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Development of Novel Secondary Hormonal Therapies for Castrate-Resistant Prostate Cancer

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1. Introduction
Androgen deprivation therapy (ADT), initially via surgical orchietomy and more contemporarily with medical castration through the use of luteinizing hormone-releasing hormone (LHRH) agonists, has been the mainstay of treatment for advanced prostate cancer for more than 60 years (Huggins and Hodges, 1941). Though initially effective in decreasing serum PSA, lessening pain from bone metastases, and delaying clinical progression, almost all men develop disease progression despite ADT within 2-3 years. Initially, this disease state was considered hormone-refractory and androgen-independent. However, more recent research has led to the understanding that many prostate cancers continue to depend on androgen receptor (AR) signalling in this state of low but still detectable circulating androgens. Thus, a more appropriate term for this disease state is castrate resistant prostate cancer (CRPC). In this chapter we will discuss the biology behind continued AR signalling in CRPC, traditional non-selective secondary hormonal therapies, and the development of novel secondary hormonal agents which selectively and potently target the AR axis in CRPC.

2. Androgen Receptor signalling in Castrate Resistant Prostate Cancer
In many cases, CRPC retains the ability to activate the AR to stimulate prostate cancer growth and progression, despite low circulating levels of testosterone induced by medical or surgical castration (i.e. less than 50 ng/dL). Various research efforts have sought to understand the mechanism through which this occurs, both as a means of understanding tumor biology and as a means of developing new targeted therapies exploiting the AR axis in CRPC. Signalling can be conceptually divided into efforts to understand ligand production and AR modification.

2.1 Ligand production in Castrate Resistant Prostate Cancer
2.1.1 Endocrine ligands
Current ADT strategies using LHRH agonists suppress gonadal androgen production, resulting in a decrease in circulating serum testosterone to castrate levels (less than 50 ng/dL). Despite gonadal androgen suppression, low levels of circulating androgens persist
in CRPC, often via production of adrenal androgens, such as dihydroepiandrosterenedione (DHEA), DHEA-sulfate (DHEA-S), and androstenedione, which are then converted to testosterone in peripheral tissues. Figure 1 below displays the steroid biosynthetic pathway and several secondary hormonal agents which block various steps of steroidogenesis, to be discussed in the following sections.

Fig. 1. Steroid Biosynthetic Pathway. Adapted from Aggarwal R and Ryan C, 2011.

Due to the peripheral conversion of adrenal steroids, low levels of circulating testosterone persists, and may account for levels up to 10% of that of pre-castrate levels (Puche, C et al. 2002). Low levels of circulating testosterone, along with circulating adrenal androgens, are hypothesized to subsequently stimulate CRPC progression through activation of the AR.
2.1.2 Intracrine ligands

More recently, research has shown that CRPC tissue has the ability to convert adrenal steroids to androgens, thereby creating an intracrine signalling system capable of converting steroid precursors to testosterone and dihydrotestosterone (DHT) which leads to continued stimulation of the AR and prostate cancer progression. The evidence for this comes from various lines of research. Direct measurements of intra-prostatic androgens including DHT demonstrates that levels of androgens in CRPC tissue is not significantly different compared with normal prostate tissue, despite significantly lower levels of circulating testosterone in the castrate men (Nishiyama T, et al. 2004). This finding implies that CRPC tissue acquires the ability to produce testosterone and DHT in an intracrine fashion, a finding which has been supported by further studies showing up-regulation of many of the steroid enzymes involved in androgen synthesis (see figure 1).

For example, Stanbrough et al. analysed oligonucleotide microarrays from 33 CRPC bone metastasis samples and compared their gene expression with samples from 22 hormone-sensitive primary cancers. The CRPC bone metastases demonstrated up-regulated expression of several enzymes involved in the steroid synthetic pathway: 17-beta hydroxysteroid dehydrogenase which converts androstenedione to testosterone; 3-beta hydroxysteroid dehydrogenase, which converts DHEA to androstenedione, and increased ratio of 5-alpha reductase isoform 1 to 2, which converts testosterone to DHT (Stanbrough M, et al 2006).

In a follow up study, Montgomery et al. evaluated androgen levels and transcripts encoding steroidogenic enzymes in benign prostate tissue, untreated primary prostate cancer, metastases from patients with castration-resistant prostate cancer, and xenografts derived from castration-resistant metastases. In this study, castrate-resistant tissues displayed increased expression of several key enzymes involved in androgen synthesis, including: CYP17A1 (C17,20 lyase), a key enzyme which converts progesterone and pregnenolone to 17-hydroxyprogesterone and 17-OH pregnenolone, as well as subsequent conversion of these steroids to androstenedione and DHEA respectively; 3-beta hydroxysteroid dehydrogenase as in the prior study. Furthermore, metastatic prostate cancers from CRPC patient samples express transcripts encoding androgen-synthesizing enzymes and maintain intratumoral androgens at concentrations capable of activating AR target genes and maintaining tumor cell survival in a xenograft model (Montgomery R et al, 2008). Finally, in an innovative study by Locke et al., it was demonstrated that tumor explants isolated from CRPC progression are capable of de novo conversion of [14C] acetic acid to dihydrotestosterone and that uptake of [3H] progesterone allows detection of the production of six other steroids upstream of dihydrotestosterone.

This cumulative body of evidence suggests that CRPCs are capable of adapting to lower circulating levels of androgens induced by castration, in which steroid enzymes involved in the synthetic pathway are upregulated, and thereby maintain high levels of intra-tumor androgens capable of stimulating the AR and driving prostate cancer progression. Understanding this mechanism of castration resistance has led to the development of targeted secondary hormonal therapies which specifically inhibit key enzymes of the androgen synthetic pathway, as will be discussed in the later section.

2.2 Androgen Receptor modification in Castrate Resistant Prostate Cancer

In addition to modification in the enzymes involved in steroid hormone production, the AR itself undergoes adaptation in the castrate state, and is implicated in disease progression to
CRPC. Mechanisms by which the AR adapts to the castrate state have been extensively studied in the past several decades, and include: (1) AR amplification and overexpression (2) heightened AR sensitivity to ligand activation through increased AR stabilization, enhanced nuclear localization, and overexpression of nuclear co-activators (3) increased AR promiscuity through various point mutations (4) ligand-independent activation of the AR through various signal transduction pathways, (5) AR splice variants with constitutive activity. In the following sections we will examine some of the evidence behind these modifications to the AR.

2.2.1 Androgen Receptor gene amplification and overexpression
In the late 1990s, research was starting to show that AR activation continued to play an important role in prostate cancer progression despite low circulating testosterone levels, and a potential mechanism through which this might occur was AR gene amplification and overexpression. In a study by Koivisto, et al, AR gene amplification was analyzed in 54 patient tumor samples at the time of recurrence after prior therapy, as well as in 26 cases, paired primary tumor samples prior to any therapy. In this study, 28% of the recurrent therapy-resistant tumors, versus none of the primary tumor samples, displayed AR gene amplification. Furthermore, through genomic analysis, the AR gene was wild type in all but one of the 15 AR gene amplified tumor samples. Interestingly, this study went on to show a clinicopathologic correlation between AR gene amplification and prior responsiveness to ADT, as well as improved subsequent prognosis (Koivisto P et al. 1997). In a follow up study by Linja et al., in which real-time quantitative reverse transcriptase polymerase chain reaction (RT-PCR) was used to analyze AR expression levels in eight benign prostate hyperplasias, 33 untreated and 13 castrate-resistant locally recurrent carcinomas, as well as 10 prostate cancer xenografts. All castrate-resistant tumors showed on average, 6-fold higher expression than androgen-dependent tumors or benign prostate hyperplasias (P < 0.001). Four of 13 (31%) castrate-resistant tumors contained AR gene amplification detected by fluorescence in situ hybridization. Finally, and equally as important, two of the ten prostate cancer xenograft models displayed AR overexpression, thus providing a key model for testing future drugs targeting the AR in the AR-amplified disease state (Linja MJ, et al. 2001).

Early studies such as these provided compelling evidence that AR gene amplification and thus overexpression may represent an important mechanism by which prostate cancers overcome low circulating androgen levels. Given this, a logical therapeutic strategy is the development of potent AR antagonists which would have activity in this AR-amplified disease state, and indeed, there are several novel potent, AR antagonists which are in clinical phase of drug development (see section below).

2.2.2 Androgen Receptor stabilization and heightened activity
In addition to numerical increase in the number of ARs per cancer cell, increased stabilization and nuclear localization of the AR may also factor into the mechanism of prostate cancer progression in the castrate resistant disease state. In a prior study by Gregory et al, recurrent prostate cancer cell lines had an AR degradation half-life that was 2-4 times longer than that of androgen-sensitive cancer cell lines. Furthermore, IHC staining showing that AR localization was entirely nuclear in the recurrent cancer cell lines; while localizing to both the cytoplasm and nucleus in the androgen sensitive cell lines (Gregory
CW, et al. 2001). This data suggests that AR activation and subsequent AR-mediated gene expression may in part be stimulated in CRPCs by mechanisms to prevent AR degradation and enhance localization to the nucleus. The mechanism of AR stabilization in CRPCs may in part related to increased cyclin-dependent kinase 1, which has been shown to phosphorylate and stabilize the AR and is also upregulated in castrate-resistant cell lines in prior pre-clinical study (Chen S, et al. 2006).

2.2.3 Androgen Receptor point mutations
Estimating the true frequency of acquired point mutations with functional significance in advanced prostate cancer has been difficult, due to various factors including patient selection, tumor heterogeneity, tissue source (prostate gland v metastases), method of tissue preservation, and molecular methods. They appear to be fairly uncommon in early prostate cancer and more prevalent in advanced prostate cancer. In a correlative analysis of bone marrow samples from patients with CRPC being treated with first generation anti-androgen withdrawal (CALGB study 9663), 10% of the patient samples had an AR point mutation, which was found within the hormone binding domain involved with transcription factor binding (Taplin M, et al. 2003). From a functional standpoint, it appears that certain AR point mutations lead to a more promiscuous AR, capable of being activated by a wider range of ligands. In a prior study of a mutant AR transfected into various cell lines, the adrenal androgen DHEA was capable of inducing greater AR-mediated transcriptional activity in the mutant AR cell line compared with wild type AR (Tan J, et al. 1997). In this way, the increase in AR promiscuity may complement the changes in ligand production as outlined in the previous section, in which point mutations in the AR confer a greater ability for the AR to be activated by alternative ligands in the presence of low circulating testosterone levels, including the adrenal androgens such as DHEA. Mutations in the AR may also lead to partial agonistic activity of the first generation anti-androgens, such as flutamide, nilutamide, and bicalutamide, as will be discussed in the following section.

2.2.4 Ligand-independent activation of the Androgen Receptor
There is a wide-ranging body of evidence which suggests that for a subset of prostate cancers, ligand-independent activation of the AR, via activation from other signal transduction pathways, can independently activate the AR and lead to disease progression in the absence of hormone binding to the AR. Though not the focus of the current book chapter, the various signaling pathways that have been implicated in such a manner include the insulin-like growth factor pathway, epidermal growth factor receptor, and keratinocyte growth factor pathways, among others (Feldman B & Feldman D, 2001).

2.2.5 Androgen Receptor splice variants
Over the past several years a growing body of research implicates the generation of AR splice variants as a potential mechanism of driving disease progression to CRPC. Such AR splice variants have “hidden exons” within introns that are not normally transcribed in the wild type AR. The alternate splicing that incorporates such hidden exons into the variant mRNA transcripts creates pre-mature stop codons prior to the translation of the C-terminal ligand binding domain. Thus, variant AR proteins are created which lack the traditional ligand binding domain (see figure 2 below). In a seminal paper by Hu et al. prostate cancer tissue from primary hormone-sensitive and metastatic CRPC cancer tissue was analyzed by

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in silico DNA sequencing for the presence of AR splice variants. In total, 7 variant AR transcripts were discovered, AR-V1 through AR-V7. The two most abundantly expressed were AR-V1 and AR-V7. On average, there was 20-fold higher expression of these two variant transcripts in CRPC as opposed to hormone-sensitive prostate cancer. Functionally, AR-V7 was found to localize to the nucleus of prostate cancer cell line under androgen depleted conditions, and most importantly, was constitutively active in driving the expression of androgen-responsive genes (Hu, R, et al. 2009).

Fig. 2. Androgen Receptor Transcript and Splice Variants. NTD = N terminal domain. DBD = DNA binding domain. The hatched areas represent “hidden” exons spliced into the DNA binding domain exons (2 and 3), thus creating variant AR transcripts. The hidden exons of the variant AR transcripts encode stop codons, leading to premature termination and exclusion of the C-terminal ligand binding domain (exons 5-8 in green). Figure adapted from Guo, Z & Qiu, Y, 2011.

The exciting discovery of AR splice variants represents another potential mechanism by which cancer cells modify AR processing to adapt to a low circulating testosterone environment, creating AR splice variants which are not dependent on hormone binding to drive gene expression and cancer cell division and metastasis. Targeting the variant AR proteins, perhaps at the more ubiquitous N-terminal domain, represents a potential therapeutic approach to overcome this mechanism of resistance.

3. Traditional secondary hormonal therapies for Castrate Resistant Prostate Cancer

Traditional hormonal manipulations can be of some benefit to patients with CRPC; however significant responses are not seen in the majority of patients, and responses tend to be short-lived. Furthermore, the response duration and magnitude of benefit tend to diminish with
each successive hormonal manipulation. Chemotherapy has traditionally been the mainstay of treatment for CRPC patients who have failed secondary hormonal therapy; however, the median increase in overall survival with first-line docetaxel chemotherapy is a modest 3 months, and fewer than 20% of patients with CRPC live beyond 3 years (Tannock, et al. 2004; Petyrlak DP, et al. 2004). Clearly, novel therapies are needed which applied together or in succession can lead to meaningful improvement in the quality and quantity of time for patients with CRPC. In the following sections we will first discuss the traditional secondary hormonal agents which have been used to treat CRPC. We will then continue onwards with a discussion of the novel secondary hormonal therapies currently in clinical development, which more selectively and potently inhibit either steroid ligand production or AR activation.

3.1 First generation antiandrogens

First generation antiandrogens, which competitively inhibit the binding of androgens to the ligand binding domain of the AR, remain in widespread use in the treatment of prostate cancer of various disease stages. The addition of a first generation antiandrogen (i.e. flutamide, nilutamide, or bicalutamide) to medical castration (combined androgen blockade) demonstrates only modest benefits in the hormone-sensitive disease population, with a small absolute survival benefit of less than 5% in most studies and meta-analyses. Similarly, the addition of an anti-androgen after ADT fails has demonstrated only modest benefit in prior clinical studies. In a prior clinical trial of flutamide 250 mg orally three times daily versus prednisone 5 mg orally four times per day, the median time to symptomatic progression on flutamide was only 2.3 months (as compared to 3.4 months with prednisone), and the proportion of patients with a greater than 50% decline in PSA was 23% in the flutamide group vs. 21% in the prednisone group (Fossa SD, et al. 2001).

Similar rates of biochemical response were noted in a trial of 232 men who received either flutamide 375 mg/day or bicalutamide 80 mg/day after disease progression on combined androgen blockade. The percentage of men with a greater than 50% decline in PSA was 35.8%; the response duration was a little over 6 months (Suzuki H, et al. 2008). In another small trial of 31 men with CRPC treated with high dose bicalutamide 150 mg/day, only 22.5% of men had a PSA decline of > 50% for more than 2 months, almost all in men without prior treatment with flutamide (Joyce R, et al. 1998). The modest efficacy and limited duration of response of first generation anti-androgens may in part be due to the fact that these molecules can act as partial agonists of the AR, especially AR which develop point mutations as a mechanism of resistance to these anti-androgens. Clinically, this partial agonist effect is observed with the phenomenon of anti-androgen withdrawal, a therapeutic maneuver in which the anti-androgen is discontinued in a patient who is progressing despite combined androgen blockade. In a prior study of anti-androgen withdrawal, 11% of patients demonstrated a decline of 50% or more in serum PSA after anti-androgen withdrawal (Small E, et al. 2004). Presumably, in these small subsets of patients who respond to antiandrogen withdrawal, the AR may have developed mutations which confer the ability to be activated by the antiandrogen.

Novel second generation antiandrogens which lack any agonist activity against the AR and demonstrate markedly more potent AR inhibition, including MDV-3100, will be discussed in the upcoming section.
3.2 Estrogens
Estrogens have long known to have been active in the treatment of prostate cancer; however the exact mechanism of actions remains uncertain. Putative mechanisms include inhibition of LH hormone release from the pituitary gland, inhibition of adrenal androgen production, and a direct cytotoxic effect on prostate cancer cells (Robertson CN, et al. 1996). In a prior phase randomized phase II trial comparing the estrogenic herbal compound PC-SPES with diethylstilbestrol, a greater than 50% decline in baseline PSA was noted in 40% and 24% of patients respectively; median time to progression was 5.5 vs. 2.9 months respectively (Oh W, et al. 2004).

There is clearly a modest degree of activity of estrogenic compounds in the treatment of CRPC; however current use of these agents (i.e. diethylstilbestrol, Premarin, etc.) is limited by the small but not insignificant risk of venous thromboembolic events and possibly increased risk of myocardial infarction and stroke; these particular co-morbidities are especially concerning in a disease population of elderly men. Concomitant prophylactic anticoagulation is recommended when using these agents.

3.3 Ketoconazole
Ketoconazole is a broad, non-specific inhibitor of multiple cytochrome p450 enzymes involved in androgen biosynthesis, including the conversion of cholesterol to pregnenolone, 11-beta hydroxylation, and 17-alpha hydroxylase/C17, 20 lyase (CYP17) activity. In a previously referred to randomized phase II study of 260 men with CRPC, with progressive disease despite combined androgen blockade, randomized to treatment with antiandrogen withdrawal alone or in combination with ketoconazole, 27% of patients assigned to the ketoconazole arm had a 50% or greater decline in serum PSA level, and 20% of patients had an objective response (Small EJ, et al. 2004). Interestingly, at the time of disease progression on ketoconazole, levels of adrenal androgens including DHEA, DHEA-S, and androstenedione had all increased compared to month 1 levels, which suggest that ketoconazole resistance may in part reflect inadequate androgen production suppression. This mechanism of resistance has implications for the development of novel androgen synthetic enzyme inhibitors such as abiraterone acetate. In an intriguing analysis of adrenal androgen hormone levels from the study by Small et al., patients who had higher baseline levels of androstenedione had a higher likelihood of response to treatment with ketoconazole (Ryan CJ, et al. 2007). This suggests that baseline adrenal androgen levels may be used as predictive biomarker for the use of adrenal androgen blockade as a therapeutic maneuver for CRPC; however this hypothesis requires prospective validation in larger studies.

Ketoconazole is a relatively non-specific inhibitor of multiple enzymes involved in the steroid synthetic pathway, and as such, as blocks normal corticosteroid production and causes iatrogenic adrenal insufficiency. Accordingly, side effects of this medication include lethargy, rash, nausea, and liver toxicity. Supplementation with physiologic replacement doses of hydrocortisone (i.e. 20 mg in the morning, 10 mg in the evening) is required while patients are taking ketoconazole. Furthermore, given the relatively non-specific CYPP450 inhibition, ketoconazole interacts with a wide number of other medications. Its oral absorption and bioavailability can be variable, depending on the acidity of the stomach and fed/fasting state and use of acid suppressing medications. Despite these potential side effects and drug interactions, ketoconazole represents a viable and widely used secondary hormonal agent for CRPC, especially in the patient population.
with asymptomatic or minimally symptomatic bone-only metastatic or rising PSA-only disease.

4. Novel secondary hormonal therapies for Castrate Resistant Prostate Cancer

Insights into the mechanisms of continued AR signaling in CRPC, as discussed above, including (1) adrenal and intra-tumoral androgen ligand production, and (2) modifications of the AR, including gene amplification, over-expression, point mutations, ligand-independent activation, and splice variants, have led to the development of novel secondary hormonal therapies for CRPC. These new therapies are more selective and potent than their traditional counterparts. In the following subsections we will discuss the clinical development of several of the new hormonal therapies for CRPC.

4.1 Selective inhibition of CYP17

As displayed in figure 1, CYP17 (17-alpha hydroxylase/C17, 20 lyase) catalyzes two key steps of androgen synthesis within the steroid biosynthetic pathway: the 17-hydroxylation of progesterone and pregnenolone and subsequent conversion to DHEA and androstenedione respectively. Inhibition of this enzyme would divert cholesterol derivatives away from androgen production, and towards mineralocorticoid production (corticosterone and aldosterone). As outlined above, intra-tumoral upregulation of CYP17 has been previously implicated in the progression to CRPC. Logically then, selective inhibition of CYP17 represents an attractive strategy for inhibiting adrenal and intra-tumor androgen production in CRPCs and thereby slowing disease progression.

4.1.1 Abiraterone acetate

Abiraterone acetate is the prodrug of abiraterone, a potent, highly selective, irreversible inhibitor of CYP17. In pre-clinical in vivo study using WHT mice, this compound was able to markedly decrease the level of serum testosterone to less than 0.1 nanomolar concentration, despite 3-4 fold increase in serum LH concentration (Barrie SE, et al. 1994). In the first phase 1 study of abiraterone, O’Donnell et al. studied various dosing schedules ranging from 10 to 500 mg x 1 dose in castrate resistant men. At a dose level of 500 mg, there was suppression of serum testosterone to less than lower limit of detection (< 0.14 nmol/L) with parallel reduction androstenedione levels, supporting its mechanism of action of CYP17 inhibition. The duration of testosterone suppression after a single dose was variable, but generally ranged from days 2-5 post-dose (O’Donnell A, et al. 2004). In a follow up phase I trial by Attard and colleagues, 21 patients with CRPC and progression through multiple prior traditional secondary hormonal therapies were treated with abiraterone with doses ranging from 250 mg to 2000 mg/day. Pharmacodynamic effects on serum hormone levels showed a plateau at a dose of 1000 mg/day, which was the dose level of an expanded cohort of 9 patients and the subsequent recommended phase II/III dose. There were no treatment-related grade 3 or 4 adverse events from this trial. As expected, increases in levels of ACTH, corticosterone, and 11-deoxycorticosterone were observed, and there were adverse events related to subsequent mineralocorticoid excess, namely hypokalemia and hypertension. This was effectively managed with the use of eplerenone, a mineralocorticoid antagonist. The median baseline serum testosterone level was 7 ng/mL in this study; at all
dose levels serum testosterone was decreased to < 1 ng/mL within 8 days of treatment initiation. In a separate phase I dose escalation study of abiraterone acetate in 33 men, including 19 with prior ketoconazole treatment, daily dosing from 250 mg to 1000 mg was well tolerated with no dose-limiting toxicities (DLTs) (Ryan CJ, et al. 2010). Hypertension and hyperkalemia, signs of mineralocorticoid excess, as might be expected by the mechanism of action, were the most common serious toxicities (grade 3 or higher 12% and 9% respectively), which responded to medical management including low dose corticosteroids or mineralocorticoid receptor antagonists such as eplerenone. Spironolactone was avoided given its potential androgenic properties. Overall, 55% of patients in this study had a confirmed 50% or greater decline in serum PSA level at 12 weeks. In the subset of 19 patients with prior ketoconazole exposure, 46% had a greater than or equal to 50% decline in serum PSA at 12 weeks. Importantly, this data suggests that CRPCs which are resistant to ketoconazole may still be sensitive to the effects of abiraterone, which is a more potent and selective inhibitor of androgen synthesis compared to ketoconazole. In contrast to prior studies of ketoconazole in CRPC, in which adrenal androgens levels rose at the time of disease progression, serum hormone levels including testosterone and DHEA-S did not rise at the time of disease progression on abiraterone. This data suggests the mechanism of resistance to abiraterone may be unrelated to a rise in androgen levels. The phase II portion of this study included added prednisone 5 mg orally twice daily, and excluded patients with prior chemotherapy or ketoconazole (Ryan CJ, et al. 2009). Preliminary results indicated a 50% or greater decrease in PSA in 88% of patients; median time to PSA progression was 337 days. Subsequent various phase II studies have evaluated abiraterone as monotherapy and combined with low dose prednisone in men with CRPC and prior docetaxel chemotherapy. In a two stage phase II trial by Reid and colleagues of 47 men with CRPC and previous treatment with docetaxel, treated with abiraterone 1000 mg/day monotherapy, 51% of patients demonstrated a 50% or greater decline in serum PSA level. Furthermore, the median time to PSA progression was 169 days; the objective response rate was 28% among men with measurable disease at baseline. 8 patients had prior ketoconazole treatment; all but one had prior treatment with a first generation antiandrogen. Adverse events were as expected due to secondary mineralocorticoid excess, including 55% with hypokalemia, 17% with hypertension, and 15% with fluid retention. In a phase II trial of abiraterone 1000 mg/day + prednisone 5 mg twice daily in 58 men with CRPC and prior docetaxel treatment, a confirmed ≥ 50% decline in PSA was observed in 36% of patients, including 27% of patients with prior ketoconazole treatment (Danila DC, et al. 2010). The median time to PSA progression was 169 days. The addition of prednisone decrease the incidence of clinical mineralocorticoid excess, and no patients required treatment with eplerenone while on study. Results of the follow up confirmatory randomized phase III trial of abiraterone in the post-docetaxel CRPC population were recently reported (de Bono JS, et al. 2011). In this trial, 1195 patients with CRPC and prior docetaxel were randomized in a 2:1 fashion to receive either the combination of abiraterone 1000 mg/day + prednisone 5 mg twice daily versus placebo + prednisone 5 mg twice daily. After a median follow up of 12.8 months, overall survival was longer in the abiraterone group vs. the placebo group (median overall survival of 14.8 vs. 10.9 months; HR = 0.65, p < 0.0001). The data was unblinded at the time of interim analysis, as the results exceeded the pre-planned stopping rule for efficacy. All secondary
endpoints, including progression-free survival, objective response rate, and PSA response rate favored the abiraterone treatment arm. Hypokalemia was noted in 17% of abiraterone group patients, and 10% of patients experienced hypertension of any grade severity. As a result of the overall survival benefit demonstrated in this phase III trial, abiraterone acetate was granted FDA approval on April 28\textsuperscript{th}, 2011 for use in men with metastatic CRPC who had received prior chemotherapy containing docetaxel. An ongoing phase III trial of prednisone with or without abiraterone in men with metastatic CRPC without prior chemotherapy has finished accrual; study results are expected within the next year (NCT00887198).

The drug development of abiraterone acetate has unfolded rapidly over the past decade, based on a strong scientific rationale, pre-clinical and early clinical phase data indicating potent blockade of CYP17, a rational phase II/III dose selection, and the selection of clinically relevant endpoints for confirmatory phase III trials. Development of this drug remains ongoing, and many questions remain to be answered, including: (1) mechanisms of abiraterone resistance (2) optimal sequencing in the therapy of men with CRPC (e.g. before or after docetaxel?) (3) potential combination with other secondary hormonal agents (4) activity in patients with prior ketoconazole (patients treated with ketoconazole were excluded from the above mentioned phase III trials) (5) population pharmacokinetic analysis, and (6) development of predictive biomarkers that might allow for individualized patient selection for those most likely to benefit from abiraterone. This last issue is likely to become increasingly more relevant in an era of rising medical costs and the choice of multiple new agents for the treatment of CRPC. Preliminary data suggests that patients with higher levels of baseline adrenal androgen levels are more likely to respond to abiraterone, similar to the results obtained with prior studies of ketoconazole (Logothetis CJ, et al. 2008).

4.1.2 TAK-700 and TOK-001
Orteronel (TAK-700) is a selective CYP17 inhibitor which has reached clinical development in CRPC. Preliminary phase 1 data of 26 men with CRPC treated with dose levels ranging from 100 through 600 mg twice daily as well as 400 mg twice daily + low dose prednisone were recently presented (Dreicer R, et al. 2010). No dose limiting toxicities were seen. Fatigue was the most common adverse event, seen in 62% of patients, including 3 patients with grade 3 fatigue at the 600 mg twice daily dose. Other common adverse events included nausea, vomiting, anorexia, and constipation. Doses at or above 300 mg twice daily produced a 50% or greater decline in PSA in 70% of patients, of whom 29% had an impressive > 90% decline in serum PSA. Phase 3 trials of orteronel in men with metastatic CRPC pre and post docetaxel are ongoing (NCT01193244 and NCT01193257 respectively).

TOK-100, in a pre-clinical model, selectively inhibits CYP17 enzymatic activity and down regulates AR expression. In the LAPC4 xenograft model, TOK-100 combined with castration inhibited tumor growth and down-regulated AR expression, in contrast to treatment with castration or bicalutamide alone, in which AR expression was up-regulated (Vasaitis T, et al. 2008). Phase I/II trials of TOK-001 are underway in CRPC. The potential for down regulation of AR expression in addition to CYP17 inhibition may lead to more potent suppression of AR-mediated disease progression in CRPC, a hypothesis that warrants testing in current and future clinical trials of this compound.
4.2 Selective and potent inhibition of the Androgen Receptor

AR gene amplification and over-expression appears to be a relatively common phenomenon as tumors adapt to a low circulating testosterone environment, and may lead to progression to CRPC. First generation AR antagonists such as flutamide or bicalutamide inhibit ligand binding to the AR and thereby decrease nuclear localization and activation of AR-mediated gene expression. However, in the AR-amplified state, the first generation antiandrogens may not block the AR in a potent enough manner to block ligand-mediated AR activation. Furthermore, acquired point mutations in the AR may cause first generation antiandrogens to exhibit partial agonistic activity towards the AR, as supported by the clinical phenomenon of response to antiandrogen withdrawal. Pre-clinically, first generation antiandrogens exhibit partial agonist activity towards the AR in prostate cancer cell lines engineered to express higher amounts of AR. More potent AR antagonists, which are capable of inhibiting the AR even in cells with AR overexpression, and do not possess any agonistic activity towards the AR, would be highly desirable as a hormonal therapy in CRPC, a potentially AR-amplified disease state.

4.2.1 MDV3100

MDV3100 was developed pre-clinically in an iterative screening process of various compounds that retain AR antagonistic activity in an AR-overexpressed cell line. MDV3100 binds to AR with 5-8 fold greater affinity compared to the first generation antiandrogen bicalutamide (Tran C, et al. 2009), impairs AR nuclear translocation, and inhibits AR binding to DNA, and blocks binding of AR to co-activators to a greater degree than bicalutamide. In tumor xenograft models known to overexpress AR, treatment with MDV3100 led to substantial tumor shrinkage.

MDV3100 was studied in a phase I/II clinical trial of 140 men with CRPC, including 45% of patients with prior ketoconazole and 54% with prior chemotherapy, in doses ranging from 30 mg to 600 mg/day. The maximum tolerated dose for ≥ 28 days was 240 mg/day. At doses of 360 mg/day and higher, 13% of patients discontinued treatment due to an adverse event, including three patients with seizures and one patient with a myocardial infarction. In contrast, at doses of 240 mg/day or lower, 1% of patients (1 out of 87 patients) discontinued treatment due to an adverse event. The most common grade 3 or higher dose-limiting toxicity was fatigue, which generally resolved with dose reduction. Anti-tumor activity was noted at all dose levels. In total, 56% of patients showed a 50% or greater reduction in serum PSA level; 22% of patients had an objective radiographic response among those with measurable disease at baseline, and conversion from unfavorable to favorable circulating tumor cell (CTC) count in 49% of patients. Similar PSA response rates were seen in patients with and without prior chemotherapy, though among patients with prior ketoconazole exposure, there was a lower percentage of patients with a 50% or greater decline in serum PSA (37% vs. 71% for those with and without prior ketoconazole respectively). The median time to radiographic progression was 47 weeks. Based on the encouraging results of this phase I/II clinical trial, ongoing phase III trials of MDV3100 vs. placebo, at a dose of 160 mg/day, are ongoing in patients with metastatic CRPC with and without prior docetaxel treatment (NCT00974311 and NCT01212991 respectively).

4.2.2 Other Androgen Receptor antagonists

Several other second generation, highly potent, pure AR antagonists have reached clinical development in CRPC. BMS-641988 is a highly potent AR inhibitor was designed based on

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AR crystal structure. In pre-clinical study, this AR antagonist showed a > 1 log increase in potency of AR inhibition compared with bicalutamide, both in regards to AR binding and inhibition of AR-mediated gene expression (Attar RM, et al. 2009). Furthermore, in a human xenograft model, BMS-6419888 displayed greater growth inhibition compared with bicalutamide. Based on the encouraging pre-clinical data, this compound was subsequently tested in a phase I dose escalation study (Rathkopf D, et al. 2010). In this trial, doses of BMS-6419888 were escalated from 5 mg to 150 mg. In total, 61 men were treated. One patient experienced an epileptic seizure at a dose of 60 mg twice daily. Antitumor activity was limited to one partial response, and partial agonism was seen as evidenced by a decrease in serum PSA upon drug withdrawal. Based the limited anti-tumor activity despite achieving target therapeutic levels, as well as the epileptic seizure, the study was closed prematurely and further clinical development of this compound discontinued.

ARN-509 is a potent AR antagonist in the early phases of clinical development. It inhibits AR nuclear translocation and DNA binding, thereby modulating expression of genes which drive prostate cancer growth. It is currently being tested in a phase I/II clinical trial of men with metastatic CRPC with up to two prior chemotherapy regimens (NCT01171898). The primary endpoint is maximum tolerated dose; secondary endpoints include change in PSA, number of new bone lesions, and objective response by RECIST criteria. Enrollment began in July of 2010 and results are expected in 2012. Likely due to the several seizure events during prior clinical trials of MDV3100 and BMS-6419888, patients with a history of seizures or potentially lower seizure threshold are excluded from this phase I/II trial of ARN-509.

5. Future directions

The clinical activity of the novel secondary hormonal therapies which attack the AR axis continues to lend credence to the now widely held hypothesis that continued activation of the AR plays an important role in the progression of disease to CRPC and ultimately to prostate cancer death. Much progress has been made over the past several decades in the drug development of secondary hormonal therapies for CRPC. However, there are many questions that remain yet to be answered, including: (1) optimal timing and sequence of hormonal therapies in relation to chemotherapy and each other (2) relative risks and benefits of combination versus sequential hormonal monotherapy (3) mechanisms of resistance (4) patterns of disease progression on these novel therapies (5) potential predictive biomarkers to help individualize patient therapy, including the molecular characterization of circulating tumor cells (6) pharmacokinetic studies across various study populations and ethnicities (7) pharmacogenomics analysis of potential associations between germ line mutations and response (8) long term safety data, and (9) optimal phase II/III clinical trial endpoints to assess efficacy of these agents, including the potential use of surrogate markers such as change in number of circulating tumor cells. Furthermore, there are new treatment strategies which target the AR axis that are in the infancy of drug discovery and development. Among them is EPI-001, a compound which inhibits transactivation of the N-terminal domain of the AR, without interacting with the AR ligand-binding domain, and thus may serve as a potential inhibitor of the AR splice variants that are hypothesized to play a role in the resistance to androgen ablation therapy (Andersen et al, 2010). Additionally, inhibitors of heat shock proteins, which act to stabilize the AR among other proteins, are also in clinical development.
6. Conclusions

AR activation continues to play a role in the progression of CRPC, despite low circulating serum testosterone levels in this disease state. This is accomplished through endocrine ligand production via adrenal androgen synthesis, intracrine ligand formation via up-regulation of the enzymes involved in androgen synthesis, including CYP17, AR overexpression and point mutations which confer receptor promiscuity and promote agonistic activity of traditional antiandrogen therapy, ligand-independent AR activation, and generation of constitutively active AR splice variants, among others. Pre-clinical drug discovery and development targeting specific steps in these mechanisms has led to the clinical development of numerous secondary hormonal agents which specifically and potently target the AR axis. Ongoing research is directed at optimizing and personalizing the use of the current novel secondary hormonal therapies as well as developing new therapeutic strategies to overcome treatment resistance in CRPC.

7. References


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This book represents a case study based overview of many different aspects of drug development, ranging from target identification and characterization to chemical optimization for efficacy and safety, as well as bioproduction of natural products utilizing for example lichen. In the last section, special aspects of the formal drug development process are discussed. Since drug development is a highly complex multidisciplinary process, case studies are an excellent tool to obtain insight in this field. While each chapter gives specific insight and may be read as an independent source of information, the whole book represents a unique collection of different facets giving insight in the complexity of drug development.

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