Identification of a Clinically Relevant Androgen-Dependent
Gene Signature in Prostate Cancer

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Abstract

The androgen receptor (AR) is the principal target for treatment of non–organ-confined prostate cancer (PCa). Androgen deprivation therapies (ADT) directed against the AR ligand–binding domain do not fully inhibit androgen-dependent signaling critical for PCa progression. Thus, information that could direct the development of more effective ADTs is desired. Systems and bioinformatics approaches suggest that considerable variation exists in the mechanisms by which AR regulates expression of effector genes, pointing to a role for secondary transcription factors. A combination of microarray and in silico analyses led us to identify a 158-gene signature that relies on AR along with the transcription factor SRF (serum response factor), representing less than 6% of androgen-dependent genes. This AR-SRF signature is sufficient to distinguish microdissected benign and malignant prostate samples, and it correlates with the presence of aggressive disease and poor outcome. The AR-SRF signature described here associates more strongly with biochemical failure than other AR target gene signatures of similar size. Furthermore, it is enriched in malignant versus benign prostate tissues, compared with other signatures. To our knowledge, this profile represents the first demonstration of a distinct mechanism of androgen action with clinical relevance in PCa, offering a possible rationale to develop novel and more effective forms of ADT. Cancer Res; 71(5); 1978–88. ©2011 AACR.

Introduction

Prostate cancer (PCa) remains the most frequently diagnosed cancer of an internal organ and the second leading cause of cancer-related death in men (1). One in 6 American men will be confronted with PCa, which makes this disease a significant health problem.

Localized PCa is treated with surgical or radiation therapies that have a curative intent (2). For patients with locally advanced PCa, those with metastatic disease, or whose cancer recurs after initial treatment, treatment options are limited to prevent disease progression. As PCa progression depends on androgen signaling, the androgen receptor (AR) is the principal target for treating non–organ-confined disease. Traditional androgen deprivation therapy (ADT) interferes with the systemic production of androgens and/or involves administration of antiandrogens (3). Initially, ADT prevents tumor growth and leads to a favorable clinical response. Unfortunately, ADT does not eradicate disease and eventually PCa recurs as castration-recurrent PCa (CRPC), which is invariably lethal. Intriguingly, the emergence of CRPC is due, at least in part, to inappropriate activation of the AR (4–7). Recent therapeutic approaches that are tailored specifically to target aberrant AR action in CRPC lead to antitumor activity in a substantial subset of patients (8–10). However, these effects are partial and temporary, which indicates that AR activity is not inhibited fully by current ADTs (11, 12). Developing more effective means to interfere with AR signaling requires an in-depth understanding of the molecular mechanism(s) by which AR governs clinically relevant events in PCa.

The AR is a ligand-dependent transcription factor belonging to the nuclear receptor superfamily. On androgen binding, the AR translocates from the cytoplasm to the nucleus, binds as a dimer to “androgen response elements” (ARE) in the regulatory regions of target genes, and recruits a productive transcriptional complex (reviewed in ref. 13). Considerable efforts have been directed toward identifying AR-dependent genes which contribute to PCa progression. Large-scale gene expression profiling studies in model systems have identified dozens of androgen-regulated genes (14–19). Many of these have been proposed to play a role in differentiated cell function, cell proliferation, and cell survival (20). Nonetheless, correlation of androgen-responsive mRNA expression profiles obtained from in vitro model systems with transcriptomes derived from clinical PCa specimens has been challenging. To date, specific genes and transcriptional programs that are
critical for PCa cell proliferation and metastasis and that are regulated by androgens remain largely elusive. These difficulties may reflect, in part, that attempts at classification have encompassed all androgen-dependent gene expression, which assumed little or no variation in the manner by which AR controls transcription of target genes. Recent systems approaches, however, suggest variability in the composition of the AR transcriptional complex at regulatory sites in effector genes, indicate that not all androgen-dependent genes are subject to direct ARE-driven mechanisms of regulation and provide evidence that AR signaling in PCa cells relies on secondary transcription factors (TF; refs. 21–25). Some TFs interact directly with the AR to affect its ability to bind to AREs and compete for coregulators or to cooperate in the transcription of AR target genes (13). Other TFs mediate critical effects on PCa cells by mechanisms that do not rely on physical interaction with the AR but involve androgen regulation of their activities (26, 27). These ‘indirect’ mechanisms of androgen action convey androgen responsiveness to target genes that do not contain AREs and can induce coordinated responses of genes and/or cells. Identification of TFs whose transcriptional program contributes to the development of aggressive disease may, therefore, open novel avenues to target clinically relevant androgen signaling in PCa.

We recently identified a novel indirect mechanism of androgen action in which effects of androgens on PCa cells are mediated by serum response factor (SRF; ref. 28), which is a MADS box-containing TF that was originally identified by its ability to convey the effects of serum to immediate early response genes (29). Since then, SRF has also been shown to control expression of genes involved in the organization of the cytoskeleton and to be critical for embryonic development, experimental metastasis, and angiogenesis (30–33). Androgen exposure induces expression of four-and-a-half-LIM domain protein 2 (FHL2) in a manner that is AR-dependent but independent of any AREs in the FHL2 gene. Instead, androgens stimulate expression of FHL2 through action of SRF on its consensus binding site (CARG box) in the FHL2 promoter (28). In view of these cellular and physiologic roles, it is tempting to speculate that androgen control over the SRF transcriptional program may have important implications for PCa progression.

Materials and Methods

Cell culture

LNCaP and VCaP cells were purchased from American Type Culture Collection and were maintained as described (28, 34). Behavior of cells was monitored throughout the study by assessing overall androgen responsiveness, morphology, and transcriptional regulation, which were consistent with previous observations for these cell lines.

siRNA transfection

LNCaP and VCaP cells were seeded in 60-mm dishes at a density of $5.5 \times 10^5$ or $1 \times 10^6$ cells per dish, respectively, in antibiotic-free medium. The next day, cells were transfected with siGENOME SMARTpool siRNA targeting SRF (Dharmacon) or a custom-made control SMARTpool targeting luciferase (Luc condition) using Lipofectamine 2000 (Invitrogen) following the manufacturer’s instructions. Forty-two hours after transfection, cells were treated with 5 mmol/L R1881 or ethanol vehicle. Three biological triplicates were included per treatment group. Forty-eight hours later, cells were harvested in TRIzol reagent (Invitrogen).

Cell line RNA preparation and microarray analysis

RNA was isolated from cells with TRIzol (Invitrogen), purified on RNeasy columns (Qiagen), and checked for integrity by Agilent testing. cDNA was generated and hybridized to Human Genome U133 Plus 2.0 Arrays (Affymetrix) according to the manufacturer’s instructions at the Mayo Clinic Advanced Genomics Technology Microarray Shared Resource core facility. The microarray data sets have been deposited in Gene Expression Omnibus under accession number GSE22606. A detailed description of the microarray data analysis can be found in Supplementary Data.

Patient material and microarray data analysis

A detailed description of the patient materials and microarray data set analysis is included in Supplementary Data.

Ingenuity Pathway Analysis

Ingenuity Pathway Analysis (IPA) was done using the 158 SRF-dependent androgen-responsive gene signature as a focus gene set and Ingenuity curated knowledge base as a reference.

Real-time reverse transcriptase PCR

cDNA was prepared and real-time reverse transcriptase (RT)-PCR was done as before (28). Primers targeting human FHL2, SRF, prostate-specific antigen (PSA), AR, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) have been described (28). Primer sequences used to analyze SRF-dependent gene expression are listed in Supplementary Table S1.

Results

Identification of an SRF-dependent androgen-responsive gene expression profile

To identify and characterize genes and cellular processes that are androgen-regulated in an SRF-dependent manner in PCa, Affymetrix HG-U133 Plus 2.0 GeneChip array analysis was done starting from RNA obtained from LNCaP cells in which androgen stimulation was combined with siRNA-mediated SRF silencing. Biological triplicates were processed for each treatment group. The efficacy of the SRF knockout and its effect on the expression of the positive control gene FHL2 were verified by real-time RT-PCR and are shown in Supplementary Figure S1. Microarray data analysis focused on identifying genes which, for each replicate, show at least 2-fold androgen-dependent changes in expression, rely entirely on the presence of SRF for androgen-dependence, and show basal expression that is not affected by loss of SRF. This approach detected 158 unique genes (178 probe sets), 113 (131 probe sets) and 45 (47 probe sets) of which were upregulated and downregulated, respectively, in an SRF-dependent manner following androgen...
Overall androgen- and SRF-responsiveness of this expression profile, which represents less than 6% of androgen-regulated genes (Fig. 1B), was validated by real-time RT-PCR (Fig. 2) and immunoblotting (Supplementary Fig. S2). AR involvement was further confirmed using AR-specific siRNA and the AR antagonist bicalutamide and by obtaining dose–response curves with the natural ligand dihydrotestosterone (DHT) and the
Figure 2. Real-time RT-PCR validation of microarray results. LNCaP cells were transfected with siRNAs targeting SRF or nonspecific control siRNAs (c siRNA) as described. SRF-dependency and androgen-responsiveness of genes identified by the microarray approach were evaluated by real-time RT-PCR, using the primer pairs listed in Supplementary Table S1. Target gene mRNA levels were normalized with the values obtained from GAPDH expression and are expressed as relative expression values, taking the value obtained from one of the vehicle-treated, control-transfected conditions as 1. Columns, means of values obtained from 3 independent biological replicates; bars, SEM values. SLITRK6, SLIT and NTRK-like family, member 6; SSR3, signal sequence receptor, as relative expression values, taking the value obtained from one of the vehicle-treated, control-transfected conditions as 1. Columns, means of values obtained from GAPDH expression and are expressed as described.

SRF-dependent androgen-responsive gene functions are relevant to cancer biology

Although some of the genes belonging to the newly identified 158-gene signature had been reported to be androgen-regulated (14, 18, 35), the majority of these genes have not been described previously as targets for androgen action in PCa cells. Interestingly, genes belonging to the SRF- and AR-dependent gene profile fulfill roles in processes as diverse as cell division (e.g., CDC25A), lipid synthesis (e.g., DGAT2), chemokine activity (e.g., CCL8), immediate early response (e.g., IER5), and extracellular matrix binding (e.g., CYR61), all of which are relevant to cancer cell biology. Moreover, IPA primarily assigned functions in cell cycle, cell morphology, and cellular movement, development, assembly, and organization to this gene signature. IPA indicated a significant association between this 158-gene expression profile and cancer and genetic disorders. Reproductive, respiratory, and cardiovascular diseases were also associated with this gene signature (Fig. 4A). These observations suggest that the novel mechanism of androgen action may play a critical role in PCa.

SRF-dependent androgen-responsive gene signature is sufficient to separate benign and malignant prostate tissues

To validate the relevance of the SRF-dependent androgen-responsive gene signature for the clinical situation, the expression of the 178 probe sets was analyzed against mRNA expression data sets derived from human prostate specimens that were generated before (36). Prostate tissues included in this profiling study consist of normal epithelium (n = 17), benign prostatic hyperplasia (BPH; n = 10), prostatic intraepithelial neoplasia (PIN; n = 4), PCas of Gleason pattern (GP) 3 (n = 31), GP4 (n = 20), GP5 (n = 10), and lymph node (LN) metastases (n = 7). An increase in GPs corresponds to a poorer prognosis, as does the presence of LN metastases at the time of prostatectomy (37, 38). RNA was obtained from prostate tissue that was isolated by laser capture microdissection from radical prostatectomy specimens from patients with no preoperative treatment as described (36) and was analyzed using U133 Plus 2.0 microarrays. For initial analysis, normal epithelium and BPH samples were designated as noncancer cases, whereas PIN lesions and GP3, GP4, GP5, and LN were considered cancer cases. Unsupervised clustering of these 99 samples by the 178-probe set signature alone generated 2 major clusters, which strikingly separated “normal” versus “malignant” prostate tissues. One case of PIN, considered a premalignant lesion to PCa, was the only exception and clustered with “normal” prostate tissue (Fig. 4B). A t-test
comparison revealed that this separation is due to differential expression of 78 probe sets between "normal" and "cancerous" prostate samples (Fig. 4C; Supplementary Table S4). Subsequent analyses did not include BPH samples. Pairwise comparison between normal epithelial prostate samples and PIN, GP3, GP4, GP5, and LN specimens, respectively, showed differential expression of 28, 69, 71, 56, and 67 probes sets. Notably, altered expression of some probe sets was unique to a particular tissue type whereas changes in expression of others were common to 2 or more tissue types (Fig. 5; Supplementary
Table S5). As shown in Figure 5, a core of 20 probe sets was found to be consistently deregulated with altered expression in GP3, GP4, GP5, and LN tissues compared with normal prostate epithelium. For validation purposes, the expression patterns of these 20 probe sets were examined in prostate tissue mRNA profiles available through the Oncomine database. This search indicated that the 20 core probe sets are consistently differentially expressed between normal and malignant prostate samples in 12 independent profiling studies which had used different tissue procurement methods, RNA extraction procedures, and microarray platforms (Supplementary Table S6). In contrast, similar analyses for random sets of 20 direct AR target genes indicate that 35% to 40% of gene expression is inconsistently altered between malignant and benign prostate samples in different data sets (data not shown). These findings confirm the significance of the SRF- and AR-dependent core gene signature in PCa and corroborate the validity of our microarray experiment. Literature review provided additional evidence to support differential expression of target genes at the RNA and protein level (e.g., 39–43). Moreover, comparisons between paired normal prostate epithelium and localized PCAs (n = 9) and between matched localized cancer and LN metastases (n = 4) yielded 52 and 23 differentially expressed probe sets (paired t test, P < 0.05), respectively (Supplementary Tables S7 and S8).

**SRF-dependent androgen-responsive gene signature correlates with aggressive disease**

The relevance of the SRF-dependent androgen-responsive gene signature to PCa progression was assessed by exploring its correlation with GP number and metastatic status. Application of a linear regression model showed that expression of 67 transcripts is positively (n = 17) or negatively (n = 50) associated with aggressive disease (P < 0.05; Fig. 6; Supplementary Table S9). These results suggest that this gene signature may also be indicative of clinical outcome after...
mRNA expression was derived from 131 localized primary prostate tumors (27 of which experienced biochemical recurrence), 19 metastatic prostate tumors, and 29 normal prostate specimens (Supplementary Table S13). Tissues were macro-dissected, mRNA profiling was done without amplification and Affymetrix Human Exon 1.0 ST Arrays were used. The 178 probe sets correspond to 142 annotated and unique genes, 139 of which mapped to the Exon Array data set by gene symbol. Survival analysis was done for the 139 genes by the Cox proportional hazard model in which PSA recurrence was the end point. Eighteen genes were identified that are associated significantly with biochemical failure (Supplementary Table S14). The overlap with Supplementary Table S11 consists of 1 gene, DGAT2, which is positively associated with biochemical recurrence. As limited overlap for outcome markers between microarray-based profiling studies is common (e.g., ref. 45), gene set analysis was conducted for the 139 gene set as a whole, which showed that it is significantly associated with biochemical failure ($P = 0.02$; Table 1). Next, gene set analysis was performed for both the 139 SRF- and AR-dependent genes and 10 randomly selected sets of 142 AR-dependent genes ($142 = \text{same number of unique and annotated genes}$), using LS/KS permutation statistics. These 2 tests find gene sets that have more genes correlated with survival times (here time to PSA failure) than expected by chance through 100,000 permutations. Table 1 shows that the SRF- and AR-dependent gene set ranks number 1 in both tests with permutation $P$ values of 0.02 and 0.08, respectively. These results indicate that the SRF- and AR-dependent gene set is associated more significantly with PSA recurrence than sets of AR target genes of similar sizes and that the association with biochemical recurrence is less likely a chance finding. Gene set analysis of totally random gene sets of similar size also failed to show a significant association with biochemical failure (Supplementary Table S15). Evaluation of gene set enrichment between PcA and normal prostate tissues indicated that all 10 random AR target gene sets are significantly enriched in normal tissues (false discovery rate, (FDR) $< 0.25$, negative enrichment scores), which is consistent with previous observations (46). In contrast, the SRF- and AR-dependent gene set is enriched in cancer tissue ($FDR = 0.12$, positive enrichment score; data not shown). Moreover, evaluation of 10 totally random gene sets found one set to be enriched in normal prostate tissues whereas the remaining 9 gene sets were not significantly enriched in either benign or malignant prostate tissue (data not shown).

Discussion

Here, we report the isolation of, to our knowledge, the first discrete androgen-dependent signaling pathway that is relevant to the clinical situation in PCa. Despite the dependence of PCa cells on AR signaling (3–12), previous attempts to identify genes that are critical for disease progression and metastasis and are under androgen control have been largely unsuccessful. The difficulties in validating the androgen-responsive transcriptomes derived from in vitro model systems using expression profiles from clinical samples may in part be due to

Figure 5. Differentially expressed SRF-dependent androgen-responsive probe sets in normal epithelium, localized cancer, and metastatic cancer. Pairwise comparisons were made between PIN, GP3, GP4, GP5, and LN metastases and normal epithelium, respectively, using the limma package implemented in R to identify differentially expressed probe sets. Expression patterns of probe sets that are common or unique in GP3, GP4, GP5, and LN metastatic tissues are summarized in a 4-way Venn diagram. A detailed description of probe set tissue distribution is listed in Supplementary Table S5.
the use of different platforms and variations in RNA procurement and processing protocols. More likely, the analysis was hampered by the inherent assumptions that all androgen regulation of AR target genes occurs via a similar transcriptional mechanism and that every gene found to be subject to androgen regulation in model systems also plays a significant role in the clinical setting. Efforts to sort gene expression profiling data on the basis of the extent, direction, and kinetics of androgen regulation have isolated distinct clusters of genes (16, 18, 19) but do not allow for correlation between cell-based models and clinical specimens.

We reasoned that codependency of the AR on secondary TFs, which are increasingly recognized to convey selectivity to the regulation of subsets of AR target genes (21–25), can be exploited to delineate distinct mechanisms of androgen action in PCa and that thoughtful selection of a candidate TF with potentially important roles in PCa cell biology can identify gene signatures that contribute to disease progression. To test this hypothesis, a microarray-based approach was undertaken to identify the spectrum of genes that rely on SRF, a versatile TF which functions in the immediate early response and the organization of the cytoskeleton (29, 30), to achieve full

Figure 6. Expression of SRF-dependent androgen-responsive probe sets correlates with aggressive disease. A linear regression model assesses the correlation of probe set expression with GP number and presence of LN metastatic disease. Probe sets that correlate significantly ($P < 0.05$) are plotted in a stacked line graph. The $y$-axis represents a log 2 scale. Probe set expression is plotted as relative expression levels. A, probe sets that correlate positively with tumor aggressiveness. B, probe sets that correlate negatively with aggressiveness of disease. Probe sets that associate with aggressive disease are listed in Supplementary Table S9.
androgen responsiveness. This approach revealed a gene profile that corresponds to less than 6% of the androgen-dependent transcriptome in the PCa cell line LNCaP. Strikingly, even without prior knowledge of levels of expression for these genes or further manipulation of the data, this gene signature could successfully separate benign from malignant prostate tissues. Moreover, the gene expression profile correlated with aggressive disease and poor postoperative outcome. Validation studies using an independent PCa profiling study with suitable tissue and RNA procurement methods, complete clinical annotation, and reliable follow-up data (44) confirmed the association of the SRF- and AR-dependent gene signature with biochemical recurrence. Moreover, fewer genes that are both androgen-regulated and harbor genomic AR-binding sites (Supplementary Table S12) correlate with PSA failure. In stark contrast with the SRF- and AR-dependent gene signature, random sets of AR target genes are significantly enriched in normal rather than malignant prostate tissues.

The overall design of the experiment, particularly the concentration of androgens used and the timing of the different steps, aimed to avoid skewing the results toward effects that are merely attributable to changes in cell proliferation and survival. In keeping with this premise, the resulting 158-gene signature displayed a striking enrichment for genes that function in cell adhesion, cell–cell communication, and cell–cell interaction. IPA associated this profile with development and function of the cardiovascular, connective tissue, and skeletal and smooth muscle systems (data not shown). Independent Gene Ontology Analysis of the probe sets which are expressed differentially between benign and malignant prostate tissues confirmed involvement in musculature and central nervous system (data not shown), both systems in which SRF and AR have been shown to fulfill indispensable roles (47, 48). At the cellular and molecular levels, IPA and Gene Ontology Analysis point toward a disproportional contribution (~30%) of genes with actin cytoskeleton–related functions to the aberrantly expressed SRF- and androgen-dependent gene signature. In addition to the differentially expressed genes that encode components and regulators of the cytoskeleton (e.g., ACTA2, CNN2), many are associated with cellular events that rely heavily on the cell’s actin cytoskeleton such as chemotaxis (e.g., CYR61), cell division (e.g., CDC25A), formation of cellular protrusions (e.g., WWTR1), and endosomal and vacuolar transport (e.g., VPS26B). (Re)organization of the cytoskeleton is vital for cancer cells to invade surrounding tissue and migrate and generate metastatic lesions and may underlie the correlation of the SRF-dependent mechanism of androgen action with more aggressive disease. It should be noted that the 158-gene signature also contains genes involved in lipid synthesis, transcription, and protein synthesis, which have been shown to be important in PCa, and several genes involved in ion homeostasis. Ion channels have been implicated in cancer cell invasive behavior and may be viable pharmacologic targets (49).

Apart from its clinical significance, this novel mechanism of androgen action represents a different means of SRF activation at the molecular level. According to its classical model of action, SRF is bound constitutively to CARG boxes in target genes, where its activity is regulated by signaling cascades and/or by interaction with one or more of its cofactors (50). Induction of SRF activity by extracellular stimuli typically results in rapid changes in the levels of its target genes. In contrast, androgen responsiveness of CARG box containing genes for which SRF binding has been confirmed by chromatin immunoprecipitation (e.g., COG3, SDK1; data not shown) requires 8 to 16 hours of androgen treatment. The need for even longer androgen exposure for some genes (e.g., CCL8) most likely reflects indirect regulation by SRF. Ongoing work in our laboratory indicates that androgens affect the activity but not expression levels, cellular localization, or CARG box–binding potential of SRF. Moreover, SRF is not differentially expressed between benign and malignant prostate specimens (data not shown). These observations suggest AR- and ARE-dependent modulation of regulators of SRF activity.

### Table 1. Gene set analysis using LS/KS permutation statistics for evaluation of the association of gene expression with biochemical failure

<table>
<thead>
<tr>
<th>Gene set</th>
<th>Number of genes</th>
<th>LS permutation P value</th>
<th>KS permutation P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-SRF focus set</td>
<td>139</td>
<td>0.02882</td>
<td>0.07976</td>
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<tr>
<td>AR random set 8</td>
<td>142</td>
<td>0.06031</td>
<td>0.54397</td>
</tr>
<tr>
<td>AR random set 6</td>
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<td>0.07680</td>
<td>0.76182</td>
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<tr>
<td>AR random set 1</td>
<td>142</td>
<td>0.13604</td>
<td>0.74264</td>
</tr>
<tr>
<td>AR random set 2</td>
<td>142</td>
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<td>0.72544</td>
</tr>
<tr>
<td>AR random set 10</td>
<td>142</td>
<td>0.18899</td>
<td>0.90306</td>
</tr>
<tr>
<td>AR random set 5</td>
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<td>0.21640</td>
<td>0.94449</td>
</tr>
<tr>
<td>AR random set 9</td>
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<td>0.95764</td>
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<tr>
<td>AR random set 3</td>
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</tr>
<tr>
<td>AR random set 7</td>
<td>142</td>
<td>0.67887</td>
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Clinically Relevant Mechanism of Androgen Action in Prostate Cancer

Taken together, the data presented here provide a proof-of-principle for the existence of discrete modes of AR action with clinical relevance. Thus, novel ADT approaches may be developed that are geared selectively toward the molecular events by which AR controls PCA progression, metastasis, and the lethal phenotype.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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5. Attard G, Reid AH, Olmos D, de Bono JS. Antitumor activity with clinical relevance. Thus, novel ADT approaches may be developed that are geared selectively toward the molecular events by which AR controls PCA progression, metastasis, and the lethal phenotype.

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Disclosure of Potential Conflicts of Interest

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