The androgen receptor and clinical challenges

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This report is based on a seminar held during the 10th Annual Meeting of the British Uro-oncology Group in London, 13–14 September 2013. The seminar focused on all aspects of the role of the androgen receptor in prostate cancer, from an overview of the molecular mechanisms and underlying pathways to the development of therapeutic agents designed to inhibit the androgen receptor.

In 1941, Charles Huggins first described scientifically the relationship between androgens and the pathogenesis and progression of prostate cancer. Since then, androgen deprivation therapy (ADT) through surgical or chemical castration has been the cornerstone of treatment for advanced and metastatic prostate cancer. Following the seminal work by Huggins, numerous approaches to androgen deprivation have been used successfully. However, in all cases, patients eventually experience disease relapse, and go on to develop more aggressive, castrate-resistant tumours.

ROLE OF THE ANDROGEN RECEPTOR IN CASTRATE-RESISTANT PROSTATE CANCER

Androgen receptor (AR) signalling is a feature of prostate cancer across the spectrum of the disease, with the majority of androgen-independent or castrate-resistant tumours continuing to express AR. The androgen signalling pathway involves the conversion of testosterone into dihydrotestosterone (DHT) in the prostate tissue. Testosterone and DHT are then translocated to the cytoplasm and bind to the AR before translocation to the nucleus and activation of the DNA.

ROLE OF THE ANDROGEN RECEPTOR IN CASTRATE-RESISTANT PROSTATE CANCER

Figure 1. Potential androgen receptor (AR) therapeutic targets

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The British Uro-oncology Group was formed in 2004 as a professional association with the specific aim of providing a network for doctors working in uro-oncology.
In hormone-sensitive disease, the tumour responds to a reduction in serum testosterone to castrate levels (<50ng/dl) allowing the disease to be controlled,1–3 while in castrate-resistant prostate cancer (CRPC), the tumour progresses in spite of castrate levels of testosterone. However, even in CRPC, progression is often still dependent on androgen signalling,4 and AR therefore remains a logical target in this disease state.

Immunohistochemical studies have shown that AR expression is heterogeneous in prostate cancer; however, the degree of heterogeneity does not generally correlate with response to ADT.

There are many complex pathways involved in AR signalling in CRPC, a selected number of which are shown in Table 1.

Many attempts have been made to consider targets to prevent or delay endocrine therapy resistance by proactive intervention with the known CRPC pathways. For example, it has been shown that approximately only 10 per cent of CRPC specimens harbour genetic mutations in the AR,4 and as such, the role of AR mutations in CRPC progression is not clear. However, it is thought that the presence of this mutation expands the capability of the AR to be activated by other ligands and may allow activation of the AR by some anti-androgens.1

Another potential genetic instability for tumour development is AR gene amplification. Indeed, amplification of the AR gene has been suggested as a mechanism that enables prostate cancer cells to become sensitive to the reduced level of androgens present after androgen ablation therapy. Although AR amplification occurs rarely in untreated primary prostate cancer, it has been shown that 50–85 per cent4 of CRPC samples exhibit AR overexpression, causing increased sensitivity to reduced levels of androgens.5 Further, increased AR protein expression is characteristic of aggressive prostate cancer in various disease settings, and may thus serve as a prognostic marker in some patients.

CRPC tissues tend to have raised levels of splicing variants,4–6 particularly in aggressive CRPC. The role of these variants is not fully understood, but their presence may represent a mechanism of early resistance to treatment.

Steroidogenesis is another interesting feature of CRPC. After a period of ADT, de novo androgen synthesis is initiated by the prostate tumour cells, reactivating the androgen-driven processes and promoting tumour regrowth. The role of steroidogenesis in CRPC remains controversial, but there is some evidence to suggest that it may be an important factor.

The recent advances in characterising the molecular pathways leading to CRPC, including the discovery of splicing variants and AR overexpression, suggest that the AR remains a logical target for therapy and offers opportunities for the rational development of new approaches to predict and/or control disease progression in the castrate setting (Figure 1).

THE ANDROGEN RECEPTOR: CLINICAL CHALLENGES

Since Huggins first established the link between androgen levels and progression of prostate cancer, ADT has become the key systemic treatment against prostate cancer.

Dual androgen blockade

There remains some controversy over the use of dual androgen blockade, involving surgical or pharmacological androgen suppression with a luteinising hormone-releasing hormone agonist (LHRHa) in addition to an antiandrogen agent as a first-line approach in the treatment of metastatic prostate cancer.

A collaborative meta-analysis reported in 2000 of around 8000 patients in 27 randomised trials demonstrated that dual androgen blockade improved the five-year survival rate by 2 or 3 per cent, with a range of uncertainty of approximately

<table>
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<th>Pathway</th>
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<td>Upregulation of the AR, maintenance of AR signalling under androgen deprivation therapy</td>
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<td>Outlaw pathway</td>
<td>Ligand-independent activation of the AR by growth factors (eg HER-1/HER-2)</td>
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<td>Steroidogenesis</td>
<td>Enhanced ligand-dependent activation of the AR by increase of de novo synthesis of testosterone and dihydrotestosterone</td>
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Table 1. Selected pathways involved in androgen receptor (AR) signalling in castrate-resistant prostate cancer

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0–5 per cent, compared with LHRHa therapy alone (Figure 2). In spite of the statistical significance of this difference, the size of the clinical benefit is marginal and has not generally been adopted as standard initial therapy in the UK. The use of 'step-up' dual androgen therapy is, however, commonly associated with the addition of an antiandrogen, most typically bicalutamide, at the time of first relapse with LHRHa therapy. This may change in the future with the emergence of a number of newer and apparently more efficacious hormone agents.

Abiraterone
Abiraterone inhibits androgen biosynthesis in the testes, adrenal glands and the tumour tissues. In 2012, publication of the final results of the COU-AA-301 trial marked a new milestone in the management of metastatic CRPC by demonstrating a significant median overall survival (OS) benefit of abiraterone acetate in combination with prednisolone (15.8 months) compared with placebo plus prednisolone (11.2 months) among patients who had previously received docetaxel.

Similarly, the COU-AA-302 pre-chemotherapy trial showed a significant increase in the time to radiographic progression-free survival (rPFS) for abiraterone and prednisolone (16.5 months) compared with prednisolone alone (8.3 months). There was also a strong trend towards improvement in OS, a co-primary endpoint in this trial, with median values of 35.3 versus 30.1 months in favour of abiraterone. Although the use of rPFS as a clinical trial outcome remains controversial, it is known to correlate closely with clinically relevant findings. Serological responses were also significantly improved with a reduction in PSA of 50 per cent or more demonstrated in 62 per cent of patients in the prednisolone control arm also had a PSA decline and 29 per cent had a reduction in PSA of at least 50 per cent, indicating some activity of steroids alone.

Enzalutamide
Enzalutamide is a very potent AR antagonist that directly targets three stages of the AR signalling pathway.

In 2012, the AFFIRM trial, a phase 3, double-blind, placebo-controlled trial of enzalutamide in metastatic CRPC post-chemotherapy, showed a clear median survival benefit of 4.8 months over best standard of care (18.4 versus 13.6 months; p<0.0001). The OS benefit was demonstrated across all pre-specified subgroups, and enzalutamide showed a significant increase in median rPFS (8.3 versus 2.9 months; p<0.001) and time to PSA doubling (8.3 versus 3.0 months; p<0.001). Time to first skeletal-related event was also delayed (16.7 versus 13.3 months; p<0.0001).

Although only a small number of patients were evaluable for pain response in the AFFIRM trial, significantly more enzalutamide patients experienced at least a 30 per cent reduction in pain compared with the control group (p=0.0079), while time to pain progression was also increased in the whole group (p=0.0004). All health-related quality-of-life (HRQoL) responses were higher among the enzalutamide group (43 per cent of enzalutamide patients showed an improvement in HRQoL total score compared with 18 per cent of control patients). This HRQoL response was observed even in the social and family domain, which is rarely observed in trials of this nature. Enzalutamide was found to be generally well tolerated.

Immediately prior to study unblinding, it was observed that 24 per cent of patients in the control group had subsequently received abiraterone after withdrawal of study drug, potentially impacting on survival in favour of the control arm. The results of the AFFIRM trial thus clearly demonstrate that directly targeting the AR is an effective therapeutic strategy in metastatic CRPC. To ascertain whether enzalutamide has a role in the pre-chemotherapy setting, a randomised phase 3 study of enzalutamide versus placebo in men with chemotherapy-naïve metastatic CRPC is ongoing (NCT01212991). The co-primary endpoints of this trial...
(PREVAIL) are OS and rPFS. In October 2013, following the 10th Annual Meeting of the British Uro-oncology Group, a press release advised that PREVAIL is to terminate early as the trial was positive for both its primary endpoints at interim analysis.14

An additional ongoing study, the TERRAIN trial (NCT01288911), is designed to assess the efficacy and safety of enzalutamide compared with bicalutamide when added to castration therapy on failure of initial castration therapy alone.

Orteronel
Another agent that targets androgen biosynthesis is orteronel, a novel inhibitor of the CYP17 pathway. Orteronel more specifically inhibits CYP17 20 lyase versus CYP17 hydroxylase.15 A phase 3 study of orteronel in patients with metastatic CRPC who progressed post-chemotherapy was recently stopped early after it was reported that a pre-specified interim analysis indicated that the study was unlikely to meet its primary endpoint of improved OS.16 A pre-chemotherapy trial of this agent is currently ongoing.

SUMMARY
The AR has played a pivotal role in the management of prostate cancer for over 70 years and continues to be a key area of research in the development of novel and emerging therapies. Advancing prostate cancer is not uniformly refractory to further hormonal manipulation and disease progression is frequently dependent on androgen synthesis and AR interactions. Castration-resistant prostate cancer, which is still hormone sensitive, has been clearly characterised, with new drugs such as abiraterone acetate and enzalutamide.

Declaration of interests
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