PROSTATE CANCER:

ANDROGEN RECEPTOR, ANDROGEN DEPLETION THERAPIES, BONE METASTASIS & EVOLUTION TO CASTRATION RESISTANCE

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DISCLOSURE - ΔΗΜΟΣΙΟΠΟΙΗΣΗ

Είμαι μέλος της Εθνικής Επιτροπής «Βιοηθικής & Δεοντολογίας» για τις Κλινικές Μελέτες στην Ελλάδα, Υπουργείου Υγείας.

Δεν παίρνω αμοιβή για τις ομιλίες μου και δεν είμαι επ' αμοιβή σύμβουλος σε καμία Φαρμακευτική Εταιρεία στην Ελλάδα ή στο εξωτερικό.

Το Εργαστήριο Πειραματικής Φυσιολογίας, το οποίο διευθύνω από το 2004, έχει τα τελευταία χρόνια χρηματοδοτηθεί με "Institutional Support" από σειρά Φαρμακευτικών Εταιρειών στα πλαίσια Ερευνητικών Προγραμμάτων και του ΜΠΣ «Μοριακή & Εφαρμοσμένη Φυσιολογία» μέσω του ΕΛΚΕ (2007-2017):

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ELPEN

ΕΙΝΑΙ ΣΟΒΑΡΟ ΠΡΟΒΛΗΜΑ ΝΑ ΕΧΕΙΣ ΚΑΡΚΙΝΟ ΤΟΥ ΠΡΟΣΤΑΤΗ ?

1930: Η εφημερίδα ΕΣΤΙΑ έγραφε…

…άμαξα παρέσυρε και φόνευσε γέροντα 50 ετών…

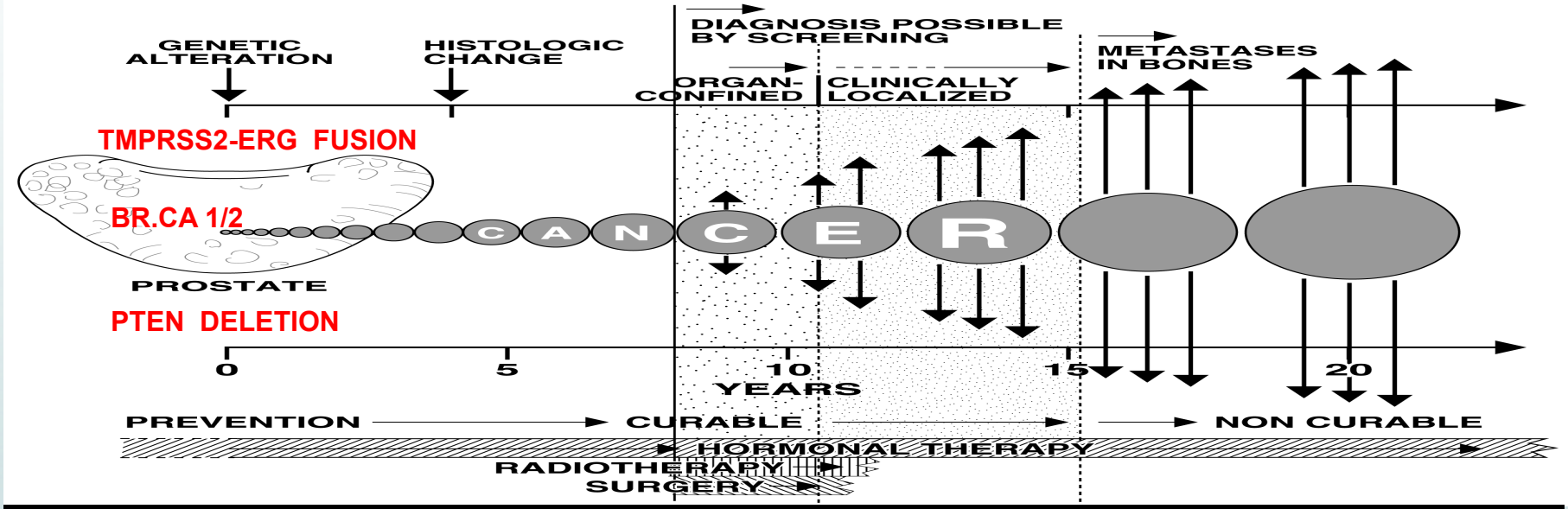
1948: Swedish Study on Prostate Cancer Pathology

…detection of PR.CA in 80 % of cadavers > 80 yrs....<latent PR.CA>...

1942: Huggins & Hodges Nobel Laureates in Physiology-Medicine

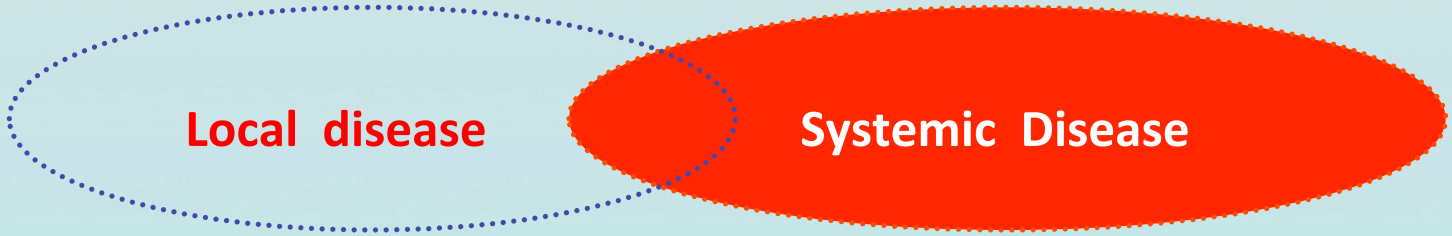
…castration & estrogens produce clinical response in metastatic prostate CA…

Clinical Evolution of Prostate Cancer



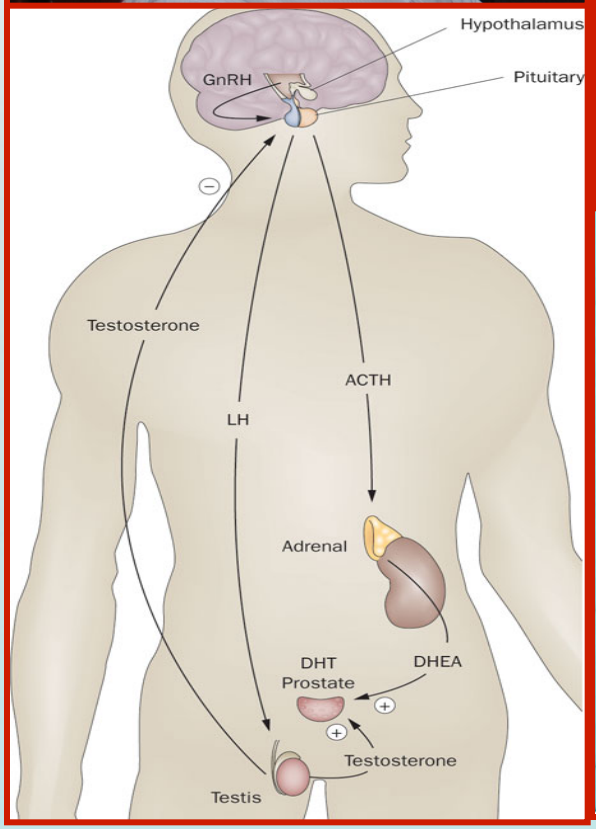
Castration Responding		Castration Resistant
PIN	CANCER	Lymph nodes (+)

PRE - OPERATIVE PREDICTORS: PSA (>20) , Gleason score (>7), CTCs (+) Bone Scan (+)

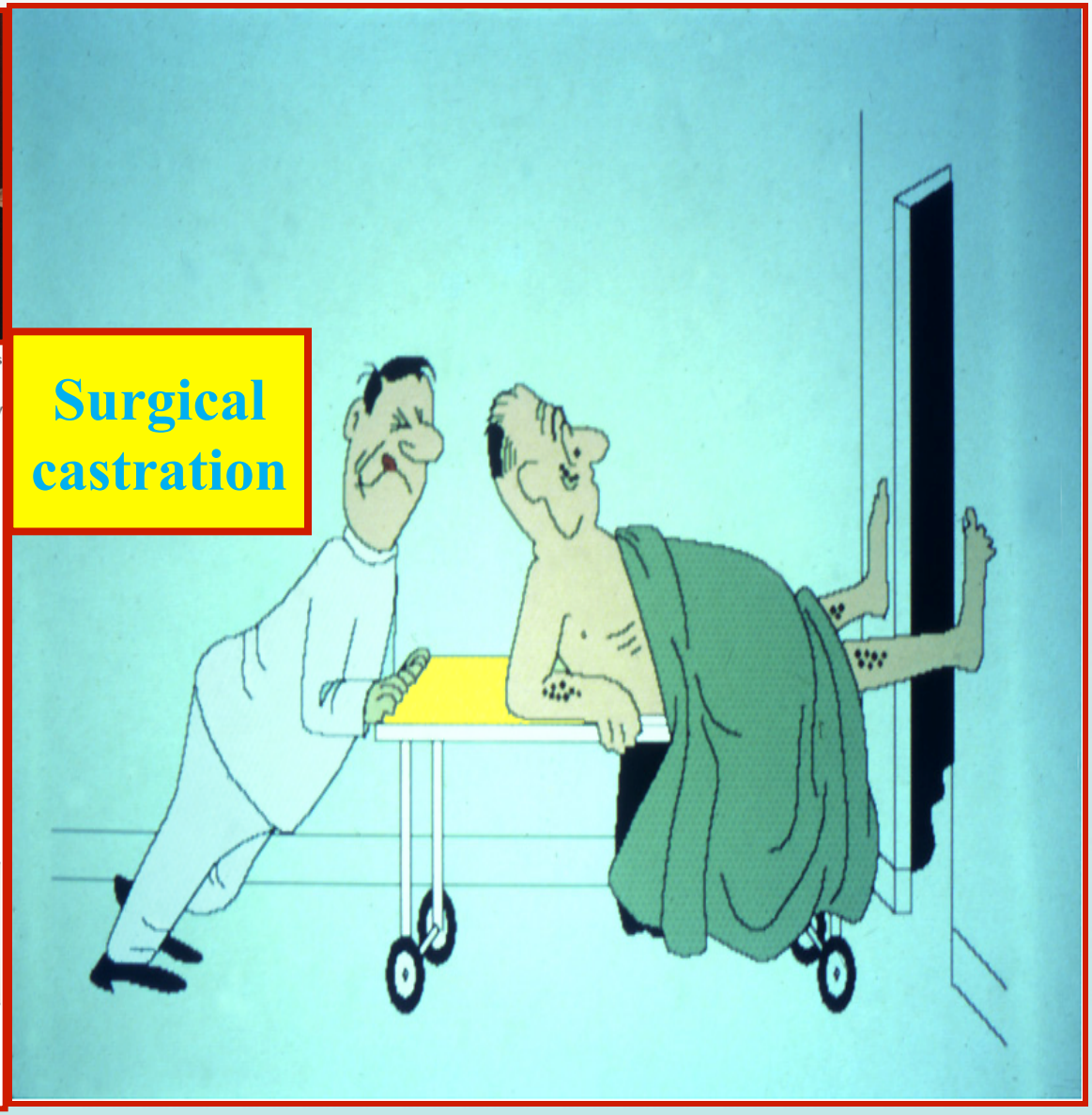


PROSTATE CANCER : Understanding The Pathophysiology and Re-Designing A Therapeutic Approach
(Editors: F. Labrie & M. Koutsilieris, 2004)

LHRH-A (MEDICAL CASTRATION) IN THE TREATMENT OF ADVANCED PROSTATE CANCER

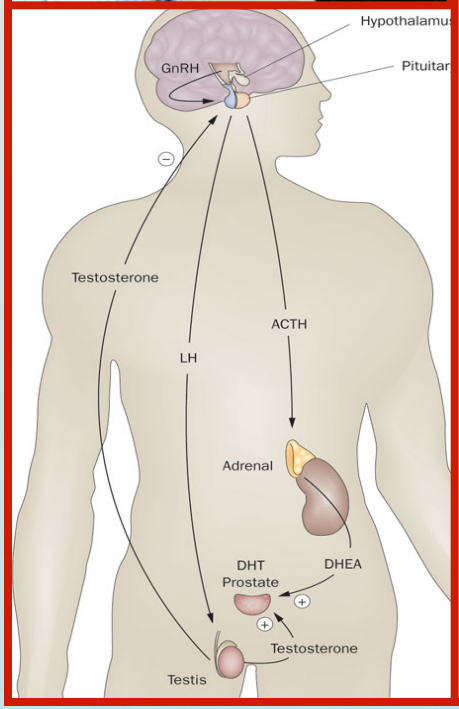


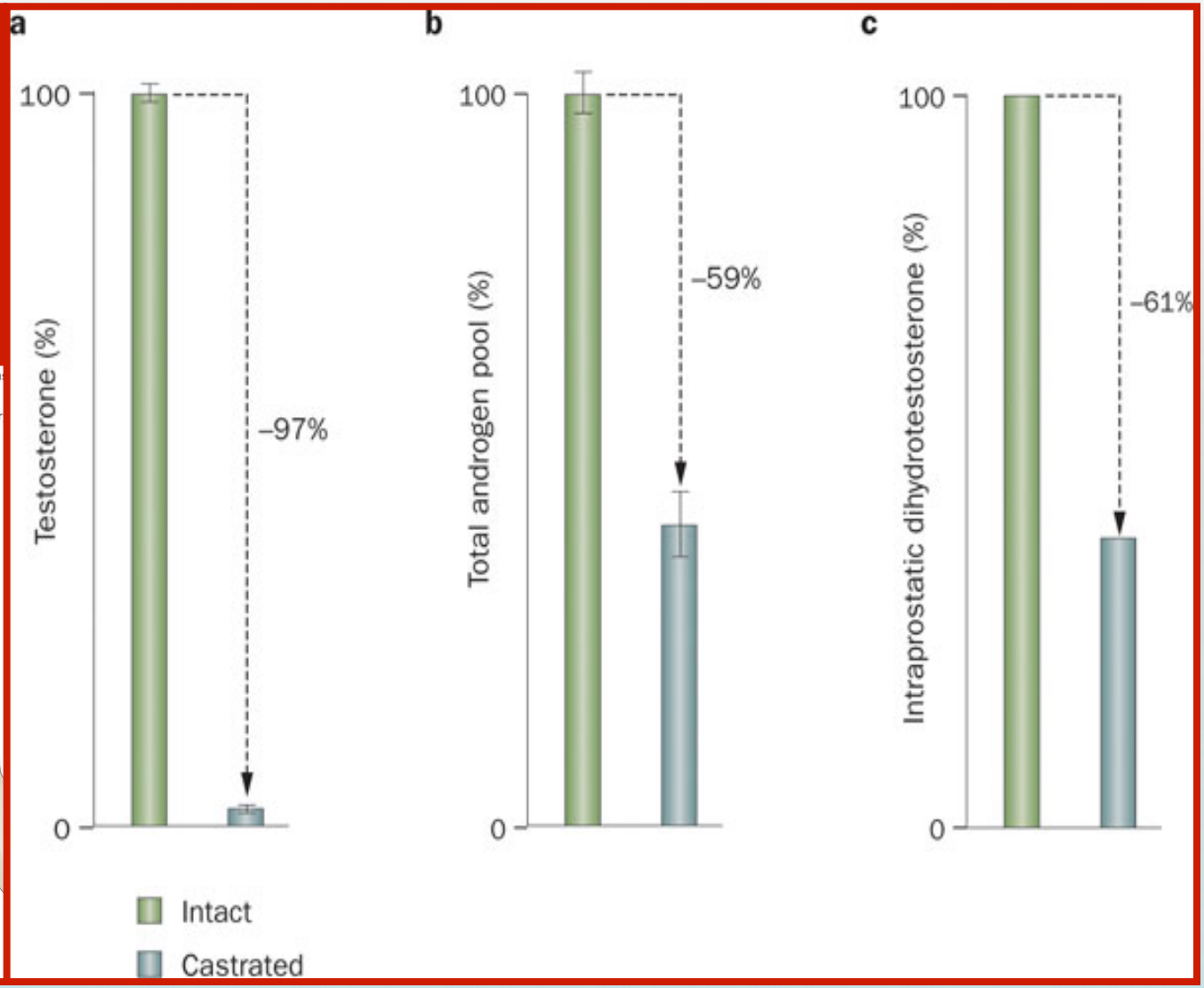
Surgical castration



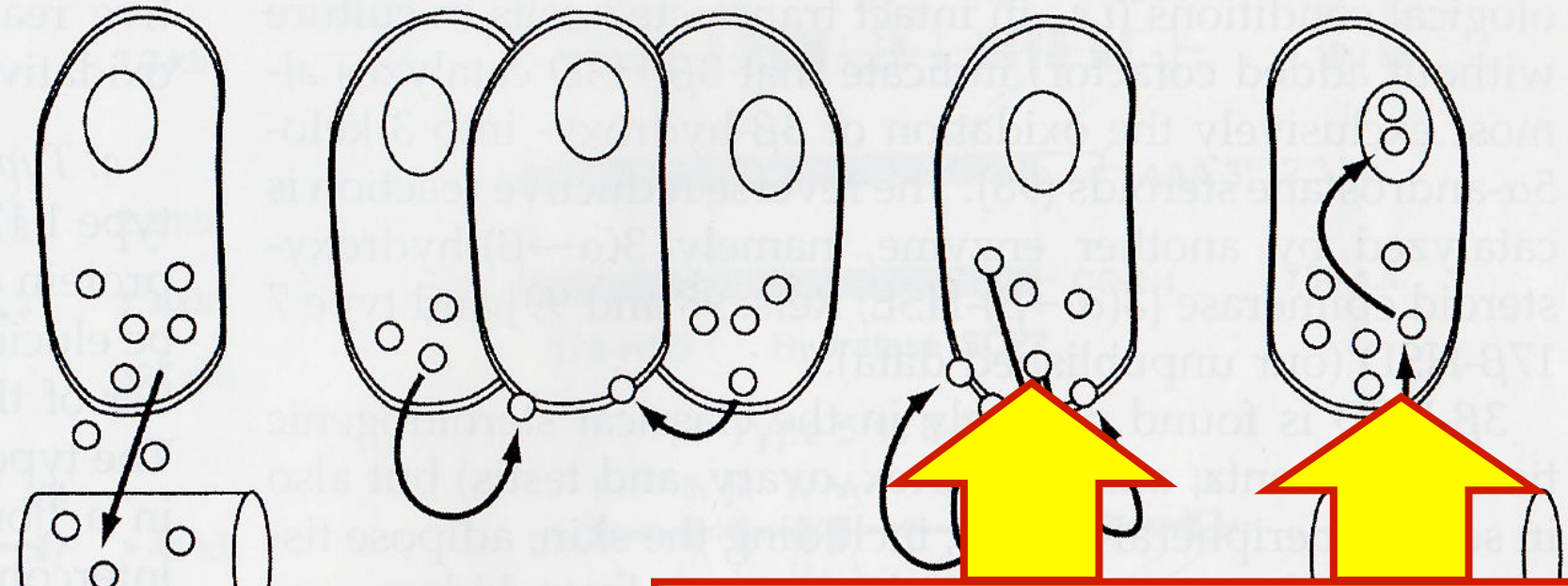
George Tolis et al, PNAS (USA), 1981

THE CONCEPT OF RESIDUAL ANDROGEN IN PROSTATE CANCER COMBINATION THERAPY (LHRH-A plus ANTIANDROGEN)





Fernand Labrie et al, CJCI, 1982



Production & Transformation Of Steroid Hormones In the Peripheral Tissues

COMPLETE / COMBINED ANDROGEN BLOCKADE (CAB)

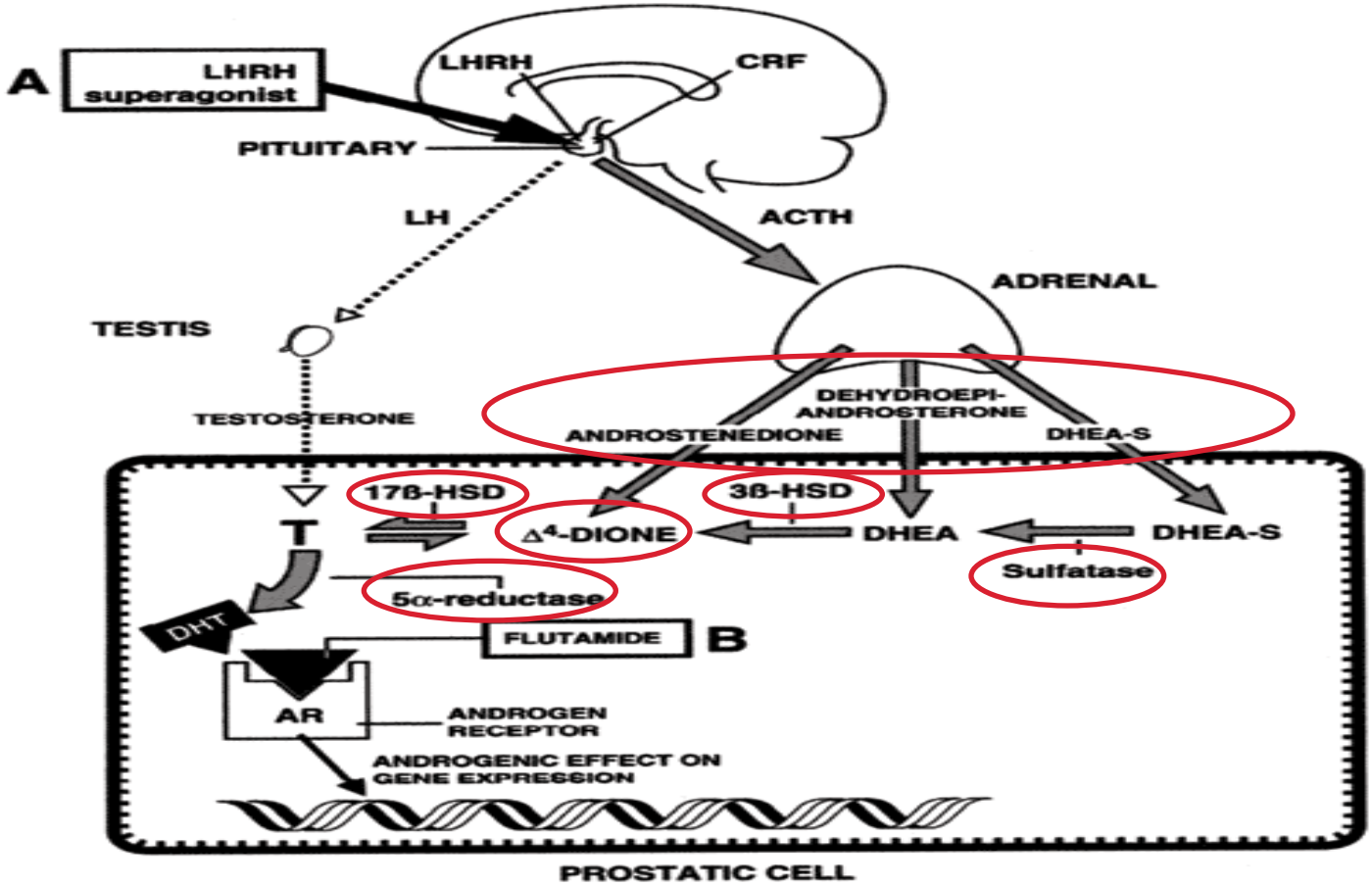
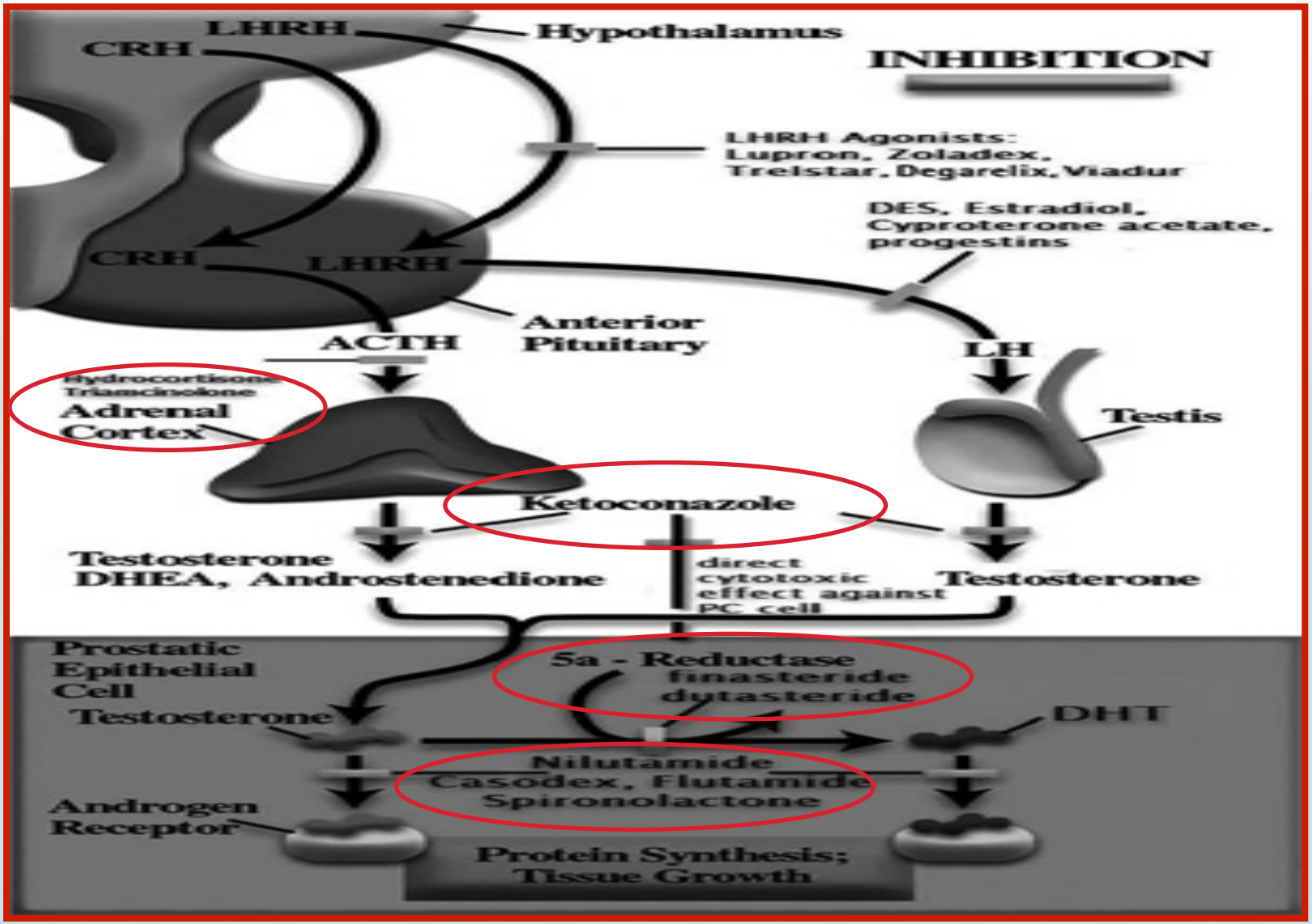
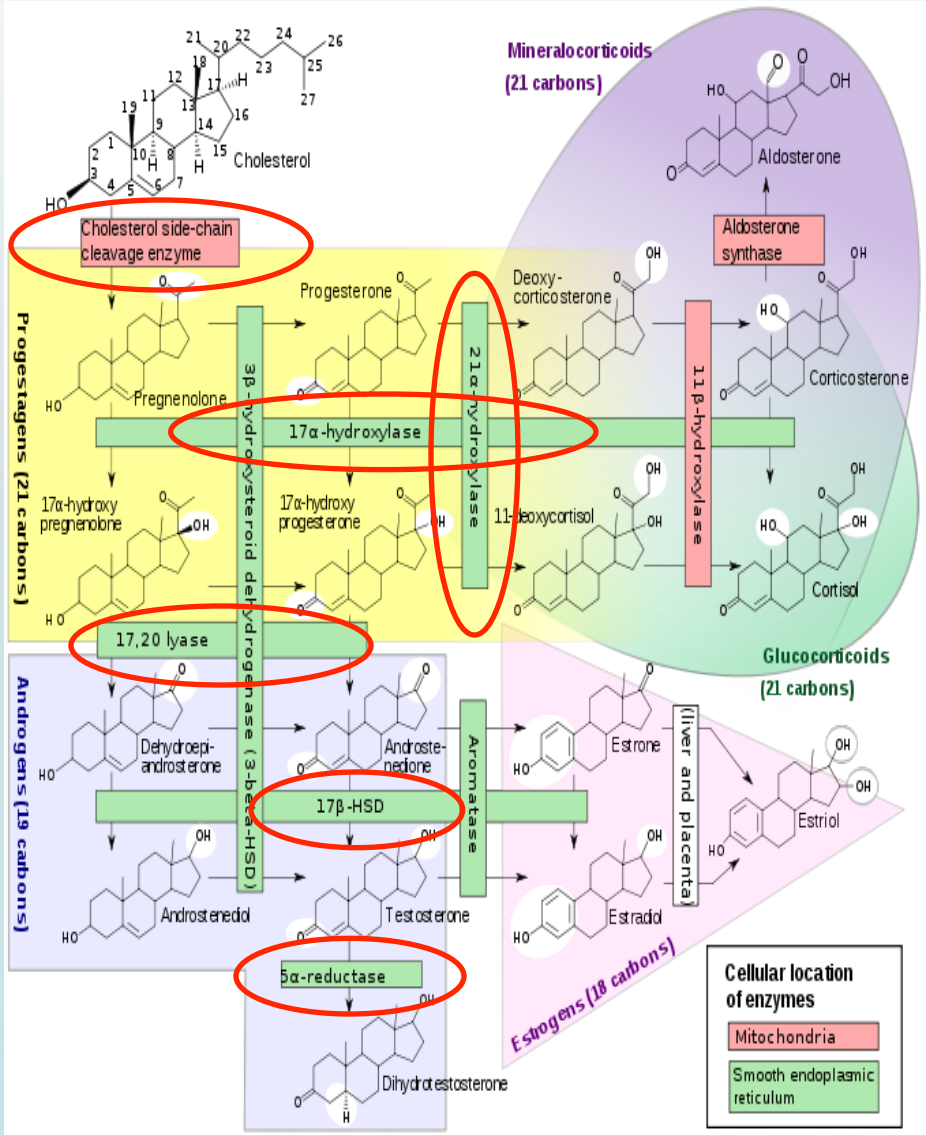


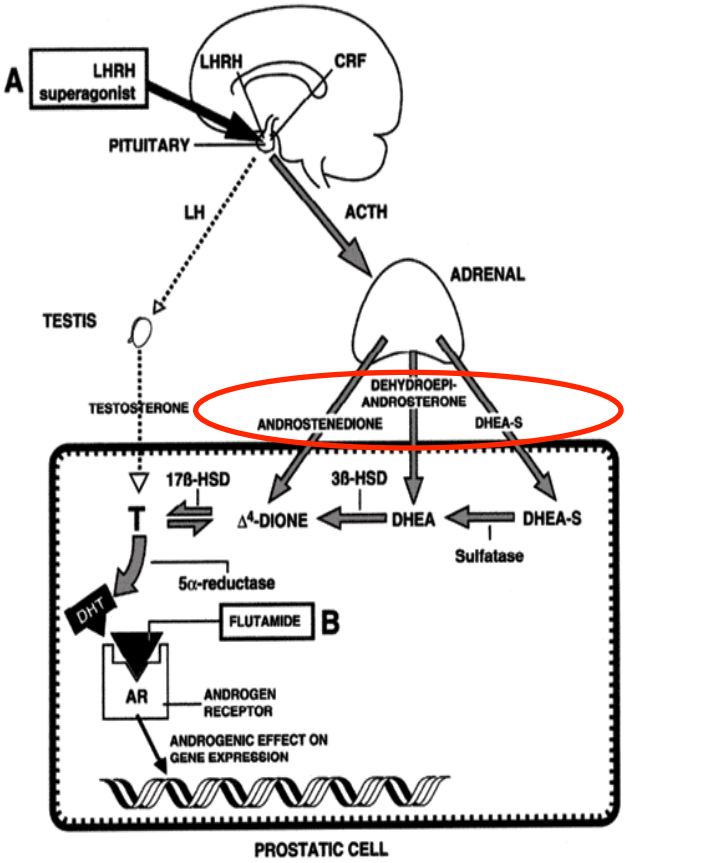
Figure 3 *— Intracrine activity of the human prostate or biosynthetic steps involved in the formation of the active androgen dihydrotestosterone (DHT) from testicular testosterone as well as from the inactive adrenal precursors DHEA, DHEA-sulfate (DHEA-S), and 4-dione in human prostatic tissue. 17β-hydroxysteroid dehydrogenase; 3β-HSD = 3β-hydroxysteroid dehydrogenase/Δ⁵-Δ⁴-isomerase. The widths of the arrows indicate the relative importance of the sources of DHT in the human prostate: 60% originating from the testes and 40% from the adrenals in 65-year-old men. The testis secretes testosterone (T) which is transformed into the more potent androgen DHT by 5α-reductase in the prostate. Instead of secreting T or DHT directly, the adrenal secretes very large amounts of DHEA and DHEA-sulfate (DHEA-S), which are transported in the blood to the prostate and other peripheral tissues. These inactive precursors are then transformed locally into the active androgens T and DHT. The enzymatic complexes DHEA sulfatase, 3β-HSD, 17β-HSD and 5α-reductase are all present in the prostatic cells, thus providing 40% of total DHT in this tissue. (From Labrie F: Androgen blockade in prostate cancer in 2002: major benefits on survival in localized disease. Mol Cell Endocrinol. 2002; 198: 77-87.)*

Clinical trials in 80's & 90's



ANDROGEN SYNTHESIS IN PERIPHERAL TISSUES





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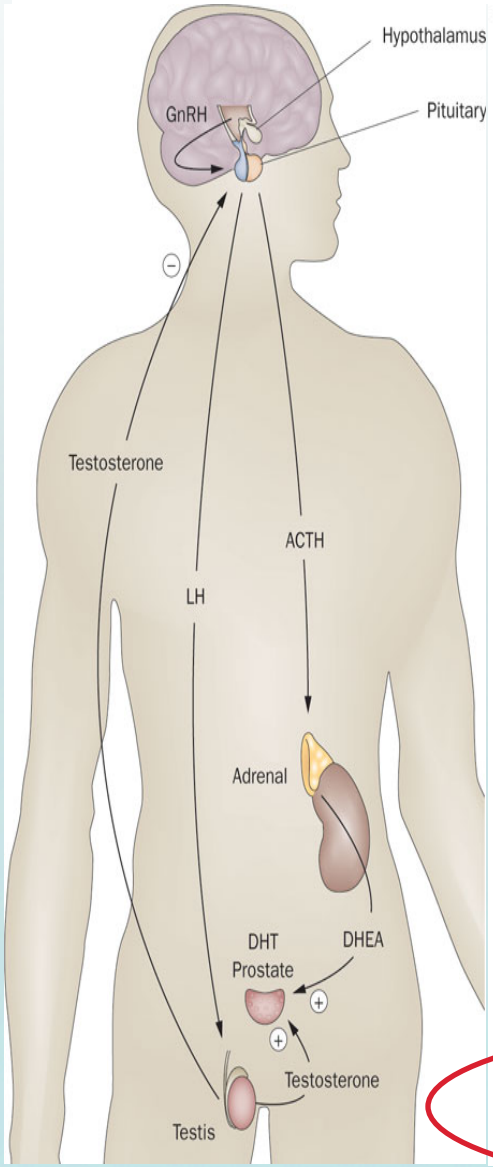
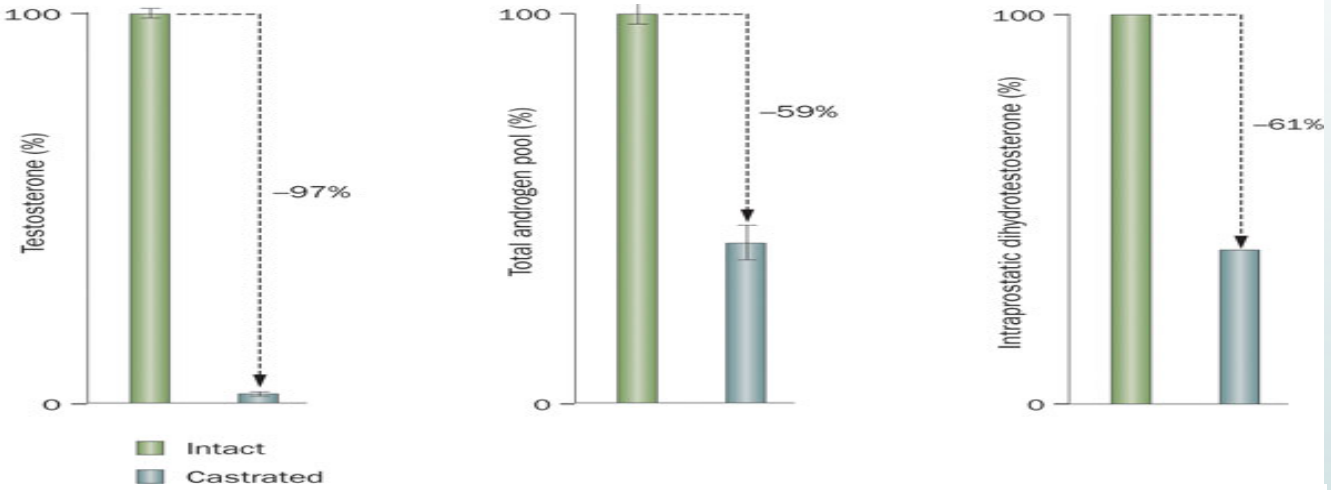
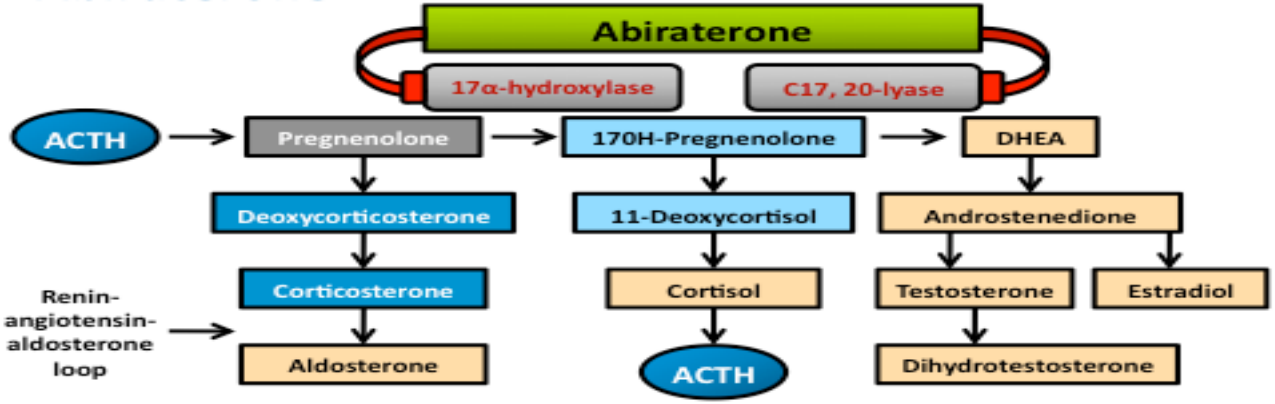
TARGETING THE SYNTHESIS OF ANDROGENS LOCALLY





Targeting Androgen Biosynthesis

Abiraterone



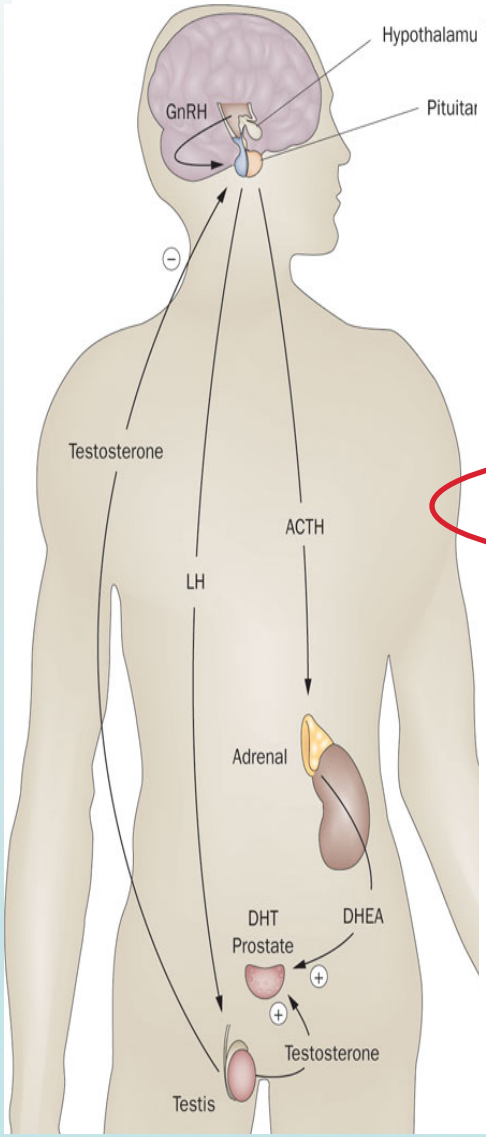
- **Inhibitor of CYP17A1**
- **Pre- and post-docetaxel antitumor activity**

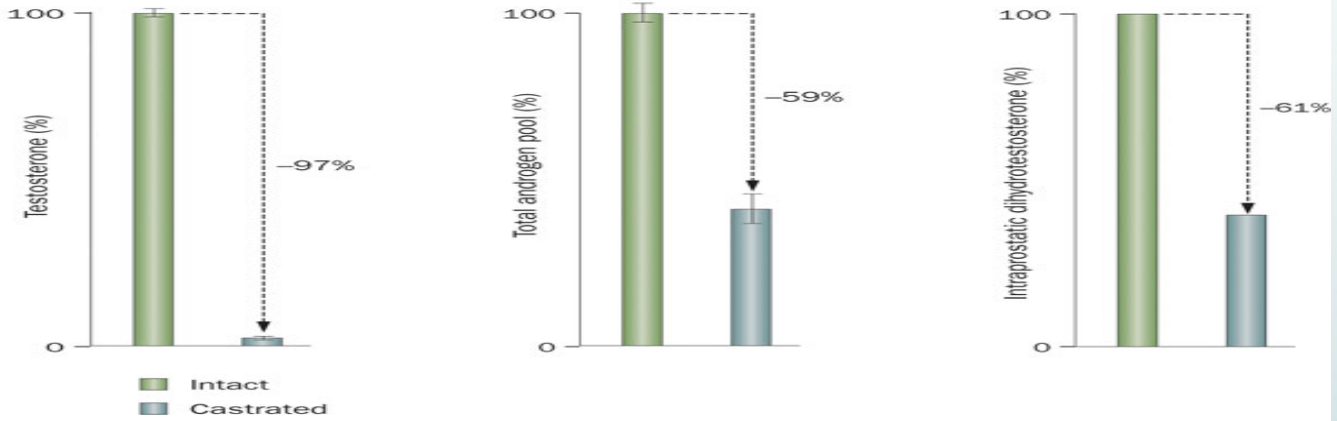
ACTH = adrenocorticotropic hormone; DHEA = dehydroepiandrosterone

Ang JE, et al. *Br J Cancer.* 2009;100:671-675.

Medscape EDUCATION

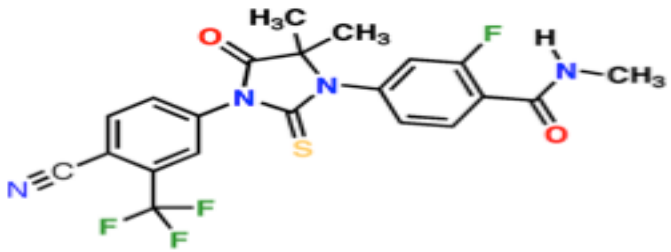
TARGETING THE ACTIVITY OF THE ANDROGEN RECEPTOR





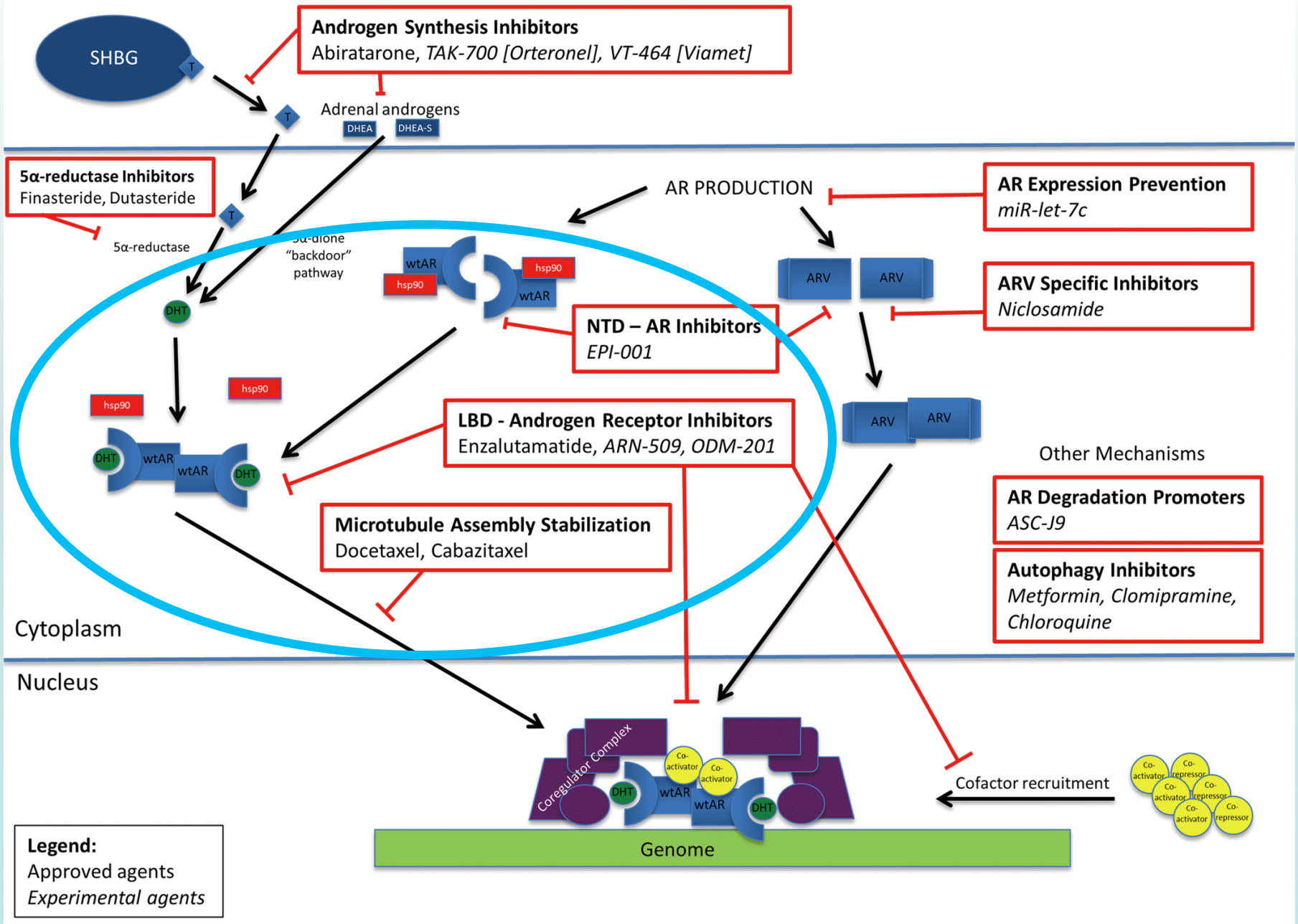
Targeting AR Function
MDV3100

- Small AR antagonist
- Binds AR more potently than bicalutamide
- Inhibits AR nuclear translocation

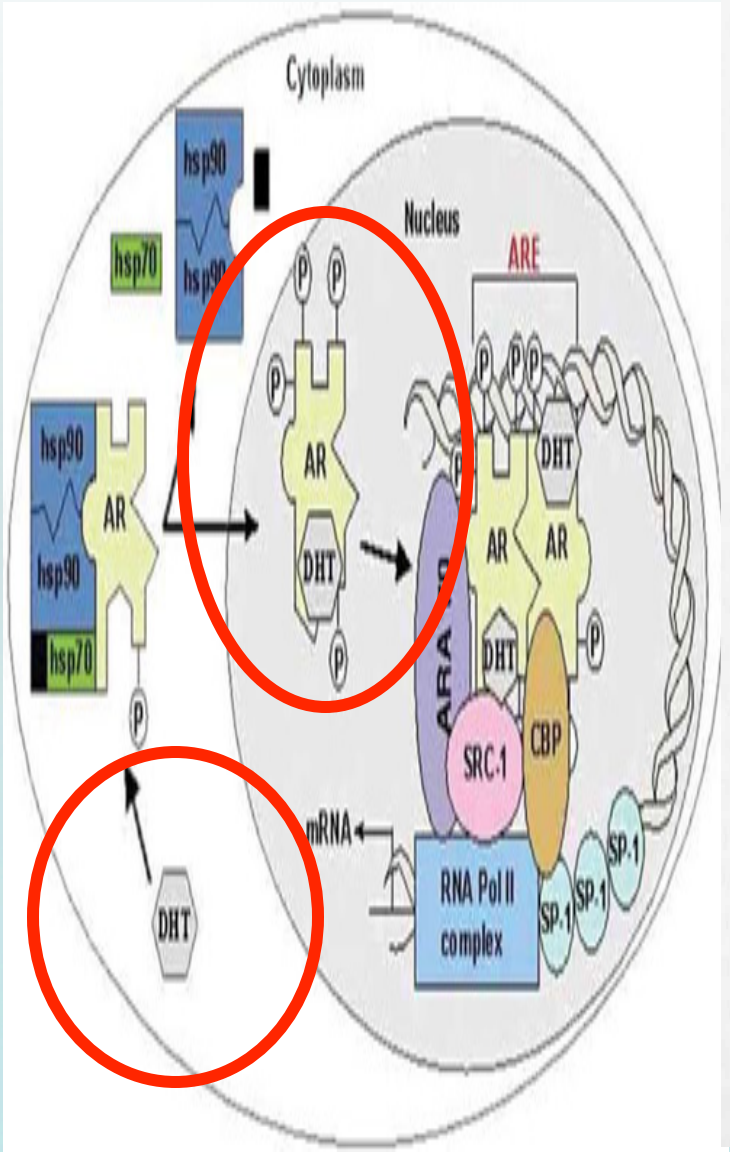


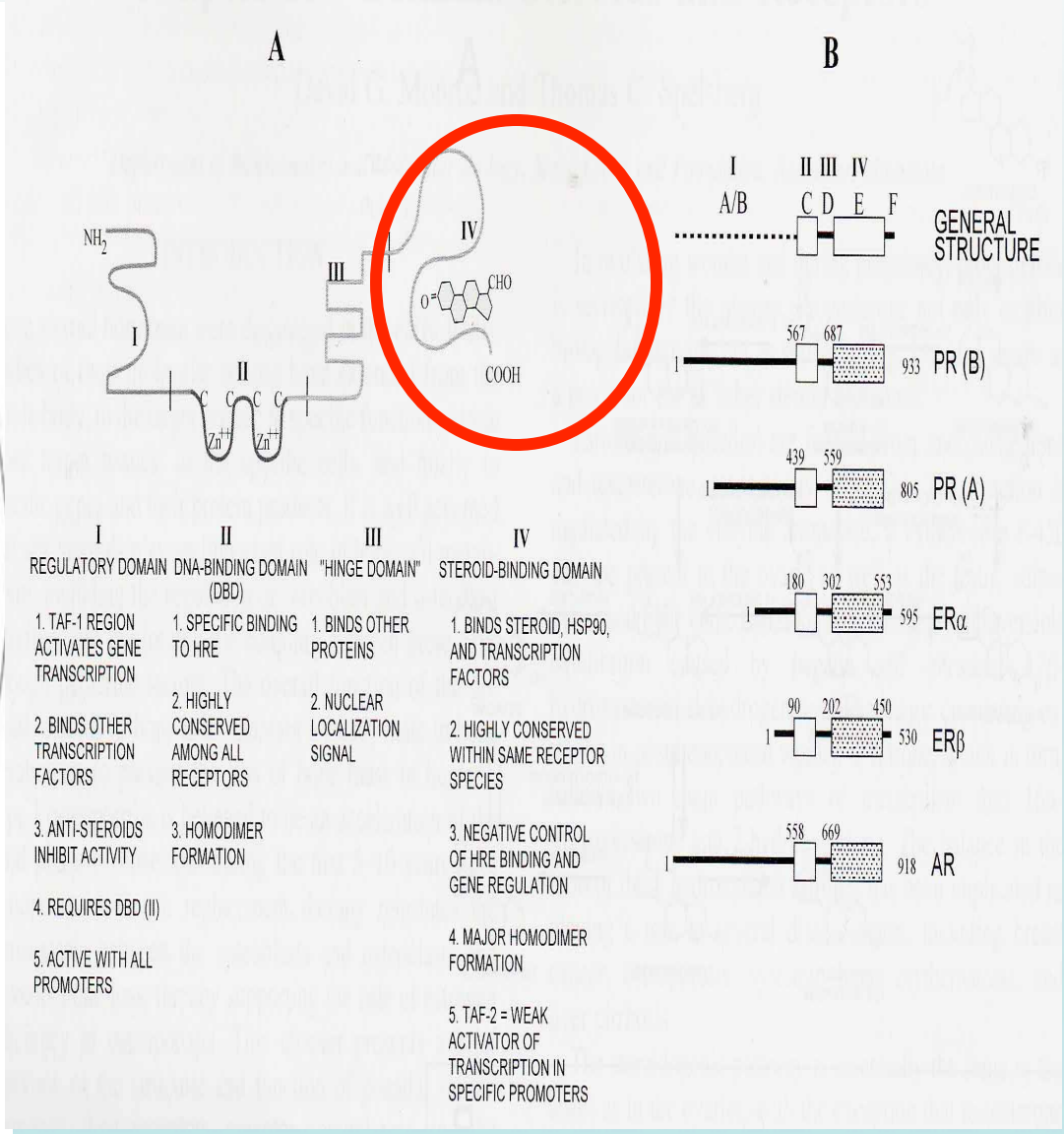
Scher HI, et al. *Lancet*. 2010;375:1437-1446.

Medscape EDUCATION

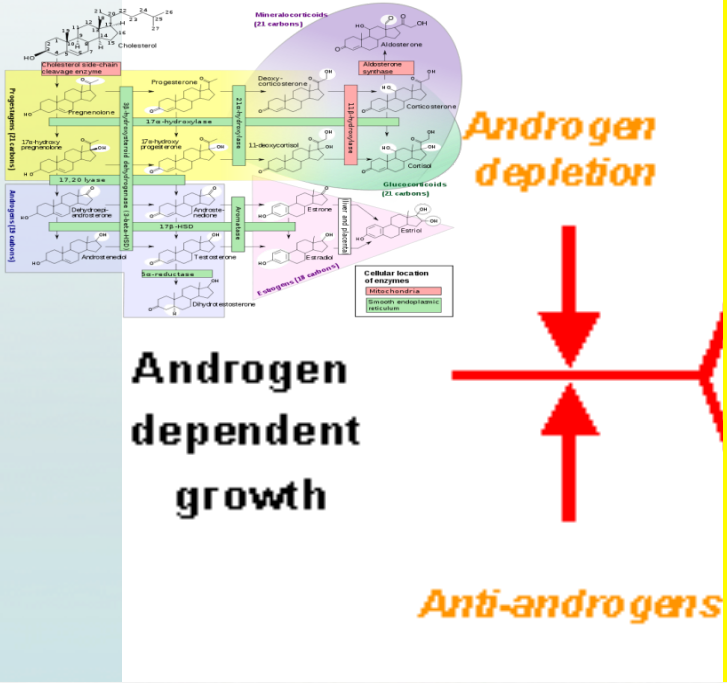

SHBG
T
Androgen Synthesis Inhibitors
Abiratarone, TAK-700 [Orteronel], VT-464 [Viamet]
Adrenal androgens
DHEA
DHEA-S
5α-reductase Inhibitors
Finasteride, Dutasteride
5α-reductase
5α-dione "backdoor" pathway
AR PRODUCTION
AR Expression Prevention
miR-let-7c
ARV Specific Inhibitors
Niclosamide
NTD – AR Inhibitors
EPI-001
LBD - Androgen Receptor Inhibitors
Enzalutamatide, ARN-509, ODM-201
Microtubule Assembly Stabilization
Docetaxel, Cabazitaxel
Other Mechanisms
AR Degradation Promoters
ASC-J9
Autophagy Inhibitors
Metformin, Clomipramine, Chloroquine
Cytoplasm
Nucleus
wtAR
hsp90
DHT
ARV
Coregulator Complex
Co-activator
Co-repressor
Cofactor recruitment
Genome
Legend:
Approved agents
Experimental agents

ANTI – ANDROGENS / ANDROGEN RECEPTOR ACTIVITY





CASTRATION RESISTANT PROSTATE CANCER



Castration Resistant Growth

&

Disease Evolution

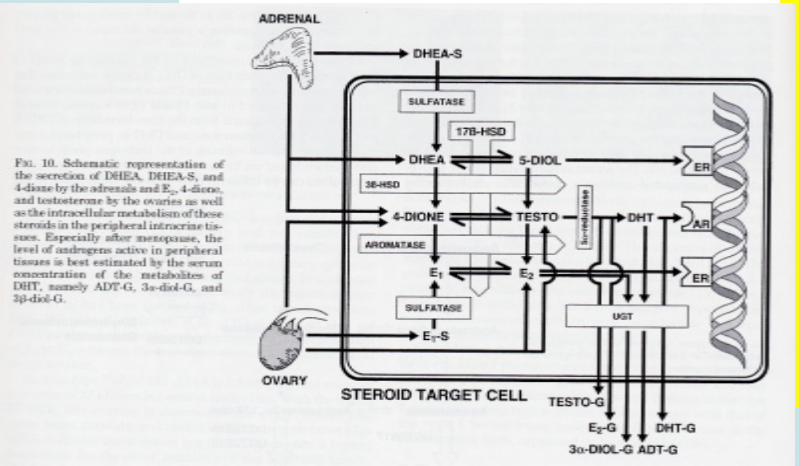
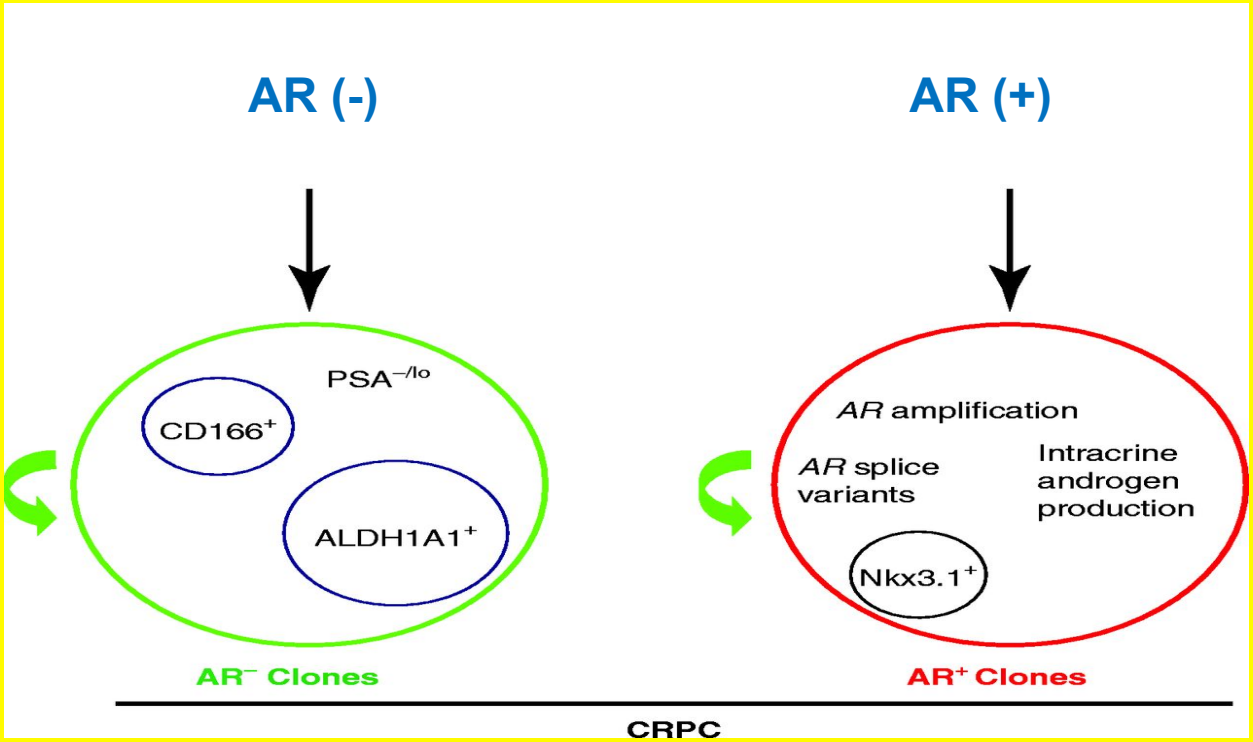


FIG. 10. Schematic representation of the secretion of DHEA, DHEA-S, and 4-dione by the adrenals and E_1, 4-dione, and testosterone by the ovaries as well as the intracellular metabolism of these steroids in the peripheral intracrine tissues. Especially after menopause, the level of androgens active in peripheral tissues is best estimated by the serum concentration of the metabolites of DHT, namely ADT-G, 3α-diol-G, and 3β-diol-G.

CASTRATION RESISTANT PROSTATE CANCER

Is that all ????

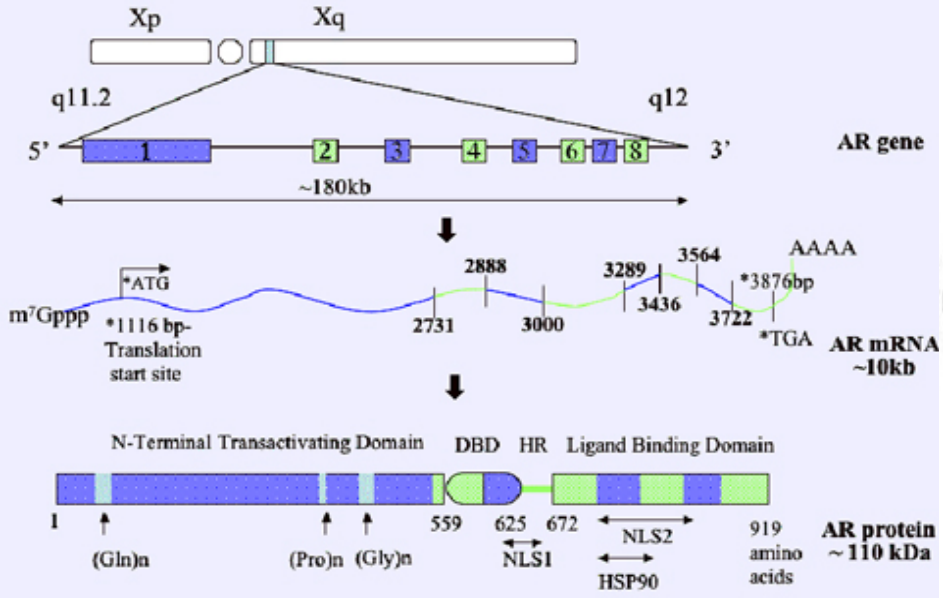
Castration Resistant Prostate Cancer

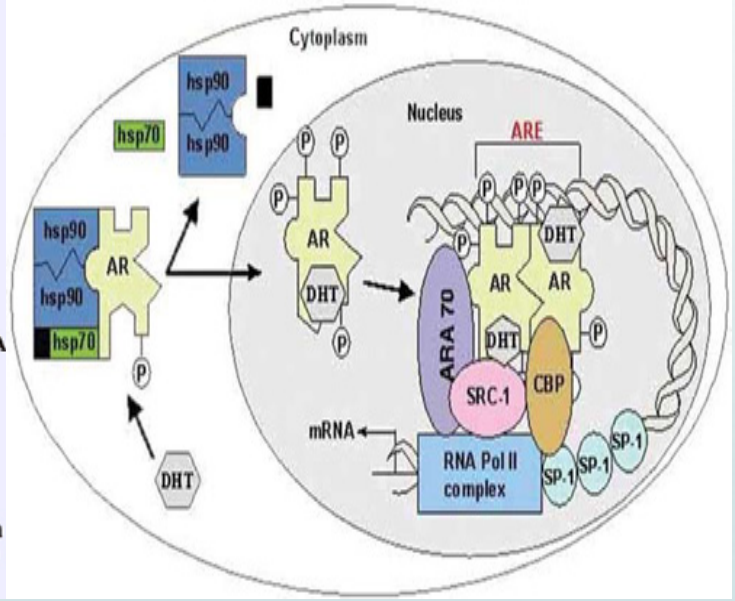


DONALD COFFEY's THEORY

Urology. 1981 Mar;17(Suppl 3):40-53. Prostate tumor biology and cell kinetics--theory.
Coffey DS, Isaacs JT.

AR EXPRESSION AND PROSTATE CANCER PROGRESSION





Androgen receptors in endocrine therapy resistant human prostate cancer.

van der Kwast TH, Schalken J, Ruizeveld de Winter JA, van Vroonhoven CC, Mulder E, Boersma W, Trapman J.

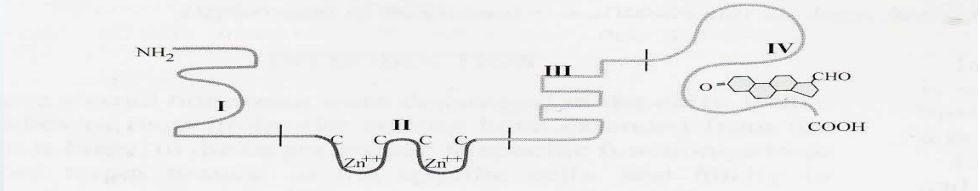
Int J Cancer. 1991 May 10;48(2):189-93

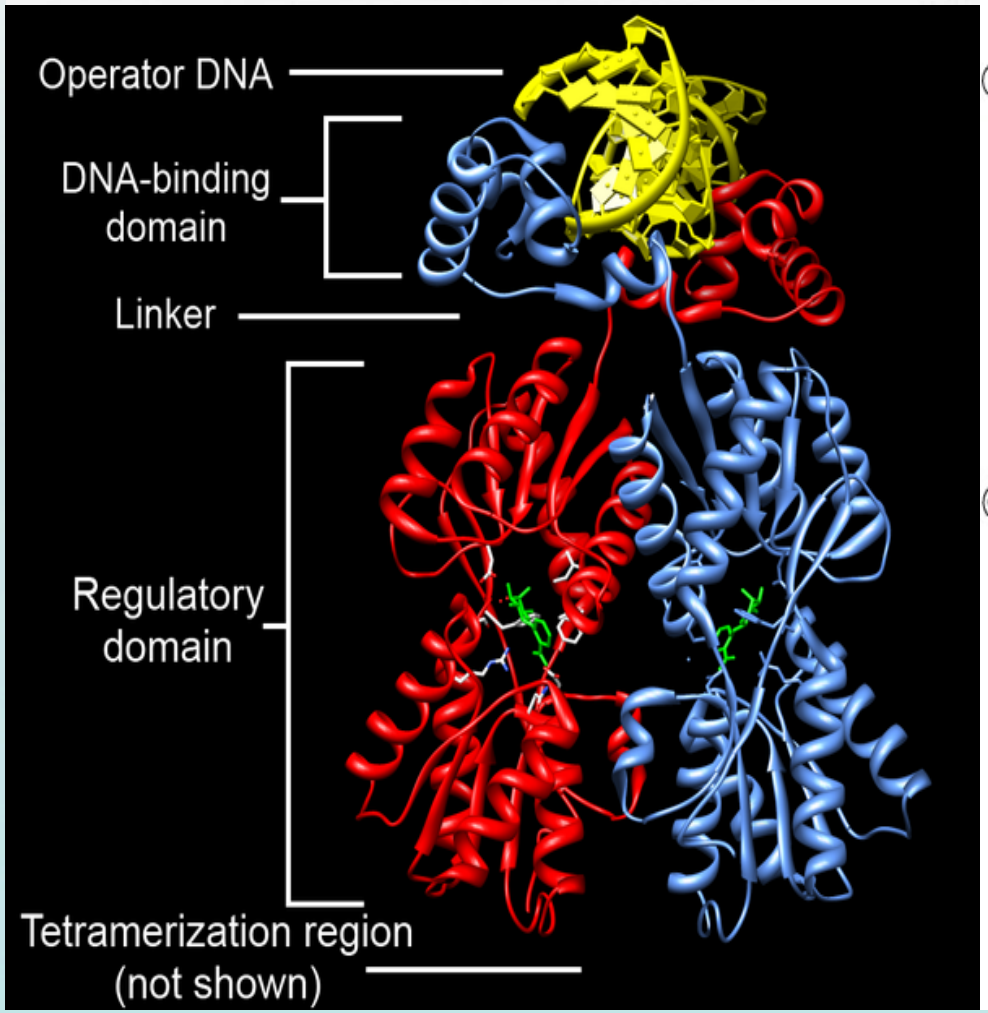
In vivo amplification of the androgen receptor gene and progression of human prostate cancer.

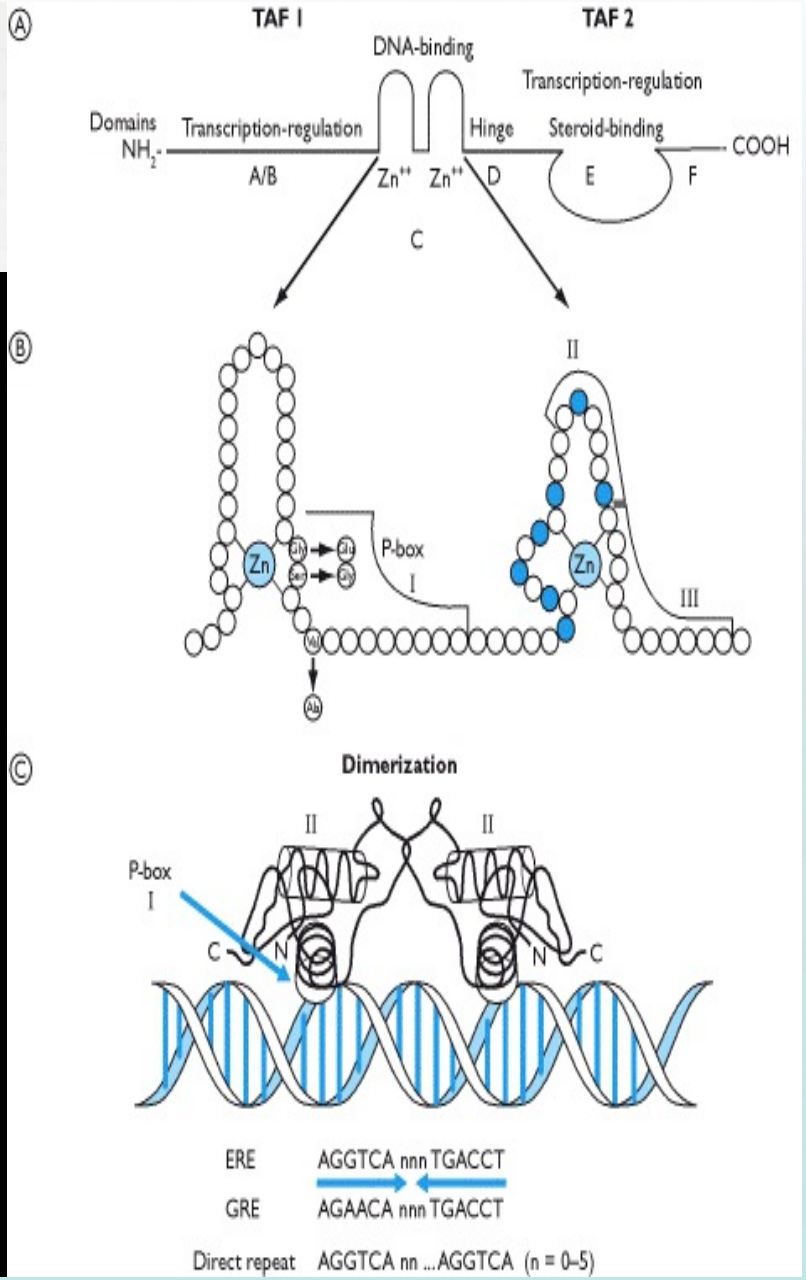
Visakorpi T, Hyytinen E, Koivisto P, Tanner M, Keinänen R, Palmberg C, Palotie A, Tammela T, Isola J, Kallioniemi OP.

Nat Genet. 1995 Apr;9(4):401-6.

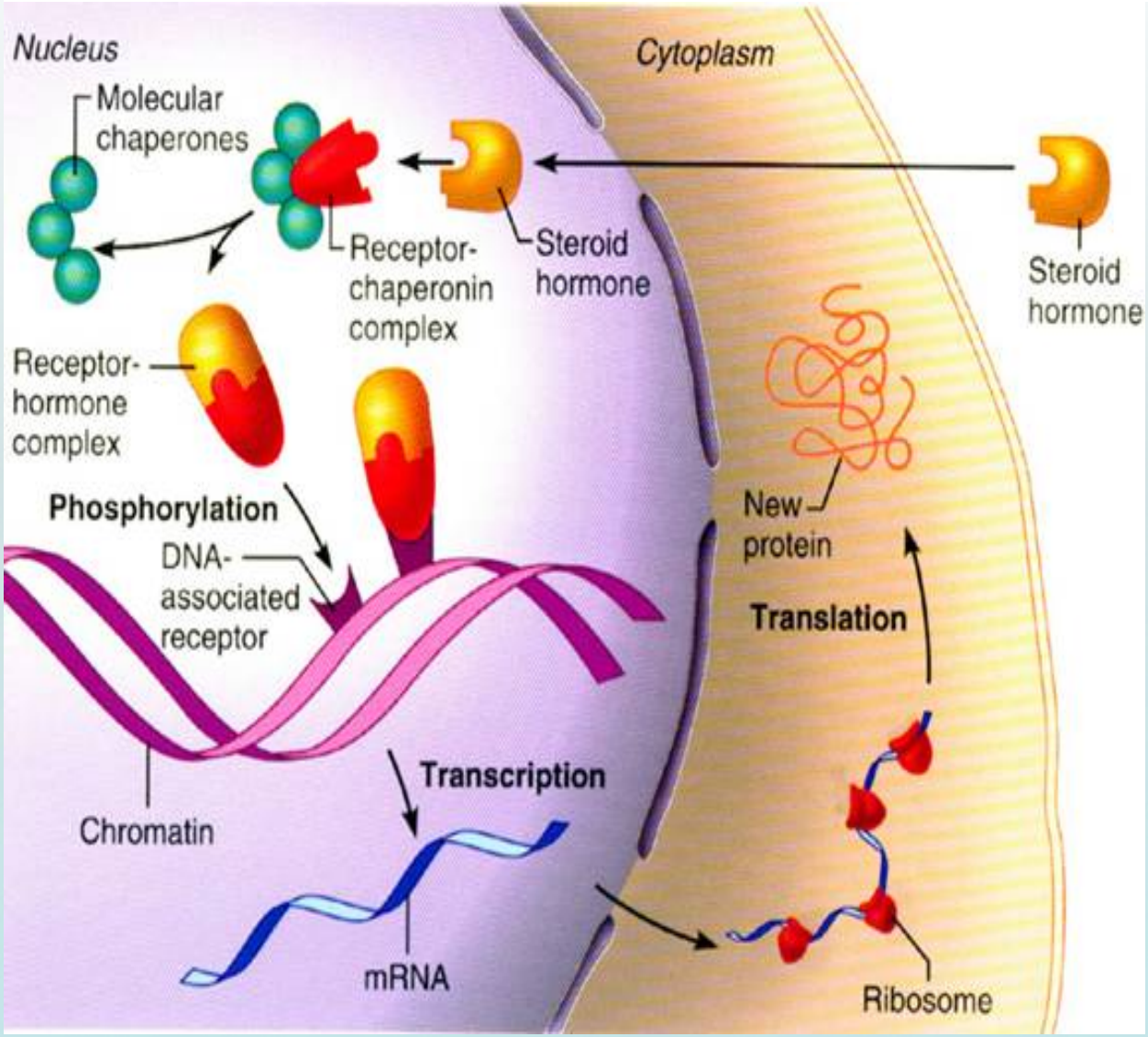
ANDROGEN RECEPTOR ACTIVITY

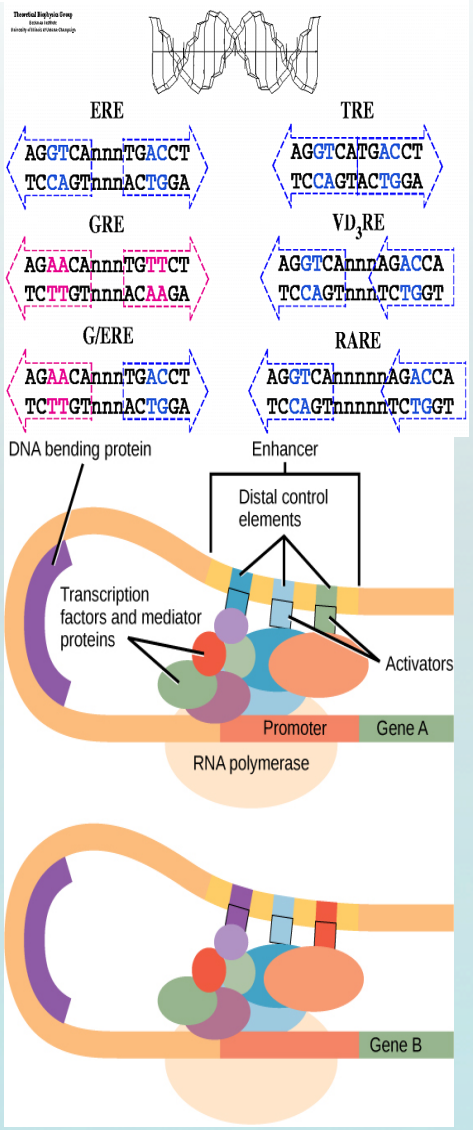




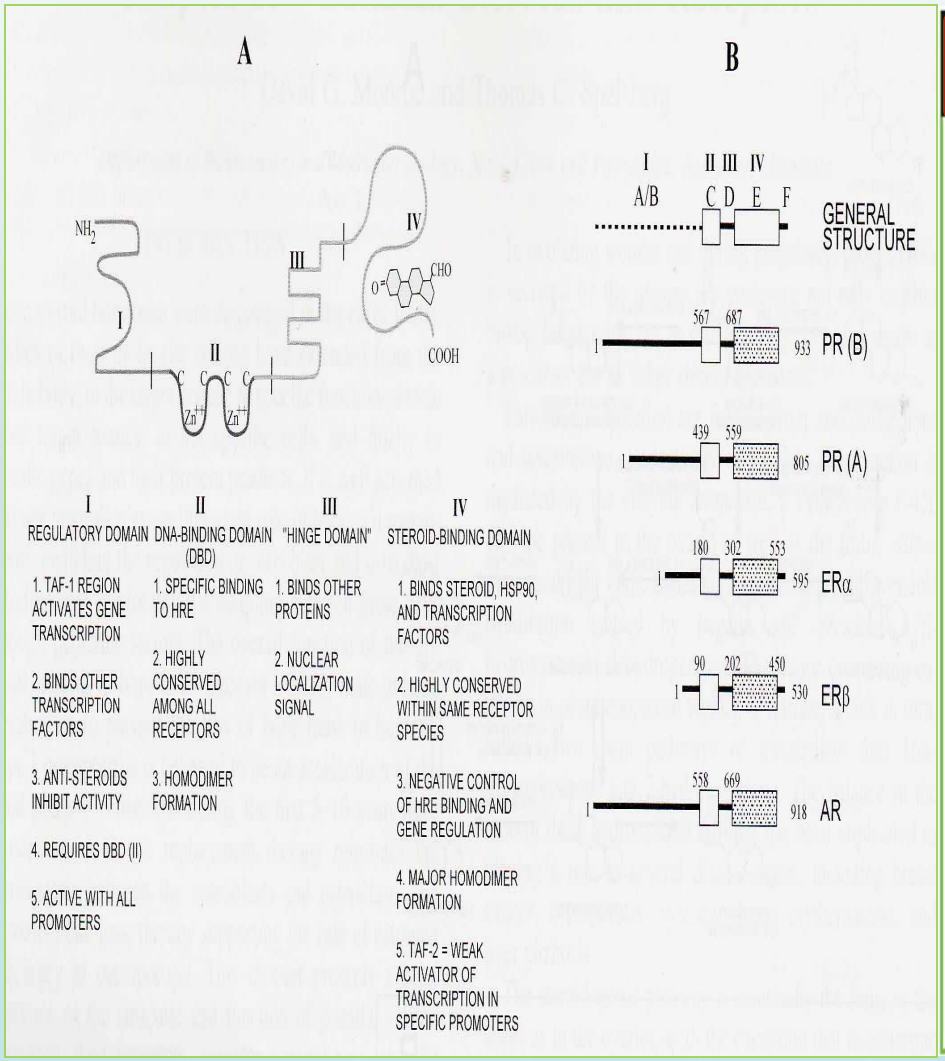


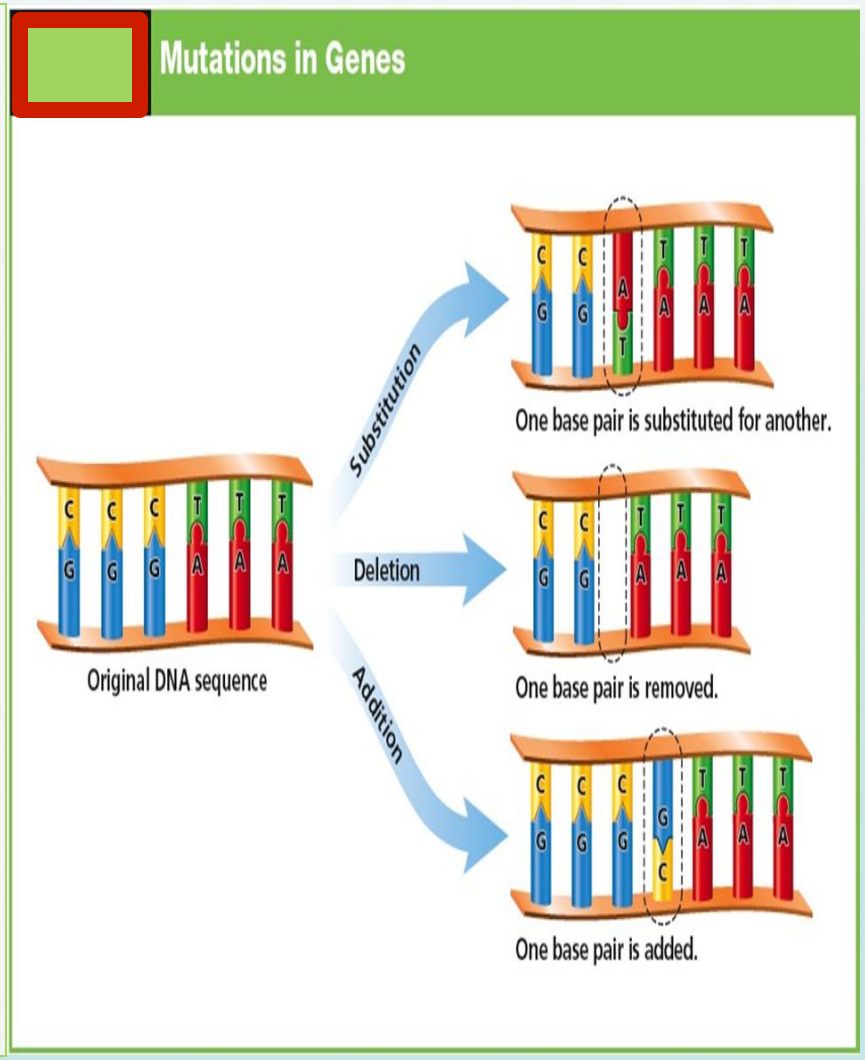
ANDROGEN RECEPTOR ACTIVITY



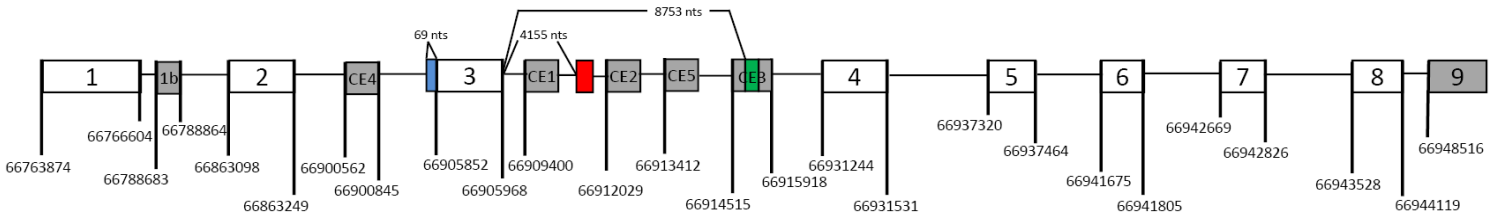


ANDROGEN RECEPTOR MUTATIONS



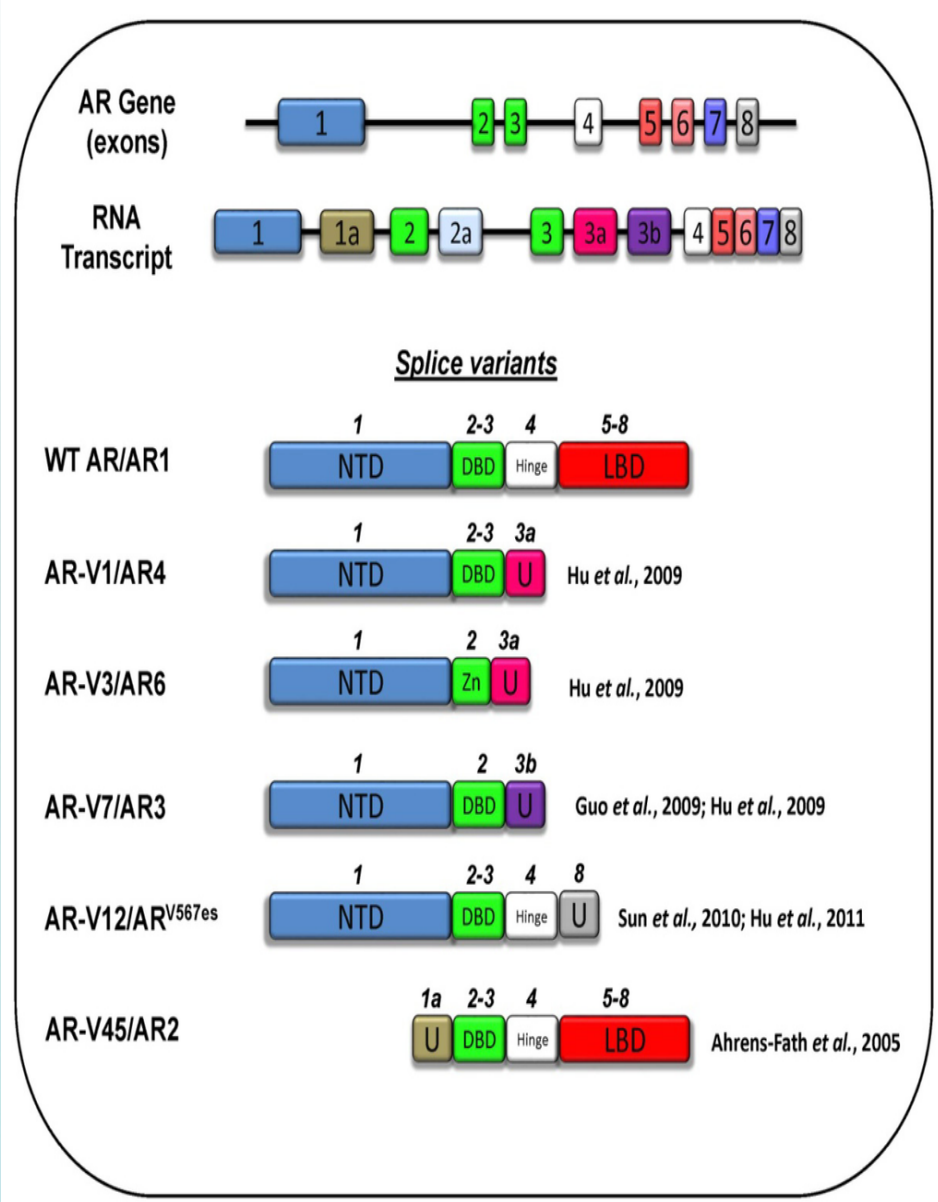


A

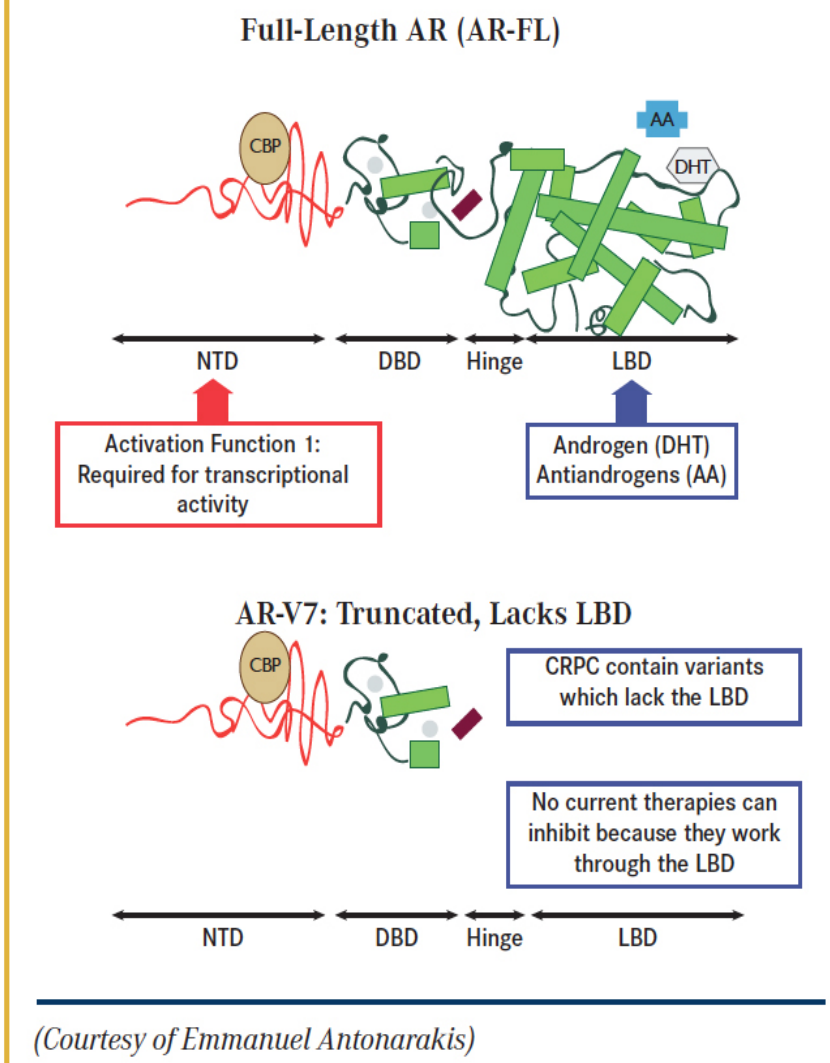


B

AR-Vs	Alternative names	Transcriptional activity	Transcripts	Proteins
AR-FL		Ligand-stimulated	1 2 3 4 5 6 7 8	**AR-FL:MTLG**DNLPEQAAFWRHLHIFWDHVVKK stop
AR-45		Conditional	1b 2 3 4 5 6 7 8	**AR45:** start MILWLHS**LETARDHVLPIDYY---FHTQ stop**
AR-23		Ligand-stimulated	1 2 3 4 5 6 7 8	**AR23: KVFFKRAAE**EIPEERDSGNSCSELSTLVFVLP**GKQKYLCA---FHTQ stop**
AR-V1	AR4	Conditional	1 2 3 CE1	**AR-V1:MTLG**AVVVSERILRVFGVSEWOP stop
AR-V2		Unknown	1 2 3 3 CE1	**AR-V2:MTLG**AVVVSERILRVFGVSEWOP stop
AR-V3	AR1/2/2b	Constitutive	1 2 CE4 3 CE1	**AR-V3:RAAE**GFFRMNKLKESSDTNPKPYCMAAPMGLTENNRNRKKSYRETNLKAVSWPLNHT stop
AR-V4	AR1/2/3/2b, AR5	Constitutive	1 2 3 CE4 3 CE1	**AR-V4:MTLG**GFFRMNKLKESSDTNPKPYCMAAPMGLTENNRNRKKSYRETNLKAVSWPLNHT stop
AR-V5		Unknown	1 2 3 CE2	**AR-V5:MTLG**D stop
AR-V6		Unknown	1 2 3 CE2	**AR-V6:MTLG**AGSRVS stop
AR-V7	AR3	Constitutive	1 2 3 CE3	**AR-V7:MTLG**EKFRVGNCKHLKMTRP stop
AR-V8		Unknown	1 2 3	**AR-V8:MTLG**GFDNLCELSS stop
AR-V9		Conditional	1 2 3 CE5	**AR-V9:MTLG**DNLPEQAAFWRHLHIFWDHVVKK stop
AR-V10		Unknown	1 2 3	**AR-V10:MT**PSSGTNSVFLPHRDVVRTGCRSNSGYHSCSCEYHDYCFL stop
AR-V11		Unknown	1 2 3	**AR-V11:MTLG**GKILFFLFLLLPLSPFSLIF stop (EXON RUNON)
AR-V12	AR^{v567es}	Constitutive	1 2 3 4 8 9	**AR-V12:KALP**DCERAASVHF Stop
AR-V13		Inactive	1 2 3 4 5 6 9	**AR-V13:LFSI**NHT Stop
AR-V14		Unknown	1 2 3 4 5 6 7 9	**AR-V14:SVQP**ITPDAMYL Stop
AR-8		Inactive	1 3 CE3	**AR8: YSGPYGDMR**NTRRKRLWKLIIRSINSCICSPRETEVPVRQQK stop

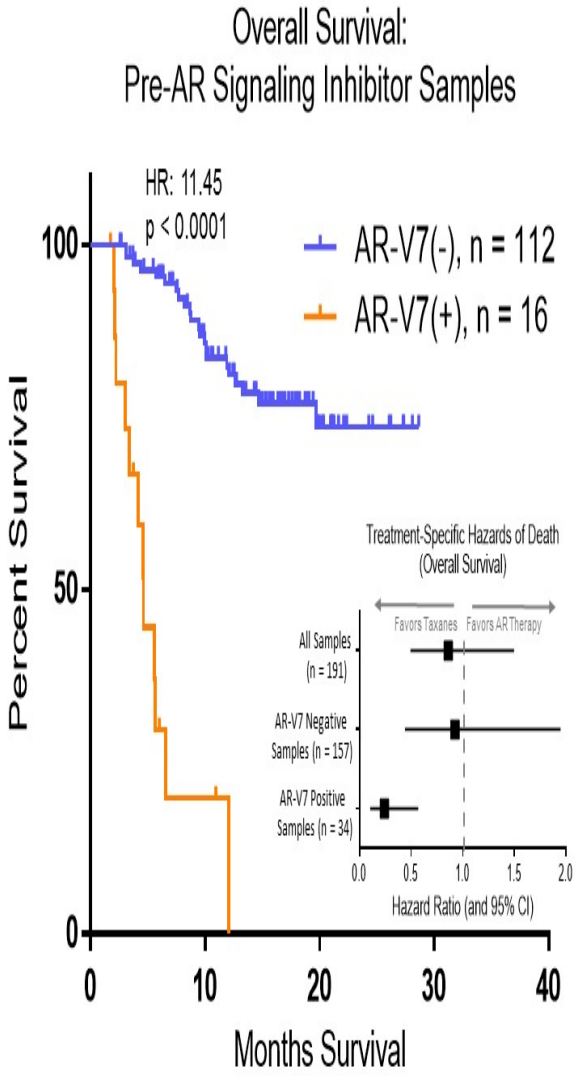


ANDROGEN RECEPTOR ACTIVITY



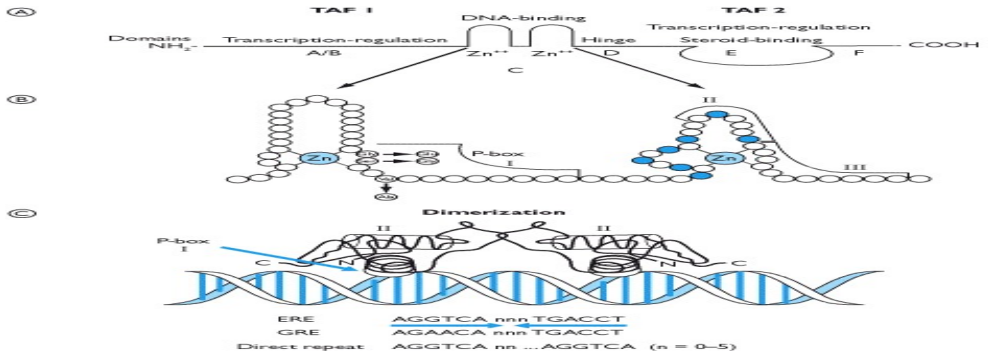
(Courtesy of Emmanuel Antonarakis)

CRPC: ANDROGEN RECEPTOR ACTIVITY - MEDIATED POOR SURVIVAL

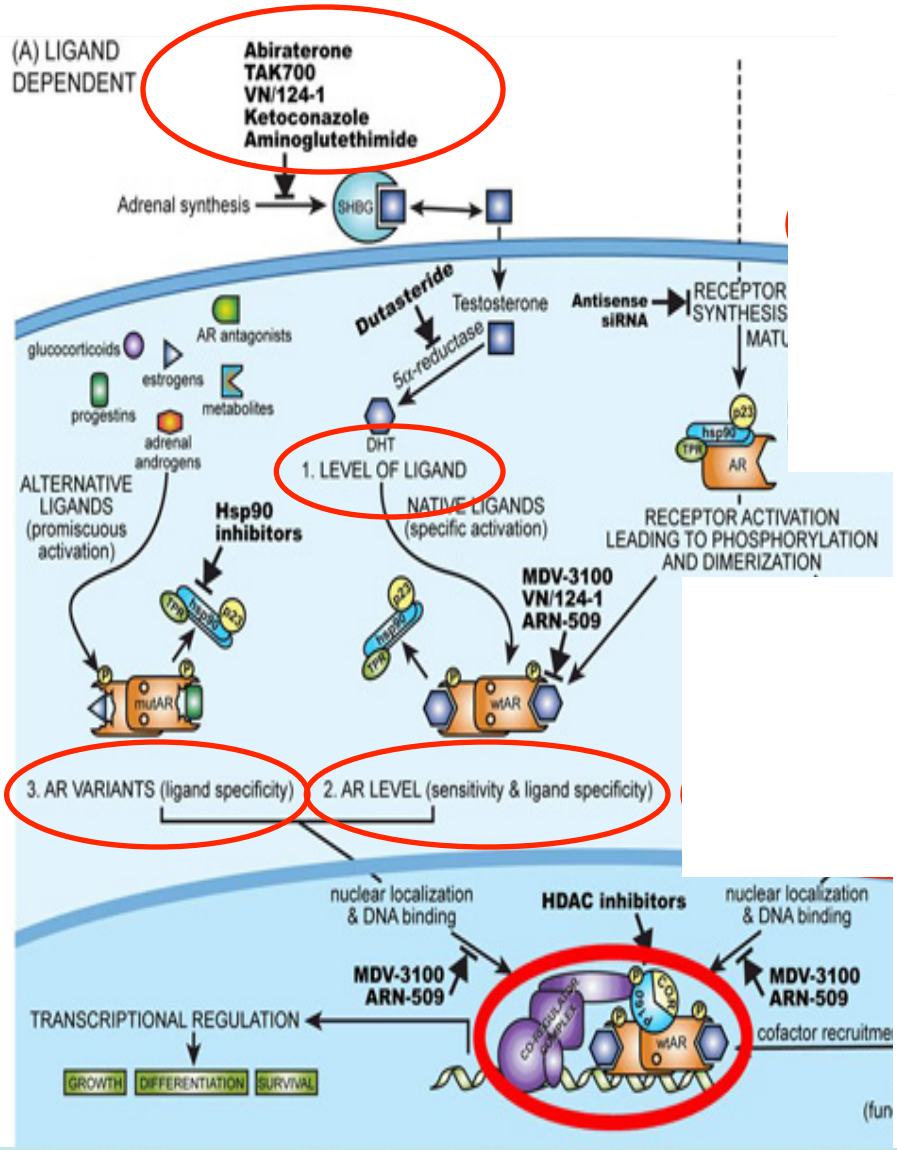


	Abiraterone			Enzalutamide		
	AR-V7 positive	AR-V7 negative	P value	AR-V7 positive	AR-V7 negative	P value
PSA response rate	0%	62%	0.004	0%	53%	0.004
Median PFS (months)	2.3	NR	<0.001	2.1	6.1	<0.001
Median OS (months)	10.6	NR	0.006	5.5	NR	0.002

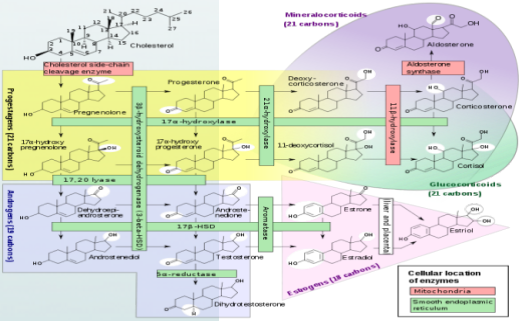
NR=not reached



CASTRATION RESISTANT PROSTATE CANCER



CASTRATION RESISTANT PROSTATE CANCER



Androgen depletion

Androgen dependent growth

Castration-Resistant Growth & Disease Evolution

Anti-androgens

AR involved

- AR mutations
- AR overexpression (amplification)
- Aberrant AR activation
- Aberrant AR coactivators

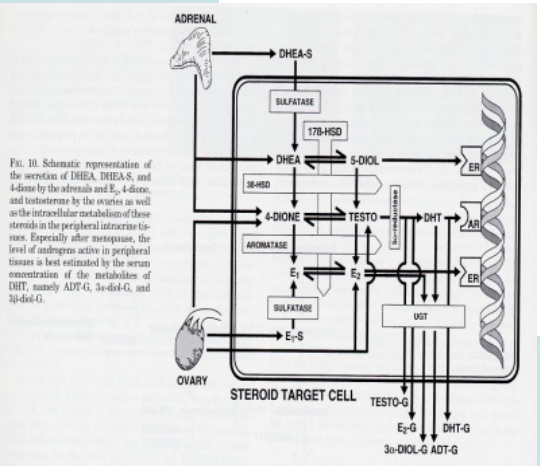
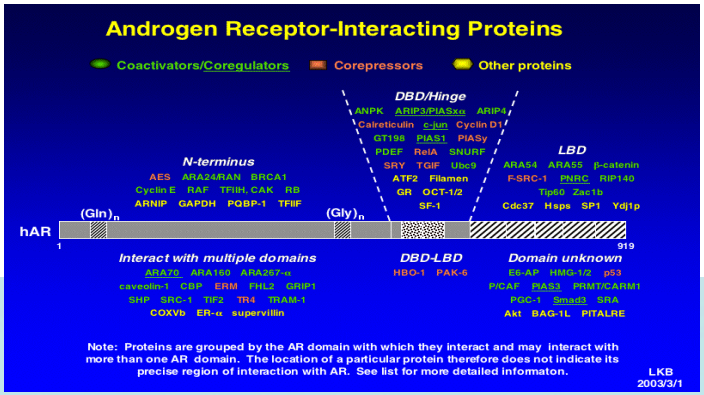


FIG. 10. Schematic representation of the secretion of DHEA, DHEA-S, and 4-dione by the adrenals and E_2, 4-dione, and testosterone by the ovaries as well as the intracellular metabolism of these steroids in the peripheral intracrine tissues. Especially after menopause, the level of androgens active in peripheral tissues is best estimated by the serum concentration of the metabolites of DHT, namely ADT-G, 3α-diol-G, and 3β-diol-G.



CASTRATION RESISTANT PROSTATE CANCER

Is that all ????

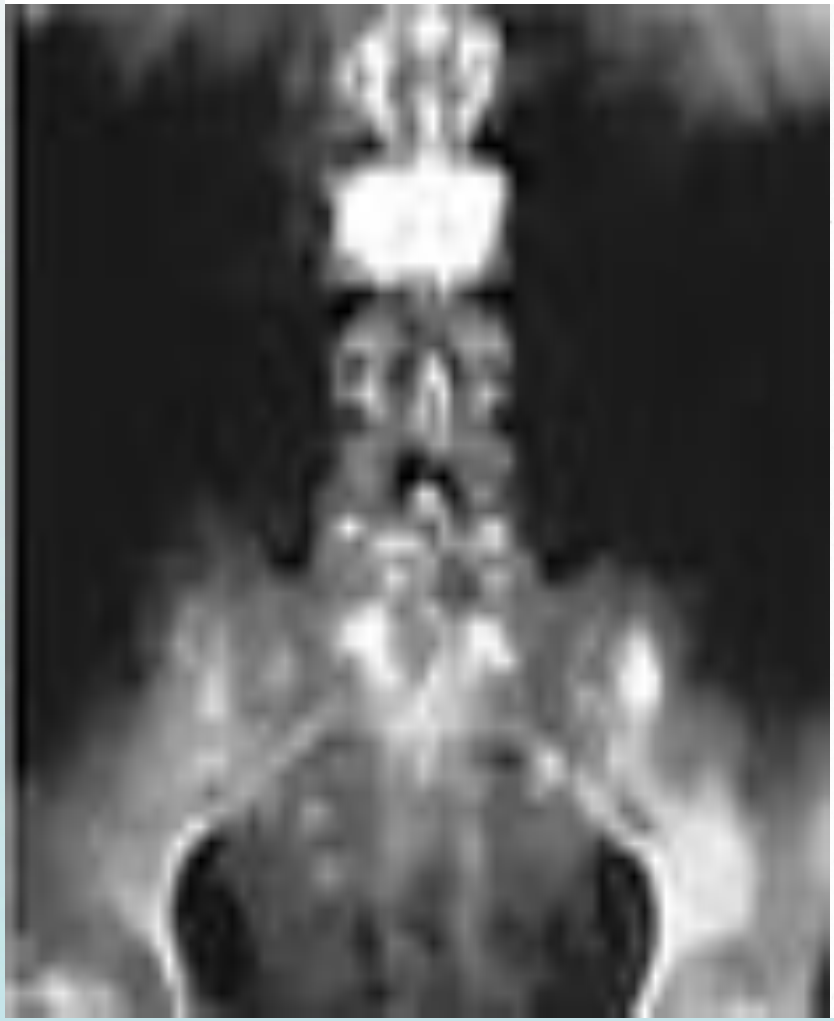
ANDROGEN DEPLETION THERAPIES IN PROSTATE CANCER

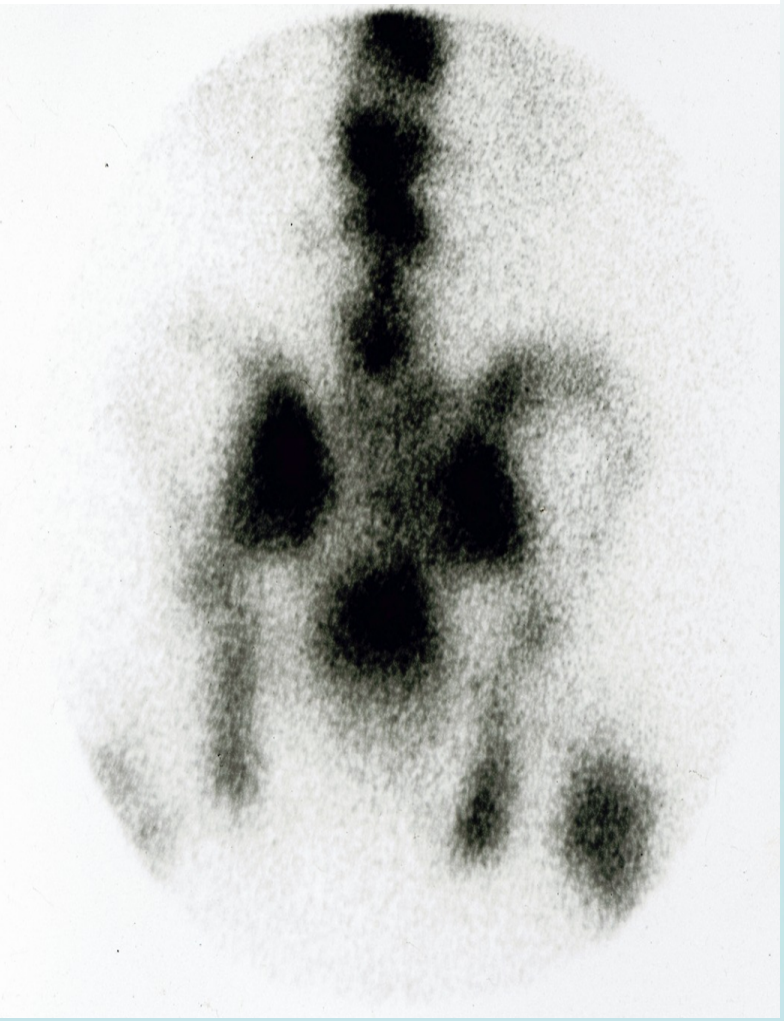
The number of bone lesions is the most important factor predicting disease response & outcome to androgen depletion therapies

Objective response and disease outcome in 59 patients with stage D2 prostatic cancer treated with either Buserelin or orchiectomy. Disease aggressivity and its association with response and outcome.
Koutsilieris M, Faure N, Laroche B, Robert G, Ackman CF.
Urology. 1986 Mar;27(3):221-8.

The assessment of disease aggressivity in stage D2 prostate cancer patients.
Koutsilieris M, Laroche B, Thabet M, Fradet Y.
Anticancer Res. 1990 Mar-Apr;10(2A):333-6

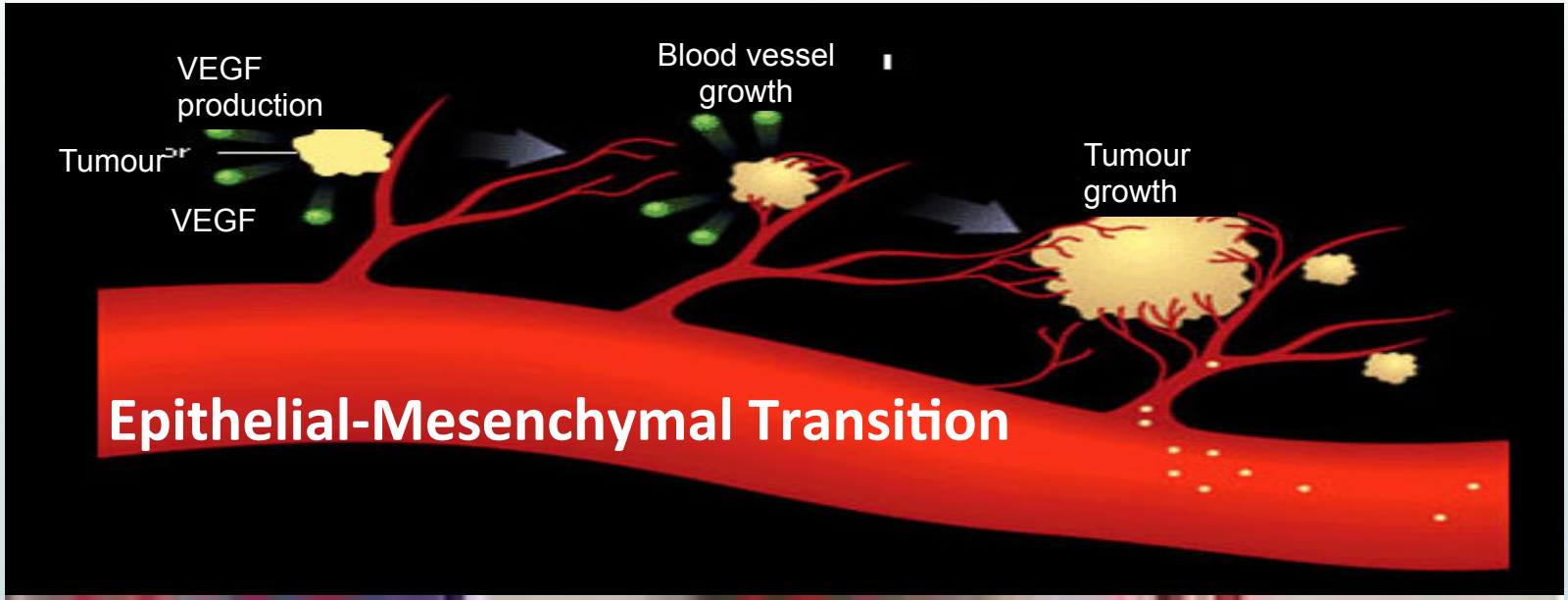
BONE LESIONS: OSTEOBLASTIC NATURE - THE MAIN SITE OF DISEASE EVOLUTION TOWARDS CASTRATION RESISTANT PROSTATE CANCER





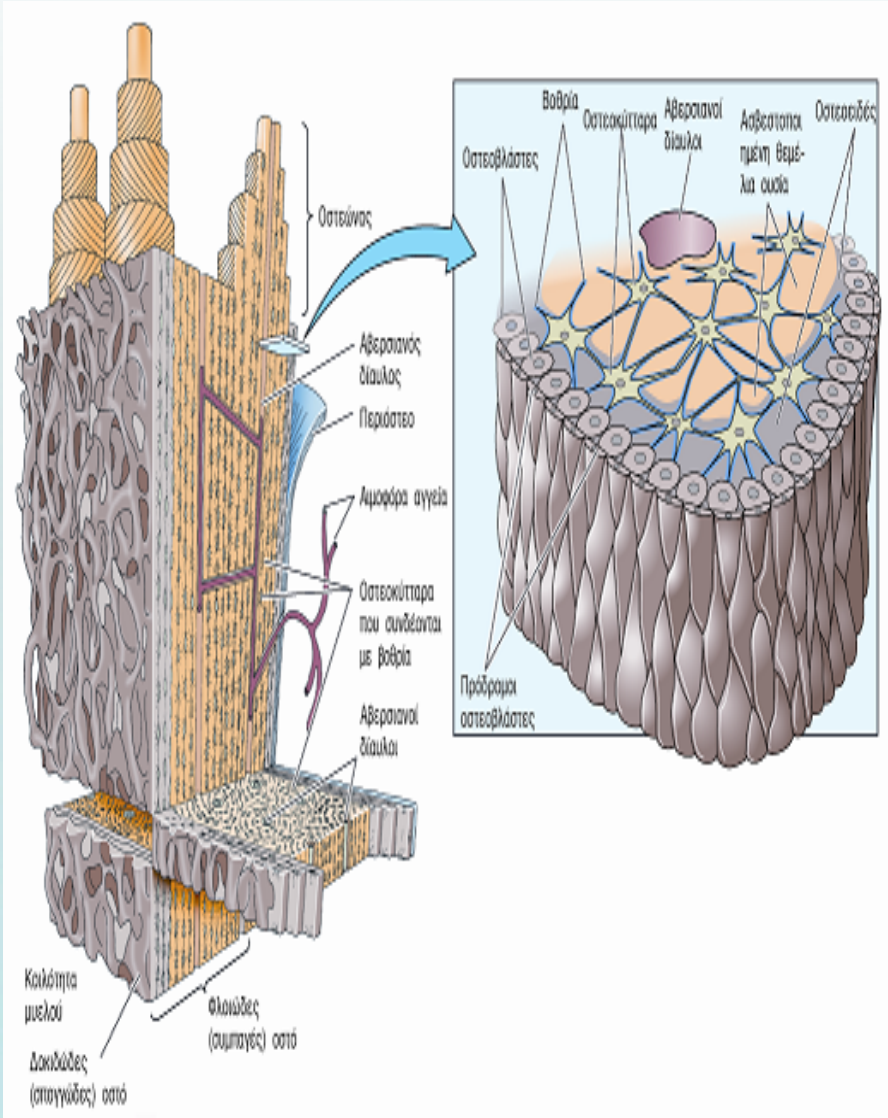
Galasko CS. Nature 1976; 263:507-508; Koutsilieris M, JCI, 1987

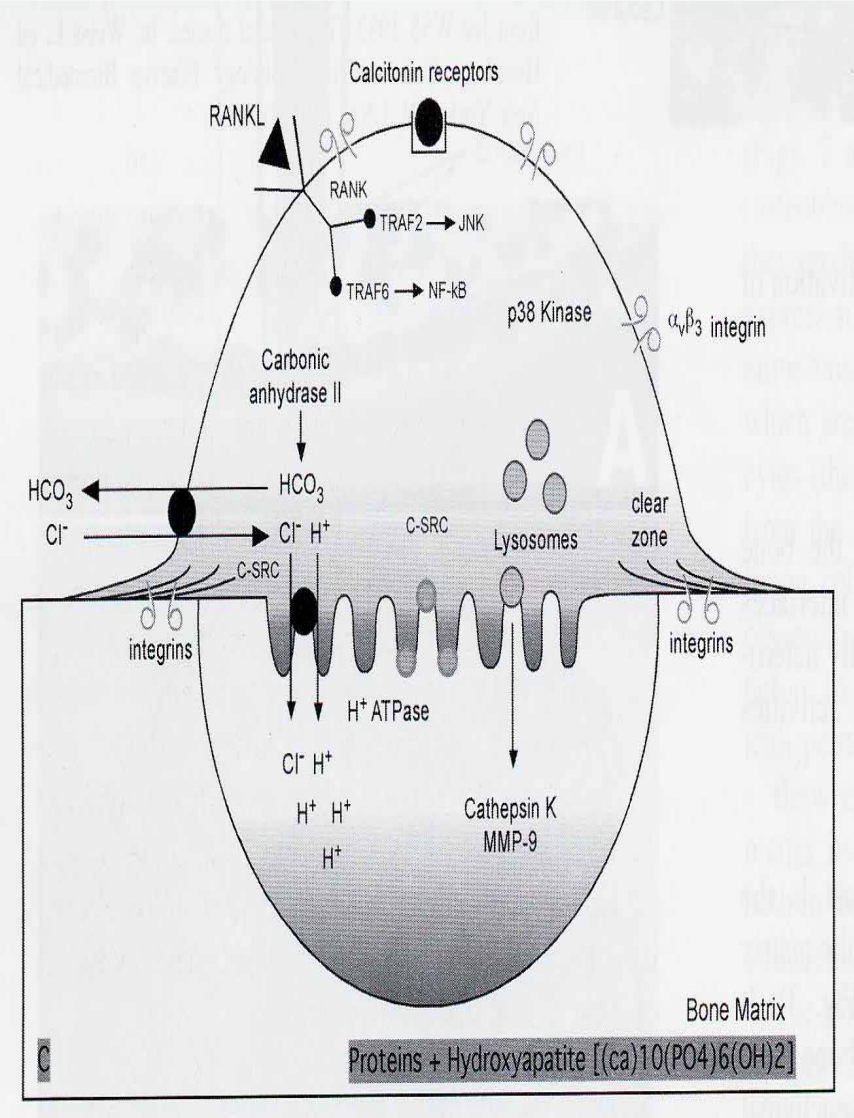
ESTABLISHMENT OF BONE METASTASIS – EARLY STAGE



Koutsilieris M, et al. In: Meadows GG, editor. Integration/interaction of oncologic growth. Springer; 2005. Ch. 19.

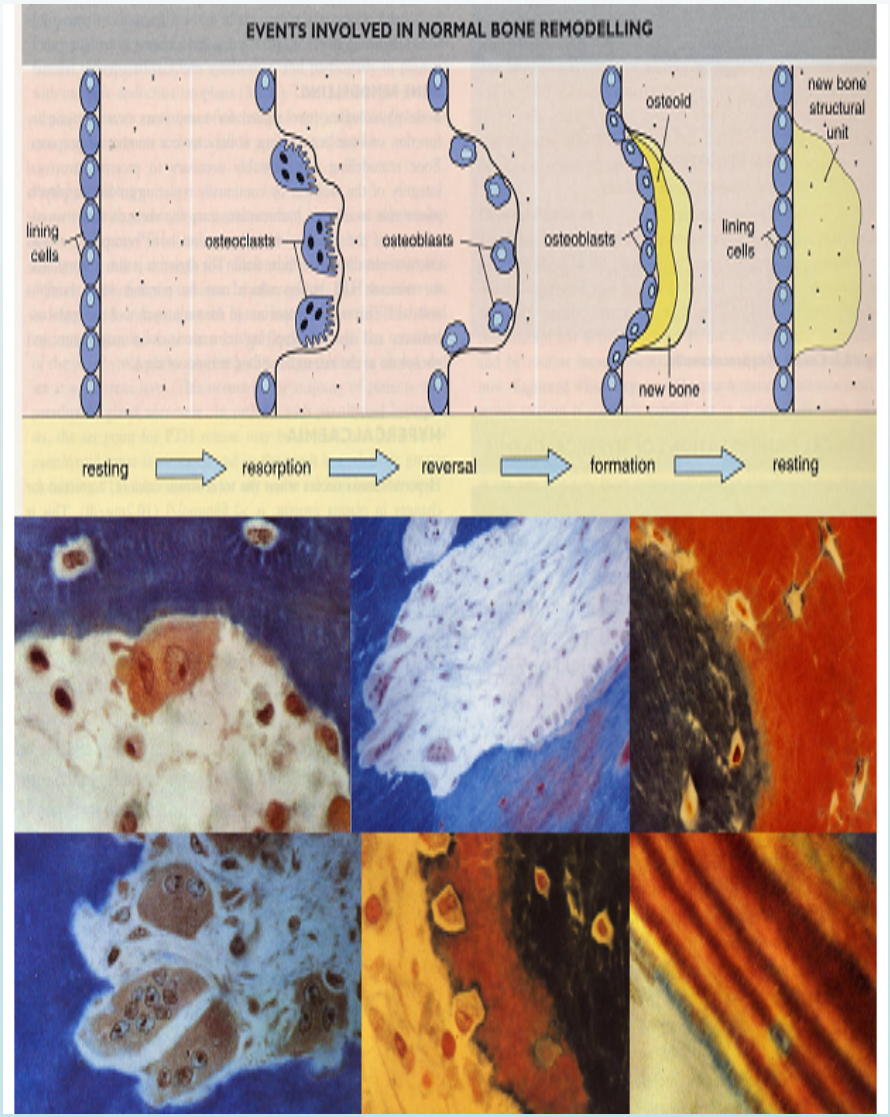
Only an osteoclast can perform bone resorption

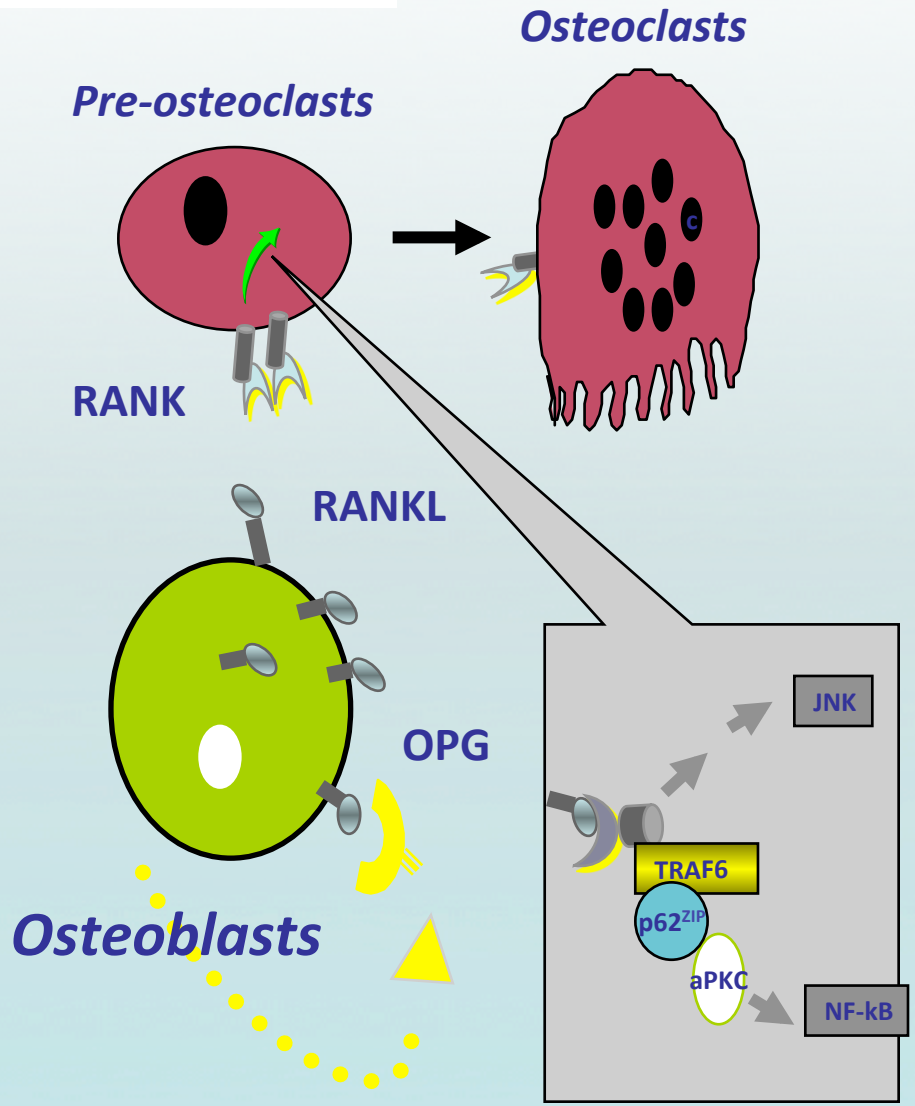




Msaouel P & Koutsilieris M, Best Pract & Res Clin Endocrinol & Metab. 2008; 1-15

OSTEOCLASTOGENESIS

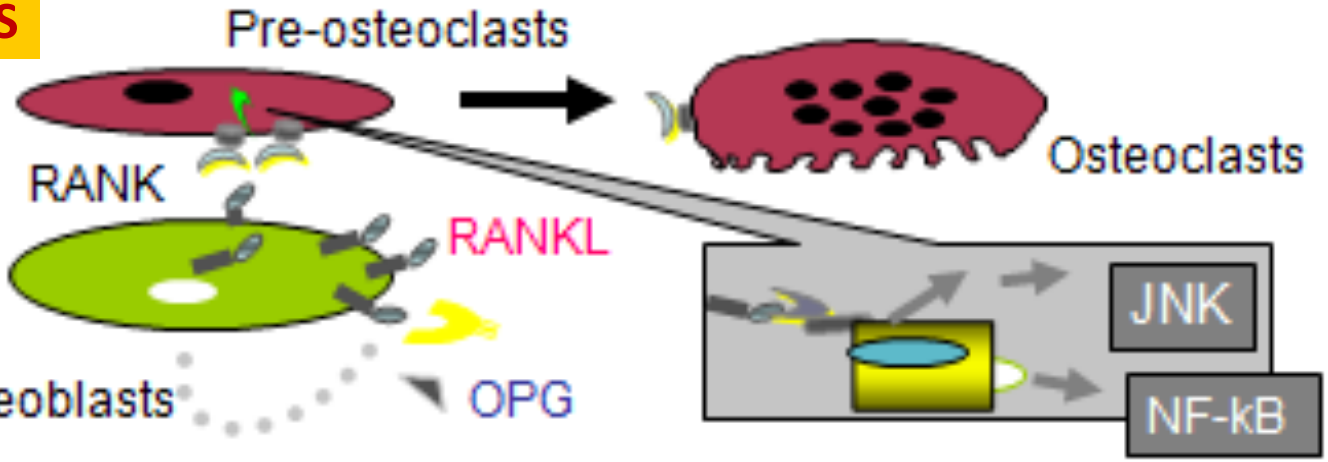




Tumour cell-orchestrated bone resorption

Tumour cell-mediated local increase of IL-6 / PTHrP / TGFβ1

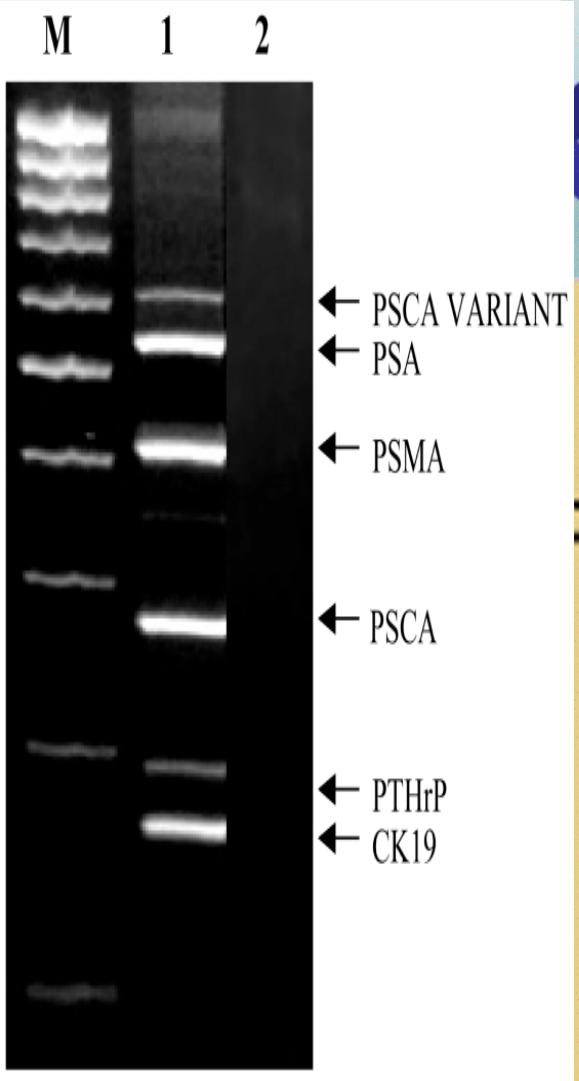
OSTEOCLASTOGENESIS

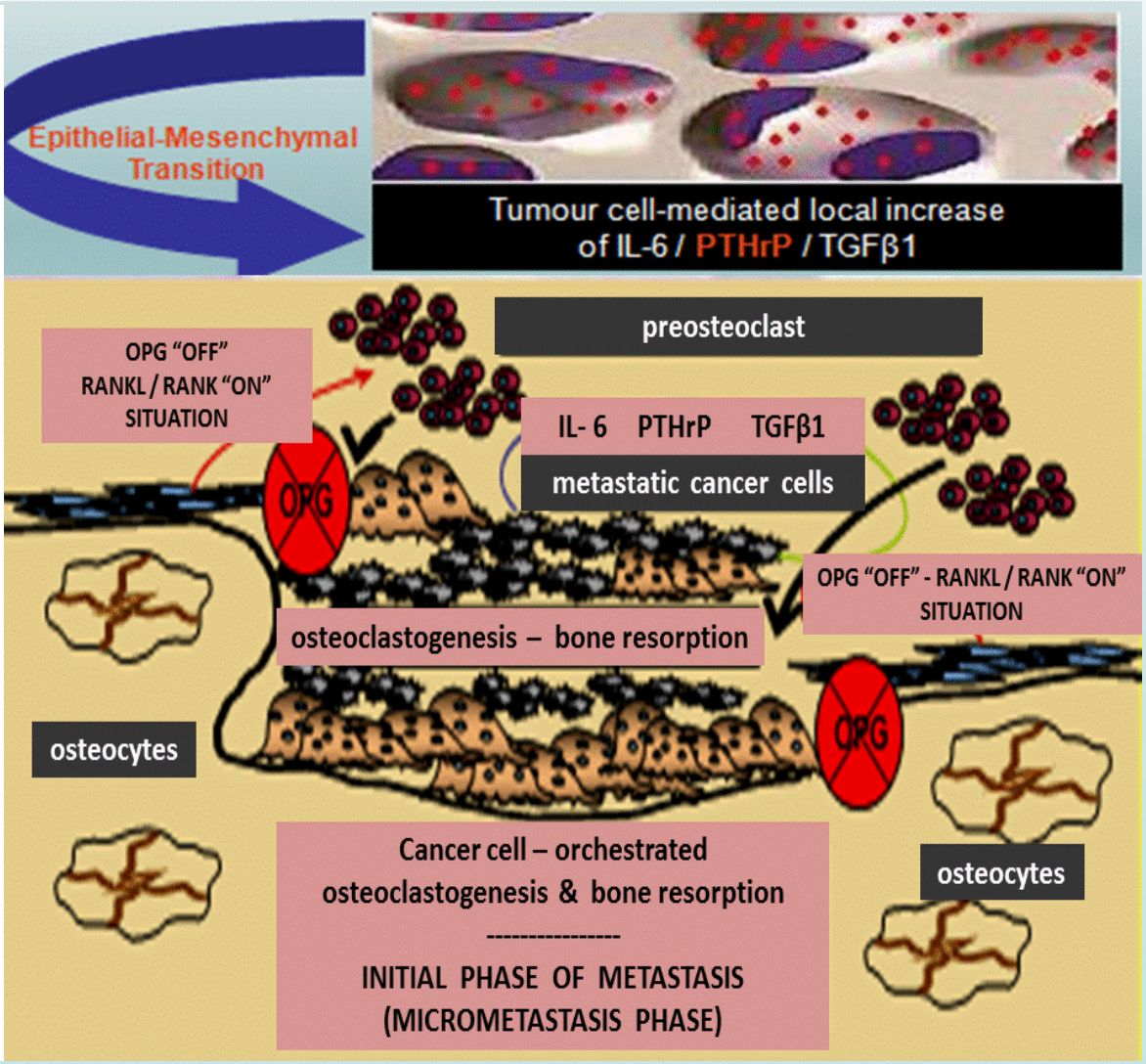


OPG = osteoprotegerin.

Koutsilieris M, et al. In: Meadows GG, editor. Integration/Interaction of oncologic growth. Springer; 2005. Ch. 19.

ESTABLISHMENT OF BONE METASTASIS – EARLY STAGE

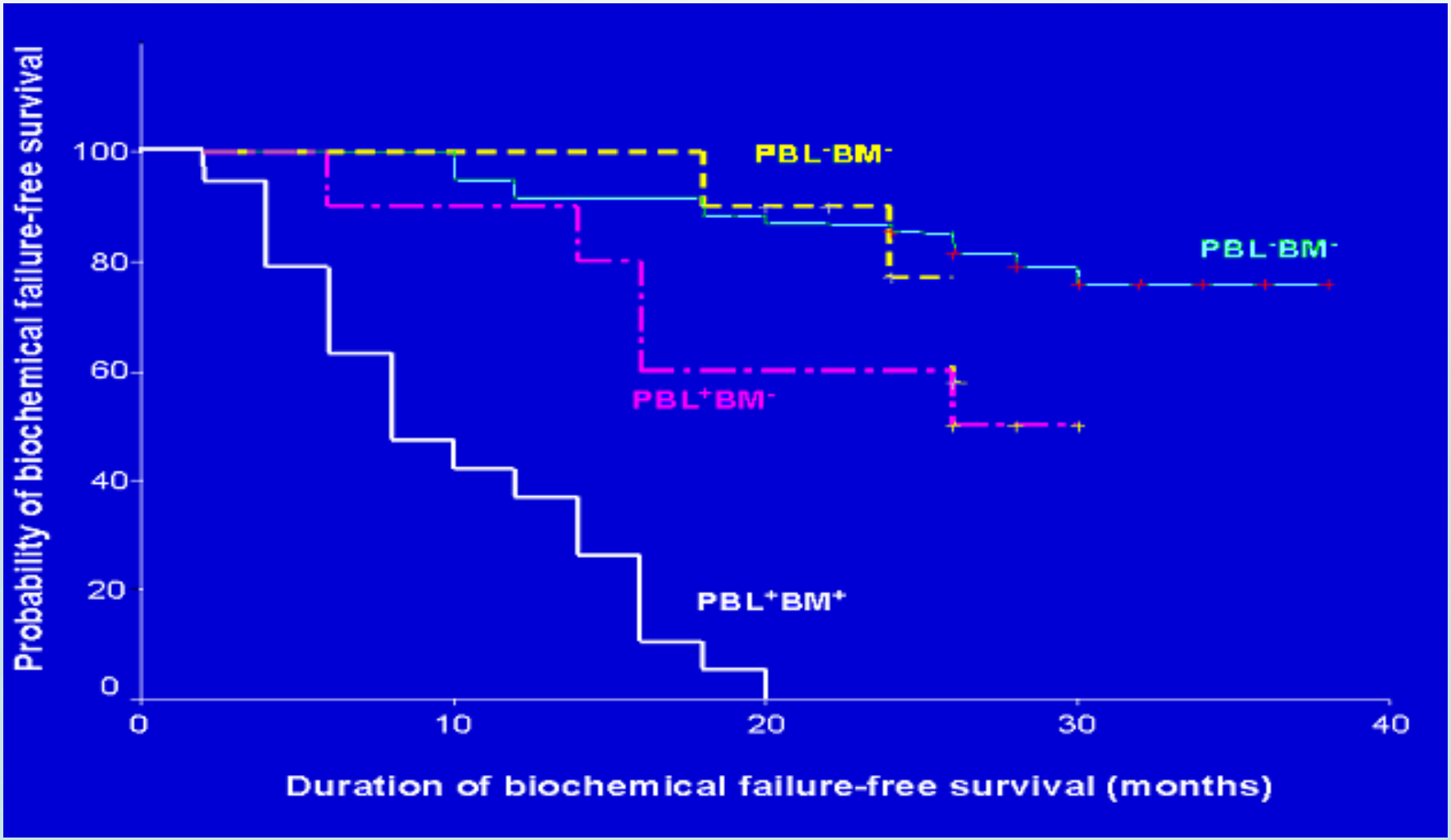




Koutsilieris M, et al. In: Meadows GG, editor. Integration/interaction of oncologic growth. Springer; 2005. Ch. 19.

Msaouel P & Koutsilieris M, Best Pract & Res Clin Endocrinol & Metab. 2008; 1-15

Molecular Staging in Clinically Localized Prostate Cancer



Lembessis P et al, Clinical Chemistry & Laboratory Medicine, 2007

Molecular Staging Using Multiplexed PCR in Clinically Localized Prostate Cancer

Detection of Circulating Tumor Cells in Prostate Cancer Patients: Methodological Pitfalls and Clinical Relevance

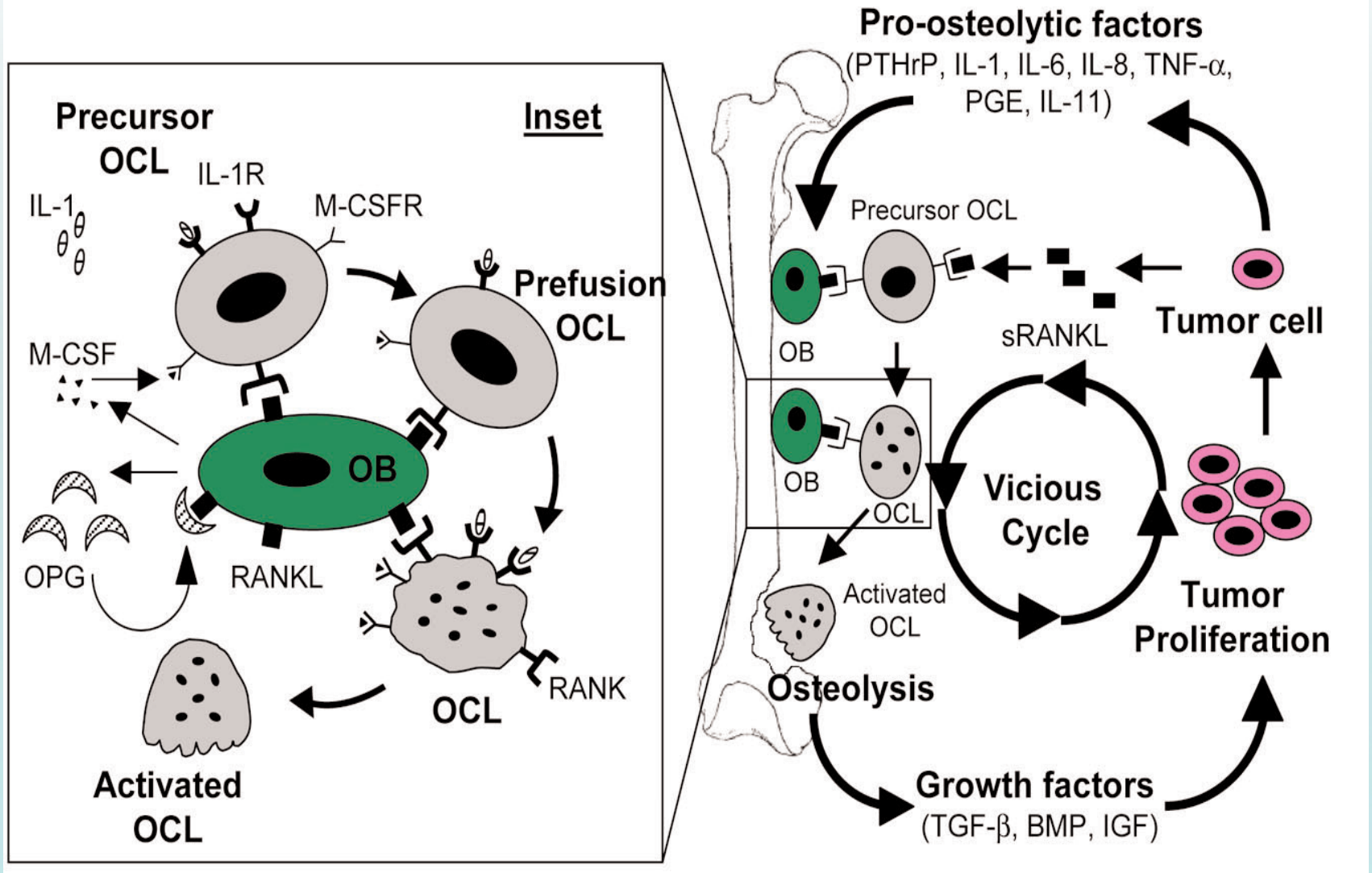
Zacharoula Panteleakou,[1] Peter Lembessis,[1,2] Antigone Sourla,[1,2] Nikolaos Pissimissis,[1] Aristides Polyzos,[3]

Charalambos Deliveliotis,[4] and Michael Koutsilieris[1]

Mol Med. 2009; Mar–Apr; 15(3-4): 101–114

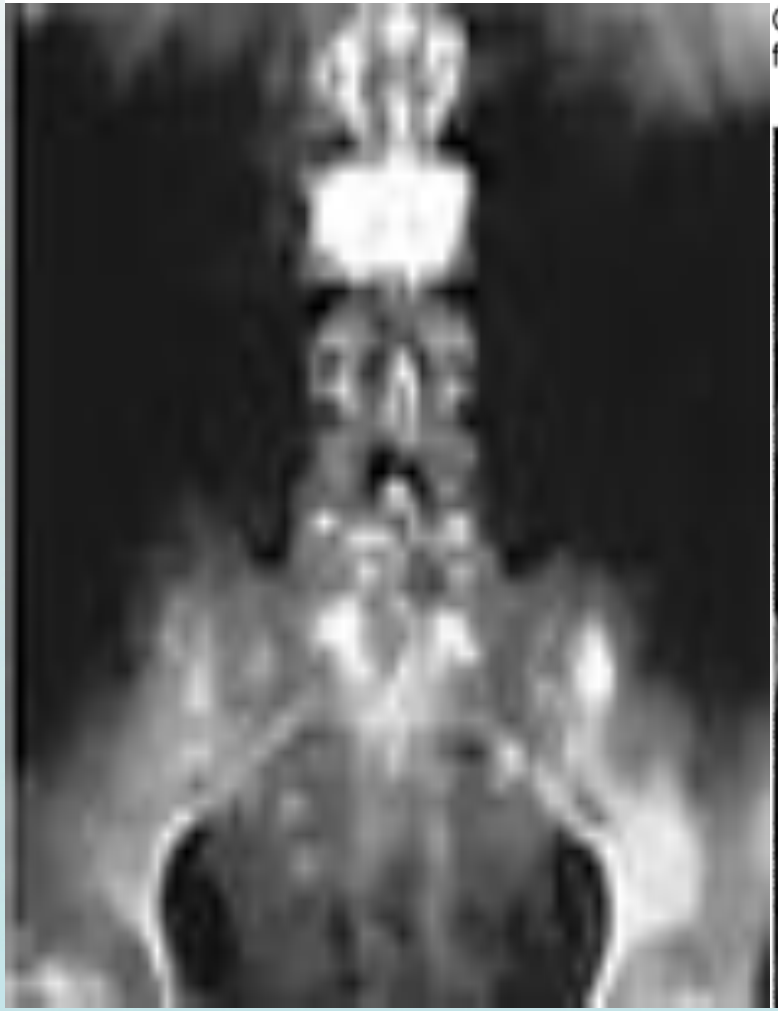
Molecular Medicine

Tumour cell - orchestrated bone resorption

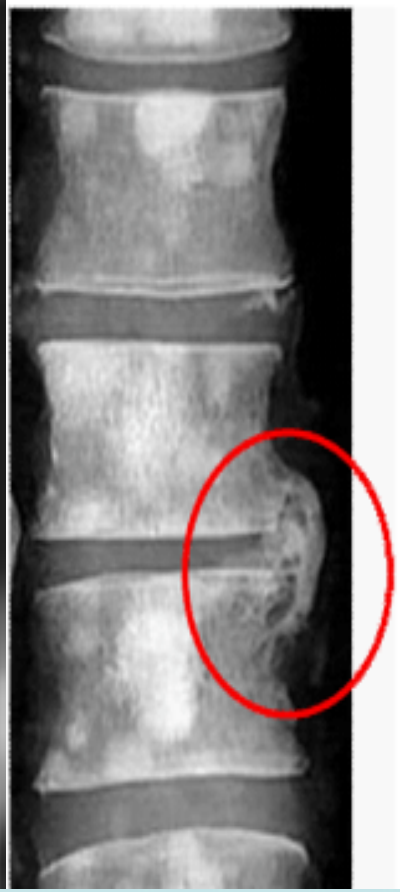


Virk MS and Lieberman JR, Arthritis Research & Therapy 2007

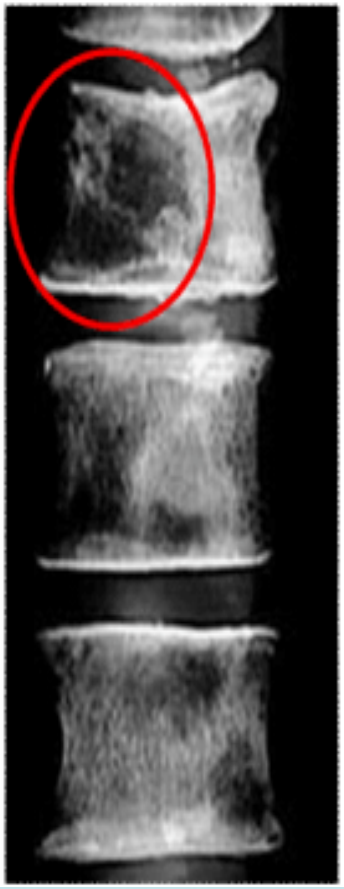
PROSTATE CANCER: LATE PHASE
WHY BLASTIC AND NOT LYTIC LESIONS ?



Osteoblastic lesion commonly found in prostate cancer



Osteolytic lesion and weakened bone commonly found in MM and breast cancer



OSTEOBLASTIC METASTASIS IN ADVANCED PROSTATE CANCER

Selective growth factors for osteoblasts are contained in extracts from prostate cancer tissues

Koutsilieris et al, The Prostate 9 : 109-115, 1985;

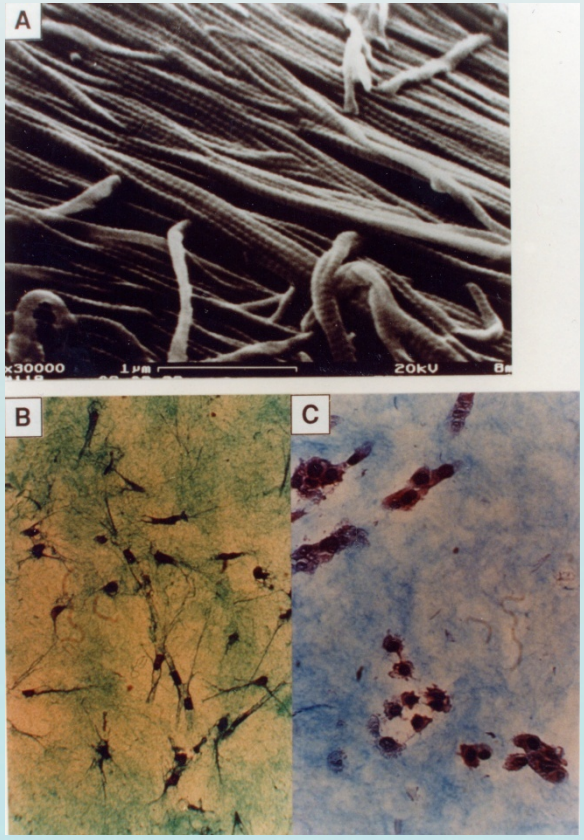
Koutsilieris et al, Journal of Endocrinology 115 : 447-454, 1987;

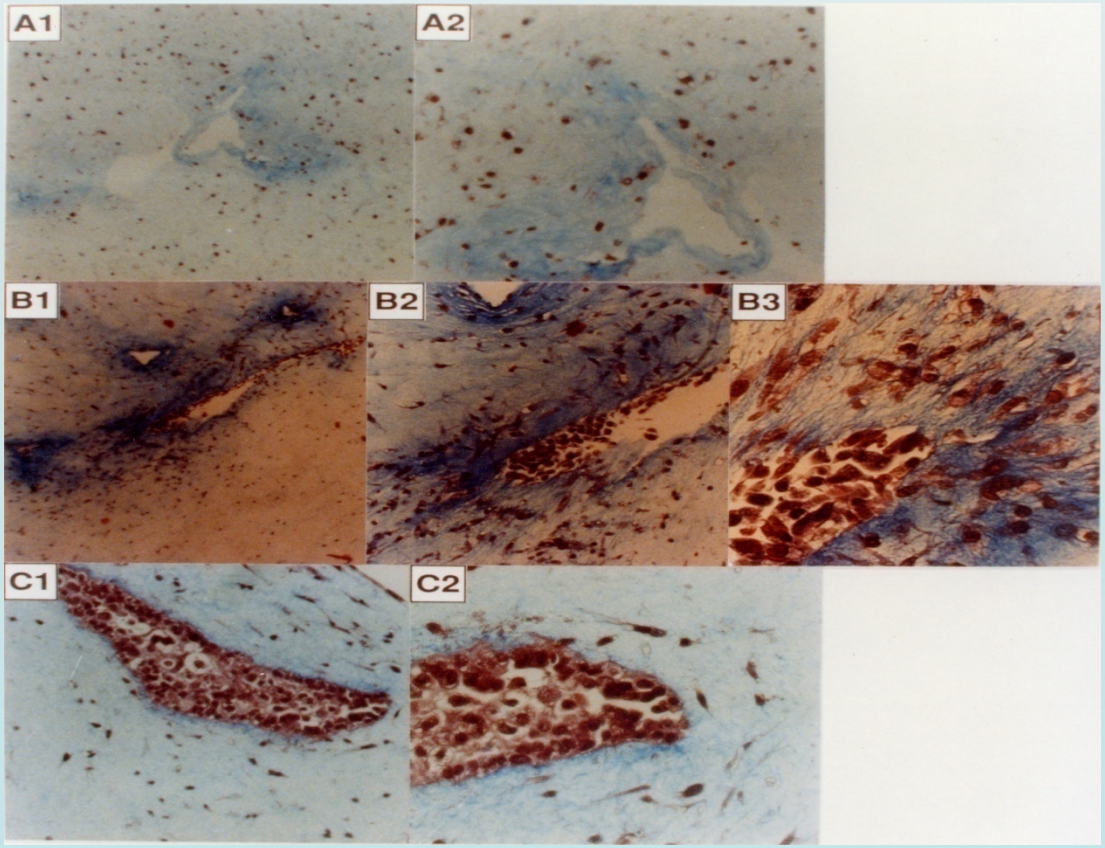
Koutsilieris et al, Journal of Clinical Investigation 80 : 941-946, 1987

J Bone Miner Res. 1994 Nov;9(11):1823-32.

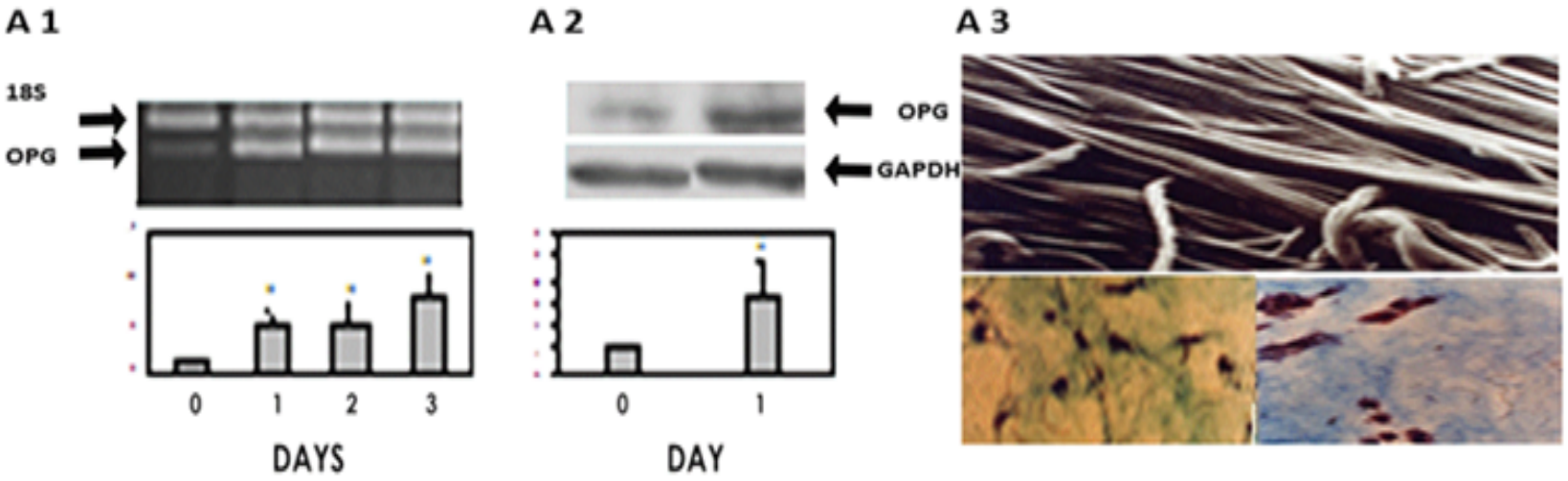
Three-dimensional type I collagen gel system for the study of osteoblastic metastases produced by metastatic prostate cancer.

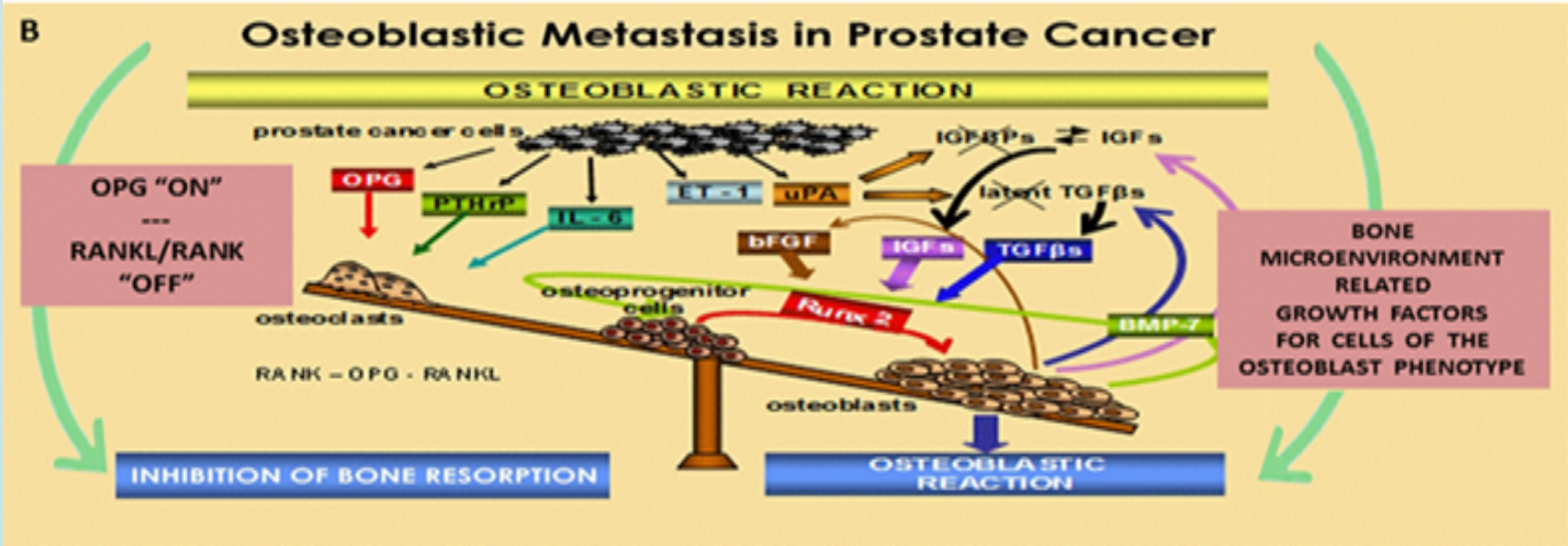
Koutsilieris M, Sourla A, Pelletier G, Doillon CJ.





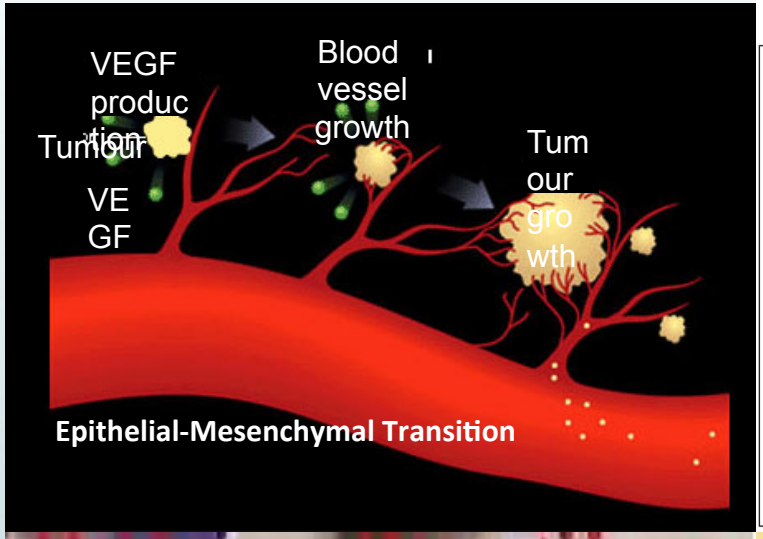
Bone metastasis: late stage - blastic metastasis in prostate cancer

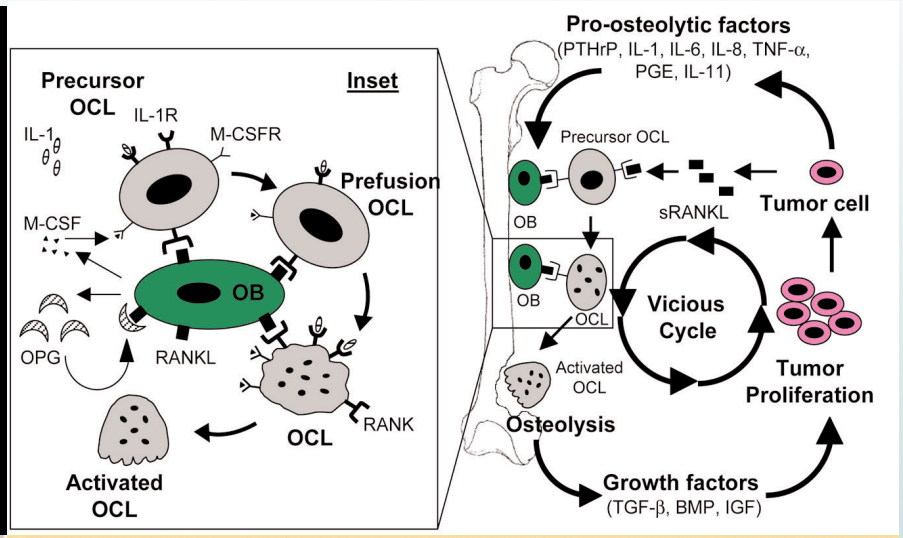


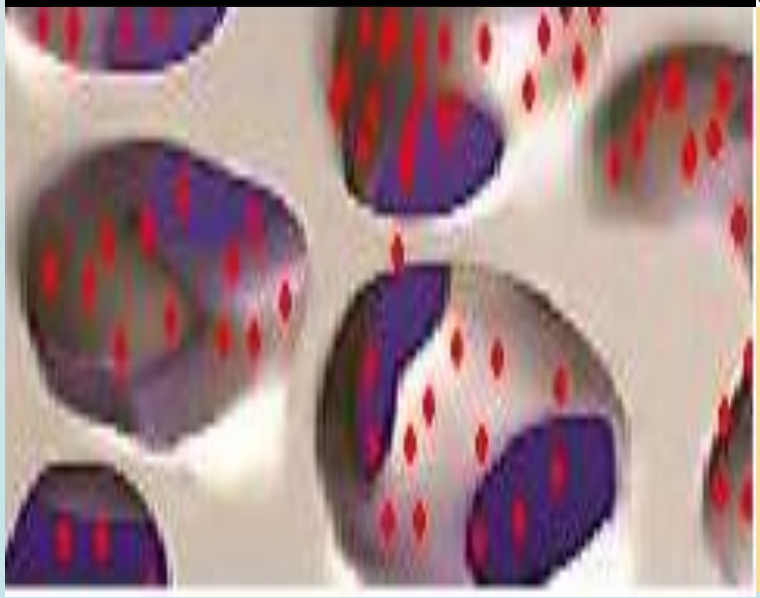


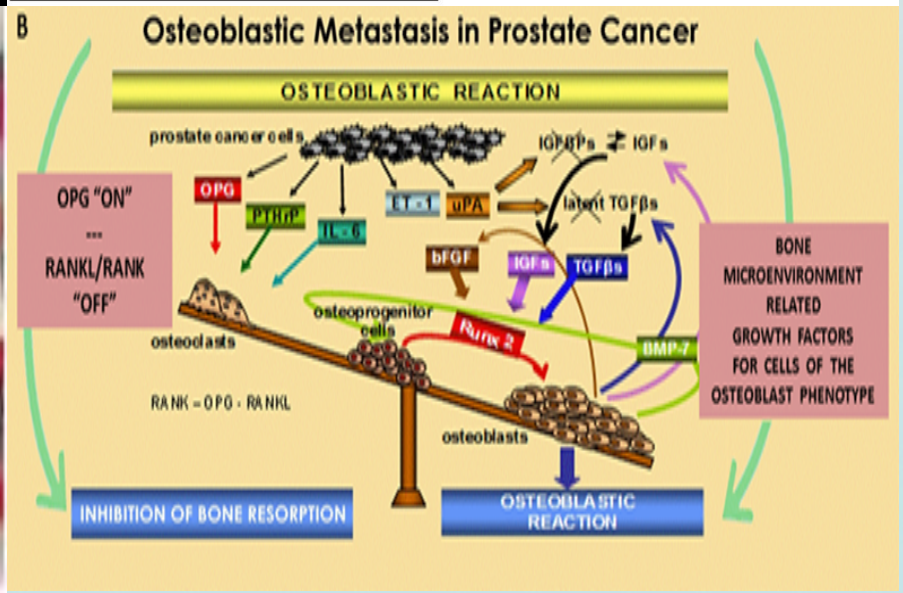
Katopodis H & Koutsilieris, In Vivo, 2008;
Msaouel & Koutsilieris M, BPRCEM 2008;
Pneumaticos S & Koutsilieris M, EOTT, 2013

ESTABLISHMENT OF BONE METASTASIS – EARLY STAGE





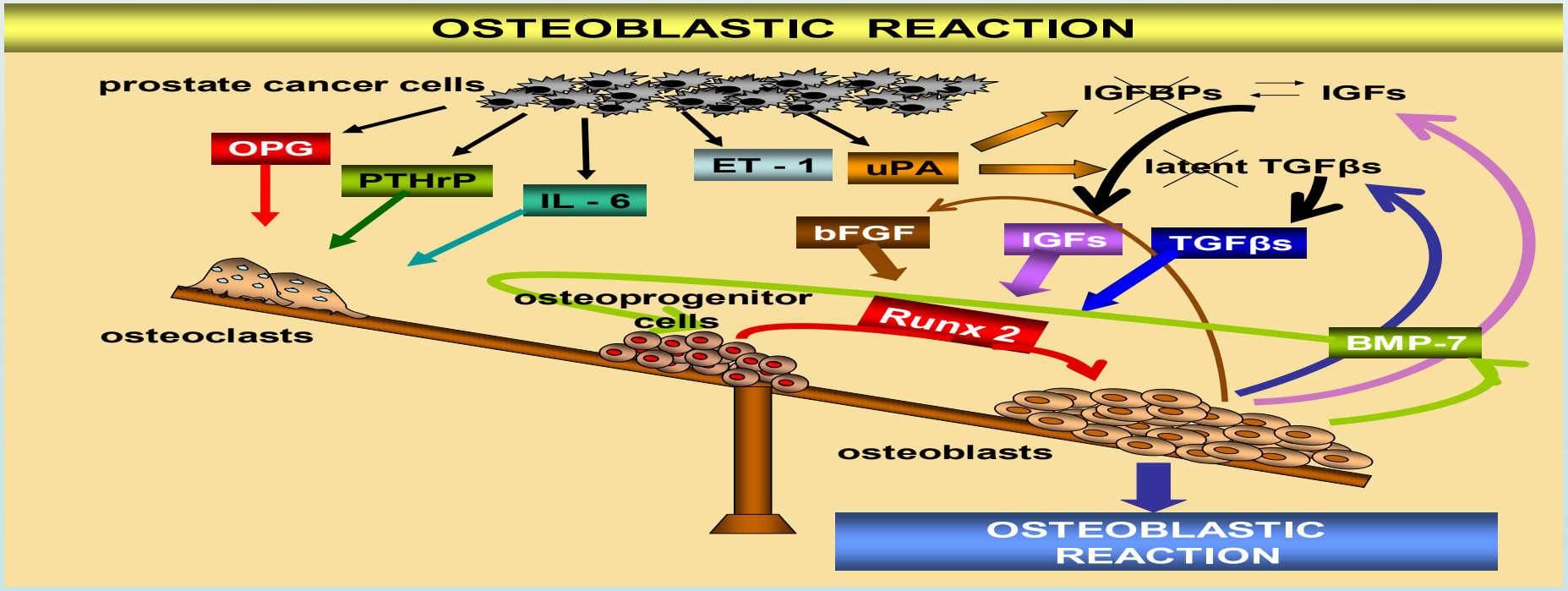




Koutsilieris M, et al. In: Meadows GG, editor. Integration/interaction of oncologic growth. Springer; 2005. Ch. 19.
Msaouel & Koutsilieris M, BPRCEM 2008; Pneumaticos S & Koutsilieris M, EOTT, 2013.

CASTRATION RESISTANT PROSTATE CANCER

Which is the clinical significance ????



Novel concept of antisurvival factor (ASF) therapy produces an objective clinical response in four patients with hormone-refractory prostate cancer: case report.

Koutsilieris M, Tzanela M, Dimopoulos T.

Prostate. 1999 Mar 1;38(4):313-6

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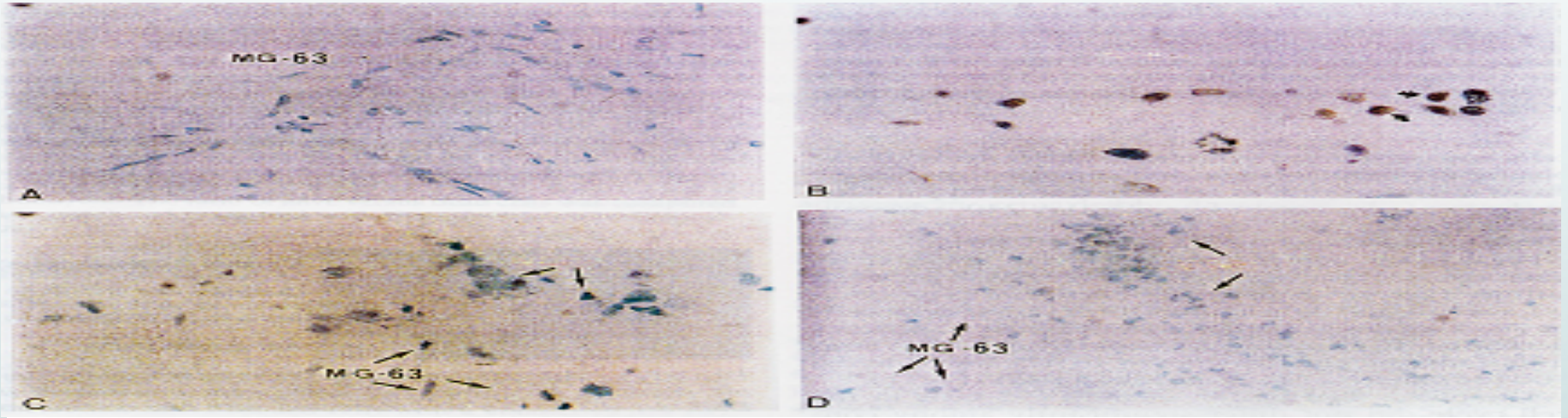
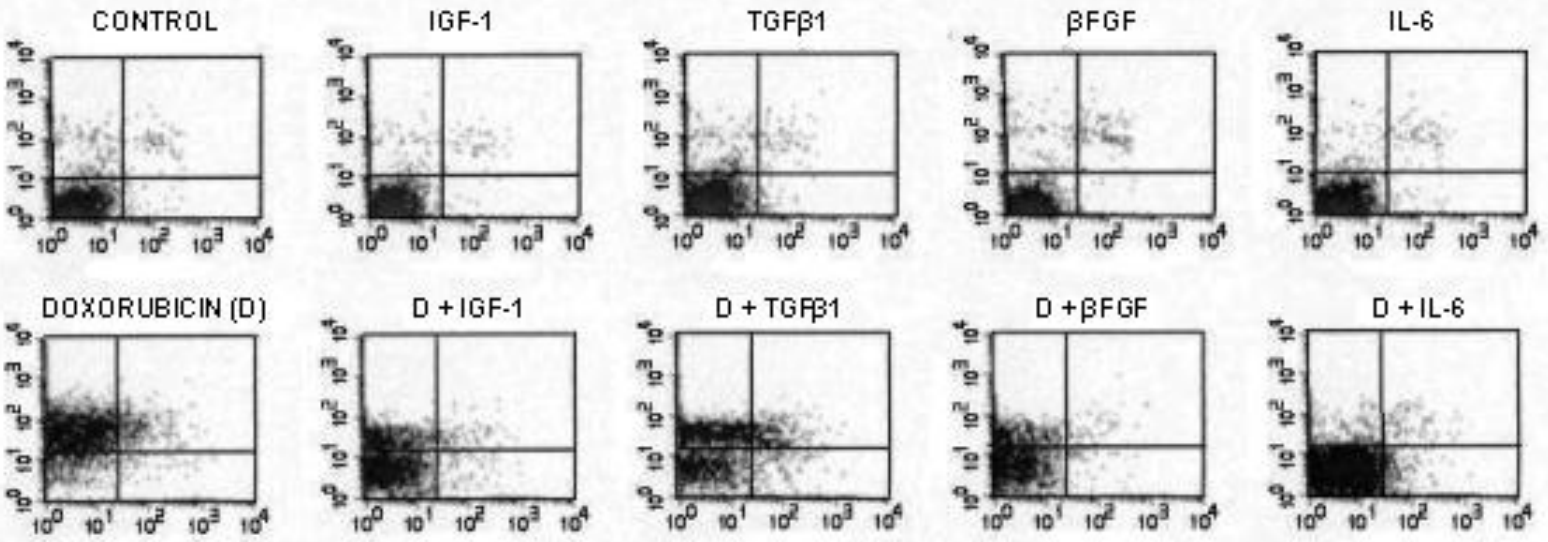
OSTEOBLASTIC METASTASIS & CHEMOTHERAPY RESISTANCE





Reyes-Moreno & Koutsilieris M et al, Urology, 1996

CROSS TALK ING OF GROWTH FACTORS WITH AR: Growth Factors (Survival Factors) Inhibit The Castration-induced Apoptosis Of Prostate Cancer Cells In Bones Microenvironment

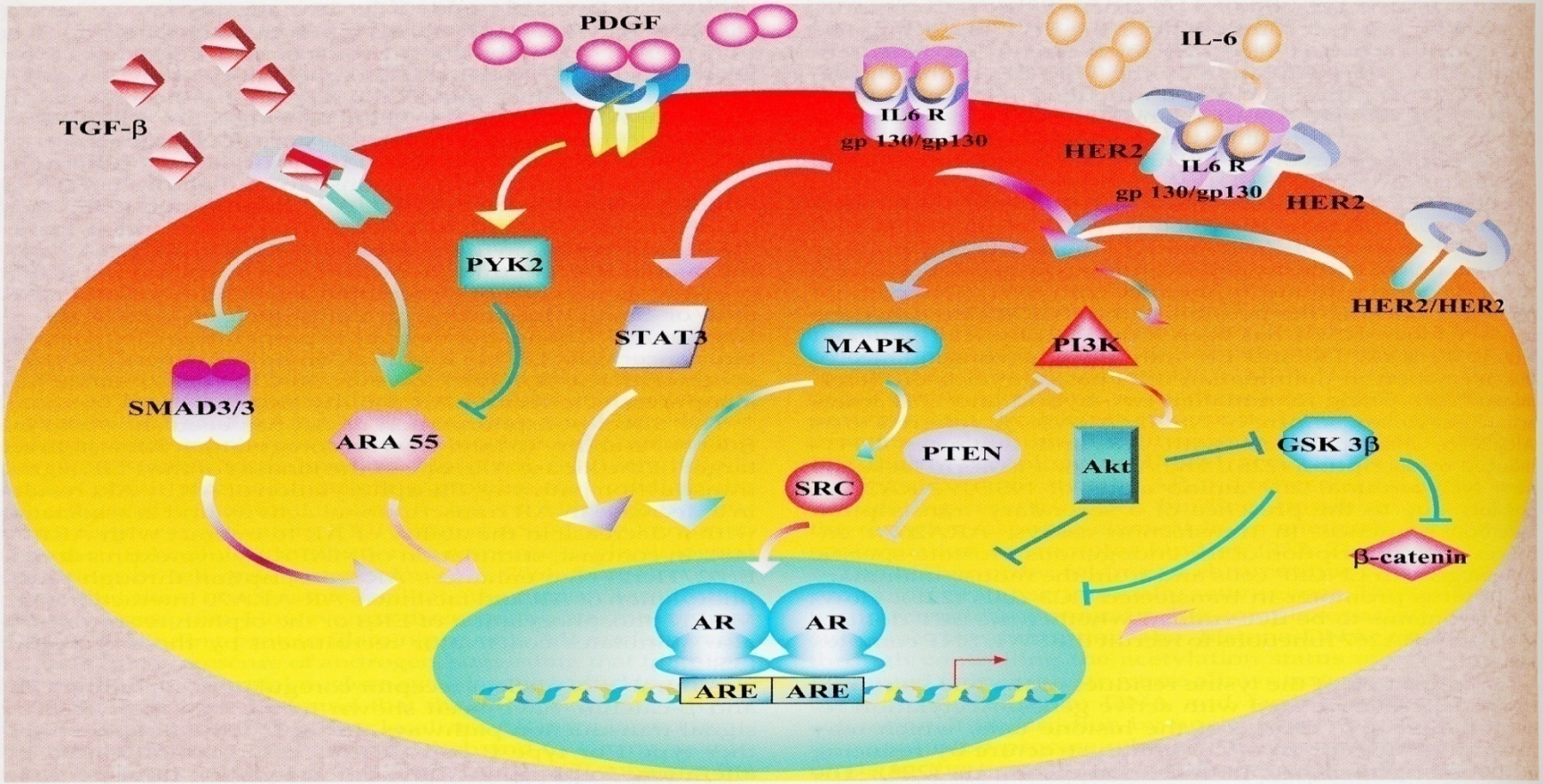
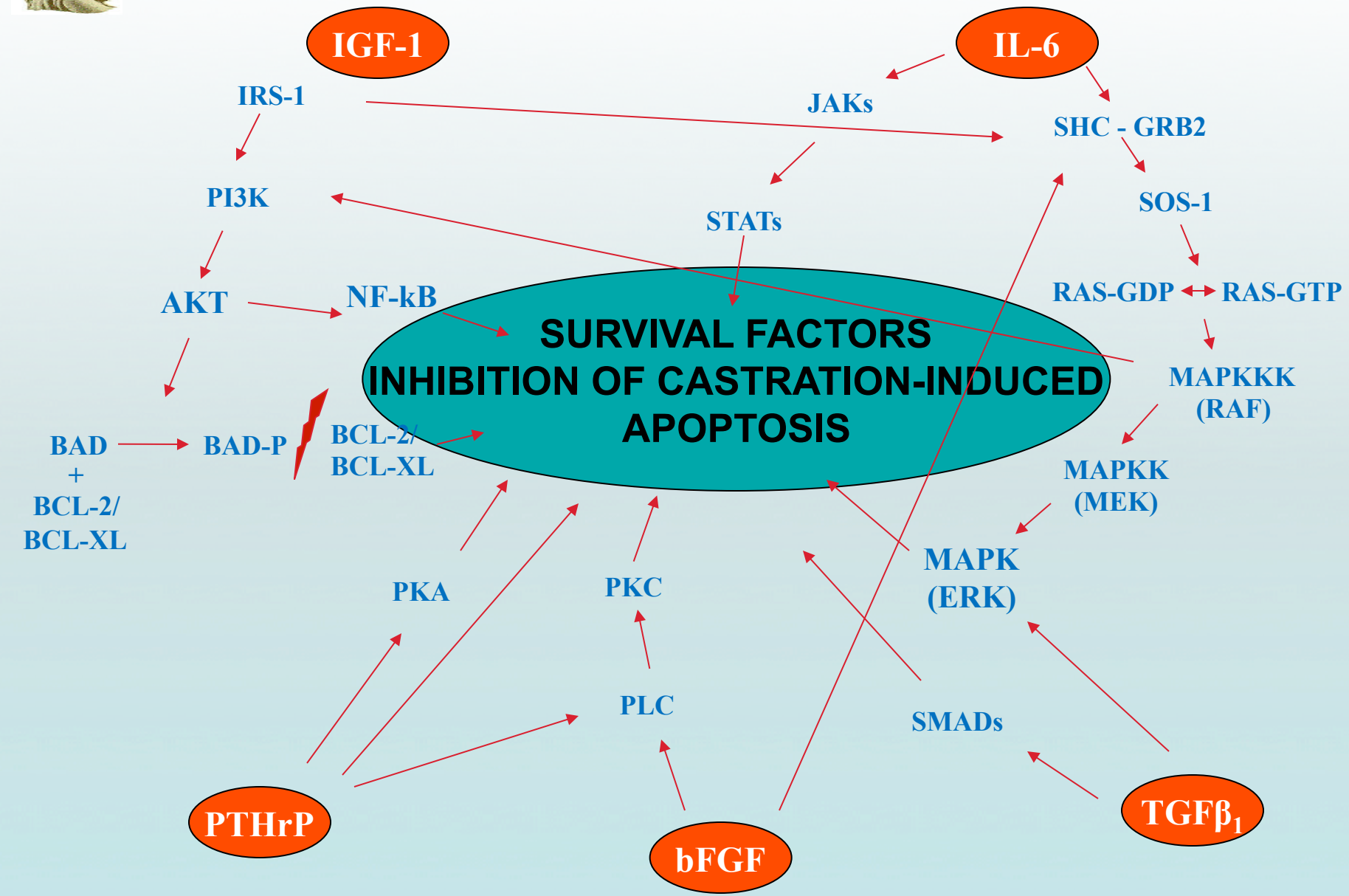


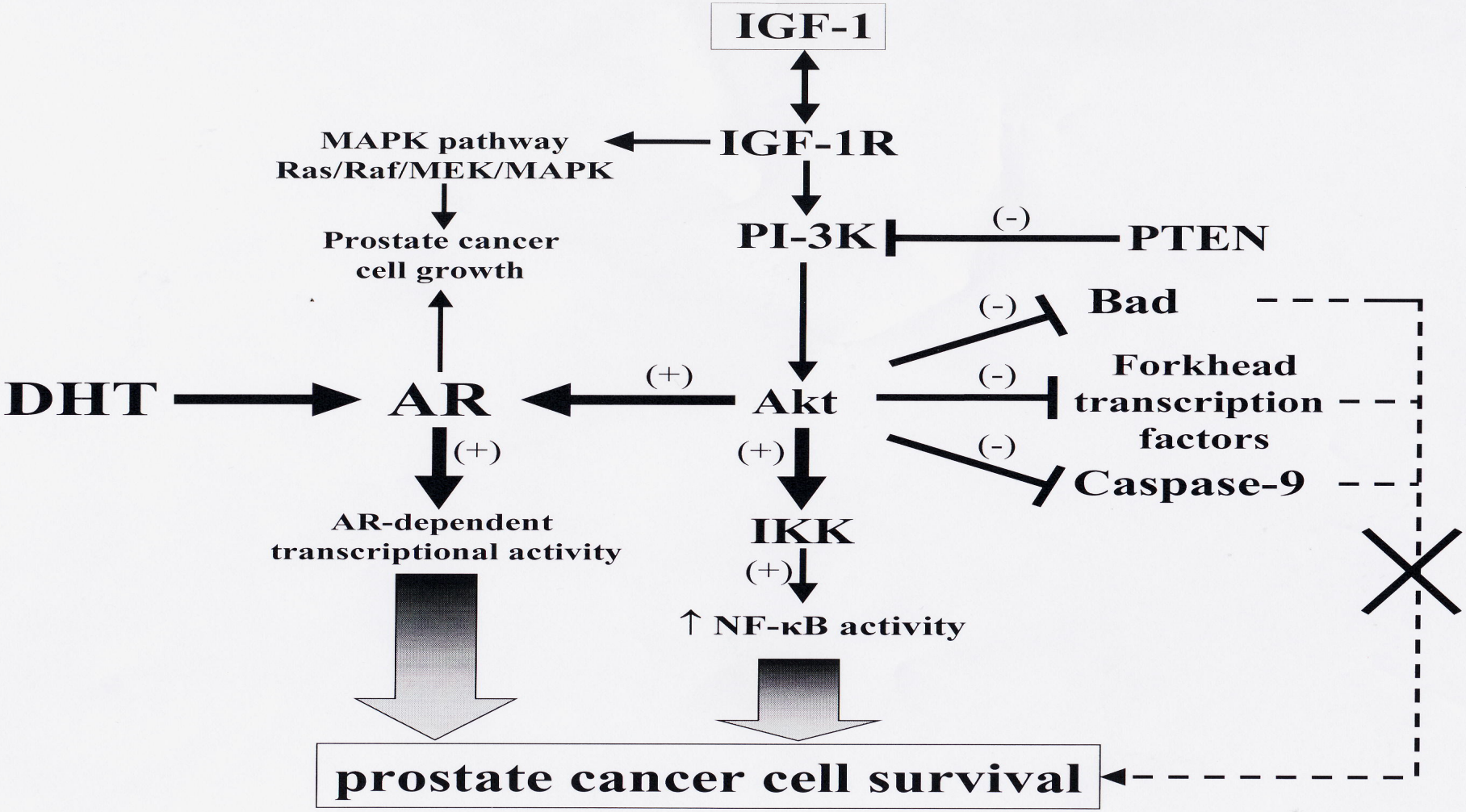
FIG. 4. Multiple signal transduction pathways are involved in the regualtion of AR and AR coregulator function. The activation of the MAPK and PI3K signal cascades occurs in response to multiple growth factor stimuli. For simplicity, IL-6 and Her2 induction of these pathways is depicted here. MAPK can directly phosphorylate AR to enhance AR interaction with coactivators and can phosphorylate coactivators, such as SRC family members, to facilitate transcription. Akt phosphorylation of AR represses AR transcription, at least in part, through reduction of AR-coactivator interaction. In addition to SRC, the coregulators β-catenin and ARA55 are targets of phosphorylative regulation as discussed in the text.

Culig Z et al, Cancer Res, 1999; Culig Z et al, Endocr Rel Cancer, 2002,; Culig Z et al, Growth Factors, 2004



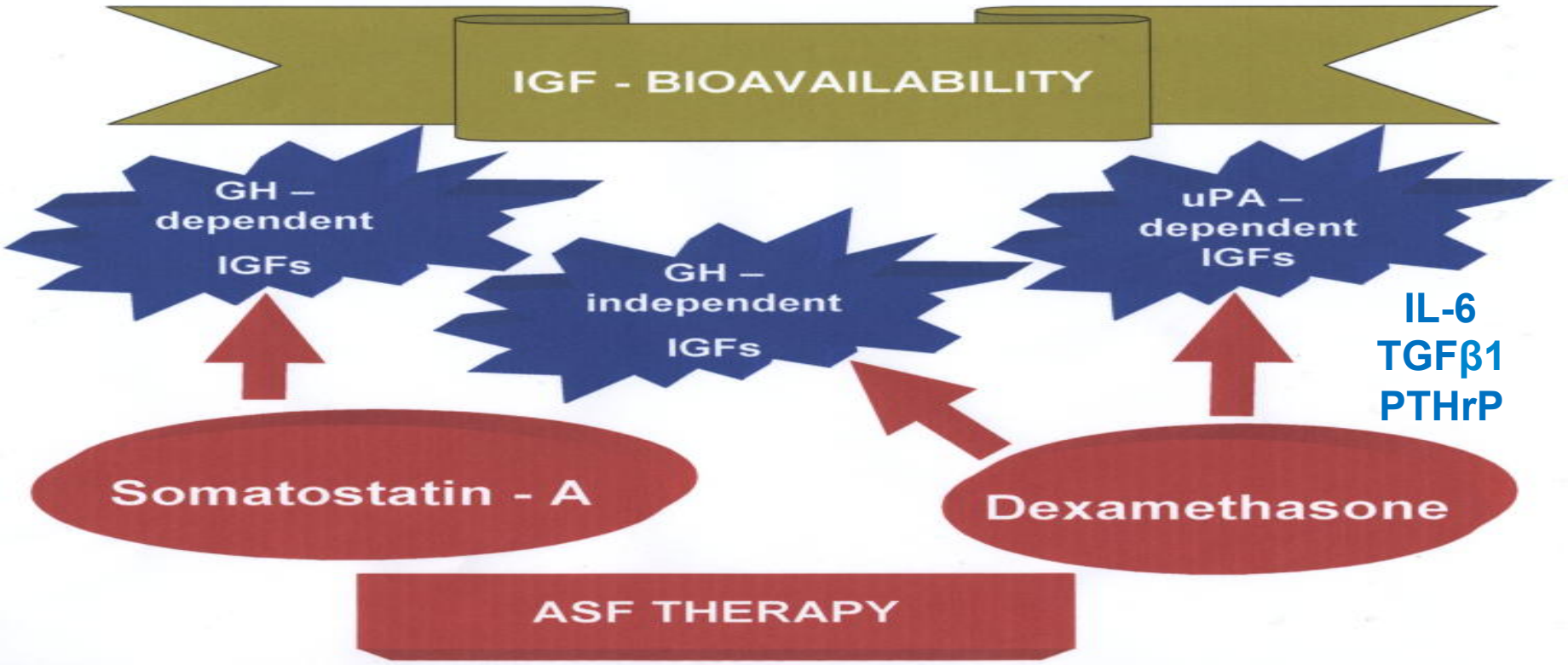
Bogdanos et al, Endocrine - Related Cancer, 10 : 279 – 289, 2003

IGF-1 Inhibits The Apoptosis (Survival Factors) Of Prostate Cancer Cells In Bones



Koutsilieris M et al, Prostate 1998; Koutsilieris M et al, J Clin Endocrinol & Metab 2001

BONE MICROENVIRONMENT-TARGETED THERAPY
Suppression of the IGF-1, TGFβs and IL-6 bioavailability can reintroduce clinical response in castration - resistant prostate cancer

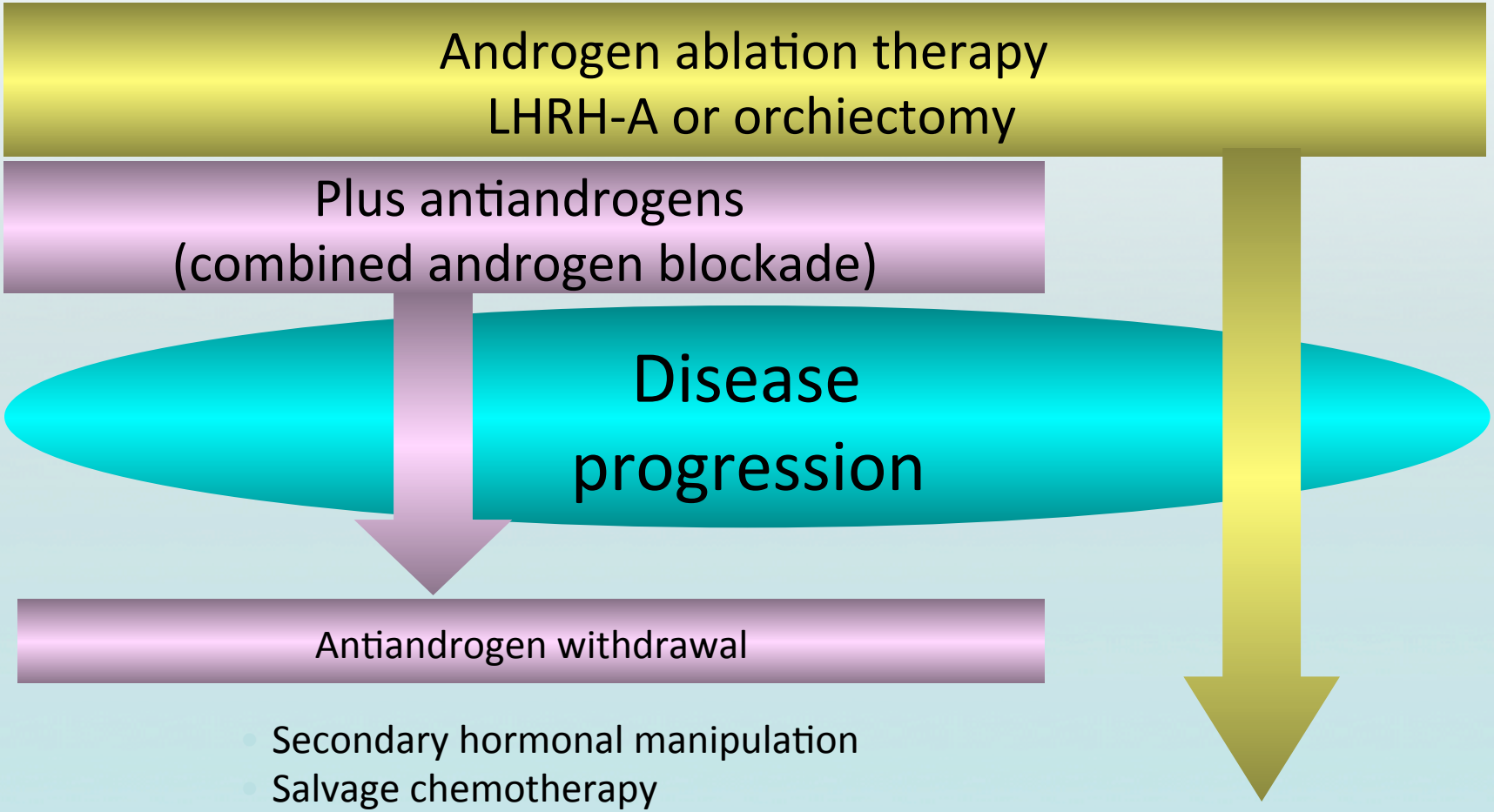


Patients had stage D3 prostate cancer.
ASF = anti-survival factor; GH = growth hormone.

Koutsilieris M, et al. Prostate. 1999; 38: 313-16;

Koutsilieris M, et al. J Clin Endocrinol Metab. 2001; 86:5729-36.

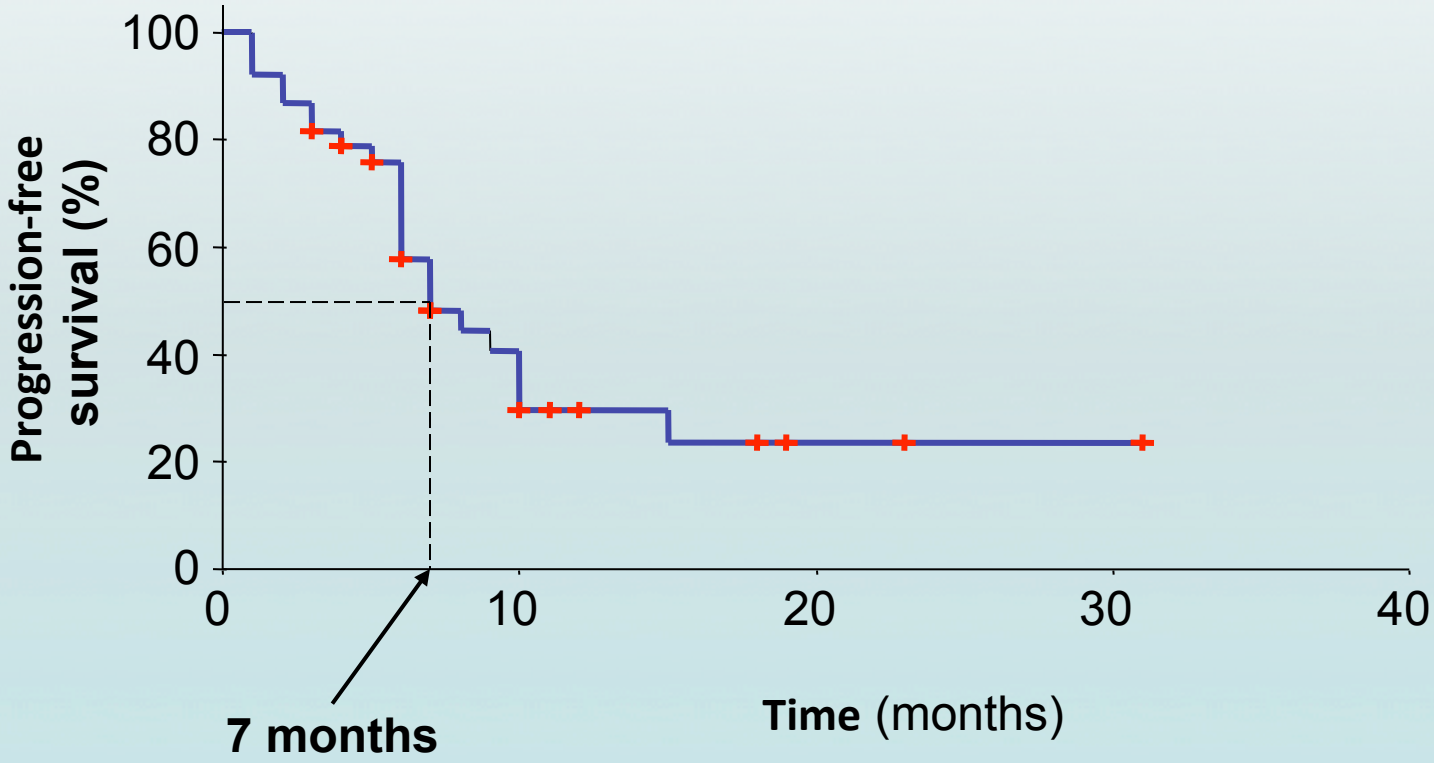
Clinical course of prostate cancer with bone involvement



- Secondary hormonal manipulation
- Salvage chemotherapy

LHRH-A = LHRH agonist.

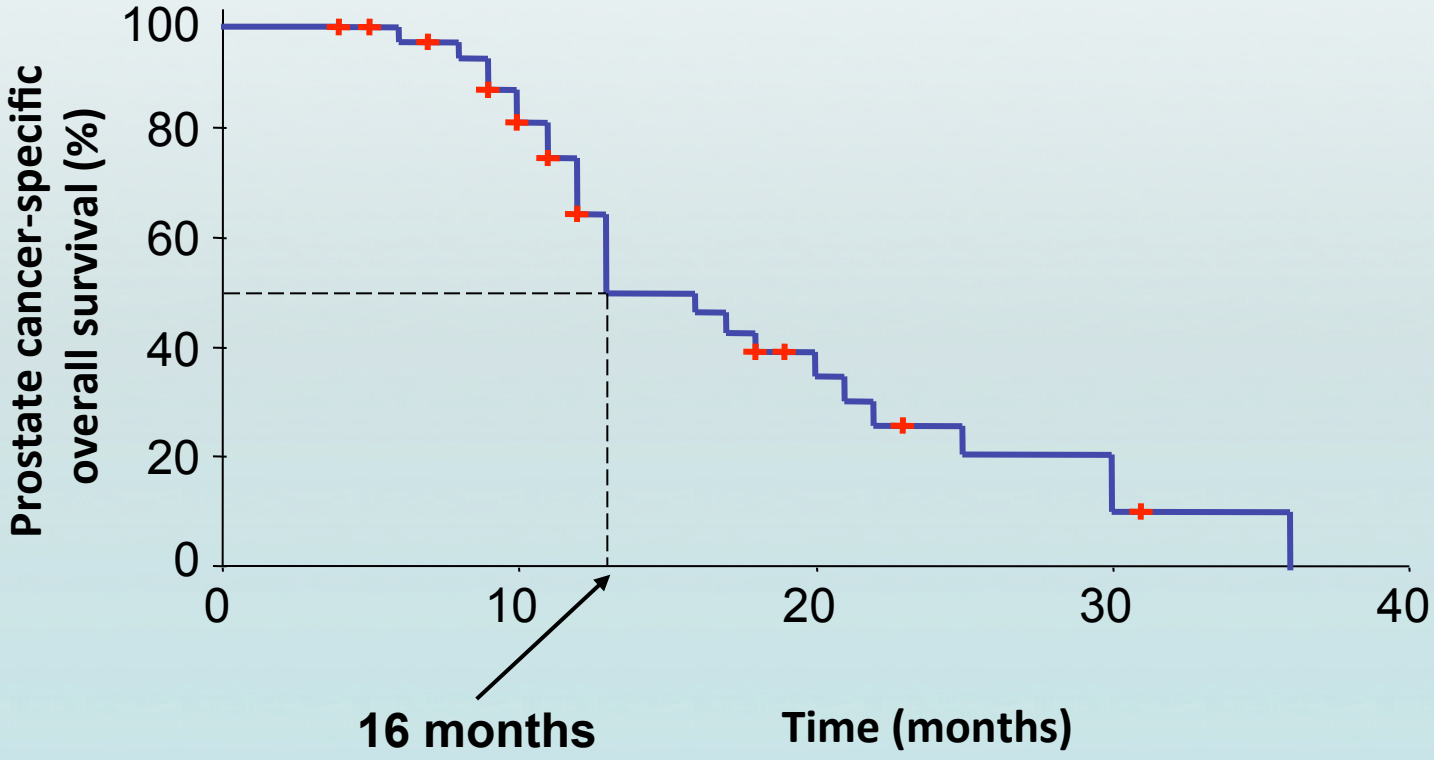
Median progression-free survival: 7 months



95% CI = 4.5–9.5 months.

Koutsilieris M, et al. Clin Cancer Res. 2004;10:4398-405.

Median disease-specific overall survival: 16 months



95% CI = 11.9–20.1 months.

Koutsilieris M, et al. Clin Cancer Res. 2004;10:4398-405.

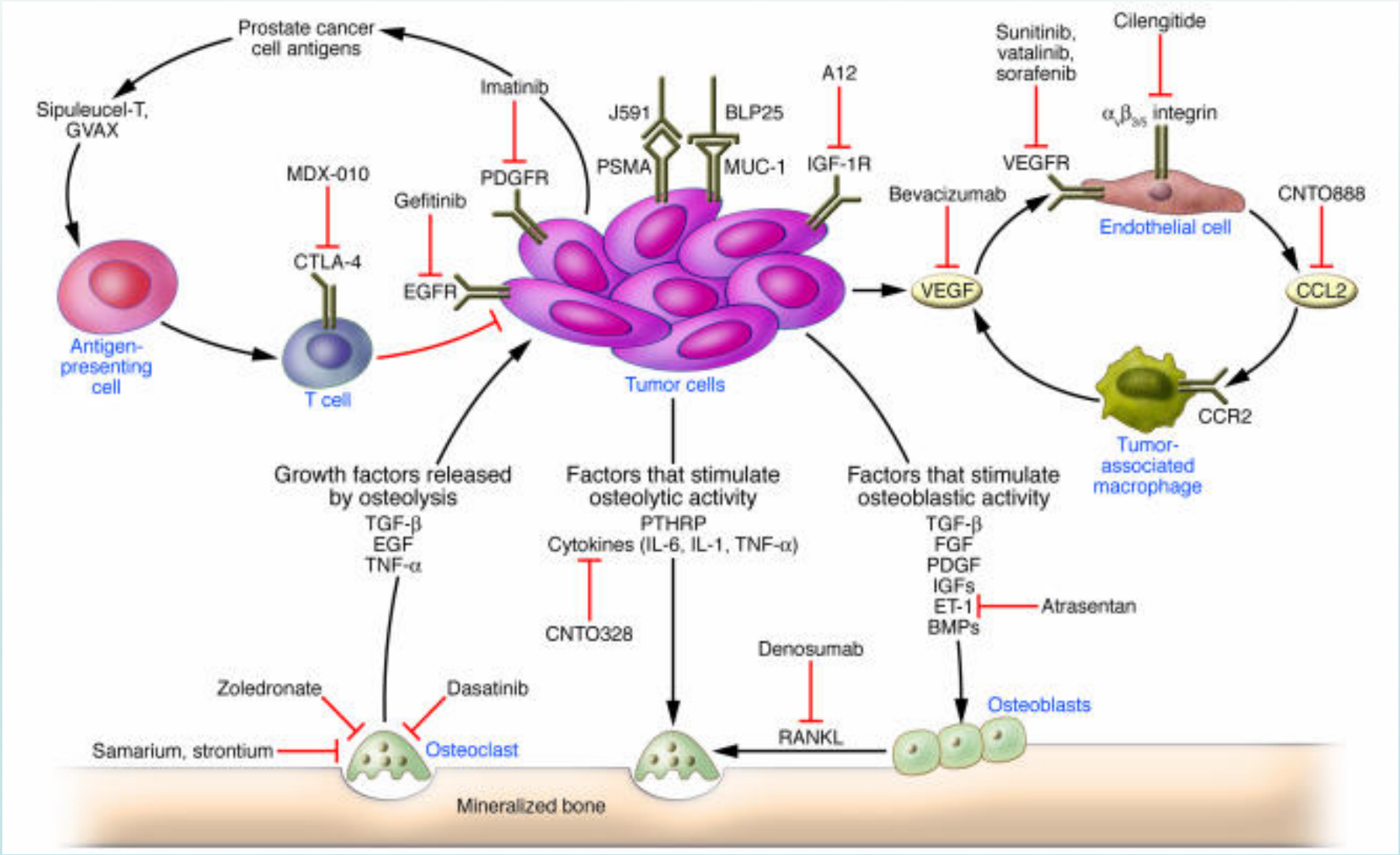
ASF therapy vs chemotherapy: results

	ASF	Chemotherapy
Median overall survival, months (95% CI)	**18 (13.0–22.7)**	**18.8 (10.8–26.7)**
Side-effects[1]		
Anaemia	**22%**	**80%*** **
Neutropenia	**0**	**60%*** **
Thrombocytopenia	**0**	**40%** **
Alopecia	**0**	**100%*** **
Nausea/vomiting	**0**	**55%*** **
Elevated blood glucose	**22%***	0

Graded according to the Eastern Cooperative Oncology Group criteria.
***p < 0.05; **p < 0.01; ***p < 0.001.**

Dimopoulos MA & Koutsilieris M. Urology. 2004;63:120-5.

Bone metastasis microenvironment - targeted therapies



BONE METASTASIS MICROENVIRONMENT TARGETED THERAPIES

Skeletal metastases and impact of anticancer and bone-targeted agents in patients with castration-resistant prostate cancer.
Vignani F, Bertaglia V, Buttigliero C, Tucci M, Scagliotti GV, Di Maio M.
Cancer Treat Rev. 2016 Mar;44:61-73.

Treating Patients with Metastatic Castration Resistant Prostate Cancer: A Comprehensive Review of Available Therapies.
Crawford ED, Higano CS, Shore ND, Hussain M, Petrylak DP.
J Urol. 2015;194(6):1537-47.

Identification of Bone-Derived Factors Conferring De Novo Therapeutic Resistance in Metastatic Prostate Cancer.
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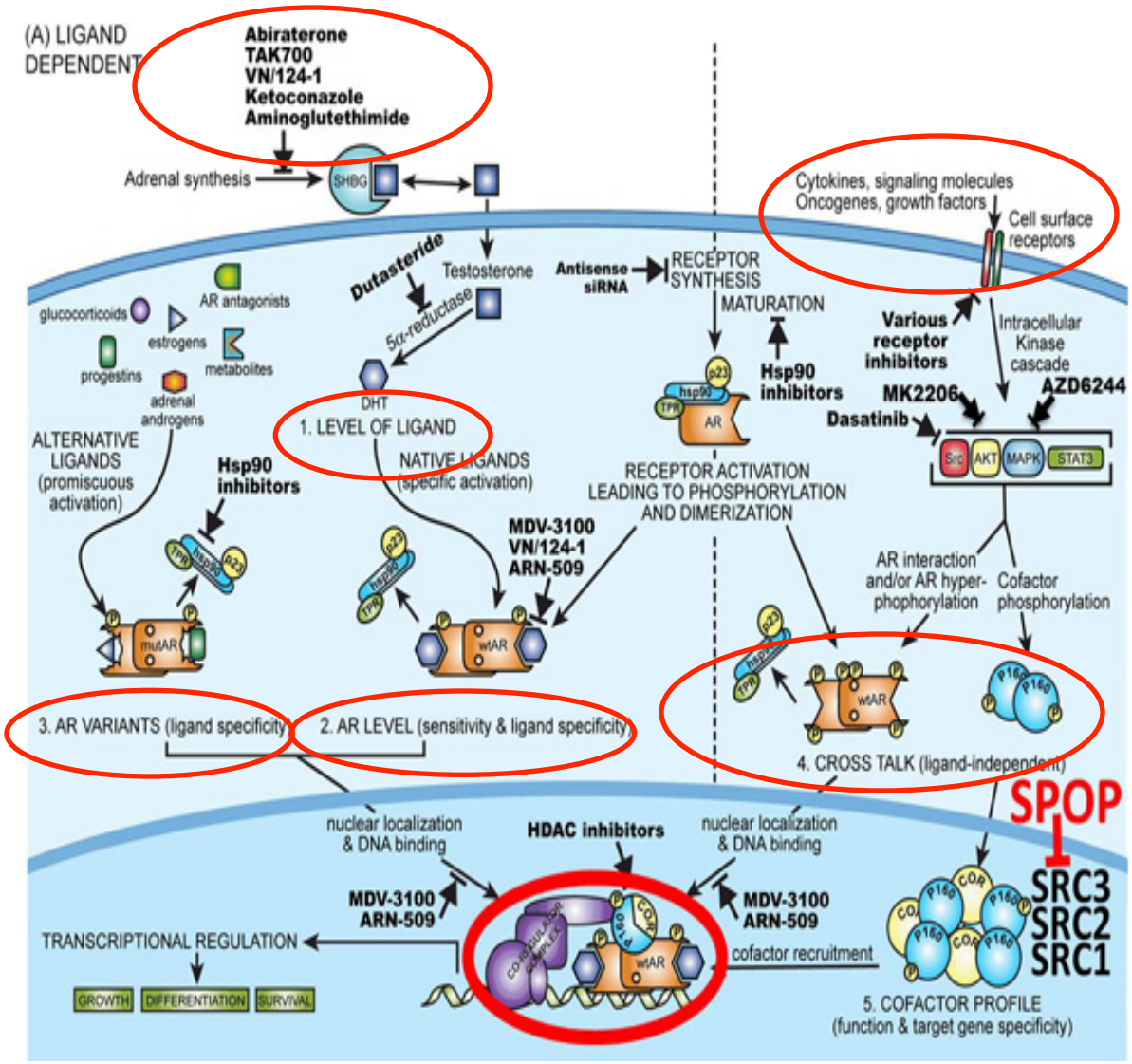
CASTRATION RESISTANT PROSTATE CANCER



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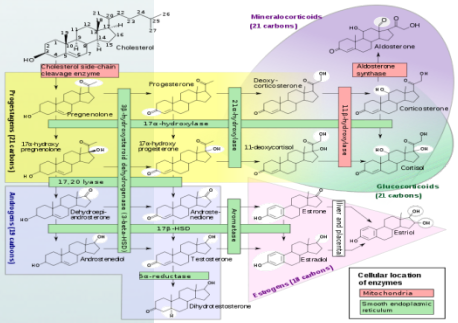
CASTRATION RESISTANT PROSTATE CANCER

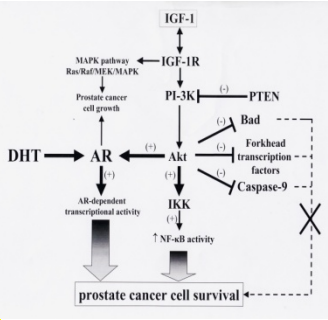


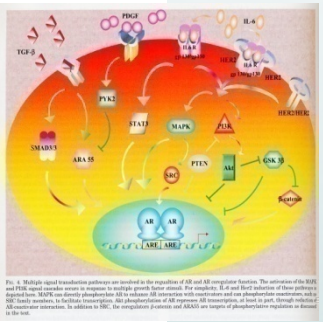
Androgen depletion

Androgen dependent growth

Anti-androgens

AR bypassed





Castration Resistant Growth & Disease Evolution

AR involved

- AR mutations
- AR overexpression (amplification)
- Aberrant AR activation
- Aberrant AR coactivators

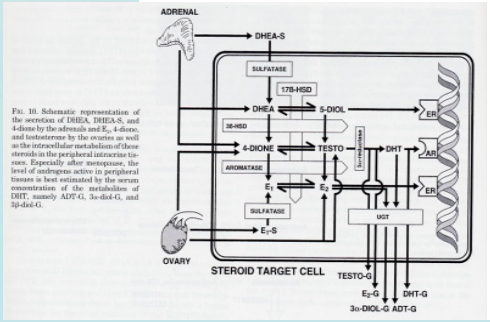
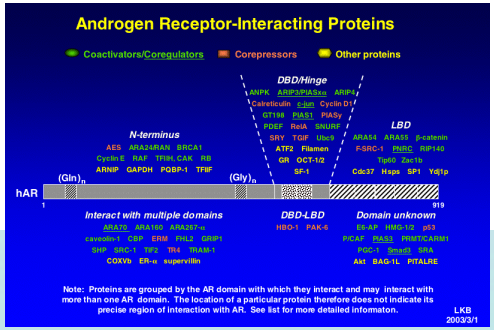


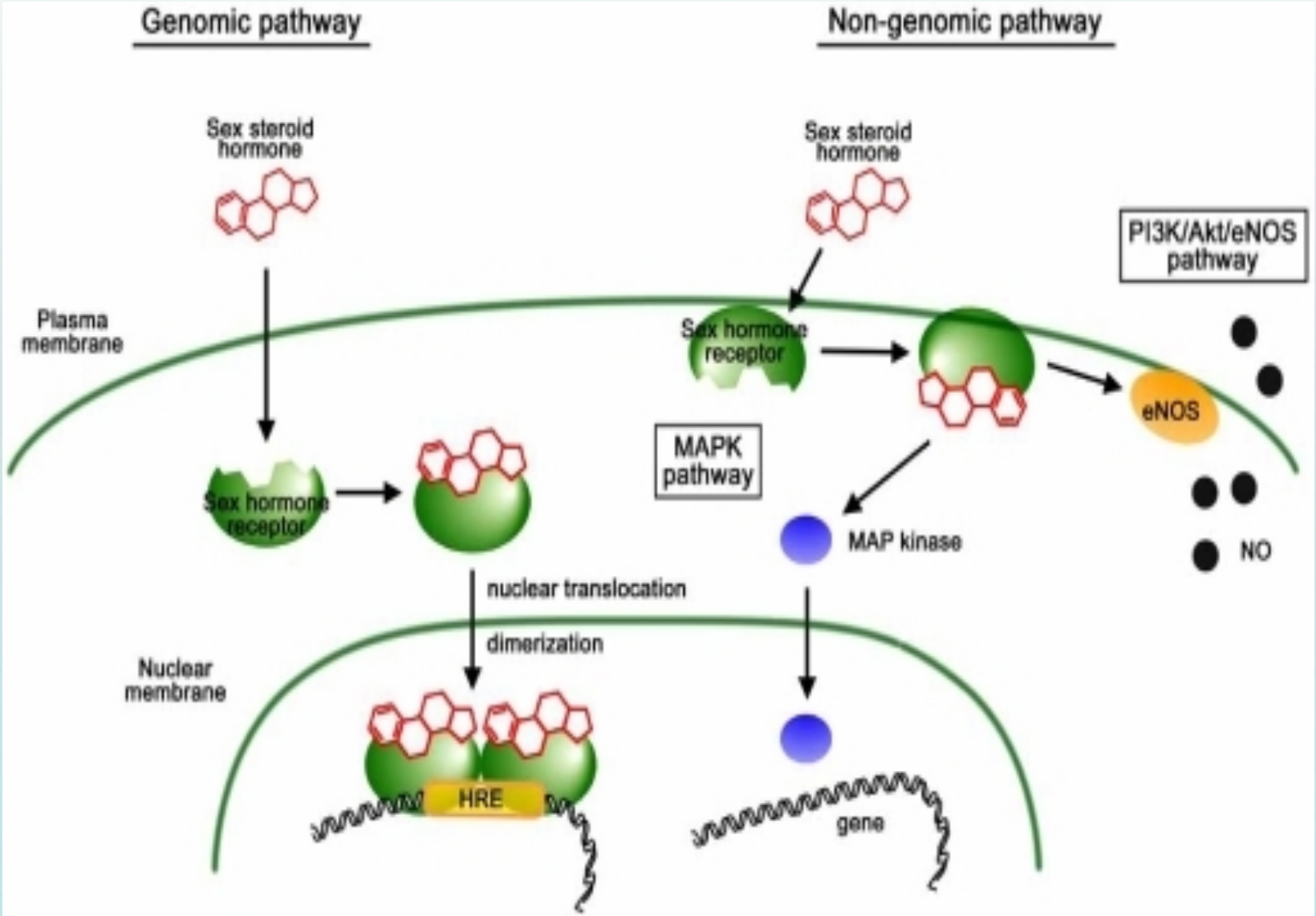
Fig. 10. Schematic representation of the secretion of DHEA, DHEA-S, and 4-dione by the adrenals and E_1, 4-dione, and testosterone by the ovaries as well as the intracellular metabolism of these steroids in the peripheral intracrine tissues. Especially after menopause, the level of androgens active in peripheral tissues is best estimated by the serum concentration of the metabolites of DHT, namely ADT-G, 3α-diol-G, and 3β-diol-G.



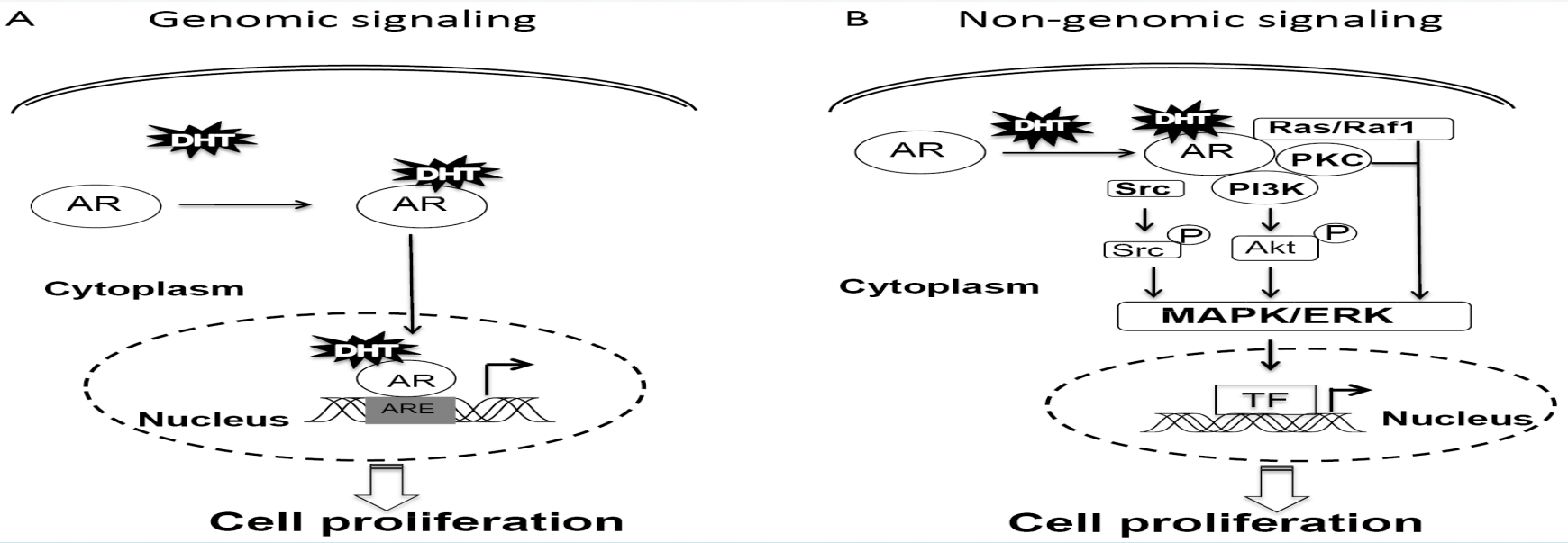
CASTRATION RESISTANT PROSTATE CANCER

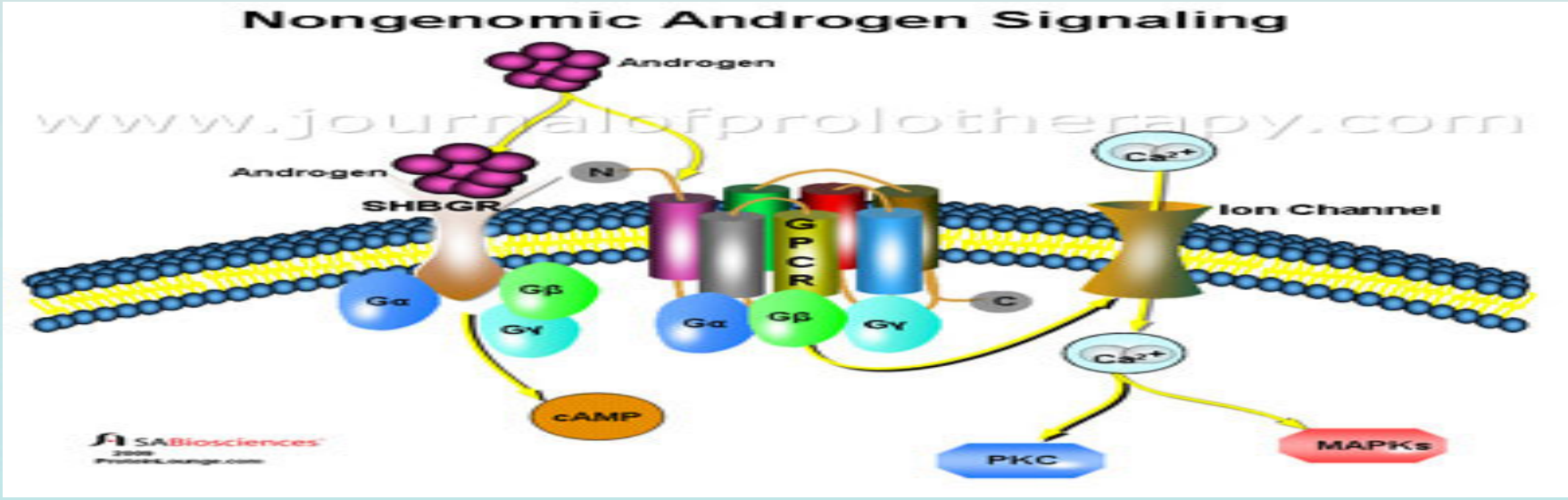
Is that all ????

NON GENOMIC ACTIONS OF STEROID HORMONES



NON GENOMIC ACTIONS OF STEROID HORMONES





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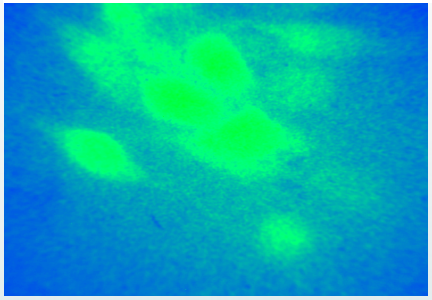
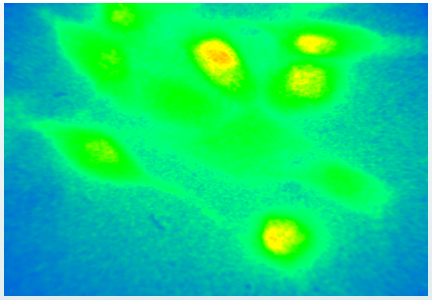
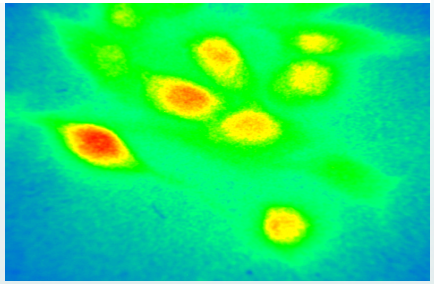
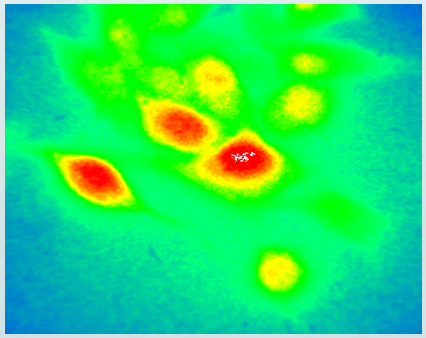
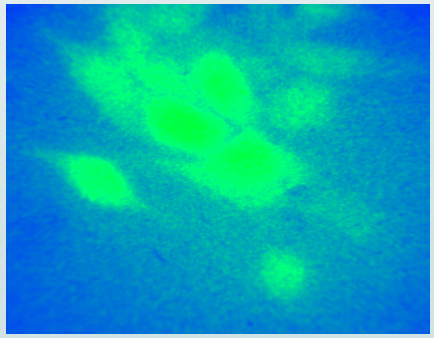
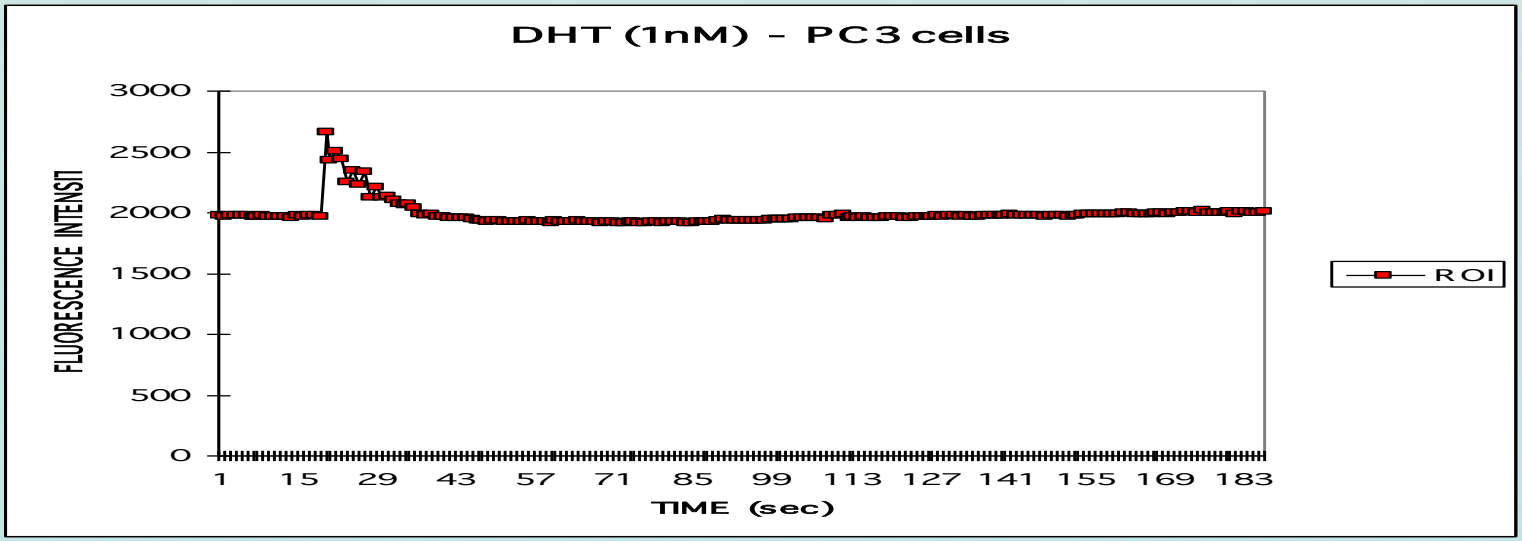








NON GENOMIC ACTIONS OF STEROID HORMONES

Several inhibitors of Src family kinases have been tested in a clinical setting for prostate cancer, notably inhibitors that target kinase activity, **dasatinib (BMSS-354825) and saracatinib (AZD0530); and KX2-391**, a peptidomimetic that blocks the substrate binding site of Src. Clinical studies indicate that targeting Src or inhibiting activated downstream kinase pathways in isolation is ineffective for CRPC.

Likewise, **inhibitors of PI3K, Akt, or mTOR** have also demonstrated limited use in clinical practice as single agents.

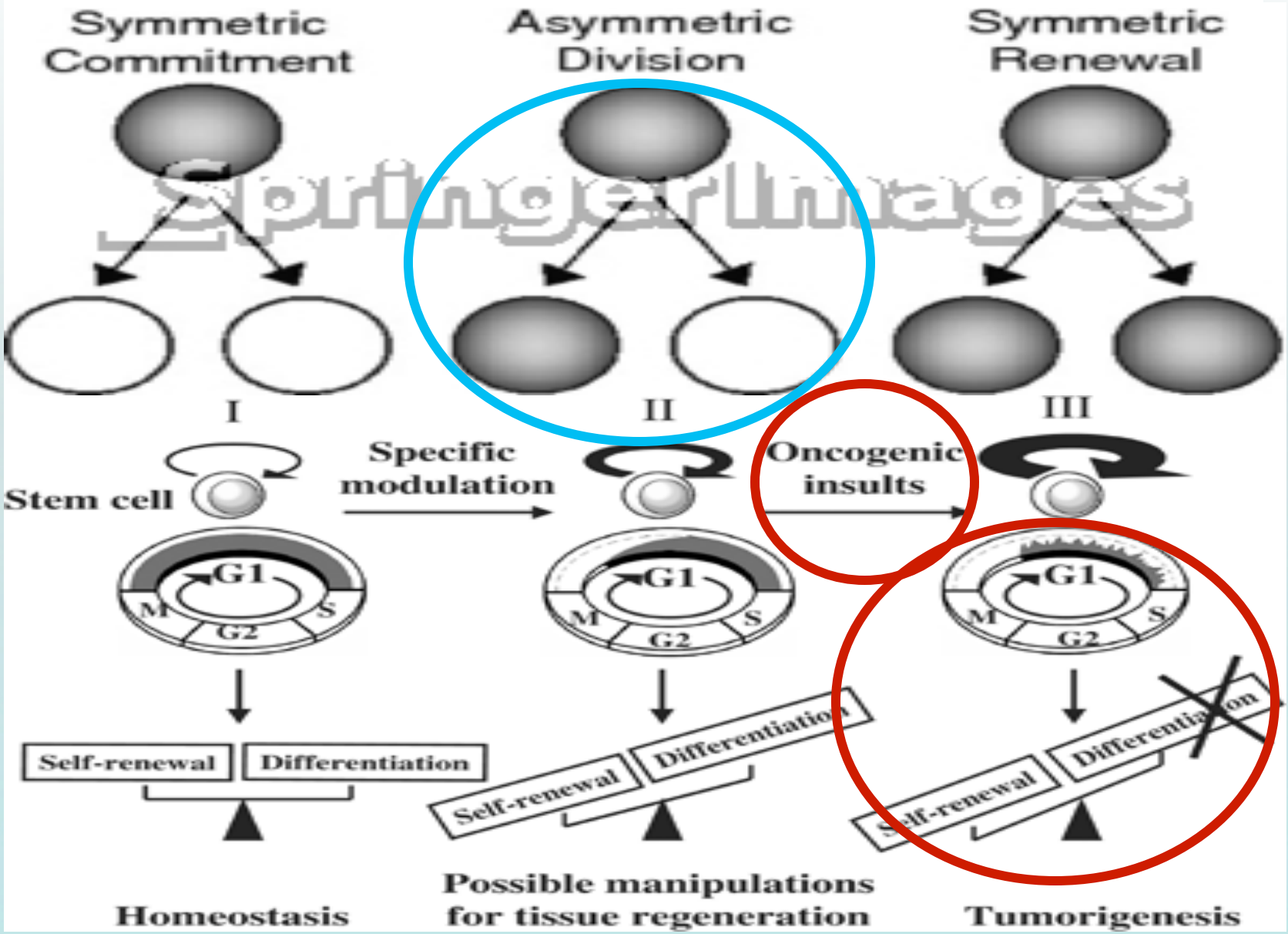
This is probably because targeting non-genomic AR signals does not protect against ligand-dependent activation of AR and transcription of AR target genes. **Inhibition of both non-genomic and genomic pathways of AR may be necessary to eradicate tumor dependency of AR.** Concurrent inhibition of AR and non-genomic AR components may prove useful for prostate cancer patients with progression after primary therapy.

Many of these strategies are currently under investigation and show promising results in preclinical models of CRPC.

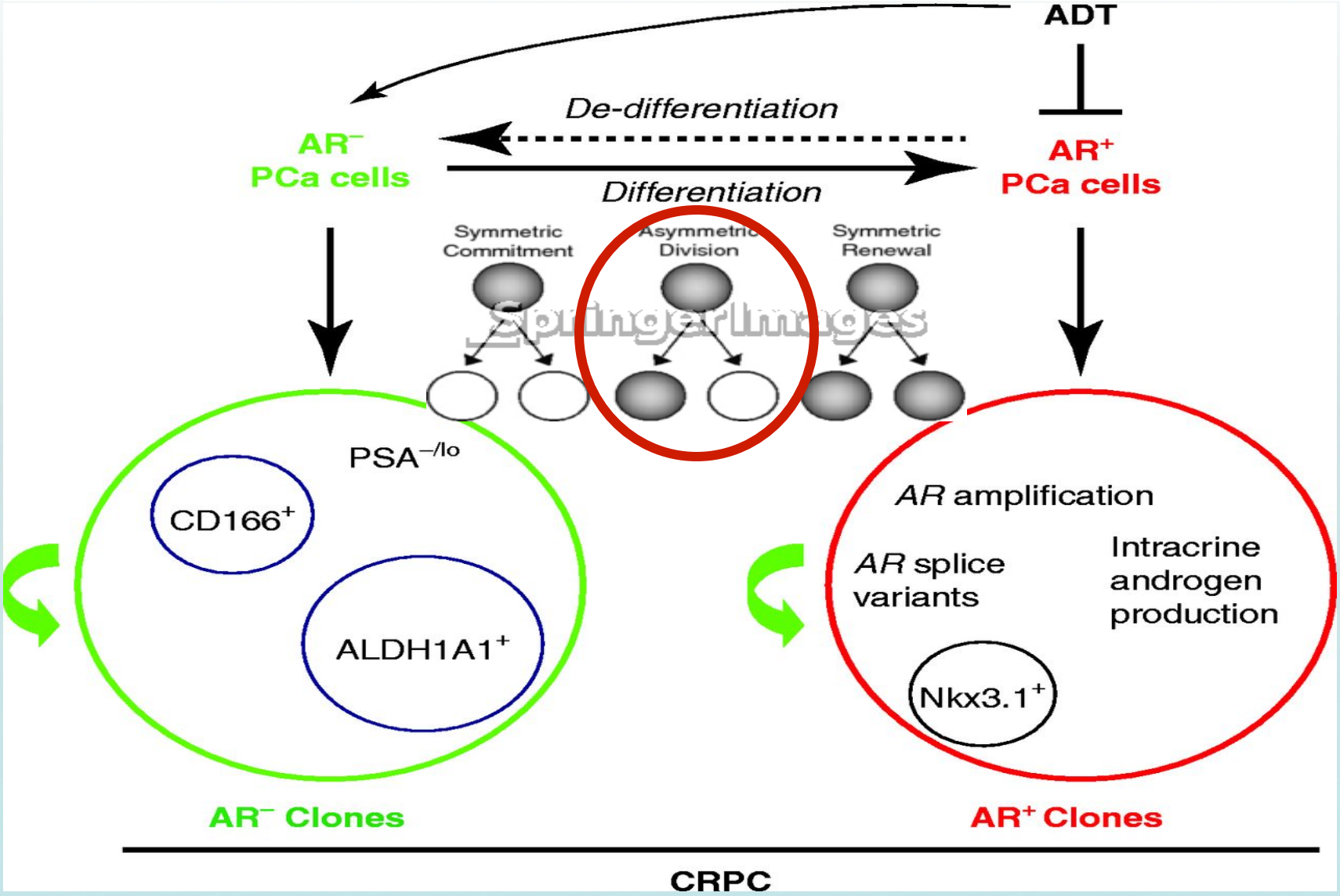
CASTRATION RESISTANT PROSTATE CANCER

Is that all ????

CANCER STEM CELL THEORY

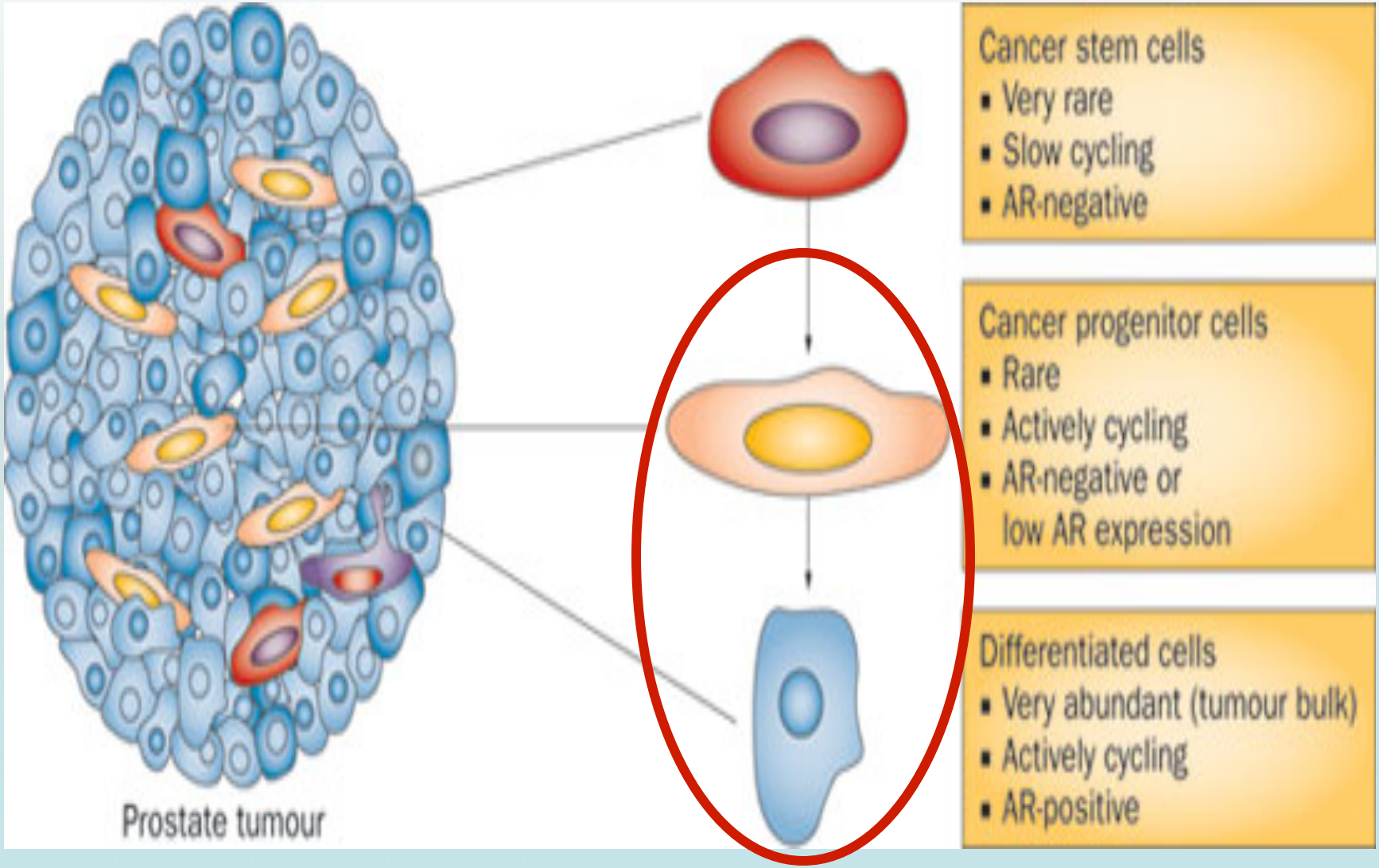


MODEL OF EPITHELIAL HOMEOSTASIS & CANCER INITIATION



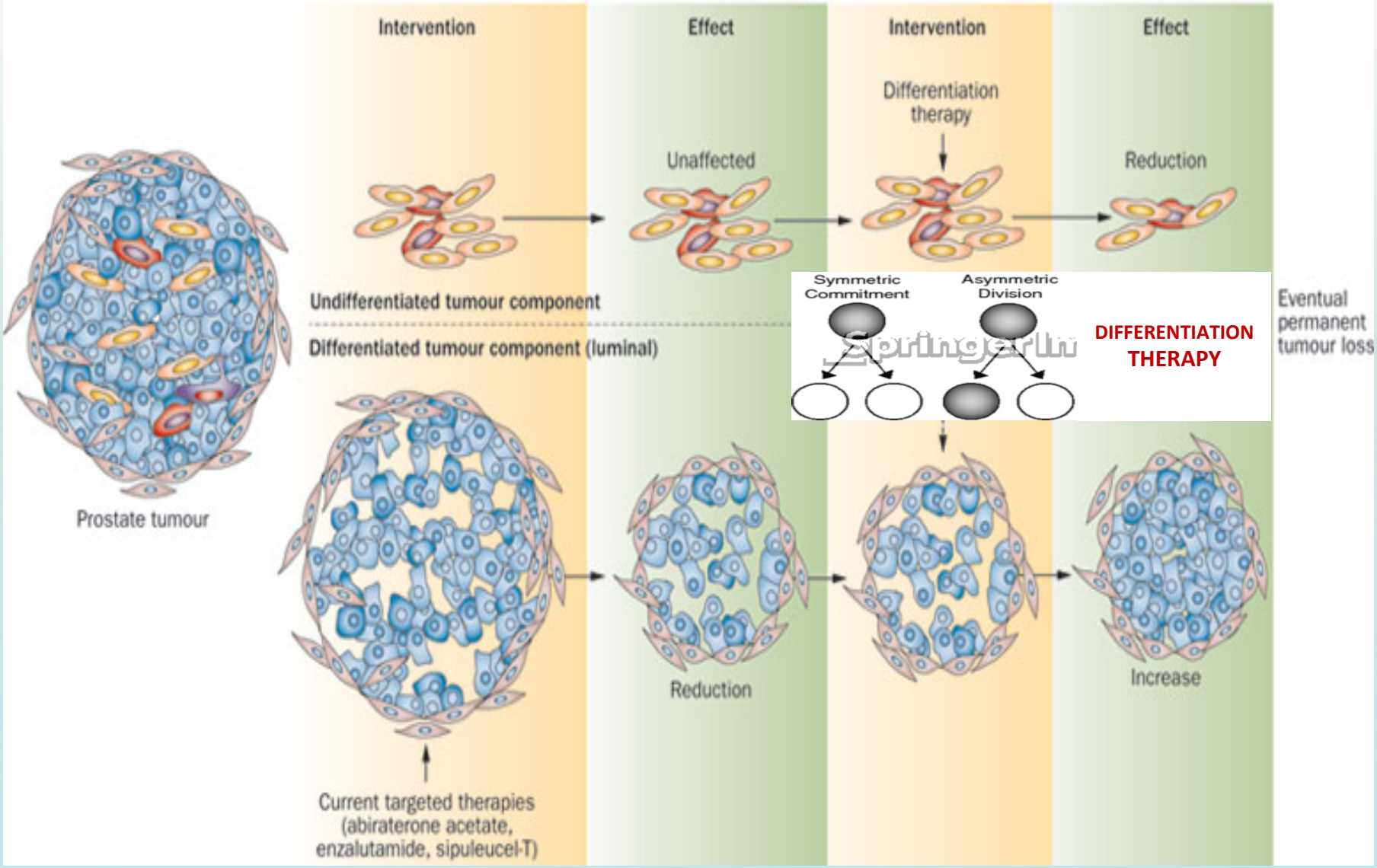
Strand DW & Golgstein AS, Endocrine-Related Cancer (2015) 22: T187-T197

MODEL OF EPITHELIAL HOMEOSTASIS & CANCER INITIATION

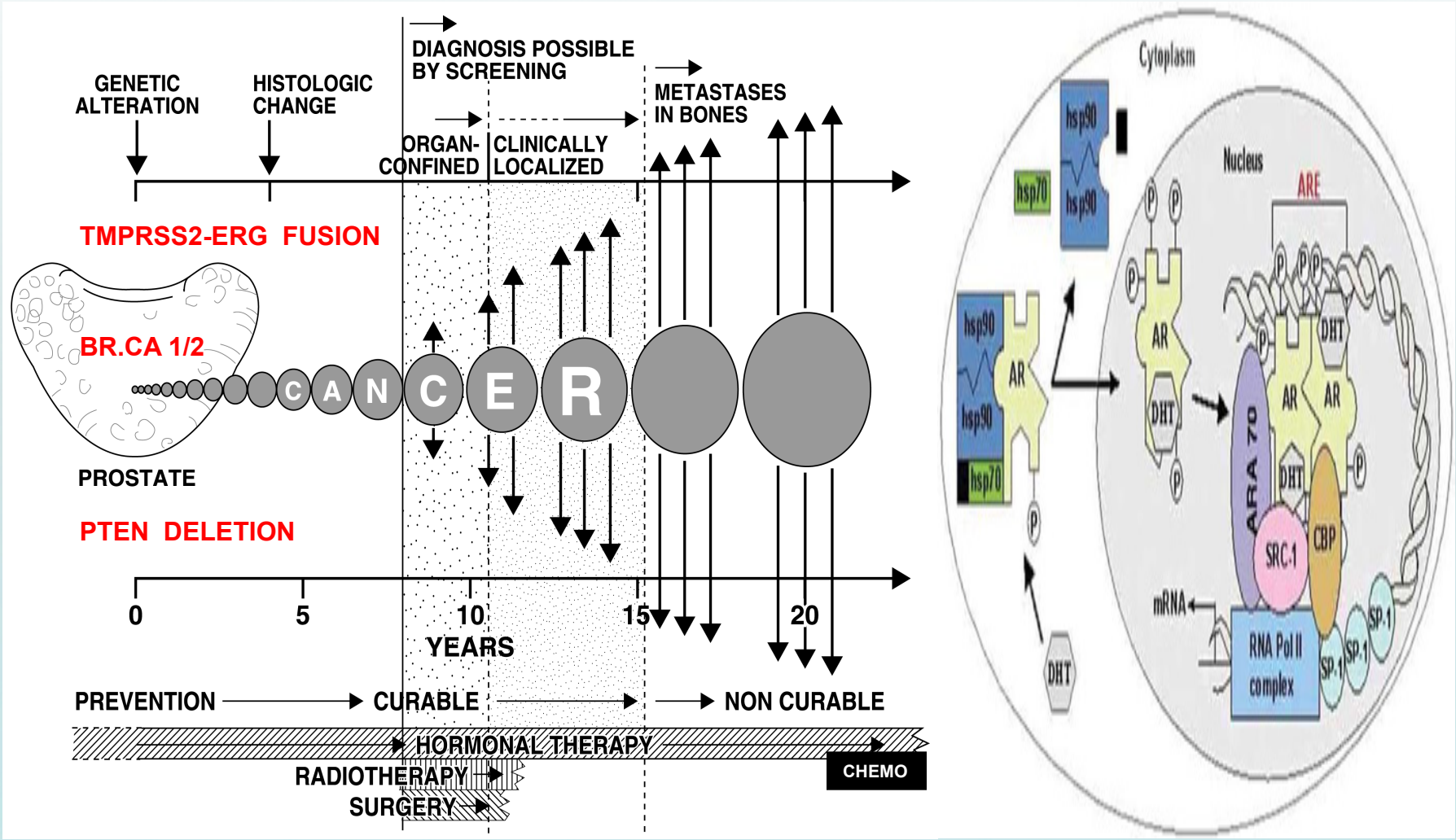


Strand DW & Golgstein AS, Endocrine-Related Cancer (2015) 22: T187-T197

DIFFERENTIATION THERAPY



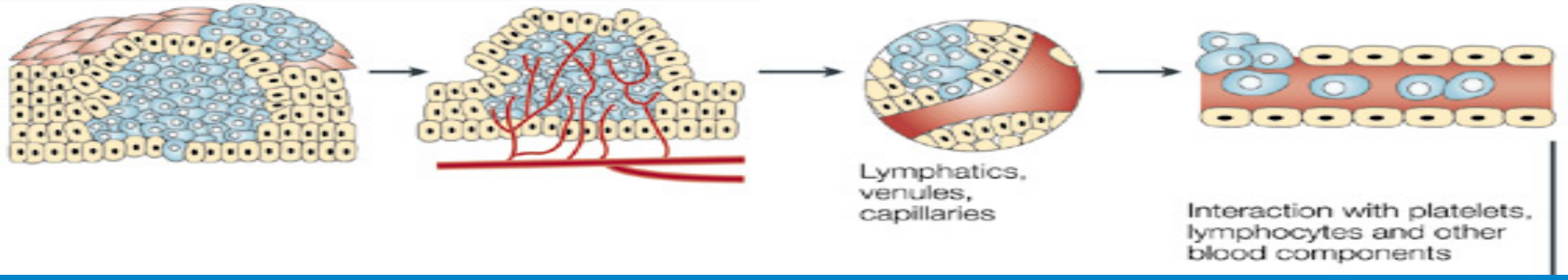
PROSTATE CANCER EVOLUTION



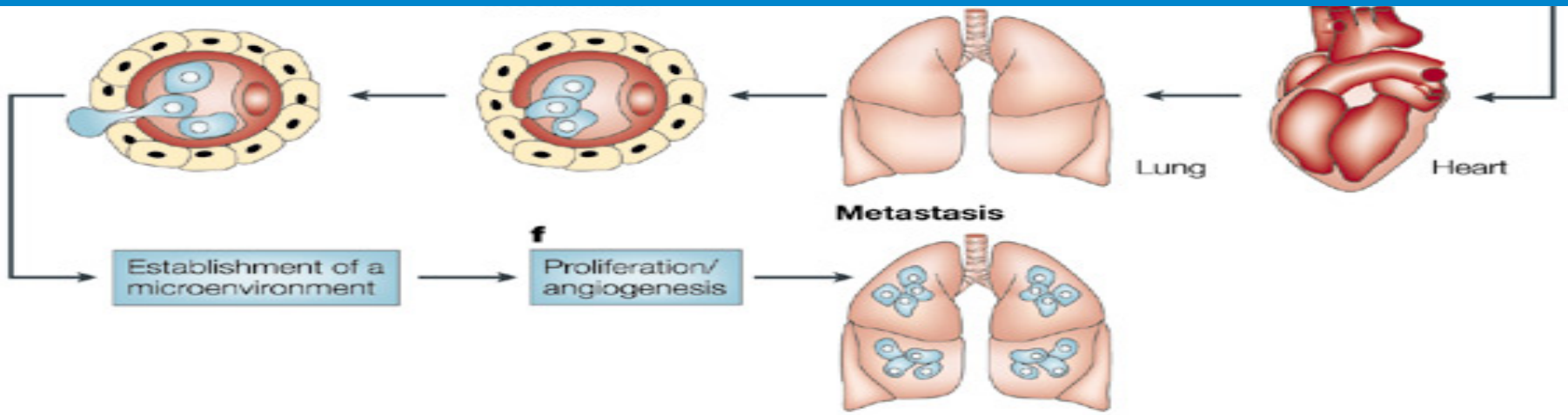
PROSTATE CANCER : Understanding The Pathophysiology and Re-Designing A Therapeutic Approach
(Editors: F. Labrie & M. Koutsilieris)

CANCER BIOLOGY I

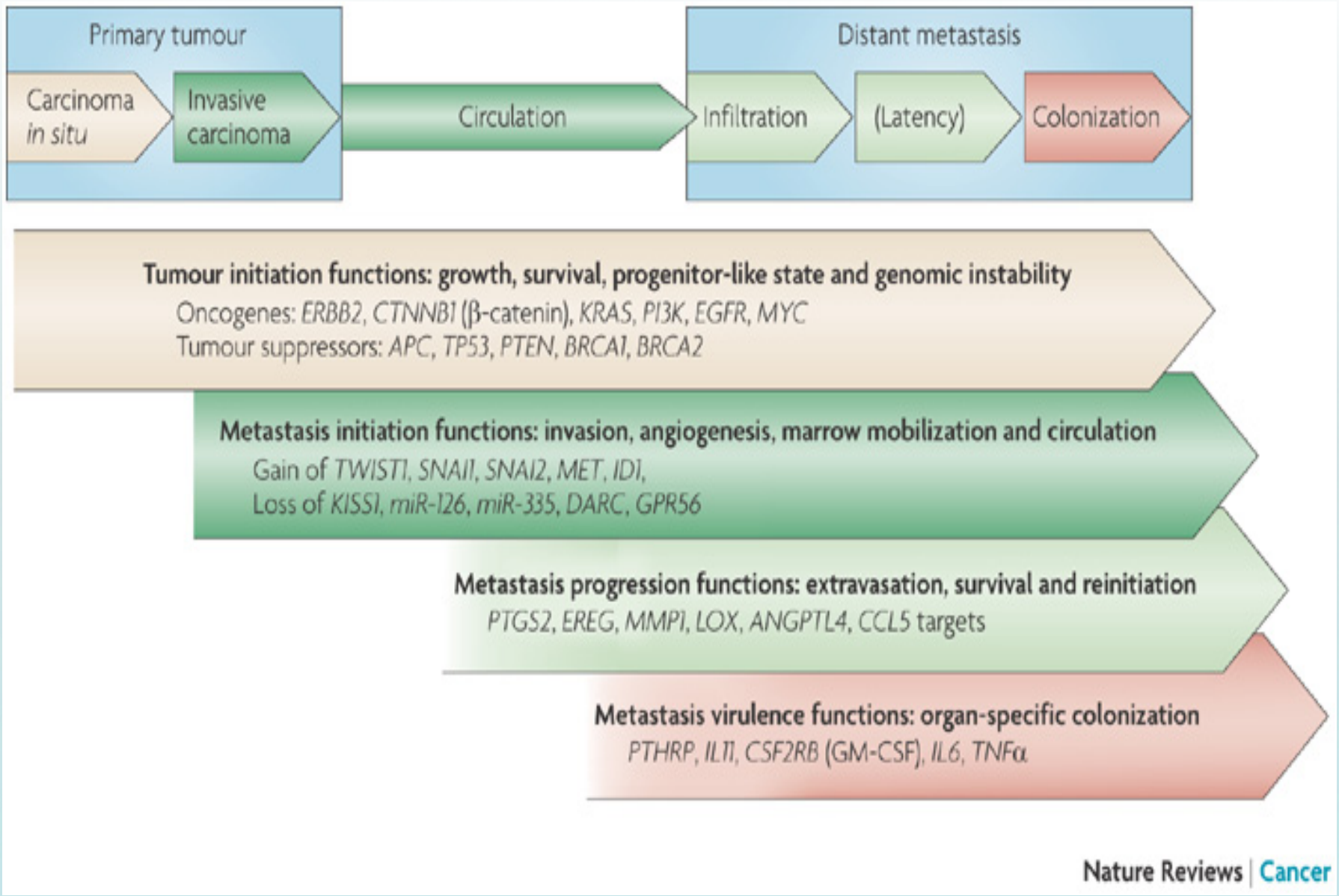
CANCER BIOLOGY II



CANCER BIOLOGY III

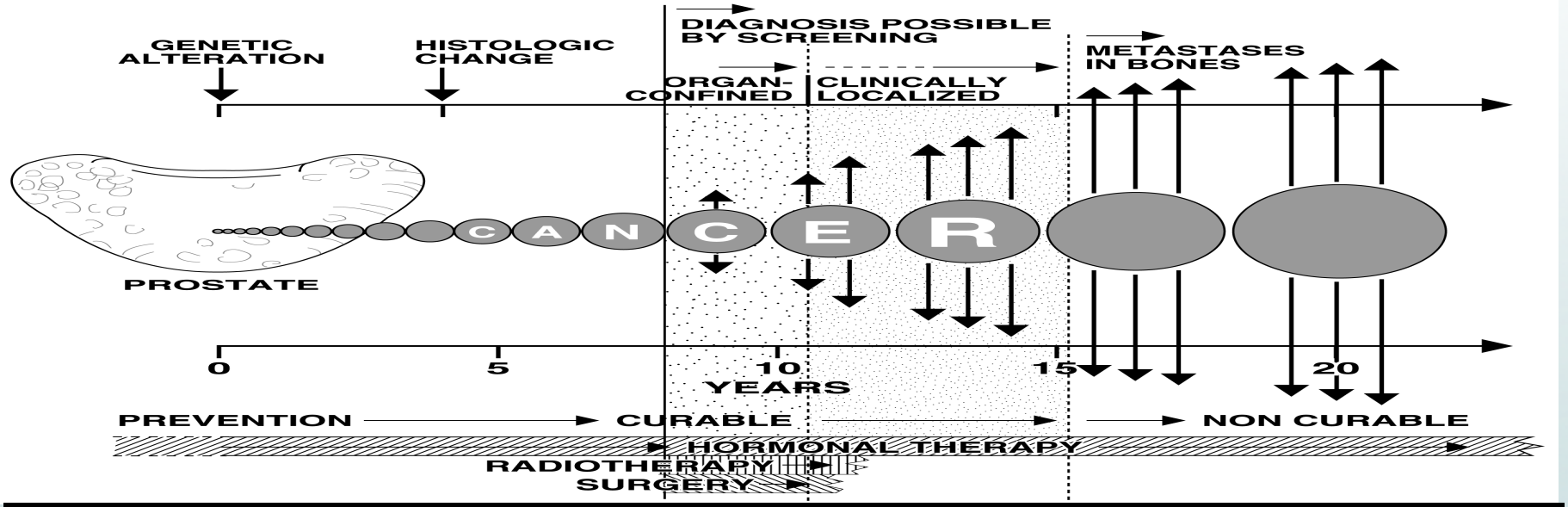


CANCER BIOLOGY IV



Pantel K et al. (2009) Cancer micrometastases
Nat Rev Clin Oncol doi:10.1038/nrclinonc.2009.44

Clinical Evolution of Prostate Cancer to Castration Resistance



Castration Responding | **Castration Resistant**

PIN | **CANCER** | **Lymph nodes (+)**

PRE - OPERATIVE PREDICTORS: PSA (>20) , Gleason score (>7), CTCs (+) Bone Scan (+)

Local disease | **Systemic Disease**

PROSTATE CANCER : Understanding The Pathophysiology and Re-Designing A Therapeutic Approach
(Editors: F. Labrie & M. Koutsilieris, 2004)

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