The development of human benign or malignant prostatic diseases is closely associated with androgens, primarily testosterone (T) and dihydrotestosterone (DHT). T is converted to DHT by 5-alpha reductase (5-AR) isozymes. Differential expression of 5-AR isozymes is observed in both human benign and malignant prostatic tissues. 5-AR inhibitors (5-ARIs) are currently used for the treatment of benign prostatic hyperplasia (BPH) and were once promoted as chemopreventive agents for prostate cancer (PCa). This review discusses the role of the differential expression of 5-AR in the normal development of the human prostate and in the pathogenesis and progression of BPH and PCa.

Keywords: 5-alpha reductase; 5-alpha reductase inhibitor; androgen; benign prostatic hyperplasia; prostate; prostate cancer

INTRODUCTION
The development of human benign or malignant prostatic diseases is androgen-dependent. Testosterone (T), the most abundant androgen in serum, is synthesized and secreted by the testes (95%) and adrenal glands (5%). However, T is not the primary androgen responsible for the development, growth and pathogenesis of the prostate. 5-alpha reductase (5-AR) converts T to dihydrotestosterone (DHT), which is the more potent ligand for androgen receptor (AR), and ligand binding to AR leads to an interaction with the androgen response elements of gene promoters. Upon ligand-AR binding and transactivation, the DHT-AR complex translocates into the nucleus and binds to androgen response elements to activate the transcription of AR-regulated genes. DHT-AR binding is more stable than T-AR binding with a three-fold lower dissociation rate and is more efficient with a 10-fold higher potency of AR signal transduction. DHT is the most prevalent and potent form of androgen in various human organs and tissues and plays a crucial role in the pathogenesis and progression of several diseases such as benign prostatic hyperplasia (BPH), prostate cancer (PCa), male pattern baldness, hirsutism and acne.

Three types of 5-AR isozymes, 5-AR1, 5-AR2 and 5-AR3, which are encoded by three distinct corresponding genes, SRD5A1, SRD5A2 and SRD5A3, exhibit differential expression patterns in the human body. 5-AR1 is primarily expressed in the skin and liver, while 5-AR2 is mainly found in the seminal vesicles, epididymis and prostate. 5-AR3 has recently been detected and described in castrate-resistant PCa. 5-AR plays a critical role in the normal development of the human prostate and in the pathogenesis and progression of prostatic diseases. As an inhibitor of the conversion of T to DHT, 5-AR inhibitors (5-ARIs) are currently used for the prevention and treatment of these conditions. The purpose of this review is to discuss the differential expression of 5-AR isozymes and their role in prostate development and the pathogenesis of prostatic diseases in an effort to define the therapeutic role of 5-AR.

THE BIOLOGY OF 5-AR ISOZYMES
Characteristics of 5-AR isozymes
The 5-AR family consists of 5-AR1, 5-AR2 and 5-AR3 (Table 1). Both 5-AR1 and 5-AR2 are microsomal nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzymes with 259 and 254 amino acid residues and molecular weights of 29.5 and 28.4 kDa, respectively. The pH optimum for 5-AR1 is 6–8.5, while that for 5-AR2 is 5–5.5. The newly detected 5-AR3 is also a microsomal NADPH-dependent enzyme made up of 318 amino acid residues. The gene architectures of SRD5A1, SRD5A2 and SRD5A3 are similar, with five exons and four introns. However, these genes are located on different chromosomes, with SRD5A1 on 5p15, SRD5A2 on 2p23 and SRD5A3 on 4q12.

Tissue distribution of 5-AR isozymes
Both 5-AR1 and 5-AR2 are expressed throughout human life. 5-AR1 is detected at quite low levels in the fetal scalp and nongenital skin, while 5-AR2 is expressed in the external genital skin early in gestation. In adults, 5-AR1 is expressed in nongenital skin, the liver and certain brain regions, and also at lower levels in the prostate, genital skin, epididymis, seminal vesicles, testis, adrenal gland and kidney. 5-AR2 is expressed at relatively high levels in the prostate, genital skin, epididymis, seminal vesicles and liver. Godoy et al. examined the expression of 5-AR3 in various benign and malignant tissues and reported that 5-AR3 was overexpressed in lung adenocarcinoma, testicular seminoma and yolk sac tumors, androgen sensitive PCa and castration-recurrent PCa relative to their benign counterparts.

MUTATION OF 5-AR GENES AND HUMAN DISEASE
The significance of 5-AR in human disease was appreciated after the discovery of 5-AR2 deficiency in 1974. The clinical syndrome of 5-AR2 deficiency, male pseudohermaphroditism, was first discovered in the Dominican Republic and the United States of America.
Subsequently, 5-AR2 deficiency syndrome was reported in many areas throughout the world.24-27 5-AR2 deficiency is caused by mutations of the 5-AR2 gene resulting in disorders of sexual development in which 46XY men possess male internal urogenital tracts but female external genitalia.28 The biochemical features of 5-AR2 deficiency include (Figure 1): (a) low normal to low levels of plasma DHT, (b) high normal to elevated levels of plasma T, (c) decreased plasma and urinary 3α-androstenediol glucuronide, a major metabolite of DHT, (d) decreased levels of urinary 5-AR metabolites of C21 and C19 steroids and increased 5β/5-α reductase urinary metabolite ratios and (e) increased plasma levels of luteinizing hormone.18,20,29,30 In 5-AR2 deficient men, Thiele et al.31 reported that 5-AR1 may play a critical role in the masculinization of 5-AR2 deficient men. Cantagrel et al.14 reported that patients with mutations in SRD5A3 exhibited a multisystemic syndrome with psychomotor delay, cerebellar vermis hypoplasia and eye malformation.

EXPRESSION OF 5-AR IN HUMAN PROSTATE TISSUE

The prostate is a ductal-acinar gland, the growth and development of which begins in fetal life and reaches completion at sexual maturity. The prostate initiates its development from the urogenital sinus in the 3rd month of fetal growth and its development is directed primarily by DHT rather than T.22,32 In the human prostate, both 5-AR1 and 5-AR2 are present in epithelial and stromal cells, while 5-AR2 is the predominant isozyme in stromal cells.5,33,34 5-AR3 is expressed by basal epithelial cells.35

EXPRESSION OF 5-AR IN BPH AND PROSTATE CANCER

Several studies have characterized the localization of the 5-AR isozymes in BPH and PCa. Habib et al.36 investigated the expression of 5-AR1 and 5-AR2 in BPH by reverse transcription-polymerase chain reaction and in situ hybridization. 5-AR1 and 5-AR2 mRNA were found in the glandular areas of BPH, while weaker signals were observed in the stroma. The 5-AR2 expression level was approximately three times that of 5-AR1. Shirakawa et al.37 found that 5-AR1 was predominantly expressed in epithelial cells, while 5-AR2 was expressed in both stromal and epithelial cells. In our experiments,38 immunostaining with the 5-AR2 antibody showed that 5-AR2 was mostly expressed in epithelial cells with some expression in the stromal compartment. Some BPH tissues (29%) exhibited no or very low 5-AR2 expression. Thomas et al.39 determined the expression of 5-AR1 and 5-AR2 in BPH and PCa by immunohistochemistry and enzyme activity assays. Low to moderate expression of 5-AR1 was observed in the nucleus of BPH cells, while high, primarily cytoplasmic expression of 5-AR1 was frequently observed in PCa. In another study, Thomas et al.38 reported that the expression of 5-AR1 was low in BPH and increased from prostatic intraepithelial neoplasia (PIN) and primary PCa to recurrent and metastatic PCa. In contrast, the expression of 5-AR2 was lower in PIN and PCa than in BPH. In contrast, Titus et al.40 observed high expression of 5-AR1 and 5-AR2 in PCa, with greater expression in high-grade PCa compared with low-grade PCa.41 Godoy et al.42 reported that the expression of 5-AR3 was restricted to the basal epithelial cells in benign prostate tissue. In high-grade PIN, 5-AR3 was expressed in both basal and neoplastic epithelial cells. Furthermore, androgen-sensitive and castration-recurrent PCa, 5-AR3 was expressed in the cytoplasm of most epithelial cells.

Overall, both 5-AR1 and 5-AR2 are present in the epithelial and stromal cells of benign prostate tissues, while 5-AR2 is the predominant isozyme in stromal cells. 5-AR3 is expressed by basal epithelial cells. Similarly, in BPH, 5-AR1 is mainly expressed in epithelial cells, while 5-AR2 is expressed in both stromal and epithelial cells. 5-AR3 is expressed in both basal and neoplastic epithelial cells of PIN and in the cytoplasm of epithelial cells in PCa. Both 5-AR1 and 5-AR2 are overexpressed in BPH compared with the normal prostate and 5-AR2 is the predominant form. Decreased expression of 5-AR2 and increased expression of 5-AR1 were observed in PIN and PCa compared with BPH. The differential expression of 5-AR1 and 5-AR2 in prostate cancer implies that dual inhibitors of 5-AR1 and 5-AR2 may be more effective in the prevention and treatment of low-risk PCa.

It is well-known that T is converted to DHT by 5-AR. Several articles have reported the levels of T and DHT in serum and prostate tissue. Olsson et al.43 investigated the local intraprostatic and peripheral serum DHT levels in patients undergoing radical prostatectomy for localized prostate cancer. They found that the local prostatic concentration of DHT was almost twofold higher than in the peripheral serum, with no difference observed between local prostatic and peripheral serum T levels. A positive correlation was observed between local prostatic and peripheral serum DHT levels and between prostate weight and local prostatic DHT levels, but not peripheral serum DHT. The prostate gland is an important source of DHT production as an endocrine organ.

### Table 1: Properties of 5-AR isozymes

| Properties     | 5AR-1                  | 5AR-2                  | 5AR-3                  |
|----------------|------------------------|------------------------|------------------------|
| Size           | 259 amino acids        | 254 amino acids        | 318 amino acids        |
| Protein        | NADPH-dependent        | NADPH-dependent        | NADPH-dependent        |
| Tissue distribution | Liver, nongenital skin, scalp, sebaceous gland, brain, ovary, prostate, testis | Prostate, epididymis, seminal vesicle, uterus, genital skin, breast, hair follicle, placenta, testis | Brain, liver, prostate, epididymis |
| Gene name      | SRD5A1                 | SRD5A2                 | SRD5A3                 |
| Gene structure | 5 exons, 4 introns     | 5 exons, 4 introns     | 5 exons, 4 introns     |
| Chromosome location | 5p15                  | 2p23                   | 4q12                   |

5-AR: 5-alpha reductase; NADPH: nicotinamide adenine dinucleotide phosphate. Data for table obtained from reference44.

### Figure 1: Pathway of steroid biosynthesis and the conversion of T to DHT by 5-AR.

C21 precursors (pregnenolone and progesterone) are converted to C19 adrenal androgens (DHEA and androstenedione) by sequential hydroxylase and lyase activities. Circulating adrenal androgens enter the prostate and can be converted to T or androstenedione by a series of reactions involving the activity of 3β and 17β enzymes. T is then converted to the potent androgen DHT by the activity of 5-AR. 17α: 17α-hydroxylase; 17,20: 17,20-lyase; 21: 21-hydroxylase; 3β: 3-HSD (hydroxysteroid dehydrogenase); 17β: 17-HSD (hydroxysteroid dehydrogenase); DHEA: dihydroepiandrosterone; AKR1C: aldo-keto reductase; 3α-diol: 5α-androstan-3α, 17β-diol; 3β-diol: 5α-androstan-3β, 17β-diol.
Androgen metabolism in the prostate not only plays an intracellular role, but more importantly serves as a systemic and locoregional androgen regulator to ensure normal prostate growth, and as such is involved in the pathogenesis of prostatic diseases. In male rats, Kashwagi et al. studied the changes of T and DHT levels in accessory sex organs, serum and seminal fluid after castration. They found that 72 h after castration, T and DHT decreased to 42% and 3% of normal levels in the prostate, respectively, while serum androgen concentrations were below the limit of quantification 6 h after castration and thereafter. The T/DHT ratio in the prostate increased with time over 72 h, while in serum, the T/DHT ratio was initially high but then rapidly decreased within 3 h after castration.

These studies demonstrate that differential expression of 5-AR isozymes is observed in both benign and malignant prostate tissues. Different 5-AR isozymes may play different roles in the development and progression of BPH and PCa. The isozymes’ differential expression in benign and malignant human prostate tissues may be relevant when examining the therapeutic effects of 5-ARIs in BPH and PCa. The mechanisms driving the differential expression of 5-AR isozymes have not been studied. In our experiments, we found that methylation of the 5-AR2 promoter region could account for its reduced expression in some adult prostate. We are currently investigating the mechanisms of differential expression of 5-AR1 and 5-AR2 in BPH and PCa.

5-ARIS FOR THE TREATMENT OF BPH

BPH is a pathological condition responsible for considerable morbidity due to urethral obstruction caused by overgrowth. The development of BPH is exclusively dependent on androgens, especially DHT, which is the major intracellular ligand mediating androgen action in prostate cells. BPH does not occur in men castrated before puberty. Both 5-AR1 and 5-AR2 are significantly overexpressed in BPH compared with the normal prostate.

5-ARI alone or in combination with an α1-adrenoreceptor antagonist is the initial treatment option that is currently available for men with BPH. Finasteride, a 4-azasteroid and analogue of T, works by acting as a potent and specific, competitive inhibitor of one of the two subtypes of 5-AR, specifically the 5-AR2 subtype. Dutasteride inhibits two of the three isoforms of 5-AR, 5-AR1 and 5-AR2; whereas, finasteride only inhibits 5-AR2 and has a much shorter half-life. Dutasteride is 45-fold more effective in inhibiting 5-AR1 and two-fold more effective against 5-AR2 than finasteride. Treatment with 5-ARIs for 3 months reduced serum and intraprostatic DHT levels in male rats. For humans, finasteride suppresses DHT by 70.8% ± 18.3% at 24 weeks, while dutasteride results in greater serum DHT suppression with less variability (94.7% ± 3.3% at 24 weeks). The intraprostatic DHT level changes with differential 5-AR isoform expression in different prostatic disease states, and different isoforms have different efficiencies of conversion from T to DHT. Thus, both finasteride and dutasteride are therapeutically effective for BPH patients because 5-AR2 is the predominant form present in BPH. 5-ARI treatment improves clinical symptoms by decreasing prostate size in patients with BPH. A number of clinical trials demonstrated that two types of 5-ARIs are effective in treating BPH.

In 1998, 3040 men with urinary symptoms and enlarged prostate glands were enrolled in the Proscar Long-Term Efficacy and Safety Study (PLESS) clinical trial. Patients were randomly assigned into one of two arms, receiving either 5 mg finasteride daily or placebo. Four years later, reduced total prostate volume (TPV), improved symptom scores and increased urinary flow rate were observed in patients in the finasteride arm of the study. Additionally, the effectiveness of finasteride in reducing the risk of acute urinary retention and the need for surgical treatment was demonstrated among men with BPH.

Pooled data from three large ARIA studies (ARIA 3001 in the United States, ARIA 3002 in the United States and ARIA 3003 in 19 countries) verified the efficacy and safety of dutasteride for the treatment of BPH. A total of 4325 men with clinical BPH were enrolled into three trials and treated daily with either 0.5 mg dutasteride or placebo. At 24 months, serum DHT and TPV were reduced by 90.2% and 25.7%, respectively, in the dutasteride group. Dutasteride also reduced the risk of acute urinary retention by 57% and that of BPH-related surgical intervention by 48%. This trial demonstrated that dutasteride was one of the optimal therapeutic options for patients with lower urinary tract symptoms (LUTS) due to BPH.

To compare the effectiveness of finasteride and dutasteride in treating BPH, the Enlarged Prostate International Comparator Study (EPICS) randomized men over the age of 50 to receive 5 mg finasteride (n = 817) or 0.5 mg dutasteride (n = 813) daily for 12 months. Finasteride and dutasteride treatment were similarly effective in reducing TPV and improving Qmax and LUTS associated with BPH.

In the Medical Therapy of Prostate Symptoms (MTOPS) and Prospective European Doxazosin and Combination Therapy (PREDICT) trials, the efficacy of treatment with finasteride and doxazosin (an α1-adrenoreceptor antagonist) were studied alone or in combination. In MTOPS, finasteride consistently reduced TPV, both alone and in combination with doxazosin. PREDICT found that the combination therapy was effective in improving urinary symptoms in men with larger (> 40 cm3) prostates. The combination of Avodart and Tamsulosin (CombAT) study demonstrated that dutasteride alone or in combination with tamsulosin (an α1-adrenoreceptor antagonist) was more effective in reducing the risk of acute urinary retention or eventual surgery than tamsulosin alone. These 5-ARI trials showed that 5-ARIs, alone or in combination with α1-adrenoreceptor antagonists, are effective in treating BPH, reducing the risk of acute urinary retention and invasive surgery.

5-ARIS FOR THE PREVENTION AND TREATMENT OF PROSTATE CANCER

PCa is the most commonly diagnosed cancer and is a leading cause of cancer death in men. In 2012, 241,740 new cases of prostate cancer were diagnosed in the US (28.50% of the total of 848,170 new cancer cases in men) with 28,170 deaths (9.33% of the total of 301,170 deaths from cancer for men). Androgens, especially DHT, play key roles in the onset and progression of prostate cancer. 5-ARIs have recently been promoted as chemopreventive or therapeutic agents. A number of clinical trials have been carried out to explore the effects of 5-ARIs (mainly finasteride and dutasteride) for the prevention and treatment of prostate cancer (Table 3).

In the Prostate Cancer Prevention Trial (PCPT), 18,882 men with normal digital rectal examinations and prostate-specific antigen (PSA) levels of 3.0 ng ml−1 or lower were randomly assigned to daily treatment with either 5 mg finasteride or placebo for 7 years. A prostate biopsy was performed for PSA > 4.0 ng ml−1 and/or abnormal digital rectal examination. The primary end-point of this trial was the prevalence of PCa during the study period. PCa was detected in 18.4% of men with either 5 mg finasteride or placebo for 7 years. A prostate biopsy was performed for PSA > 4.0 ng ml−1 and/or abnormal digital rectal examination. The primary end-point of this trial was the prevalence of PCa during the study period. PCa was detected in 18.4% of men with either 5 mg finasteride or placebo for 7 years.
Differential expression of 5-AR in the prostate

K Wang, et al

Table 2: Therapeutic trials of 5-ARIs in the treatment of BPH

| Trial | Published | Agent | Number | Duration | ▲ IPSS | Qmax (mL/s) | ▲ TPV |
|-------|-----------|-------|--------|----------|--------|-------------|-------|
| PLESS| 1988      | Finasteride | 3040  | 4 years  | Fi: -3.4 | Fr: 1.9     | Fi: -18% |
| ARIA | 2002      | Dutasteride | 4325  | 2 years  | Du: -2.2 | Du: 2.2     | Pl: 14%  |
| PREDICT| 2003     | Finasteride | 1095  | 1 year   | Pt: -5.7 | Pt: 1.4     | No data |
|       |           | Doxazosin |        |          | Fi: -6.6 | Fr: 1.8     | No data |
| MTOPS| 2003      | Finasteride | 3047  | 4.5 years| Pl: -4.9 | Pt: 2.8     | Pt: 19%  |
|       |           | Doxazosin |        |          | Fi: -5.6 | Fr: 3.2     | Di: 24%  |
|       |           |          |        |          | Do: -6.6 | Do: 4.0     | Di: 24%  |
|       |           |          |        |          | Com: -7.4| Com: 5.1    | Com: 19% |
|       |           | Dutasteride | 4844  | 4 years  | Du: -6.4 | Du: 2.0     | Du: 28%  |
|       |           | Tamulosin |        |          | Ta: -4.9 | Ta: 0.7     | Ta: 46%  |
|       |           |          |        |          | Com: -7.3| Com: 2.4    | Com: 27% |
| EPICS| 2011      | Finasteride | 1630  | 1 year   | Fi: -5.8 | Fr: 1.8     | Fi: -27.4|
|       |           | Dutasteride |        |          | Du: -6.2 | Du: 2.1     | Du: 27.4 |

5-ARI: 5-alpha reductase inhibitors; ARIA: ARIA 3001, 3002, 3003; BPH: benign prostatic hyperplasia; Com: comparison; Combat: the Combination of Avodart® and Tamulosin; Dio: doxazosin; Du: dutasteride; EPICS: Enlarged Prostate International Comparator Study; Fi: finasteride; MTOPS: medical therapy of prostate symptoms; PLESS: proscar long-term efficacy and safety study group; PREDICT: prospective european doxazosin and combination therapy; Pl: placebo; Ta: tamulosin; TPV: total prostate volume; IPSS: the international prostate symptom score

Table 3: Trials of 5-ARIs in the chemoprevention and treatment of prostate cancer

| Trial | Publish | Agent | Number | Duration | Rate of incidence or progression | High grade tumor incidence | Overall relative risk reduction in PCa vs placebo |
|-------|---------|-------|--------|----------|----------------------------------|----------------------------|-----------------------------------------------|
| PCPT  | 2003    | Finasteride | 3040  | 4 years  | Fi: 18.4% | Pt: 25.1% | Pl: 48% |
| REDUCE| 2010    | Dutasteride | 8231  | 4 years  | Du: 19.9% | Du: 6.7% | Pt: 16% |
| ARTS  | 2009    | Dutasteride | 276   | 2 years  | No data | No data | No data |
| REDUCE| 2012    | Dutasteride | 302   | 3 years  | Du: 38% | No data | No data |

5-ARI: 5-alpha reductase inhibitors; ARTS: avodart after radical therapy for prostate cancer study; DU: dutasteride; Fi: finasteride; PCa: prostate cancer; PCPT: prostate cancer prevention trial; Pl: placebo; PSA: prostate-specific antigen; REDUCE: reduction by dutasteride of clinical progression events in expectant management trial; REDUCE: reduction by dutasteride of prostate cancer events trial; RP: radical prostatectomy; RT: radiotherapy

To evaluate whether dutasteride reduces the incidence of PCa among men who are at increased risk for the disease, a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial was designed, named the Reduction by Dutasteride of Prostate Cancer Events (REDUCE). The enrolled patients met the following criteria: 50–75 years of age, PSA levels of 2.5–10.0 ng ml\(^{-1}\) and a negative 6–12 core prostate biopsy within 6 months of enrollment. The participants received a 10-core transrectal ultrasound-guided prostate biopsy at years 2 and 4. PCa was detected in 19.9% of the dutasteride arm compared with 25.1% in the placebo arm, representing an absolute risk reduction of 5.1% (\(P < 0.001\)) for men given dutasteride. Dutasteride decreased the relative risk of biopsy-detectable PCa by 22.8% (15.2 to 29.8; \(P < 0.001\)) and this risk reduction was evident across all subgroups tested. However, the absolute incidence of high-grade tumors (Gleason 8–10) was 12 cases in the dutasteride arm, much higher than the one case in the placebo arm; the 4-year difference in the number of Gleason 7–10 tumors between the two arms was not statistically significant.

To assess the effects of dutasteride on the progression of PCa in patients who have failed previous therapies, the Avodart after Radical Therapy for Prostate Cancer Study (ARTS) trial enrolled 294 patients who had increasing serum PSA levels after radical prostatectomy or radiotherapy for 2 years. The end-points of this study were time-to-PSA-doubling (PSADT), time-to-disease progression and the proportion of subjects with disease progression. This study showed that dutasteride significantly delayed PSADT and disease progression (which included PSA- and non-PSA-related outcomes) compared with placebo after 20 months of treatment (\(P < 0.001\)). This study concluded that dutasteride could delay PSA progression in patients with biochemical failure after radical prostatectomy or radiotherapy for PCa.

The Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial investigated the safety and efficacy of dutasteride in men with clinical evidence of low-risk PCa, including men with rising PSA after radical prostatectomy or radiotherapy for 2 years. The end-points of this study were time-to-PSA-doubling (PSADT), time-to-disease progression and the proportion of subjects with disease progression. This study showed that dutasteride significantly delayed PSADT and disease progression (which included PSA- and non-PSA-related outcomes) compared with placebo after 20 months of treatment (\(P < 0.001\)). This study concluded that dutasteride could delay PSA progression in patients with biochemical failure after radical prostatectomy or radiotherapy for PCa.
the differential expression of 5-AR in the prostate. Clinical trials, such as REDEEM, have reported that dutasteride delayed the progression of low-risk PCa. More mechanistic investigations are needed to understand the effects of 5-ARIs fully.

AUTHOR CONTRIBUTIONS

The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections. KW substantially contributed to the design, preparation, drafting and revising of the final version of the manuscript under the supervision of YNN. YNN also provided extremely important intellectual support, made critical revision of the manuscript for important intellectual content and obtained funding. DDF, SJ and NZX substantially contributed to the preparation, drafting and revising of the final version of the manuscript and all the authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No. 30973015) and the Beijing Natural Science Foundation (No. 7122074) at Beijing Chaoyang Hospital, Capital Medical University to YNN.

REFERENCES

1 Röhrborn CG, Mcconell JD. Benign Prostatic Hyperplasia: etiology, Pathophysiology, Epidemiology, and Natural History. 9th ed., Ch. 86. Wein: campbell-Walsh Urology; 2007. p. 2–80.
2 Klein EA, Platz EA, Thompson IM. Epidemiology, Etiology, and Prevention of Prostate Cancer. 9th ed., Ch. 90. Wein. Campbell-Walsh Urology; 2007. p. 1–43.
an important role in masculinization of 5alpha-reductase type 2 deficient males. *Eur J Endocrinol* 2005; 152: 875–80.

32 Marker PC, Donjacour AA, Dahya R, Cunha GR. Hormonal, cellular, and molecular control of prostatic development. *Dev Biol* 2003; 253: 165–74.

33 Velti R, Rodriguez R. Molecular Biology, Endocrinology, and Physiology of the Prostate and Seminal Vesicles. 9th ed. Ch. 85. Wein: Campbell-Walsh Urology; 2007, p. 1-95.

34 Habib FK, Ross M, Bayne CW, Grigor K, Buck AC, et al. The localisation and expression of 5-alpha-reductase types I and II mRNAs in human hyperplastic prostate and in prostate primary cultures. *J Endocrinol* 1998; 156: 509–17.

35 Shirakawa T, Okada H, Achariya B, Zhang Z, Hinata N, et al. Messenger RNA levels and enzyme activities of 5-alpha-reductase types 1 and 2 in human benign prostatic hyperplasia (BPH) tissue. *Prostate* 2004; 58: 33–40.

36 Niu Y, Ge R, Hu L, Diaz C, Wang Z, et al. Reduced levels of 5-alpha-reductase 2 in adult prostate tissue and implications for BPH therapy. *Prostate* 2011; 71: 1317–24.

37 Thomas LN, Douglas RC, Vesey JP, Gupta R, Fontaine D, et al. Selectivity of dihydrotestosterone in men with benign prostatic hyperplasia. *J Urol* 2006; 6: Suppl 9: S31−9.

38 Span PN, Volier MC, Smals AG, Sweep FG, Schalken JA, et al. Selectivity of finasteride as an in vivo inhibitor of 5-alpha-reductase iso-enzymes expression in the human prostate. *J Urol* 1999; 161: 332–7.

39 Schmidt LJ, Tindall DJ. Steroid 5 alpha-reductase inhibitors targeting BPH and prostate cancer. *J Steroid Biochem Mol Biol* 2011; 125: 32–8.