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Current Status of Nanotherapeutic Strategies for Prostate Cancer Management

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Prostate cancer (PCa) is one of the dreadful diseases among the common cancer-related deaths in men throughout the World. PCa prevalence diverges widely across different geographical locations and its incidence is generally higher in USA and Europe compared to Asia. Over the past few decades, the management of prostate cancer has become a great challenge worldwide. Several management options are available when prostate cancer is diagnosed at an early stage. However, for advanced cancer, none of the conventional treatments have been successful and most chemotherapeutic agents also produce undesirable side effects. Drug delivery approach coupled with nanotechnology has emerged as a front-runner in the field of cancer therapeutics. Recently, variety of drug carrier systems in nano dimensions has been developed to enhance the delivery and retention of pharmaceuticals on cancer cells and tumors and thereby augment the effectiveness of conventional chemopreventive and chemotherapeutic agents. This special issue will explore some of the exciting and emerging concepts of novel nanotherapeutic strategies either as monotherapy or combination therapy for prostate cancer management.

The concept of targeted drug delivery systems is not new but has been predicted by the German scientist and physician, Paul Ehrlich, nearly a century ago. The potential of drug delivery systems that could selectively home into the desired site had been referred to as the 'magic bullet' in earlier times and as 'guided missiles' and 'stealth delivery systems' in the contemporary era. For the past two decades, after substantial efforts, a vast array of nanocarriers has been developed as anticancer therapies for different cancers. In the case of PCa, BIND 014, a polymeric nanoparticle, composed of poly (D,L-lactide) and poly (ethylene glycol) (PEG) block copolymers encapsulating an anti-cancer agent docetaxel has been developed to target prostate-specific membrane antigen (PSMA) expressing prostate cancer cells. It was found that BIND014 could effectively inhibit the proliferation, tumor growth, and cell survival both *in vitro* and *in vivo* models [1]. Phase I studies with BIND 014 in patients with advanced solid tumors were recently presented, which included anti-tumor response in 9 out of 28 patients and a maximum tolerated dose of 60 mg/m2 [2]. Recently Phase II clinical studies were also undergoing to appraise the safety and efficacy of BIND 014 in metastatic castration-resistant prostate cancer patients [3].

Yet another recent report had highlighted the results of the cancer molecular targeting studies using anisamide-targeted stealth liposomes silencing the epidermal growth factor receptor (EGFR). This strategy was very effective against hormone-resistant stage of PCa [4]. It was inferred that EGFR-si-RNA encapsulated in the targeted nanoparticles silenced the EGFR in the tumor which in turn halts EGFR signaling and also induces apoptosis in a xenograft tumor model [4]. Gene delivery has also emerged as an attractive strategy for treating a various diseases including cancer. Recently, different anti-sense oligonucleotides designated as OGX 011, GTI 2040 and OGX427, had been developed to target hormone-resistant PCa. Particularly, OGX 011 was found to suppress the clusterin mRNA levels in human PCa, which was correlated with the Gleason score. Even preclinical studies have added evidence to this study by inducing apoptosis in response to androgen withdrawal, chemotherapy and radiation [5]. Phase I studies have indicated the use of OGX-011and its beneficial effect on PCa [6].

Next in the line is chemotherapy, the foremost therapeutic modality in which variety of cytotoxic drugs both natural and synthetic are used. The advent of nanomedicine and nano-dimensional drug delivery systems (NDDS) could enhance the efficacy of chemotherapy for prostate cancer management. Various nanoformulations encapsulating curcumin (CUR), a phytochemical with immense potential as an anticancer agent but severely limited by its poor bioavailability have been reported. These include liposomes, micelles, polymeric nanoparticles, nanogels, globular proteins and magnetic nanoparticles that have been found to improve the *in vitro* and *in vivo* biological activities of curcumin in comparison with its free form [7]. Yallapu *et al.* [7] have demonstrated that cellulose-CUR nanoparticle formulation exhibited very high anti-cancer activity and hence could be an effective nanoparticle delivery system against PCa [7]. 198AuNP-EGCG effectively reduced the tumor growth by 80% in PC-3 xenograft SCID mice [8]. Studies on combination of curcumin and resveratrol liposomal formulations revealed that they significantly inhibited cell growth and induced apoptosis *in vitro* while effectively decreasing prostatic adenocarcinoma in mice models [9].This innovative nanotechnological approach was subsequently exploited by several others and is becoming an advancing and convincing field in chemoprevention research. However, further animal studies and clinical trials are essential to conclusively validate the beneficial effects of chemopreventive agents against PCa. Combinational strategies of chemopreventive agents for PCa treatment should be carefully scrutinized because of its potential synergistic or/additive mechanisms of action. The lack of a careful understanding of the interaction that occurs between nanoparticles and many cellular processes constitutes one of the major problems, which should be taken into account during the clinical use. Let us hope that cancer nanotherapeutics will mark the beginning of a new dawn in prostate cancer management in the near future.

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