THEMATIC REVIEW

Targeting androgen receptor signaling: a historical perspective

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Abstract

The first case of prostate cancer was identified by histological examination by Adams, a surgeon at The London Hospital, in 1853. In his report, Adams noted that the condition was 'a very rare disease'. Now, over 150 years later, with increased life expectancy and screening, prostate cancer has become one of the most common cancers in men. In the United States alone, nearly 200,000 men are diagnosed with prostate cancer annually and about 33,000 succumb to their disease. Fifty years ago, men were typically diagnosed with prostate cancer in their seventies with disease that had metastasized to the bone and/or soft tissue. Diagnosis at such an advanced stage was a death sentence, with patients dying within 2 years. The pioneering work of Charles Huggins in the 1940s found that metastatic prostate cancer responds to androgen deprivation therapy (ADT), ushering in the rational use of hormone therapies that have irrevocably changed the course of prostate cancer disease management. Medical castration was the first effective systemic targeted therapy for any cancer and, to this day, androgen ablation remains the mainstay of prostate cancer therapy.

Key Words

- ▶ androgen receptor
- ▶ anti-hormone
- ▶ endocrine therapy resistance
- ▶ hormone receptor
- ▶ prostate

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Introduction

Prostate cancer was first identified by Adams in 1853. Adams noted that the condition was 'a very rare disease' (Adams 1853). Prostate cancer has become one of the most common cancers in men: nearly 200,000 men are diagnosed with prostate cancer annually in the USA alone, and about 33,000 succumb to the disease (Siegel *et al.* 2020). Medical castration was the first effective systemic targeted therapy for any cancer and, to this day, androgen ablation remains the mainstay of prostate cancer therapy (Fig. 1).

The discovery of androgen deprivation therapy

The concept of ADT to control prostate cancer can be traced back to 1789 when a Scottish surgeon, John Hunter, described seasonal variations in the size of the testicles and prostate gland in animals (Hunter 1837). He went on to demonstrate that castration in young male animals prevented further growth of the prostate, while in adults, it caused atrophy. Further evidence for Hunter's theory of a direct connection between the testes and prostate gland came from his observation that aging eunuchs

Figure 1

History/timeline of hormone therapy.

never suffered from symptoms of a hypertrophied prostate (Home 1811). On the basis of these early observations, the second half of the nineteenth century was marked by a growing interest in orchiectomy for the treatment of prostatic hyperplasia. Most notably, in 1895, the surgeon William White was the first to report symptomatic improvement in patients with an enlarged prostate treated with castration (White 1895). Numerous reports on the efficacy of castration therapy followed (Cabot 1896, White 1904); however, due to surgical morbidity prevalent at the time, the method fell into disrepute.

In the late 1930s and early 1940s, the exquisite sensitivity of prostate cancer to hormones began to be realized. Seminal work by Ethel Gutman and Alexander Gutman, which discovered serum acid-phosphatase levels are increased in patients with metastatic prostate cancer (Gutman *et al.* 1936, Gutman & Gutman 1938), laid the foundation for studying hormonal manipulations on prostatic function and measuring serum acid-phosphatase as a readout for castration. Notably, it was the pioneering experimental studies of Charles Huggins that linked androgens to malignant prostatic growth (Huggins & Hodges 1941). Huggins was born in Nova Scotia, Canada. After graduating from Harvard Medical School, he spent his internship and residency at the University of Michigan under the stewardship of the prominent surgeon Frederick A. Collier, before joining the University of Chicago in 1927.

In the original study by Huggins and his student, Clarence Hodges, eight patients with metastatic prostate cancer were treated by either castration or estrogen (stilbesterol) therapy to reduce serum testosterone levels. Remarkably, serum acid-phosphatase levels decreased in patients following oral estrogen administration, which was concordant with an appreciable improvement in patient weight, appetite, hematocrit, and, importantly, pain management (Huggins & Hodges 1941). From these findings, Huggins concluded

that prostate cancer is influenced by androgenic activity in the body and could be inhibited by eliminating androgens, either through surgical castration or neutralization of their activity by estrogen injection. The fundamental importance of these findings was acknowledged in 1966 when Charles Huggins as awarded the Nobel Prize in Physiology and Medicine, with the Nobel Committee proclaiming Huggins' work had 'already given many years of an active and useful life to patients with advanced prostate cancer over the entire civilized world – patients who would have been lost to other forms of therapy'.

Huggins' work led to larger clinical studies assessing castration in men with advanced prostate cancer. One of the most important was a series of randomized studies in the 1960s organized by the Veterans Administration Cooperative Urologic Research Group (VACURG), which assessed treating prostate cancer patients with the oral estrogen diethylstilbesterol (DES) (Byar 1972). The initial study of ~3500 patients concluded that DES treatment was as effective as orchiectomy in treating prostate cancer; however, a number of problems with systemic hormone therapy were exposed. First, lowering serum testosterone levels with estrogen yielded substantial cardiovascular and thromboembolic toxicity (Blackard 1975). Second, it became increasingly evident that androgen ablation, via surgical castration or estrogen administration, was merely palliative and not sufficient to cure patients of prostate cancer. Even Huggins, in the conclusion of his initial paper describing androgen ablation noted, 'in many cases, regression of the neoplasm is not complete' (Huggins *et al.* 1941). Knowing that, in addition to the testes, the adrenal glands produce low levels of androgens, it was postulated that adrenal androgen production may support prostate cancer recurrence. This was supported by the observation of hyper-function of the adrenal cortex, as measured by increased 17-ketosteroid secretion, in patients following orchiectomy (Satterthwaite

et al. 1941). Huggins and Scott performed the first bilateral adrenalectomy in 1945, which they showed to have a transient palliative effect in patients who failed medical or surgical castration (Huggins & Scott 1945). However, this procedure never gained acceptance due to the unpredictable results and severe side effects of hypocortisolism.

New approaches to regulating androgen production manipulating LHRH

The significant biochemical and psychosocial side effects associated with surgical orchiectomy or estrogen therapy fueled the search for new strategies to block androgen production or its interaction within prostate tissue. Two years before the publication of the first VACURG study, Andrew Schally and Roger Guillemin independently discovered the structure of the hypothalamic hormone known as luteinizing hormone (LH)-releasing hormone (LHRH; also known as gonadotrophin-releasing hormone (Schally *et al.* 1971, Guillemin & Burgus 1972)). Pulsatile release of LHRH from the hypothalamus induces the anterior pituitary to produce LH, which, in turn, travels to the Leydig cells of the testes to activate testosterone production. Schally and Guillemin investigated ways to manipulate the hypothalamic-pituitary-gonadal axis, developing the first synthetic peptide agonists of LHRH (Tolis *et al.* 1982).

Several synthetic LHRH agonists were developed for clinical use during the 1980s, including leuprolide (Lupron), goserelin (Zoladex), buserelin (Suprefact), and nafarelin (Synarel). Early studies by Schally and others showed that chronic use of LHRH agonists lowers testosterone levels by stable suppression of pituitary LH, and consequently androgen secretion from the testes (Auclair *et al.* 1977, Sandow *et al.* 1978, Vilchez-Martinez *et al.* 1979). In particular, patients with advanced prostate cancer treated daily with LHRH agonists experienced a 75% suppression in serum testosterone levels, a decrease or normalization of plasma acid-phosphatase levels, and a marked reduction in cancer-associated bone pain (Tolis *et al.* 1982). However, LHRH agonists produce a rapid, but transient increase in serum LH and hence, testosterone levels – termed a 'testosterone flare' – which was associated with pain and obstructive symptoms. Despite this, LHRH agonists have become the *de facto* method for ADT as they exhibit less cardiovascular toxicity compared to estrogen therapy (Lepor & Shore 2012). For his work, Schally received the Nobel Prize in Physiology and Medicine in 1977.

Direct inhibition of the LHRH receptor using pure antagonists has also been explored. Although

these agents were initially developed for contraceptive purposes, degarelix gained United States Food and Drug Administration (FDA) approval for the treatment of hormone-sensitive prostate cancer in 2008 (Klotz *et al.* 2008). Importantly, unlike LHRH agonist therapy, the testosterone flare is not observed with LHRH antagonists. Moreover, time to castration was reduced to 3 days compared to about a month with leuprolide (Clinton *et al.* 2017), making LHRH antagonists particularly well-suited for metastatic hormone-naïve tumors. However, these agents have not been without controversy; a recent study unexpectedly found that neoadjuvant degarelix is associated with elevated levels of intratumoral didydrotestosterone (DHT; Sayyid *et al.* 2017). Further development of LHRH antagonists has largely stalled and, presently, degarelix remains the only approved LHRH antagonist for the treatment of prostate cancer.

To combat the adverse effects and poor quality of life associated with ADT, namely sexual and endocrine dysfunction as well as changes in body composition, interest turned to cyclical administration of ADT, which enables cycling recovery of serum testosterone levels. In 1986, the first study of intermittent ADT reported improved quality of life in patients with symptomatic prostate cancer following cessation of DES therapy and, following re-emergence of symptomatic disease (mean time of 8 months), all patients demonstrated a clinical response upon re-initiation of ADT (Klotz *et al.* 1986). Following this, multiple phase II trials and meta-analyses confirmed the safety and feasibility of intermittent ADT as a treatment approach (Goldenberg *et al.* 1995, Shaw *et al.* 2007). However, while sexual outcomes and cost-savings favor intermittent therapy, recent clinical trials have shown no benefit in oncological outcomes between intermittent and continuous ADT (Perera *et al.* 2020).

The emergence of androgen receptor-targeted therapies

In the late 1960s the androgen receptor (AR) was independently discovered and characterized by three investigators: Shutsung Liao (Anderson & Liao 1968), Nicholas Bruchovsky (Bruchovsky & Wilson 1968), and Ian Mainwaring (Mainwaring 1969). The first anti-androgen, cyproterone, was discovered serendipitously through a chemical screen. An acetate group was subsequently added to generate cyproterone acetate (CPA), which exhibited increased anti-androgenic potency (Neumann 1994). The earliest studies of CPA found the administration to

decrease the size and function of the prostate in dogs and rats (Neri *et al.* 1968, Geller *et al.* 1969). Some response was also reported in human prostate adenocarcinomas (Geller *et al.* 1968). CPA directly competes with testosterone and DHT binding to the AR, while simultaneously inhibiting progesterone receptors in the pituitary to inhibit the release of LH and, in turn, decrease serum testosterone (Varenhorst *et al.* 1982). In a phase III trial, CPA was shown to be as effective as medical castration with DES (Pavone-Macaluso *et al.* 1986), leading to its approval as the first anti-androgen for the treatment of prostate cancer in the late 1980s.

The limitations of CPA, mainly its association with severe sexual dysfunction to a level mimicking surgical castration, fueled the search for non-steroidal anti-androgens (NSAAs) that do not have these side effects. This led to the discovery of flutamide in the 1970s (Liao *et al.* 1974), which became the first NSAA to be approved by the FDA in 1989 for use in treating prostate cancer. Additional NSAAs have subsequently been developed and approved for clinical use, including bicalutamide in 1995 (Newling 1990) and nilutamide in 1996 (Janknegt 1993). Although direct comparisons between the abovementioned anti-androgen therapies is not available, bicalutamide has advantages in terms of its safety profile. In particular, hepatotoxicity, a serious side effect of flutamide and nilutamide, is relatively uncommon with bicalutamide (Wirth *et al.* 2007). Today, bicalutamide remains the most widely used anti-androgen for advanced prostate cancer.

As these new agents were being developed throughout the 1980–1990s, it became clear that monotherapies targeting the AR signaling axis would be ineffective in curing patients with prostate cancer. The next logical step, accordingly, was to combine therapies to both reduce the amount of testosterone released from the testes (e.g. LHRH agonists) as well as block androgen action in prostate cells using NSAAs. This idea was initially proposed by Fernand Labrie, a Canadian endocrinologist, in 1982 (Labrie *et al.* 1982, Lefebvre *et al.* 1982). One of the earliest clinical studies of combined androgen blockade, published by David Crawford and colleagues in 1989, reported that combining leuprolide and flutamide produced a slightly longer median length of survival compared to leuprolide treatment alone (Crawford *et al.* 1989). The results of this clinical trial yield a significant shift in treatment philosophy. A total of 27 phase III clinical trials using various combinations of androgen deprivation were subsequently performed; however, shockingly, only three showed a statistically significant benefit for combined androgen blockade compared to a single agent alone (Laufer *et al.* 2000). These trials have been subjected to

independent meta-analyses (Caubet *et al.* 1997, Bennett *et al.* 1999); it was concluded that combined androgen blockade does not yield a significant survival benefit.

Doubling down on AR targeted therapy, the new generation inhibitors

Despite clinically significant responses to early systemic anti-androgen therapies, such as bicalutamide, tumors ultimately relapse to a castration-resistant state termed castration-resistant prostate cancer (CRPC). Our understanding of this phenomenon can be traced back to a pair of studies published in 1991 that reported nearly all primary prostate tumors, including those that recurred after androgen ablation therapy, continue to express the AR (Sadi *et al.* 1991, van der Kwast *et al.* 1991). A subsequent investigation found that 30% of CRPC tumors harbored genomic amplification of the AR locus, which was not detected in matched samples obtained prior to ADT (Visakorpi *et al.* 1995). A variety of AR molecular alterations, such as mutations and polymorphisms, have since been described (Watson *et al.* 2015). Notably, point mutations are associated with AR promiscuity and paradoxical responses to anti-androgen therapies; for example, bicalutamide activates the AR with a mutation in codon 741 (Hara *et al.* 2003). These findings provided the rational for drug discovery screens to identify novel anti-androgens offering a more durable response.

The azole antifungal, ketoconazole, provided the first clinical evidence that more complete androgen suppression can lead to desirable clinical outcomes in the castration-resistant setting. Ketoconazole exerts its anti-tumor activity through blockade of CYP17, the key family of enzymes responsible for adrenal and intratumoral androgen synthesis (Santen *et al.* 1983). Unfortunately, lack of potency and specificity for CYP17 yielded significant toxicities (De Coster *et al.* 1986). This led researchers at Cancer Research UK to design and evaluate more effective inhibitors of the CYP17 enzyme, which ultimately resulted in the development of abiraterone (Barrie *et al.* 1994, Potter *et al.* 1995, Rowlands *et al.* 1995). In 1996, abiraterone was out-licensed to Boehringer Ingelheim; however, developmental progress was hampered by concerns about possible side effects of blocking CYP17 as well as a lack of interest in hormonal therapies for late-stage 'hormone refractory' prostate cancer. The later realization that advanced prostate cancer remains dependent on testosterone paved the way for the licensing of abiraterone to Cougar Biotechnology (later acquired by Johnson &

Johnson) in 2004. The first phase I study, spearheaded by Dr Johan de Bono and Dr Gert Attard, enrolled 21 men with chemotherapy-naïve CRPC and found that abiraterone-treated patients experienced significant tumor shrinkage and dramatic falls in prostate-specific antigen (PSA) levels (Attard *et al.* 2008). Less than a year later, these findings were confirmed in a larger phase I/II study (Danila *et al.* 2010). In 2010, the pivotal phase III COU-AA-301 trial (NCT00638690) showed increased survival in patients given abiraterone (de Bono *et al.* 2011), paving the way for FDA approval in 2011.

In parallel with the development of abiraterone in the UK, researchers in the United States – led by Dr Charles Sawyers and Dr Michael Jung – utilized a rational drug screening and iteration strategy to identify compounds with activity in prostate cancer models overexpressing the AR (Tran *et al.* 2009). This led to the clinical development of enzalutamide (formally MDV3100). In contrast to abiraterone, enzalutamide functions to blunt AR signaling by directly binding to the ligand-binding domain of the AR, effectively inhibiting the binding of androgens as well as AR nuclear translocation and association with DNA (Tran *et al.* 2009). Given the relative efficacy and safety profile of enzalutamide in a phase I/II trial (NCT00510718 (Scher *et al.* 2010)), two multi-national phase III trials were initiated to evaluate enzalutamide in men with CRPC. The phase III AFFIRM trial (NCT00974311), which assessed enzalutamide in men with metastatic CRPC previously treated with docetaxel-based chemotherapy, demonstrated an overwhelmingly positive survival benefit (Scher *et al.* 2012). A similar survival benefit was found in the second phase III trial, PREVAIL (NCT01212991), which was conducted in men with asymptomatic metastatic CRPC without prior chemotherapy (Beer *et al.* 2014). Most recently, in the phase III ARCHES trial (NCT02677896), enzalutamide was found to significantly reduce the risk of metastatic progression or death in the castration-sensitive (CSPC) setting (Armstrong *et al.* 2019). On the basis of these trials, enzalutamide was approved by the FDA in 2012 for late-stage CRPC, which was later expanded to the setting of non-metastatic CRPC (nmCRPC) in 2018 and metastatic CSPC in 2019.

Apalutamide and darolutamide, AR antagonists designed to supersede enzalutamide, were first approved by the FDA in 2018 and 2019, respectively, for the treatment of nmCRPC. In contrast with enzalutamide, darolutamide remains active against mutated AR. It also has an improved safety profile as it does not cross the blood-brain barrier (Moilanen *et al.* 2015). However, independent clinical trials assessing enzalutamide (PROSPER (Hussain *et al.* 2018)), apalutamide (SPARTAN (Smith *et al.* 2018)), and darolutamide (ARAMIS (Fizazi

et al. 2019)) in the nmCRPC setting all reported to prolong metastasis-free survival by ~2 years. As all three drugs have a similar benefit, clinical decision-making is largely based on cost and patient co-morbidities.

Looking toward the next decade of AR targeted therapies

Despite the successes of AR pathway inhibition for the treatment of prostate cancer, the efficacy is short-lived in many patients due to emergent resistance mechanisms. Cross-resistance between currently available AR pathway inhibitors has limited treatment options following tumor recurrence. For example, adding abiraterone at the time of enzalutamide resistance was not effective (PLATO trial (Attard *et al.* 2018)) and, similarly, combining the agents upfront was also not beneficial (Alliance A031201 trial (Morris *et al.* 2019)).

To offset the possibility of persistent 'AR-driven' prostate cancer, new therapeutic paradigms are currently under investigation. Of particular promise is the development of selective AR degraders. Notably, in pre-clinical studies, these agents have shown efficacy against enzalutamide-resistant AR as well as AR splice variants (Ponnusamy *et al.* 2019, Kregel *et al.* 2020). Another innovative therapeutic strategy being explored involves alternating and/or rapid cycling of ADT and androgen therapy (termed bipolar androgen therapy, BAT) to induce supraphysiological levels of testosterone to potentially prolong or restore responses to enzalutamide. In a phase II trial, 15 of 21 patients with enzalutamide-resistant CRPC responded to a subsequent re-challenge with enzalutamide following BAT (Teply *et al.* 2018). Finally, neoadjuvant ADT has shown promise in patients with high-risk localized prostate cancer (Pignot *et al.* 2018) and, accordingly, multi-modal approaches combining local and systemic therapy could offer further therapeutic possibilities. This idea was tested in ongoing STAMPEDE clinical trials with the addition of radiotherapy to primary tumor to hormone therapy plus docetaxel in patients with newly diagnosed low burden metastatic disease. The study revealed that 32% reduction in risk of death and 41% reduction in failure-free survival while high burden disease did not reach statistical significance (Parker *et al.* 2018). This is only one example of the power of the STAMPEDE trials that has been ongoing and adding patients and different arms since 2005. This has yielded practice-changing finding and contributing to three new standard of care first-line treatment options for patient with metastatic hormone-sensitive prostate cancer

(mHSPC), including the combination of chemotherapy with hormone therapy (Sweeney *et al.* 2015).

When reflecting on the future of targeting the AR signaling pathway, it is important to appreciate the heterogeneity that exists within prostate tumors. The emergence of 'AR-indifferent' prostate cancer variants such as neuroendocrine prostate cancer (NEPC), particularly following potent AR targeted therapy (Davies *et al.* 2018), suggests that targeting the AR alone will be insufficient to cure prostate cancer. Clinical trials combining AR pathway inhibitors with AR agnostic therapeutic strategies, such as immunotherapy (e.g. PD1/PDL1 blockade) or epigenetic therapies (e.g. EZH2 inhibition) as well as targeting the DNA repair using PARP inhibitor are ongoing. These types of combination approaches might be the next generation of prostate cancer therapies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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