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Mechanisms of prostate cancer progression to androgen independence☆

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Prostate cancer is a major health problem in the United States and worldwide. In 2007, more than 27,000 men were estimated to have died from prostate cancer in the United States alone. Although important advances have been made in the diagnosis and treatment of prostate cancer, therapies focused on the removal or inhibition of androgen action remain the most important components of therapy for individuals with metastatic disease. Despite the application of such modalities, the vast majority of patients with metastatic disease progress with a median survival of less than 2 years. A number of different mechanisms have been identified that may potentially contribute to the progression of prostate cancer. These insights suggest that signaling via the androgen receptor (AR) – either via alternate signaling pathways impinging on the AR or through the in situ formation of androgens within progressive tumors – is an important contributor to such progressive disease. It is anticipated that such mechanistic insights will lead to the development of useful new therapies in the future.

Key words: prostate; cancer; androgen; androgen receptor; mutations; steroidogenesis; signalling.

Prostate cancer is a major health problem in the United States and worldwide. In 2007, in the United States alone, the American Cancer Society has estimated that more than 218,000 new cases of prostate cancer were diagnosed, while more than 27,000 men died of the disease.[1,2] This problem is even more substantial when viewed from a global perspective, with prostate cancer accounting for more than 220,000 deaths worldwide annually.[3]

Significant changes have occurred in the way that prostate cancer is diagnosed and treated. Advances employing the use of serum markers have resulted in a shift toward

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more localized forms of the disease at the time of diagnosis. The development of more selective and sparing surgical techniques has substantially reduced patient morbidity and minimized patient mortality. Major advances have been made in hormonal and also to some extent in chemotherapeutic therapies. Despite these advances, patients with metastatic disease progress to the point where their tumors no longer respond to hormonal – or non-hormonal – based therapies. Such cancers do not respond to available modalities and have limited survival.[4–6]

In the last two decades, an increased effort has been focused on understanding the biology of prostate diseases, particularly prostate cancer. As a result of these efforts, an immense body of work has emerged regarding the genetics and biology of prostate cancer development, metastasis, and progression. The present manuscript is focused principally on reviewing insights into the mechanisms by which prostate cancer progresses to exhibit androgen-independent growth.[a]

THE ANDROGEN RECEPTOR, THE NUCLEAR RECEPTOR FAMILY, AND MECHANISMS CONTROLLING ANDROGEN ACTION

The nuclear receptor family is a gene family that contains 48 members in the human genome.[7] Members of this protein family were originally identified on the basis of characteristically conserved protein motifs and overall protein sequence similarities.[8,9] Each protein within this family is believed to serve as a regulator of gene expression. This group contains members that appear to display constitutive activities, as well as those that are regulated by specific ligands, including the androgen receptor.

The androgen receptor (AR) is a typical member of the nuclear receptor family (Figure 1). Like other members of this family, it contains specific domains that mediate the binding of high affinity ligands (ligand binding domain, LBD), and modulate its interaction with specific target DNA sequences within the genome (DNA-binding domain, DBD) (Figure 1). The androgen receptor is one of the larger members of the nuclear receptor family, with an amino terminus that comprises nearly half the coding sequence of the receptor protein. Of note, although a number of studies have demonstrated the importance of this amino terminal segment in the capacity of the receptor protein to regulate gene transcription, the mechanism by which the amino terminus contributes to gene regulation remains unclear.[11–13] Several investigators have published work suggesting the importance of an interaction between the amino terminus and the ligand binding domain in modulating AR activity.[14–17] A clear understanding of the nature of this interaction has been hampered by the lack of detailed structural analyses, as crystal structures have only been solved for individual DNA-binding and ligand-binding domains.

Within the amino terminus of the human AR are two repeated segments composed of repeated glutamine (glutamine repeat) and glycine (glycine repeat) residues. The length of these segments has been linked to variations in the activity of ARs containing varying length repeats.[13,18–23] While still viewed by many as controversial, such variations have been linked to important biological phenomena, including alterations in fertility[24], serum

[a] The terms androgen-independent, hormone-independent, castration-resistant, and hormone-refractory have all been used by different authors to describe prostate tumors that progress despite the application of available surgical or medical castration and anti-androgen therapy. None of these terms is satisfactory, as it is plausible that more than one mechanism may contribute to tumor growth. Despite these very real limitations, the term 'androgen-independent' is used in this review.

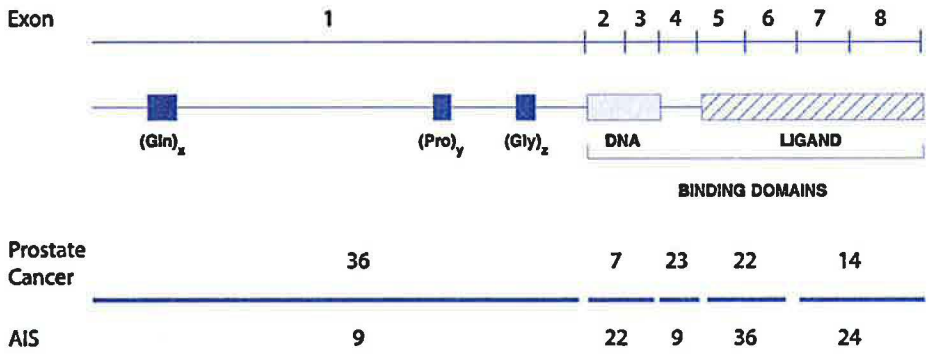

Figure 1. A schematic of the human androgen receptor (AR). Top: the AR is a typical member of the nuclear receptor family and is encoded by eight exons. It comprises segments that specifically recognize target DNA sequences (DNA-binding domain, DBD) and that bind specific ligands, such as testosterone and 5α-dihydrotestosterone (ligand-binding domain, LBD).The AR possess a large amino terminus that comprises half of the open reading frame and contains repeated elements composed of repeated glutamine (Gln), praline (Pro), and glycine (Gly) residues. These segments are of different lengths in different individuals, and contain approximately 23, 8, and 23 residues in the respective regions. Bottom: the frequency of substitution mutation in the AR open reading frame is different in prostate cancer and syndromes of androgen insensitivity (AIS). For the purpose of this figure, the%age of total mutations within the amino terminus, DBD, hinge, and LBD are shown. Mutations within the amino terminus and hinge region (36 and 23%, respectively) have been identified more frequently in prostate cancer. This is representation displays the distribution of 75 prostate cancer and 167 AIS AR mutations derived from the Androgen Receptor Database.[10] This presentation does not take into account that some mutations are repeated within each group.

testosterone levels[25], and the clinical behavior of prostate cancers.[26] The recent creation of mice engineered to express androgen receptors with differing numbers of glutamine repeats offers the possibility of examining these phenomena in greater detail.[27]

In vertebrates, testosterone and 5α-dihydrotestosterone (DHT) are the principal androgens. Testosterone is the principal circulating androgen secreted by the testis and its synthesis is regulated by the action of luteinizing hormone (LH) on the Leydig cells of the testis. Although small quantities of DHT are secreted by the testes, much of the circulating DHT is formed in peripheral tissues by the action of two 5α-reductase enzymes. Of note, distinctive pathways can give rise to androgens via selective steroidogenic pathways in specific tissues (Figure 2). Both testosterone and DHT bind to the same androgen receptor protein with high affinity. In many assays, DHT is a somewhat more potent androgen reflecting the higher affinity of the AR for DHT and the longer half life of the AR-DHT complex compared to the AR-testosterone complex.[28]

The mechanisms by which nuclear receptors regulate genes transcription have been the subject of intense scrutiny for decades. Considerable progress has been made in the last twenty years that have contributed considerable detail to our understanding of the mechanisms by which these transcription factors regulate the activity of target genes. These insights have occurred in several waves, beginning in the early 1980s with the cloning of cDNAs encoding members of the nuclear receptor family, and progressing through the last twenty years as additional modulators and pathways have been identified.

Important efforts have centered on the definition of the intermediary factors affecting interactions between components of the general transcription machinery and

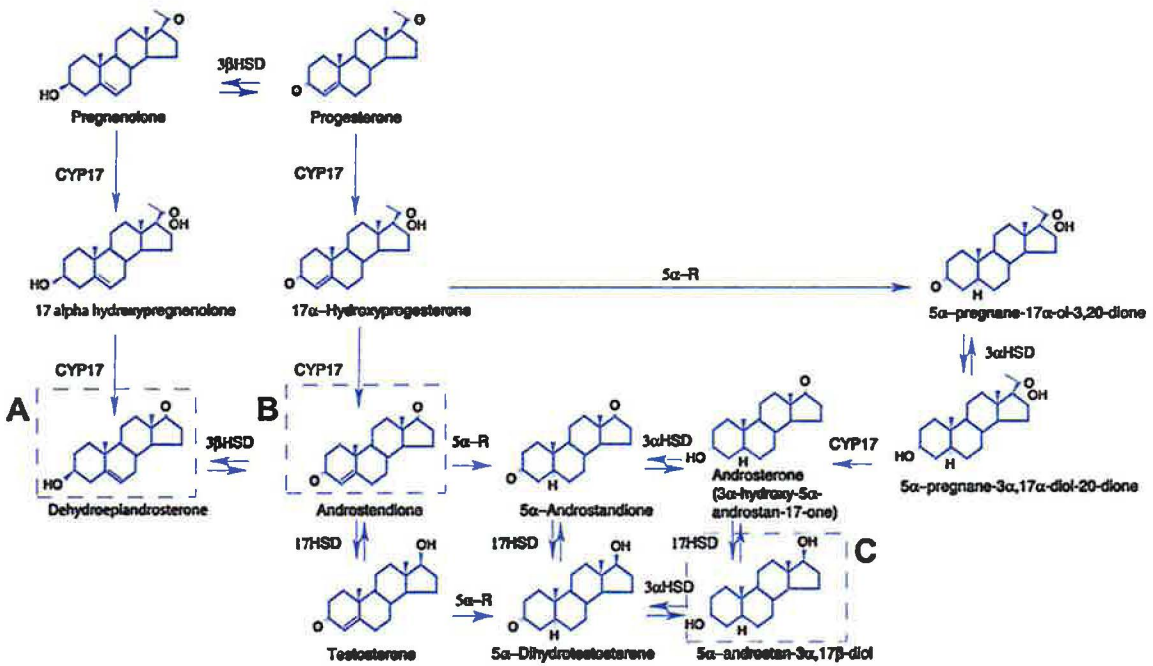

Figure 2. Interrelations and interconversions among androgens. Distinct pathways exist by which steroid precursors are converted to the active androgens, testosterone, and 5α-dihydrotestosterone. In the testis, the immediate precursor is androstenedione (box B). In the adrenal, conversion proceeds through the intermediate dehydroepiandrosterone. In the Tammar wallaby and the immature murine ovary, androgens are synthesized via 5α-androstan-3α,17β-diol. Potentially, any or all of these pathways might be the source of androgen synthesis during prostate cancer progression. These interconversions are catalyzed by families of enzymes: 17-hydroxysteroid dehydrogenases, 3α- and 3β-steroid dehydrogenases, and 5α-reductases. Reversibility or irreversibility is indicated by bi- or unidirectional arrows, respectively. Notably, synthesis of androgen via each of these pathways requires the formation of a 19-carbon steroid via the action of CYP17.

nuclear receptors themselves and the roles that these proteins play in the modulation of responsive genes.[29,30] Broad groups of 'coregulator' proteins have been identified that either enhance or repress target genes, referred to collectively as 'coactivators' and 'corepressors', respectively. Each individual protein or protein complex possesses enzymatic activity which participates in the modulation of transcriptional complex stability and/or modification of the chromatin/surrounding regulated genes. In many instances, such proteins serve as coregulators for many members of the nuclear receptor family. The participation of such proteins in the regulation of AR function has been reviewed.[31–33]

It has been clear for considerable time that members of the nuclear receptor family, including the androgen receptor, regulate gene transcription in response to ligands by alterations in the conformation of the ligand-binding domain. These changes in conformation dictate the patterns of cofactor recruitment and the subsequent patterns of gene expression. The binding of agonist ligands places the ligand binding domain of the receptor protein into a conformation that facilitates the recruitment of motifs within the primary sequence of coactivators to a specific hydrophobic cleft that is formed on the surface of the ligand-bound LBD. This recruitment facilitates the entry of proteins that enhance the stability of the transcription complex at the site of regulated genes and results in the enhancement of gene activation (Figure 3).

As was first elucidated for the estrogen receptor-α, the molecular basis of conformational changes centers on the creation of the hydrophobic cleft within the agonist-bound ligand binding domain surface that permits the recruitment of coactivators, such as members of the SRC 1 family of transcriptional coactivators.[34] The binding of antagonist ligands does not permit the formation of this coactivator cleft and instead facilitates the recruitment of proteins capable of repressing gene transcription. The molecular basis of agonism and antagonism has been observed in crystal structures of several members of the nuclear receptor family. Although it is felt that similar structural changes underlie the actions of AR antagonists, to date the crystal structure of the native androgen receptor ligand binding domain has only been solved when complexed to agonist ligands.[35–40]

In some instances, attempts have been made to map the complex interactions surrounding the regulation of responsive genes following the addition of steroid hormones. These studies have demonstrated a complex pattern of protein recruitment and dismissal from the regulatory elements within and adjacent to regulatory elements.[41–43] These changing patterns of promoter and enhancer occupancy have been associated with changes in the methylation, acetylation, SUMOylation, ubiquitination, and phosphorylation of the chromatin surrounding the regulated gene. These changes in the posttranslational modification of the chromatin are thought to mediate the state of the chromatin, permitting access to the transcription machinery and serving as a histone code.[44] Additional effects are thought to be mediated by the posttranslational modification of transcriptional machinery components themselves. Although this pattern has not been described in detail in many systems, it is anticipated that similar patterns of regulation occur at other regulated genes as well, including the AR. Importantly, it appears that patterns and gene regulation occur more broadly within regulated genes than anticipated from this study of specific model genes.[45,46]

Just as pathways have been defined with respect to gene activation by agonist ligands, similar pathways have been identified that mediate the actions of antagonists of the androgen receptor and other nuclear receptors.[47–49] The binding of androgen receptor antagonists to the ligand binding domain places the receptor into a conformation inconsistent with the recruitment of androgen receptor coactivators, and instead

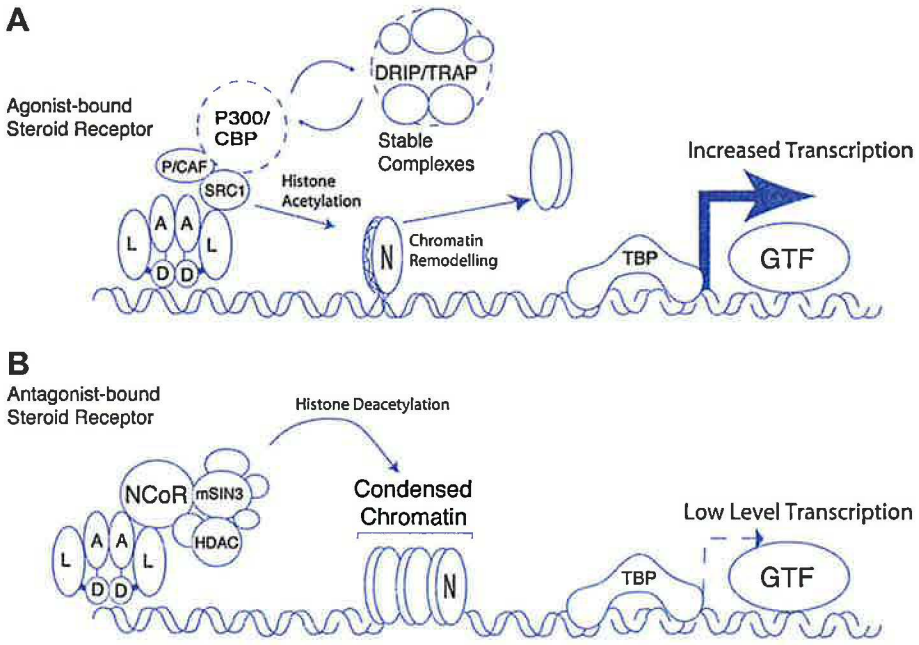

Figure 3. Coactivators and corepressors in the action of the androgen receptor and other nuclear receptors. A general model for the activities of coactivators and corepressors in the regulation of responsive genes by steroid receptors (A). The binding of a steroid receptor complexed to an agonist ligand to specific DNA sequence within or adjacent to the site of transcription initiation of a regulated gene recruits coactivator complexes containing proteins such as SRC-1, p300/CBP, and components of the mediator complex. Enzymatic activities of these proteins or by proteins within these complexes, such as histone acetyl transferase activity, modify the local chromatin structure. These changes make the transcription unit more accessible to the assembly and stability of transcription initiation complexes and results in an enhanced rate of transcription. (B) The binding of an antagonist to a steroid receptor results in the assumption of a different conformation of the receptor LBD and facilitates the recruitment of protein complexes containing corepressors such as NCoR and SMRT. The enzymatic activities associated with these corepressor complexes, such as deacetylation, leads to a condensation of chromatin structure and a decreased level of gene transcription. (A, amino terminus of NR with activation functions; D, DNA binding domain of NR; L, ligand binding domain of NR; N, nucleosome; TBP, TATA binding protein; GTF, general transcription factors.) Reprinted from Zoppi et al (2002, *Regulation of Gene Expression by the Nuclear Receptor Family in Genetics of Steroid Biosynthesis and Function* ed. J.I. Mason. Harwood Academic Publisher, pp 376–403) with permission.

places it into a conformation suitable for the recruitment of proteins that exhibit a repressive influence on the transcription of target sequences (Figure 3). As noted above, the precise structural correlates of these conformational changes remain undefined, as the crystal structure of antagonist-bound normal androgen receptor ligand binding domain has not yet been solved. Further, although most models would suggest the recruitment of coactivators such as NCoR and SMRT as a component of the action of AR antagonists, recent evidence has been presented suggesting that other pathways and mediators may be involved in the action of androgen receptor antagonists.[49,50]

It is worthwhile to note that alterations in responsiveness to individual ligands – agonist or antagonist – may be altered by the levels of nuclear coregulators that are

present within individual cell types. Enhanced expression of AR coactivators might be anticipated to enhance the responsiveness of tumors to low levels of androgens and attenuate the responsiveness to AR antagonists. Similar responses might accompany decreased expression of AR corepressors. The importance of these changes has been demonstrated in a limited number of model systems.[42,51–55]

Finally, in addition to pathways acting directly in the nucleus by the nuclear receptor activated by agonist ligands, it has become clear that alternative pathways exist in which the agonist-bound non-nuclear receptor activates alternate signaling cascade. Although these pathways have been more carefully defined with respect to the actions of estrogens and progesterone[56], similar rapid effects had been defined for androgens as well.[57,58] In some cases, these alternate signaling pathways have been associated with changes in the hormone-dependent growth patterns of the cells under study.[59]

CELL–CELL INTERACTIONS AND THE ACTIONS OF ANDROGENS IN VIVO

The biology of androgen action in the regulation of cell growth and function bears similarities to the actions of other steroid hormones. One line of evidence, however, has suggested that the actions of androgens maybe even more complex. These studies have demonstrated that androgens may not act simply within target cells, but may instead involve complex interactions between cells derived from epithelial cell populations and those derived from stromal cell populations.[60–62] Although such experiments have largely involved tissue reconstitution experiments conducted in mice, additional studies suggest that such interactions may play a role in other systems, including specific stages in development[63,64] and in the evolution of human prostate cancer to more aggressive forms.[65]

EVIDENCE THAT ALTERATIONS IN ANDROGEN ACTION MAY UNDERLIE THE PROGRESSION OF ANDROGEN-INDEPENDENT FORMS OF PROSTATE CANCER

Several lines of evidence have suggested that the androgen receptor may play an important role in the biology of progressive and recurrent prostate cancer. The demonstration that the androgen receptor is expressed in prostate cancer recurrence[66–68], the frequent amplification of the androgen receptor in prostate cancer in progression[69,70], the enhanced expression of the AR in progressive prostate cancers[71], and the emergence of mutations in the androgen receptor (see below) all have lent credence to its involvement in the progression of this disease.

Additional insights have come from examination of hormone levels in tumor samples expression and examination of gene expression patterns. In addition to demonstrating the continued expression of the androgen receptor protein in specimens of recurrent prostate cancer, Mohler and colleagues[72] demonstrated the presence of levels of testosterone and DHT in tumors that would be expected to be capable of activating the androgen receptor. These authors suggested a 'paradigm shift', in that the prostate cancer which occurs following medical or surgical castration is 'recurrent' and not 'androgen-independent'.

These experiments have been reinforced by a number of lines of evidence of a similar nature. Page et al demonstrated in healthy subjects treated with a long-acting GnRH-antagonist to effect hypogonadism, that despite a 94% decrease in serum

testosterone concentrations, intraprostatic testosterone and dihydrotestosterone levels remained a level 20–30% of control values.[73] Similarly, Nishiyama and colleagues measured levels of dihydrotestosterone in patients treated with androgen deprivation therapy (castration + flutamide).[74] In these latter studies, the investigators found that the levels of prostatic dihydrotestosterone remained at approximately 25% following androgen deprivation therapy, compared to levels measured prior to androgen deprivation. By contrast, measurements examining serum levels of dihydrotestosterone in these same individuals demonstrated that DHT levels fell by over 90%.

Mostaghel et al examined intraprostatic androgen levels and patterns of androgen-regulated gene expression in normal men and in archival prostate cancer specimens following varying lengths of androgen deprivation therapy.[75] The results of these experiments demonstrated several major features. First, intraprostatic levels of testosterone and DHT showed marked variations between individuals following short-term medical castration. Second, androgen-regulated gene expression, as indicated by the levels of PSA expression, persisted and were substantially reduced only in those subjects with the most profound suppression of intraprostatic androgen levels. Finally, examination of the levels of androgen dependent gene expression in primary prostate cancers at different time points of the androgen deprivation revealed evidence that the expression of androgen-regulated genes persisted at each of the time points examined. Further, substantial heterogeneity was observed between the levels of androgen-regulated gene expression among different samples.

MUTATIONS IN THE ANDROGEN RECEPTOR IN THE EVOLUTION OF ANDROGEN-INDEPENDENT FORMS OF PROSTATE CANCER

As noted above, several lines of evidence have suggested the involvement of the androgen receptor in prostate cancer progression, including expression of the androgen receptor in metastatic prostate cancer deposits, the frequent amplification of the androgen receptor gene in advanced forms of prostate cancer, the continued expression of androgen-dependent genes in progress of prostate cancer. In addition to these observations, two observations have increased the interest in the potential role of mutations of the androgen receptor in prostate cancer growth and progression. First was the demonstration that constitutively active forms of the androgen receptor existed raising the possibility that mutations of the androgen receptor could contribute to the behavior of some progressive prostate cancers.[76,77] The second was the identification of a mutation in the ligand binding domain of the androgen receptor expressed in the prostate cancer cell line, LNCaP, which conferred upon this cell line aberrant patterns of hormone responsiveness, including activation by anti androgens.[78]

Subsequent work by a number of laboratories has contributed to our understanding of the frequencies and circumstances where such AR mutations may contribute to the behavior of prostate cancer. To this point, numerous mutations of the androgen receptor – somatic in nature – have been identified in clinical prostate cancer specimens.

The frequency and nature of AR mutations that have been identified in prostate cancers appear to be related principally to the stage of the disease and the selective pressure that have been exerted on the cancers.[79,80] In localized primary cancers, AR mutations are believed to be uncommon and have been identified with the frequency of approximately 5%. As tumors become locally metastatic, the frequency with which AR mutations rises. In the series reported by Marcelli and coworkers,

mutations were identified in approximately 20% of microdissected locally metastatic tumor specimens.[81] When samples were examined from distant metastatic sites, an even higher frequency was demonstrated (50%).[82–84] Experiments examining the frequency and nature of mutations in distant metastatic sites in patients treated with androgen receptor antagonists showed an even higher frequency and a clustering of specific mutation types.[82] Of interest, mutations of the AR have also been identified in murine models of prostate cancer.[85,86] In some instances, mutations of the AR may themselves be oncogenic.[87]

Unlike mutations that have been identified in genetic syndromes of androgen insensitivity (loss-of-function mutations), mutations that have been identified in clinical forms of prostate cancer exhibit a somewhat different distribution within the androgen receptor open reading frame. These mutations can be viewed as comprising at least two distinct groups. In the first of these, the mutation is localized at specific regions of the receptor protein that can be shown to result in alterations of androgen receptor function. Such mutations include those that alter the ligand-binding properties of the receptor (e.g. permitting its activation by a broader range of ligands, for example) or those that result in the production of receptor protein that displays constitutive activity (as a result of either receptor truncation or amino acid substitution). The study of these mutations has been completed for a number of different mutations of the androgen receptor, and support the possibility that these changes may play a role in the pathogenesis or behavior of the prostate cancer.[82,88,89]

The second type of mutation that has been identified in the AR in prostate cancer specimens is more difficult to explain. These mutations are distributed differently in the AR open reading frame compared mutations causing AIS (Figure 1), often into regions of the receptor protein for which no clear-cut function has been identified or into segments that might be expected to lead to a loss of the androgen receptor function. These mutations may either represent disruptions of AR signaling pathways that have yet to be identified or for which the proper assay methods have not yet been tested or are not yet available.

EVIDENCE THAT ALTERNATIVE PATHWAYS MODULATE OR SUPPLANT THE REQUIREMENT FOR ANDROGENS TO STIMULATE THE ANDROGEN RECEPTOR

The demonstration that the chicken progesterone receptor could be activated in a ligand dependent fashion by cAMP dependent mechanisms[90] stimulated a large number of investigations to identify pathways capable of modulating the activities of the nuclear receptor family members, including the AR. Although early reports identified modulation of AR activity by cAMP and IGF-1 signaling pathways[91,92], subsequent investigators have implicated other potential signaling pathways.[93–100]

In subsequent studies, a number of different pathways have been examined to assess their roles in modulating the activities of the AR in the regulation of androgen receptor function and of target genes.[94] In some instances, the effects seem most clearly to exert an effect in accentuating the activity of the AR in modulating target genes and proliferation in limiting androgen levels.[95] In other instances, these effects observed indicate that the effects may signal through mechanisms that obviate the need for androgens completely. The roles that these diverse pathways play in the emergence of androgen-independent prostate cancer remain uncertain.

EVIDENCE THAT PATHWAYS OF THE ANDROGEN-REGULATED PROSTATE GROWTH ARE INTACT AND MODULATED BY ALTERNATE SOURCES OF ANDROGENS

A variety of different models has been used to study the potential mechanisms by which prostate cancers make progress to androgen independence. Experiments have been conducted using both in vitro cultured cell lines and xenografts models of prostate cancer. Each of these approaches has produced a range of interesting experimental results. Nonetheless, each of these approaches has been limited by considerations relating to influences that may be absent in these models which may be present in human prostate cancers in vivo.

In this regard, a limited number of studies has attempted to explore the molecular basis of prostate cancer progression in vivo. One such study is that reported by Stanbrough et al.[101] These intriguing experiments were conducted using bone-marrow aspirate samples obtained from individuals undergoing androgen deprivation as a part of their therapy for prostate cancer. In these studies, analyses of samples obtained from bone marrow biopsies performed in individuals with androgen-independent prostate cancer were compared to samples of primary prostate cancers following microdissection. Of note, the authors of this study took care to include in these analyses only samples that were comprised primarily of prostate cancer (i.e. with minimal contributions from bone marrow components). The results of these experiments were quite interesting. First, analysis of the microarray data permitted the grouping of the samples into metastatic androgen-independent prostate cancer groups. Inspection of the expressed genes in both groups of samples indicated that although androgen-regulated transcripts could be identified in both samples groups, the levels of these androgen-regulated genes were reduced in the androgen-independent samples. Inspection of the specific genes identified demonstrated a range of differentially expressed genes. Of particular note, was the increased level of androgen receptor expression which was noted in the majority of tumors. This finding was consistent with alterations of expression of the androgen receptor gene that have been observed in other analyses of human prostate cancers, as well as in xenograft models of prostate cancer progression.[71]

An intriguing attribute of these experiments was the identification of alterations in the expression levels of genes that would be expected to modulate the formation of androgens in situ within androgen-independent prostate cancer cells. Specifically noted were changes in the expression of genes involved in both androgen synthesis as well as breakdown. While the implications of the increase of several genes involved in the formation of androgens are obvious (HSD3B2, AKR1C3, SRD5A1 and 2) as they should lead to the formation of increased levels of active androgens within the tumors, the impact of increased levels of others are not (AKR1C1, AKR1C2, UGTB17).

The aforementioned experiments are largely consistent with the results of similar smaller trials, as well as experiments that have examined the importance of androgen levels in androgen action in prostate cancer progression. Additional support implicating in situ formation of androgens has come from additional directions as well. Some of the most compelling evidence is that centered on interim results employing agents that are capable of blocking the formation of steroid hormones that can be converted to androgens. Some of the most interesting results are the studies of Abiraterone, an inhibitor of CYP450c17 (CYP17), which blocks the cleavage of the 17/20 carbon-carbon bond that is required for the synthesis of both estrogens and androgens (Figure 3). Use of this agent in small, early stage clinical trials in patients with advanced prostate cancer who have failed

androgen deprivation and docetaxel-based chemotherapy have demonstrated that 2/3 of patients demonstrate a greater than 50% PSA decline and more than half have shown >90% PSA decline.[102,103] Of even greater interest, of 8 pts with Response Evaluation Criteria in Solid Tumors (RECIST) evaluable disease, 5/8 showed radiological partial responses, 1/8 had stable disease (7 months+), and 2/8 displayed progressive disease.[104]

Keeping in mind that conclusions cannot be reached due to the small number of patients, these results suggest that responses are likely to be heterogeneous. They also indicate that even among patients with advanced forms of prostate cancer, a substantial number of individuals with disease progressing while being treated with one type of androgen deprivation therapy could respond to therapies directed at the inhibition of the CYP17. These studies are consistent with the notion that biologically important levels of androgens are present in prostate tumors in the context of androgen deprivation therapies currently in use. These early findings suggest that these levels of androgens are important for continued tumor growth and progression and that therapies designed to further lower or eliminate them may have clinically important effects.

SUMMARY

An immense body of information has accumulated relating to the biology of human prostate cancer and prostate cancer models. Much of this information is consistent with the androgen receptor – and the gene networks that it regulates – being a central element in prostate cancer development and progression. A number of different distinct mechanisms have been identified which can participate in the modulations of prostate cancer progression (Table 1). Although no individual pathway is likely to represent a single target by which prostate cancer progression might be interrupted, it is intriguing to note the recent evidence suggesting that the ablation of low levels of androgens detected in progressive tumor specimens is likely to have important therapeutic benefits.

Table 1. Potential mechanisms of prostate cancer progression to androgen independence.

Growth mechanisms that employ the pathways that regulate prostate epithelial cell growth in normal tissues
Mutant androgen receptors
Emergence of signaling pathways that influence the androgen-regulated pathways
Augmenting the growth in response to androgens or in response to low levels of androgens
Increased expression of coactivators
Decreased expression of corepressors
Input from pathways that augment the effects of low levels of androgen
Signaling that requires the androgen receptor, but does not require hormone
Alterations in the complement of enzymes necessary to synthesize (increase) or degrade (decrease) active androgens
Emergence of growth mechanisms not normally regulated by androgen and supplanting those that are normally regulated by androgen in the prostatic epithelium

REFERENCES

1. American Cancer Society Inc. [homepage on the Internet] [cited 2008 February 11]. Cancer Statistics 2007 Presentation; [about 39 screens]. Available from: http://www.cancer.org/docroot/PRO/content/PRO_1_1_Cancer_Statistics_2007_Presentation.asp.
2. Jemal A, Siegel R, Ward E et al. Cancer statistics 2007. *CA: a Cancer Journal for Clinicians* 2007; **57:** 43–66.
3. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. *CA: a Cancer Journal for Clinicians* 2005 Mar; **55:** 74–108.
4. Huggins C & Hodges CV. Studies on prostate cancer: effect of castration, of estrogen and of androgen injection on serum acid phosphatase in metastatic carcinoma of the prostate. *Cancer Research* 1941; (1): 293.
5. Hellerstedt BA & Pienta KJ. The truth is out there: an overall perspective on androgen deprivation. *Urologic Oncology: Seminars and Original Investigations* 2003 July–August; **21**(4): 272–281.
6. Laufer M, Denmeade SR, Sinibaldi VJ, et al. Complete androgen blockade for prostate cancer: what went wrong? *The Journal of Urology* **164**:3–9.
7. Robinson-Rechavi M, Garcia HE & Laudet V. The nuclear receptor super family. *Journal of Cell Science* 2003; **116:** 585–586.
8. Mangelsdorf DJ, Thummel C, Beato M et al. The nuclear receptor superfamily: the second decade. *Journal of Cell Science* 1995 Dec 15; **83**(6): 835–839.
9. Zoppi S, Young M & McPhaul MJ. Regulation of gene expression by the nuclear receptor family in genetics of steroid biosynthesis and function. In Mason JI (ed.). Harwood Academic Publisher, 2002, pp. 376–403 [chapter 14].
10. http://androgendb.mcgill.ca/map.gif.
11. Simental JA, Sar M, Lane MV et al. Transcriptional activation and nuclear targeting signals of the human androgen receptor. *The Journal of Biological Chemistry* 1991; **266:** 510–518.
12. Jenster G, van der Korput HAGM, van Vroonhoven C et al. Domains of the human androgen receptor involved in steroid binding, transcriptional activation, and subcellular localization. *Molecular Endocrinology (Baltimore, Md.)* 1991; **5:** 1396–1404.
13. Gao T, Marcelli M & McPhaul MJ. Transcriptional activation and transient expression of the human androgen receptor. *The Journal of Steroid Biochemistry and Molecular Biology* 1996 Sept; **59**(1): 9–20.
14. He B, Kemppainen JA & Wilson EM. FXXLF and WXXLF sequences mediate the NH_2-terminal interaction with the ligand binding domain of the androgen receptor. *The Journal of Biological Chemistry* 2000; **275:** 22986–22994.
15. Kemppainen JA, Langley E, Wong CI et al. Distinguishing androgen receptor agonists and antagonists: distinct mechanisms of activation by medroxyprogesterone acetate and dihydrotestosterone. *Molecular Endocrinology* 1999; **13:** 440–454.
16. He B, Kemppainen JA, Voegel JJ et al. Activation function 2 in the human androgen receptor ligand binding domain mediates interdomain communication with the NH(2)-terminal domain. *The Journal of Biological Chemistry* 1999; **274:** 37219–37225.
17. Thompson J, Saatcioglu F, Janne OA et al. Disrupted amino- and carboxyl-terminal interactions of the androgen receptor are linked to androgen insensitivity. *Molecular Endocrinology* 2001 June 1; **15**(6): 923–935.
18. Mhatre AN, Trifiro MA, Kaufman M et al. Reduced transcriptional regulatory competence of the androgen recepto in X-linked spinal and bulbar muscular atrophy. *Nature Genetics* 1993; **5:** 184–188.
19. Chamberlain NL, Driver ED & Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. *Nucleic Acids Research* 1994; **22:** 3181–3186. Available from: http://hmg.oxfordjournals.org/cgi/ijlink?linkType=ABST&journalCode=nar&resid=22/15/3181.
20. Beilin J, Ball EM, Favaloro JM et al. Effect of the androgen receptor CAG repeat polymorphism on transcriptional activity: specificity in prostate and non-prostate cell lines. *Journal of Molecular Endocrinology* 2000; **25:** 85–96.
21. Kazemi-Esfarjani P, Trifiro MA & Pinsky L. Evidence for a repressive function of the long polyglutamine tract in the human androgen receptor: possible pathogenetic relevance for the (CAG)n-expanded neuronopathies. *Human Molecular Genetics* 1995; **4:** 523–527.

22. Irvine RA, Ma H, Yu MC et al. Inhibition of p160-mediated co activation with increasing androgen receptor polyglutamine length. *Human Molecular Genetics* 2000; **9:** 267–274.
23. Brockschmidt FF, Nothen MM & Hillmer AM. The two most common alleles of the coding GGN repeat in the androgen receptor gene cause differences in protein function. *Journal of Molecular Endocrinology* 2007 July 1; **39**(1): 1–8.
24. Tut TG, Ghadessy FJ, Trifiro MA et al. Long polyglutamine tracts in the androgen receptor are associated with reduced trans-activation, impaired sperm production, and male infertility. *The Journal of Clinical Endocrinology and Metabolism* 1997; **82:** 3777–3782.
25. Crabbe P, Bogaert V, De Bacquer D et al. Part of the interindividual variation in serum testosterone levels in healthy men reflects differences in androgen sensitivity and feedback set point: contribution of the androgen receptor polyglutamine tract polymorphism. *The Journal of Clinical Endocrinology and Metabolism* 2007 Sept 1; **92**(9): 3604–3610.
26. Nelson KA & Witte JS. Androgen receptor CAG repeats and prostate cancer. *American Journal of Epidemiology* 2002 May 15; **155**(10): 883–890.
27. Robins DM, Albertelli MA & O'Mahony OA. Androgen receptor variants and prostate cancer in humanized AR mice. *The Journal of Steroid Biochemistry and Molecular Biology* 2008 Feb; **108**(3-5): 30–36.
28. Grino PB, Griffin JE & Wilson JD. Testosterone at high concentrations interacts with the human androgen receptor similarly to dihydrotestosterone. *Endocrinology* 1990 Feb; **126**(2): 1165–1172.
29. O'Malley BW. Sequentiality and processivity of nuclear receptor coregulators in regulation of target gene expression. *Nuclear Receptor Signaling* 2003; **1:** e010.
30. Lonard DM & O'Malley BW. Nuclear receptor coregulators: judges, juries, and executioners of cellular regulation. *Molecular Cell* 2007 Sep 7; **27**(5): 691–700.
31. Heinlein CA & Chang C. Androgen receptor (AR) coregulators: an overview. *Endocrine Reviews* 2002 Apr 1; **23**(2): 175–200.
32. Gelmann EP. Molecular biology of the androgen receptor. *Journal of Clinical Oncology* 2002 July 1; **20**(13): 3001–3015.
33. Heemers HV & Tindall DJ. Androgen receptor (AR) coregulators: a diversity of functions converging on and regulating the AR transcriptional complex. *Endocrine Reviews* 2007 Dec 1; **28**(7): 778–808.
34. Brzozowski AM, Pike AC, Dauter Z et al. Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature* 1997 Oct 16; **389**(6652): 753–758.
35. Matias PM, Donner P, Coelho R et al. *The Journal of Biological Chemistry* 2000; **275:** 26164–26171.
36. Sack JS, Kish KF, Wang C et al. Crystallographic structures of the ligand-binding domains of the androgen receptor and its T877A mutant complexed with the natural agonist dihydrotestosterone. *Proceedings of the National Academy of Sciences of the United States of America* 2001 Apr 24; **98**(9): 4904–4909.
37. Kauppi B, Jakob C, Farnegardh M et al. The three-dimensional structures of antagonistic and agonistic forms of the glucocorticoid receptor ligand-binding domain: RU-486 induces a transconformation that leads to active antagonism. *The Journal of Biological Chemistry* 2003 Jun 20; **278**(25): 22748–22754.
38. Bohl CE, Wu Z, Miller DD et al. Crystal structure of the T877A human androgen receptor ligand-binding domain complexed to cyproterone acetate provides insight for ligand-induced conformational changes and structure-based drug design. *The Journal of Biological Chemistry* 2007 May 4; **282**(18): 13648–13655 [Epub [Internet] 2007 Feb 20].
39. Bohl CE, Gao W, Miller DD et al. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proceedings of the National Academy of Sciences of the United States of America* 2005 Apr 26; **102**(17): 6201–6206.
40. Cantin L, Faucher F, Couture J-F et al. Structural characterization of the human androgen receptor ligand-binding domain complexed with EM5744, a rationally designed steroidal ligand bearing a bulky chain directed toward helix 12. *The Journal of Biological Chemistry* 2007 Oct 19; **282**(42): 30910–30919.
41. Metivier R, Penot G, Hubner MR et al. Estrogen receptor-alpha directs ordered, cyclical, and combinatorial recruitment of cofactors on a natural target promoter. *Cell* 2003; **115:** 751–763.
42. Shang Y & Brown M. Molecular determinants for the tissue specificity of SERMs. *Science* 2002; **295:** 2465–2468.

43. Shang Y, Hu X, DiRenzo J et al. Cofactor dynamics and sufficiency in estrogen receptor-regulated transcription. *Cell* 2000; **103:** 843–852.
44. Rosenfeld MG, Lunyak VV & Glass CK. Sensors and signals: a coactivator/corepressor/epigenetic code for integrating signal-dependent programs of transcriptional response. *Genes & Development* 2006; **20:** 1405–1428.
45. Wang Q, Carroll JS & Brown M. Spatial and temporal recruitment of androgen receptor and its coactivators involves chromosomal looping and polymerase tracking. *Molecular Cell* 2005 Sept; **2:** 631–642.
46. Wang Qianben, Li Wei, XS Liu et al. A hierarchical network of transcription factors governs androgen receptor-dependent prostate cancer growth. *Molecular Cell* 2007 Aug 3: 380–392.
47. Privalsky ML. The role of corepressors in transcriptional regulation by nuclear hormone receptors. *Annual Review of Physiology* 2004; **66:** 315–360.
48. Burd CJ, Morey LM & Knudsen KE. Androgen receptor corepressors and prostate cancer. *Endocrine-Related Cancer* 2006 Dec 1; **13**(4): 979–994.
49. Cheng S, Brzostek S, Lee SR et al. Inhibition of the dihydrotestosterone-activated androgen receptor by nuclear receptor corepressor. *Molecular Endocrinology* 2002 Jul; **16**(7): 1492–1501.
50. Hodgson MC, Astapova I, Hollenberg AN et al. Activity of androgen receptor antagonist bicalutamide in prostate cancer cells is independent of NCoR and SMRT corepressors. *Cancer Research* 2007 Sep 1; **67**(17): 8388–8395.
51. Smith CL, Nawaz Z & O'Malley BW. Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. *Molecular Endocrinology (Baltimore, Md.)* 1997 Jun; **11**(6): 657–666.
52. Linja MJ, Porkka KP, Kang Z et al. Expression of androgen receptor coregulators in prostate cancer. *Clinical Cancer Research* 2004 Febuary 1; **10**(3): 1032–1040.
53. Agoulnik IU, Vaid A, Bingman III WE et al. Role of SRC-1 in the promotion of prostate cancer cell growth and tumor progression. *Cancer Research* 2005 Sept 1; **65**(17): 7959–7967.
54. Vijayvargia R, May MS & Fondell JD. A coregulatory role for the mediator complex in prostate cancer cell proliferation and gene expression. *Cancer Research* 2007 May 1; **67**(9): 4034–4041.
55. Gregory CW, He B, Johnson RT et al. A mechanism for androgen receptor-mediated prostate cancer recurrence after androgen deprivation therapy. *Cancer Research* 2001 Jun 1; **61**(11): 4315–4319.
56. Boonyaratanakornkit V & Edwards DP. Receptor mechanisms mediating non-genomic actions of sex steroids. *Seminars in Reproductive Medicine* 2007 May; **25**(3): 139–153.
57. Foradori CD, Weiser MJ & Handa RJ. Non-genomic actions of androgens. *Frontiers in Neuroendocrinology* 2007 Nov 7.
58. Michels G & Hoppe UC. Rapid actions of androgens. *Frontiers in Neuroendocrinology* 2007 Oct 5.
59. Unni E, Sun S, Nan B et al. Changes in androgen receptor nongenotropic signaling correlate with transition of LNCaP cells to androgen independence cancer research. *Cancer Research* 2004; **64:** 7156–7168.
60. Marker PC, Donjacour AA, Dahiya R et al. Hormonal, cellular, and molecular control of prostatic development. *Developmental Biology* 2003 Jan 15; **253**(2): 165–174.
61. Cunha GR, Cooke PS & Kurita T. Role of stromal-epithelial interactions in hormonal responses. *Archives of Histology and Cytology* 2004 Dec; **67**(5): 417–434.
62. Ricke WA, Wang Y, Kurita T et al. Hormonal and stromal regulation of normal and neoplastic prostatic growth. *Progress in Molecular and Subcellular Biology* 2005; **40:** 183–216.
63. Vanpoucke G, Orr O, Grace OC et al. Transcriptional profiling of inductive mesenchyme to identify molecules involved in prostate development and disease. *Genome Biology* 2007; **8:** R213. doi:10.1186/gb-2007-8-10-r213.
64. Welsh M, Saunders PT & Sharpe RM. The critical time window for androgen-dependent development of the Wolffian duct in the rat. *Endocrinology* 2007 Jul; **148**(7): 3185–3195.
65. Cano P, Godoy A, Escamilla R et al. Onate stromal-epithelial cell interactions and androgen receptor-coregulator recruitment is altered in the tissue microenvironment of prostate cancer. *Cancer Research* 2007 Jan 15; **67**(2): 511–519.
66. van der Kwast TH, Schalken J, Ruizeveld de Winter JA et al. Androgen receptors in endocrine-therapy-resistant human prostate cancer. *International Journal of Cancer* 1991; **48:** 189–193.
67. Ruizeveld de Winter JA, Janssen PJ, Sleddens HM et al. Androgen receptor status in localized and locally progressive hormone refractory human prostate cancer. *American Journal of Pathology* 1994; **144:** 735–746.

68. Hobisch A, Culig Z, Radmayr C et al. Distant metastases from prostatic carcinoma express androgen receptor protein. *Cancer Research* 1995; **55:** 3068–3072.
*69. Visakorpi T, Hyytinen E, Koivisto P et al. In vivo amplification of the androgen receptor gene and progression of human prostate cancer. *Nature Genetics* 1995; **9:** 401–406.
70. Koivisto P, Kononen J, Palmberg C et al. Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. *Cancer Research* 1997; **57:** 314–319.
71. Chen CD, Welsbie DS, Tran C et al. Molecular determinants of resistance to anti-androgen therapy. *Nature Medicine* 2004 Jan; **10**(1): 33–39.
*72. Mohler JL, Gregory CW, Ford 3rd OH et al. The androgen axis in recurrent prostate cancer. *Clinical Cancer Research* 2004 Jan 15; **10**(2): 440–448.
73. Page ST, Lin DW, Mostaghel EA et al. Persistent intraprostatic androgen concentrations after medical castration in healthy men. *The Journal of Clinical Endocrinology and Metabolism* 2006 Oct; **91**(10): 3850–3856.
74. Nishiyama T, Hashimoto Y & Takahashi K. The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue of patients with prostate cancer. *Clinical Cancer Research* 2004 Nov 1; **10**(21): 7121–7126.
*75. Mostaghel EA, Page ST, Lin DW et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. *Cancer Research* 2007 May 15; **67**(10): 5033–5041.
76. Picard D & Yamamoto KR. Two signals mediate hormone-dependent nuclear localization of the glucocorticoid receptor. *The EMBO Journal* 1987 Nov; **6**(11): 3333–3340.
77. Marcelli M, Tilley WD, Wilson CM et al. Definition of the human androgen receptor gene structure permits the identification of mutations that cause androgen resistance: premature termination of the receptor protein at amino acid residue 588 causes complete androgen resistance. *Molecular Endocrinology* 1990 Aug; **4**(8): 1105–1116.
*78. Veldscholte J, Ris-Stalpers C, Kuiper GG et al. A mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affects steroid binding characteristics and response to anti-androgens. *Biochemical and Biophysical Research* 1990 Dec 14; **173**(2): 534–540.
79. Avila DM, Zoppi S & McPhaul MJ. The androgen receptor (AR) in syndromes of androgen insensitivity and in prostate cancer. *The Journal of Steroid Biochemistry and Molecular Biology* 2001 Jan–Mar; **76**(1–5): 135–142.
*80. Tilley WD, Buchanan G, Hickey TE et al. Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. *Clinical Cancer Research* 1996; **2**(2): 277–285.
*81. Marcelli M, Ittmann M, Mariani S et al. Androgen receptor mutations in prostate cancer. *Cancer Research* 2000; **60**(4): 944–949.
*82. Taplin ME, Bubley GJ, Shuster TD et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *The New England Journal of Medicine* 1995; **332**(21): 1393–1398.
*83. Taplin ME, Bubley GJ, Ko YJ et al. Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. *Cancer Research* 1999; **59**(11): 2511–2515.
84. Taplin M-E, Rajeshkumar B, Halabi S et al. Androgen receptor mutations in androgen-independent prostate cancer: Cancer and Leukemia Group B Study 9663. *Journal of Clinical Oncology* 2003 July 15; **21**(14): 2673–2678.
85. Han G, Foster BA, Mistry S et al. Hormone status selects for spontaneous somatic androgen receptor variants that demonstrate specific ligand and cofactor dependent activities in autochthonous prostate cancer. *The Journal of Biological Chemistry* 2001; **276:** 11204–11213.
86. Buchanan G, Greenberg NM, Scher HI et al. Collocation of androgen receptor gene mutations in prostate cancer. *Clinical Cancer Research* 2001; **7:** 1273–1281.
87. Han G, Buchanan G, Ittmann M et al. Mutation of the androgen receptor causes oncogenic transformation of the prostate. *Proceedings of the National Academy of Sciences of the United States of America* 2005 Jan 25; **102**(4): 1151–1156.
88. Shi XB, Ma AH, Xia L et al. Functional analysis of 44 mutant androgen receptors from human prostate cancer. *Cancer Research* 2002; **62**(5): 1496–1502.

89. Zhao XY, Malloy PJ, Krishnan AV et al. Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. *Natural Medicines* 2000 Jun; **6**(6): 703–706.
90. Denner LA, Weigel NL, Maxwell BL et al. Regulation of progesterone receptor-mediated transcription by phosphorylation. *Science* 1990; **250**: 1740–1743.
91. Culig Z, Hobisch A, Cronauer MV et al. Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-I, keratinocyte growth factor, and epidermal growth factor. *Cancer Research* 1994 Oct 15; **54**(20): 5474–5478.
92. Nazareth LV & Weigel NL. Activation of the human androgen receptor through a protein kinase A signaling pathway. *The Journal of Biological Chemistry* 1996 Aug 16; **271**(33): 19900–19907.
93. Sadar MD. Androgen-independent induction of prostate-specific antigen gene expression via cross-talk between the androgen receptor and protein kinase A signal transduction pathways. *The Journal of Biological Chemistry* 1999 Mar 19; **274**(12): 7777–7783.
94. Culig Z. Androgen receptor cross-talk with cell signaling pathways. *Growth Factors* 2004 Sep; **22**(3): 179–184.
*95. Craft N, Shostak Y, Carey M et al. A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. *Natural Medicines* 1999 Mar; **5**(3): 280–285.
96. Mulholland DJ, Dedhar S, Wu H et al. PTEN and GSK3beta: key regulators of progression to androgen-independent prostate cancer. *Oncogene* 2006 Jan 19; **25**(3): 329–337.
97. Wang Y, Kreisberg JI & Ghosh PM. Cross-talk between the androgen receptor and the phosphatidylinositol 3-kinase/Akt pathway in prostate cancer. *Current Cancer Drug Targets* 2007 Sep; **7**(6): 591–604.
98. Schweizer L, Rizzo CA, Spires TE et al. The androgen receptor can signal through Wnt/beta-Catenin in prostate cancer cells as an adaptation mechanism to castration levels of androgens. *BMC Cell Biology* 2008 Jan 24; **9**(1): 4.
99. Lee SO, Pinder E, Chun JY et al. Interleukin-4 stimulates androgen-independent growth in LNCaP human prostate cancer cells. *Prostate* 2008 Jan 1; **68**(1): 85–91.
100. Araki S, Omori Y, Lyn D et al. Interleukin-8 is a molecular determinant of androgen independence and progression in prostate cancer. *Cancer Research* 2007 Jul 15; **67**(14): 6854–6862.
*101. Stanbrough M, Bubley GJ, Ross K et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Research* 2006 Mar 1; **66**(5): 2815–2825.
102. Ryan CJ, Rosenberg J, Lin A et al. Phase I evaluation of abiraterone acetate (CB7630), a 17 alpha hydroxylase C17,20-Lyase inhibitor in androgen-independent prostate cancer (AiPC)*2007 ASCO Annual Meeting Proceedings Part I. 2007 June 20 Supplement. Journal of Clinical Oncology* 2007; **25**(18S): 5064.
103. Yap TA, Attard G, Reid A et al. Abiraterone acetate, an oral irreversible inhibitor of cyp450c17, administered to castration refractory prostate cancer patients is safe, suppresses androgen and steroid precursor levels, and has a high degree of durable antitumor activity. *American Urological Association Annual Meeting, Anaheim, CA, May 19–24,* 2007: H23. [abstract 594].
104. Danila DC, Slovin S, Morris M, et al. Preliminary phase II results of abiraterone acetate in patients with castration resistant metastatic prostate cancer after failure of docetaxel-based chemotherapy Chemotherapy. In: Innovative Cancer Therapy for Tomorrow: 2007: Foundation Symposium XXV; 2007 Nov 9; New York, New York.