

Androgen Receptor and Androgen-Independent Prostate Cancer

**Edward P. Gelmann, MD
Columbia University**

Outline

AR Structure and Function

AR Amplification

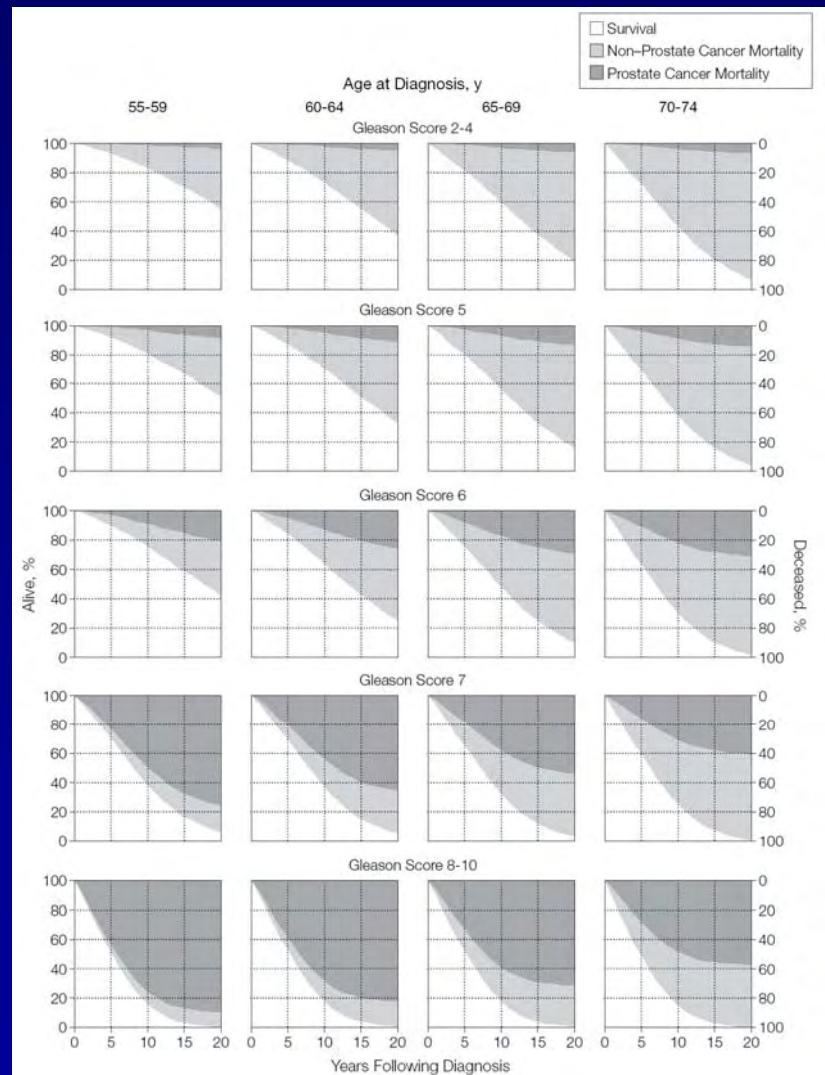
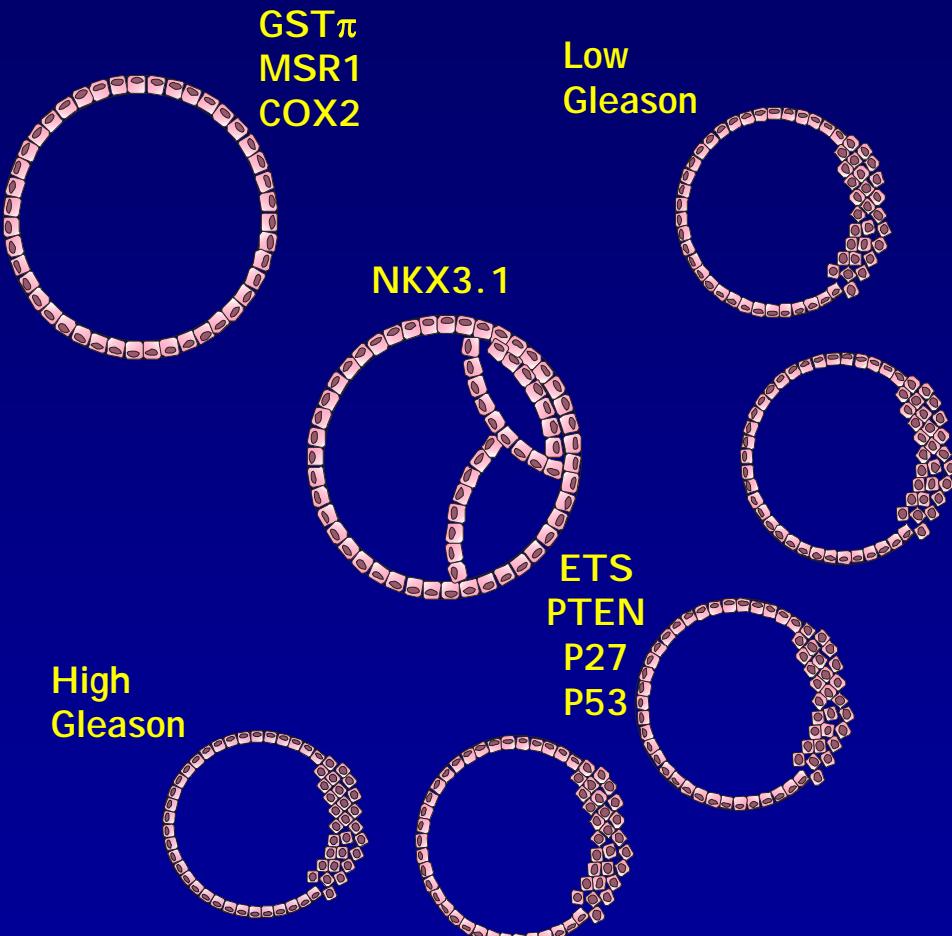
AR Mutation

AR Modification

Ligand Availability

AR Interaction

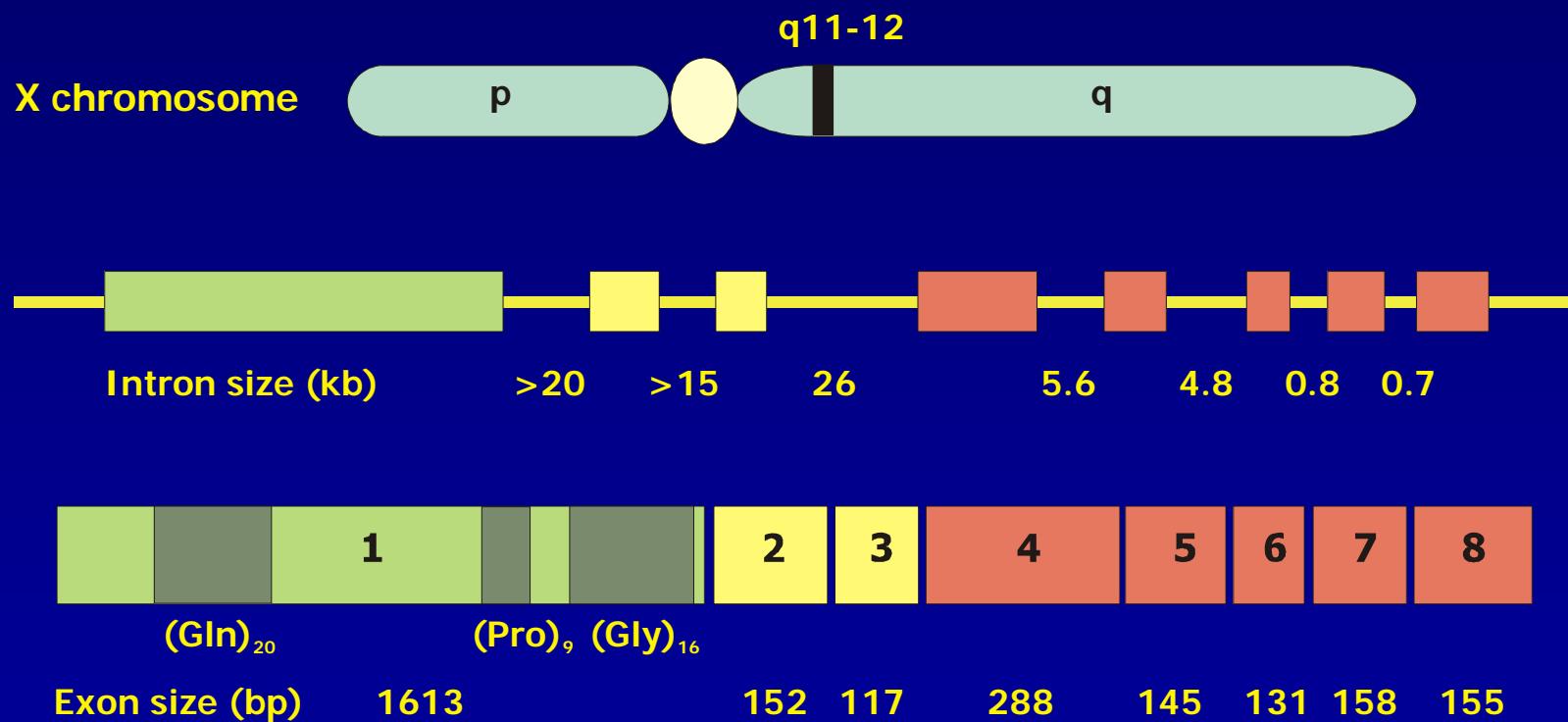
Prostate Cancer Heterogeneity



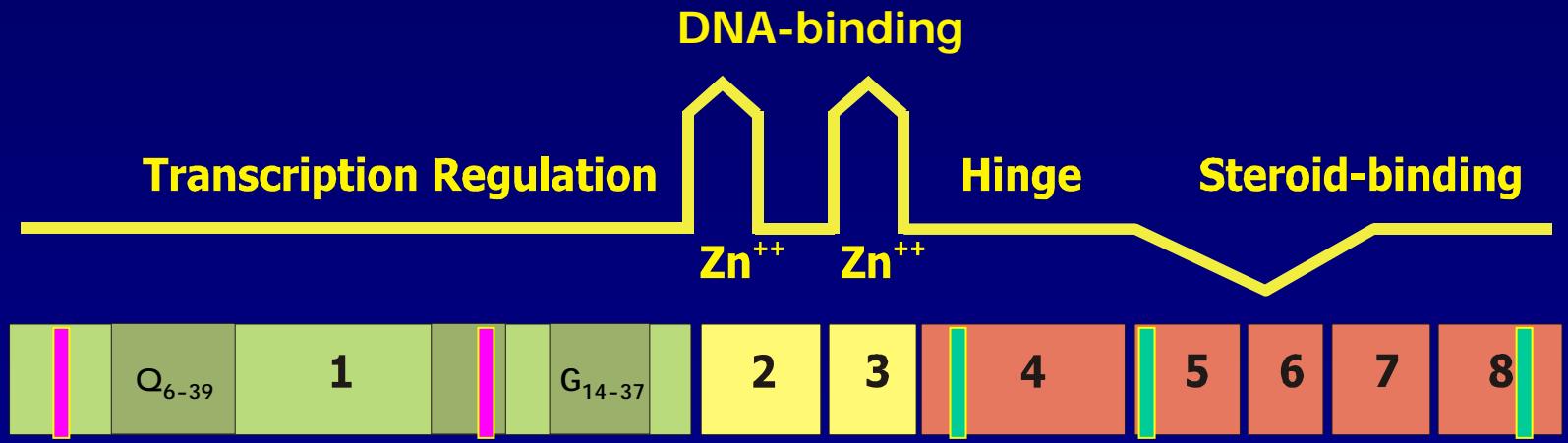
Albertsen et al,
JAMA 293:2095, 2005

2007

AR Structure



AR Structure



²³FQLNF ²⁷

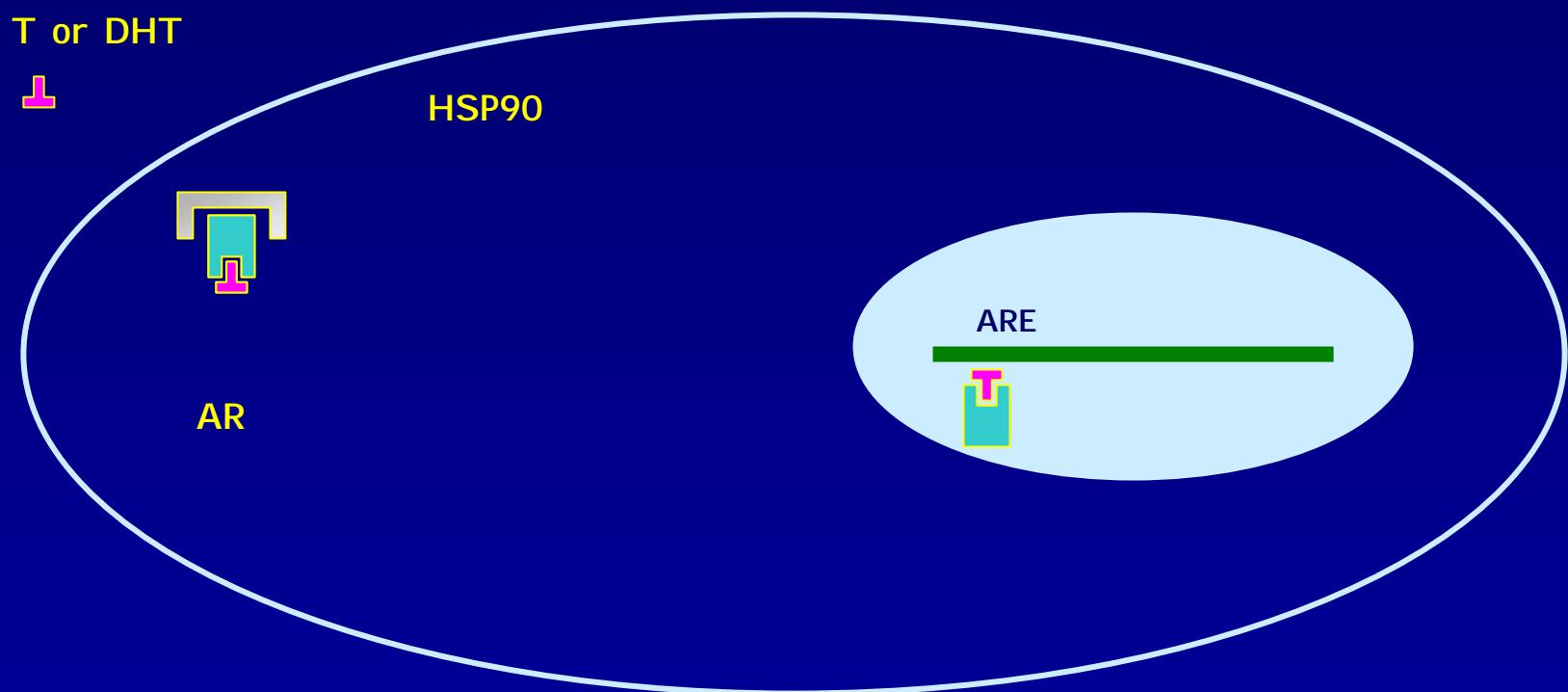
⁴³²WHTLF ⁴³⁶

716-720

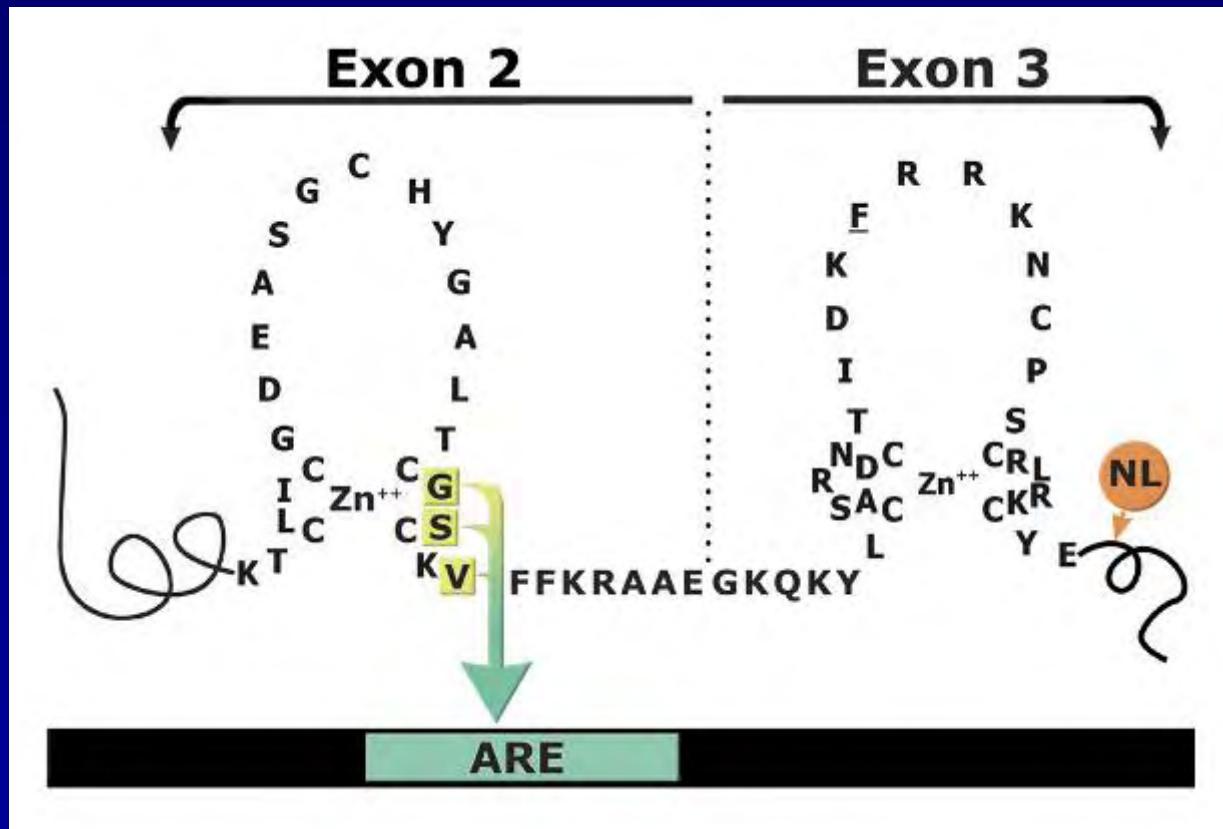
737-741

889-898 AF-2

AR Activation by Androgen

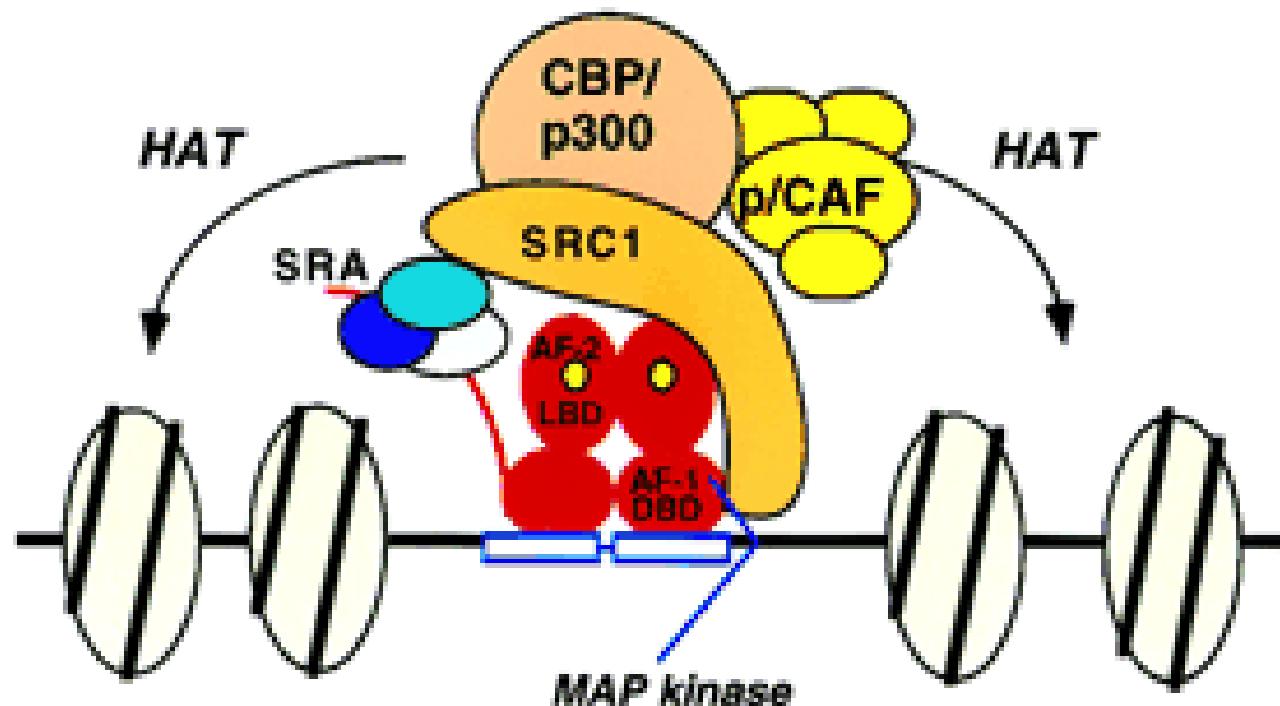


AR DNA Binding Domain

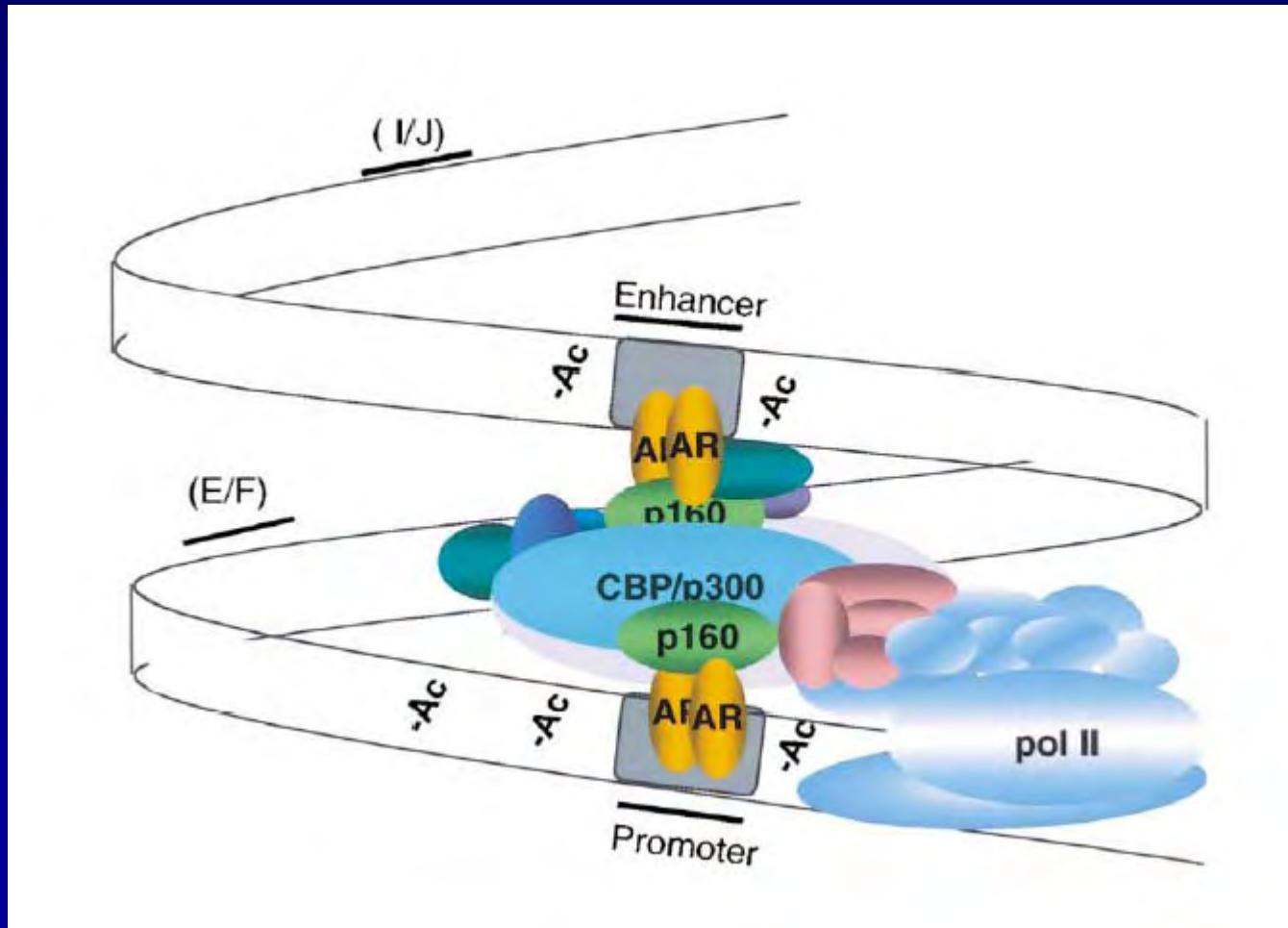


Activation of Transcription

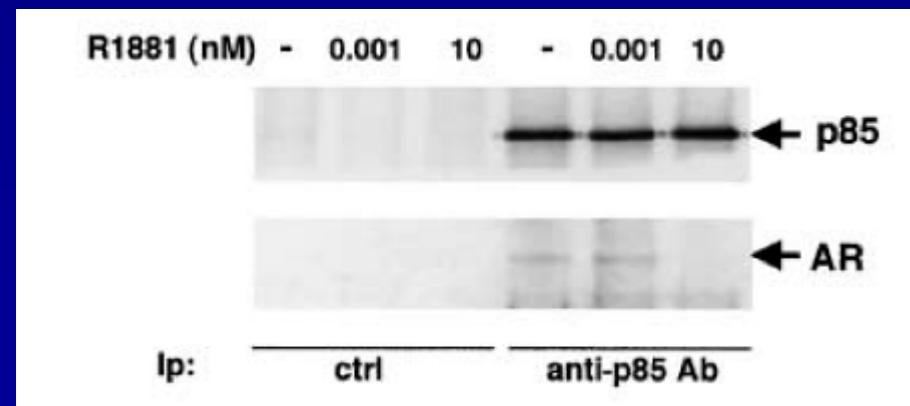
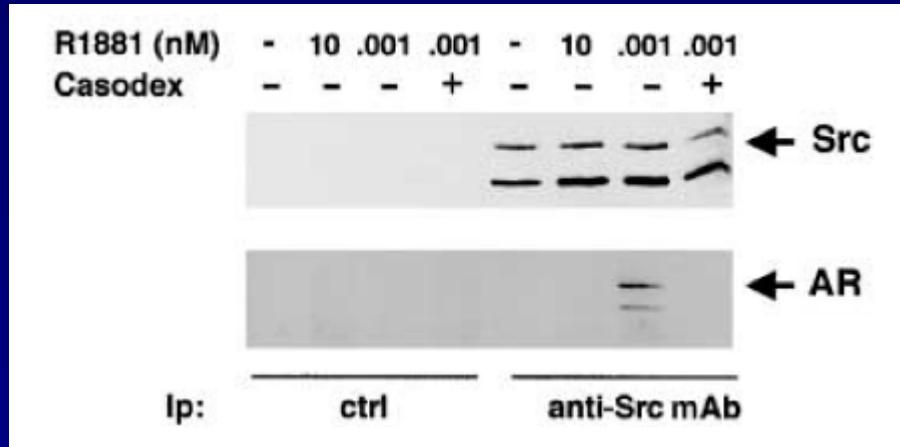
p160/CBP/PCAF Complex



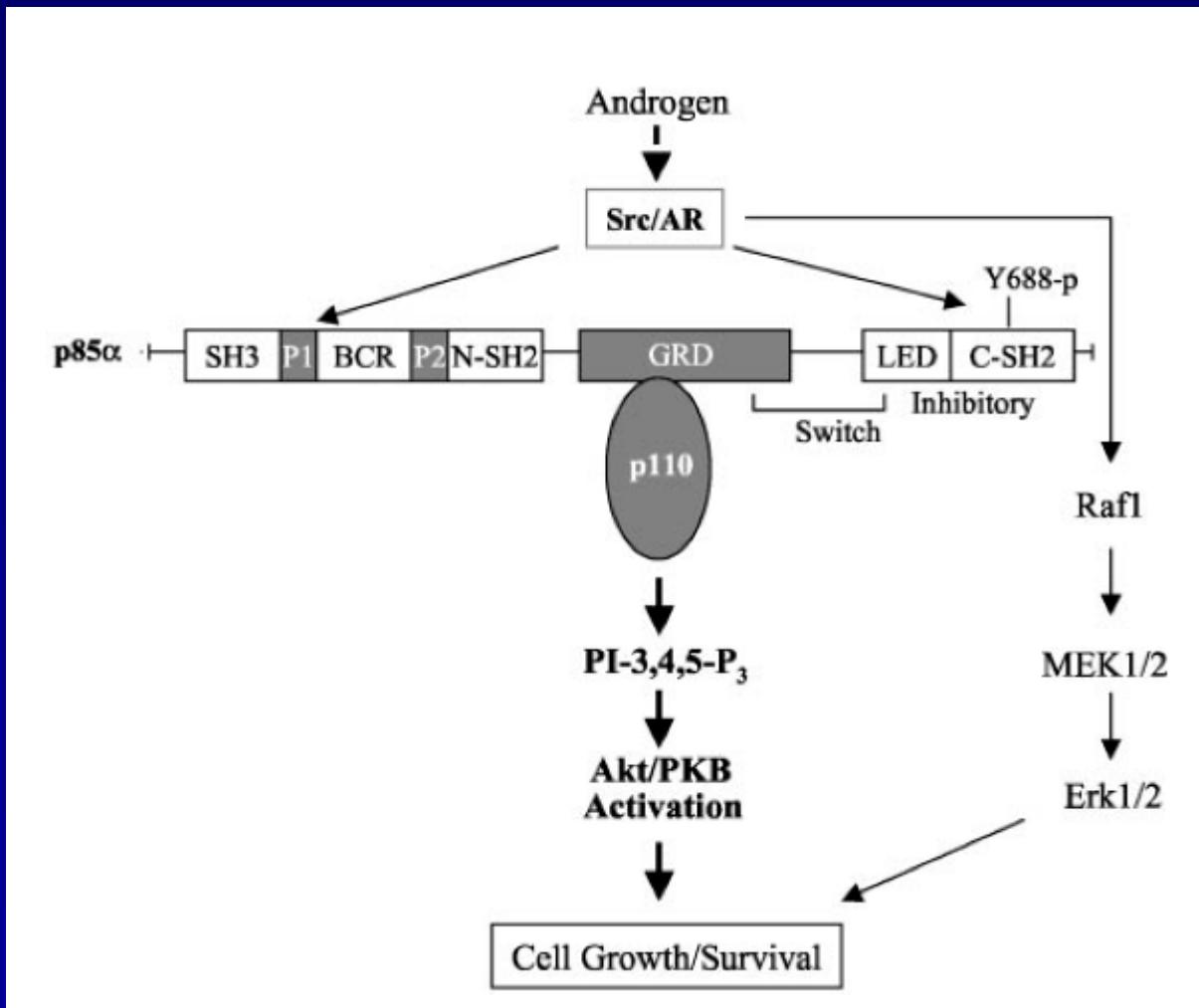
Activation of Transcription



AR Binds to SRC and PI3K



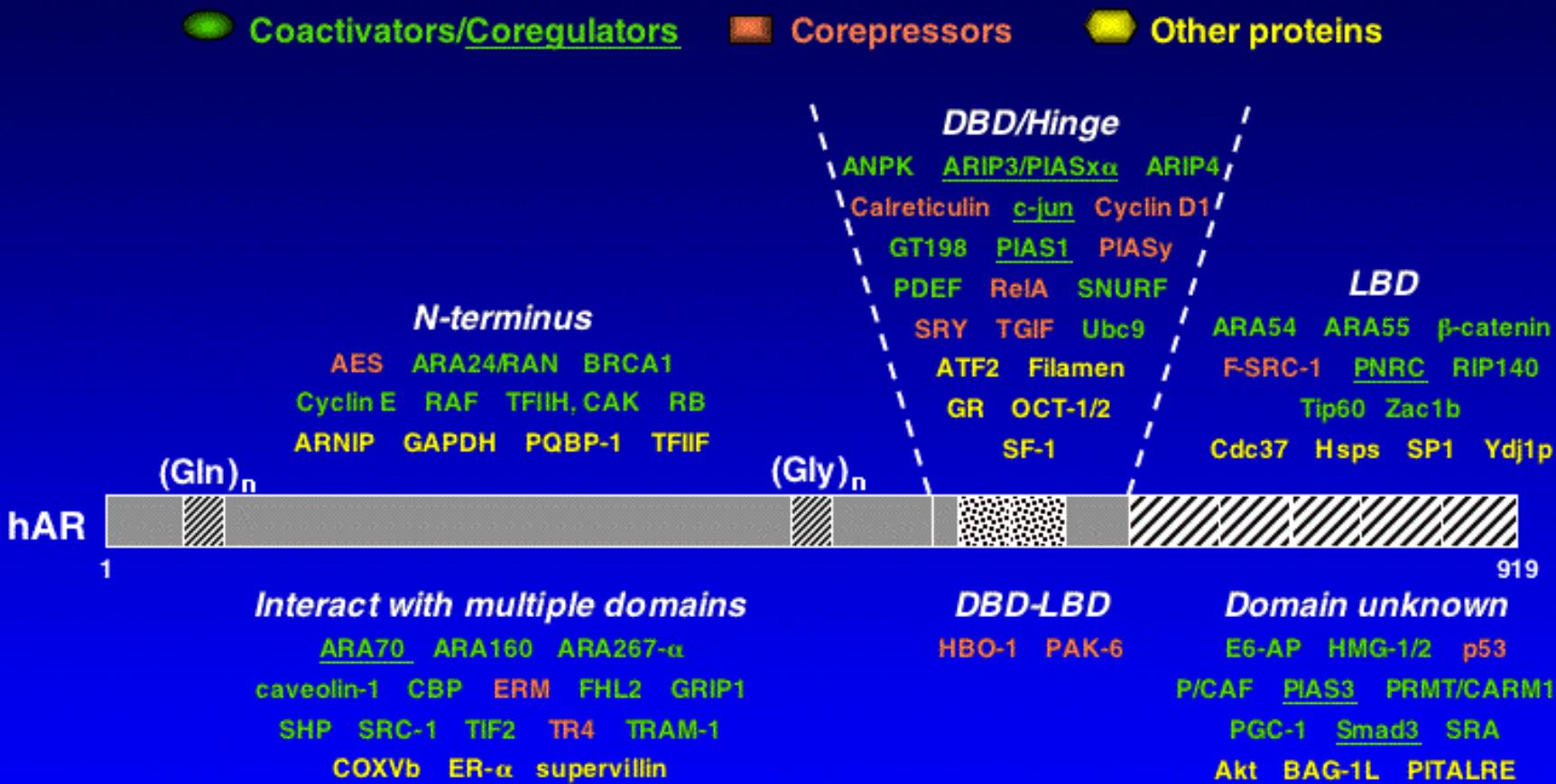
Cytoplasmic Effects of Androgen



Androgens Make a Big Difference



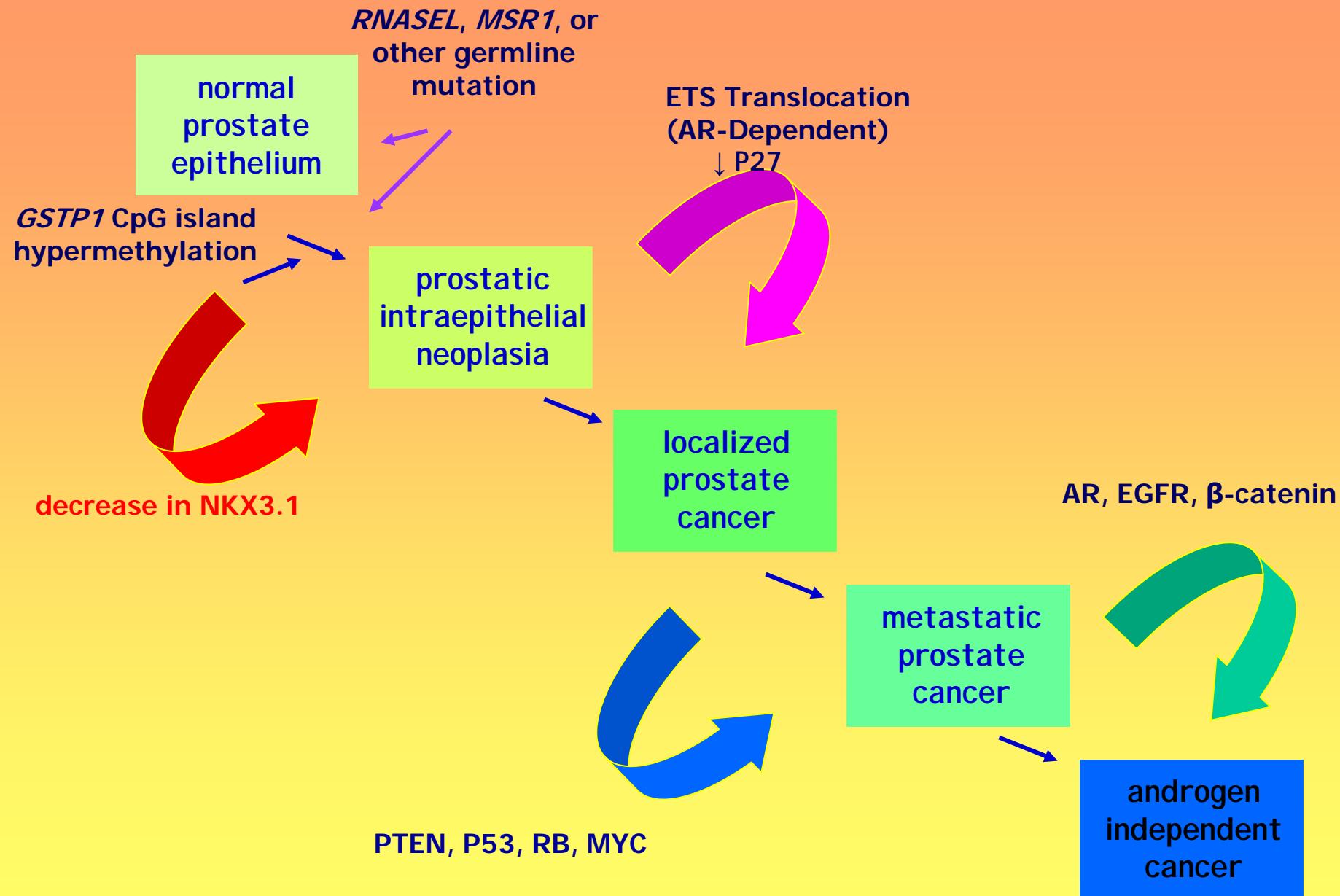
Androgen Receptor-Interacting Proteins



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 information.

LKB

2003/3/1



Outline

AR Structure and Function

AR Amplification

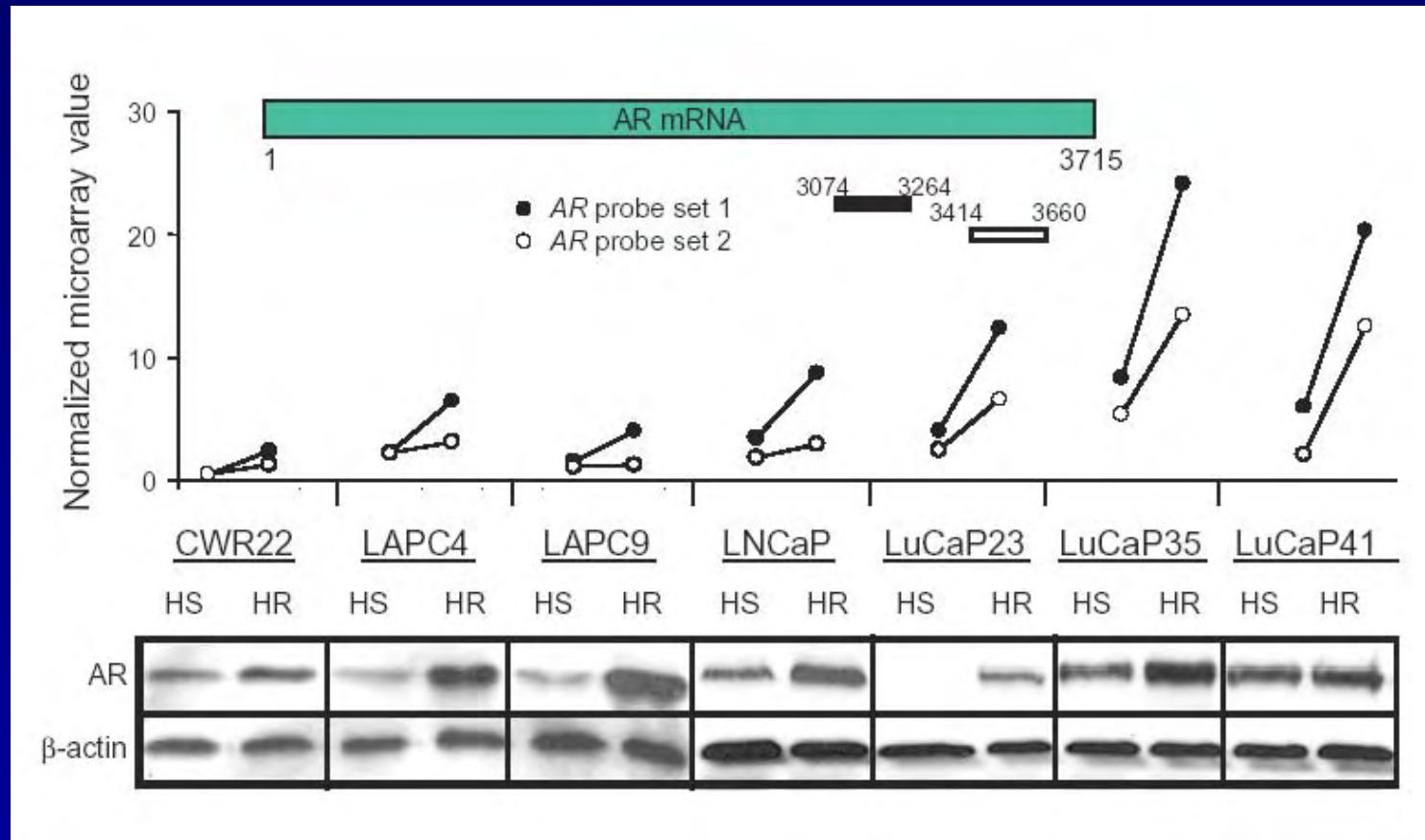
AR Mutation

AR Modification

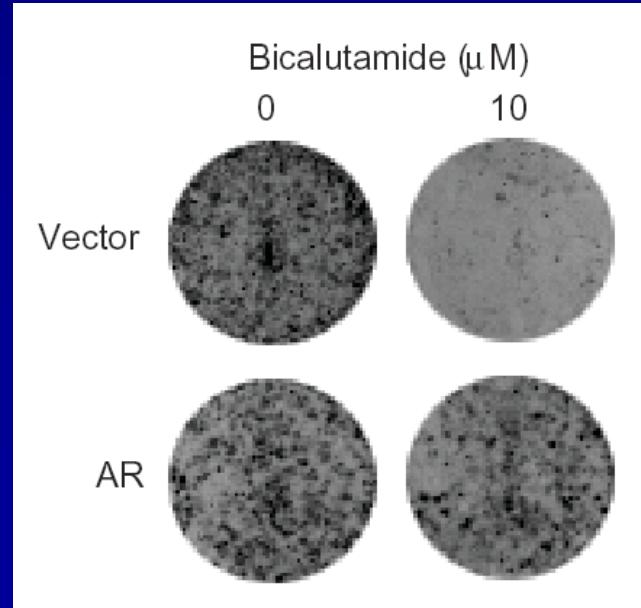
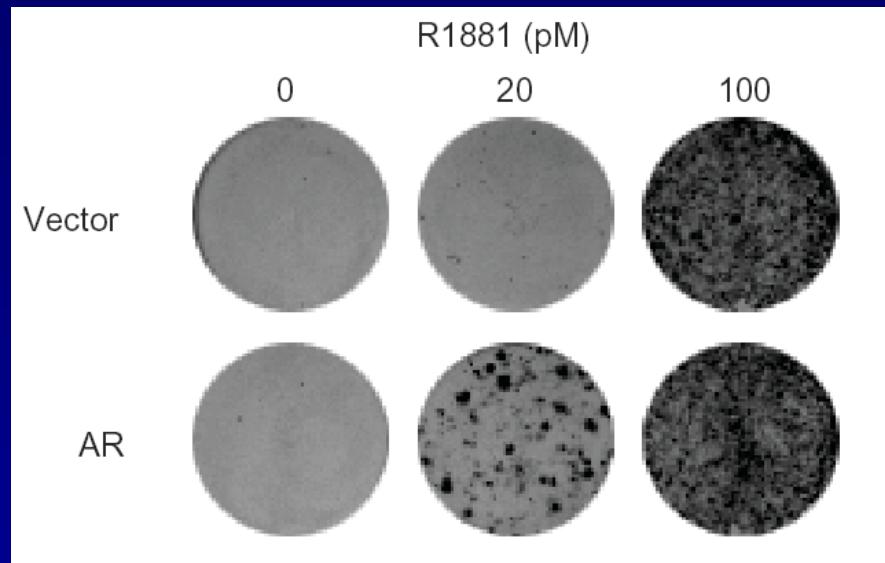
Ligand Availability

AR Interaction

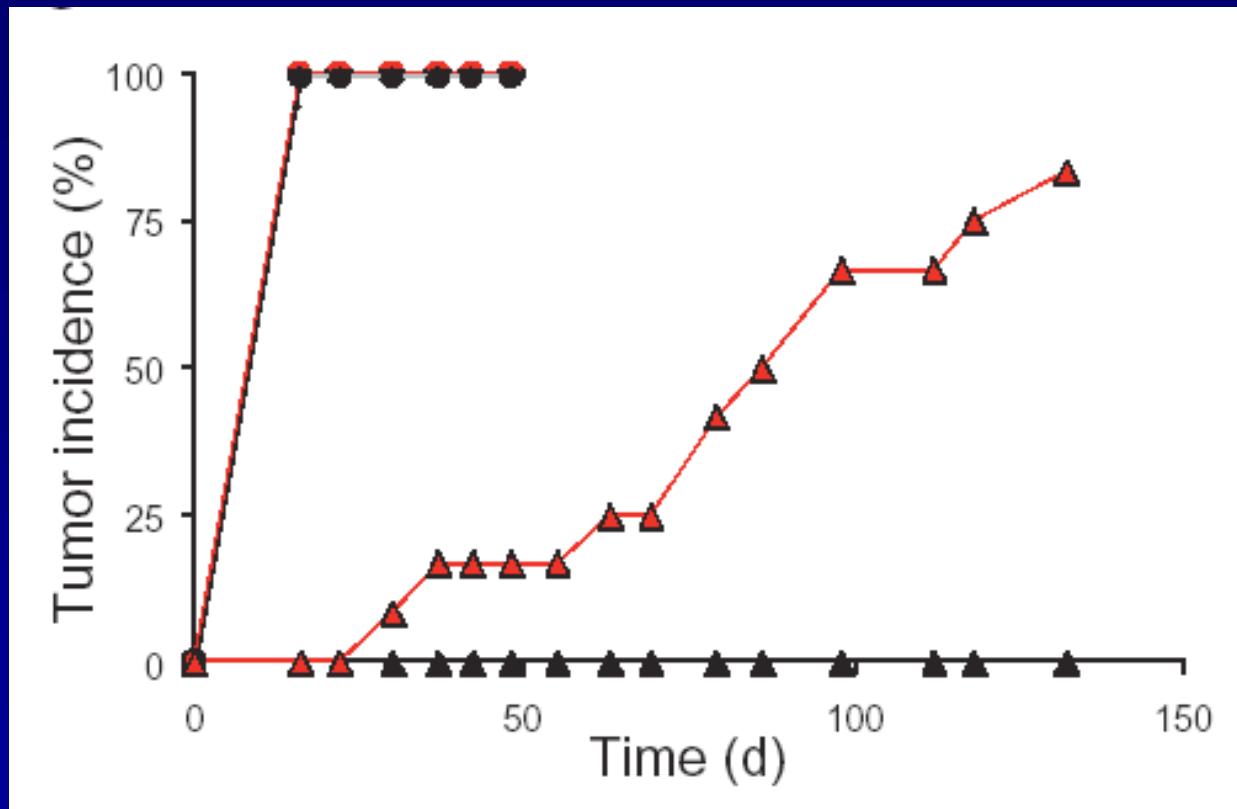
AR Gene Expression and Hormone-Independence



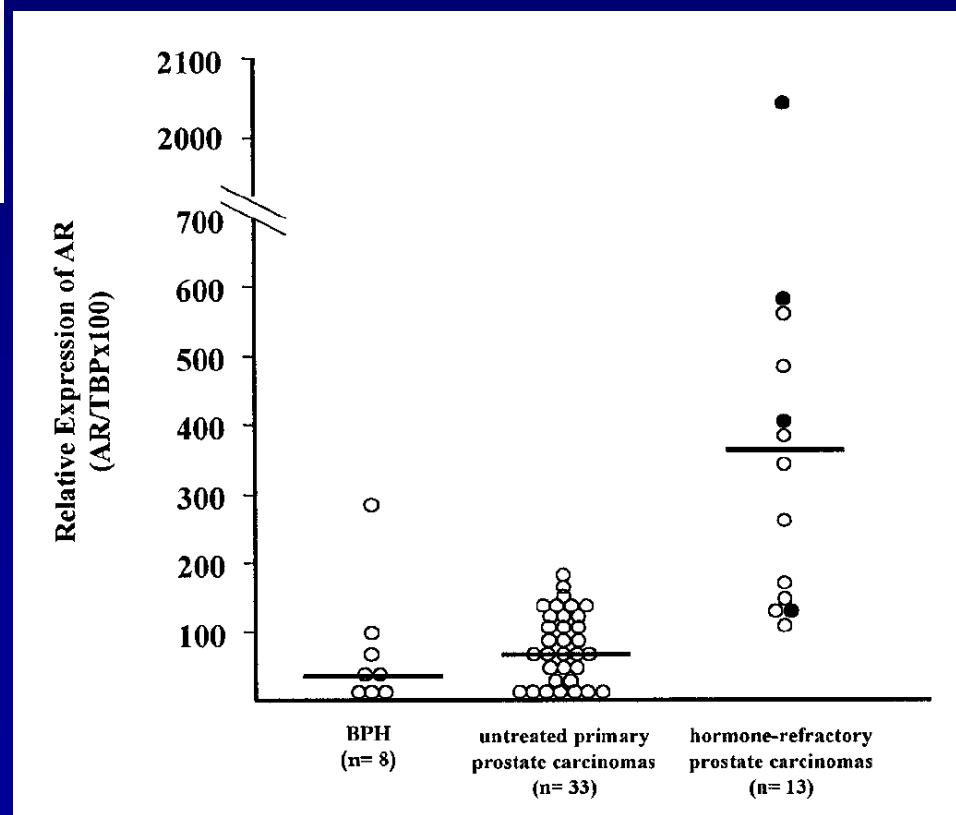
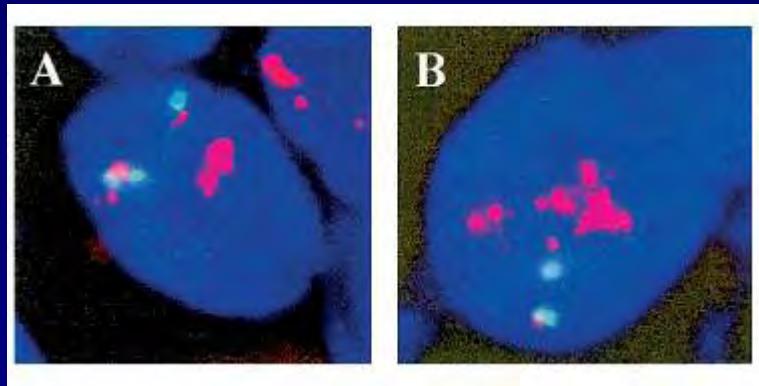
AR Gene Expression and Hormone-Independence



AR Gene Expression and Hormone-Independence



AR Gene Amplification



Outline

AR Structure and Function

AR Amplification

AR Mutation

AR Modification

Ligand Availability

AR Interaction

AR Mutations - CaP

Frequency of AR mutations

prior flutamide therapy

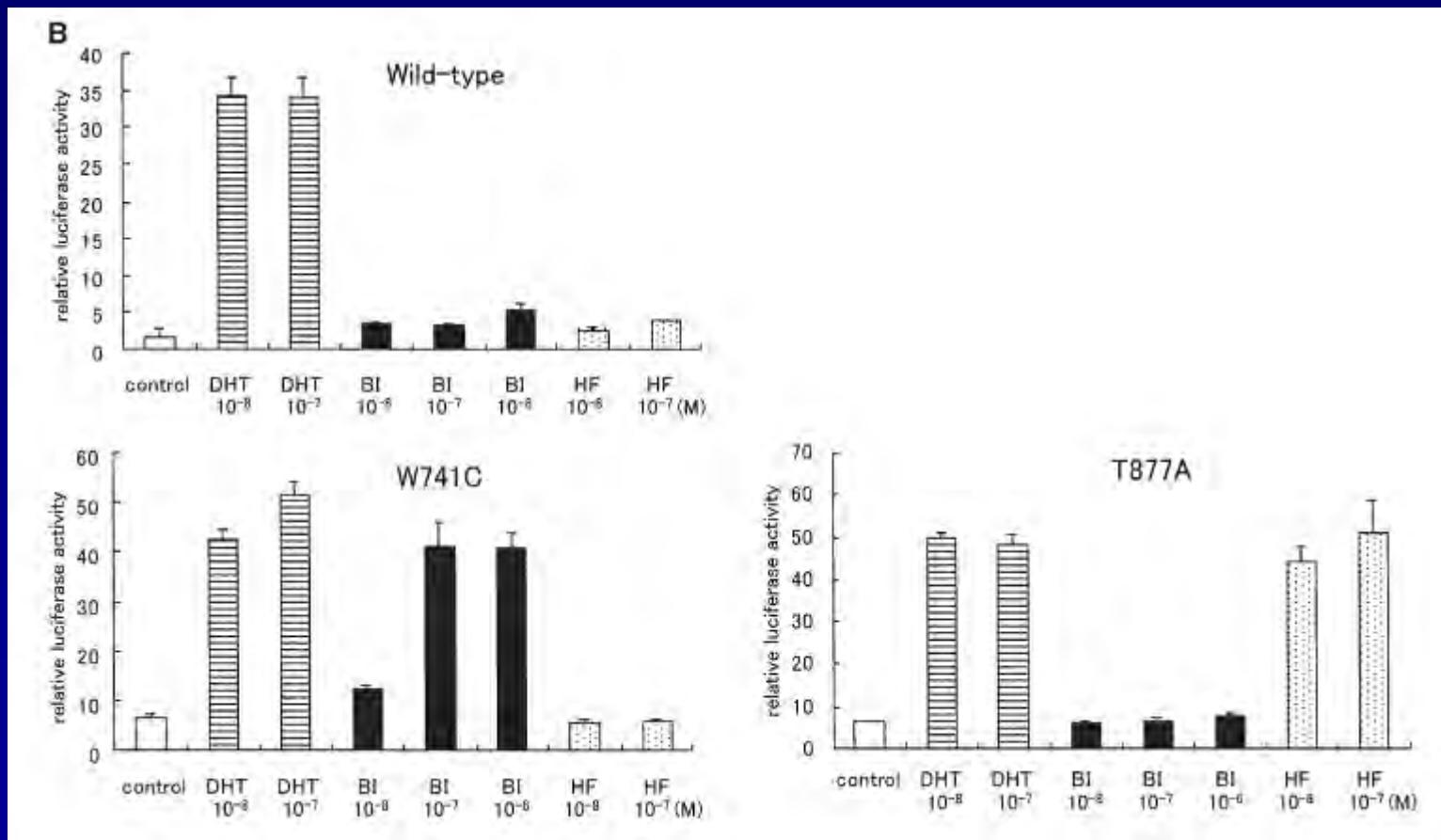
5/16

no prior flutamide therapy

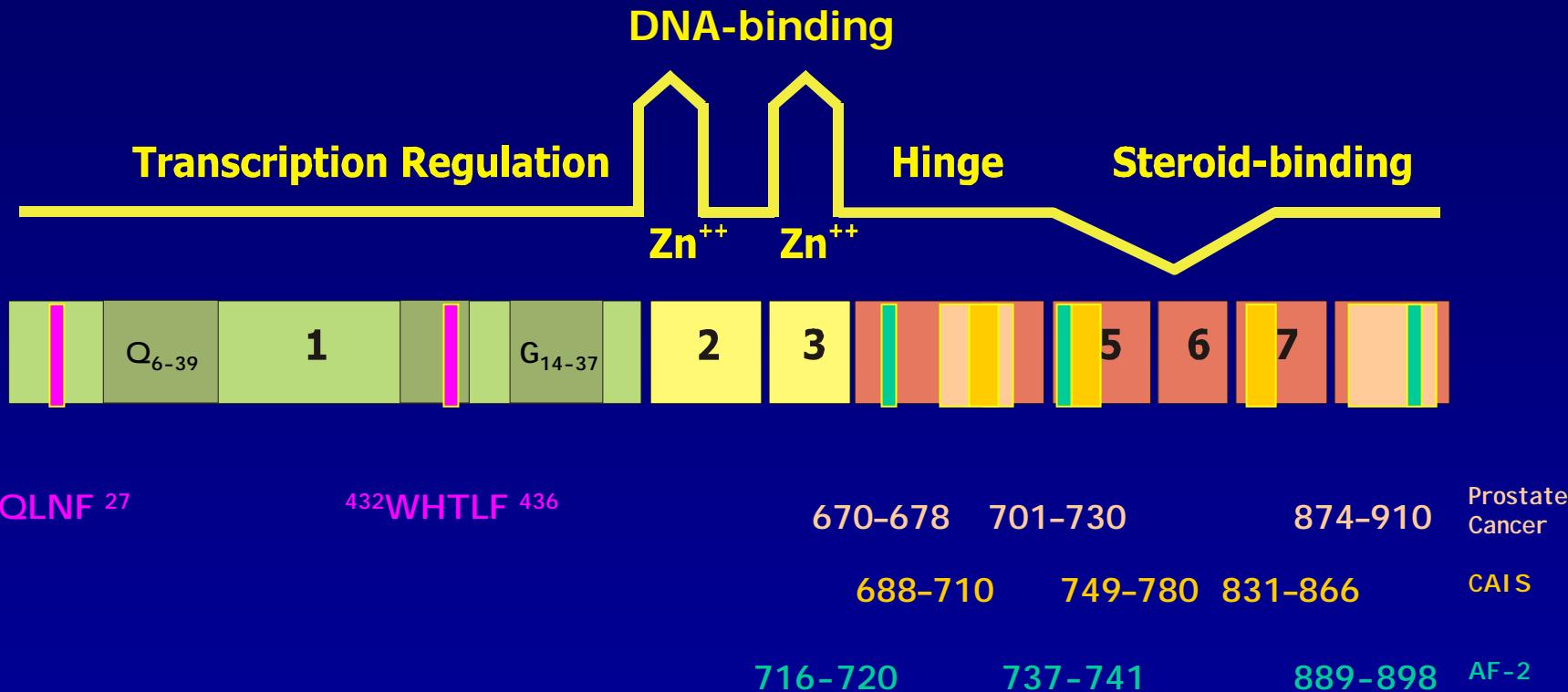
1/17

AR Mutations

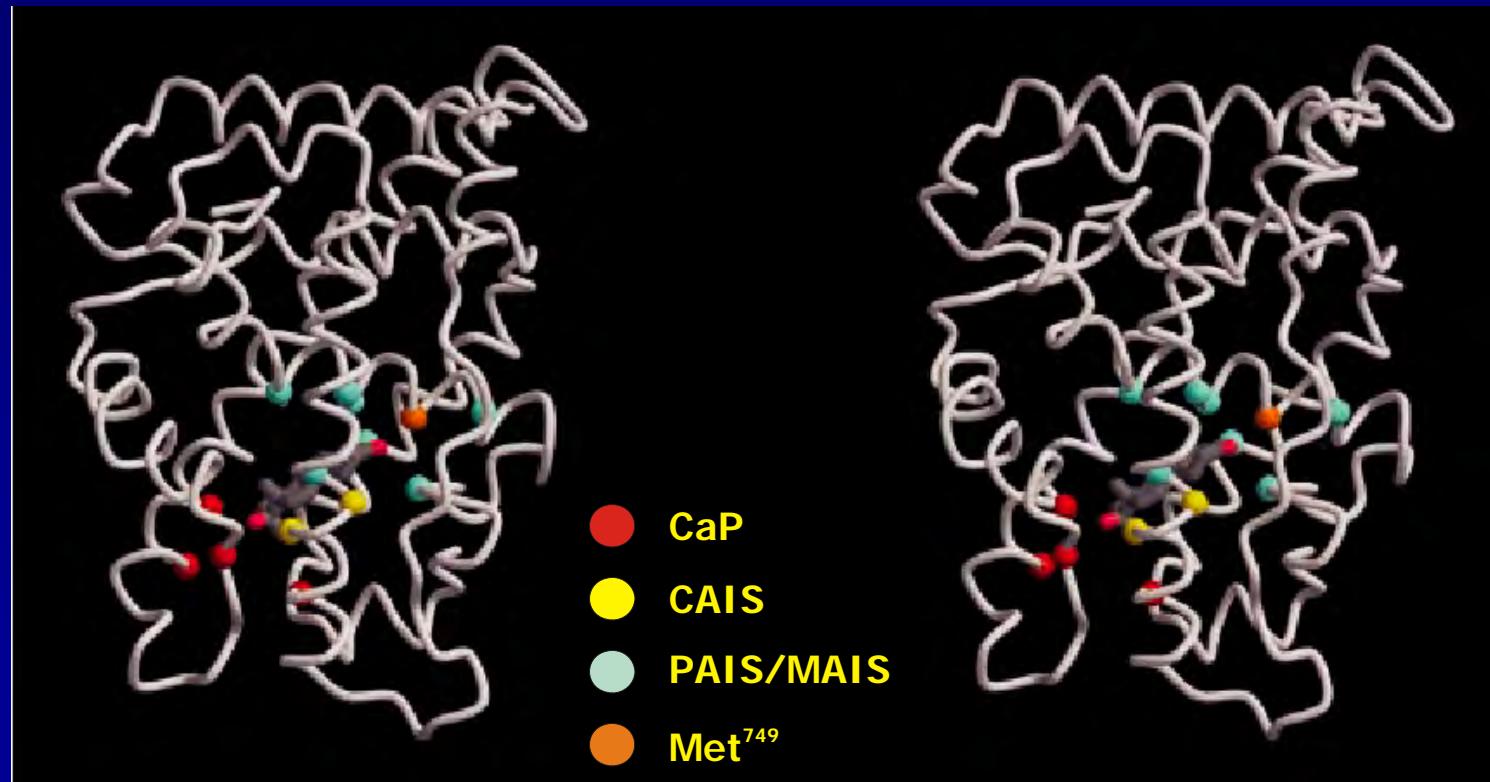
Bicalutamide resistance



AR Structure



LBD Mutations in Cap and AIS



Outline

AR Structure and Function

AR Amplification

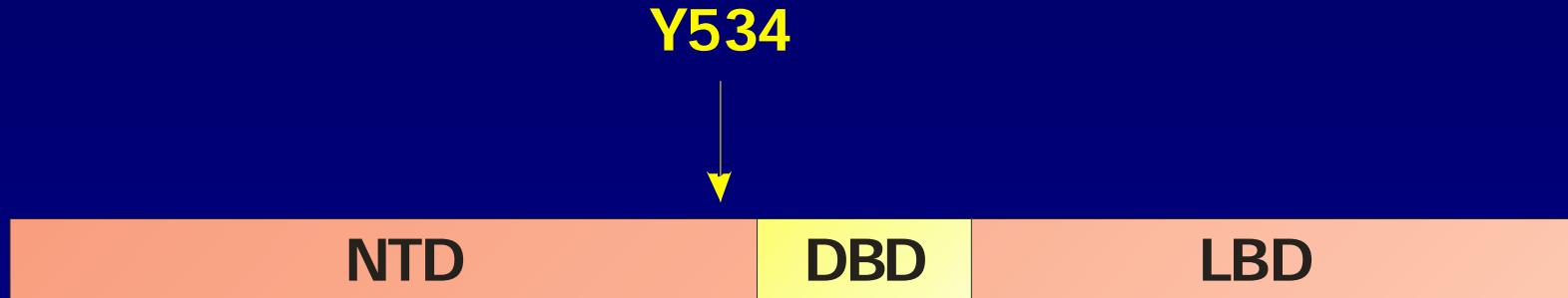
AR Mutation

AR Modification

Ligand Availability

AR Interaction

AR Phosphorylation

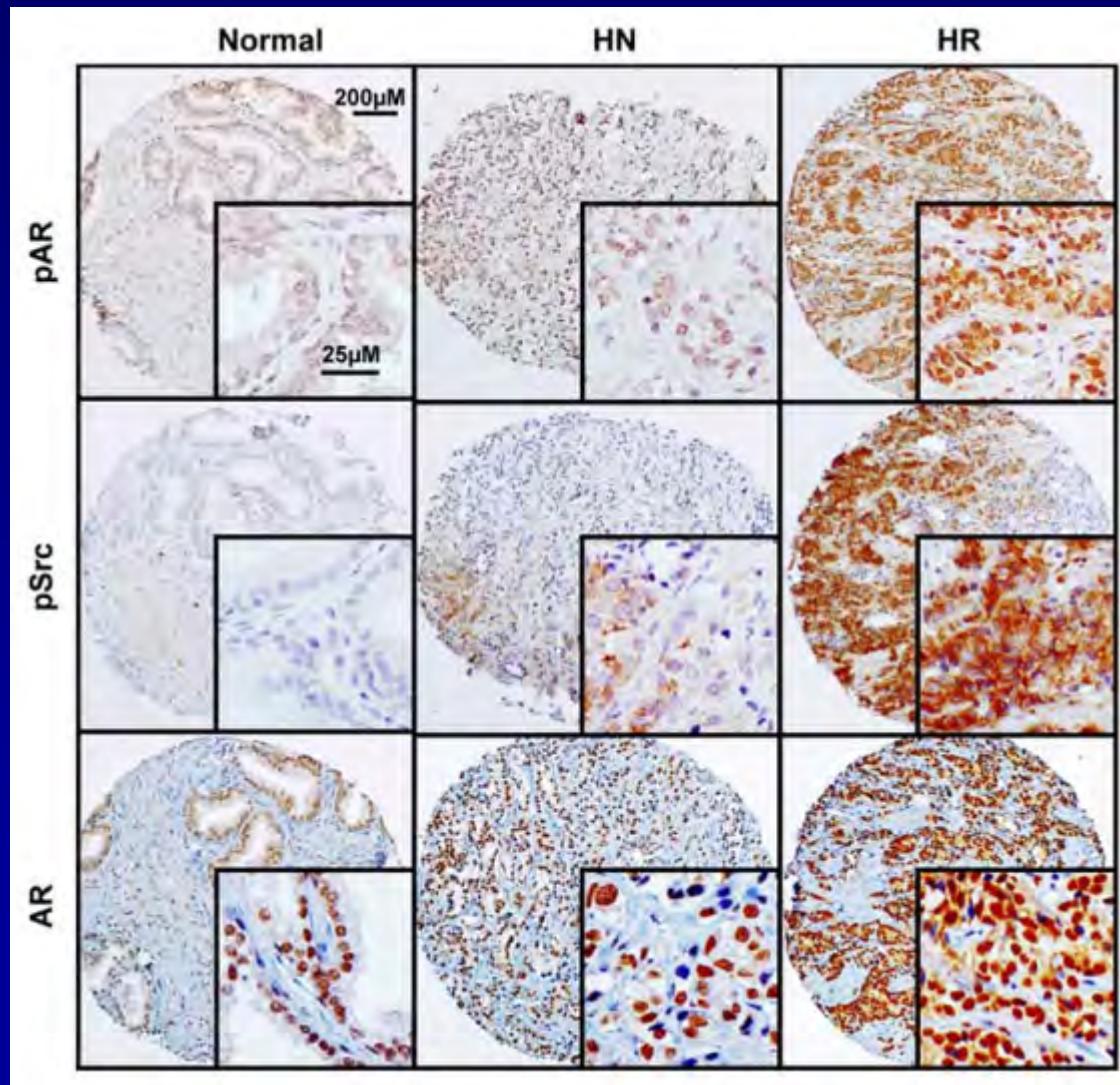


SRC tyr kinase site in AR

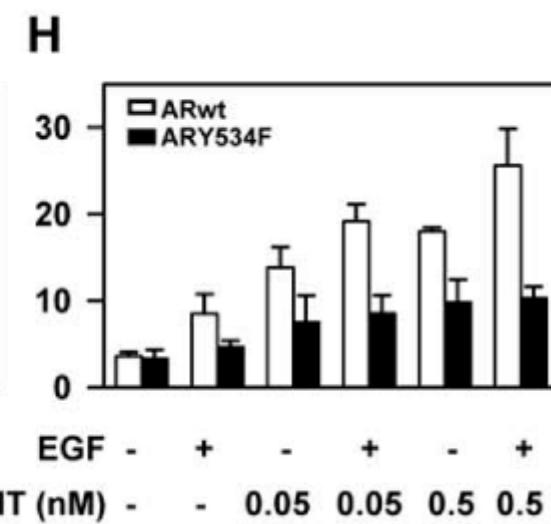
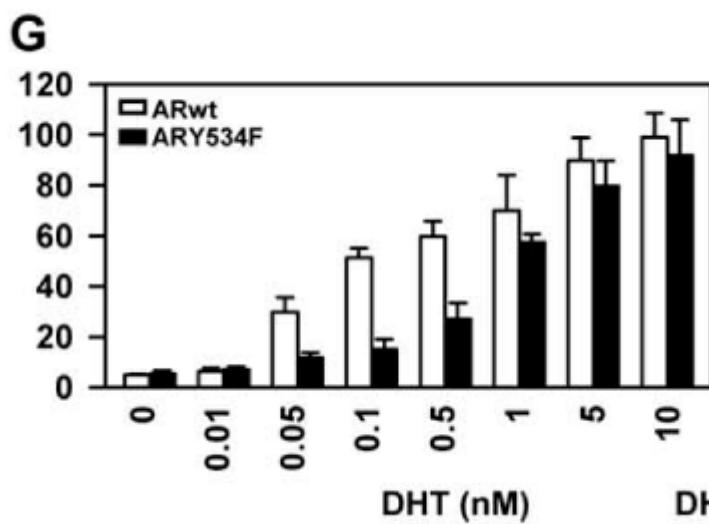
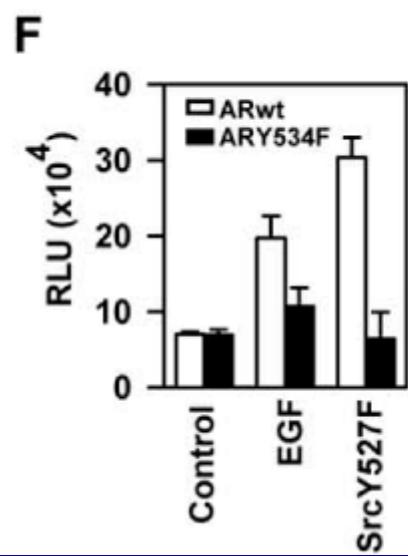
AR(p-Tyr⁵³⁴) increased in AIPC

Y534 Phosphorylation activates AR

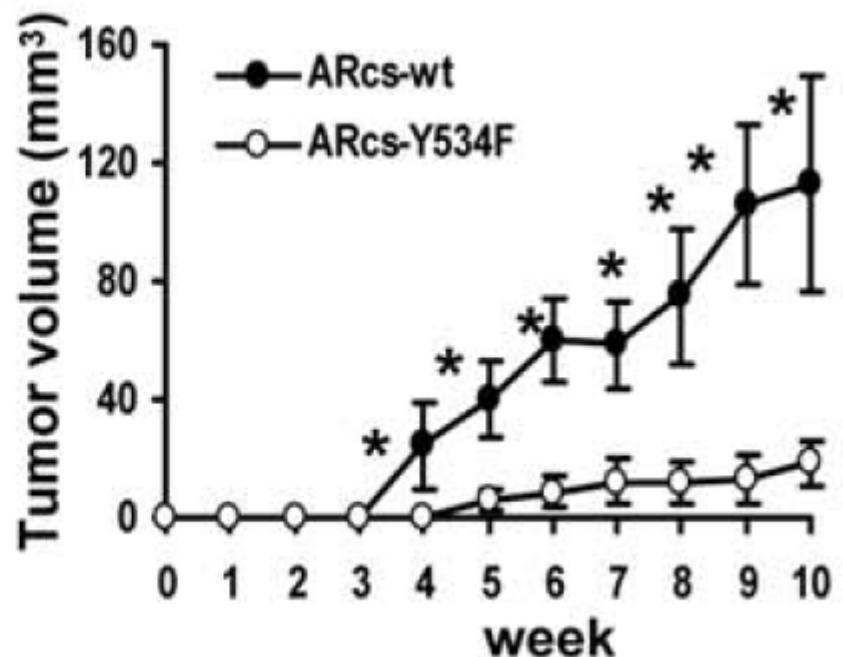
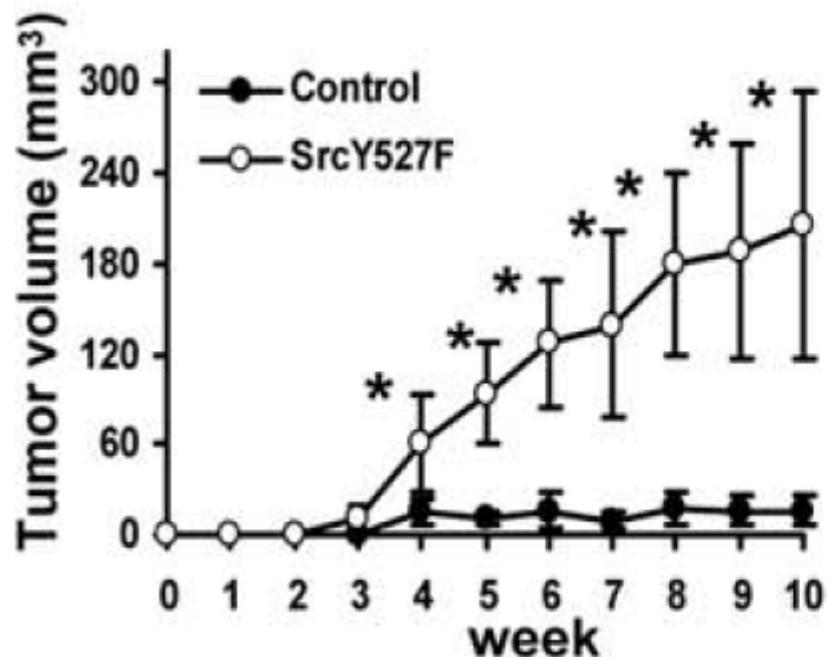
AR Phosphorylation



AR Phosphorylation



AR Phosphorylation



AR Phosphorylation

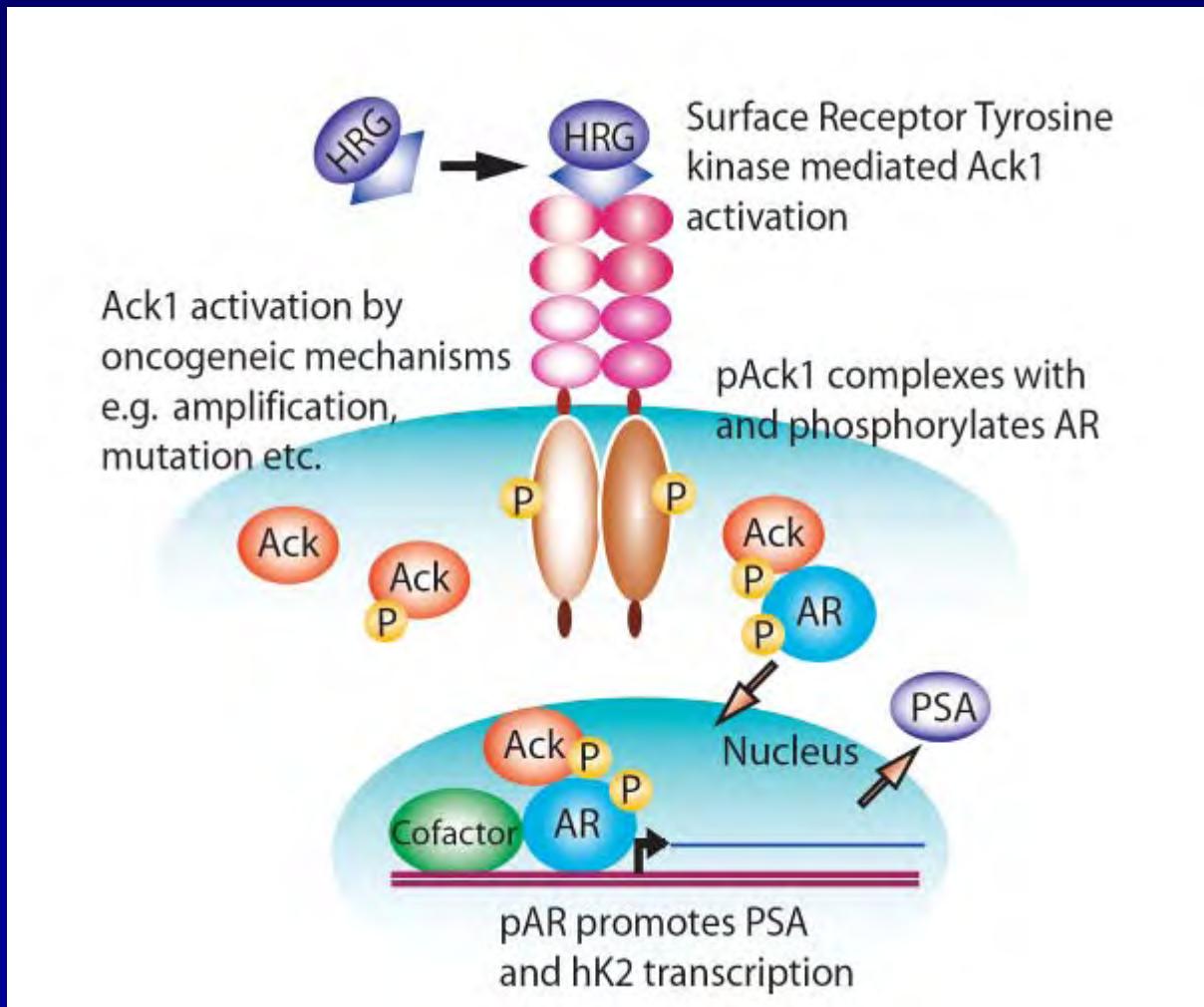


ACK1 tyr kinase site in AR

AR(p-Tyr) increased in AIPC

Y267 and Y363 Phosphorylation activate AR

AR Phosphorylation



Outline

AR Structure and Function

AR Amplification

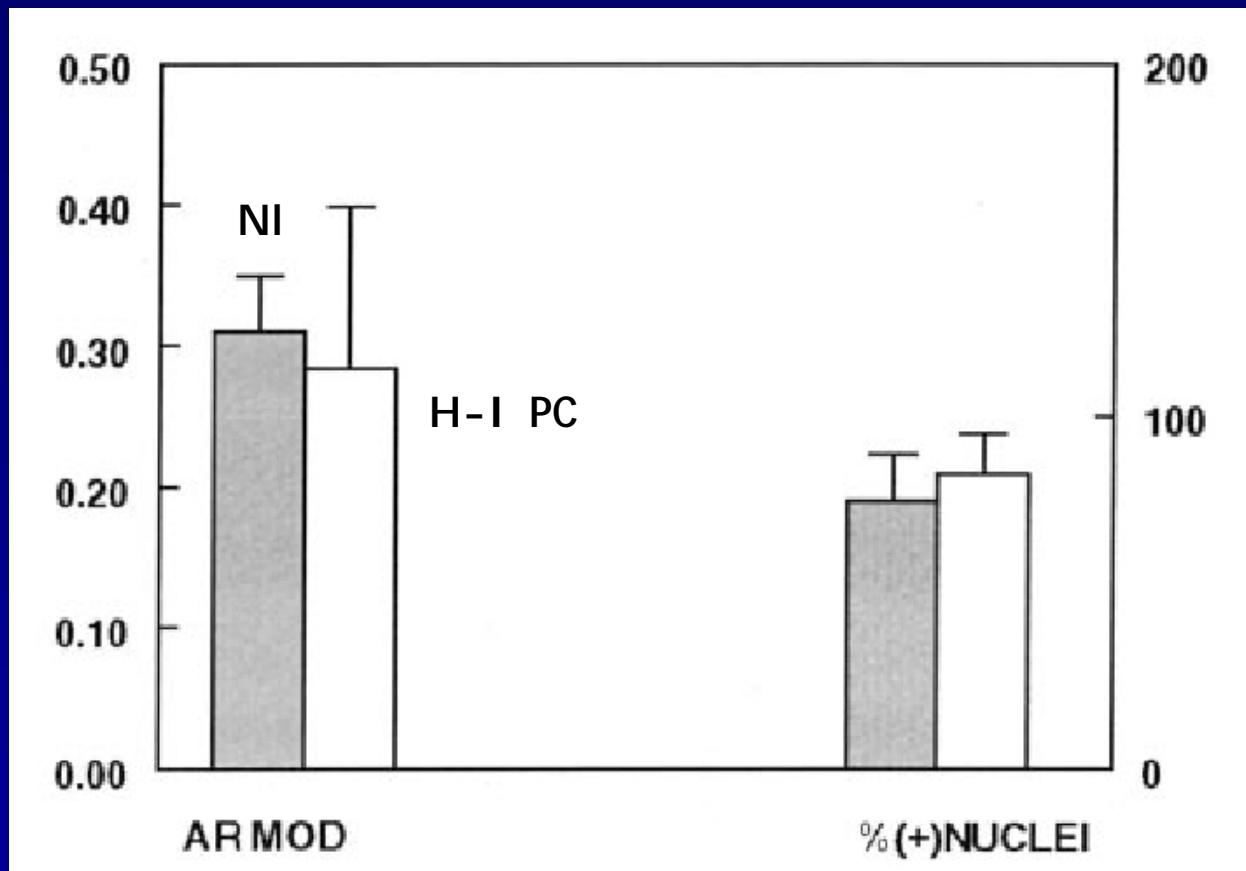
AR Mutation

AR Modification

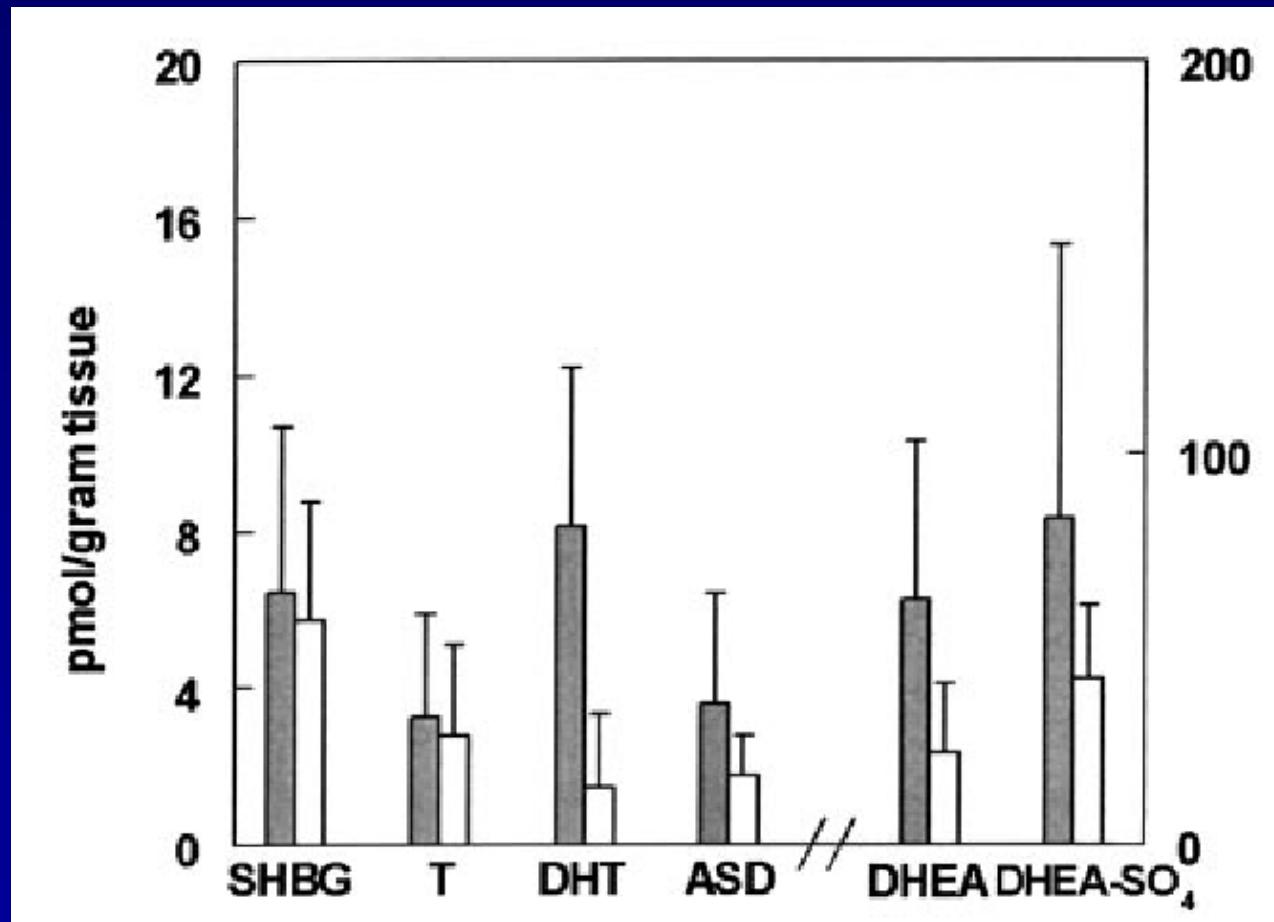
Ligand Availability

AR Interaction

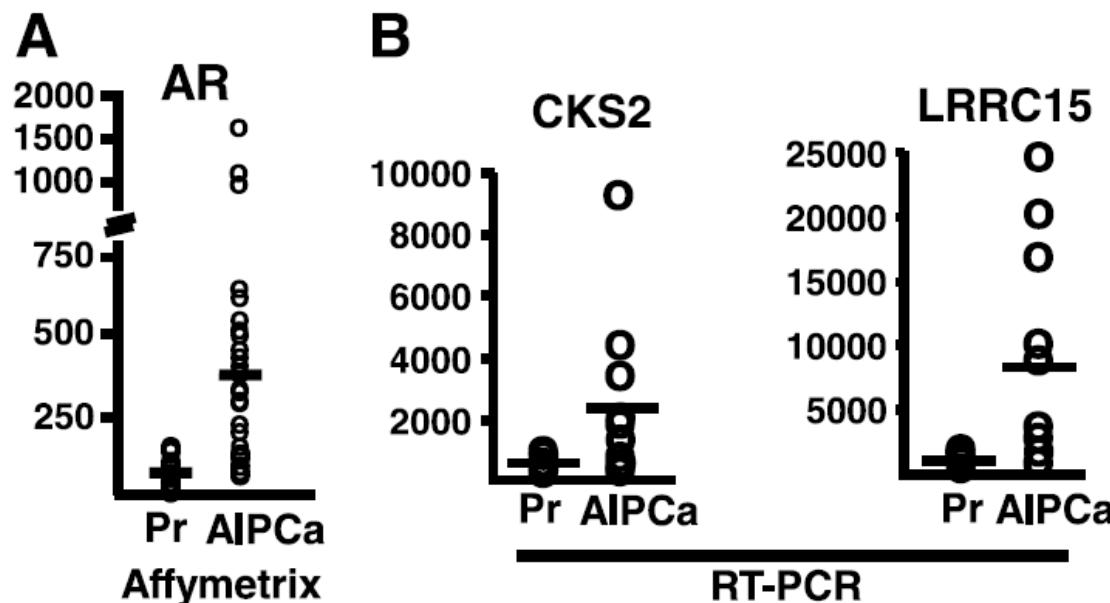
AR Expression – Channel TURPs



Tissue Hormone Levels – Channel TURPs



Increased Level of Enzymes to Make Testosterone



Outline

AR Structure and Function

AR Amplification

AR Mutation

AR Modification

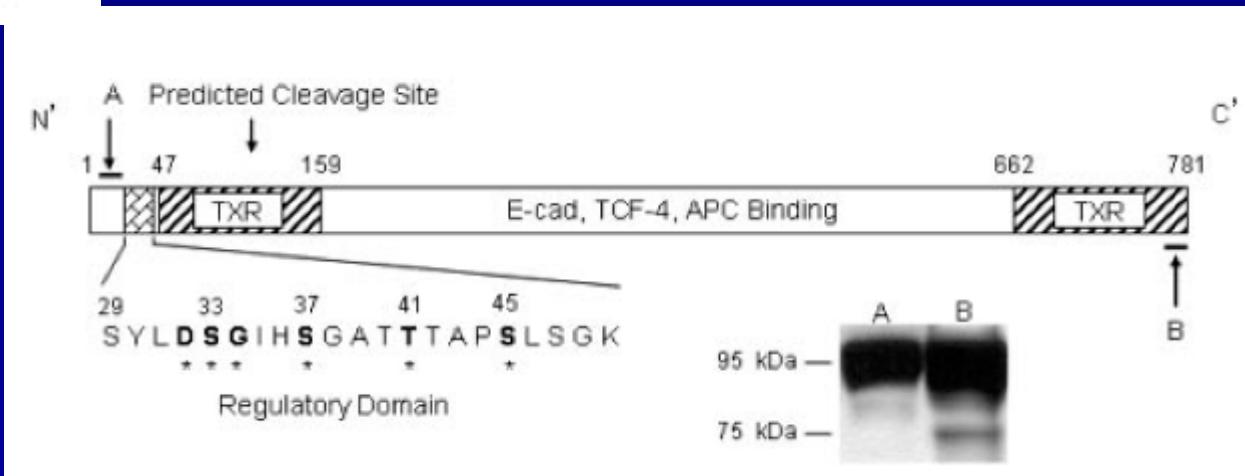
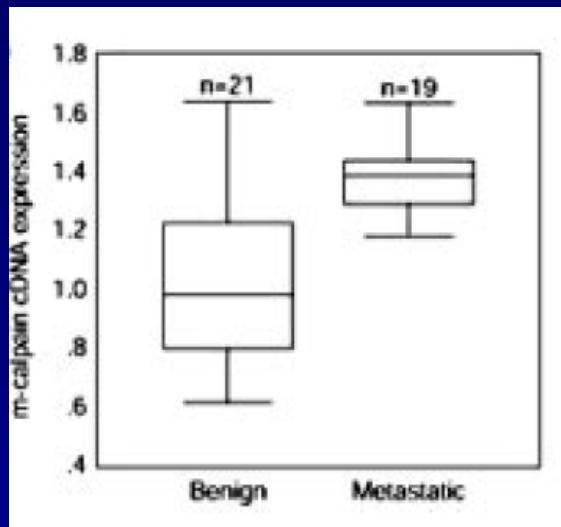
Ligand Availability

AR Interaction

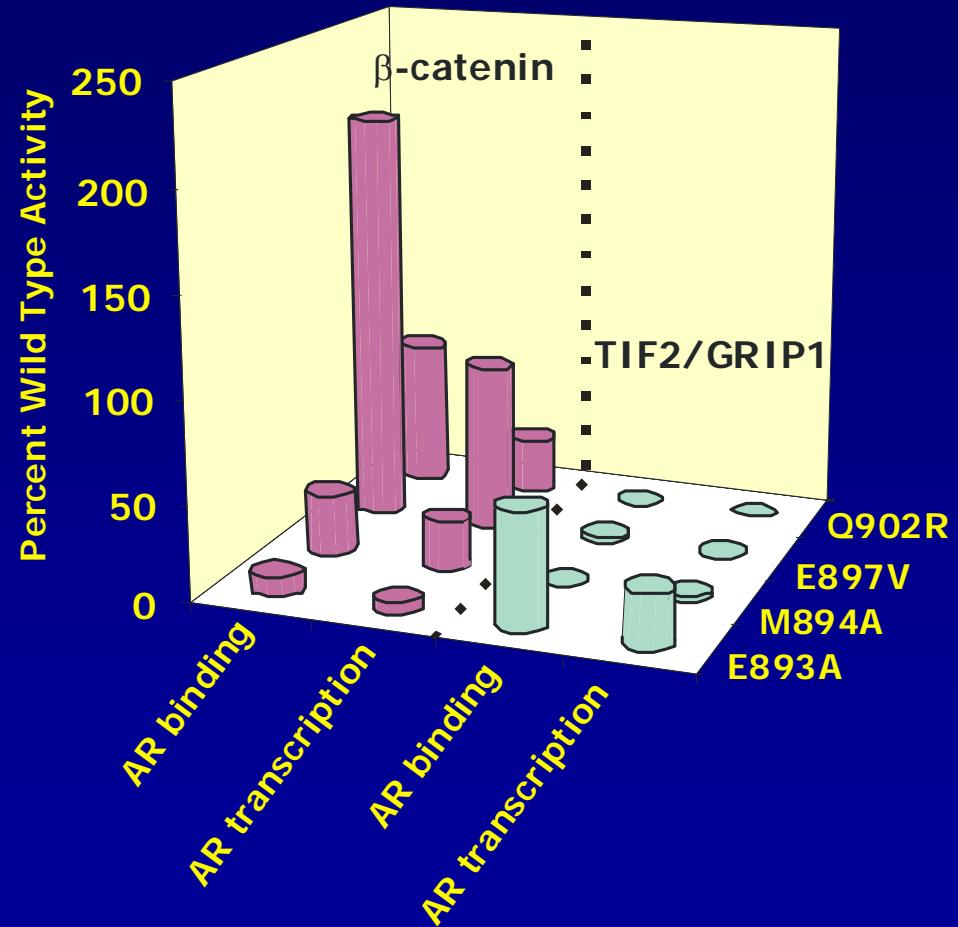
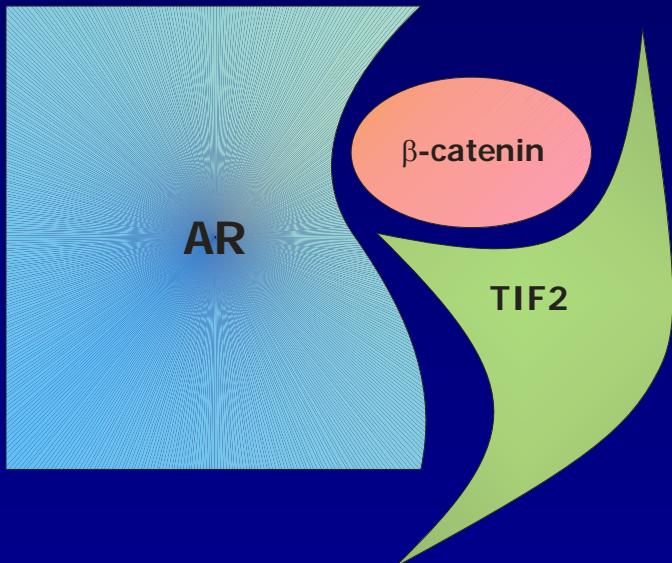
Protein Binding to LBD

1. Coactivators
2. Corepressors
3. NTD

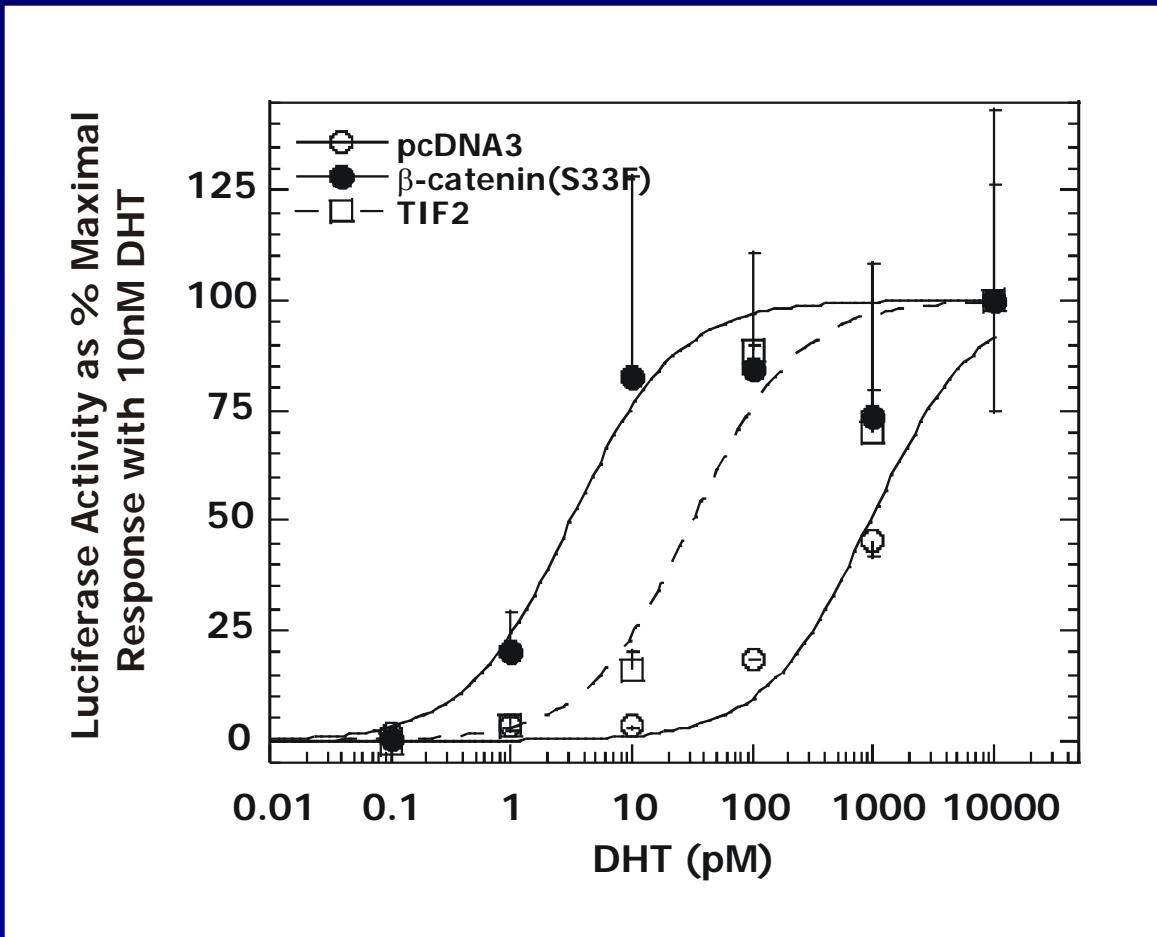
β -Catenin Truncation in Advanced Prostate Cancer



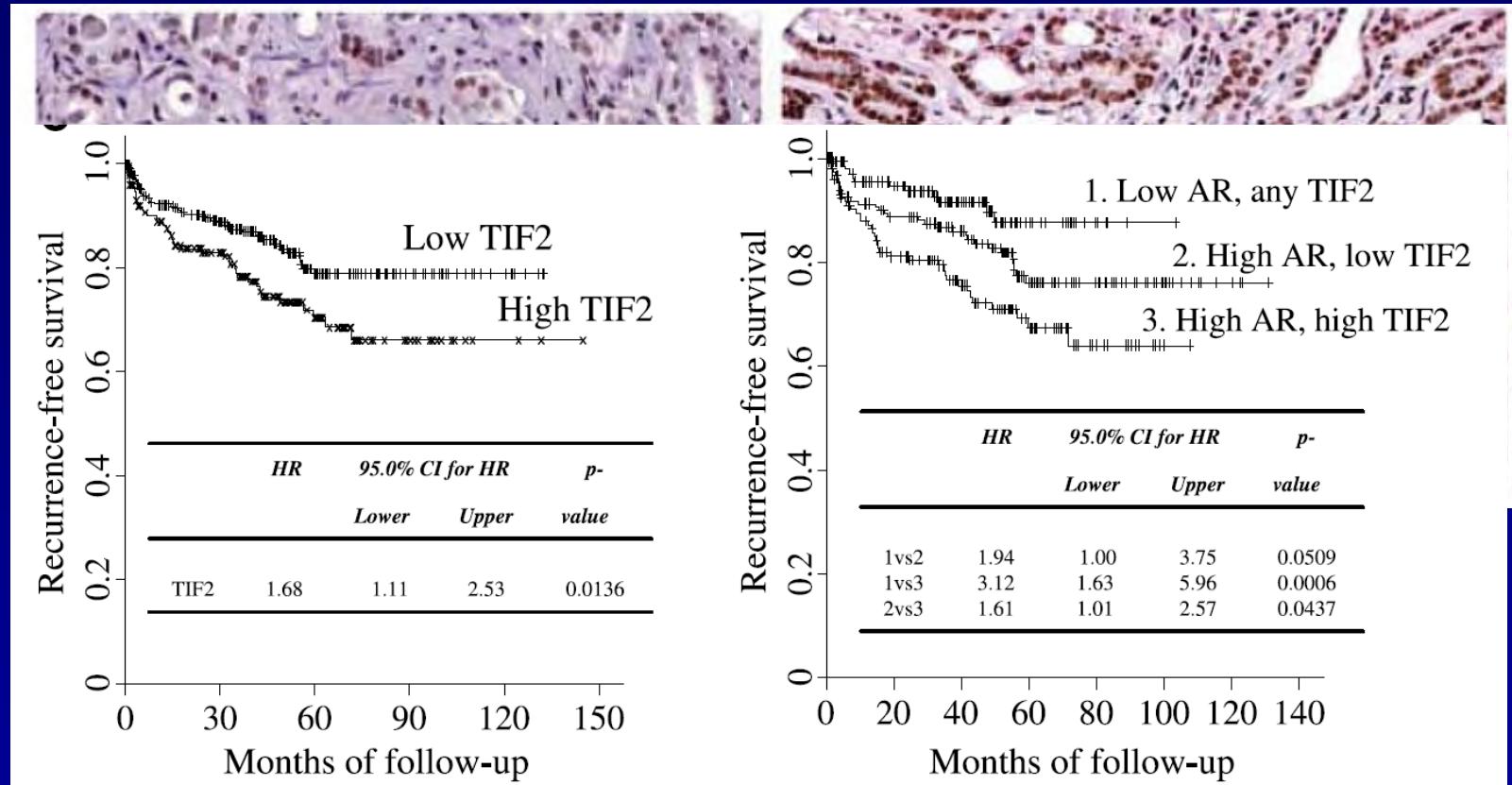
β -Catenin TIF2 and AR



AR Response to DHT



TIF-2 Expression in Prostate Cancer



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 AI PC occurs via many mechanisms.
4. Successful blockade of the receptor pathways will confer greater therapeutic control on metastatic prostate cancer.