



Review

Potential impact of combined inhibition of 3α -oxidoreductases and 5α -reductases on prostate cancer



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Abstract Prostate cancer (PCa) growth and progression rely on the interaction between the androgen receptor (AR) and the testicular ligands, testosterone and dihydrotestosterone (DHT). Almost all men with advanced PCa receive androgen deprivation therapy (ADT). ADT lowers circulating testosterone levels, which impairs AR activation and leads to PCa regression. However, ADT is palliative and PCa recurs as castration-recurrent/resistant PCa (CRPC). One mechanism for PCa recurrence relies on intratumoral synthesis of DHT, which can be synthesized using the frontdoor or primary or secondary backdoor pathway. Androgen metabolism inhibitors, such as those targeting 5α -reductase, aldo-keto-reductase family member 3 (AKR1C3), or cytochrome P450 17A1 (CYP17A1) have either failed or produced only modest clinical outcomes. The goal of this review is to describe the therapeutic potential of combined inhibition of 5α -reductase and 3α -oxidoreductase enzymes that facilitate the terminal steps of the frontdoor and primary and secondary backdoor pathways for DHT synthesis. Inhibition of the terminal steps of the androgen metabolism pathways may be a way to overcome the shortcomings of existing androgen metabolism inhibitors and thereby delay PCa recurrence during ADT or enhance the response of CRPC to androgen axis manipulation.

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Figure 1 Pathways to DHT synthesis (modified from Ref. [62]). 5 α -reductase (SRD5A) 1, 2 or 3 (frontdoor pathway; pink) metabolize testosterone to dihydrotestosterone (DHT). 3 α -oxidoreductase (primary backdoor pathway; purple) or aldo-keto reductase (secondary backdoor pathway; green) enzymes convert androstanediol or androstanedione, respectively to DHT.

The CYP17A1 inhibitor, abiraterone, impairs both the 17 α -hydroxylase and 17,20-lyase activities of the enzyme, thus blocking adrenal androgen synthesis [28,29]. Abiraterone depletes PCa or CRPC tissue androgen levels and extends patient survival approximately 4 months when used for CRPC, which garnered Food and Drug Administration (FDA) approval [30–33]. However, inhibition of CYP17A1 by abiraterone can lead to glucocorticoid insufficiency and mineralocorticoid excess. Hypertension, hypokalemia and peripheral edema occur with sufficient frequency that abiraterone is co-administered with prednisone [34–36].

The earlier clinical failure of abiraterone (and other CYP17A1 inhibitors) has been attributed to several mechanisms that involve AR splice variants [37], circulating DHEA-SO₄ that remains in spite of abiraterone treatment [38], increased expression of CYP17A1 [39,40], or other primary [37,41] and/or secondary backdoor pathway [39] androgen metabolism enzymes. CYP17A1 inhibition induces progesterone accumulation, which competes with abiraterone for CYP17A1 [42]. CYP17A1 inhibition may result in up-regulation of CYP11A1 and the aldo-keto reductase family 1 member C3 (AKR1C3); both enzymes are capable of increasing intra tumoral *de novo* androgen synthesis by activating different androgen metabolism pathways [42]. Chang et al. [43] reported HSD3B1 mutations promote DHT synthesis despite therapeutic intervention. The concept of interrupting intratumoral androgen metabolism has merit, but CYP17A1 inhibition occurs too early in the DHT synthesis pathways, which enables PCa cells to alter the pathways used to produce DHT.

Therefore, inhibition of the terminal steps of the primary and secondary backdoor pathways using a combination of SRD5A and 3 α -oxidoreductase enzyme inhibitors may improve PCa response. Inhibition of the steps immediately proximal to DHT synthesis will render pathway switching

ineffective, which may lower DHT levels better than any androgen metabolism inhibitor used alone.

3. 5 α -reductase inhibition alone is insufficient to deplete intratumoral DHT levels

The 5 α -reductases (types I–III) encoded by SRD5A1, 2 or 3 play an essential role in metabolism of progestagens, glucocorticoids and androgens. These enzymes irreversibly reduce the double bond at C4 and C5 in Ring A (Fig. 2; purple) [44–46] of substrates such as progesterone, cortisone, and testosterone, to produce dihydroprogesterone, dihydrocortisone, and dihydrotestosterone (DHT), respectively [46]. The type II reductase encoded by SRD5A2 is predominant in benign hyperplastic prostate and is the target of finasteride. Dutasteride inhibits type I and type II 5 α -reductase, and may also inhibit type III as well [47]. PCa may depend more on SRD5A1 and SRD5A3 [48]. Finasteride treatment enhanced the extent of response to ADT when initiated simultaneously with ADT [49–53], which suggests 5 α -reductase inhibition may be useful when used earlier for advanced PCa. However, finasteride and dutasteride both have proven ineffective in CRPC because of variable patient response, accumulation of T that enables AR activation, and/or insufficient depletion of intratumoral DHT levels due to active SRD5A3 or primary or secondary backdoor pathway metabolism [54–57].

4. 3 α -oxidoreductases inhibition lowers intratumoral DHT levels *in vitro*

Redox enzymes, such as hydroxysteroid dehydrogenases (HSD), aldo-keto reductases or retinol dehydrogenases (RDH) oxidize or reduce steroid substrates [8,9,58]. These enzymes are responsible for steroid metabolism, which

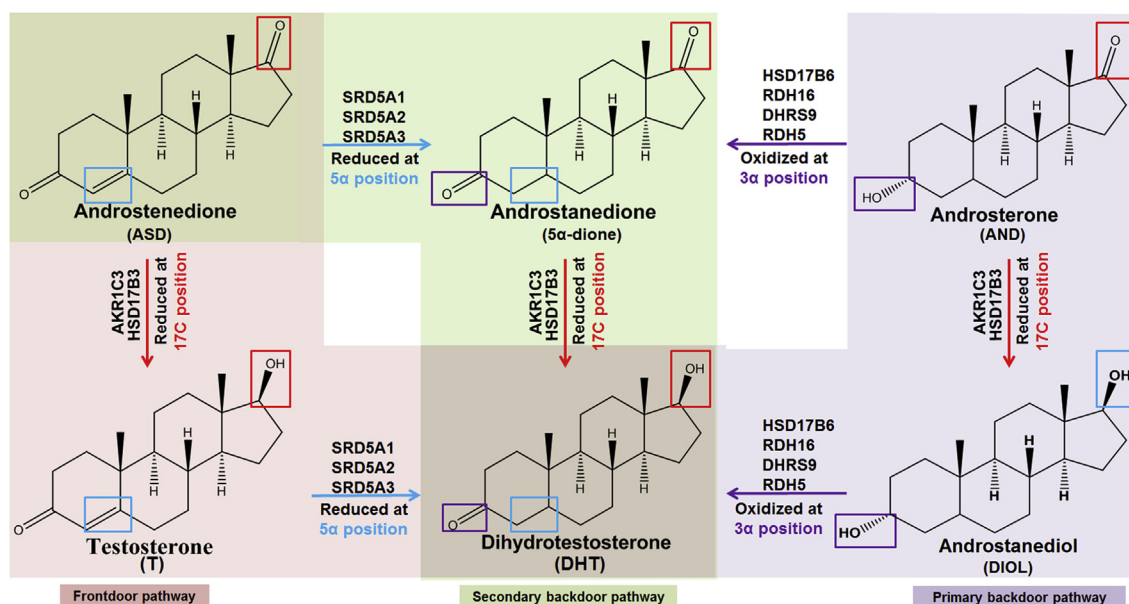


Figure 2 5 α -reductase (SRD5A) (blue) and 3 α -oxidoreductase (oxidation [purple]; reduction [red]) target sites on steroid rings. SRD5A activity (blue) occurs at the 5 α position of Ring A, 3 α -oxidoreductase oxidation sites (purple) occur at the 3 α position of Ring A and aldo-keto reduction (red) occurs at the 17 β position of Ring D.

includes glucocorticoid, mineralocorticoid and androgen synthesis or degradation [59–61].

The terminal step in the primary backdoor pathway of androgen metabolism uses one of four 3 α -oxidoreductases (HSD17B6; RDH5; RDH16; and dehydrogenase/reductase family member 9 [DHRS9]) to convert androstenediol to DHT [8,62]. The 3 α -oxidoreductases have conserved catalytic amino acids (Fig. 3) and co-factor binding sites [63–66], and carry out similar reactions, despite having different K_m values [62,67]. Preclinical studies using castration-recurrent CWR-R1 human xenografts demonstrated that androstenediol is converted to DHT [68]. The secondary backdoor pathway requires a combination of SRD5A, to 5 α -reduce ASD to 5 α -dione, the four 3 α -oxidoreductases, AKR1C3 or HSD17B3, to finally reduce 5 α -dione to DHT [11–13,17].

A pre-clinical study using the AKR1C3 inhibitor, indomethacin, demonstrated a proof of principle that AKR1C3 inhibition overcame PCa resistance to abiraterone and enzalutamide. The study provided evidence for the necessity for identification and development of AKR1C3 inhibitors [13,69]. A Phase 1/2 clinical trial that tested the efficacy of an AKR1C3 inhibitor, ASP9521, ended without evidence of clinical response. The authors suggested that insufficient PCa cell expression of AKR1C3 may have caused therapeutic failure [70].

No 3 α -oxidoreductase inhibitors are used in the clinic to inhibit the four enzymes that metabolize androstenediol to DHT or 5 α -dione to DHT. Recently, our group showed that combined inhibition of the four 3 α -oxidoreductases and SRD5A1 or SRD5A2 lowered DHT levels better than inhibition of either enzyme group alone using *in vitro* PCa cell line models [62].

One challenge with using 3 α -oxidoreductase inhibition therapy is enzyme redundancy. Dutasteride treatment and expression of catalytically inactive 3 α -oxidoreductases impaired PCa cell line production of DHT, but did not reduce DHT levels completely in all experimental conditions [62]. Expression data showed that clinical PCa specimens and PCa cell lines express at least one or more 3 α -oxidoreductase enzymes [62]. Inhibition of one 3 α -oxidoreductase enzyme may impair DHT production, but remain insufficient to deplete DHT levels and inactivate AR. An ideal inhibitor would target all four 3 α -oxidoreductases. However, the enzymes have low protein sequence homology. This implies that there are variations in the precise substrate recognition regions of the enzymes despite their sharing 100% identity among their catalytic residues [62,63].

Finally, the role of post-translational modification and activity regulation in 3 α -oxidoreductase remains unclear in clinical prostate specimens. These regulators of 3 α -

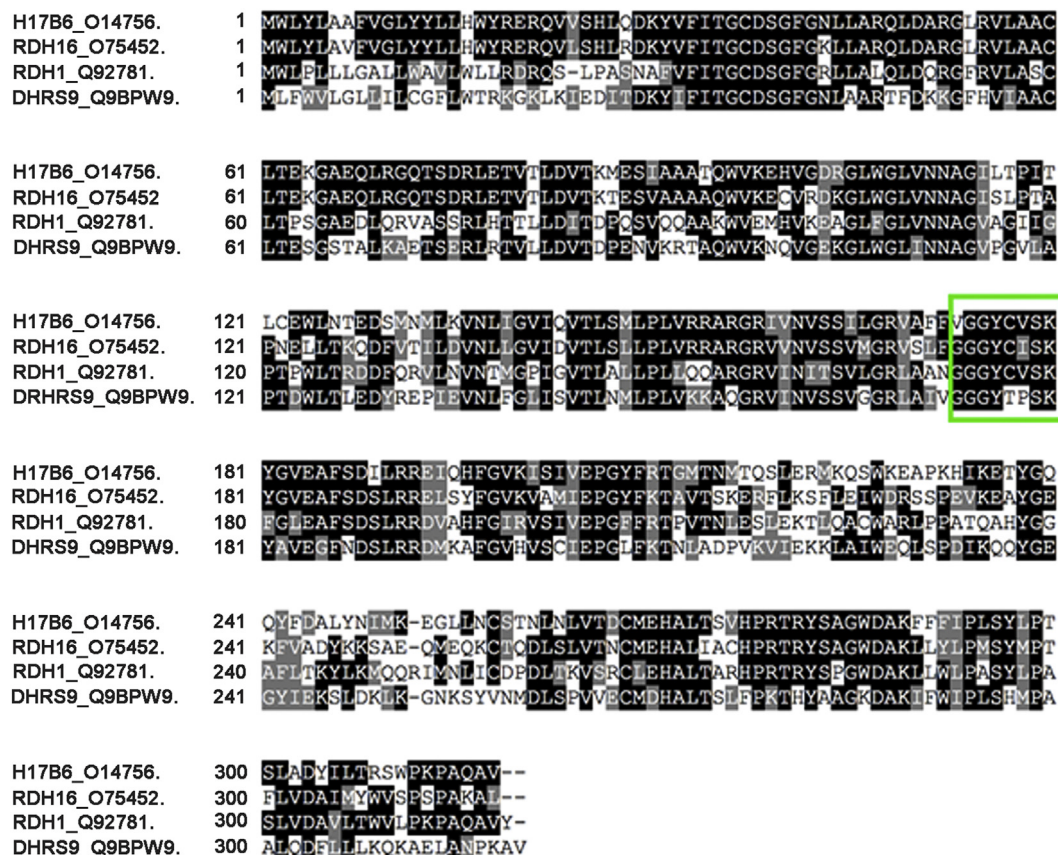


Figure 3 Sequence alignment of the four 3 α -oxidoreductases showed that their catalytic amino acid residues are conserved (green box). COBALT protein sequence alignment shows the conserved catalytic amino acid residues among the four 3 α -oxidoreductases.

oxidoreductase activity may provide an alternative target for catalytic inhibition.

5. Conclusion

The inhibition of androgen metabolism enzymes to improve PCa response to ADT or impair or prolong PCa transition to CRPC has merit. Despite success with CYP17A1 inhibition (an upstream androgen metabolism enzyme), PCa recurs or CRPC persists during treatment and remains lethal [37,39–41]. Inhibition of SRD5A to block the terminal step of the frontdoor pathway (conversion of T to DHT) has proven ineffective against CRPC [55–57]. AKR1C3 inhibition also has been unsuccessful [70]. Inhibition of the enzymes that catalyze terminal steps in the primary backdoor androgen metabolism (conversion androstenediol to DHT) or the secondary backdoor androgen metabolism pathways (conversion androstenedione to DHT) has not been tested clinically because of a lack of candidate inhibitors.

Once inhibitors of the four 3α -oxidoreductases are developed, the lead candidate can be tested alone or combined with ADT, CYP17A1 and SRD5A1 inhibitors (Fig. 4) in order to impair upstream and downstream androgen metabolism and thereby minimize the ability of PCa cells to adapt their androgen metabolism pathways during ADT. This therapy is similar to the proposed androgen annihilation therapy [71], however, this new “complete” androgen annihilation includes 3α -oxidoreductase inhibition to impair both terminal steps of the primary and secondary backdoor androgen metabolism pathways. 3α -oxidoreductase

inhibition may need to be combined with anti-androgens or AR splice variant therapeutics if 3α -oxidoreductase inhibition alone reveals AR is stimulated despite inhibition of the backdoor pathway or if AR-splice variants develop. Complete androgen annihilation should improve ADT and delay or prevent death from CRPC.

Author contributions

Study design: James L. Mohler and Michael V. Fiandalo.

Data acquisition: Michael V. Fiandalo.

Data analysis: James L. Mohler and Michael V. Fiandalo.

Drafting of manuscript: James L. Mohler, Michael V. Fiandalo and Daniel T. Gewirth.

Figure development: All figures were developed by Drs. Mohler, Fiandalo and Gewirth.

Critical revision of the manuscript: James L. Mohler, Michael V. Fiandalo and Daniel T. Gewirth.

Conflicts of interest

The authors declare no conflict of interest.

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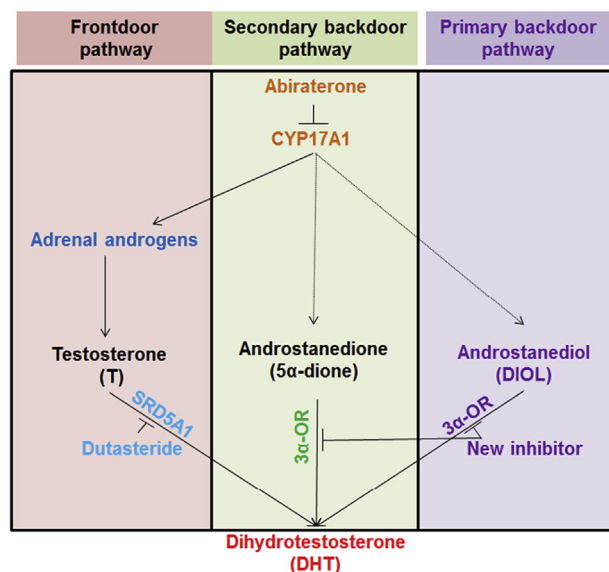


Figure 4 Model of a coordinated attack on enzymes that drive dihydrotestosterone (DHT) production that should lower DHT levels better than an upstream attack of any specific enzyme. Androgen metabolism inhibitors against CYP17A1, 3α -oxidoreductase, aldo-keto reductase and SRD5A used simultaneously should lower DHT levels better than individual enzyme inhibition alone. CYP17A1, cytochrome P450 17A; SRD5A, 5-reductases; 3α -OR, 3α -oxidoreductase.

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