Prostate Cancer: Molecular Mechanisms and Therapeutics.

Author: Raveen S. Rathnasinghe[1,2,*]

[1]BSc (HONS), AMSB, and [2]School of Science & Engineering, Teesside University, Middlesbrough, Tees Valley, UK, TS1 3BA.
[*]Correspondence: R.Rathnasinghe@Tees.ac.uk (+44794 6445663)

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ABSTRACT **Prostate cancer (PC) is a malignancy which develops within the male prostate resulting from dietary habits, environmental aspects and hereditary factors. At early stages, the disease is asymptomatic and often can remain undiagnosed. Symptoms are regularly seen in advanced-metastatic stages of the cancer, which gives ample opportunities to administrate effective treatment. Nevertheless, extensive researches focusing on the molecular biology of the disease has provided insights on diagnosing and understanding the disease to facilitate effective therapeutic-interventions. Molecular-markers including prostate specific antigen and oncogenes such as *Bcl-2* and *c-Myc* have been used to diagnose PC to contemplate treatments. Underpinning molecular mechanisms such as aberrations in the androgen receptor, disrupted microtubule dynamics and effector molecules such as CYP17 has been targeted to design drugs in order to sustain the pathogenesis and metastasis of PC. Novel therapeutics such as Proscar® and Provenge® have been approved by the FDA on the basis of the results observed in clinical trials, *in vivo* and *in vitro* studies. Despite the increasing knowledge of underpinning molecular mechanisms of PC has supported early diagnosis and effective therapeutics, a significant percentage of patients' die of drug-resistant metastatic disease. Evolution by natural selection where tumours acquire mutations as a response to changes caused by therapeutics is an elucidation for such drug resistance. Knowledge gaps in respect to tumour metastasis to the skeletal system and transformation to hormone-independent state of the disease hinders drug design and treatment. Additional research in regards to the molecular mechanisms of prognosis to develop effective therapeutics and tactical use of such therapeutics may provide opportunities to sustain PC.**

INTRODUCTION

Prostate cancer (PC) is identified as the most common malignancy and leading source of cancerous deaths among Caucasian males and considered as a global health and economic burden (Swinnen *et al*., 2004). Persistent studies have suggested multiple risk factors such as age, race, diet and environmental aspects for PC. Provided that PC is a slow growing tumour, symptoms are often seen in advanced stages of the disease, giving less opportunities for effective treatment (Li, Okino, & Dahiya, 2004). Diagnosis of PC associates with fluctuations in the molecular marker prostate specific antigen (PSA), as a consequence of molecular changes implicated by the malignancy. However, there is no cut-off level for PSA in order to confirm PC, despite high levels of serum-PSA being regarded as suspicious (Chiam, Ricciardelli, & Bianco-Miotto, in press). Additionally, several genetic and epigenetic biomarkers such as a-methylacyl-CoA racemase (AMACR) have been studied for both diagnosis and drug-design. Such oncogenes/oncogenic products are summarised in Table 1.

Statistical studies indicated an increase of 54,720 diagnosed PC cases between years 2002 and 2012, arguably by the advancements of diagnostic techniques and extensive use of PSA levels to diagnose PC (Hessels, Rittenhouse, & Schalken, 2005; Jemal, Thomas, Murray, & Thun, 2002; Siegel, Naishadham, & Jemal, 2012). Intriguingly, a decrease of 2050 deaths has been observed between 2002 and 2012 arguably due to the use of effective therapeutics based on research of underpinning molecular mechanisms (Siegel *et al*., 2012).

Primarily, PC begins as a non-invasive stationary tumour, followed by metastasis to lymph-nodes close to the prostate. Consequently, PC proceeds to a highly-metastatic phase where tumours spread throughout the body signifying an advanced stage of PC (Sternberg, 2002). Further to the discovery of PC in 1940s, it was established that PC is dependent on male sex-hormones and androgens, providing opportunities to produce drugs targeting androgens and the androgen receptor (AR) which mediates it (Chiam *et al*., in press). Inconveniently, PCs inevitably renovate to an androgen-independent (AIPC) state, making hormonal-therapy ineffective.

Molecular basis of this phenomenon is yet to be fully understood (Schröder, 2008). In this review, developments and evolution in underpinning molecular mechanisms for drug design has been critically analysed, suggesting areas requiring further research.

Gene/ Gene Product	Description and function	Abnormality	Drug design	References
Androgen receptor gene (*AR*)	Codes for a TF that binds with androgens at defined DNA motifs to promote healthy cell proliferation.	Alterations in short CAG-repeats leading uncontrolled proliferation of PC cells. ǂ	Inhibition of transcriptional activity by Casodex † and use of MDV3100 to irreversibly bind to AR. †	Chng & Cheung, ; Fu, Madan, Yee, & Zhang, 2012; Linja & Visakorpi, 2004
Glutathione S-transferase π gene (*GSTP*)	Detoxifies glutathione (carcinogen) to protect DNA in order to avert carcinogenesis.	Hyper-methylation of promoter region resulting in a non-functional protein.	HDAC inhibitor molecules to promote de-methylation. ǂ	Hauptstock *et al*., 2011; Porkka & Visakorpi, 2004
***p53* (TSG)**	Codes for a TF that protects cellular DNA from chemical insults and tumour suppression.	Missense mutations/ Loss of heterozygocity resulting in non-functional p53 with high half-life.	Use of adenovirus vectors with wild type *p53* for treatment. †	Downing, Jackson, & Russell, 2001; Heidenberg, Bauer, McLeod, Moul, & Srivastava, 1996; Navone *et al*., 1999
K-Ras	Mediates inducible signalling pathways for cell proliferation and apoptosis.	Mutations in codons 12 and 13, resulting in constitutive tumour proliferation.	FTS drug for *Ras* inhibition and use of antisense therapy to down regulate *Ras*. ǂ †	Erlich *et al*., 2006; Kloog & Cox, 2000; Shen, Lu, Yin, Zhu, & Zhu, 2010
c-Src	Codes for kinases that transduce signals involved in adhesion, migration and cytoskeletal alteration.	Hereditary mutations ǂ and overexpression leading to bone metastasis of PC. ǂ	Dasanitib & ATP analogue drug which inhibits tyrosine kinase activity, inhibiting *Src* activity. †	Fizazi, 2007; Ishizawar & Parsons, 2004; Recchia *et al*., 2003
Insulin-like growth-factor (IGF) I & II	IGF-I is a mitogen which increases DNA synthesis; IGF-2 promotes cell proliferation. ǂ	Differential expression caused by epidemiological factors leading to tumour mobility.	MCAb to bind with IGF receptors to effectively halt its function.	Fu *et al*., 2012; Gennigens, Menetrier-Caux, & Droz, 2006
***NKX3.1*homeo box gene (TSG)**	Codes for TF which regulates prostate epithelial cell proliferation and tumour suppression. ǂ	Haploinsufficiency and loss of heterozygocity. ǂ	siRNA mediated gene silencing. †	Bhatia-Gaur *et al*., 1999; DeMarzo, Nelson, Isaacs, & Epstein, 2003; Pengju *et al*., 2010

Table 1. TF – Transcription factor; TSG- Tumour suppressor gene; FTS - trans-farnesylthiosalicylic acid; siRNA- small interfering RNA; HDAC- Histone deacetylases; MCAb – Monoclonal antibody; ‡- underlying molecular mechanism/other mechanisms fully not understood, requires further investigation; †- Drug activity fully not understood/ early trials.

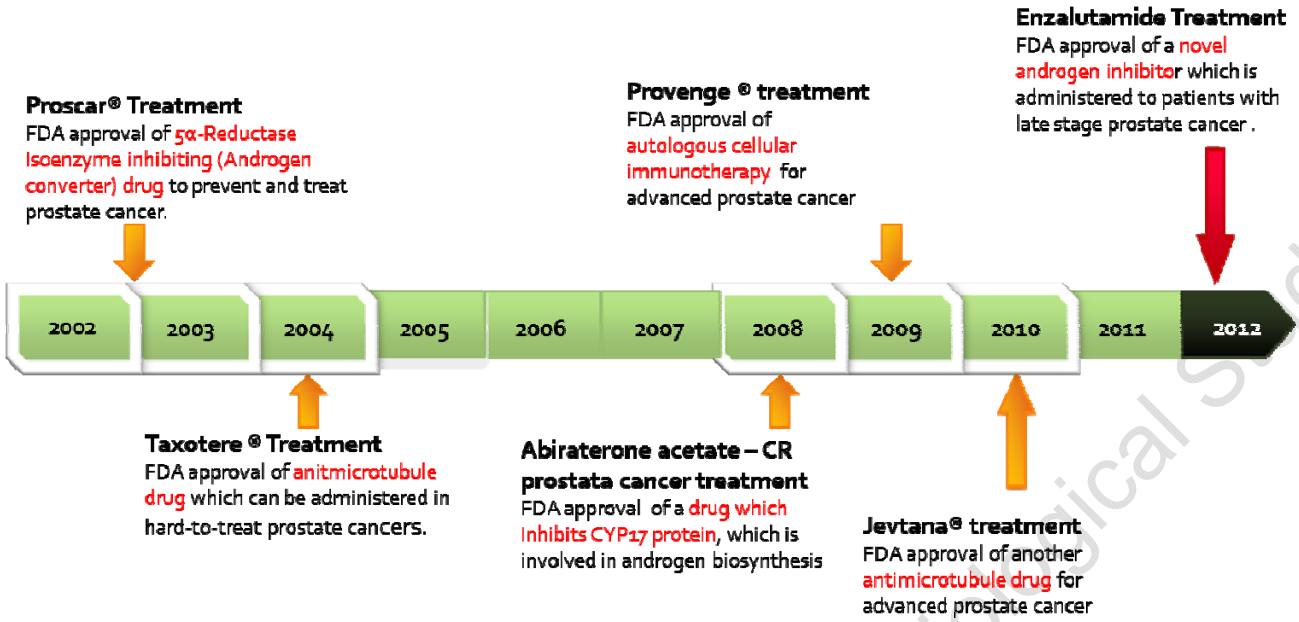

Figure 2. A decade (2002 – 2012) of drug-designs on underpinning molecular mechanisms which have been approved by the food and drug administration.

DECADE OF MOLECULAR-THERAPEUTIC ADVANCEMENTS

Researches involving these molecular mechanisms have provided interesting insights which served as focal points for therapeutic design. Such drugs are then subject to various trials at various timescales to obtain the approval of the Food and Drug Administration (FDA) which enables the commercialisation. Some of the major therapeutic advancements which are currently in clinical practice are discussed.

PROSCAR® (FINASTERIDE)

Androgen-AR interactions facilitate the equilibrium of prostate cell proliferation and apoptosis in healthy prostates. Upon entrance to the prostate from testis and adrenal glands, the primary androgen testosterone is converted to dihydrogentestosterone (DHT) by the enzyme 5α-reductase (5AR) which has a higher affinity to bind to AR (Schröder, 2008). However, DHT-AR interactions lead to an uncontrolled state of cell proliferation of the prostate in PCs with bypassed apoptotic pathways (Taplin, 2007). Thus, the inhibition of 5AR was a target to treat and prevent PC. Evidently by large clinical trials involving placebos in combination with other *in vivo* and *in vitro* studies, it was determined that the 5AR inhibitor finasteride (Proscar) was a potent drug which can destroy cancer cells by inducing apoptotic pathways such as the expression of caspase 7 & 8 pathways inducing TNF-α associated pathways (Tindall & Rittmaster, 2008). Evidence for the drug effectiveness was depicted by clinical and histological changes of patients subject to proscar treatment. Decisively, finasteride drugs are ineffective against metastatic androgen-independent cancers which are a result of various AR mutations (Thompson *et al.*, 2003).

TAXOTERE® (DTX)

Microtubules are pivotal components in facilitating mitosis, wherein duplicated chromosomes are divided into two daughter cells. Thus, anti-microtubule drug design has been extensively investigated for the treatment of hormone-refractory PC (HRPC) (Mediavilla-Varela *et al.*, 2009). Anti-carcinogenic properties of DTX are underpinned by its ability to exert cell-death by caspase-2/caspase-3 dependent apoptosis and mitotic catastrophe. Functionality of this drug relies on the dosage and the ability of DTX to bind with β-subunits of microtubules which stabilises microtubule dynamics to promote depolymerisation of microtubules by conformational shape changes of tubulin (Jordan & Wilson, 2004; Williams, Muenchen, Kamradt, Korenchuk, & Pienta, 2000). Hence, the cell cycle of DTX-induced tumours will reside in a blocked mitotic state.

As a consequence of prolonged DTX administration, PCs become resistant to DTX which is underpinned by poorly understood mechanisms and evolutionary concepts. More recent *in vitro* and *in vivo* research suggested that

DTX is able to induce non-apoptotic/caspase-independent cell death of tumours (Williams *et al*., 2000). However, the precise molecular mechanisms remain to be elucidated.

ABIRATERONE ACETATE

HRPC functions independently from androgens, which makes conventional hormone therapies ineffective. However, in advanced PCs, a sudden rise of serum-PSA levels indicates reactivation of AR signalling activity. Traditional therpeutics for anti-androgen production solely targets the cessation of androgen production in testis (Attard *et al*., 2009). Nonetheless, recent researches suggest evidence for intra-tumoral androgen production in addition to androgen production in adrenal glands which are not affected by traditional therapy (De Bono *et al*., 2011). Furthermore, overexpression of ARs by genetic mechanisms has enabled ARs to function under trivial amounts of androgens. Thus, androgen synthesis other than by the testis has been investigated for drug design.

Consequently, researchers have identified the protein CYP17 as a key component on oestrogen and androgen biosynthesis within testis and adrenal glands. Therefore, CYP17 is able to increase the activity of the AR which results in favourable environment for PC. The therapeutic Abiraterone acetate is a molecule which can irreversibly bind to CYP17, to halt androgen production. Treatments as such are referred to as total ablation therapy (Vasaitis, Bruno, & Njar, 2011). As a result of all the clinical trials and experimental studies carried out, it can be said that this drug is able to improve the quality of life (QOL) of patients suffering from PC (Attard *et al*., 2009; De Bono *et al*., 2011; Vasaitis *et al*., 2011).

PROVENGE®

Autologous cellular-immunotherapy (Provenge) is the inaugural vaccine-based treatment for HRPC, which has evidently shed light on improving the QOL of patients who do not respond to conventional chemotherapy. The underlying concept of this particular treatment is the induction of tumour-specific immunity within the patient which is reliant on a compatible target antigen and subsequent presentation of it to the immune system (Beinart, Rini, Weinberg, & Small, 2005). Dendritic cells (DC) are a type of antigen-presenting cells (APC) which play a crucial role in presenting antigens to T-cells as class I and II molecules to prime an immune response. Provenge vaccine has exploited this mechanism to treat tumours by ingesting DCs with tumour specific antigens such as prostatic acid-phosphatase (PAP), antigen-cytokine fusion protein PA2024 and granulocyte-macrophage colony stimulating factor (GM-CSF) *ex vivo*. Consequently, cytokine-mediated resilient cellular immune responses are directed at tumours which express PAP, resulting in disrupted tumour growth (Small *et al*., 2000).

Clinical studies have justified the suitability, specificity and efficiency of this vaccine by positive results observed in trail patients (Kantoff *et al*., 2010). Further optimisation of the Provenge vaccine dosage schedule, combinatorial therapy with other drugs and suitability for patients with non-advanced PC are areas which are currently being investigated to enhance this particular therapeutic.

JEVTANA® (CABATZITAXEL)

Jevtana was developed as an intravenous injectable product to treat metastatic-HRPC. Its functionality is identical to DTX; however several improvements have been made to make this drug more effective than DTX (Nightingale Dr. & Ryu Dr., 2012). Jevtana binds with *N*-terminal amino-acids of β-tubulin subunits and inhibits actin depolymerisation to effectively terminate cell tumour proliferation and cell cycle by halting microtubule extension during mitosis. It was suggested that tumour resistance for such drugs are based on its strong-affinity to bind P-glycoprotein (P-gp) which is often found in tumour cells (Liu *et al*., 2012; Liu, Sakya, O'Donnell, Flick, & Ding, 2012). The newly improved Jevtana exhibits a weaker binding affinity to P-gp, allowing it to function within a tumour cell in an effective manner without interference. Another improvement of Jevtana is that the therapeutic has supplanted hydroxyl groups with methyl groups resulting in loss of anti-tumour drug resistance by deactivating ATP-dependent efflux pumps (Nightingale Dr. & Ryu Dr., 2012).

Additionally, several trials have administered Jevtana to treat DTX resistant tumours of patients suffering HRPC. Side effects such as diarrhoea and neutropenia have been observed in Jevtana treated patients (Liu *et al*., 2012).

ENZALUTAMINDE

Indicatively, AR is often a target for therapeutics due to the greater involvement in HRPC. Mutations and overexpression of AR is believed to shorten the tumour latency period resulting in resistance to typical anti-androgen therapeutics (Vogelzang, 2012). Enzalutamide is a non-steroidal androgen inhibitor which is much more effective in comparison to other conventional AR-inhibitors. This

completely inhibits AR signalling by binding to *AR* without stimulating the AR, which inhibits AR-androgen interactions in tumour cells which facilitate DNA binding and nuclear translocation phases, resulting in shrinkage of the tumour (Scher *et al*., 2012). These observations were present among drug resistant ARs and overexpressed ARs. Further research is required to determine the precise dosage to counter act any side effects and opportunities for resistance.

As discussed above, research involving the molecular biology of the disease has provided avenues to design therapeutics to sustain the disease and many of the proposed therapeutics have proven to be effective treatment. Nevertheless, knowledge other than the molecular mechanisms should be considered to understand and treat PC. In particular, several other factors such as evolution dynamic and tumour adaptability should be closely studied to facilitate the effective treatments which are less prone to resistance of relapse.

EVOLUTION DYNAMICS OF PC

Comparative cancer-cell phylogenetic studies have concluded that Darwin's evolution theory by natural selection can be used as frame for understanding PC and developing drugs. It is evident that the fundamental process of neoplasm ascendance, malignancy and drug resistance is underpinned by evolution and somatic-cellular selection (Pepper, Findlay, Kassen, Spencer, & Maley, 2009).

ADAPTION TO TUMOUR-MICROENVIRONMENTS

Neoplastic progression is a process of somatic evolution where cells acquire mutations by the influence of environmental conditions. This is exemplified by the inflammatory conditions in early prostate-lesions where macrophages produce reactive oxygen and nitrogen species which induce DNA damage in prostate cells leading to carcinogenesis (Basanta *et al*., 2012). These cells adapt and evolve according to microenvironment to divide uncontrollably to form large tumours which are able function within hypoxic conditions (Josson, Matsuoka, Chung, Zhau, & Wang, 2010). Thus, tumours up regulate transcription-factors inducing angiogenesis and tumourgenesis. Intriguingly, there is ample evidence to suggest that in advanced stages of PC, tumours evolve to carry out autocrine-like functions mimicking the functionality of the testes making ablation therapy ineffective (Small & De Bono, 2011).

RESISTANCE FOR THERAPEUTICS

In clinical context, patients who are introduced to drugs are prone to relapse despite initial response. For example, extensive use of conventional anti-androgen therapies enables PC to select for mutations which makes the AR hypersensitive resulting in resistance for therapeutics aimed at it (Pepper *et al*., 2009). Typically, drug resistance occur as a result of changes in the tumour-microenvironment consequently by the chemotherapeutic action. Changes within the tumour membrane play a pivotal role in drug resistance by averting the drug from reaching its target. Mutations through evolution allows manipulation of various signalling pathways such as nuclear factor-kappa B (NFκB/IL-6) pathway, MAPK/ERK and somatostatin receptor pathways to initiate drug-resistance in advanced PCs (Semenas, Allegrucci, Boorjian, Mongan, & Persson, 2012).

DISCUSSION

PC cancer is a highly permeating disease which causes fatality in men predominantly in western countries. Despite diet and environmental factors being risk factors for PC, hereditary genes such as *HPC1* and *PCAP* have been identified to increase the risk of PC (Gonzalgo & Isaacs, 2003). Research focusing on molecular markers to diagnose PC in early stages has shed light on contemplating effective treatment plans to improve the QOL of PC patients. The past decade of research involving the molecular biology of PC has enabled design drug resulting in production of effective therapeutics which target molecular pathways of PC to minimise malicious effects.

Despite the increasing knowledge and awareness of PC which has enabled early detection and administration of effective drugs, a significant proportion of PC patients die of drug-resistant metastatic disease (Wang, Beebe, Pwiti, Bielawska, & Smyth, 1999). Extensive use of conventional therapeutics is a main culprit for drug resistant tumours (Semenas *et al*., 2012). Evolution of tumours according to Darwin's theory has permitted to selectively acquire mutations to expedite resistance to therapeutics (Josson *et al*., 2010). Subsequently, tumour metastasis to the skeletal system and lymphatic system and the transformation to hormone-independency denote advanced stages of PC (Schröder, 2008). Evolution within tumours to carry out abnormal physiological tasks which act in favour for tumours is another plausible explanation for such observations. Further research on effective biomarkers and underpinning molecular mechanisms to develop effective

therapeutics and tactical use of such developments is the key to controlling PC.

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