Androgen Receptor and Androgen-Independent Prostate Cancer

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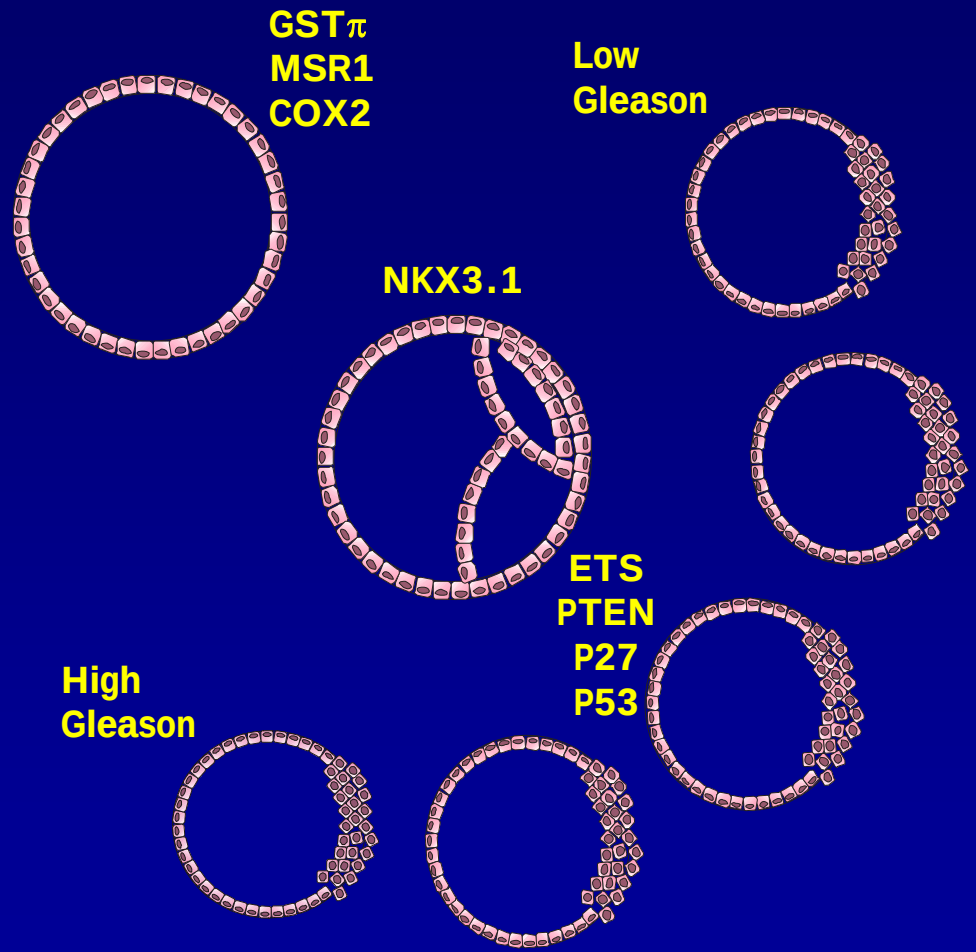
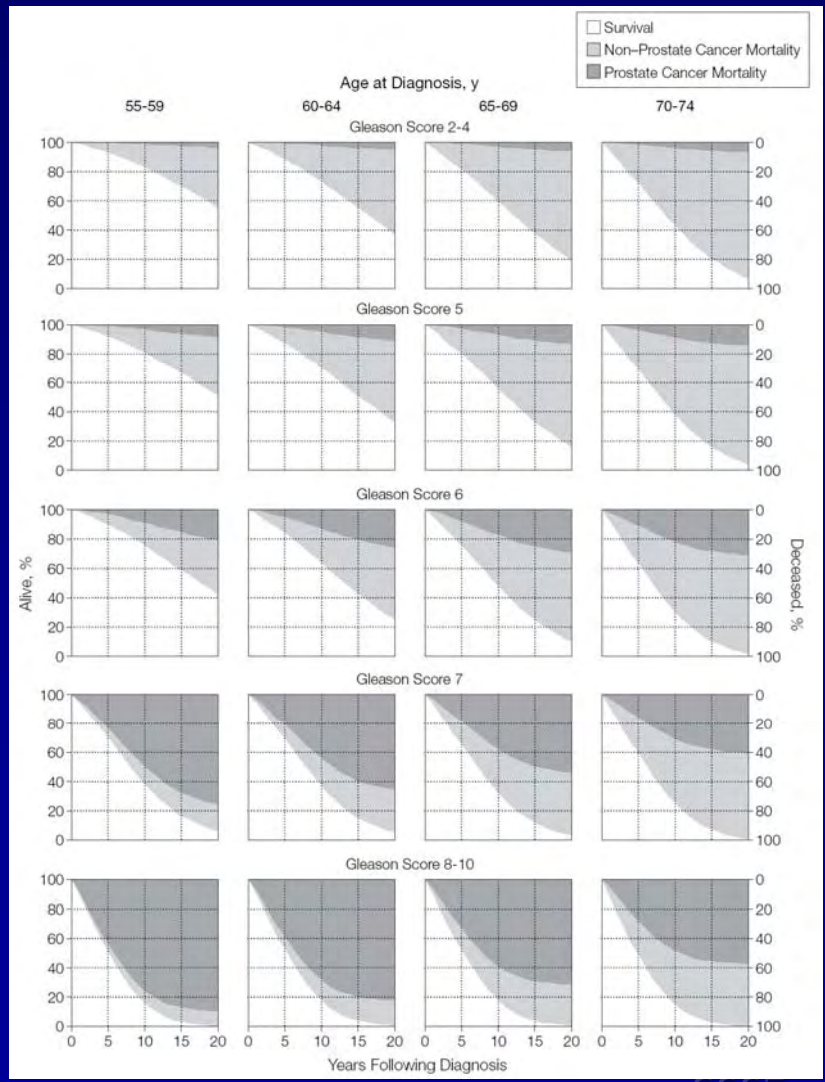
Columbia University

Outline

- AR Structure and Function
- AR Amplification
- AR Mutation
- AR Modification
- Ligand Availability
- AR Interaction

Prostate Cancer Heterogeneity

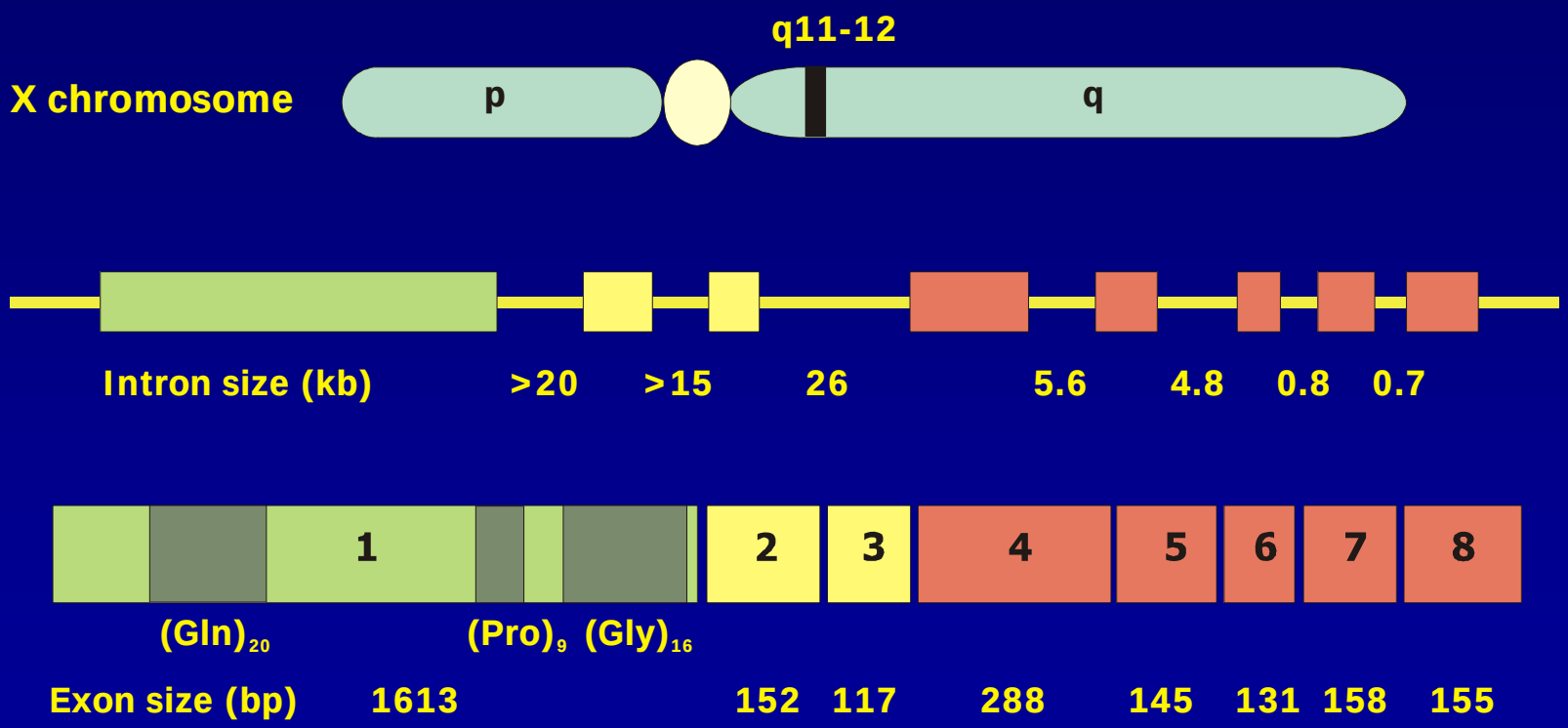




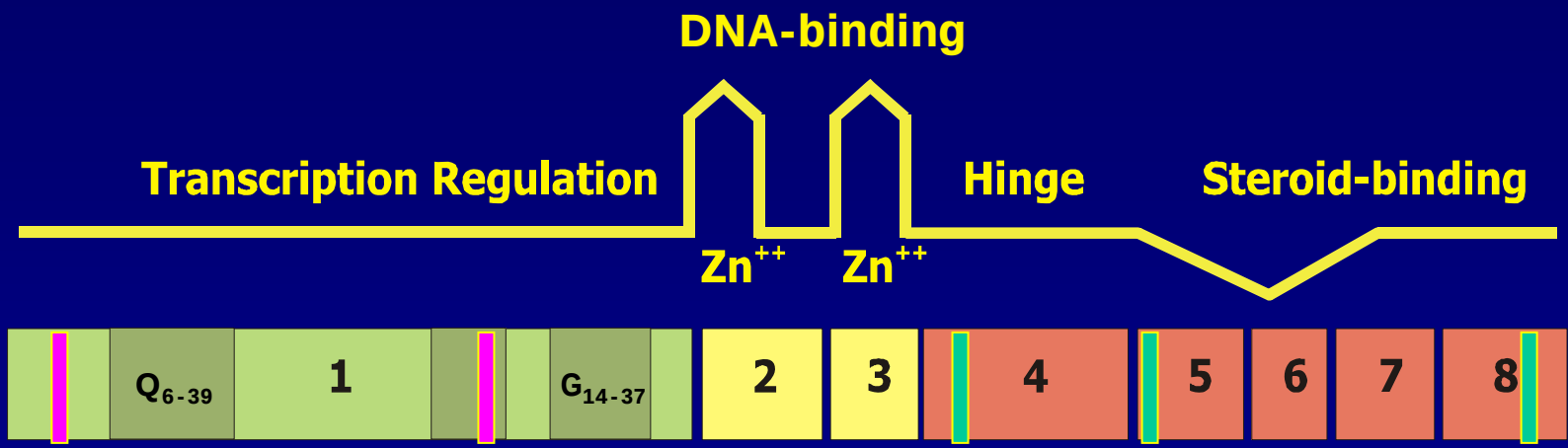
Albertsen et al,
JAMA 293:2095, 2005

2007

AR Structure



AR Structure



^{23}FQLNF ^{27}

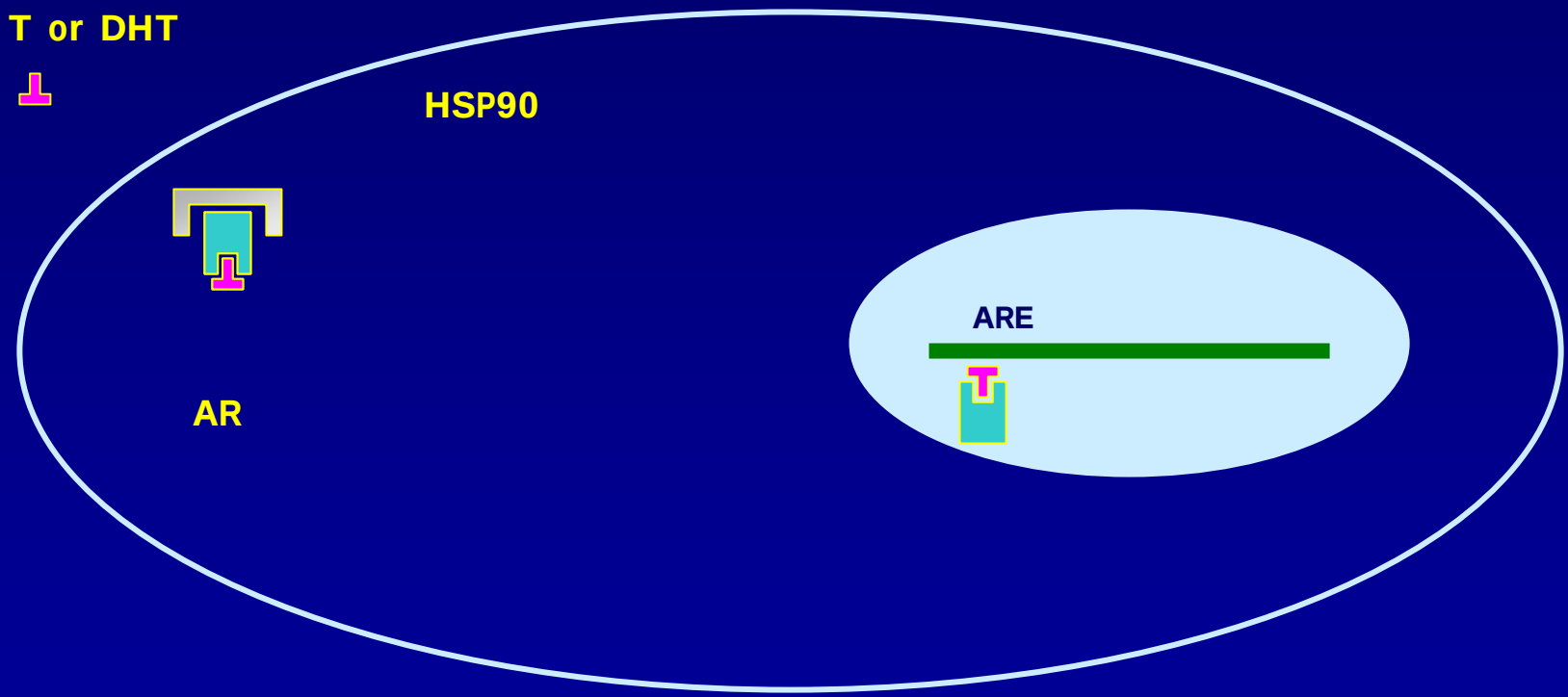
^{432}WHTLF ^{436}

716-720

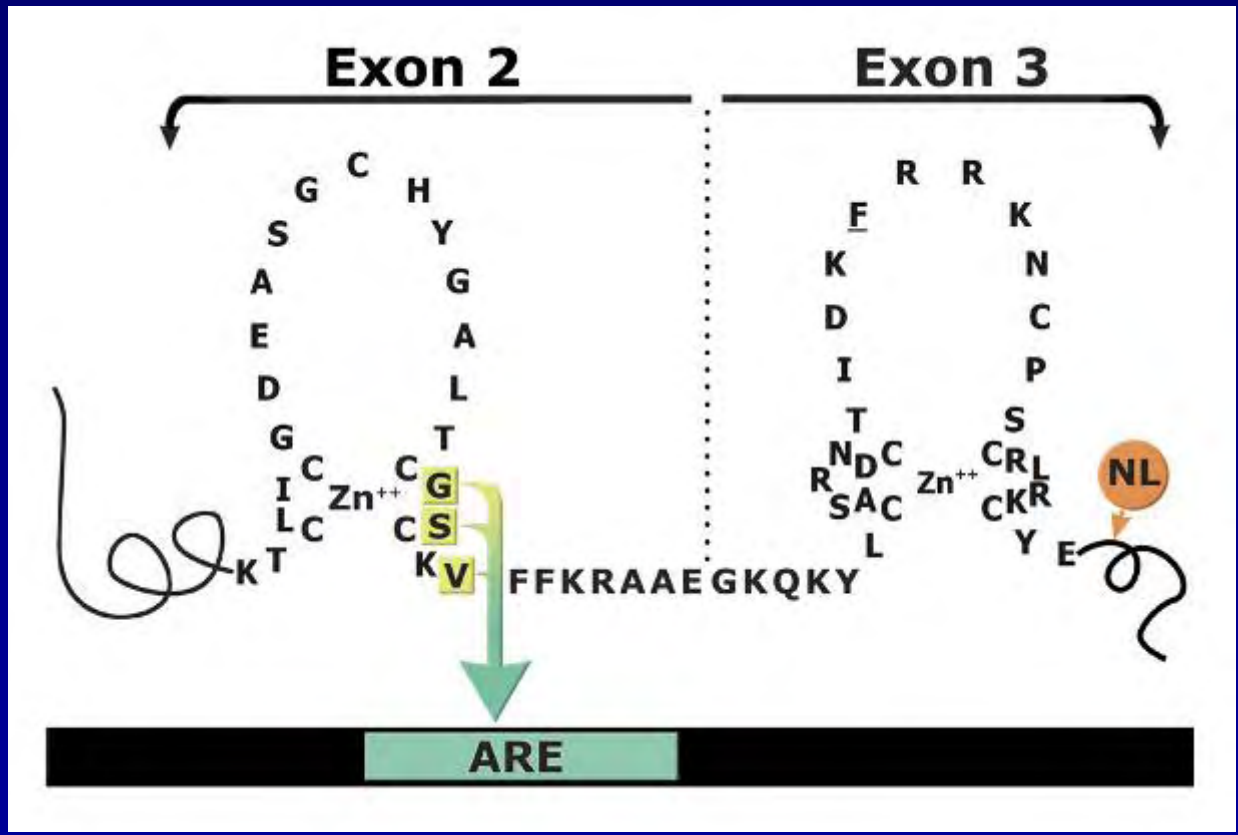
737-741

889-898 AF-2

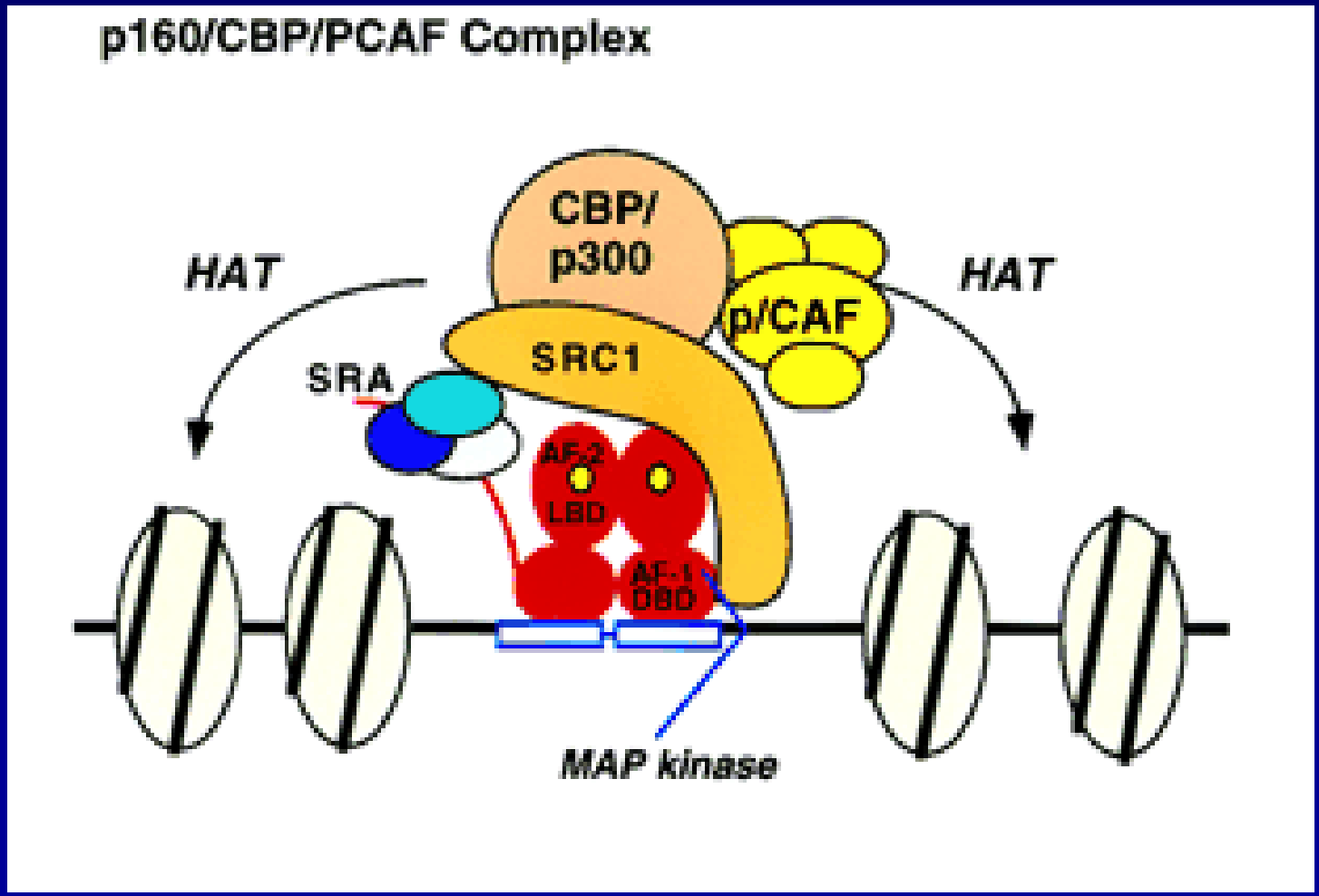
AR Activation by Androgen



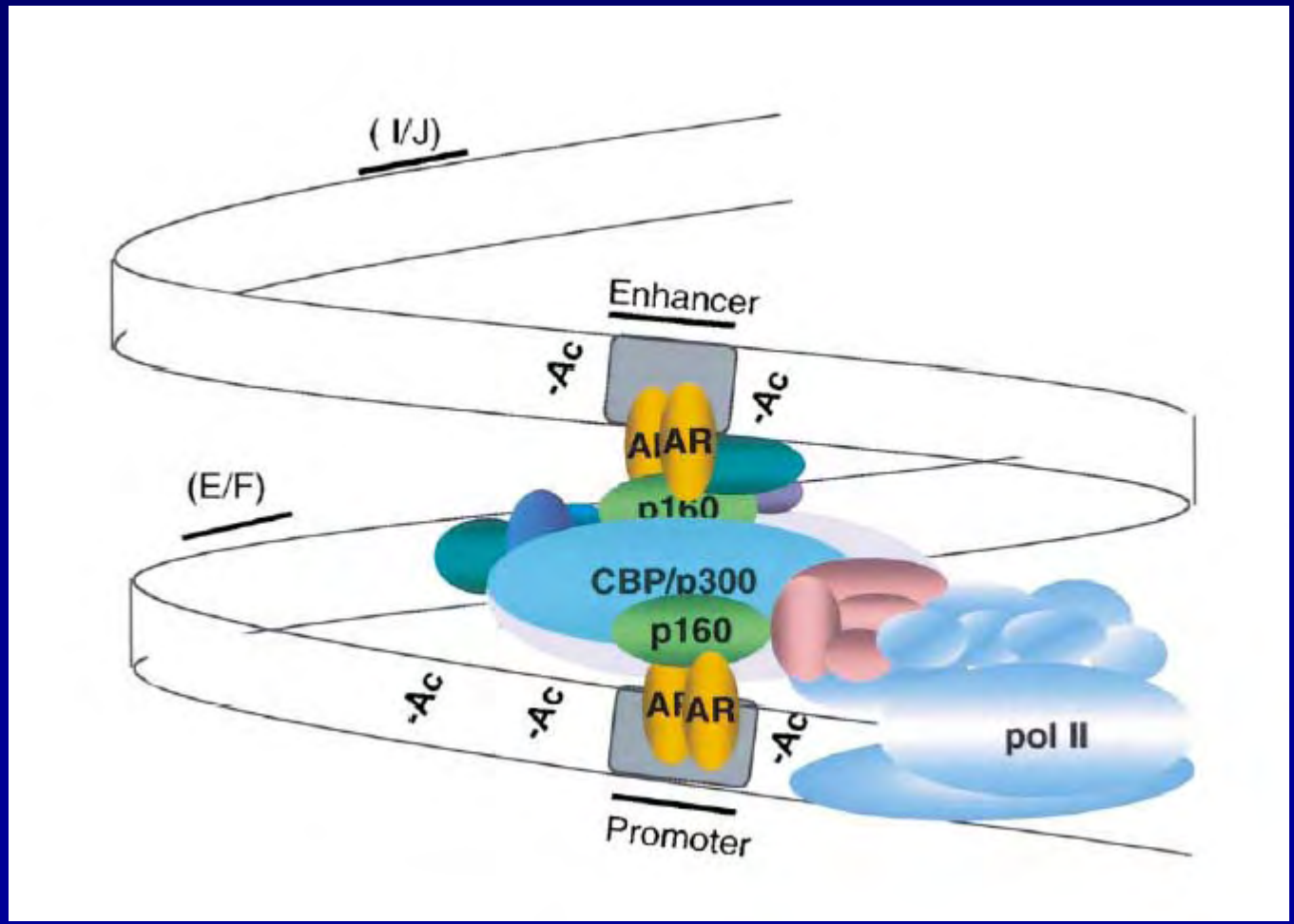
AR DNA Binding Domain



Activation of Transcription

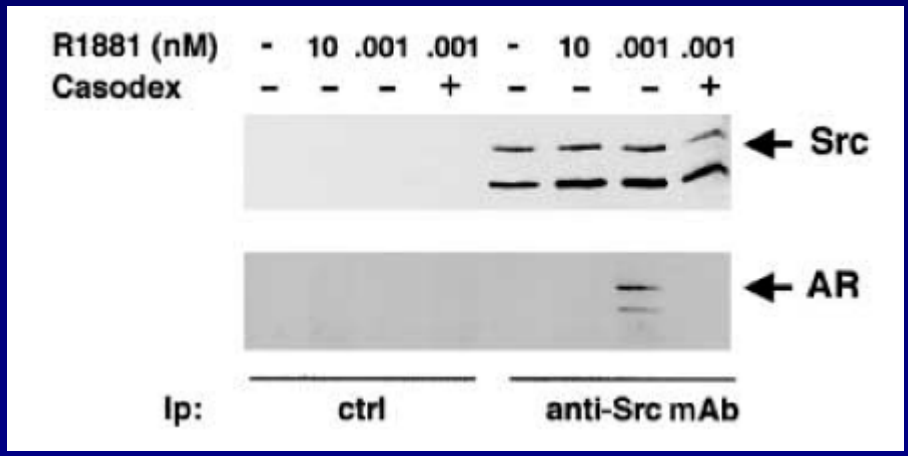


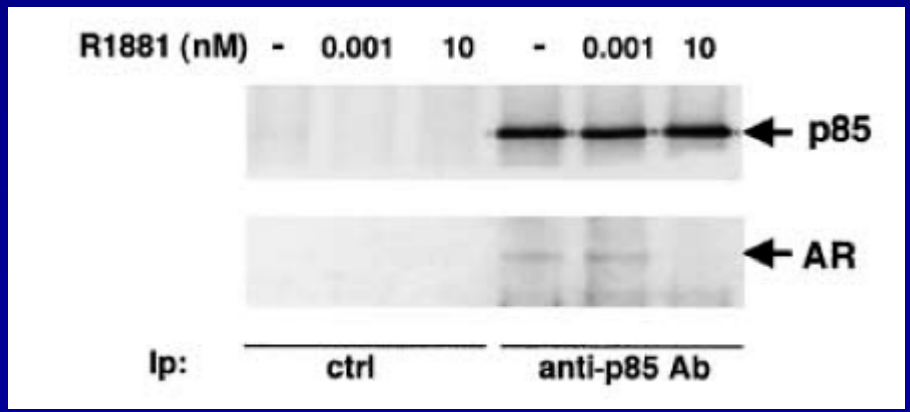
Activation of Transcription



Shang Mol Cell 9:601, 2002

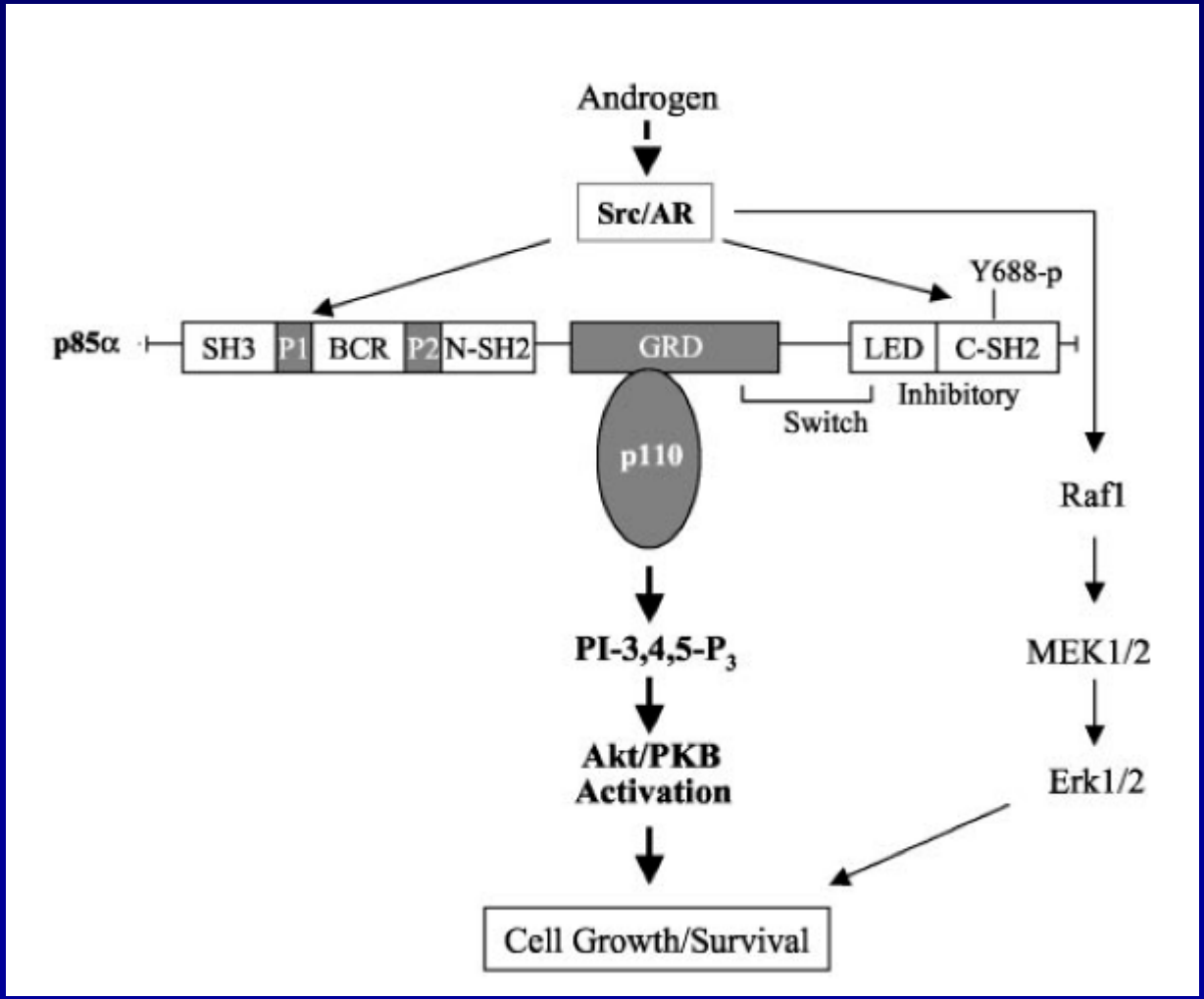
AR Binds to SRC and PI3K





Castoria JCB 161:547, 2003

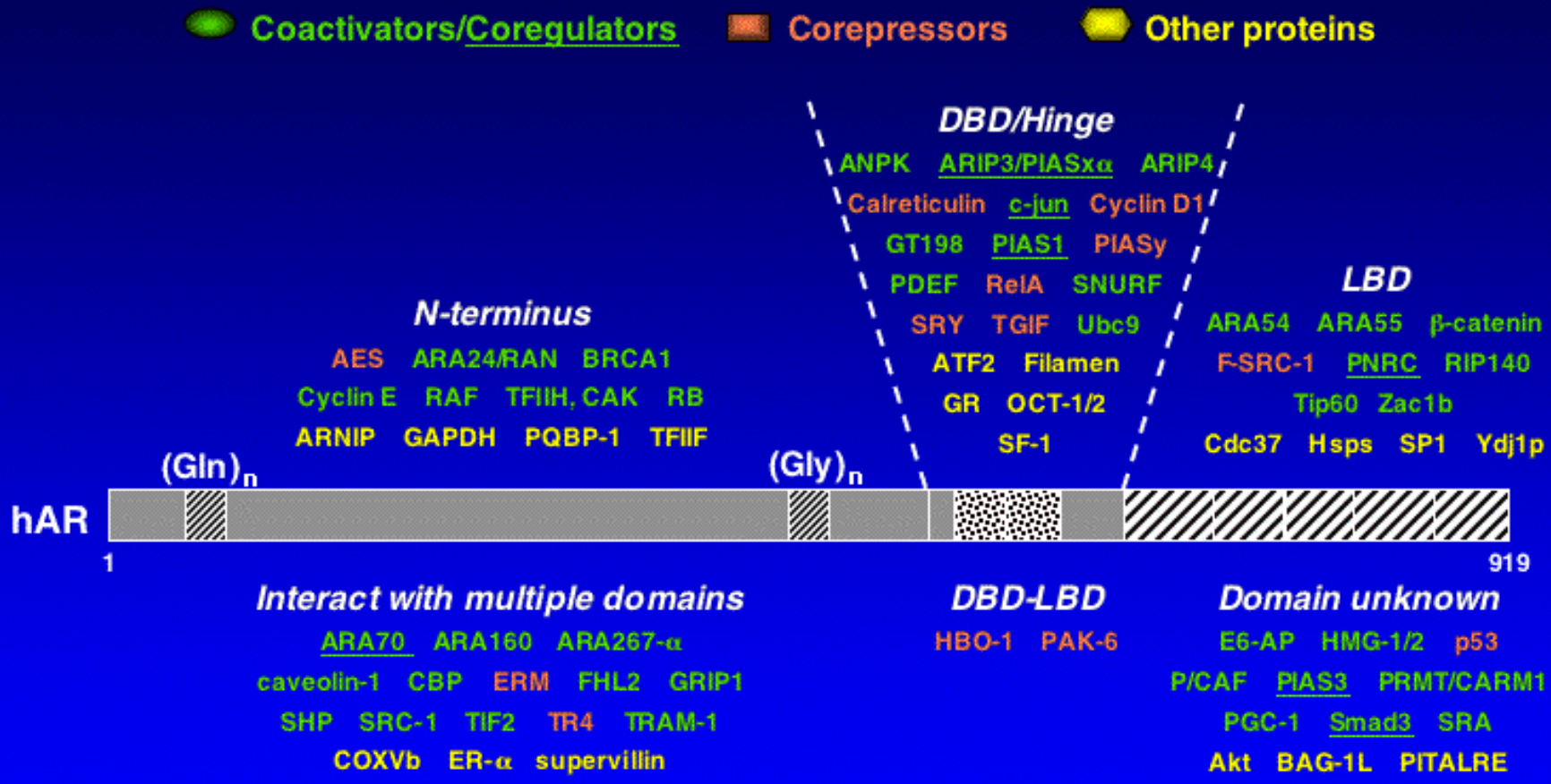
Cytoplasmic Effects of Androgen



Sun JBC 278:42992, 2003

Androgens Make a Big Difference

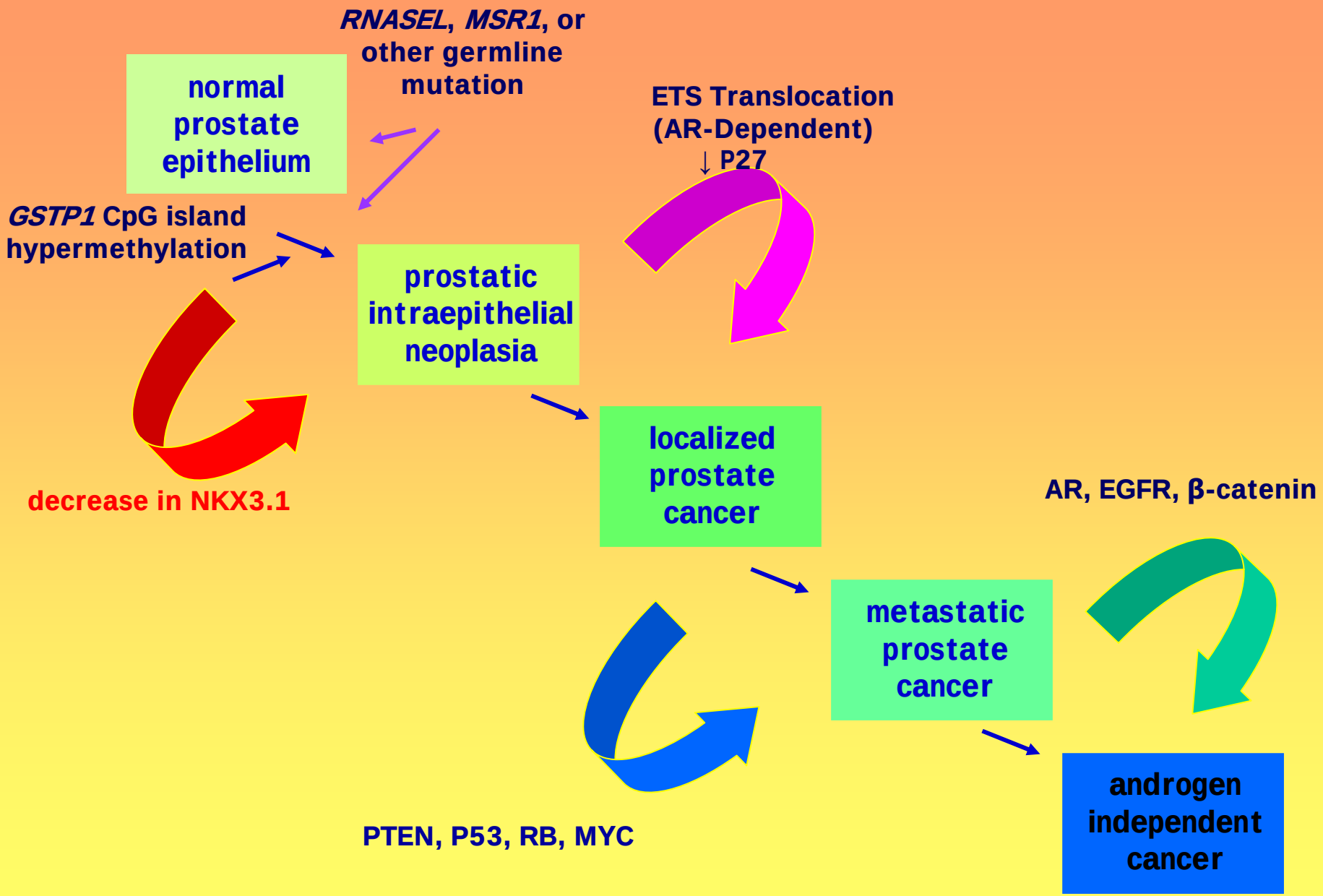
Androgen Receptor-Interacting Proteins



Note: Proteins are grouped by the AR domain with which they interact and may interact with more than one AR domain. The location of a particular protein therefore does not indicate its precise region of interaction with AR. See list for more detailed informaton.

LKB
2003/3/1

http://androgendb.mcgill.ca/


RNASEL, *MSR1*, or other germline mutation
normal prostate epithelium
ETS Translocation (AR-Dependent) ↓ P27
GSTP1 CpG island hypermethylation
prostatic intraepithelial neoplasia
decrease in NKX3.1
localized prostate cancer
AR, EGFR, β-catenin
metastatic prostate cancer
PTEN, P53, RB, MYC
androgen independent cancer

Outline

AR Structure and Function

AR Amplification

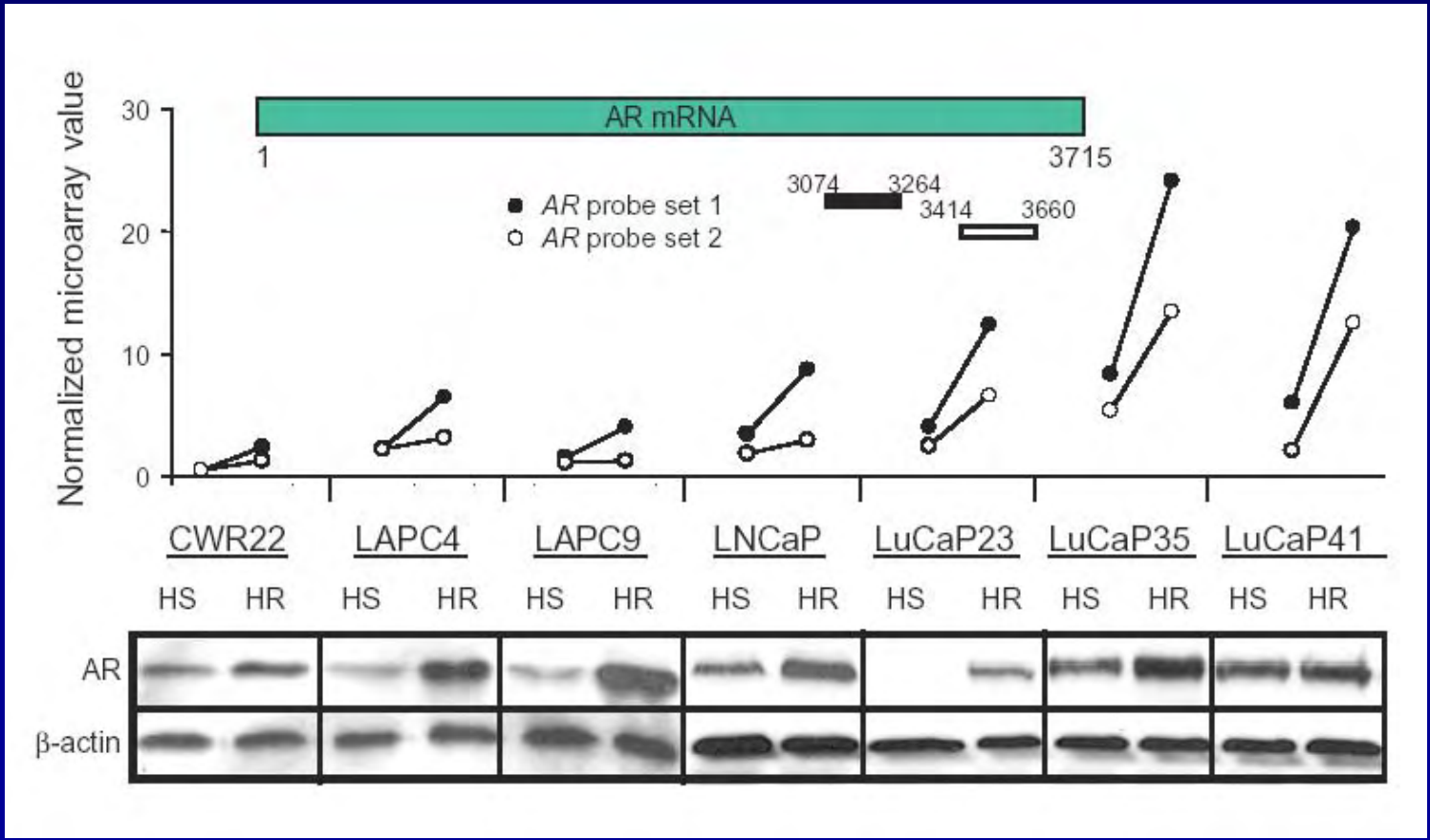
AR Mutation

AR Modification

Ligand Availability

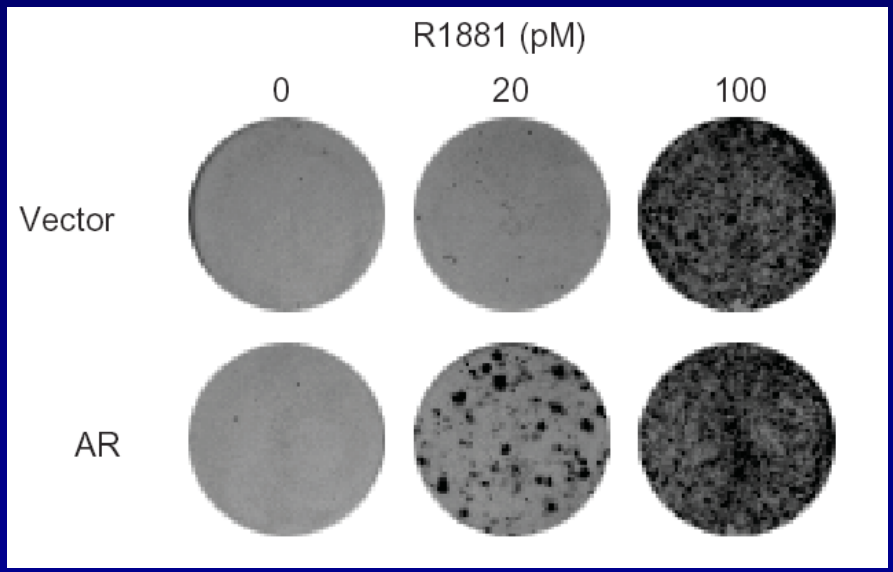
AR Interaction

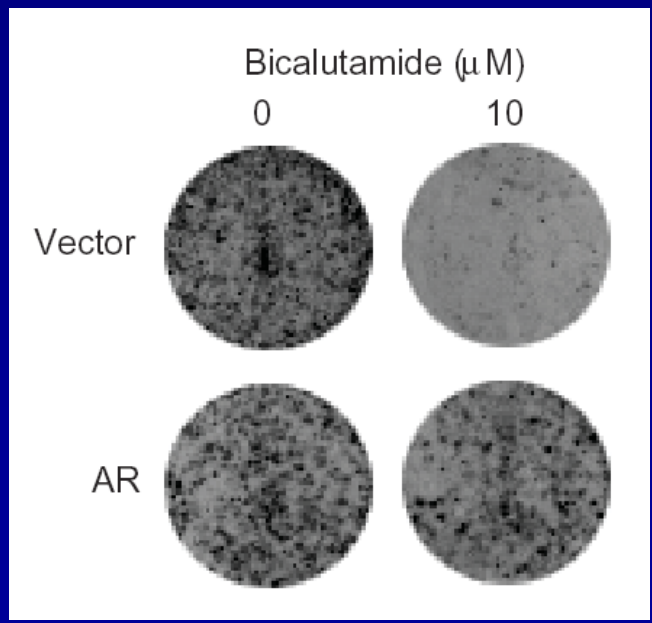
AR Gene Expression and Hormone-Independence



Chen Nat Med 10:33, 2004

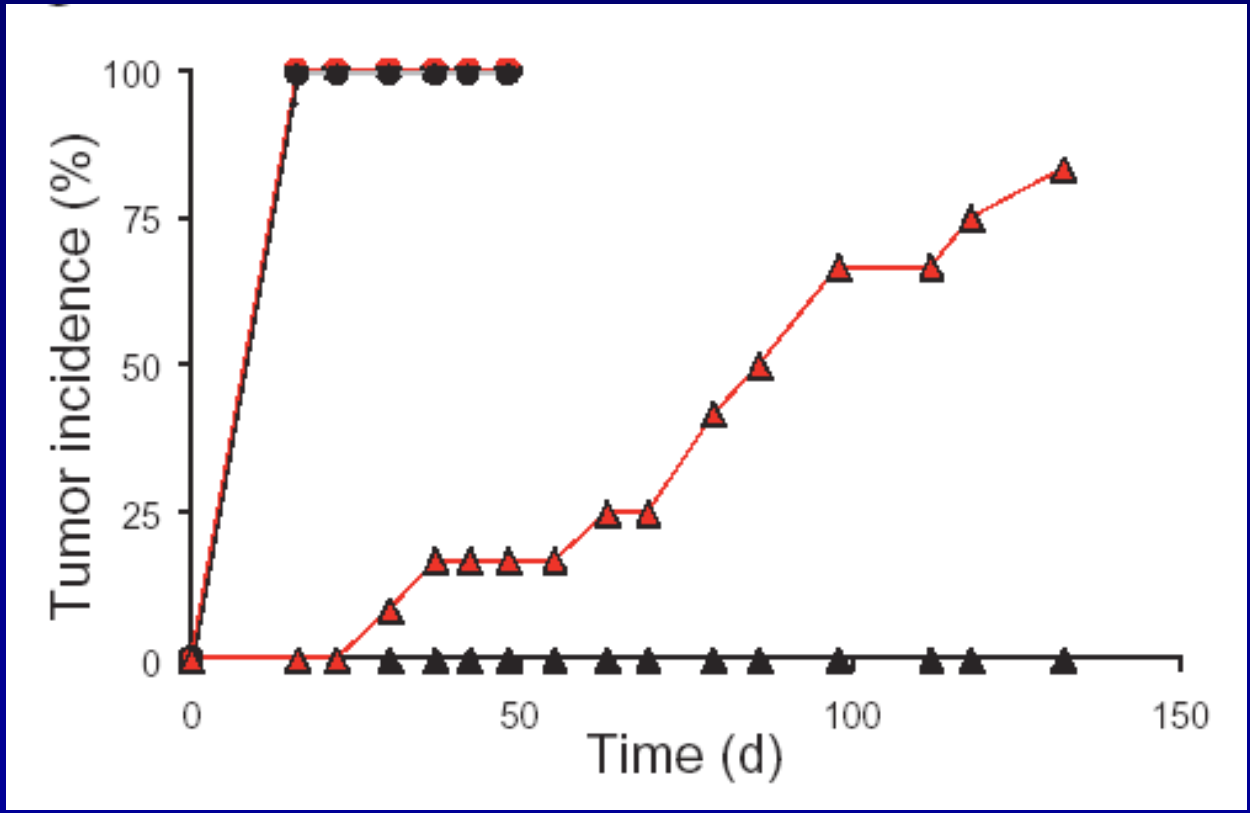
AR Gene Expression and Hormone-Independence





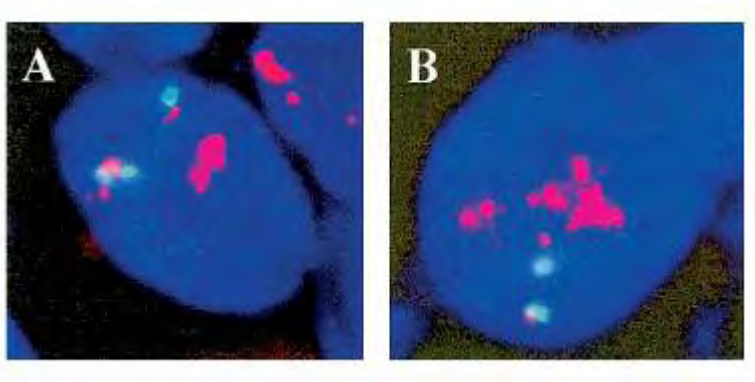
Chen Nat Med 10:33, 2004

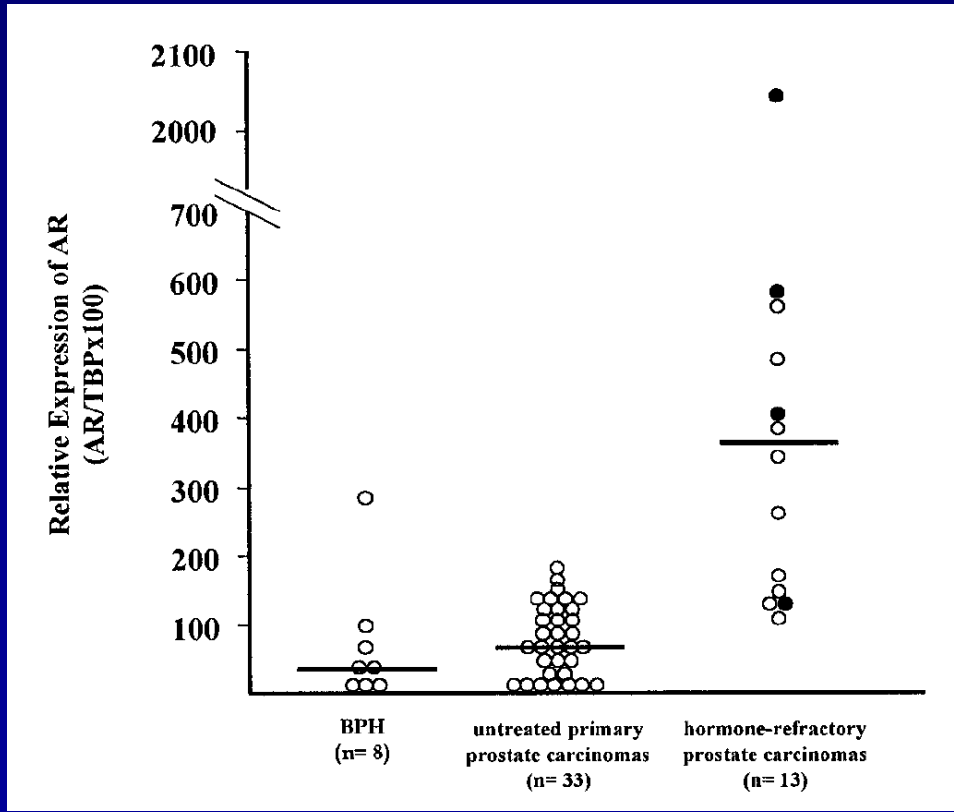
AR Gene Expression and Hormone-Independence



Chen Nat Med 10:33, 2004

AR Gene Amplification





Linja Can Res 61:3550, 2001

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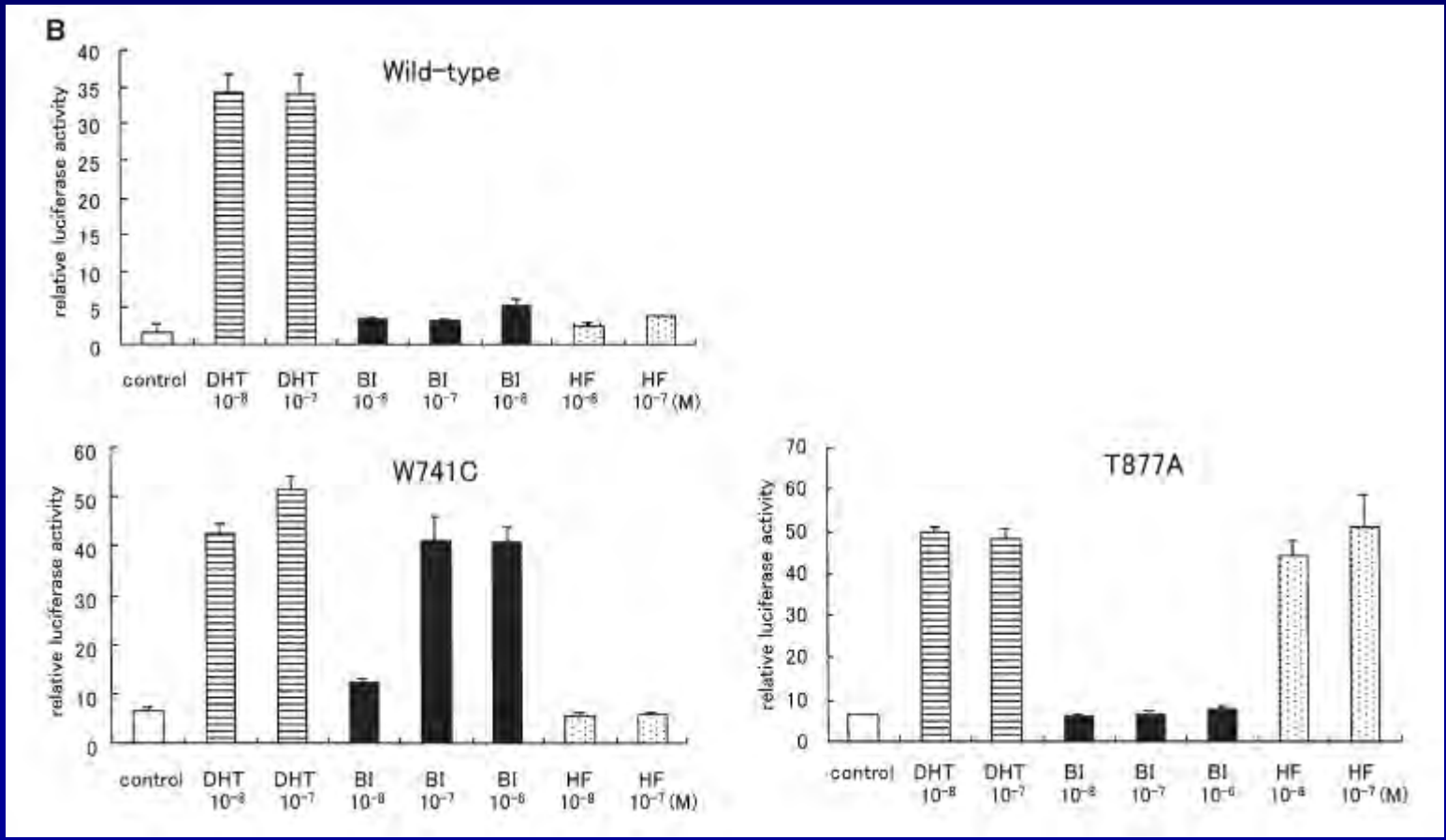
AR Mutations - CaP

Frequency of AR mutations

prior flutamide therapy	no prior flutamide therapy
5/16	1/17

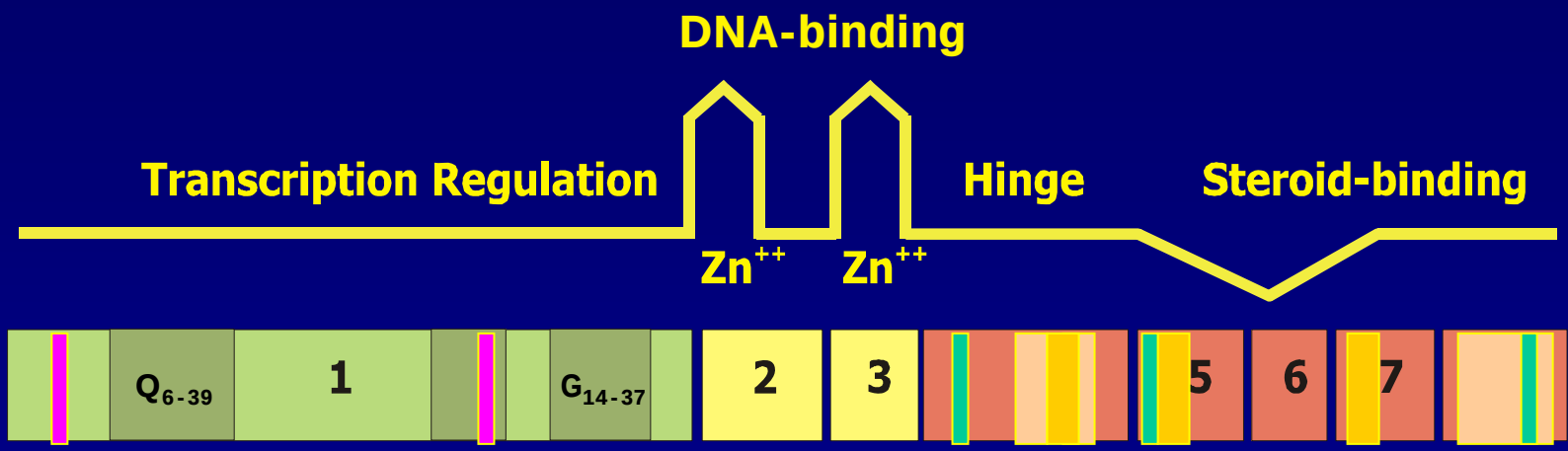
Taplin et al, Cancer Res 59:2511-15, 1999

AR Mutations
Bicalutamide resistance



Yoshida Cancer Res 65:9611, 2005

AR Structure

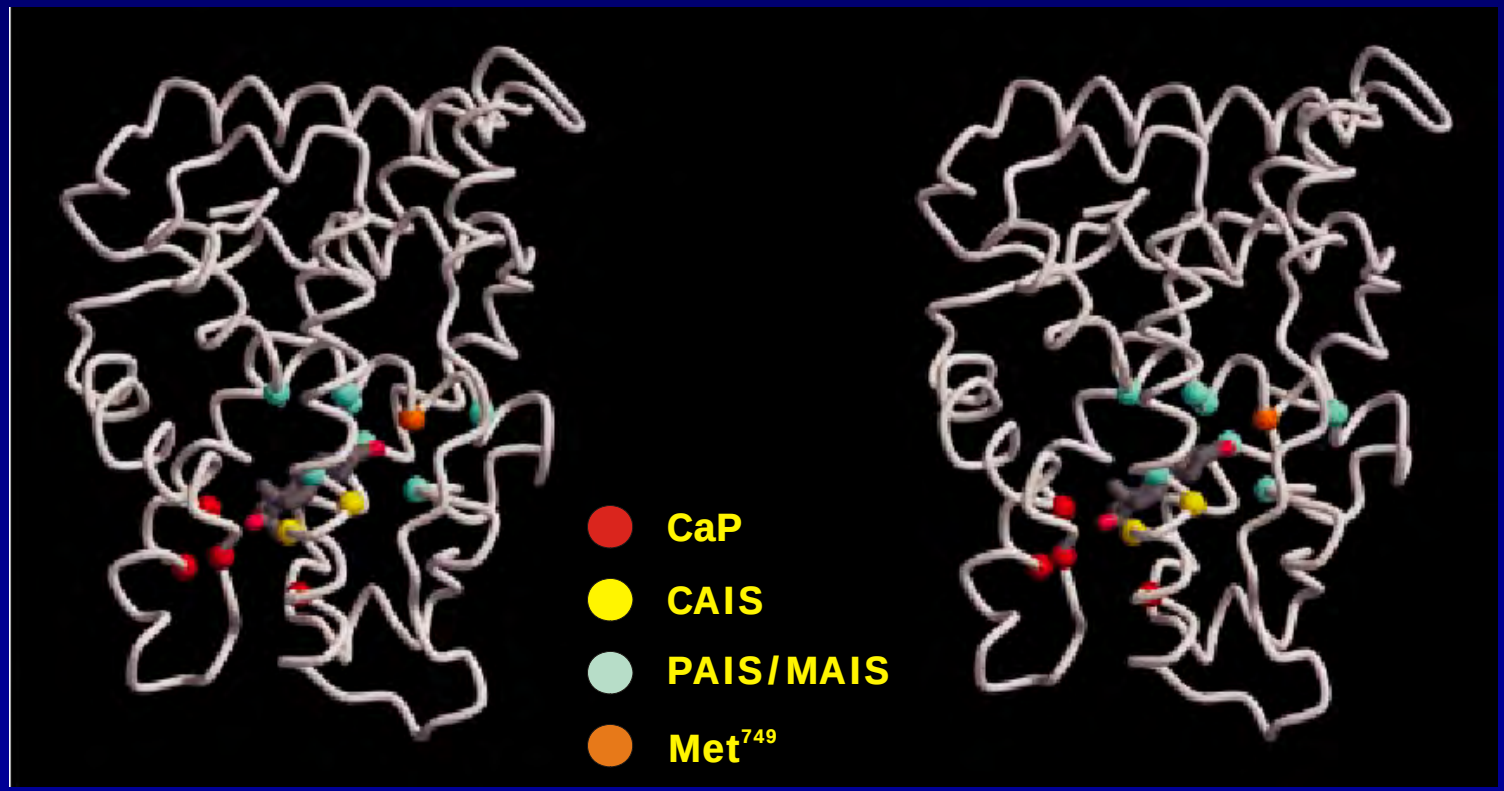


^{23}FQLNF ^{27}

^{432}WHTLF ^{436}

670–678	701–730	874–910	Prostate Cancer
688–710	749–780	831–866	CAIS
716-720	737-741	889-898	AF-2

LBD Mutations in Cap and AIS



Matias, JBC 275:26164, 2000

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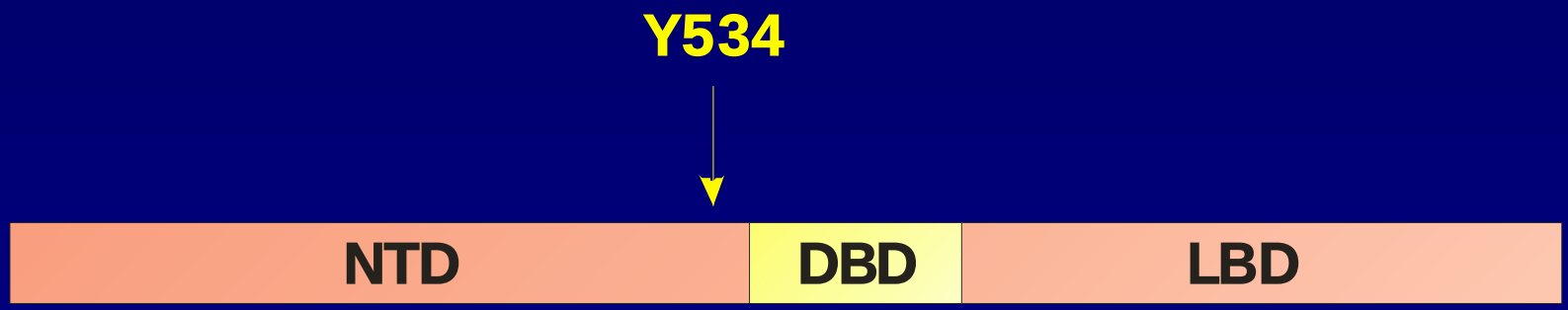
AR Interaction

AR Phosphorylation



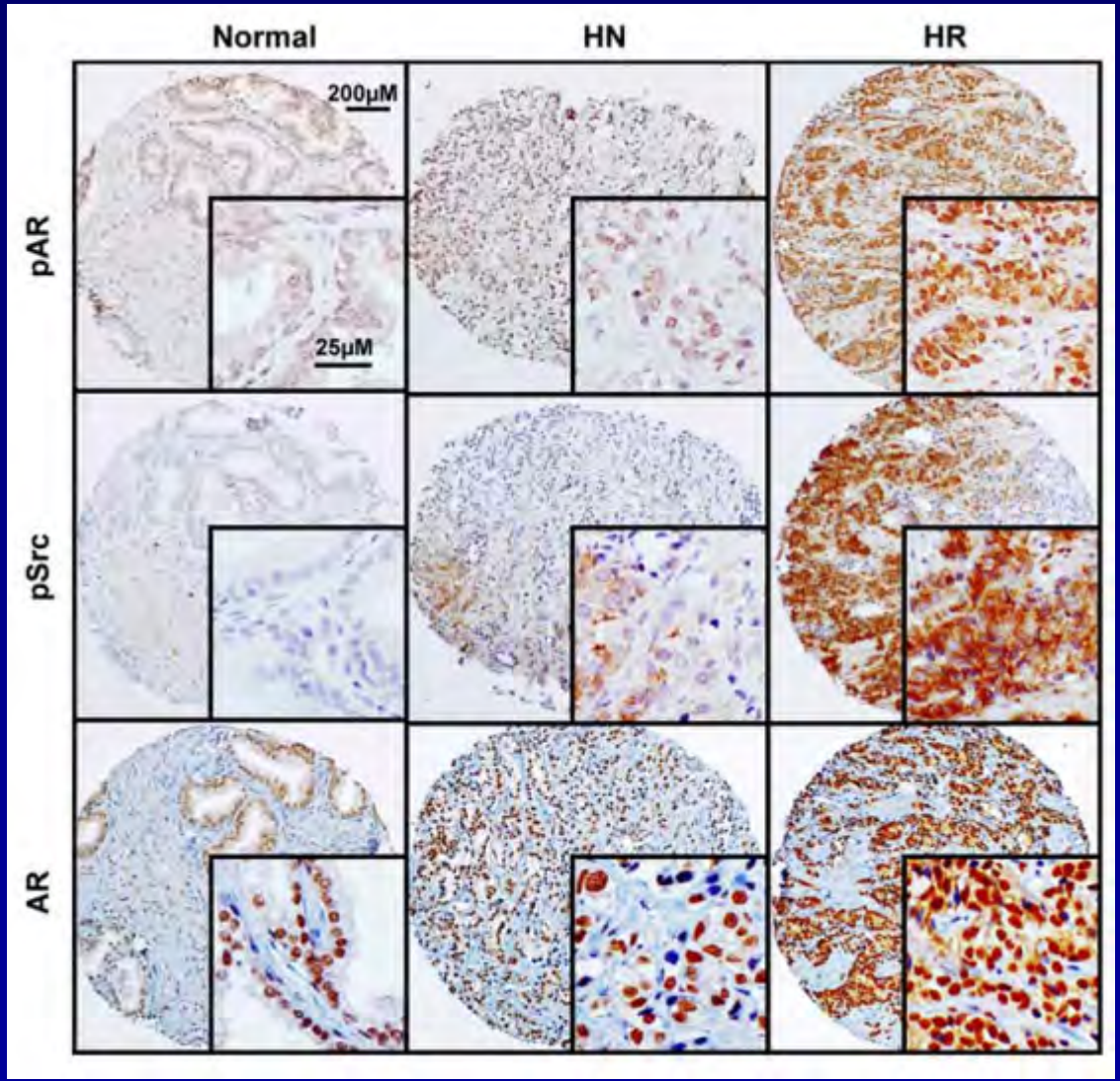
SRC tyr kinase site in AR

AR(p-Tyr^{534}) increased in AIPC

Y534 Phosphorylation activates AR

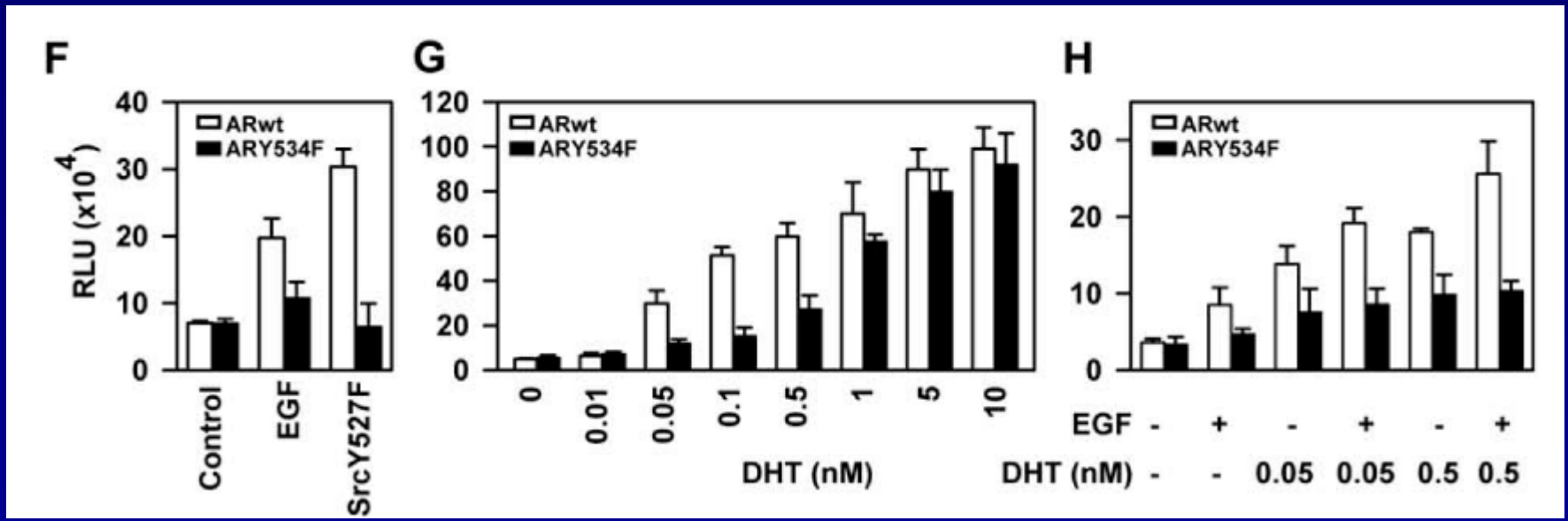
Guo Can Cell 10:309, 2006

AR Phosphorylation



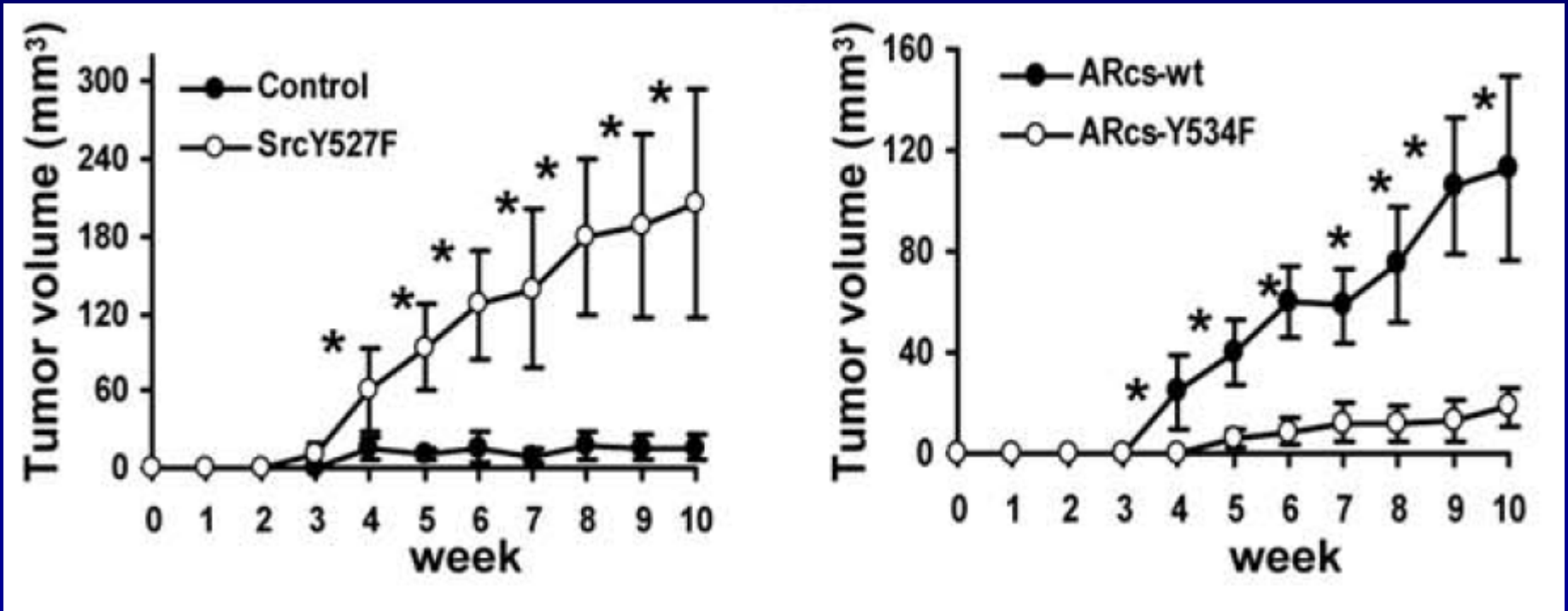
Guo Can Cell 10:309, 2006

AR Phosphorylation



Guo Can Cell 10:309, 2006

AR Phosphorylation



Guo Can Cell 10:309, 2006

AR Phosphorylation

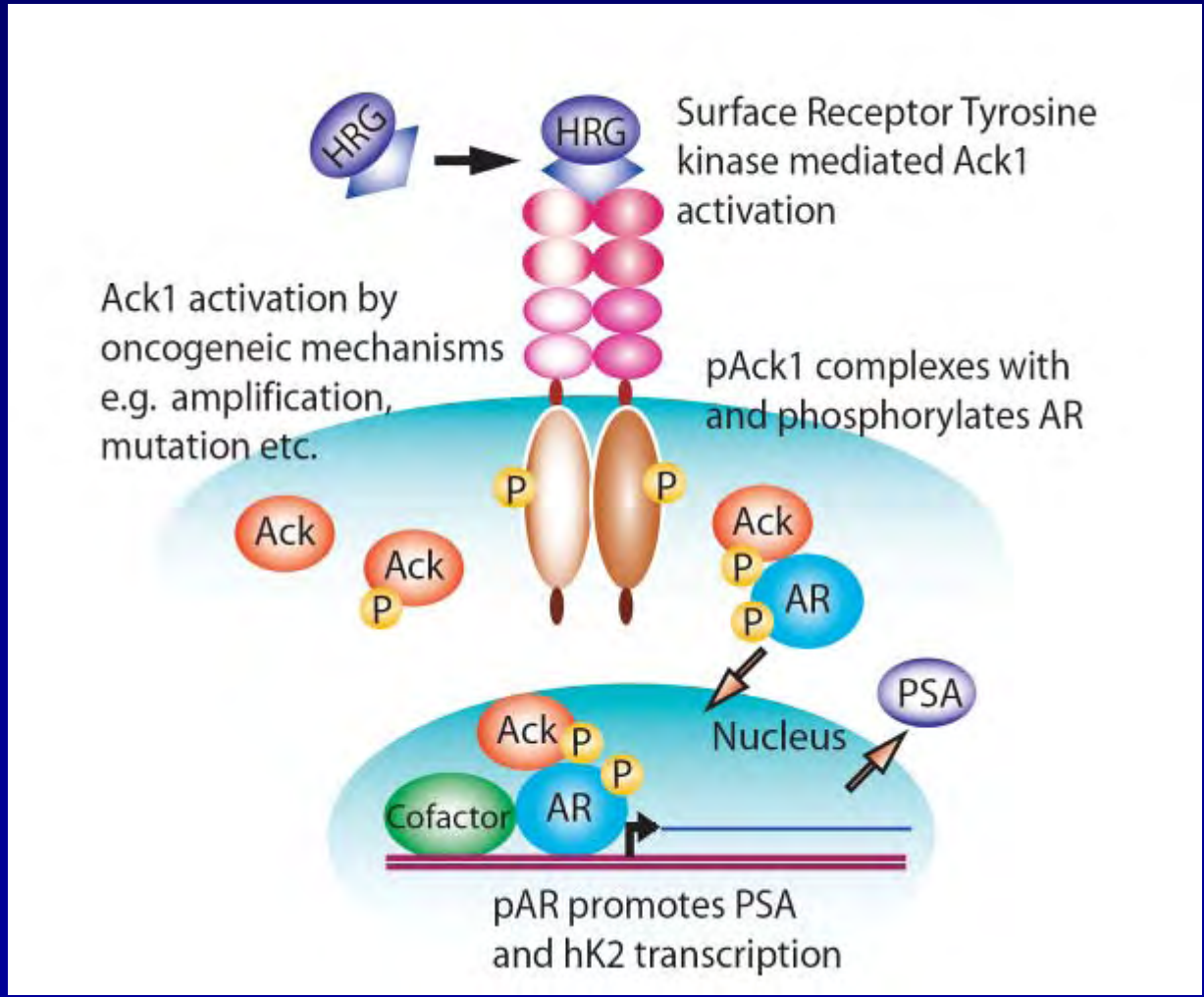
ACK1 tyr kinase site in AR

AR(p-Tyr) increased in AIPC

Y267 and Y363 Phosphorylation activate AR

Mahajan PNAS 104:8438, 2007

AR Phosphorylation



Mahajan PNAS 104:8438, 2007

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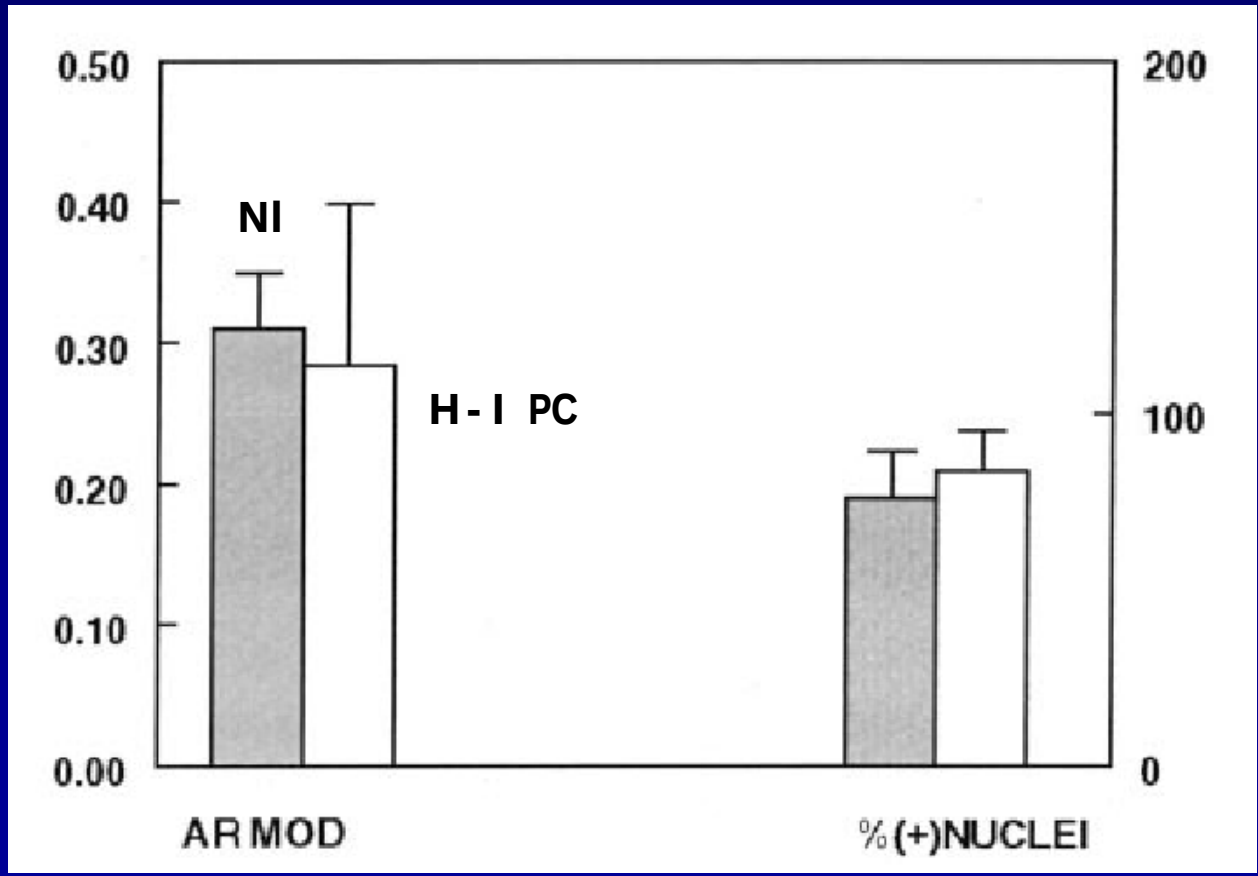
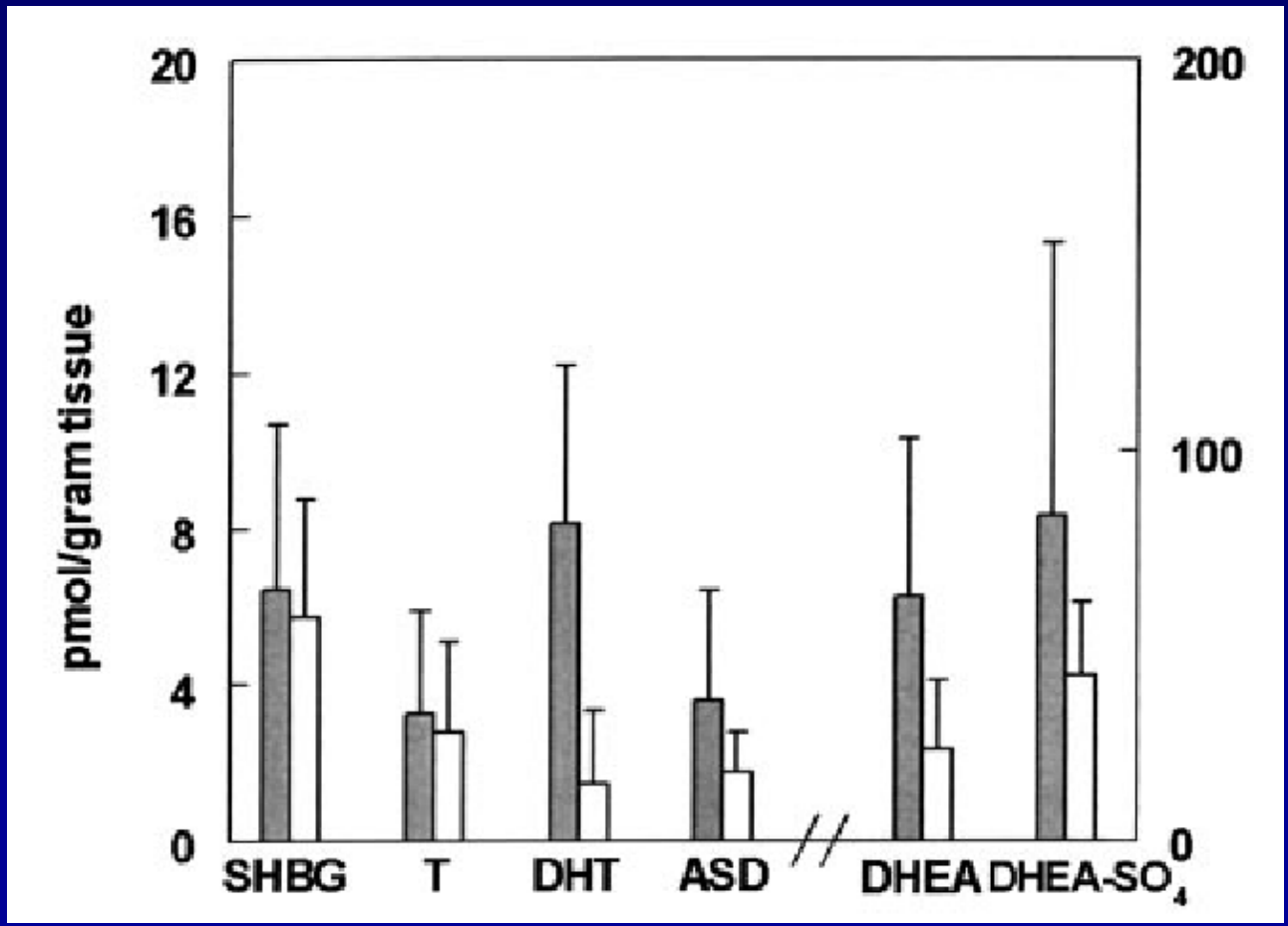
AR Expression – Channel TURPs



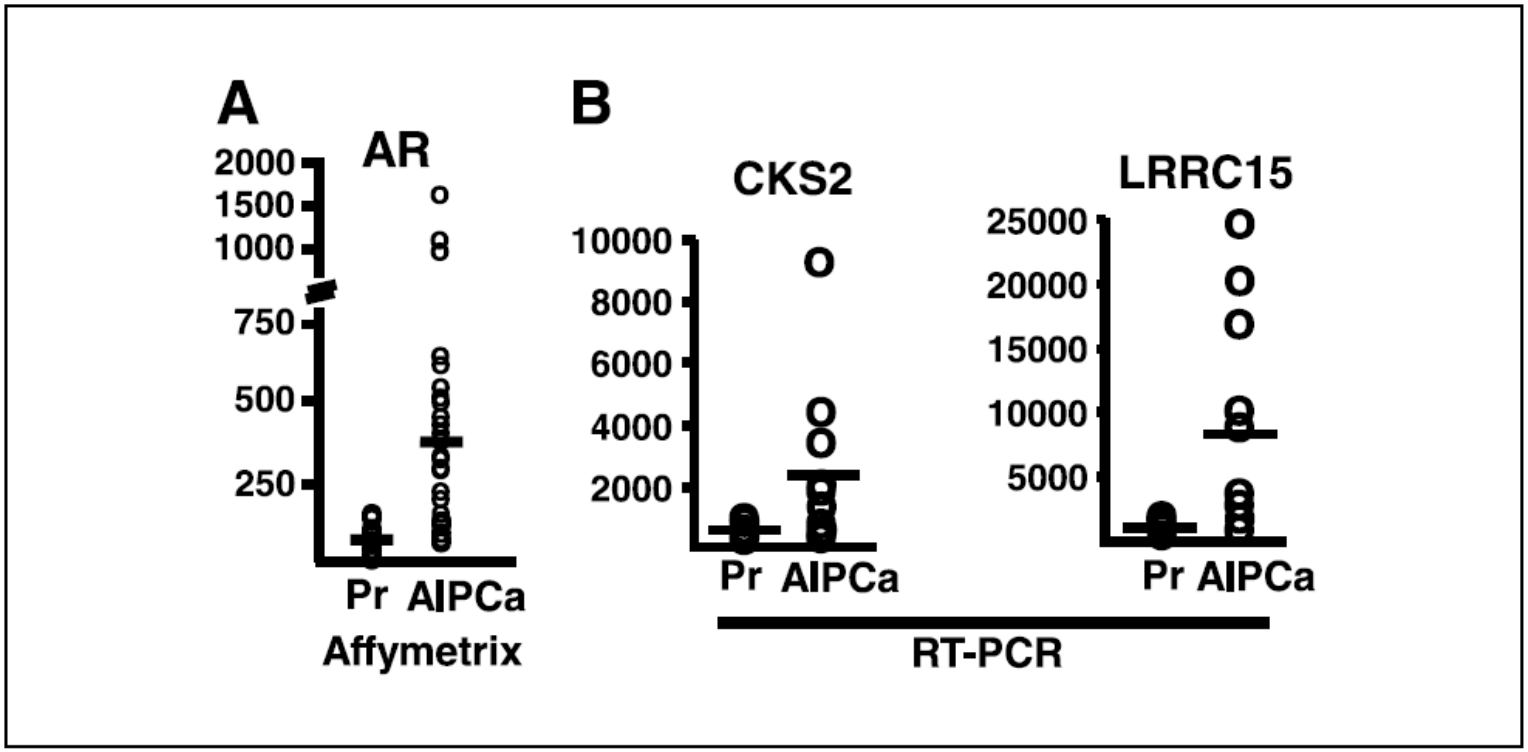
Mohler CCR 10:440, 2004

Tissue Hormone Levels – Channel TURPs



Mohler CCR 10:440, 2004

Increased Level of Enzymes to Make Testosterone



Stanbrough Can Res 66:2815, 2006

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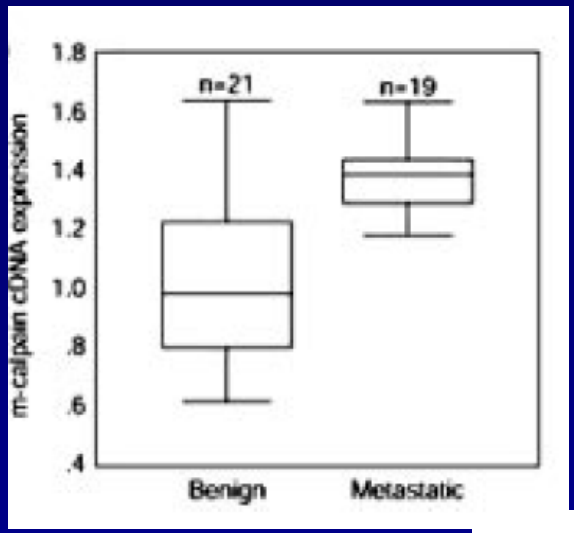
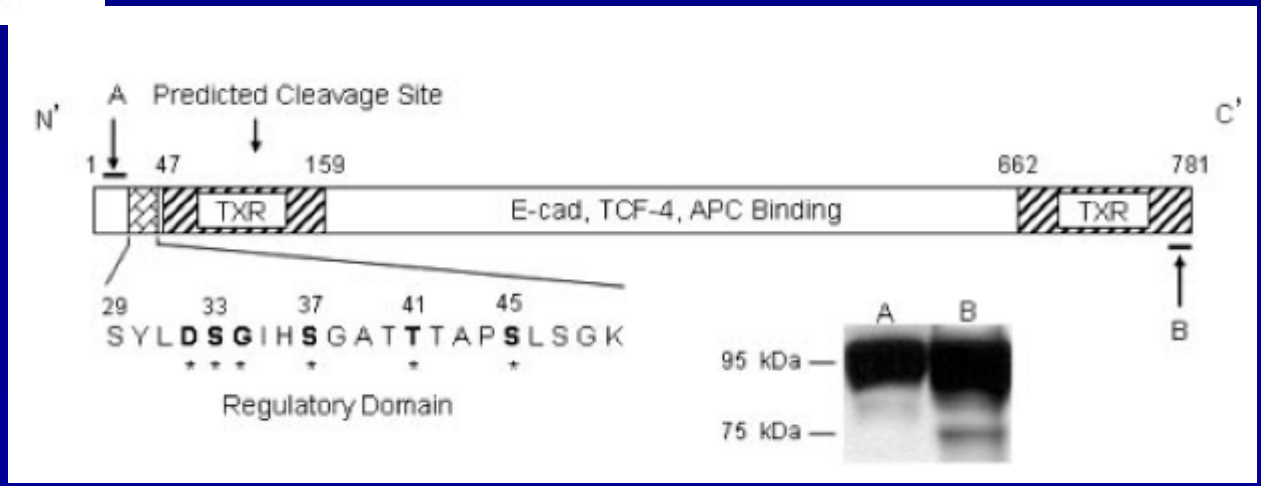
Protein Binding to LBD

1. Coactivators
2. Corepressors
3. NTD

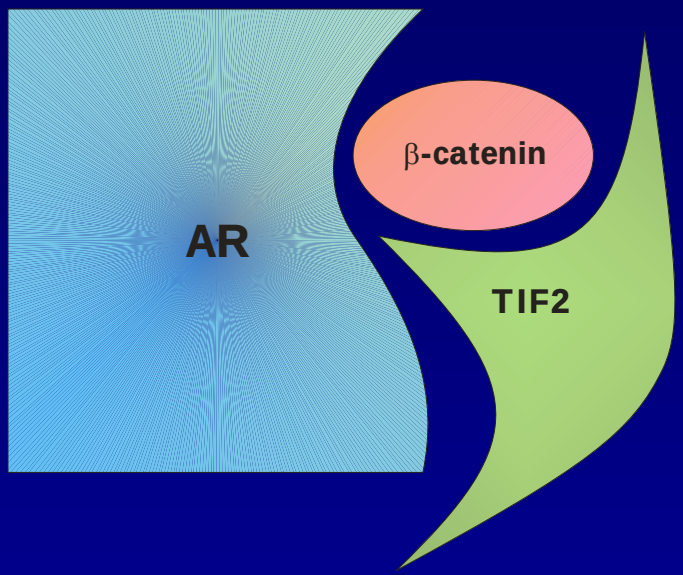
β-Catenin Truncation in Advanced Prostate Cancer

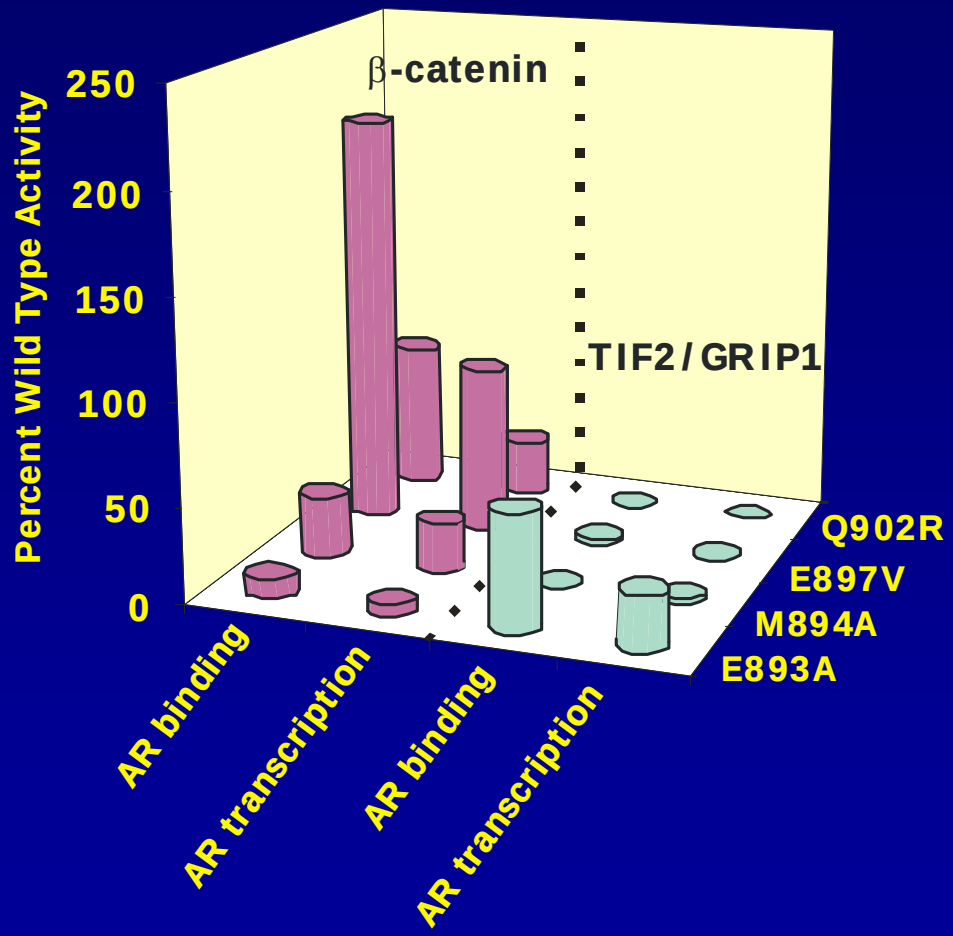




Rios-Doria Can Res 64:7237, 2004

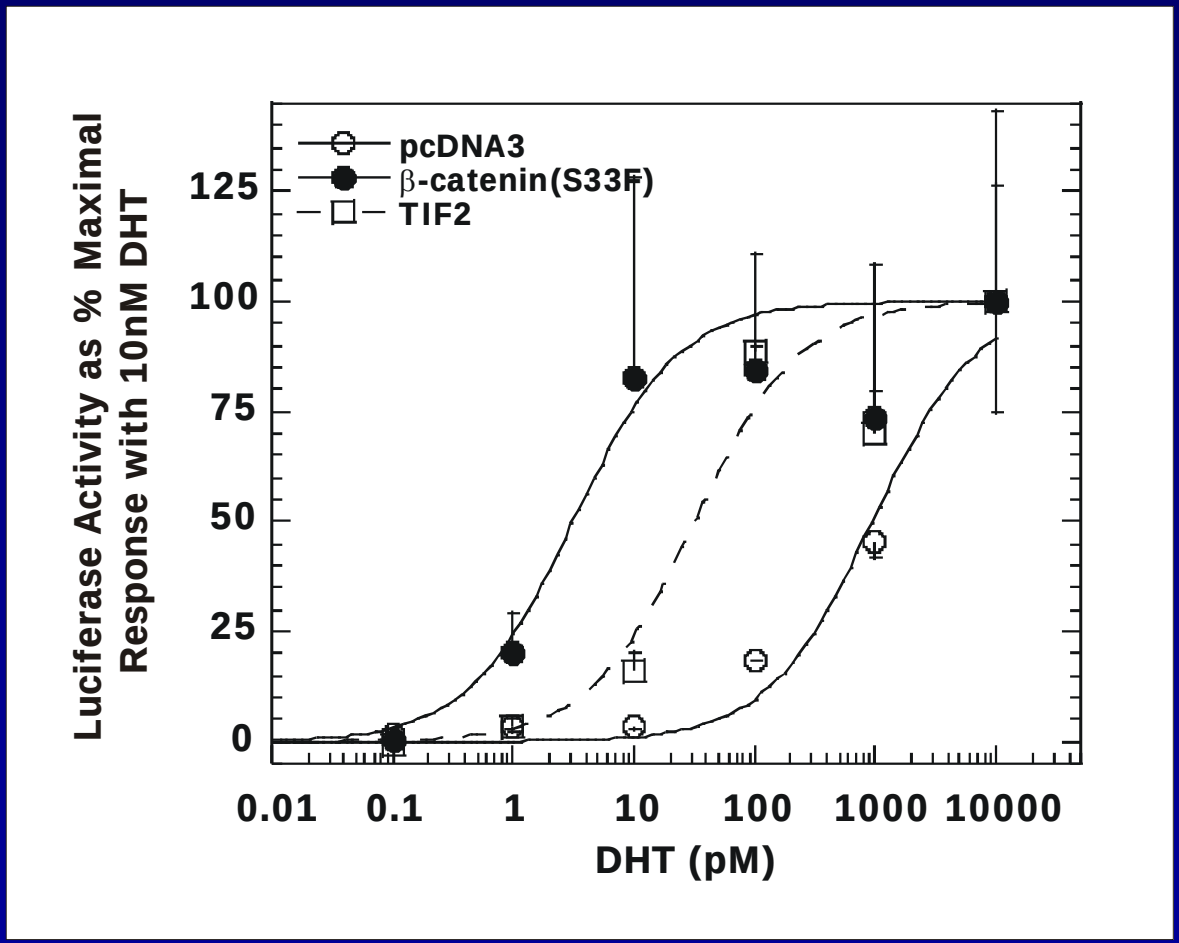
β-Catenin TIF2 and AR



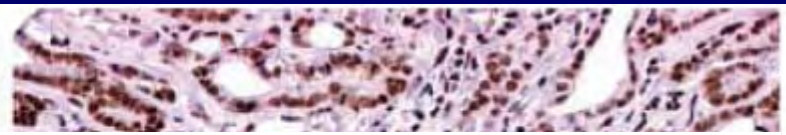


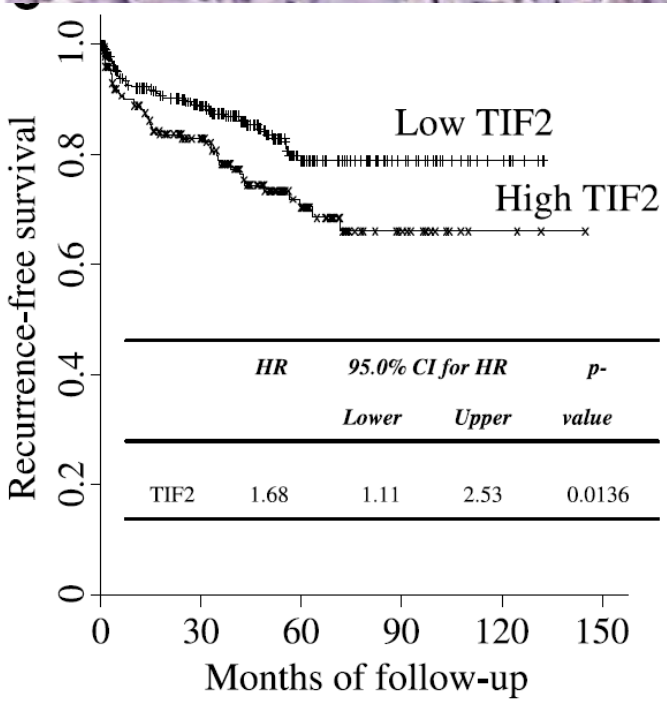
Song & Gelmann JBC 280 37853, 2005

AR Response to DHT

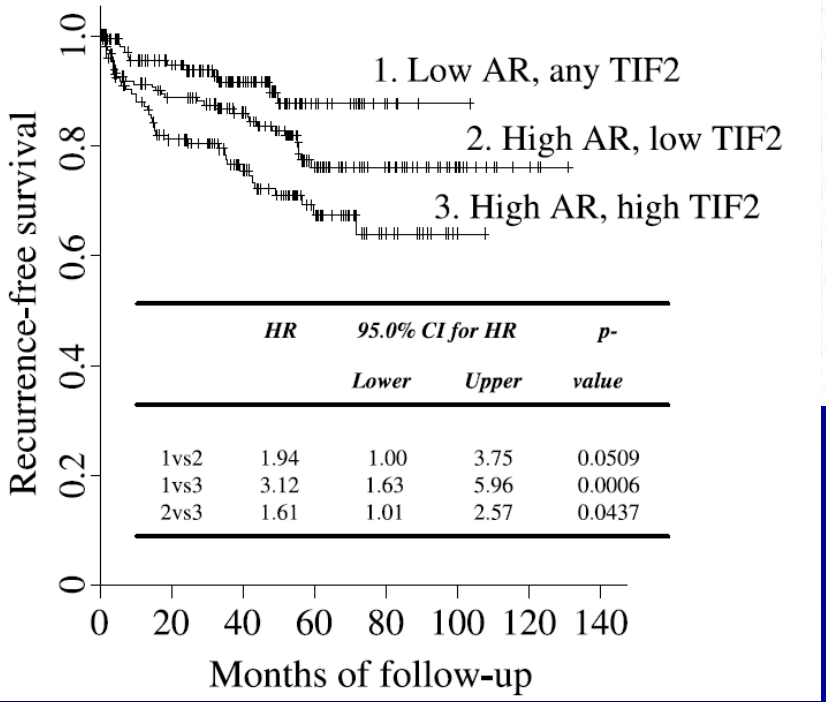


TIF-2 Expression in Prostate Cancer





	HR	95.0% CI for HR		p-value
		Lower	Upper	
TIF2	1.68	1.11	2.53	0.0136



	HR	95.0% CI for HR		p-value
		Lower	Upper	
1vs2	1.94	1.00	3.75	0.0509
1vs3	3.12	1.63	5.96	0.0006
2vs3	1.61	1.01	2.57	0.0437

Agoulnik Can Res 66:10594, 2006

Conclusions

1. Prostate cancer requires AR signaling for development and sustenance.

2. AR activation is required throughout the natural history of prostate cancer.

3. AR activation in AIPC occurs via many mechanisms.

4. Successful blockade of the receptor pathways will confer greater therapeutic control on metastatic prostate cancer.