Improving the Outcome of Patients with Castration-resistant Prostate Cancer Through Rational Targeting of the Androgen Receptor

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Abstract

Castration-resistant prostate cancer (CRPC) is now the second most common cause of male cancer-related mortality. Recent evidence confirms that androgen receptor signalling continues to drive a significant proportion of progressing prostate cancers despite castrate serum levels of testosterone and multiple hormonal interventions. An increased understanding of the molecular biology underlying CRPC is informing on therapeutic targets for this disease, and we hypothesise that this will lead to the development of more efficacious drugs.

Keywords

Prostate cancer, androgen receptor, castration resistance, hormone therapies

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Prostate cancer is the most common malignancy in western societies and the second most common cause of male cancer-related death in the UK.[1,2] When confined to the prostate gland, the disease is potentially curable with local therapy (radical prostatectomy or external-beam radiotherapy). However, in the UK one in five men has metastatic prostate cancer at presentation, and 15–33% of men fail local therapy and develop incurable metastatic disease.[3,4] Evidence emerging over the past five years has increasingly identified androgen receptor (AR) signalling as critical to all stages of the disease, and the terminal, incurable stage of prostate cancer is now widely referred to as castration-resistant prostate cancer (CRPC) in preference to the previously utilised terminology hormone-refractory prostate cancer.[6]

Current Treatments for Castration-resistant Prostate Cancer

Activation of the androgen receptor (AR) regulates transcription of a diverse range of target genes involved in prostate cell proliferation, differentiation and apoptosis.[6] Drugs that reduce circulating levels of androgens or that competitively inhibit the action of androgens at the AR (anti-androgens) remain central to the treatment of prostate cancer. Gonadotrophin-releasing hormone (GnRH)/luteinising-hormone-releasing hormone (LHRH) agonists, such as goserelin and leuprorelin, inhibit luteinising hormone (LH) secretion and suppress testicular testosterone generation (medical castration). Castration is the first line of treatment for the majority of patients with metastatic prostate cancer. Virtually all patients have a biochemical and clinical response to medical or surgical castration. The duration of response varies significantly from less than 12 months in some patients to several years in others.[4] The adverse effects of androgen deprivation therapy include osteopenia or osteoporosis with attendant danger of bone fracture,[7] loss of muscle mass, low-grade anaemia, sexual dysfunction, hot flushes and gynaecomastia, all of which may reduce quality of life, and there is low-level evidence that androgen deprivation therapy (ADT) may hasten cognitive decline. There is no approved strategy to prevent the adverse metabolic effects of ADT, and as more men are diagnosed with prostate cancer and at a younger age, the scale of the health problem secondary to long-term ADT may increase significantly.[8]

The first therapeutic approach for patients who become resistant to castration is usually the addition of a secondary hormone manoeuvre while maintaining castrate levels of testosterone. Competitive inhibitors of androgen interaction with the AR ligand binding site, such as the anti-androgens (e.g. bicalutamide or flutamide), are routinely used to treat patients in combination with GnRH agonists or after relapse on GnRH agonists to achieve 'maximum androgen blockade'. However, although low levels of androgens remaining after castration are thought to play a role in the onset of CRPC, this combination strategy has not been proved to prolong survival. These drugs have been shown to prevent nuclear translocation of the AR,[9] but their effect is reversible and the clinical benefit derived from their use is modest at best,[10] leading to a response rate of about 15%.[11] In addition, up to 30% of patients experience a drop in prostate-specific antigen (PSA) after discontinuing anti-androgens.[12] This is explained in part by the development of AR gene mutations,[13] gene amplification

to behave as agonists.[14] Continuous oral glucocorticoids (dexamethasone 0.5mg once daily [od] or prednisolone 10mg od) can also result in temporary PSA responses in up to 50% of patients, presumably due to adrenal androgen suppression.[15–17] A further effective hormone therapy, albeit more toxic, is the use of oestrogens, by mouth or by skin patch. The oestrogenic compound diethylstilboestrol (DES) is not approved for use in the US but is the most commonly used oestrogen in UK practice. Small studies of DES 1mg per day in CRPC reported a response rate of 40–70% of patients.[18,19] As oestrogens may cause painful gynaecomastia, gastrointestinal upset and, occasionally, fluid retention, and also increase the risk of thromboembolism, they are usually deferred to third-line hormonal therapy.

Treatment with docetaxel 75mg/m^2 three times weekly and daily prednisolone 10mg has been shown to confer a survival advantage of a median of 2.5 months and improve quality of life in patients with CRPC compared with mitoxantrone, and is now regarded as the standard of care in patients for whom chemotherapy is indicated.[16] Platinum-containing regimens such as epirubicin, carboplatin and 5-flurouracil have also shown antitumour activity in phase II studies,[20] and their activity in patients who fail docetaxel treatment is undergoing evaluation. The major impact on the quality of life of most patients with CRPC occurs as a result of their disease metastasising to bone. Single-fraction palliative radiotherapy can be used to control pain from solitary sites of disease. The use of bisphosphonates such as zoledronic acid in prostate cancer remains controversial, and although one study suggests a reduction in skeletal-related complications, overall no improvement in patient quality of life or survival has been reported.[21] For patients with widespread painful bone involvement, treatment with bone-seeking radiopharmaceuticals, e.g. strontium-89, is available in specialist centres and offers a targeted approach for providing rapid pain relief. The less myelosuppressive radioisotope, the α-emitter radium 223, is also currently in phase II studies and may be superior to strontium, as administration of higher doses is not as limited by marrow toxicity.[22]

Optimising the Successful Development of Agents for Castration-resistant Prostate Cancer

The limited therapeutic options available to prostate cancer patients underscore the urgent need for the development of novel agents to tackle the castration-resistant state, provide palliation and improve survival in this group of patients. In addition, drugs that are targeted specifically against cancer cells, allowing a better toxicity profile than standard cytotoxic agents, are sought. The rational development of such novel targeted agents requires a greater understanding of the molecular biology underlying castration resistance. In addition, with the earlier use of castration and the frequent use of PSA for monitoring, the development of CRPC is now commonly identified by an increasing PSA rather than by new or worsening symptoms. Patients are often asymptomatic when this initially occurs, providing a large cohort of patients who refuse docetaxel or for whom chemotherapy is not suitable and thus presenting a window for the conduct of clinical trials of drugs of low toxicity.[5]

The key to drug development lies in identification and characterisation of targets and pathways driving cancer growth in this disease. With our increasing understanding of the genes and pathways that drive CRPC, therapeutic agents can be developed that act on the molecular targets defined by the key genetic and molecular abnormalities responsible. With a plethora of new agents becoming increasingly available, a thorough evaluation of the use of pharmacokinetic (PK) and pharamcodynamic (PD) end-points allows a pharmacological 'audit trail' to be constructed (see *Table 1*).[23] PK end-points provide information on how much drug gets into the body and ideally into target tissues; PD end-points allow understanding of what the drug does with respect to modulation of the molecular target and biochemical pathway, and whether this translates into achieving the desired biological effect. This ensures that all of the main stages in drug development (from drug administration through the biological effect to the clinical outcome) can be monitored and interpreted. The audit trail thus provides a basis for answering critical questions in a rational, hypothesis-driven fashion and ensures that the drug development process is more scientific and rigorous. As our understanding of the molecular biology of CRPC advances, rational drug development will exploit the targets and pathways of prime importance.

Table: New Drugs Under Investigation for the Treatment of Castration-resistant Prostate Cancer

Target	Biological Effect	Examples of Drugs	Stage of Clinical Development
17α hydroxylase/ C17,20 lyase	Suppression of adrenal androgen precursors	Abiraterone acetate	Phase III (accrual completed in post-docetaxel study); chemotherapy-naïve phase III studies planned
Novel AR antagonists	Inhibition of AR signalling	MDV-3100	Phase III
HSP90	Inhibition of AR signalling	17-AAG 17-DMAG	Phase II Phase I/II
HDAC	Downregulation of AR	SAHA FK228	Negative phase II studies Negative phase II studies
PI kinase	Inhibition of AKT/PI3K signalling axis	PI620	Phase I
mTOR	Inhibition of downstream effectors in AKT/PI3K	CCI-779 RAD001	Phase II
IGF1-R	Inhibition of IGF1-R signalling axis	CP-751-851	Phase II
ErbB receptor family	Inhibition of erbB signalling axis	Gefitinib Pertuzumab (2C4)	Negative phase II trials Negative phase II trials

HSP = heat shock protein; AR = androgen receptor; HDAC = histone deacetylase; IGF = insulin-like growth factor.

The Androgen Receptor as a Therapeutic Target for Castration-resistant Prostate Cancer

The presence of high AR messenger RNA (mRNA) levels in almost all tumour samples from patients with CRPC strongly suggests that prostate tumours evolve mechanisms to reactivate AR expression and AR-responsive pathways.[14] Molecular changes to the AR that have been proposed to cause castration resistance include R gene amplification,[24] mutations in the AR gene,[6,25] post-transcriptional causes of increased AR expression[26] and alterations in AR co-repressor/co-activator function.[27,28] These could result in continued androgen-dependent activation of a 'hyper-sensitive' AR,

a promiscuous AR that is activated by alternative ligands or constitutive, non-ligand-dependent activation of the AR.

AR gene amplification is reported in one-third of CRPC tumours, and as amplifications are significantly less common in untreated tumours it has been proposed that gene amplification is the result of selective pressure exerted by androgen deprivation.[24,29] This could result in AR activation by low levels of androgens or by alternative ligands, such as mineralocorticoids or anti-androgens. Similarly, the prevalence of

As our understanding of the molecular biology of castration-resistant prostate cancer advances, rational drug development will exploit the targets and pathways of prime importance.

AR mutations in tumour tissue appears to increase with increasing exposure to castration, anti-androgens and other lines of hormone treatment.[6,30] The vast majority of these mutations result in conformational promiscuity of the ligand-binding domain (LBD) of the AR,[31] thus providing a molecular explanation for the androgen withdrawal phenomenon. More recently, AR variants have also been described in CRPC patients who lack the LBD. These constitutively active variants can induce canonical androgen-responsive gene expression in the absence of androgens,[32] resulting in resistance to therapeutic strategies aimed at suppressing ligands.

The transcriptional activity of the AR is mediated, in part, by co-activators that enhance or co-repressors that reduce receptor function. The three co-activators – ARA70, steroid receptor co-activator 1 and RAC3/ACTR – can enhance AR transcriptional activity in the presence of 'castrate' levels of androgens, and co-activator proteins such as ARA54 and ARA70 can selectively enhance the activity of the AR to alternative ligands such as estradiol and hydroxyflutamide.[27,28,33] Decreased expression of co-repressors such as nuclear receptor co-repressor (NCoR) and silencing mediator of retinoid and thyroid receptors (SMRT), which mediate, in part, the antagonist action of bicalutamide, flutamide and mifepristone, may contribute to the agonist activity that can be observed with these agents.[34] A change in the co-activator to co-repressor ratio can alter AR transactivation activity in the presence of low concentrations of DHT. Conversely, the co-repressors SMRT and NCoR can inhibit AR function in a ligand-dependent manner. Experimental models show that alterations in the co-activator to co-repressor ratio can also explain the paradoxical agonistic effects of anti-androgens and other steroid hormones on prostate cancer growth.[35] However, this relationship has not been exploited therapeutically to date, especially as a result of the complex nature of these interactions.

Kumar-Sinha et al. recently reported that 40–70% of prostate cancers have a chromosomal rearrangement that results in hormonal regulation of oncogenic ETS (ERG, ETV1, ETV4, ETV5) gene expression.[36] The most common rearrangement results in fusion of TMPRSS2 with ERG. Transcription of TMPRSS2 or other ETS gene fusion partners is regulated by the AR, oestrogen receptor or, potentially, other steroid receptors such as the vitamin D receptor.[37] ETS gene fusions have introduced the interesting hypothesis that inhibition of AR signalling results in suppression of oncogenic ETS gene expression, explaining the significant antitumour activity of castration and other hormonal therapies. The corollary of this hypothesis is that ETS gene fusions could serve as biomarkers that predict response to hormone therapy. In addition, disease progression secondary to a rising PSA in castrate patients occurs in a significant proportion of patients following re-induction of ETS gene over-expression.[38] ETS genes could therefore serve as valid therapeutic targets, although as they are transcription factors they are notoriously hard to target therapeutically. Activation of the AR by residual androgens in CRPC can be inhibited by: suppressing non-gonadal synthesis of hormones that bind the AR;[39] novel, potent AR antagonists;[14] and ablation of the AR with drugs such as the histone deacetylase inhibitors and heat shock protein 90 (HSP90) inhibitors.[40]

Targeting Androgen Receptor Signalling

Inhibition of the Steroid Synthesis Pathway

Plasma testosterone is not completely suppressed by castration, in part due to the peripheral conversion of adrenal androgenic steroids to testosterone by 17-ketoreductase.[4] It has also been reported that, despite castration, intraprostatic levels of androgens in CRPC may remain sufficient to maintain tumour growth. Studies measuring testosterone and DHT report a decline at institution of castration with a subsequent rise in testosterone in CRPC to levels equivalent to prostate tissue obtained from non-castrate men.[41,42] The source of these androgens is unclear, but altered regulation of enzymes involved in the synthesis and inactivation of androgens may be one cause of their accumulation. In support of this, increased expression of enzymes involved in the androgen synthesis pathway have been reported in CRPC, suggesting the possibility of either *de novo* production of androgenic steroids from cholesterol precursors or the enhanced conversion of adrenal androgens to testosterone by CRPC.[43–45]

Adrenal androgen synthesis can be inhibited by targeting the pituitary–adrenal axis or by the inhibition of key enzymes in the steroid biosynthesis pathways. Suppression of the pituitary–adrenal axis and consequently the generation of adrenal androgens by low-dose steroids have not been shown unequivocally to occur in patients with CRPC, but it could be one explanation for their antitumour activity.[46,47] Ketoconazole, an imidazole antifungal agent that weakly and non-selectively inhibits several cytochrome P450 (CYP) enzymes involved in adrenal steroid synthesis, induces a short-lived PSA response in 20–30% of CRPC patients.[12] Importantly, patients who respond to ketoconazole and subsequently progress show a significant decrease associated with an increase in disease progression of adrenal androgens (dehydroepiandrosterone sulphate [DHEA-S] and androstenedione), suggesting that ketoconazole resistance is caused by adrenal androgens.[12] Although suppression of adrenal androgen biosynthesis is probably important, targeting of the steroid biosynthesis pathway at other sites, most notably CRPC itself where several key enzymes have been reported to be over-expressed,[44,45] could also prove critical to significant and durable therapeutic responses.

A more specific inhibitor of steroid synthesis is currently in phase III clinical development. Abiraterone acetate is a potent, orally bioavailable and irreversible inhibitor of CYP17, which is a key enzyme involved in the 17-hydroxylation of pregnenolone and

progesterone and their subsequent conversion to the adrenal androgens, dehydroepiandrosterone (DHEA) and androstenedione. Its inhibition causes suppression of serum androgens and oestrogens that could activate the AR, TMPRSS2 and other hormone-regulated genes.[48] Declines in PSA by ≥50 and ≥90% with abiraterone acetate have been reported in 50–60 and 20–30% of CRPC patients, respectively, despite prior progression with castrate on several hormonal agents. Importantly, declines in PSA were associated with radiological tumour regression, declines in circulating tumour cell count and symptomatic benefit.[48,49] In addition, prior treatment with docetaxel chemotherapy did not significantly alter sensitivity to abiraterone acetate.[50] In these studies, concomitant castration was continued to prevent a compensatory LH surge that can overcome CYP17 blockade.[20] Continuous CYP17 inhibition results in raised levels of ACTH that increase steroid levels upstream of CYP17, including corticosterone and deoxycorticosterone. These raised upstream steroids prevent adrenocortical insufficiency but can result in a syndrome of secondary mineralocorticoid excess characterised by fluid retention, hypertension and hypokalaemia. This can be ameliorated by mineralocorticoid antagonists or low-dose glucocorticoids, which decrease ACTH and steroids upstream of the CYP17 blockade. Secondary responses were observed on addition of steroids to abiraterone acetate, possibly due to suppression of raised upstream steroids that were driving a 'promiscuous' AR.[48,49] The current clinical development strategy of abiraterone acetate includes combination with steroids.

Novel, Potent Androgen Receptor Antagonists

Another strategy for inhibiting AR signalling is with potent AR antagonists that prevent nuclear translocation. Inhibitors of steroid synthesis could abrogate ligand-dependent AR signalling but will not prevent constitutive activation of the AR, which can occur following AR amplification. The novel anti-androgen MDV-3100 binds to the AR and inhibits nuclear translocation much more potently than bicalutamide. In pre-clinical LNCaP-based models, MDV-3100 does not become agonistic.[51] This agent is now in phase I/II clinical trials in the Prostate Cancer Consortium in the US, and presentations at scientific meetings suggest ≥50% declines in PSA in 40–60% of CRPC patients. A novel series of isoindoledione-based compounds have also been identified as potent antagonists of the wild-type and several mutant isoforms of the AR.[52-54] These compounds are being developed by Bristol-Myers Squibb.

Ablation of Intracellular Androgen Receptor Signalling

HSP90 is a member of the family of heat shock proteins that acts as an adenosine triphosphatase (ATPase)-driven molecular chaperone. HSP90 is as an ATPase-driven molecular chaperone that maintains the molecular stability, conformation and function of oncogenic tyrosine and serine-threonine kinases, such as erbB2 and AKT, and steroid hormone receptors, including the androgen and oestrogen receptors.[40,55–57] LAQ824 can induce the hyperacetylation of HSP90, disrupting the complex between HSP90 and its client proteins, such as the AR, inhibiting their synthesis and function.[58] Treatment of androgen-dependent and -independent prostate cancer cell lines with LAQ824 depletes wild-type and mutated AR through HSP90 inhibition; LAQ824 also blocks androgen-induced PSA production, induces apoptosis and inhibits cell proliferation in LNCaP cells.[40] In prostate cancer animal models, the first-in-class HSP90 inhibitor 17-allylaminogeldanamycin (17-AAG) causes the degradation of these client proteins at non-toxic doses and inhibits the growth of hormone-naïve and castration-resistant tumours.[59] 17AAG-induced cell-cycle arrest and apoptosis *in vitro* and *in vivo* and phase I trials have been completed.[60]

HSP90 chaperone activity is regulated by histone deacetylase (HDAC) enzymes. In HDAC6-deficient cells, HSP90-dependent post-translational maturation of nuclear steroid receptors is abrogated.[61,62] Recently, aberrations of 'global' histone modification have been observed in prostate cancer. Global levels of the acetylation or methylation of five different residues in histones H3 and H4 were examined in prostate tumour samples. These histone modification patterns could predict tumour grade and recurrence.[63] Expression of HDAC1 is associated with high expression levels of ERG, linking HDAC inhibitors with transcriptional activity of hormone-dependent ERG gene fusions.[64] In addition, HDAC inhibitors, including SAHA (vorinostat) and LBH589, block the AR-mediated transcriptional activation of many genes, including the TMPRSS2 gene, and genetic knockdown of either HDAC1 or HDAC3 can suppress expression of AR-regulated genes.[57] In addition to suppressing AR protein levels in prostate cancer cells, HDAC inhibitors can also block AR activity through inhibition of the assembly of co-activator/RNA polymerase II complex after AR binds to the enhancers of target genes.[57] Several HDACs, including SAHA and romidepsin (depsipeptide), are undergoing clinical investigation. However, these studies have reported very limited antitumour activity in CRPC. In the recently presented but as yet unpublished phase II trial of romidepsin, a cyclic depsipeptide with pre-clinical prostate cancer antitumour activity administered intravenously weekly for thee weeks in a four-week cycle, only one radiological and biochemical response was observed.[65] However, this may be a reflection of an inadequate pharmacodynamic effect, with current HDAC inhibitors achieving insufficient levels for maximal AR blockade.[57] Improved formulations and further evaluation of the correct schedule could be required to achieve the clinical benefits that have been reported in pre-clinical models.

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Targeting Alternative Signalling Pathways

Other Steroid Receptors

Resistance to AR-targeting therapies could develop following induction of downstream AR targets by other steroid receptors or alternative cell signalling pathways. In the prostate cancer cell line NCI-H660, transcription of TMPRSS2:ERG is modulated by a functional oestrogen receptor.[66] Computational analysis of expression array data suggests a central role for oestrogen-receptor-related pathways in prostate cancer. In addition, increased expression of oestrogen receptor-α and decreased expression of oestrogen receptor-β has been associated with prostate cancer progression.[67] Oestrogens are suppressed by abiraterone and could account in part for some of the antitumour activity reported.

Studies of aromatase inhibitors have reported no evidence of antitumour activity, but this could be a result of the complex interplay of oestrogen receptor-α and oestrogen receptor-β in CRPC. Similarly, response elements upstream of TMPRSS2 can be activated by other steroid receptors, including vitamin D.[37] Calcitriol (1,25-dihydroxycholecalciferol), the principal active metabolite of vitamin D, demonstrates significant antineoplastic activity in pre-clinical models of prostate cancer.

The development of agents to specifically target the upstream genes and proteins potentially deregulated in prostate cancer also provides an opportunity for reversing resistance to endocrine treatments.

Human Epidermal Growth Factor Receptor 2

Experimental models have shown that the AR can be activated indirectly by cross-talk with other non-steroidal receptors. Epidermal growth factor receptor, other growth factors such as keratinocyte growth factor, insulin-like growth factor-1 and epidermal growth factor and cytokines such as interleukin-6 can activate the AR and minimise or possibly even negate the requirement for ligand.[68–71] The development of agents to specifically target these upstream genes and proteins potentially deregulated in prostate cancer also provides an opportunity for reversing resistance to endocrine treatments. Human epidermal growth factor receptor 2 (HER-2)/neu, a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases, is consistently over-expressed in some castrate prostate cancer cell lines and in the human disease at a higher frequency in castration-resistant as opposed to hormone-naïve primary tumours.[68,72,73] In addition, HER-2/neu was shown to promote DNA binding and AR stability through activation of mitogen-activated protein kinase (MAPK) and Akt, which could also bind directly to the receptor.[74,75] However, phase II clinical studies of therapeutics targeting HER2 failed to demonstrate any clinical benefit, despite proven antitumour activity with the same dose and regimen in other tumour types.[76–78] As it becomes increasingly evident that a significant proportion of CRPC remains driven by ligand activation of the AR, the role of cross-talk between the HER kinase family and AR signalling must at best be of limited relevance. However, in the future there may be a role for combination regimens that include therapeutics targeting cross-talk pathways in patients in whom AR signalling has been truly abrogated with CYP17 inhibitors and novel anti-androgens, etc.

Phosphatase and Tensin Homologue and Phosphoinositide 3-kinase Signalling

The phosphoinositide 3-kinase (PI3K) pathway regulates many key cellular processes. There is now overwhelming evidence implicating the PI3K/AKT/mTOR pathway as a regulator in the malignant progression of prostate cancer. Functional loss of phosphatase and tensin homologue (PTEN) (which is the negative regulator of PI3K) is thought to occur in up to half of all prostate cancers and is associated with increased activation of AKT and the downstream kinase mTOR, which is involved in regulating protein synthesis. Loss of PTEN and increased AKT-1 phosphorylation is typically associated with higher Gleason grading, advanced stage and poorer prognosis.[79]

The PI3K pathway appears to be critical in the development of CRPC. *In vitro* data suggest that over-expression and activation of AKT can trigger prostate cancer androgen escape via altered sensitivity and activation of AR.[80] The PI3K pathway therefore presents a number of attractive kinase targets for drug development. The first generation of PI3K inhibitors were limited by lack of potency, poor selectivity for the oncogenic class I PI3K isoforms and unsuitable pharmaceutical properties. Newer-generation inhibitors have improved pharmacological properties, appear highly selective and have demonstrated growth inhibition *in vitro* and *in vivo*. A number of these inhibitors are shortly to enter the clinic.[81] Preliminary data from these inhibitors show that the likely molecular response is G1/S phase arrest, with no significant apoptosis. PI3K inhibitors may therefore be best used in combination with inhibitors of other survival signalling pathways, e.g. EGFR/ MEK/MAPK,[82] or following treatment with cytotoxics. Similarly, a number of specific small-molecule inhibitors of AKT are in development and should enter clinical trials shortly. Proof of principle that the PI3K pathway can be targeted successfully for clinical use in cancer has been demonstrated by the development of rapamycin analogues (CCI-779, RAD-001) that inhibit the mTOR kinase and are now undergoing evaluation in phase II trials in CRPC. RAD-001 has been shown to completely reverse the PIN phenotype in murine transgenic AKT models. In addition, mTOR-dependent regulation of HIF1-α may produce an anti-angiogenic effect.[83] One of the main concerns regarding the use of mTOR inhibitors is the possibility of 'negative feedback' with activation of upstream targets such as insulin-like growth factor (IGF)1-R and p-AKT.

Insulin-like Growth Factor Receptor Signalling

Activation of IGF-1R by IGF-1 or IGF-2 results in phosphorylation and membrane recruitment of insulin receptor substrate proteins and activation of intracellular signalling pathways, including PI3K and MAPK. The activated receptor is thus able to induce AR signalling in the absence of AR ligand activation. IGF-1R expression has been reported to alter as prostate cells progress from a normal to a malignant phenotype, and IGF-1R is implicated in resistance to therapy.[84] Targeting of IGF-1R signalling in pre-clinical tumour models has suppressed growth of prostate cancer cells, induced apoptosis *in vitro* and *in vivo* and sensitised cancer cells to conventional chemotherapeutic treatment and irradiation.[85] An IGF-1R-targeting monoclonal antibody is now being evaluated for the treatment of CRPC.[86]

Ongoing Challenges

It is envisioned that the next decade will result in significant changes in the treatment of prostate cancer. As new and better drugs targeting the AR are developed (see *Table 1*), patients may become truly AR-independent. Also, therapeutic targeting of ETS genes or their downstream targets could achieve the antitumour effectivity of hormone therapies while sparing patients the adverse effects of androgen deprivation. A key challenge that remains to be addressed is the identification of suitable surrogate end-points for survival. PSA does not predict survival and therefore is not suitable for evaluating response to drugs. Recently, the rate of the rise of

PSA (PSA velocity) has been associated with the length of survival after treatment and may prove to be a suitable surrogate for survival.[87] However, PSA secretion is driven by AR signalling, and new drugs that directly target AR signalling could be ineffective treatments yet modulate PSA levels. New technology allows the isolation and enumeration of circulating tumour cells (CTCs) in patients with advanced prostate cancer. The number of CTCs pre- and post-chemotherapy above and below a set threshold is associated with survival in CRPC, and a decline in CTC count with treatment is associated with an improvement in survival.[88] Dynamic-weighted magnetic resonance imaging and positron emission scans using 18F-fluoro-2-deoxy-D-glucose or 18-F-fluoro-3'deoxy-3'-L-fluorothymidine may also be valuable tools to assess CRPC and may allow early assessment of disease response. Overall, these surrogates could become primary endpoints in efficacy trials, thereby expediting future advances and drug approval. ■

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