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Drug discovery: Hit to lead, lead to possible clinical candidates-development of androgen receptor down-regulating agents for the treatment of castration resistant prostate cancer

Purushottamachar Puranik
University of Maryland School of Medicine, USA

Abstract

Prostate cancer (PC) remains a significant medical burden in the United States. The American Cancer Society's estimates for PC in the US for 2013 are: about 238,590 new cases, 29,720 deaths. Suppression of gonadal androgens by medical or surgical castration remains the mainstay of treatment for patients with advanced PC. However, the response to treatment is not durable, and transition to a castration-resistant prostate cancer (CRPC) state is inevitable and incurable. The CRPC cells overexpress functional AR, mutated AR, and most importantly AR isoforms called AR splice variants devoid of the ligand-binding domain. Therefore, current drugs have no effect on AR splice variants implicated in the progression of PC into CRPC. We envision that effective treatment of CRPC patients will require new drugs that can modulate all forms of AR such and AR down-regulating (ARD) agents (ARDAs).

For the development of ARDAs, we applied combined analog-based, random screening and medicinal chemistry approaches. Initially, we generated a pharmacophore model for virtual screening and also screened in house compound library. We found VN/124-1 (Phase II clinical candidate) a potent CYP17 inhibitor as hit with mild ARD and anti-androgen activities. Synthetic modification of VN/124-1 resulted into a lead with specific ARD activity (full length and splice variant AR) with no observed secondary activity. Further lead optimization resulted in steroidal and nonsteroidal agents as potential clinical candidates. All approaches and stages involved in the development novel ADRAs will be presented.

Biography

Dr. Purushottamachar Puranik is currently a Research Associate in Dr. Vincent Njar's laboratory at University of Maryland Baltimore. He received his Ph. D. degree (2003) from University Institute of Chemical Technology, Mumbai University, India. Thereafter, he worked for Chemical Process Research Laboratory of US Vitamins Ltd., Mumbai before he join Dr. Vincent Njar laboratory in 2005. Dr. Puranik applies computational and synthetic chemistry techniques in discovery and development of prostate and breast cancer agents. He has published more than 25 research articles in reputed journal, and he is editorial board member of Biochemistry and Pharmacology: open access of OMICs publishing group and other.