SUMMARY
The androgen receptor (AR) and the androgen–AR signaling pathway play a significant role in male sexual differentiation and the development and function of male reproductive and non-reproductive organs. Because of AR’s widely varied and important roles, its abnormalities have been identified in various diseases such as androgen insensitivity syndrome, spinal bulbar muscular atrophy, benign prostatic hyperplasia, and prostate cancer. This review provides an overview of the function of androgens and androgen–AR mediated diseases. In addition, the diseases delineated above are discussed with respect to their association with mutations and other post-transcriptional modifications in the AR. Finally, we present an introduction to the potential therapeutic application of most recent pharmaceuticals including miRNAs in prostate cancer that specifically target the transactivation function of the AR at post-transcriptional stages.

INTRODUCTION
Androgens are responsible for a wide array of physiological effects on the reproductive and non-reproductive systems of the male body during different periods of development (Mainwaring, 1977, HM, 1998). In particular, testosterone (T) and its metabolite 5β-dihydrotestosterone (DHT) are the two most active androgens responsible for these effects. Testosterone is most abundant in circulation throughout the body, while its sterically altered counterpart, DHT is more mitogenic and concentrated in the cells of androgen-sensitive tissues (Mainwaring, 1977, HM, 1998). During fetal life, androgens are primarily responsible for sexual differentiation through virilizing the Wolffian duct structures and external genitalia. During puberty, they regulate the growth and function of the penis, prostate, seminal vesicles, vas deferens, epididymis, and scrotum, as well as stimulating growth spurts, development of the larynx, and skeletal muscle growth. In adults, they function in regulating behavior, spermatogenesis, muscle mass/function, bone metabolism, and certain aspects of the cardiovascular system (HM, 1998). In addition to stimulating and maintaining sexual function in men, androgens may also be responsible, in part, for aggressive behavior.

Androgens act through both genomic (direct) and non-genomic (indirect) mechanisms. The most extensively studied and prominent form of androgen action is through direct interactions with androgen receptor (AR), member of the steroid hormone receptor family of nuclear transcription factors that is present in primary/secondary sexual organs as well as non-reproductive organs such as kidneys, skeletal muscles, adrenal glands, skin, and nervous system (Verhoeven & Swinnen, 1999). AR action is a vast and active field of research that needs an up-to-date stand-alone comprehensive summarization to encompass various modes of androgen-dependent and androgen-independent actions in normal development as well as in...
disease state. Here, we attempt to discuss on the concise action of androgen-dependent and -independent actions of AR. Typically, via the androgen-dependent pathway, AR is bound to heat shock proteins (HSPs; such as Hsp90) which act as inhibitors to the AR, maintaining its inactive state and allowing hormones to bind (Fang et al., 1996). Once androgen binds to the AR, the HSPs are released as AR is phosphorylated and undergoes conformational changes necessary for dimerization and translocation to the nucleus (Fang et al., 1996). In the nucleus, the dimerized AR binds to a DNA androgen response element (ARE), a 15 base pair sequence found in numerous AR target genes to initiate a complex transcriptional program in target cells. Other transcription factor proteins/coactivators then bind to the AR-ARE complex to ensure stability of the gene’s promoter complex (Busu & Tindall, 2010; Schmidt & Tindall, 2013) (Fig. 1). Such paracrine action and signaling is pivotal to prostate development as well as prostate carcinogenesis. Extensive literature exists describing the androgen-independent actions of AR. However, here we summarize only a few key cellular signaling pathways of interest that modulates AR transactivation function independent of androgen action (Fig. 1). Among many, extracellular growth factors, cytokines, G-protein-coupled receptors, multiple kinases, and recently alternatively spliced isoforms of AR have been implicated in AR androgen-independent function. Two cytokines, viz. interleukin-6 (IL-6) and interleukin-8 (IL-8) have been implicated in androgen-independent function of AR (Blaszczyk et al., 2004; Seaton et al., 2008). IL-6 is expressed in multiple cells types and organs including leukocytes, osteoblasts, Leydig cells, kidney, lung, prostate, etc. Human osteoblasts-derived IL-6 stimulates growth of prostate cancer through the action of AR (Blaszczyk et al., 2004; Malinowska et al., 2009). Activation of Janus Kinase and signal transducer and activator of transcription pathways by IL-6 may also be a result of chronic inflammation thus setting the stage for the development and progression of prostate cancer. In addition, IL-6 is also shown to modulate differential recruitment of AR coactivator p300 to AR target gene transcription initiation complex by inhibiting histone acetyltransferase acetylation. Interestingly, this effect of IL-6 was independent of MAPK or AKT pathways suggesting pleiotropic actions of IL-6 in castration-sensitive and - resistant prostate cancer (Jia et al., 2004).

Interleukin-8 signaling also promotes androgen-independent proliferation via AR expression and transactivation (Seaton et al., 2008). It appears that IL-8’s effect on AR activation may be linked through tyrosine kinase Src and focal adhesion kinase (Lee et al., 2004). Mitogen-activated protein kinases or MAPK pathways mediate cellular signaling to modulate cell proliferation, differentiation, apoptosis, and cell survival. Three members of the serine/threonine kinases including stress-activated c-Jun NH2-terminal kinase, stress-activated protein kinase 2 (MAPK2/p38) and extracellular signal-regulated protein kinase (ERK1/2) appears to play a distinct role in the development of castration-resistant prostate cancer (Rodriguez-Berriguete et al., 2012). MAPK2/p38 sensitizes the cells to promote IL-6-induced activation of androgen-independent function of AR (Lin et al., 2001; Ueda et al., 2002). Protein Kinase A has also been shown to upregulate AR-mediated transactivation via increasing cellular levels of cyclic AMP (cAMP) (Nazareth & Weigel, 1996). Many kinases including Ack1, Src, Aurora-A, and Erk1/2 (p42/44) appears to phosphorylate AR through a variety of mitogen and cytokine signaling modulating ligand-independent transactivation of AR thus promoting castrate-resistant prostate cancer (Ueda et al., 2002; Guo et al., 2006; Kraus et al., 2006; Agoulnik et al., 2008). Many paracrine regulated growth factors such as insulin-like growth factor (IGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF) also promote prostate epithelial cell proliferation by paracrine pathways (Zhu & Kyprianou, 2008). In brief, several molecular players including kinases, cytokines, growth factors, AR coactivators, and alternatively spliced isoforms of AR can activate androgen-independent activation of AR to promote castrate-resistant prostate cancer and many extensive reviews have been dedicated to summarize this field (Heemers & Tindall, 2007, 2009; Zhu & Kyprianou, 2008; Lamont & Tindall, 2011; Lu et al., 2015).

Androgen receptor-mediated transcriptional activation is central to the development and proliferation process to maintain physiological homeostasis. However, AR autocrine modulation can lead to undesirable proliferation and development of prostate cancer. While the aforementioned mechanism of ligand-dependent AR activation is most prominent, studies have shown that receptors with deleted ligand-binding sites may still exhibit transcriptional activity, suggesting that a binding domain without a ligand sterically represses AR activity (Jenster et al., 1991; Bruggenwirth et al., 1997). In addition, growth factors (IGF, keratinocyte growth factor, and EGF) and protein kinase A activators may induce ligand-independent AR activation by acting upon AR phosphorylation (Culig et al., 1995; Nazareth & Weigel, 1996). As mentioned before, androgens may also act independently of the AR. Some androgen-sensitive tissues lack ARE interactions, whereas others lack functional AR because of AR insensitivity or AR blockade by AR-antagonists or LHHR agonists (Denis & Griffiths, 2000; Lonergan & Tindall, 2011). Therefore, androgens such as T and DHT may function independently of AR signaling pathway. It has been hypothesized that androgens may influence the regulation of autocrine and paracrine mediators of gene expression, mediate secondary transcription factors, affect secretion of hormones that control androgen action in distal tissues, or bind to plasma proteins that have extracellular receptors (HM, 1998; Verhoeven & Swinnen, 1999; Lonergan & Tindall, 2011). AR’s role has been implicated in various disorders including androgen-insensitivity syndrome (AIS) (Tadokoro-Cuccaro & Hughes, 2014; Tadokoro-Cuccaro et al., 2014), hypospadias (Huang et al., 2015; Zhao et al., 2015), gynecomastia (Hellmann et al., 2012), X-linked spinal and bulbar muscular atrophy (SBMA, AKA Kennedy’s disease) (La Spada et al., 1991; Greenwood & Zajac, 2004; Cortes et al., 2014), cryptorchidism (Cain et al., 1994, 1995; Massart & Saggese, 2009), male infertility (Wang et al., 2009), alopecia (Zhuo et al., 2012), polycystic ovary syndrome (Lin et al., 2013), prostatic hypertrophy (Izumi et al., 2013), and prostate and breast cancers (Yuan & Balk, 2009; Basu & Tindall, 2010; Lonergan & Tindall, 2011; Green et al., 2012; Shafi et al., 2013; Balk, 2014; Culig & Santer, 2014; Ricciardi et al., 2015).

Although various effects and mechanisms of the androgen-AR signaling pathway in males have been studied in detail and are well understood, these processes in female are significantly less well established because of the lack of a viable model system. This is because of the fact that AR gene is located on the X chromosome (Migeon et al., 1981; Brown et al., 1989). Recent studies involving cre-lox conditional knockout AR female mice, however,
have shown that such female mice produce fewer offspring than their wild-type counterparts and exhibit defective folliculogenesis. This indicates that AR may function in female fertility, ovulation, follicular maturation, as well as uterine development (Yeh et al., 2002). In addition, AR’s differential roles in multiple hormone-related cancers including prostate, bladder, lung, liver breast, and kidney underlies the clinical importance of the molecule (Chang et al., 2014).

Androgen receptor is a single-strand polypeptide having a modular structure with four functional domains: the N-terminal domain (NTD) contains activation function-1 (AF-1) region, the DNA-binding domain (DBD), the hinge domain, and the C-terminal ligand-binding domain (LBD) that contains AF-2 region (Tsai & O’Malley, 1994; Mangelsdorf et al., 1995) (Fig. 2).

The NTD of AR is the most poorly conserved in sequence homology and length of all the domains, and comprises over half of the entire protein (amino acid residues 1–537). Besides transcriptional activation region, the NTD also includes homopolymeric amino acid regions (polyglutamine and polyglycine repeats) that function in transcriptional regulation in interaction with other receptor regions, and in determining the three-dimensional structure of the receptor (Evans, 1988; Jenster et al., 1991; Pereira de Jesus-Tran et al., 2006; Myung et al., 2013). The length of the polyglutamine repeat is inversely related to AR transcriptional activity (Kazemi-Esfarjani et al., 1995). In other words, the longer the polyglutamine repeat, the less the AR trans-activation activity – possibly because of interactions with coregulators – and AR mRNA and protein expression (McPhaul et al., 1991; Choong et al., 1996a,b; Hsiao et al., 1999). On the other hand, shorter polyglutamine repeats may prevent proper N-terminal phosphorylation and interaction between AR domains (McPhaul et al., 1991; Jenster et al., 1994; Shi et al., 2011; Ryan & Crespi, 2013). As for the polyglycine repeats, it has been shown that complete deletion of the region results in...
significant reduction of AR transactivation activity (Gao et al., 1996; Sasaki et al., 2003). AF-1 region (residues 360–494) is responsible for AR stabilization through interactions with the LBD and mediates most of AR transactivation (Beato et al., 1996; Ikonen et al., 1997; He et al., 1999, 2000; Moilanen et al., 1999), and the region between residues 141–338 are necessary for ligand-dependent AR activity (Jenster et al., 1991; Simental et al., 1991). Furthermore, the NTD of the AR may interact with various transcription factors or get phosphorylated by kinases, both of which regulate AR transactivation (Weigel, 1996; Gioeli et al., 2002). Finally, the domain can be modified by sumoylation proteins; when sumoylation sites are mutated, AR transactivation activity (Weigel, 1996; Gioeli et al., 1991). The AR protein also contains a DNA-binding domain (DBD) composed of two zinc finger structures. In addition, the C-terminal domain (CTD) of AR contains a ligand-binding domain (LBD), which has a transcriptional activation function domain-2 (AF-2) that connects to the DBD by a hinge region [AF-2, activation function domain-2; CTD, C-terminal domain; DBD, DNA-binding domain; LBD, ligand-binding domain; NTD, amino terminal domain; ORF, open reading frame; UTR, untranslated region].

**Androgen-insensitivity syndrome**

Androgen-insensitivity syndrome is an X-linked recessive disorder in which masculinization of external and internal genitalia does not occur properly. AIS patients exhibit end-organ resistance to androgens because of defects in the AR gene and thus in the resulting protein (Brown, 1995). This makes the condition distinct from other forms of male pseudo-hermaphroditism such as 17α-hydroxy-steroid dehydrogenase type 3 deficiency or 5α-reductase type 2 deficiency (Wilson et al., 1974, 1993; Geissler et al., 1994). The syndrome consists of two major categories: complete androgen-insensitivity syndrome (CAIS) or partial androgen-insensitivity syndrome (PAIS), depending on the extent to which the body lacks functional AR (Brown, 1995). Despite the fact that both PAIS and CAIS patients have XY karyotype (making them genetically male), CAIS patients exhibit various female phenotypic characteristics including: female external genitalia, underdeveloped vagina, absence of prostate, epididymis, vas deferentia, seminal vesicles, no sexual hair growth, and gynecomastia development (Brown, 1995; Quigley et al., 1995; Boehmer et al., 2001). On the other hand, phenotypic characteristics of PAIS patients are generally more variable, ranging from an overall female appearance (with external female genitalia, female growth patterns in pubic hair) to ambiguous genitalia or a predominantly male phenotype (Quigley et al., 1995; Boehmer et al., 2001). Patients that belong to this latter group normally exhibit characteristics such as micropenis, cryptorchidism, and perineal hypospadias. Although levels of testosterone, luteinizing hormone, and estradiol increase in PAIS patients during puberty, there is decidedly less feminization compared with that of CAIS patients. Infertility in some patients has also been attributed to mild forms of AIS (Batch et al., 1993; Imasaki et al., 1994; Evans et al., 1997; Boehmer et al., 2001). Despite the myriad of phenotypic characteristics in AIS patients, they all have fully functional testes which produce normal levels of hormones such as testosterone and Mullerian-inhibiting factor. This accounts for the fact that AIS patients do not have Mullerian-derived structures such as proximal vagina, uterus, or the fallopian tubes (Brown, 1995). The etiology of AIS is a loss-of-function mutation in the AR gene, which resides on the long arm of the X-chromosome (Xq11–13). Loss of function means loss of hormonal function on tissues despite normal levels of androgen synthesis (Brown, 1995).
types of mutations have been studied extensively in 46, XY patients with AIS: single point mutations (which results in misplaced stop codons or amino acid substitutions), insertions and deletions of nucleotides which causes shifts in the translations reading frame, complete/partial gene deletions, and mutations in introns that affect splicing of the AR RNA (Gottlieb et al., 2004).

As the NTD of the AR receptor is a highly conserved region, deleterious mutations are relatively rare (mutations have been found in only 8% of the codons in this domain). The majority of the mutations prematurely terminate the translational process through stop codons or frameshift mutations from nucleotide insertions/deletions (Gelmann, 1996). One study discovered a mutation in the fourth nucleotide which decreases the translational efficiency of the AR mRNA in a PAIS patient (Choong et al., 1996a,b). Other mutations, in combination with mosaicism or mutations in other regions of the gene have been cited in the NTD.

The DNA-binding domain (including the two prominent zinc fingers), on the other hand, contains a significantly higher percentage (27%) of codons that exhibit mutations (Gelmann, 1996). Mutations in this domain – which consist mainly of single nucleotide substitutions – cause the DNA-binding/dimerization activity of the protein to be defective, leading to impaired or absent transcriptional activation by the AR (Gast et al., 1995). However, two studies have shown – through 3D-modeling of the mutated DBD – that certain mutations in this region indeed do not result in the loss of function in the AR (Lobaccaro et al., 1996; Bruggenwirth et al., 1998). A mutation (G577R) in a region involved with recognizing AREs was detected in a PAIS individual. It was shown that this mutation affected the transactivation of various synthetic and natural promoters differently, suggesting that androgen target genes did not respond the same way to the mutation (Nguyen et al., 2001). The Ala596Thr mutation in the second zinc finger inhibited dimerization of AR upon contact with androgens in one PAIS patient (Gast et al., 1995). Finally, a Ser579Arg mutation has been shown to have unpredictable and varying effects on the individual, ranging from feminization to normal male phenotype (Gwercman et al., 2004).

Only six mutations have been reported in the hinge region of the AR (only 8% of codons exhibited mutations) (Gelmann, 1996), possibly signifying that this region affords flexibility in its genetic makeup. Some variations in the gene sequence are not significantly detrimental to AR function (Greep, 1978). Nevertheless, studies have reported an I664N substitution on the border of the hinge region that resulted in lowered hormone-binding efficiency (Pinsky et al., 1992).

The ligand-binding domain of the AR is the site of the largest number of mutations: 56% of the codons contain mutations (Gelmann, 1996). Both complete and partial AIS have been described in association with certain mutations, precluding a strict match between genotypes and phenotypes of patients. Mutations in the LBD affect many functional aspects such as receptor stability, ligand-binding efficiency, interaction with coactivator receptors, and ligand binding (Greep, 1978).

Instances of partial/complete gene deletions in the AR have been relatively few, possibly because the AR gene itself does not often exhibit these kinds of defects (Gelmann, 1996). Deletion of exon 3 results in an AR protein that lacks the second zinc finger, whereas loss of exon 4 leads to a missing hinge region and N-terminal part of the LBD. Nevertheless, a sole deletion in exon 3 still results in a functional LBD (Greep, 1978).

Splice donor and splice acceptor mutations in the AR gene are also exceedingly rare in AIS individuals (Gelmann, 1996). In one study, seven out of eight reported cases of substitution mutations in donor splice sites, were patients with CAIS (Greep, 1978). Insertion of a nucleotide at a splice donor site in intron 6 caused PAIS in one case (Trifiro et al., 1997). As for splice acceptor sites, only three mutations have been reported which all alter the effective splicing of the AR mRNA. A substitution mutation in the acceptor site at intron 2 caused activation of a cryptic splice acceptor site and a mass insertion of 69 nucleotides between exons 2 and 3 of the AR mRNA (Bruggenwirth et al., 1997). Because insertion corresponded to the region between the first and second zinc clusters of the DBD, the protein was unable to bind DNA effectively (Greep, 1978).

Mutations of the AR in AIS patients can cause a variety of functional abnormalities: from a complete loss of receptors on cell surfaces because of premature termination of the synthesis process, or defective AR that cannot bind substrates as effectively. This latter condition ultimately results in impairment or loss of signal transmission from AR, regardless of the concentration of androgens or functionality of AR (Brown, 1995).

Data are not yet available regarding the incidence of CAIS/PAIS in the United States. However, AIS incidence internationally is reported to be 1 in 20,400 live born males (CAIS occurs at a higher rate than PAIS). The medical morbidity of AIS is very limited. Even if untreated patients develop testicular malignancies, these are readily curable provided that they are limited to the testes. Comparatively speaking, the psychological morbidity of AIS patients is much more substantial. The psychological issues engendered by being treated as oddities during medical examinations (perhaps being examined in unnecessarily number of times simply for teaching students and residents), lack of self-confidence, and confused gender perceptions are considerable. As of yet, no racial differences have been attributed to the incidence of AIS (Brown, 1995). Readers are encouraged to review the most recent and comprehensive update on numerous mutations found in AR protein in McGill University, Montreal, Canada website at http://androgendb.mcgill.ca/ (Gottlieb et al., 2012).

**Spinal and bulbar muscular atrophy**

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy’s disease, is a rare hereditary X-linked recessive disease characterized by death of nerve cells in the spinal cord and bulbar region of the brainstem, leading to muscle weakness and atrophy of limb, facial, and bulbar muscles (McEwan, 2001; Katsumo et al., 2004). SBMA is caused by an abnormal number of trinucleotide CAG (polyglutamine tract) repeats in the AR gene. SBMA only affects males; its incidence is 1–2 per 100,000 without correlation to certain ethnic and racial backgrounds (Fischbeck, 1997).

The onset of muscle weakness usually occurs between the ages of 30 and 60 years, although there are often non-specific symptoms earlier in life, such as muscle cramping and tremors. Fasciculations (slight involuntary muscle contractions) conspicuous in the face, neck, and tongue are present in the early stages, and those of the extremities are easily induced by muscle stress.
Bilateral weakness in facial and masseter muscles, impaired palatal and uvula movements coupled with atrophy and tremors of the tongue eventually lead to impaired speech, aspiration, and choking. The speech of SBMA patients often has a nasal quality because of reduction of the velopharyngeal closure. Muscle tone is often hypotonic and deep tendon reflexes are impaired; sensory involvement is largely restricted to loss of vibration sense which is evident distally in the legs. Electromyograms show reduced sensory nerve action potentials and endocrinological tests reveal elevated testosterone levels (possibly caused by partial androgen resistance). Although patients with SBMA do not experience cognitive impairment, cerebellar symptoms, or dysautonomia (malfunction of the autonomous nervous system), they may suffer from a variety of disorders including gynecomastia, reduced fertility, erectile dysfunction, testicular atrophy, abdominal obesity, hyperlipidemia (elevated lipid levels in the blood), liver impairment, and glucose intolerance. Patients often develop difficulty walking in their fifties and sixties, and many suffer life-threatening respiratory tract infections. As expected, fatigability after any kind of stressful movement or exercise is common (Greenland & Zajac, 2004). Female patients with SBMA usually remain asymptomatic, although some patients have reported frequent muscle fasciculations and mild facial weakness later in life (Sobue et al., 1993; Fischbeck, 1997; McEWan, 2001; Greenland & Zajac, 2004; Katsuno et al., 2004).

As mentioned before, etiology of SBMA is an expansion of the CAG repeat (polyglutamine tract) in the AR gene which leads to neurodegeneration (La Spada et al., 1991; Gatchel & Zoghbi, 2005). Unaffected individuals exhibit between 9 and 36 repeats, but patients with SBMA often display 38 to 62 repeats upon gene analysis. SBMA belongs to a larger class of diseases known as polyglutamine diseases (because of the abnormalities in the polyglutamine tract) (Gatchel & Zoghbi, 2005). Therefore, like other polyglutamine diseases, SBMA exhibits anticipation, somatic mosaicism, and selective neuronal/non-neuronal involvement even though the mutant gene is expressed throughout the body. The age of onset of the disease and the severity of SBMA is inversely correlated with the amount of CAG expansion in the AR gene, with longer expansions inducing earlier onset and more severe cases of the disease, and vice versa (Doyu et al., 1992).

The expansion of the polyglutamine tract in the AR gene influences the pathogenesis of SBMA by two different mechanisms: impaired or absent AR function leading to neurodegeneration, and pathogenic AR function leading to toxic damage of neurons. The abnormally large number of CAG repeats inhibits interaction between the N-terminal transactivation domain and the coactivators (Poletti, 2004), but the chief cause of neurodegeneration in SBMA is believed to be acquired toxicity attributed to the production of abnormal AR proteins (Adachi et al., 2001). Aggregation is favored among the altered AR proteins that have abnormally long stretches of polyglutamine repeats. The rate-limiting step of aggregation is the formation of oligomeric nuclei, resulting from a repeat length-dependent conformational change in the polyglutamine monomer (Wytenbach, 2004). Studies have shown that these oligomers (intermediates) are toxic and thus lead to cellular events causing neurodegeneration (Muchowski & Wacker, 2005). Furthermore, AR proteins with long polyglutamine tracts can be cleaved by capase-3 proteins (with longer tracts being more susceptible to cleavage and vice versa), liberating a polyglutamine-containing toxic fragment and thus increasing the toxicity of AR protein (Kobayashi et al., 1998). A recent study found AR polyglutamine reduced long-term protein turnover and impaired autophagic flux in motor neuron-like cells and blocked autophagy pathway progression. The transcriptional regulation of autophagy revealed a functional association between transcription factor EB (TFEB) and AR. The normal polyglutamine tract containing AR promoted TFEB transactivation while long-tract inhibited it (Cortes et al., 2014). Autopsy studies of patients with SBMA reveal that there is often diffuse nuclear accumulation of pathogenic AR in the anterior horn of the spinal cord (Adachi et al., 2005); the frequency of this accumulation is correlated with the length of CAG repeat in the AR gene. Thus, it seems that aggregation of the pathogenic AR protein in the nucleus is significant in causing cell dysfunction and degeneration (Katsuno et al., 2004). More specifically, such accumulation in the nuclei of motor neurons in diffusible form leads to neuronal dysfunction and cell death (Gatchel & Zoghbi, 2005). Because AR is expressed in almost every organ in the body, it is not surprising that accumulation of pathogenic AR occurs not only in the central nervous system, but also in other tissues such as scrotal skin. In fact, the amount of accumulation in scrotal skin is correlated with that of the spinal motor neurons and the number of CAG repeats present, but is inversely correlated with motor functional scale (Banno et al., 2006). This indicates that scrotal skin biopsy for polyglutamine tracts of the pathogenic AR protein may serve as an efficient biomarker to monitor SBMA (Katsuno et al., 2004).

Several factors that are not involved directly with pathogenic AR have also been hypothesized to contribute to the pathogenesis of SBMA: HSPs, transcription dysregulation, and axonal trafficking in motor neurons. HSPs are stress-inducible molecular chaperones that play crucial roles in folding, assembling and transporting proteins (Macario & Conway de Macario, 2005). For example, HSP70 and HSP90 cooperate exclusively with AR protein and regulate its function, nuclear translocation, and degradation. Also, HSP are responsible for abrogating toxic conditions in the cell by refolding certain proteins (Heinlein & Chang, 2004). However, several studies have shown that polyglutamine expansion inhibits proper cellular responses to cytotoxic stress (Wytenbach, 2004). Truncated AR with a long polyglutamine region delays the induction of HSP such as HSP70 (Cowen et al., 2003).

Disruption of transcriptional processes may also underlie the pathogenesis of polyglutamine diseases such as SBMA (Sugars & Rubinsztein, 2003). For example, cAMP response elements (CREB-binding protein or CBP) are transcriptional coactivators that act as a histone acetyltransferase – regulating gene transcription and chromatin structure. However, CBP’s activity is inhibited in cells of patients with polyglutamine diseases. Therefore, this malfunction of transcriptional machinery may lead to neurodegeneration observed in polyglutamine diseases. In support of this hypothesis, acetylation of nuclear histone H3 has been reported to be greatly reduced in SBMA mice (Minamiyama et al., 2004).}

© 2016 American Society of Andrology and European Academy of Andrology

Andrology, 2016, 4, 366–381 371
of motor neurons. Recently, obstruction of axonal transport has been shown to be a major component of neurodegeneration in diseases such as SBMA (Gunawardena & Goldstein, 2005). A mutation in the genes encoding proteins dynein and dynactin 1 (responsible for regulating axonal transport) causes motor neuron degeneration in both human and mice (Hafezparast et al., 2003; Puls et al., 2003). Although experimental data suggest that axonal transport may be inhibited by pathogenic AR containing expanded polyglutamine tracts, accumulation of pathogenic AR is rarely found in axons of the motor neuron. Therefore, further studies need to be made before a definitive conclusion can be drawn (Szabó et al., 2003).

**Hypogonadism**

As discussed above because of mutations of AR and its defective transactivation function variable phenotypes of androgen insensitivity is a common phenomenon in both, male and female. Low levels of serum testosterone in human manifests hypogonadism. Hypogonadism is characterized by lack of production of enough testosterone which can be congenital or may develop later in adulthood. Congenital male hypogonadism may delay puberty and impede normal development. The adulthood hypogonadism is characterized by altered masculine physical characteristics, decrease in muscle mass, erectile dysfunction, gynecomastia, and osteoporosis. Serum testosterone levels decreases, whereas the increase in sex hormone-binding globulin ensues progressively during the normal aging process. In addition, a variety of other conditions including Kallmann syndrome, pituitary and hypothalamic disorders, inflammatory diseases, and obesity causes andropausal symptoms resulting in decrease activity of AR and hypogonadism (Kumar et al., 2010). These conditions are basically linked to the downregulation albeit, differential transactivation function of the AR. Such subtle modulation of androgen effect has also been attributed to the presence of CAG repeat polymorphism in the AR gene (Zitzmann, 2009). Clinical testing of CAG repeat numbers for diagnosis and treatment of hypogonadism is still debatable. CAG polymorphism in AR has also been directly correlated with insulin, triglycerides, and blood pressure in men undergoing testosterone replacement therapy (Stanworth et al., 2014). It may be of importance to determine the CAG repeat number to tailor the testosterone dosage for differential pharmacological treatment of hypogonadism (Francomano et al., 2013; Morgentaler et al., 2014). Studies have shown a direct correlation between the level of serum testosterone and the number of polyglutamine CAG repeats (Crabbe et al., 2007). Interestingly, longer CAG repeat polymorphism of AR gene correlates with increased androgen/estrogen ratio in males (Hulthaniemi et al., 2009), which has also been implicated in decreased potency (Harkonen et al., 2003). On the other hand, short AR CAG repeat number is associated with infertility, defective spermatogenesis, and azoospermia. These variable phenotypes because of polymorphism in AR CAG repeat is also likely to influence modalities of testosterone treatment in hypogonadal men (Zitzmann, 2007, 2009).

**Benign prostatic hyperplasia**

Benign prostatic hyperplasia (BPH) is a prevalent disorder in men (Webber, 2006; Donnell, 2011). More than 50% of men 60 years of age and 90% of men 85 years of age will exhibit some histologic evidence of BPH, and about one in four men have clinical symptomology related to it. The disease results from hyperplasia of prostatic stroma and/or glandular elements. Both the enlarged prostate and increased smooth muscle tone in the gland obstruct urinary flow, resulting in voiding symptoms, including hesitancy, frequency, urgency, intermittency, weak stream, urinary dribbling, nocturia, incomplete voiding, and urinary incontinence (involuntary loss of urine). As BPH progresses, incomplete emptying of the bladder may supervene favoring the development of urinary tract infections, formation of bladder stones, hydronephrosis (dilation of kidneys from obstructed urine), and reduced renal function. The incidence of these symptoms significantly increases with age (Webber, 2006; Donnell, 2011). So far, only age and an intact androgen system have been documented as risk factors for BPH. Changes in the regulation/production of androgens (which promote the growth of various organs such as the prostate) and estrogens are thought to effect the development of BPH, but the actual mechanisms through which this occurs has not yet been elucidated. However, because androgens mainly act through cooperation with AR, variations in the function of AR gene (and thus its protein product) may significantly influence the pathogenesis of BPH (Roberts et al., 2004).

As mentioned in previous sections, the two highly variable polymorphisms in the AR gene (both in exon 1 of the N-terminal region) are the CAG polyglutamine and GGN polyglycine repeats. A short CAG repeat causes increased AR transactivation, whereas a longer CAG stretch results in reduced activity (Chamberlain et al., 1994; Choong et al., 1996a,b; Tut et al., 1997). Consequently, a shorter CAG tract could lead to over-stimulated growth of the prostate, resulting in BPH. The effects of GGN repeats on the function of AR are not yet clear, although one study has shown that deletion of the polyglycine resulted in reduced receptor function (Gao et al., 1996). Studies examining the effects of polyglutamine repeats in the receptor gene and BPH have been inconsistent (Roberts et al., 2004). Some researchers have reported an association between short repeat numbers and BPH, whereas others have reported the contrary (Bousema et al., 2000; Schatzl et al., 2002). This discrepancy may be related to the use of different criteria to define BPH (Roberts et al., 2004). In a recent study of the association between the polymorphism lengths (CAG and GGN repeats) in the AR gene and the incidence of BPH in a cohort of men it was found that the risk of BPH and the age of incidence was increased and decreased, respectively, for a small number of CAG (<21) and GGN (<16) repeats. The results regarding the CAG repeats concur with previous studies showing that fewer CAG repeats increase AR transactivation activity (such as prostate growth), and increased numbers of CAG repeats are associated with reduced receptor function and mRNA expression (Choong et al., 1996a,b; Tut et al., 1997). Although no association between GGN repeat numbers and BPH had so far been documented, results from the aforementioned studies suggest that they may be related. Because AR gene is located on the X-chromosome, the two alleles may have an additive effect on the incidence of BPH, where the presence of both high-risk polymorphisms could considerably influence the function of AR. However, the effect of deletion of GGN repeat region of the AR gene in this study was inconsistent with findings in a previous
study in which reduced AR transcriptional activity was observed in such settings (Gao et al., 1996). Furthermore, BPH is a condition influenced by multiple genes, and the relative importance of AR gene and its polymorphisms is difficult to evaluate in isolation (Roberts et al., 2004).

Prostate cancer

Prostate cancer is the most prevalent non-skin cancer in the United States, affecting one in every six men and is the second leading cause of cancer-related deaths in males (Siegel et al., 2015). Its incidence increases with the age of the individual. It is estimated that more than 65% of all prostate cancer patients are men over the age of 65. Ethnicity, family history, and high animal fat intake also influence the risk for prostate cancer. African American men are 61% more likely to have the disease in comparison to Caucasian men, and are 2.5 times more likely to die from prostate cancer. Men who have a first-degree relative (father, brother, son) diagnosed with prostate cancer are twice as likely to be diagnosed with this disease. The risk is four-fold for those who have two or more affected relatives. Furthermore, the risk is even higher if such relatives were diagnosed before the age of 60. Social and environmental factors including diet, smoking, and alcohol consumption also appear to influence the risk for prostate cancer (Brawley et al., 1998a,b; Hsing & Chokkalingam, 2006). Prostate cancer in its earlier stages usually does not exhibit any symptoms. However, as cancer progresses, symptoms develop and gradually become more pronounced. Symptoms include, but are not limited to frequent urination (especially at night), hesitancy, urinary urgency with or without incontinence, weak or interrupted stream, dysuria, impotence, painful ejaculations, blood in the urine or semen, recurring pain/stiffness in the lower back, hips, and upper thighs. Unfortunately, these symptoms overlap with symptoms related to other prostate diseases such as BPH or prostatitis. Therefore, thorough check-ups and testing are necessary to pinpoint accurate cause of these symptoms.

Prostate development and normal prostate function is dependent upon androgens and their actions on target hormones (such as growth factors) through the androgen-AR signaling pathway (Roy et al., 1999). Therefore, AR and the modulators of AR activity are considered significant factors in the progression of prostate cancer. In fact, 80–90% of prostate cancers are initially dependent upon androgens, which is why initial therapy of prostate cancer is targeted toward decreasing circulating androgens and AR activity (Denis & Griffiths, 2000). Unfortunately, androgen ablation therapy eventually fails, and cancer develops into a hormone-refractory stage (Heinlein & Chang, 2004). Once cancer becomes hormone refractory, AR may be activated through other means to stimulate growth besides binding to androgen ligands. Studies have shown that such an activation is dependent on the NTD of the AR (Gao et al., 1996). Recently investigators have created AR NTD decoy molecules that competitively bind to proteins required for ligand-independent activation of AR. Evidence from in vitro expression showed that such decoys decrease tumor incidence and inhibit prostate cancer growth in NOD-SCID mouse xenograft (Quayle et al., 2007). It seems clear that loss of AR function is not the cause of androgen deprivation therapy failure, but instead that prostate cancer progresses through the alteration of the AR activity and molecular interactions (Schmidt & Tindall, 2013; Antonarakis et al., 2014a,b; Chan & Dehm, 2014; Culig & Santer, 2014).

As mentioned previously, the two major polymorphisms in the AR gene are the CAG and the GGN repeats. AR that have shorter CAG polymorphic regions show increased transcriptional activity. Their effects in altering AR transcriptional activity may cumulatively contribute to cancer risk and age of diagnosis (Heinlein & Chang, 2004). In fact, short CAG repeat lengths have been reported to be associated with an earlier age at diagnosis (Bratt et al., 1999; Beilin et al., 2001), higher cancer grade at the time of diagnosis, and more aggressive biologic behavior (Giovannucci et al., 1997; Ingles et al., 1997). Furthermore, short CAG repeat regions may also act in tandem with AR co-regulators or polymorphic promoters of AR target genes to increase prostate cancer susceptibility (Heinlein & Chang, 2004). For example, the steroid receptor coactivators (SRC) co-regulator in the prostate and its interaction with AR genes that have shorter CAG repeat lengths is hypothesized to increase the risk for prostate cancer because of its ultimate effect on the transcriptional activity of the AR (Culig et al., 2000, 2004; Heinlein & Chang, 2004; Heemers et al., 2010; Culig & Santer, 2014). Also, individuals homozygous for relatively shorter CAG repeat lengths (<20) and the G allele of a PSA target gene promoter (which contains an ARE) have been reported to show a five-fold increase in the risk for prostate cancer (Xue et al., 2001). The greater binding affinity of the AR with this allele of PSA gene promoter (PSA encodes for a protease that cleaves extracellular matrix proteins) and increased activity of the short CAG AR, is hypothesized to additively contribute to prostate carcinogenesis (Xu et al., 2000; Ding et al., 2004). On the other hand, other polymorphic repeat GGN, of the AR gene is less studied than the CAG repeat region in its relation with the risk for prostate cancer (Heinlein & Chang, 2004). The conclusions drawn from various studies are inconsistent. Two studies reported that short GGN repeat lengths increase susceptibility to the development of prostate cancer (Hakimi et al., 1997; Stanford et al., 1997), whereas another study reported that a longer GGN repeat length is associated with increased risk for the disease as well as death (Edwards et al., 1999). AR gene amplification has been proposed as a mechanism by which prostate cancer cells can continue to grow despite the low levels of androgen associated with androgen ablation therapy (Culig et al., 2003; Debes & Tindall, 2004). Although most of the amplification cases involve wild-type AR gene, two cases have been reported in which point mutations have taken place (Koivisto et al., 1997; Wallen et al., 1999). Unfortunately, AR amplification has not been consistent with an increase in the expression of AR target genes. Therefore, this mutational event may simply be because of genomic instability during prostate cancer progression.

In several prostate cancer cases, the coactivators ARA70 and SRC have been found to be over-expressed (Yeh & Chang, 1996; Heinlein & Chang, 2004). Because coactivators enhance transcriptional activity of AR and activate these receptors at lower ligand concentrations, the observed over-expression of AR coactivators may contribute to carcinogenesis of the prostate (Gao et al., 1996; Heinlein & Chang, 2004). For example, an increase in SRC-3 coactivator expression was found to be associated with an increase in prostate cancer aggressiveness and decreased disease-free survival (Gnanapragasam et al., 2001). However, it remains to be determined which specific coactivators are
significantly over-expressed in prostate cancer. The over-expression of coactivators may also allow cancer cells to proliferate despite androgen deprivation because of enhanced sensitivity of AR to androgens (Gregory et al., 2001).

Tumor suppressor genes – retinoblastoma susceptibility gene (Rb), breast and ovarian cancer susceptibility gene (BRCA1), and phosphate and tensin homolog (PTEN) have been shown to interact with AR to influence transactivational activity. Rb normally enhances AR transcription; inhibition of the Rb-AR complex leads to the reduction in AR functionality (Lu & Danielsen, 1998; Yeh et al., 1998; Barbieri et al., 2013). In prostate cancer, Rb expression is decreased despite the fact that AR expression is increased (Tricoli et al., 1996). This suggests Rb’s role as a negative regulator of the cell cycle is dominant to its interaction with AR proteins. BRCA1, responsible for regulating cell cycle and DNA repair has been shown to enhance AR transcriptional activation (Yeh et al., 2000; Rosen et al., 2001). Although some researchers report that prostate cancer risk is exacerbated with certain BRCA1 mutations, others have failed to find such an association (Sinclair et al., 2000; Vazina et al., 2000). PTEN, on the other hand, is found to inhibit AR protein through its degradation (Lin et al., 2004). PTEN negatively regulates PI3K/Akt kinases to control the amount of cellular proliferation and apoptosis (Simpson & Parsons, 2001). In prostate cancer, studies have shown that in the absence of PTEN, AR is no longer degraded properly and aberrant regulation of these kinases results in increased AR transcriptional activity. Loss of PTEN correlates with higher Gleason scores in prostate cancer specimens (McMenamin et al., 1999).

Alteration of growth factor or growth factor receptor expression by tumor cells can also affect prostate cancer progression (Russell et al., 1998; Djkiew, 2000). Growth factors and cytokines regulate cells through membrane receptor binding, whereupon a phosphorylation cascade is initiated that eventually leads to phosphorylation of transcription factors. AR is one of the transcription factors that is modulated by these cascades, so disruption of these interactions may play a role in the evolution of prostate cancer. Mediation of the AR in prostate cancer – through phosphorylation of AR directly or its coregulators – by these signal transduction cascades may involve enhancing AR activity to allow proliferation despite low androgen levels (Kyprianou & Isaacs, 1987; Gelmann, 2002; Heinlein & Chang, 2004; Montgomery et al., 2014).

Lastly, AR may develop the ability to become activated by a broader range of ligands (such as adrenal androgens, estrogen, progesterone, cortisol, and antiandrogens) (Gelmann, 2002; Heinlein & Chang, 2004). The majority of these mutations are point mutations with single amino acid substitutions that are focused to the LBD of the AR, thus relaxing the binding specificity of ligands (Buchanan et al., 2001; Gelmann, 2002; Taplin et al., 2003). In some metastatic prostate cancers, ligand-relaxation mutations in the AR allow anti-androgens to function as AR agonists, and allow adrenal androgens to activate AR transactivation activity. The most frequent mutation of the former type – T876A – can also be activated by dehydroepiandrosterone (DHEA) (Tan et al., 1997; Shi et al., 2002), androstenediol (Miymoto et al., 1998), estradiol, and progesterone (Veldscholte et al., 1990; Miyamoto et al., 1998; Shi et al., 2002). Up to 30% of metastatic prostate cancer samples show enhanced AR transcriptional activity because of binding with adrenal androgens (Culig et al., 1993; Suzuki et al., 1993; Taplin et al., 1995; Tilley et al., 1996; Marcelli et al., 2000), suggesting that adrenal androgens alone, or together with antiandrogens may cause failure of androgen ablation therapy and facilitate progression of prostate cancer.

Ligand-binding relaxation of AR may be caused by interactions with various AR coactivators. For example, the coactivator ARA70 allows wild-type AR to bind to anti-androgens and bicatalumidine (Yeh & Chang, 1996). ARA70 also enables adrenal androgens to activate AR. DHEA and androstenediol may only enhance AR transcriptional activity if there is a mutant T876S AR interacting with ARA70 (Labrie et al., 1988; Miyamoto et al., 1998). Supervillin and a mutant of β-catenin S33F have also been reported to enable AR transcriptional activation when adrenal androgens are present (Truica et al., 2000; Ting et al., 2002). Estradiol may sometimes act as an AR activator when ARA70, β-catenin S33F, or ARA55 interacts with the AR protein (Thin et al., 2002; Ting et al., 2002; Rahman et al., 2003).

AR-TARGETING AGENTS IN PROSTATE CANCER

Targeting of AR functions using AR-antagonist in both, castration-sensitive and castration-resistant prostate cancer remain the mainstay in prostate cancer therapy. However, the development of drug resistance because of the scores of ligand-independent cellular tricks covertly played by AR leads to ineffective treatment of castrate-resistant prostate cancer. Hence, exclusive targeting of AR function at protein level does not appear to be effective in ~27,000 patients who die from this deadly form of prostate malignancy every year alone in the United States. Hence, novel approaches to target AR transactivation function at post-transcriptional or at translation stages appears to be an innovative approach. It is interesting to note that, in response to Enzalutamide (XTandi-AR antagonist) and Abiraterone acetate (Zytiga-targets CYP17A1) treatment of novel alternatively spliced aberrant AR variants are produced by unknown RNA-splicing mechanisms (Dehm et al., 2008; Dehm & Tindall, 2011; Chan et al., 2012; Li et al., 2013). A majority of prostate cancer relapsed tumors express wild-type AR as well as an aberrantly spliced short form of AR, which along with intratumoral androgens promotes oncogenic AR signaling, proliferation, and survival. (Antonarakis, 2014; Antonarakis et al., 2014a,b; Nakazawa et al., 2014). These AR splice variants appears to have a common 3'UTR. Hence, targeting AR mRNA at the post-transcriptional stage by novel RNA-based strategies would have superior and desirable results in prostate cancer therapies. Because of ~6.8 kb long 3' UTR of AR mRNA, the post-transcriptional control of the expression is likely to be regulated by hundreds of miRNAs in normal as well as in disease state (Sikand et al., 2011; Ebron et al., 2013). We have previously demonstrated that miR-488* has ability to post-transcriptionally regulate AR expression in human prostate cancer cells and downregulation has been observed in prostate cancer (Sikand & Shukla, 2011; Ebron et al., 2013). The use of miRNAs as potential therapeutic targets has been examined in several studies that have shown to target specific miRNA deregulation (both over-expression and down-regulation) in cancer cells is associated with pathogenic effect. Studies have demonstrated that modulating the expression levels of miRs in various cancers including prostate cancer by miR mimics or antagonims improves their therapeutic index. Osling et al. have shown that miR-34a over-expression lead to
downregulation of AR expression (Ostling et al., 2011). We have also observed that miR-34a has ability to target the transactivation function of AR and downregulate AR-androgen signaling that fuels growth factor over-expression. Recently, miR-34a mimetic was systemically delivered to lung tumor in murine model which inhibited tumor growth to provide therapeutic relief (Wiggins et al., 2010). Moreover, miR-34a mimetic delivery in animals did not influence non-specific immune responses. In addition, miR-34a blocked cell-cycle progression and induced apoptosis in lung cancer cells (Daige et al., 2014). Interestingly, miR-34a is a transcriptional target of tumor suppressor gene, p53 suggesting its molecular connection with the tumor suppressor pathway in cancers (He et al., 2007). From these studies, it is clearly established that miRNA replacement therapeutics is not a distant dream. Currently, miR-34a as ‘MIRX34’ is in phase I clinical trials to treat primary lung tumors, solid tumors, lymphoma, AML, CLL, ALL, and multiple myelomas (https://clinicaltrials.gov/ct2/show/NCT01829971?term=MIRX34&rank=1). In addition, there are >200 studies currently listed in clinicaltrials.gov which highlights the therapeutic and prognostic value of miRNAs in diseases including cancers. Detail description of these miRNAs is beyond the scope of the manuscript. We suggest readers to consult several excellent reviews published in last several years with extensive details of miRNA biogenesis, differential regulations, biomarkers, and therapeutics potentials (Bar tel, 2009; Garofalo & Croce, 2011; Shukla et al., 2011).

CONCLUSION AND FUTURE DIRECTIONS
Androgen receptor is one of the most important and extensively studied steroid receptors because of its important physiologic function in many organs and its involvement in the pathogenesis of various diseases including cancers (Cai et al., 2009; Yap et al., 2011; Friedlander et al., 2012; Izumi et al., 2013; Schmidt & Tindall, 2013; Egan et al., 2014; Barbieri & Rubin, 2015). However, despite numerous studies addressing AR role in growth and development as well as its pivotal role in prostate cancer, the molecule remains enigmatic and has remained a resilient foe (Nelson, 2014). In this review, we have provided a brief summary on the function and mechanics of the androgen-AR signaling pathway and the diseases (AIS, SBMA, BPH, and prostate cancer) that may result from abnormalities in the expression of AR and its downstream targets. The common pharmacological agents and surgical therapies utilized to manage above diseases have been discussed. We provided a snapshot of mutations which renders the function of AR useless as in AIS, SBMA, or makes AR a number one ‘villain’ in the development of prostate carcinogenesis and failure of treatments (Isaacs, 1999; Culig et al., 2005; Singh et al., 2006; Ang et al., 2009; Antonarakis & Armstrong, 2011; Lorente & De Bono, 2014; Mostaghel et al., 2014). It is needless to say that a lot more research and investigations are needed to continue to clarify the relation between aberrations in signaling pathways and onset or progression of prostate cancer to develop efficient drugs to target AR transactivation function that fuels the development of metastatic castration-resistant prostate cancer. The recent development with respect to AR nuclear pre-mRNA splicing is intriguing. In response to treatment with Abiraterone acetate (ZYTIGA CYP17A1 inhibitor) and Enzalutamide (XTANDI-AR mCRPC antagonist) AR pre-mRNA splicing produces multiple spliced variants which appears to promote treatment failures and development of metastatic castrate-resistant prostate cancer (Dehm et al., 2008; Sun et al., 2010; Watson et al., 2010; Dehm & Tindall, 2011; Haile & Sadar, 2011; Zhang et al., 2011; Beltran et al., 2014; Robinson et al., 2015). However, molecular mechanism(s) orchestrating the production of alternatively spliced AR mCRPC isoforms remains unexplored. In fact, substantial research has been dedicated to study AR DNA and protein, however, not much work has been performed in relation to AR mRNA and its regulatory activities in cellular functions. We emphasize that significant information may be obtained about AR activities and function through studies focusing toward post-transcriptional stages of AR mRNA processing. It is known that alternatively spliced isoforms may be a result of numerous germ line or somatic mutations that disrupts cis-acting splice sites and RNA purine or pyrimidine-rich enhancer elements found within the exons of the pre-mRNA, execution of such studies will generate information about AR function in normal and disease state. These studies will provide unique opportunities to learn about the subversive characteristics of AR in the development of hormone and therapy-resistance phenotype.

ACKNOWLEDGMENTS
The research work in SG laboratory is supported by United States Public Health Service Grant R01CA108512, R21CA193080, R03CA186179, VA Merit Award 1I01BX002494, and Department of Defense grant W81XWH-15-1-0538. Research in GCS lab is supported by Department of Defense grants W81XWH-14-1-0508 and W81XWH-14-1-0509. The research work cited was partially supported by Faculty Research Development Grant of Cleveland State University and Center for Gene Regulation in Health and Disease grant.

REFERENCES


Evans BA, Hughes IA, Bevan CL, Patterson MN & Gregory JW. (1997)
ANDROGEN RECEPTOR-RELATED DISEASES ANDROLOGY
Friedlander TW, Roy R, Tomlins SA, Ngo VT, Kobayashi Y, Azameera A,
Endocr Relat Cancer 12, 229–244.
Andrology 2016, 4, 366–381


Kyrianou N & Isaacs JT. (1987) Biological significance of measurable androgen levels in the rat ventral prostate following castration. Prostate 10, 313–324.


Thin TH, Kim E, Yeh S, Sampson ER, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, ANDROGEN RECEPTOR-RELATED DISEASES ANDROLOGY

Thin TH, Kim E, Yeh S, Sampson ER, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, ANDROGEN RECEPTOR-RELATED DISEASES ANDROLOGY


