Molecular Pathways: Inhibiting steroid biosynthesis in prostate cancer.

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Keywords: abiraterone acetate, 5α-androstane-dione, backdoor pathway, prostate cancer

Disclosure: Abiraterone acetate was developed at The Institute of Cancer Research, which therefore has a commercial interest in the development of this agent. N.S. has received consulting fees from Janssen and Medivation. R.J.A. has received consulting fees from Cougar Biotechnology, now a unit of Johnson and Johnson. G.A. has received consulting fees and travel support from Janssen-Cilag, Veridex, Roche/Ventana, Astellas, Novartis and Millennium Pharmaceuticals, speakers fees from Janssen, Ipsen, Takeda and Sanofi-Aventis, and grant support from AstraZeneca and Genentech. G.A. is on The ICR rewards to inventors list of abiraterone acetate.
Funding: R.F. and G.A are employees of the Section of Medicine that is supported by a Cancer Research UK programme grant and an Experimental Cancer Medical Centre (ECMC) grant from Cancer Research UK and the Department of Health (Ref: C51/A7401). R.F is funded by The Wellcome Trust (Clinical PhD Programme) G.A. is also supported by a Cancer Research UK Clinician Scientist Fellowship. The authors acknowledge NHS funding to the Royal Marsden NIHR Biomedical Research Centre. N.S. is supported by a Howard Hughes Medical Institute Physician-Scientist Early Career Award, the Prostate Cancer Foundation, an American Cancer Society Research Scholar Award, grant PC080193 from the U.S. Army Medical Research Command and 1R01CA172382 from the National Cancer Institute.
Abstract

A significant proportion of castration-resistant prostate cancers (CRPC) remain driven by ligand activation of the androgen receptor. Although the testes are the primary source of testosterone, testosterone can also be produced from peripheral conversion of adrenal sex hormone precursors dehydroepiandrosterone (DHEA) and androstenedione (AD) in the prostate and other tissues. CYP17A1 catalyzes two essential reactions in the production of DHEA and androstenedione: the hydroxylation (hydroxylase activity) and the subsequent cleavage of the C17-20 side-chain (lyase activity). Potent and selective inhibition of CYP17A1 by abiraterone depletes residual non-gonadal androgens and is an effective treatment for CRPC. Elucidation of the mechanisms that underlie resistance to abiraterone will inform on the development of novel therapeutic strategies post abiraterone. Preclinical evidence that androgen biosynthesis in prostate cancer cells does not necessarily follow a single dominant pathway and residual androgens or alternative ligands (including administered glucocorticoids) can reactivate androgen receptor signaling supports co-targeting of more than one enzyme involved in steroidogenesis and combining a CYP17A1 inhibitor with an anti-androgen. Furthermore, given the drawbacks of 17α-hydroxylase inhibition, there is considerable interest in developing new CYP17A1 inhibitors that more specifically inhibit lyase activity and are therefore less likely to require glucocorticoid co-administration.
BACKGROUND

For the past 70 years, gonadal androgen depletion by medical or surgical castration has been the standard of care for men with metastatic prostate cancer. Despite significant initial responses, patients invariably relapse and several studies suggest intra-tumoral androgens (most commonly testosterone) in castration-resistant prostate cancer (CRPC) tumors are restored to equivalent levels found in non-castrate prostates. Intra-tumoral testosterone and/or dihydrotestosterone (DHT) in men could be generated from conversion of circulating adrenal androgens or could be synthesized de novo from cholesterol. The latter has been suggested in a number of preclinical models but remains unproven in patients. High doses of ketoconazole, which inhibits many cytochrome P450 enzymes, have been used for over a decade to inhibit androgen biosynthesis and induce tumor responses in CRPC. The high doses of ketoconazole required to inhibit cytochrome P450c17 (17α-hydroxylase/17,20-lyase, CYP17A1), however, are associated with significant toxicity in up to 30% of patients. Moreover, CYP17A1 inhibition with ketoconazole is incomplete, and a rise in adrenal androgens has been reported at disease progression. The development of abiraterone as a specific and irreversible inhibitor of CYP17A1 offered a less toxic and more effective option. Abiraterone acetate is now approved in combination with prednisone for the treatment of CRPC, based on demonstration of an improvement in survival when administered with prednisone to docetaxel-treated and chemotherapy-naïve patients. Abiraterone acetate and prednisone also significantly delay pain progression and skeletal-related events and improve quality of life and pain control. These data have unequivocally confirmed that directly targeting androgen biosynthesis is a valid therapeutic option for prostate cancer. This review will discuss the challenges of inhibiting CYP17A1 and other enzymes involved in steroid synthesis and review strategies that are being evaluated to further improve results achieved to date with abiraterone.

Androgen biosynthesis pathways

Steroidogenesis entails processes by which cholesterol is converted to biologically active steroid hormones. Steroidogenesis begins with the irreversible cleavage of a 6-carbon group from cholesterol, producing pregnenelone, by cytochrome P450sc (side chain cleavage enzyme, CYP11A1). A small repertoire of cytochrome P450 and non-P450 enzymes then convert pregnenelone to other 21-carbon steroids (including progestins, glucocorticoids, and mineralocorticoids), 19-carbon steroids (androgens) and 18-carbon steroids (estrogens). The transformations catalyzed by the P450s, 5α-reductases, and 3β-hydroxysteroid
dehydrogenase-Δ⁵/Δ⁴-isomerases (3βHSDs) are all irreversible reactions, giving rise to the general pathways of steroidogenesis (Figure). In contrast, the 3α-, 11β-, and 17β-HSD reactions at the terminal stages of the pathways are reversible pseudoequilibria, with each isoenzyme strongly favoring either steroid oxidation or reduction in intact cells. In human beings, each steroidogenic P450 derives from one gene yielding one isoform, whereas all other enzymes exist as two or more isoenzymes, each with a unique cognate gene expressed in a tissue-specific fashion. Consequently, steroidogenesis generally follows a canonical pathway up to a point, but the final steps vary amongst tissues and cells, particularly in cancer cells, where genetic changes are frequent and ectopic expression of various genes is typical. CYP17A1 is the key enzyme for the synthesis of 19-carbon sex steroid precursors from 21-carbon pregnanes. CYP17A1 catalyzes both the 17α-hydroxylation (hydroxyl addition to pregnenolone and progesterone) and the subsequent 17,20-lyase cleavage (side-chain cleavage from 17-hydroxyprogesterone and 17-hydroxypregnenolone). The latter activity requires the presence of adequate amounts of cytochrome b₅. Exploiting the requirement of the 17,20-lyase but not 17α-hydroxylase reaction for cytochrome b₅ could allow development of therapeutics that specifically inhibit the former reaction. As cytochrome b₅ is involved in a multitude of other essential processes, this approach will be challenging but could be possible since the critical residues of b₅ for stimulating 17,20-lyase activity are E48 and E49 and these are not required for enhancing the activities of CYP2E1 or CYP2C19. In addition to its two primary activities, human CYP17A1 also 16α-hydroxylates progesterone during 25% of turnovers and cleaves pregnenolone and allopregnanolone directly to their Δ¹⁶, 19-carbon homologs in the presence of b₅.

Although small amounts of androstenedione (AD), testosterone, and other 19-carbon steroid metabolites can be directly produced by the adrenal glands, most Δ⁴-androgens in the castrated male are produced in peripheral tissues, where 3βHSD converts DHEA to AD and Δ⁵-androstenediol to testosterone, respectively (Figure). In the testis, 17βHSD3 efficiently converts AD to testosterone and DHEA to Δ⁵-androstenediol, respectively, but in the adrenal and peripheral tissues, the much slower type 5 (17βHSD5) enzyme catalyzes these conversions, and 17βHSD1 also reduces DHEA to Δ⁵-androstenediol. Testosterone is then irreversibly 5α-reduced to the higher affinity ligand DHT by steroid 5α-reductase (SRD5A) isoenzymes (this is referred to as the canonical or “conventional” pathway for DHT synthesis). DHT is inactivated in part by 3-keto-reduction to 5α-androstane-3α,17β-diol through a single
step, catalyzed by the AKR1C isoenzymes 1-4 (reductive 3α-HSDs; mainly AKR1C2) and to 3α-androsterone through two steps (Figure). DHT, 5α-androstane-3α,17β-diol and 3α-androsterone can all be inactivated by the enzymes UDP glycosyltransferase 2, B15 (UGT2B15) or UGT2B17 15. The sulfotransferase SULT2A1 rapidly sulfonates the majority of DHEA synthesized in the adrenal gland, and most of the adrenal androgenic product therefore circulates as DHEA-sulfate (DHEA-S).

The inter-conversion of the 5α-reduced androgens occurs through reversible HSD reactions with the possibility of “back conversion” of inactive terminal products to DHT. 5α-reduction of upstream steroids, as opposed to 5α-reduction of testosterone, leads to DHT synthesis that bypasses testosterone through at least two pathways. In the 5α-androstanedione pathway, AD is converted by SRD5A1 to 5α-androstanedione, which is then converted into DHT by 17βHSD(s) 16 (Figure). The alternative or “backdoor” pathway to DHT synthesis occurs when progesterone and 17-hydroxyprogesterone (17OHP) accumulate and SRD5A enzymes are present. In this pathway, 17OHP is 5α- and 3α-reduced prior to the 17,20-lyase reaction of CYP17A1, yielding the 5α-reduced androgen androsterone (Figure). If 17βHSD activity is also present, 3α-androsterone is converted to 5α-androstane-3α,17β-diol via oxidative 3α-HSD activity, possibly catalyzed by 17βHSD6 17. This pathway yields DHT without DHEA, AD and testosterone as intermediates and occurs naturally in tammar wallaby pouch young testes, in the neonatal testes of several rodent species, and in certain types of congenital adrenal hyperplasia 18,19.

CLINICAL-TRANSLATIONAL ADVANCES

Metabolic Consequences of Therapeutic Inhibition of CYP17A1

Abiraterone was rationally designed in the early 1990s using pregnenolone as a backbone to bind the active site of CYP17A1 and inhibit its activity 20. This inhibition occurs secondary to formation of an essentially irreversible coordination complex between the heme iron—that is required in the CYP17A1 active site for enzymatic activity—and the azole nitrogen atom of abiraterone, plus hydrogen bonding interactions between the abiraterone 3β-OH and conserved polar residues in CYP17A1 21,22. The structural similarities between the latter interactions and ligands binding to steroid receptors could explain abiraterone’s (and other CYP17A1 inhibitors’) weak (relatively) antagonism of the androgen receptor (AR) 23. The
specificity of abiraterone for inhibition of 17,20-lyase versus 17α-hydroxylase is low (1.4-fold, IC50=2.9 nM compared with 4 nM) 21 and treatment with abiraterone acetate therefore blocks both activities. When used as a single-agent, abiraterone acetate suppresses cortisol and causes a rise in ACTH with a consequent increase in 11-deoxycorticosterone (DOC) and corticosterone, mimicking the effects observed in families with congenital inactivating CYP17A1 mutations 24. When administered to noncastrate men, abiraterone acetate (a maximum of 750mg was evaluated) suppresses testosterone, but a subsequent LH surge overcomes inhibition of gonadal testosterone synthesis 25. Significantly higher doses than the currently approved 1000mg would be required to suppress androgens if abiraterone acetate was administered to noncastrate men, probably without any obvious sparing of the side-effects associated with pharmacologic castration with gonadotropin-releasing hormone agonists (GnRHa). Importantly, when administered with GnRHa, significant suppression of circulating DHEA, DHEA-S, AD, testosterone and estradiol is achieved with no obvious rise at disease progression 26-28. Evaluation of the latter has however been limited by the sensitivity of assays used.

CYP17A1 inhibition with single-agent abiraterone acetate is not associated with adrenocortical insufficiency, because a compensatory increase in ACTH leads to very high levels (30-40 fold rise) of the weak glucocorticoid corticosterone that maintains the glucocorticoid requirements of patients. However, raised levels of corticosterone precursors that have mineralocorticoid properties, particularly DOC, lead to a syndrome of mineralocorticoid excess, characterized by hypokalemia, hypertension and fluid retention 26,29,30. In order to effectively prevent or treat ACTH-induced side-effects of mineralocorticoid excess, two different strategies could be adopted: 1) the administration of exogenous glucocorticoids to prevent a compensatory ACTH rise, 2) the administration of mineralocorticoid receptor antagonists (MRA) that inhibit the peripheral effects of raised mineralocorticoids.

Prednisone (prednisolone in the UK) 5mg bid was used in the regulatory Phase III studies of abiraterone, primarily because most CRPC patients are already receiving this glucocorticoid during taxane treatment. Prednisone is a glucocorticoid prodrug that is converted by 11β-HSD in the liver into the active form, prednisolone. Prednisolone is four times a more potent glucocorticoid than cortisol, and 5-7.5 mg daily is used to manage adrenal insufficiency 31.
However, in the COU-301 and COU-302 Phase III studies up to 40% of patients treated with prednisone and placebo suffered side-effects associated with mineralocorticoid excess \(^8,9\) suggesting prednisone (or prednisolone) or their metabolites could activate the mineralocorticoid receptor. Moreover, as anticipated side-effects of mineralocorticoid excess were significantly more common in the abiraterone-prednisone arm in both studies. The half life of prednisone is three hours and the biological effect of 5mg lasts up to twelve hours \(^32\) although this can be variable due to prednisone’s interconversion with prednisolone. Once daily prednisone dosing is being used in several clinical studies in early prostate cancer and breast cancer (for example NCT01751451, NCT01381874, NCT00268476) but there is a hypothetical increased risk of more mineralocorticoid excess due to a compensatory nocturnal rise in ACTH, Modified-release formulations or higher doses could be considered for once daily dosing if these studies report significant mineralocorticoid excess. Overall, hypokalemia is usually corrected with oral potassium supplementation, and fewer than 2% of patients treated with prednisone 5mg BID and abiraterone require MRA or intervention to control these side-effects \(^8\). Dexamethasone is a potent glucocorticoid, and a dose of 0.5 mg daily is usually used. In retrospective studies, dexamethasone was reported to have a significant response rate (equivalent or potentially superior) to prednisone as monotherapy for CRPC \(^33\). Dexamethasone has no mineralocorticoid activity and a long duration of action: this could make it the preferred combination glucocorticoid. Orthostatic hypotension has been rarely reported (~2/100 patients) after addition of dexamethasone to patients on single-agent abiraterone, presumably due to dexamethasone’s absence of mineralocorticoid properties coupled with a rapid decline in raised mineralocorticoids \(^28,29\). Hydrocortisone (cortisol) could be administered at a daily dose of 10–12 mg/m²/daily in divided doses (corresponding to a total daily dose of 15-25 mg). However, due to its short duration of action even thrice daily dosing is unlikely to completely suppress ACTH without over-dosing.

Overall, it is challenging to suppress ACTH whilst not administering supra-physiological glucocorticoid doses and avoiding Cushingoid symptoms from long-term treatment. Moreover, it is possible that long-term use of exogenous glucocorticoids is detrimental (see final section). The alternative option is to use abiraterone acetate alone and treat patients who develop mineralocorticoid excess with a MRA. However, spironolactone, the first-generation, cheapest and most readily available (competitive) MRA binds to the AR as a mixed agonist/antagonist and could lead to disease progression \(^34,35\). Eplerenone, a second-generation MRA was
developed as a more selective MRA that does not bind wild-type AR but can activate AR mutations previously detected in prostate cancer \(^{23}\). Also, significantly raised levels of steroids upstream of CYP17A1 in patients on single-agent abiraterone acetate could activate mutant AR, and very high levels of 17α-hydroxylase substrates could overcome CYP17A1 inhibition by abiraterone. In fact, when dexamethasone was added to single-agent abiraterone in patients with a rising PSA, a secondary PSA decline \(\geq 50\%\) was reported in 25\% of patients regardless of prior treatment with the same dose and regimen of dexamethasone suggesting high levels of upstream steroids were causing resistance \(^{29}\). Amiloride and triamterine, which are potassium-sparing diuretics and inhibitors of the epithelial sodium channel in the distal nephron, are useful agents for controlling the hypokalemia and hypertension of mineralocorticoid excess states and might be effective treatments for these complications of abiraterone therapy without activating AR.

**Novel CYP17A1 inhibitors in clinical development**

Given the drawbacks of 17α-hydroxylase inhibition, there is considerable interest in developing new CYP17A1 inhibitors that more specifically inhibit 17,20-lyase and are therefore less likely to require glucocorticoid co-administration. Orteronel (TAK-700; Millennium Pharmaceuticals) inhibits 17,20-lyase activity 5.4 times more potently than 17α-hydroxylase activity \(^{36}\). This relative specificity might however require a compromise between higher doses that achieve maximum profound inhibition of 17,20-lyase with the risk of a decrease in cortisol and consequent raised ACTH and mineralocorticoid excess versus lower doses that do not suppress cortisol. Orteronel is currently undergoing evaluation in Phase III studies in chemotherapy-naïve and chemotherapy-treated CRPC (NCT01193244; NCT01193257). Both studies utilize a dose of 400mg twice daily and combine orteronol with prednisone. Lower doses of orteronel (for example 300mg bid) that may not require concomitant exogenous glucocorticoids are also being evaluated. Another CYP17A1 inhibitor, galeterone (VN/124-1, TOK-001; Tokai Pharmaceuticals), is a combined inhibitor of CYP17A1, AR and SRD5A \(^{37}\), which has recently completed phase I testing \(^{38}\). VT-464 (Viamet Inc) has a 60-fold greater specificity for C17,20-lyase than 17α-hydroxylase. Treatment of monkeys with VT-464 did not cause a rise in steroids upstream of CYP17A1 in contrast to abiraterone \(^{39}\). This agent is now in early clinical trials.
Reactivation of AR signaling in patients progressing on abiraterone – will combination therapy prove more effective?

The mechanisms that underlie resistance to abiraterone are unknown, and their elucidation will inform on the development of novel therapeutic strategies post abiraterone and biomarkers for selecting patients for treatment. The majority of patients progressing on abiraterone have a rise in PSA, suggesting reactivation of AR or other steroid signaling pathways that could increase PSA transcription. Several studies have shown that the AR can become promiscuously activated by very low levels of androgens (that could persist in patients treated with abiraterone acetate), other steroid metabolites and drugs that bind the AR. The latter could include abiraterone or co-administered glucocorticoids. AR mutations previously described in prostate cancer can be activated by cortisol and other glucocorticoids at levels significantly lower than are reported in patients. Studies are required to evaluate whether the development of or clonal selection of mutant AR-expressing clones occur on inhibitors of steroid biosynthesis as was described nearly two decades ago with first-generation anti-androgens. Moreover, glucocorticoid receptor signaling could activate AR regulated genes in the absence of ligand activation of AR signaling. These or other mechanisms of AR stimulation on abiraterone therapy may explain persistent or resumed AR signaling observed in circulating tumor cells that appear to portend a poorer prognosis.

Gene expression studies have identified alterations in the expression of multiple steroidogenic enzymes in CRPC tissue including increased levels of SRD5A1, 3βHSD, 17β-HSD5 (also called AKR1C3) and a new isoform of SRD5A (SRD5A3) and reduced expression of SRD5A2. Moreover, CYP17A1 and other steroidogenic enzymes have been shown to become upregulated as a consequence of abiraterone treatment in preclinical models. Although increased expression of steroidogenic enzymes does not necessarily equate with increased androgen production, these observations raise the possibility that resistance to abiraterone may be due in-part to mechanisms that maintain androgen synthesis. Translational studies to date have failed to identify a rise in circulating androgens on treatment but measurement of intracellular androgens has been limited by the availability of CRPC tissue and the technical and analytical challenges of controlling for losses during extraction and processing, and definitively separating, detecting, and identifying particular steroids amongst highly related compounds. It is hypothesized that androgen biosynthesis in prostate cancer cells does not necessarily follow a single dominant pathway, particularly under therapy pressure.
model would support co-targeting of more than one enzyme involved in steroidogenesis. Nonetheless, both the conventional and alternative pathways of androgen biosynthesis are dependent on CYP17A1 17,20-lyase for production of androgens, and to date a CYP17A1-independent mechanism for androgen biosynthesis has not been identified. The role of non-CYP17A1 steroidogenesis inhibitors may therefore be limited to combinations with CYP17A1 inhibitors when 17,20-lyase blockade is incomplete, potentially reversing resistance or allowing the use of doses that do not concurrently suppress 17α-hydroxylase activity.

Significant pathway diversity and redundancy pose a challenge to targeting steroidogenesis downstream of CYP17A1. SRD5A1 is highly expressed in prostate cancer and mediates the 5α-androstanedione pathway synthesis of DHT that appears preferentially activated in prostate cancer cell lines and freshly collected CRPC patient tissue 16,54-56. Although most studies to date suggest that testosterone concentrations are higher than DHT in CRPC, this could be explained by inefficient testosterone 5α-reduction by SRD5A1, leading to its accumulation.4,16,57. Furthermore, studies of intratumoral androgens disproportionately sample the interstitial space and cellular cytoplasm and DHT concentrations are enriched in the cellular nucleus, which is where most of the AR protein resides in the presence of agonist 58. Combinations of a 5α-reductase inhibitor with 17,20-lyase inhibition would prevent 5α-reduction of 17OHP and could prevent the accumulation of “backdoor pathway” steroids upstream of CYP17A1 27. A phase II study is evaluating the addition of dutasteride to abiraterone acetate in metastatic CRPC and studying levels of testosterone and DHT at baseline and at progression (NCT01393730). Dutasteride is preferred to finasteride as the latter is relatively specific for the type 2 enzyme, whilst dutasteride inhibits all three isoforms 17. 17β-HSDs play an important role by catalyzing the reduction of 19-carbon-17-ketosteroids to their corresponding 17β-hydroxy forms, as well as the reverse reaction (oxidation). To date, 14 different 17β-HSD genes and cognate isoenzymes have been identified; consequently, specific inhibition of one isoform could be by-passed if other 17β-HSDs are also expressed. For example, inhibition of 17β-HSD3 would not prevent DHT synthesis due to SRD5A-mediated conversion of AD to 5α-androstanedione, followed by 17β-HSD5-mediated conversion to DHT (Figure). Similarly, inhibition of 17βHSD5 could be by-passed by the 5α-androstanedione pathway. Inhibition of 3βHSD could effectively block the conventional pathway at the less active metabolite DHEA, but the backdoor pathway to DHT synthesis would not be suppressed and 3βHSD inhibitors developed to date demonstrate unfavorable properties such as AR agonism 59. Interestingly,
abiraterone also inhibits 3βHSD1 and 3βHSD2 in vitro (albeit less potently than CYP17A1) and could therefore prevent conversion to active androgens of any DHEA that leaks through abiraterone’s block of 17,20-lyase 60. Steroid sulfatase hydrolyzes steroid sulfates, such as estrone sulfate and DHEA-S, to their unconjugated, biologically active forms estrone and DHEA. The first trial with a first-generation single-agent steroid sulfatase inhibitor (SXT64, 667 COUMATE) in postmenopausal women with locally advanced or metastatic breast cancer confirmed inhibition of sulfatase that was associated with reductions in serum Δ5-androstenediol, AD and testosterone 61. Second- and third-generation steroid sulfatase inhibitors have now been developed 62. Inhibiting sulfatase activity in combination with abiraterone in men with prostate cancer could reduce the production of AR-activating androgens from DHEA-S, which would be particularly of relevance in select patients for whom DHEA-S rises on abiraterone treatment.

Increasing drug exposure of abiraterone could reverse resistance through more potent CYP17A1 (and 3βHSD) inhibition and increasing AR antagonism. This strategy could potentially be achieved by exploiting increased absorption of abiraterone in the presence of a high fat meal. To date, anti-tumor activity data is not available from randomized trials of different abiraterone doses. The hypothesis that reactivation of AR signaling by residual low levels of androgens, reactivation of steroid biosynthesis or alternative ligands (including administered glucocorticoids) supports the combination of an anti-androgen with a CYP17A1 inhibitor. Moreover, this combination would prevent a rise in androgens that could occur on treatment with an anti-androgen: as testosterone and DHT have a higher affinity for the AR than enzalutamide and other anti-androgens developed to date, out-competing of the anti-androgen by natural ligand could reverse AR inhibition. A phase Ib/II safety evaluation of enzalutamide (MDV3100, Medivation) in combination with abiraterone acetate and prednisone in CRPC with bone metastases is currently ongoing (NCT01650194). Finally, inhibition of steroid biosynthesis merits evaluation in early-stage prostate cancer when greater efficacy and increased cure rates could be achieved – the STAMPEDE study (NCT00268476) is currently comparing abiraterone with androgen deprivation therapy (ADT) to ADT alone in high-risk M0 or newly diagnosed M1 patients.
Figure. Androgen biosynthesis pathways

The basic pathways are demarcated with respect to CYP17A1 and SRD5A activities. The 17-deoxy, 21-carbon steroids upstream of CYP17A1 are shown at left in green box, including 11-deoxycorticosterone (DOC). The 17-hydroxy, 21-carbon steroids are in center in peach box, and 19-carbon steroids are at right in blue box, generated via 17-hydroxylase and 17,20-lyase reactions of CYP17A1, respectively. The 5-reduced steroids are highlighted with darker background at lower right. Reversible interconversions catalyzed by HSDs are shown with double arrows at terminal steps. CYP17A1, cytochrome P450c17; 3β-HSD, 3-beta-hydroxysteroid dehydrogenase/isomerase; 11α-HSD, 11-beta-hydroxysteroid dehydrogenase; 17β-HSD, 17-beta-hydroxysteroid dehydrogenase; 3α-HSD, 3-alpha-hydroxysteroid dehydrogenase; SRD5A, steroid 5α reductase; DHEA, Dehydroepiandrosterone; DHEA-S, Dehydroepiandrosterone sulfate; STS, steroid sulfatase; SULT2A1, sulfotransferase 2A1
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Figure 1:

- **Cholesterol**
  - 17-deoxy-21-carbon steroids
    - Pregnenolone → 17α-OH-pregnenolone
    - Progesterone → 17α-OH-progesterone
    - 11-deoxycorticosterone → Cortisol
    - Corticosterone → 18-OH-corticosterone → Aldosterone

- **17-hydroxy-21-carbon steroids**
  - 17α-OH-pregnenolone → 17α-OH-progesterone
  - 11-deoxycortisol → Cortisol

- **19-carbon steroids (androgens & metabolites)**
  - Dehydroepiandrosterone → Δ4-androstenedione
  - Testosterone → Androsterone

**Enzymes:**
- CYP17A1
- 3βHSD
- SRD5A
- SULT2A1
- STS
- 17βHSD2
- AKR1C2
- 17αHSD3/5
- 17αHSD6
- 11βHSD

**Metabolites:**
- 5α-pregnane-3α,17α-diol-20-one
- 5α-pregnane-17α-ol-3,20-dione
- 5α-androstane-17α-ol-3,20-dione
- 5α-androstane-3α,17α-diol-20-one
Clinical Cancer Research

Molecular Pathways: Inhibiting steroid biosynthesis in prostate cancer.


Clin Cancer Res Published OnlineFirst March 7, 2013.

Updated version
Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-12-0931

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