

Novel Approach: Androgen Receptor Down-Regulating Agents for the Treatment of All Stages of Prostate Cancer Disease

Puranik Purushottamachar*

Department of Pharmacology & Experimental Therapeutics, and Center for Biomolecular Therapeutics, University of Maryland School of Medicine, 685 West Baltimore Street, Baltimore, MD 21201-1559, USA

Editorial

Prostate Cancer (PC) is the most commonly diagnosed neoplasm among the males in industrialized countries. For the patients with localized PC, initial treatment includes surgery or radiation. Since the involvement of androgens and Androgen Receptor (AR) in development and progression of PC [1], Androgen Deprivation Therapy (ADT) remains the critical therapeutic option for advanced/metastatic forms of PC.

ADT can be achieved either by surgical (removal of testicles) or chemical castrations using GnRH agonists (eg. Leuprolide Figure 1). Unfortunately, most men eventually fail ADT and disease transforms from androgen dependent to an androgen-independent and this etiology is commonly known as Castration-Resistant Prostate Cancer (CRPC) [2]. At present no therapy has been shown to be effective.

The circulating androgens can also be reduced by interfering with their biosynthesis which is catalyzed by 17, 20-lyase enzyme (CYP17) [3]. Recently Abiraterone has been launched to treat advanced PC, where VN/124-1 is in advanced Phase-II and TAK700 is in Phase-III clinical trials (Figure 1) [4]. Long term treatment of PC with these new agents may shed light on possible development of drug resistance as in the case of other CYP inhibitors in fungal infection treatment.

Another approach for the treatment of advanced PC is anti-androgens. The therapeutic agents used clinically such as steroidal anti-androgens (cyproterone acetate Figure 1) are known for side effects, such as erectile dysfunction, gynecomastia etc [1]. Whereas nonsteroidal anti-androgens (Bicalutamide etc Figure 1) show fewer side effects but long-term drug usage leads to mutation of the AR which resulting in CRPC [3]. Recent second-generation AR antagonist retain antagonism in over-expressing cell lines, and among these MDV3100 (Figure 1) has now progressed to late-stage clinical trials [5].

Anti-androgen failure and CRPC is driven by continued AR signaling, which has been linked to elevated AR expression, AR mutation and ligand-independent AR activation and persistent intraprostatic androgens [6]. With this evidence it is reasonable to suggest that effective strategy that leads to AR down-regulation may be useful for treating PC. Hence AR down-regulation is an attractive target for the treatment of all stages of PC.

Recently, we have discovered first synthetic small molecules as Androgen Receptor Down-regulating Agents (ARDAs) through the development of a pharmacophore modeling [2]. Two CYP17 inhibitors (i.e., VN/124-1 and abiraterone) are also ARDAs [7, 8]. Recognizing the potential of ARDAs, leading pharmaceutical industry like AstraZeneca (Figure 1) has also turned their attention towards development of ARDAs [4]. However the definite mechanism of AR down-regulation action of these agents is unknown. Early discovery of specific ARDA

and their mode of action would enable medicinal chemists to rationally design novel ARDAs which may be useful for treating all stages of PC patients.

In summary progression of advanced PC to CRPC pose a big challenge to biologists, pharmacologist, medicinal chemist and clinicians. Indeed, prostate cancer is the second leading cause of cancer-related death among men in the United States. More knowledge leads to better outcomes, as President Obama noted in his 2009 address to the American Medical Association. More researchers (multi-disciplinary) with knowledge of PC biology, pharmacology and chemistry needed to beat the current challenges of CRPC. As mentioned in the summary of letter (SCIENTIFIC PROGRESS IS ESSENTIAL -July 1945) from US former President Franklin D. Roosevelt to Vannevar Bush, former Director of the Office of Scientific Research and Development, 'The responsibility for basic research in medicine and the underlying sciences, so essential to progress in the war against disease, falls primarily upon the medical schools and universities' [9]. There are number of universities (let alone individuals) in the US and abroad in resource-poor settings, who cannot afford subscription for traditional articles. Publishing the research findings in Open-Access (OA) journals provide scholarly articles with no subscription fees or restrictions on access and is the key to the advancement of scientific creativity and innovation. One such OA journal is Biochemistry and Pharmacology: Open Access of OMICS publishing group is providing the same services available through traditional scholarly journals, such as a peer-review process, filtering, production and distribution. Providing OA to the researchers may result into early discovery of novel therapeutic agents for all life threatening diseases including dreaded PC disease.

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*Corresponding author: Purushottamachar Puranik, Department of Pharmacology & Experimental Therapeutics, and Center for Biomolecular Therapeutics, University of Maryland School of Medicine, 685 West Baltimore Street, Baltimore, MD 21201-1559, USA, Tel: 240-314-6450; E-mail: PPuranik@som.umaryland.edu

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