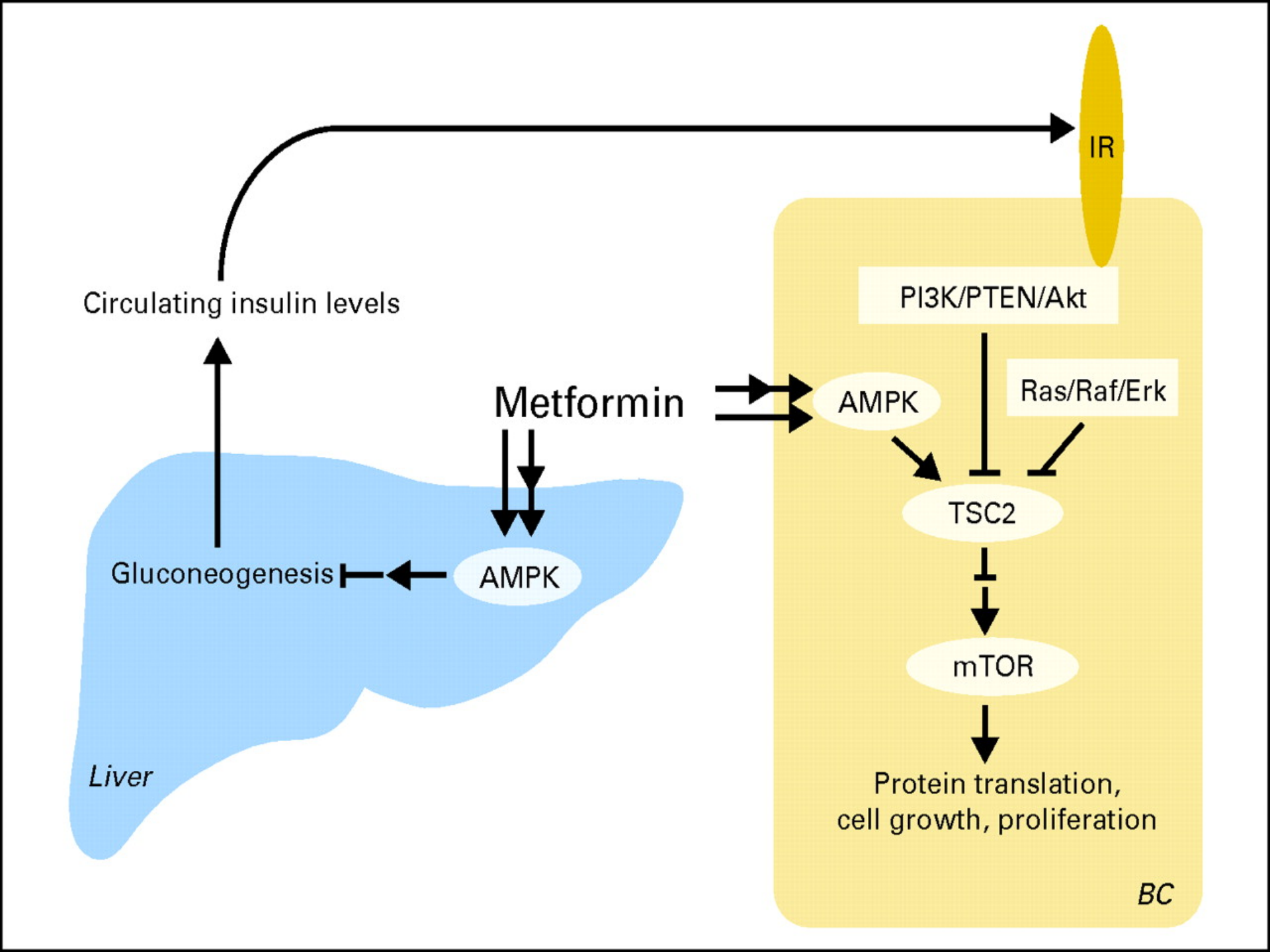

IR
Circulating insulin levels
PI3K/PTEN/Akt
Metformin
AMPK
Ras/Raf/Erk
TSC2
Gluconeogenesis
AMPK
mTOR
Liver
Protein translation,
cell growth, proliferation
BC

Metformin and Prostate Cancer

Prostate Cancer and Prostatic Disease (2014), 1–7

www.nature.com/pcan

ORIGINAL ARTICLE

A pilot 'window of opportunity' neoadjuvant study of metformin in localised prostate cancer

AM Joshua[1], V Zannella[1,6], MR Downes[1,2,6], B Bowes[1], RN Karen Hersey[1], M Koritzinsky[1], M Schwab[3], U Hofmann[3], A Evans[1,2], T van der Kwast[1,2], J Trachtenberg[1,3], A Finelli[1,3], N Fleshner[1,4], J Sweet[1,2] and M Pollak[5]

- Decrease in the Ki67 index (p=0.015, 28.7% decrease)
- Reduction in phosho-4EBP1 immunostaining (p<0.001)
- Preliminary assessment revealed tissue metformin levels of ~80 ng/mg
- These results indicate that metformin may have anti-proliferative activity mediated at least in part by its action of the mTOR pathway

Metformin Use and All-Cause and Prostate Cancer–Specific Mortality Among Men With Diabetes

David Margel, David R. Urbach, Lorraine L. Lipscombe, Chaim M. Bell, Girish Kulkarni, Peter C. Austin, and Neil Fleshner

VOLUME 31 · NUMBER 25 · SEPTEMBER 1 2013

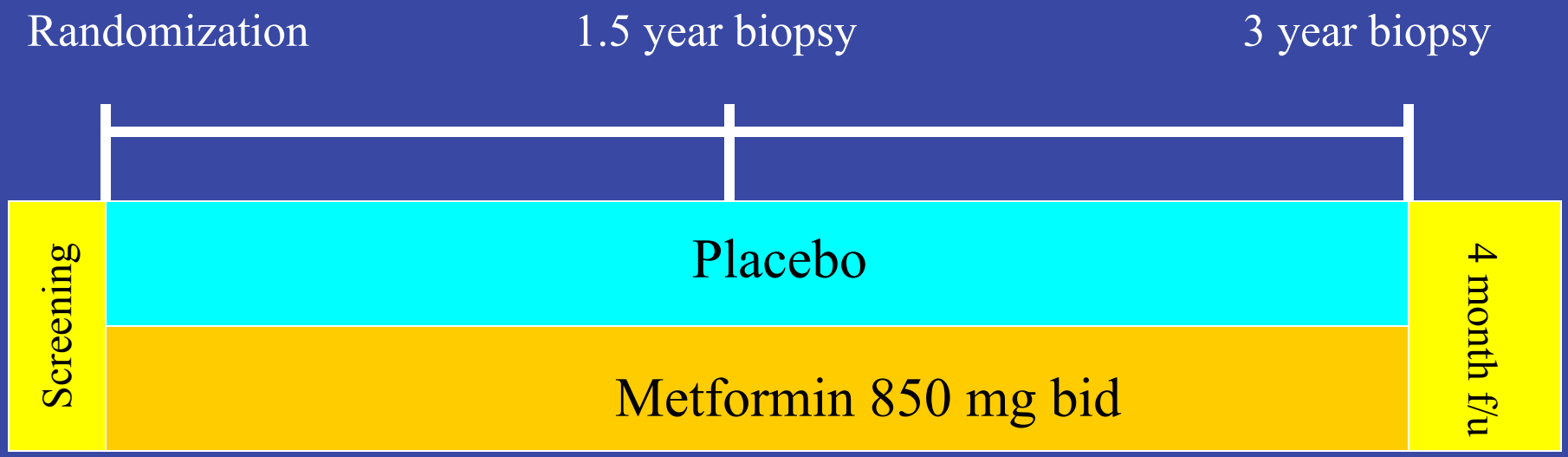
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

	Prostate cancer specific (number of events 291) HR 95%CI		Overall mortality (number of events 1343) HR 95%CI	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Cumulative metformin	0.64* (0.54-0.76)	0.76* (0.64-0.89)	0.86* (0.82-0.9)	0.92* (0.88-0.97)
Cumulative sulfonylurea	1.01 (0.93-1.02)	1.01 (0.89-1.12)	0.96* (0.92-0.99)	1.02 (0.98-1.06)
Cumulative TZD	0.69 (0.4-1.2)	0.98 (0.54-1.79)	0.80* (0.63 -0.96)	0.89 (0.78-1.1)
Cumulative insulin	0.97 (0.68-1.01)	0.86 (0.69-1.5)	1.1 (0.98-1.23)	1.1 (1.01-1.2)

MAST STUDY : TERTIARY PREVENTION

Multicenter, randomized, placebo-controlled trial



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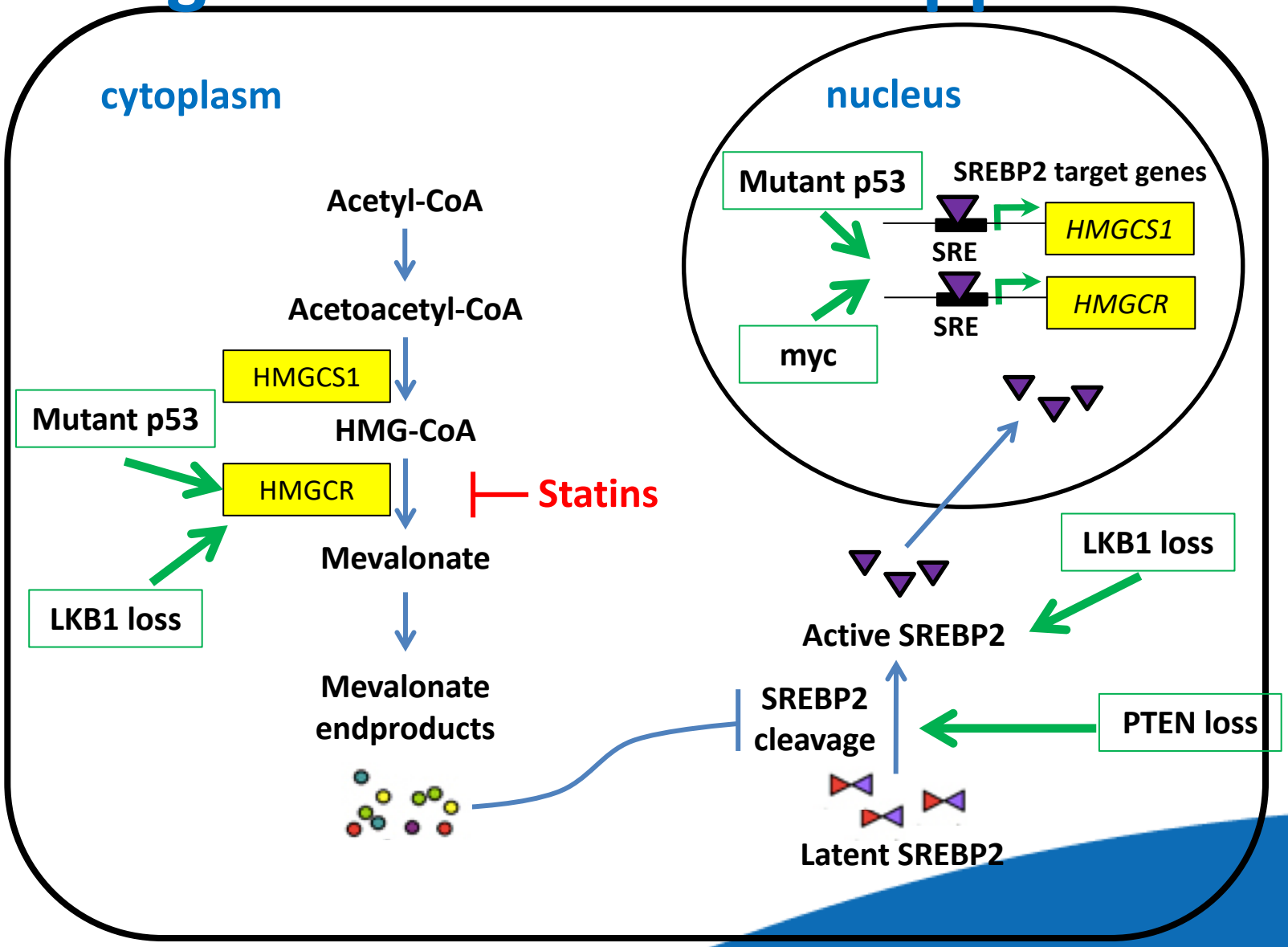
Control of Mevalonate Pathway by Oncogenes and Tumour suppressors



Statins in Prostate Cancer

The Influence of Statin Medications on Prostate-specific Antigen Levels

Robert J. Hamilton, Kenneth C. Goldberg, Elizabeth A. Platz, Stephen J. Freedland

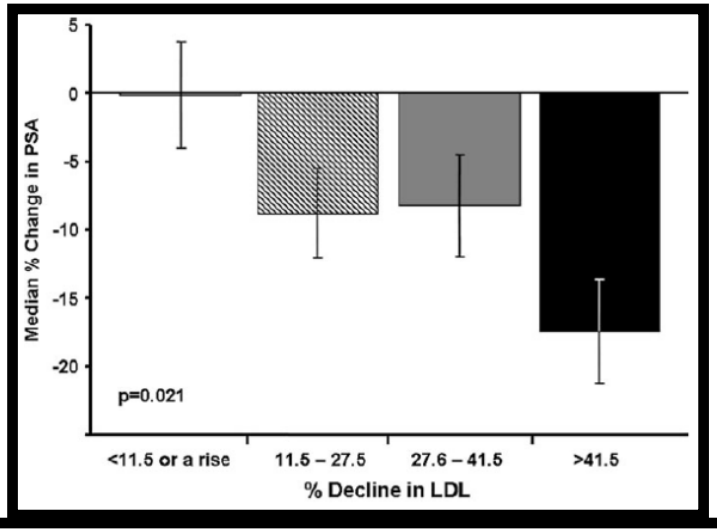


Table 3. Factors independently associated with change in PSA after starting a statin*

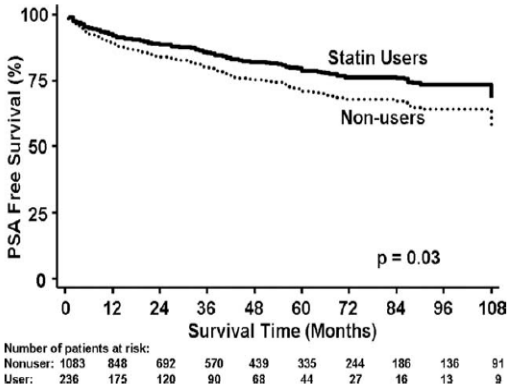
Covariate parameter	% decline in PSA	95% CI	*P* value†
10% decline in LDL after starting statin	1.64	0.64 to 2.65	.001
Statin dose equivalent			
<simvastin 20 mg	Ref	—	—
=simvastin 20 mg	8.53	2.65 to 14.41	.005
>simvastin 20 mg	9.35	3.29 to 15.42	.003

J Natl Cancer Inst 2008;100:1511–1518

Statin Medication Use and the Risk of Biochemical Recurrence After Radical Prostatectomy

Results From the Shared Equal Access Regional Cancer Hospital (SEARCH) Database

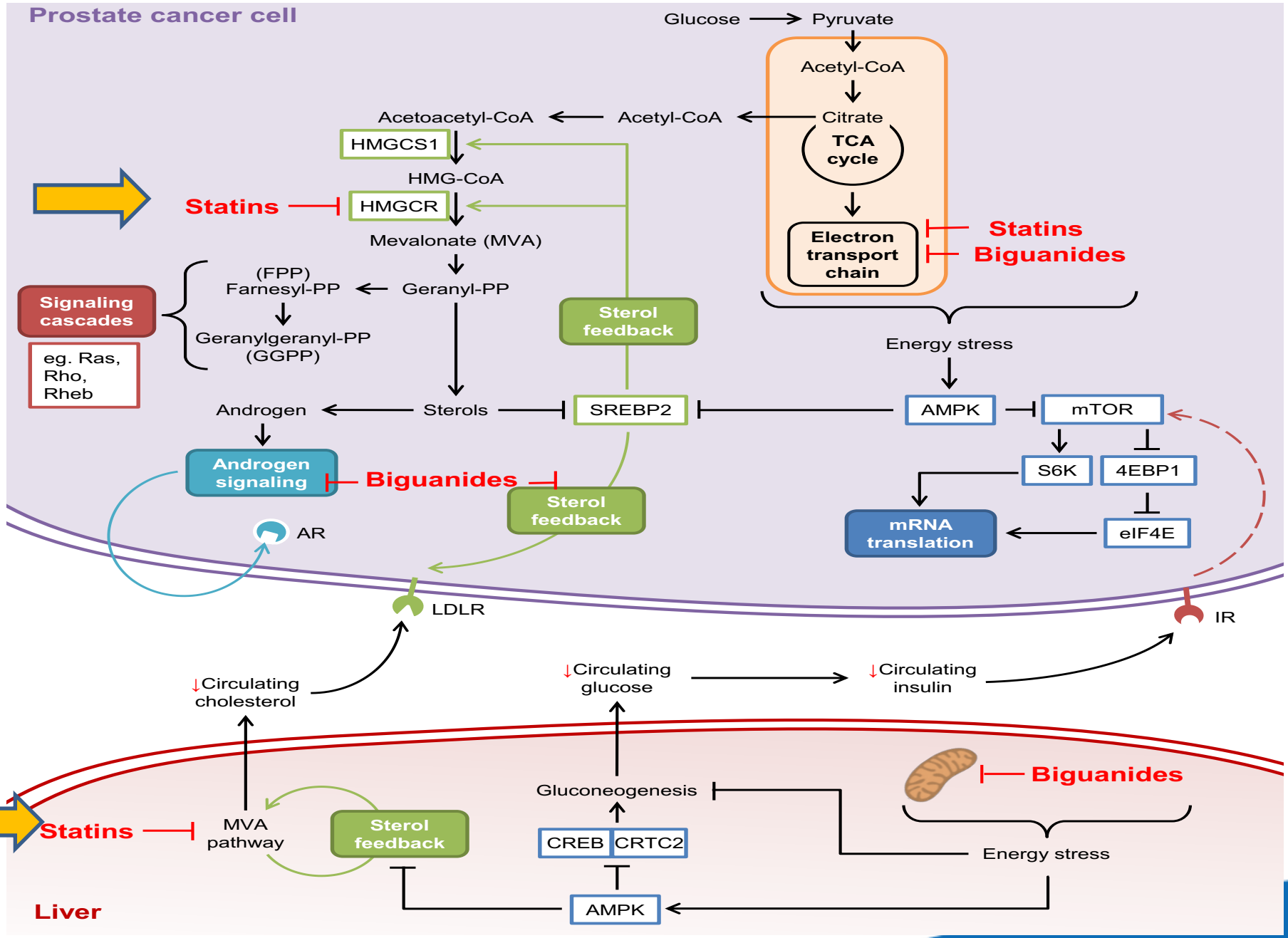
Robert J. Hamilton, MD, MPH[1,2]; Lionel L. Banez, MD[1,3]; William J. Aronson, MD[4,5]; Martha K. Terris, MD[6,7]; Elizabeth A. Platz, ScD, MPH[8,9]; Christopher J. Kane, MD[10]; Joseph C. Presti, Jr, MD[11,12]; Christopher L. Amling, MD[13,14]; and Stephen J. Freedland, MD[1,3]



Analysis	HR	95% CI	p-value
Crude	0.90	0.45-1.19	0.45
Multivariate	0.70	0.51-0.98	0.03

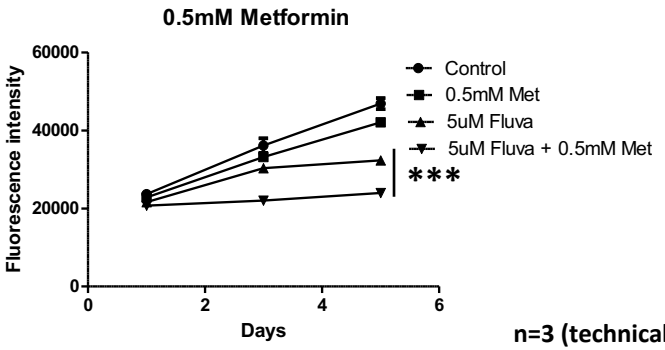
Dose	HR	95% CI	p-value
No statin	1.00	--	--
Dose Eq <1	1.08	0.66-1.73	0.78
Dose Eq =1	0.57	0.32-1.00	0.05
Dose Eq >1	0.50	0.27-0.93	0.03

Cancer 2010;116:3389–98.

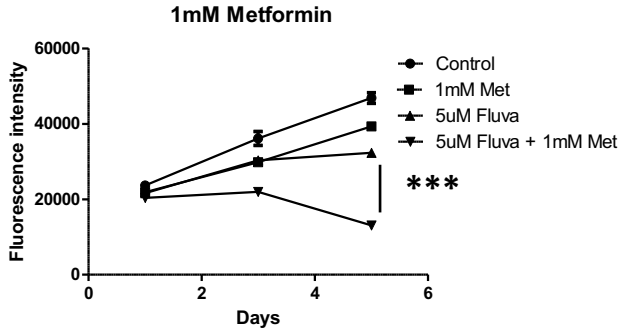

Prostate cancer cell
Glucose
Pyruvate
Acetyl-CoA
Citrate
TCA cycle
Electron transport chain
Statins
Biguanides
Acetoacetyl-CoA
Acetyl-CoA
HMGCS1
HMG-CoA
Statins
HMGCR
Mevalonate (MVA)
(FPP) Farnesyl-PP
Geranyl-PP
Geranylgeranyl-PP (GGPP)
Signaling cascades
eg. Ras, Rho, Rheb
Sterol feedback
Energy stress
Androgen
Sterols
SREBP2
AMPK
mTOR
S6K
4EBP1
Androgen signaling
Biguanides
Sterol feedback
AR
mRNA translation
eIF4E
LDLR
IR
↓Circulating cholesterol
↓Circulating glucose
↓Circulating insulin
Biguanides
Gluconeogenesis
Statins
MVA pathway
Sterol feedback
CREB
CRTC2
Energy stress
AMPK
Liver

STATINS AND METFORMIN CO-OPERATE TO SIGNIFICANTLY INDUCE PCA CELL DEATH

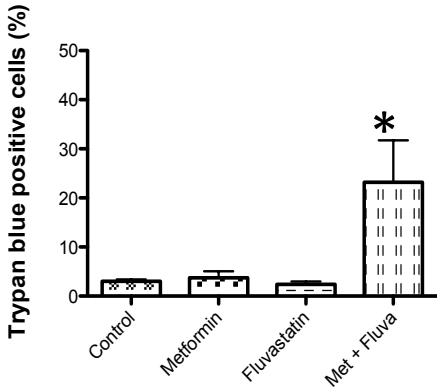
1. Significantly reduced LNCaP viability compared to single agents alone

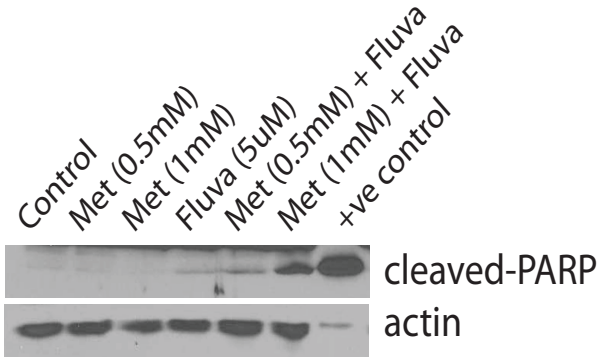


n=3 (technical quadruplicates)
Error bars = SEM
***** p<0.001, One-way ANOVA**

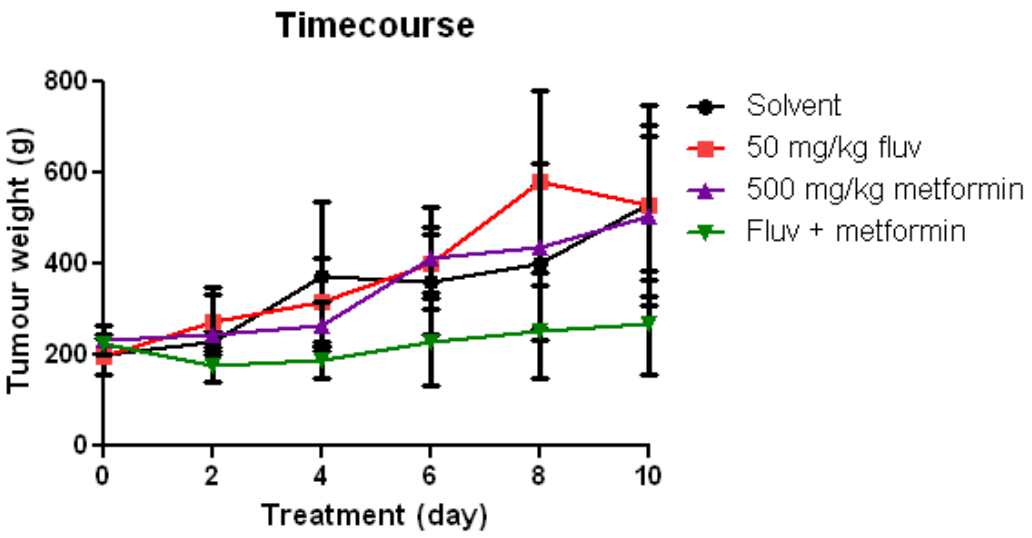


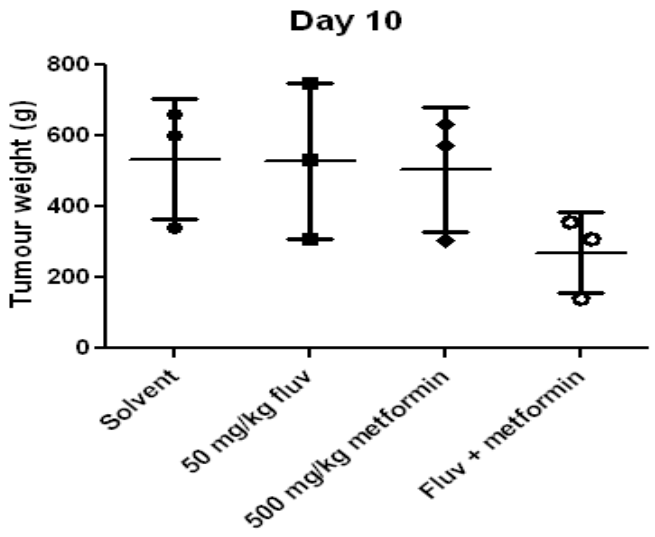
2. Cell death in LNCaP cells





FLUVASTATIN-METFORMIN COMBINATION SLOWS THE GROWTH OF LNCaP XENOGRAFTS





Metformin and Prostate Cancer

VOLUME 31 · NUMBER 25 · SEPTEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Metformin Use and All-Cause and Prostate Cancer–Specific Mortality Among Men With Diabetes

David Margel, David R. Urbach, Lorraine L. Lipscombe, Chaim M. Bell, Girish Kulkarni, Peter C. Austin, and Neil Fleshner

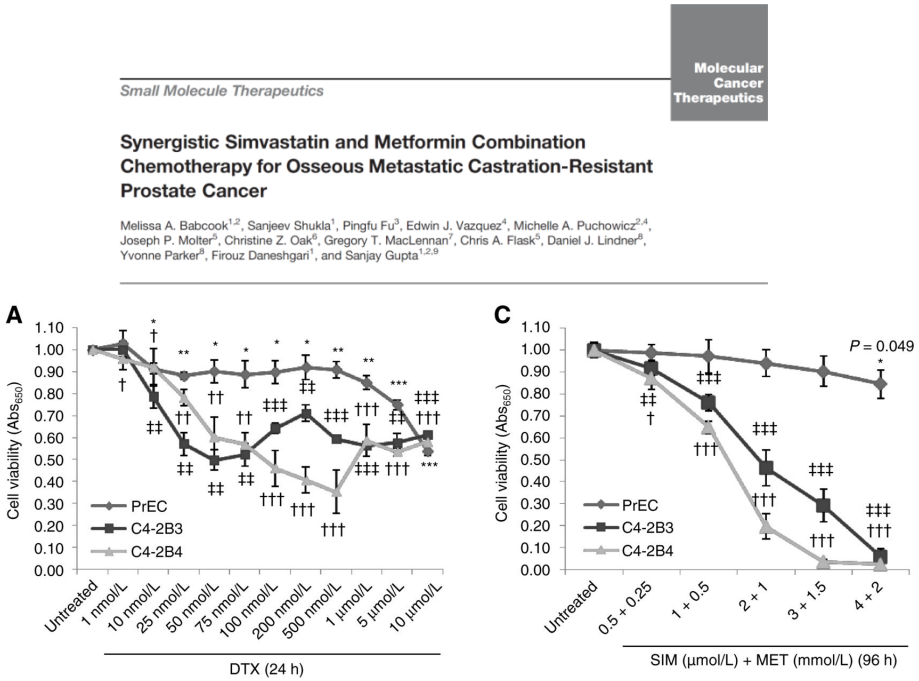
Table 5. Sensitivity Analyses of the Association Between Cumulative Use of Metformin and PC-Specific and All-Cause Mortality

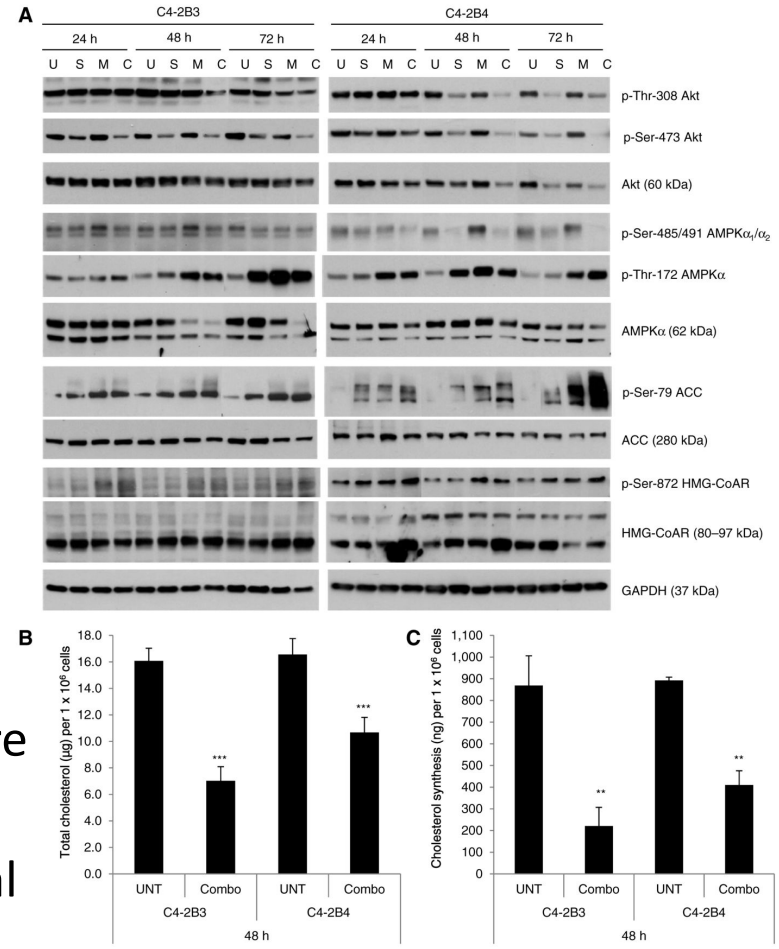
		PC-Specific Mortality			All-Cause Mortality		
Variable	No. of Patients	HR	95% CI	*P*	HR	95% CI	*P*
Metformin monotherapy *v* diet control	850 of 1,702	0.56	0.51 to 0.70	.0013	0.8	0.77 to 0.85	.005
Statin users	2,405	0.78	0.62 to 0.99	.004	0.92	0.84 to 1.01	.1
Low comorbidity*	1,940	0.78	0.54 to 1.14	.03	0.91	0.85 to 0.98	.0015
Metformin users	1,619	0.81	0.75 to 0.87	.003	0.95	0.91 to 1.02	.2
Localized PC	955	0.59	0.41 to 1.2	.24	0.95	0.8 to 1.08	.81
Advanced PC	1,109	0.71	0.62 to 0.83	.006	0.92	0.86 to 0.99	.01
Tracer analysis- cataract surgery		0.98	0.96 to 1.1		0.98	0.96 to 1.1	

NOTE. Each unit represents 6 months of follow-up with prostate cancer (PC) –specific and all-cause mortality. The same primary multivariable analysis was repeated separately for each of the eight sensitivity analyses.
Abbreviation: HR, hazard ratio.
*Weighted score of 4 or more by using Johns Hopkins Adjusted Clinical Groups Case-Mix System.

HR for interaction: 0.77,
p=0.0001

Statin / Metformin Combination





- Combination of simvastatin and metformin synergistically inhibits mCRPC cell viability more effectively then docetaxel
- Minimal adverse viability effect on PrEC normal prostate epithelial cells
- Statin/metformin combination ameliorates metabolic abnormalities

LIPITOR AND BIGUANIDE TO ANDROGEN DELAY (LIGAND) TRIAL

LIGAND Trial

Aims:

A. Determine if combo biguanide/statin can delay PSA rise among men with biochemical failure and M0 disease

B. Determine predictors of response to therapy in this group

C. Secure biospecimens for other projects

- Aim: 40% (HR 0.6) improvement in time to PSA > 10 ng/mL or development of metastases
- N = 110 patients in a randomized phase 2 setting (80% power α 0.1)
- Stratified by
  - PSA doubling time
  - Centre
  - Past treatment

Metabolic Syndrome and its Components in Prostate Cancer Patients under Androgen Deprivation Therapy

Juan Morote , Antonio Gómez-Caamaño , José L. Alvarez-Ossorio , Daniel Pesqueira , Angel Tabernero , Francisco Gómez Veiga , José A. Lorente , Mariano Porras , Juan J. Lobato , María J. Ribal , Jacques Planas

PII: S0022-5347(14)05140-4
DOI: 10.1016/j.juro.2014.12.086
Reference: JURO 12093

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Accepted Date: 15 December 2014

Table 3. Changes in the prevalence of MetS after one year of androgen deprivation therapy, according to the definition criteria.

Time	WHO (1998)	ATP III (2001)	AACE (2003)	AHA/NHLBI (2005)	IDF (2005)
Baseline	29 (9.4)	71 (22.9)	104 (33.5)	133 (42.9)	155(50.0)
After12 months of ADT[a]	42 (13.5)	83 (26.8)	119 (38.4)	158 (51.0)	173 (55.8%)
Percent increase (%)	4.1	3.9	4.9	8.1	5.8
p Value	0.049*	0.075	0.211	0.001*	0.061

[a]ADT: androgen deprivation therapy. *Significant difference.

ADT vs Classic Metabolic syndrome

	Metabolic Syndrome	ADT-induced Metabolic Syndrome
Abdominal obesity	Yes	Yes
Insulin sensitivity	Decreased	Decreased
Trigylycerides	Increased	Increased
Fat accumulation	Visceral	Subcutaneous
HDL cholesterol	Decreased	Increased

Slide courtesy of Matthew Smith

BJUI
BJU INTERNATIONAL

A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy

Jenny P. Nobes, Stephen E.M. Langley, Tanya Klopper, David Russell-Jones* and Robert W. Laing

*St Luke's Cancer Centre, and *Department of Diabetes and Endocrinology, The Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK*

Accepted for publication 10 June 2011

TABLE 3 Between group comparisons of percentage change from baseline to 6 months

Variable	Control arm ($n = 20$), % change, mean (SD)	Intervention arm ($n = 20$), % change, mean (SD)	*P*
Abdominal girth (cm)	2.15 (4.30)	−0.58 (3.53)	0.05
Weight (kg)	2.18 (3.63)	−3.19 (3.82)	<0.001
BMI (kg/m^2)	2.10 (3.58)	−3.15 (3.73)	<0.001
Body fat (%)	6.47 (20.60)	−5.48 (14.95)	0.08
Systolic BP (mmHg)	1.77 (5.96)	−5.96 (10.13)	0.01
Diastolic BP (mmHg)	2.85 (10.54)	0.99 (13.68)	0.66
Glucose 0 (mmol/L)	−3.14 (5.40)	0.36 (8.30)	0.16
Glucose 60 (mmol/L)	16.34 (55.30)	19.70 (40.89)	0.84
Glucose 120 (mmol/L)	−10.07 (26.42)	−5.98 (35.63)	0.71
Triglycerides (mmol/L)	17.08 (48.03)	26.07 (66.98)	0.66
HDL cholesterol (mmol/L)	10.88 (15.37)	10.14 (12.04)	0.87
LDL cholesterol (mmol/L)	−2.34 (19.84)	7.05 (13.61)	0.12
Total cholesterol (mmol/L)	2.01 (16.91)	8.37 (12.36)	0.22
Insulin 0 (pmol/L)	21.74 (119.57)	40.58 (242.40)	0.78
Insulin 60 (pmol/L)	16.87 (75.24)	0.93 (46.35)	0.48
Insulin 120 (pmol/L)	24.52 (140.22)	69.41 (216.54)	0.51
C-peptide 0 (pmol/L)	46.17 (107.38)	20.81 (119.19)	0.52
C-peptide 60 (pmol/L)	14.07 (53.10)	6.65 (27.89)	0.64
C-peptide 120 (pmol/L)	29.69 (74.70)	23.01 (32.24)	0.76
IGF-1 (nmol/L)	−6.85 (27.24)	7.32 (22.05)	0.10
IGF BP3 (mg/L)	1.09 (15.34)	0.33 (21.03)	0.91
HbA1c (%)	−0.23 (3.62)	−2.23 (3.09)	0.07
Leptin (ng/mL)	64.77 (95.10)	24.16 (64.32)	0.24
Adiponectin (ng/mL)	17.65 (25.39)	28.18 (21.81)	0.20
Ghrelin (pg/mL)	3.51 (29.12)	1.22 (29.94)	0.82

BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; IGF BP3, IGF binding protein 3; LDL, low-density lipoprotein.

TABLE 4 Within group change in mean value for each parameter from baseline to 6 months

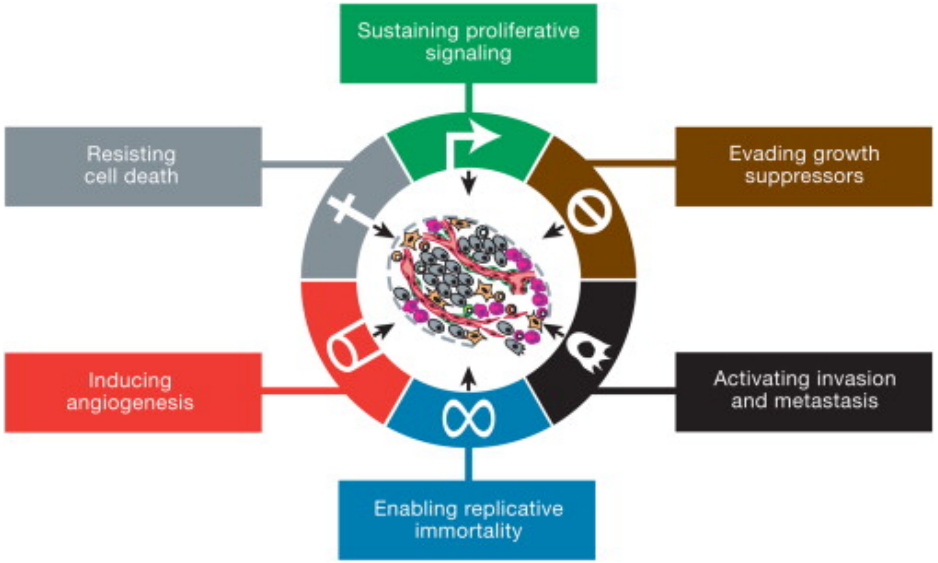
	Control arm ($n = 20$), mean (SD)			Intervention arm ($n = 20$), mean (SD)		
Variable	Baseline	6 months	*P*	Baseline	6 months	*P*
Metabolic syndrome, *n*	2	2	1.00	7	3	0.04
Abdominal girth (cm)	101.6 (9.6)	103.7 (10.2)	0.08	100.1 (6.8)	99.4 (5.9)	0.41
Weight (kg)	81.0 (14.7)	82.7 (14.8)	0.04	82.0 (10.3)	79.3 (10.0)	<0.01
BMI (kg/m^2)	25.9 (3.7)	26.4 (3.7)	0.04	27.0 (3.1)	26.1 (3.0)	<0.01
Body fat (%)	23.4 (4.8)	24.5 (4.5)	0.22	25.5 (5.2)	24.1 (5.9)	0.11
Systolic BP (mmHg)	130.3 (11.9)	132.4 (12.2)	0.26	134.8 (16.0)	125.8 (12.1)	0.02
Diastolic BP (mmHg)	74.5 (10.2)	76.3 (10.5)	0.40	76.4 (8.6)	76.4 (7.5)	1.00
Glucose 0 (mmol/L)	5.39 (0.46)	5.21 (0.47)	0.03	5.49 (0.61)	5.48 (0.38)	0.88
Glucose 60 (mmol/L)	7.44 (3.00)	8.39 (5.75)	0.46	9.19 (2.77)	10.33 (2.71)	0.12
Glucose 120 (mmol/L)	6.49 (1.91)	5.62 (1.80)	0.03	7.56 (2.34)	6.62 (2.05)	0.11
Triglycerides (mmol/L)	1.41 (1.27)	1.75 (2.10)	0.18	1.17 (0.53)	1.34 (0.67)	0.18
HDL cholesterol (mmol/L)	1.46 (0.28)	1.61 (0.37)	0.02	1.44 (0.36)	1.57 (0.31)	<0.01
LDL cholesterol (mmol/L)	3.48 (1.27)	3.21 (0.74)	0.32	2.96 (0.64)	3.17 (0.89)	0.05
Total cholesterol (mmol/L)	5.59 (1.34)	5.55 (0.94)	0.88	4.92 (0.75)	5.32 (0.98)	0.01
HOMA IR	1.17 (0.74)	1.25 (0.99)	0.63	1.41 (1.45)	1.33 (1.49)	0.76
Insulin 0 (pmol/L)	61.69 (40.0)	66.6 (53.7)	0.59	107.0 (160.0)	92.4 (153.3)	0.76
Insulin 60 (pmol/L)	583.3 (428.3)	499.9 (234)	0.51	556.9 (287.1)	502.3 (256.4)	0.43
Insulin 120 (pmol/L)	307.3 (183.0)	277.1 (204.5)	0.50	273.8 (156.8)	280.5 (120.7)	0.88
C-peptide 0 (pmol/L)	800.4 (349.0)	1 058.3 (715.1)	0.15	954.2 (773.1)	917.2 (792.7)	0.89
C-peptide 60 (pmol/L)	3 527.6 (1 341.8)	3 523.1 (810.8)	0.99	3 656.3 (1 386.7)	3 636.6 (877.3)	0.95
C-pep 120 (pmol/L)	2 719.9 (1 258.1)	2 906.0 (938.4)	0.50	2 625.7 (770.2)	3 188.0 (1 032)	0.01
IGF-1 (nmol/L)	20.38 (4.57)	19.03 (7.23)	0.35	17.51 (3.45)	18.73 (4.90)	0.17
IGF BP3 (mg/L)	2.84 (0.64)	2.87 (0.73)	0.81	2.75 (0.57)	2.72 (0.63)	0.83
HbA1c (%)	5.37 (0.27)	5.35 (0.26)	0.73	5.51 (0.20)	5.38 (0.21)	<0.01
Adiponectin (ng/mL)	12 286 (2 872)	14 132 (3 040)	0.01	11 718 (5 652)	14 349 (5 017)	<0.001
Ghrelin (pg/mL)	1 030.73 (612.97)	994.58 (493.99)	0.65	1 289.14 (428.65)	1 286.24 (486.29)	0.98
Leptin (ng/mL)	3.76 (2.23)	5.37 (2.53)	0.02	4.72 (2.06)	5.63 (3.62)	0.21

BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; IGF BP3, IGF binding protein 3; LDL, low-density lipoprotein.

ADT + METFORMIN (Jarrad)2017

- VA database (n=87,344)
- DM pts on metformin
  - HR 0. 77(0.74-0.81)
- DM not on Metformin
  - HR 0.99
  - OS prolongation 7.4->9.1 yrs

Hallmarks of Cancer: Evolving Perspective



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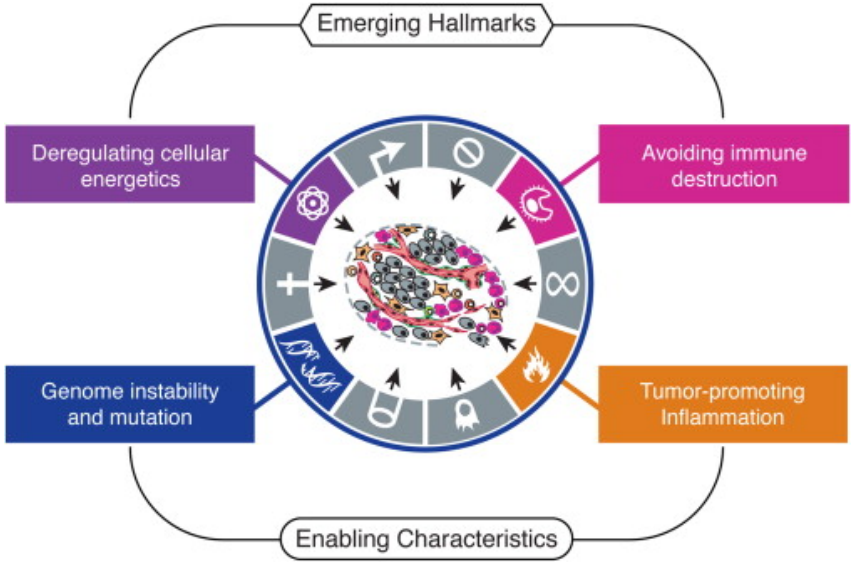
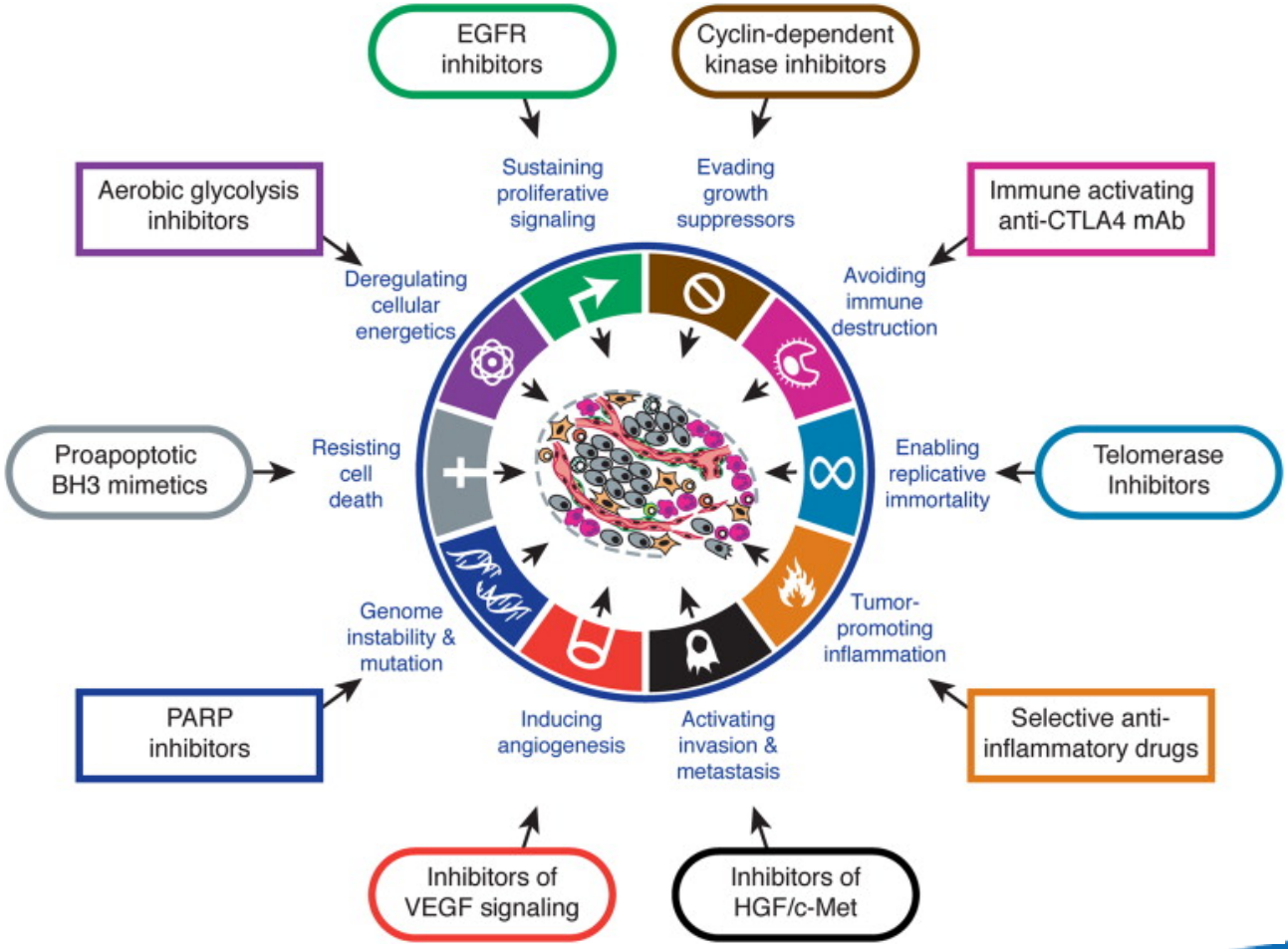


2011

Douglas Hanahan , Robert A. Weinberg
Hallmarks of Cancer: The Next Generation
Cell, Volume 144, Issue 5, 2011, 646 - 674
http://dx.doi.org/10.1016/j.cell.2011.02.013

Hallmarks of Cancer: Evolving Perspective



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CONCLUSIONS

- Urologist's need to recognize MetS
- ADT increases risk of MetS and may explain cardiovascular risk changes
- MetS components are viable targets not only for minimizing risk of ADT but potentially as anticancer therapies