Novel Targeted Therapies for Prostate Cancer

Prostate cancer is a cancer that starts in the prostate gland. It is the third most common cause of death from cancer in men of all ages and is the most common cause of death from cancer in men over the age of 75. Prostate cancer is rarely found in men younger than 40. More than 1.1 million cases of prostate cancer were recorded in 2012 worldwide, accounting for approximately 8 percent of all new cancer cases and 15 percent in men. In 2018, the American Cancer Society predicts that there will be around 164,690 new diagnoses of prostate cancer, and that around 29,430 fatalities will occur because of it in the United States.

Treatment is different for early and advanced prostate cancers. In early stage prostate cancer, If the cancer is small and localized, it is usually managed by one of the following treatments: Watchful waiting or monitoring, based on PSA blood levels; Radical prostatectomy where the prostate is surgically removed; Brachytherapy using radioactive seeds that are implanted into the prostate to deliver targeted radiation treatment; Conformal radiation therapy; and Intensity modulated radiation therapy. Patients may receive radiation therapy combined with hormone therapy for 4 to 6 months.

In advanced prostate cancer chemotherapy may be recommended, as it can kill cancer cells around the body. Androgen deprivation therapy (ADT), or androgen suppression therapy, is a hormone treatment that reduces the effect of androgen. The patient will likely need long-term hormone therapy. Radical prostatectomy is not currently an option for advanced cases, as it does not treat the cancer that has spread to other parts of the body.

Systemic delivery of chemotherapy is often ineffective in the treatment of prostate-confined cancer. *In-vivo* results from regional delivery of chemotherapy in prostate cancer show potential higher efficiency in tumor arrest but still have major issues to be solved. One general cause of anticancer drug resistance is the limited ability of drugs to penetrate tumor tissue and to reach all of the tumor cells in a potentially lethal concentration Extravasation and interstitial transport (via diffusion and convection) are diminished in the intratumoral space by high interstitial pressure, hypovascularity, high tumor cell density and/or a large stroma fraction; these problems are more serious in larger, bulky tumors. Chemotherapy drugs are more effective against proliferating vs. quiescent cells; thus, slowly proliferating cells at greater distances from tumor blood vessels are likely to be resistant to therapy. Chemotherapeutic drugs also are typically inefficient against tumor stem cells.

Recently, targeted therapies aimed to target key aberrations arising from cancer associated mutated genes (usually called oncogenes), rather than employing a cancer-wide cytotoxic therapy, were proposed. Targets now (2017) in clinical trials include EGFR, HER2, targets belonging to the PI3K/Akt/mTOR signaling pathway, ALK, BCR-Abl and BRCA1/2 (Stuchbery et al., 2015).

RNA interference (RNAi)

Non-coding RNAi molecules regulate genes post-transcriptionally and can lead to gene silencing. Endogenous dsRNA initiates RNAi by activating the ribonuclease protein Dicer, which binds and cleaves double-stranded RNAs (dsRNAs) to produce double-stranded fragments of 20–25 base pairs with a 2-nucleotide overhang at the 3' end, known as siRNAs. These interfering RNAs (siRNAs) are integrated into an active RNA-induced silencing complex (RISC), while being separated into single “sense” and “antisense” strands. Within the RISC, the antisense strand then base-pairs to its target mRNA and induces cleavage of the mRNA, thereby preventing it from being used as a translation template. Synthetic siRNAs can vary widely in their design, including the specific targeted sequence along the mRNA, accessibility to Dicer and RISC, the length of each strand, optional symmetrical, asymmetrical, blunt, and loop structures, and chemical modifications of many types.

The delivery of RNAi to target tissue is a major challenge. Systemic injection of siRNA into the vascular system needs to overcome renal filtration and phagocytosis and degradation in the bloodstream, and needs to achieve targeting to the diseased site, transport across the vascular endothelial barrier, diffusion through the extracellular matrix, uptake into the cell, escape from the endosome, and unpackaging and release of the siRNA to the cell RNAi machinery. Systemic delivery today is limited to a small number of target tissues, in particular to the liver.

RNAi enables effective targeting of some specific oncogenes that constitute potential therapeutic targets in prostate cancer, including HSP90, BMI-1 and Neto2.

Hsp90 (Heat shock protein 90) is a molecular chaperone that regulates the maturation, activation, and stability of critical signaling proteins that drive the development and progression of prostate cancer, including androgen receptor signaling. Prostate adenocarcinoma, as a primarily endocrine disease, is frequently dependent (at least initially) on androgens to maintain growth and viability of the tumor (Foley & Mitsiades, 2016). Androgen receptor, Akt and Her-2 (epidermal growth factor receptor) are all important pathways in prostate cancer and significantly, all are Hsp90 client proteins. Therefore, treatments that target Hsp90 would simultaneously disrupt multiple pathways in prostate cancer (Ischia et al., 2013). First-generation Hsp90 inhibitors in prostate cancer resulted only with poor clinical responses. Recent advances in compound design and development, use of novel preclinical models and further biological insights into Hsp90 structure and function have now stimulated a resurgence in enthusiasm for these drugs as a therapeutic option, as single agents or in combination, for prostate cancer (Centenera et al., 2017). Today (2017) about 10 Hsp90 inhibitors representing multiple drug classes, with different modes of action, are undergoing clinical evaluation.

BMI1 (B-cell-specific Moloney murine leukemia virus integration site 1) is a known stem cell marker that belongs to the Polycomb group transcriptional repressor family. BMI1 and another Polycomb group family member, enhancer of zeste homolog 2 (EZH2), have been

implicated in regulating the prostate cancer stem cell phenotype (Kerr & Hussain., 2014). The expression of BMI1 has been found to be upregulated in various human cancers, including, liver, head and neck, nasopharyngeal, prostate, colorectal, breast, endometrial, cervical, and ovarian cancers, and usually is associated with chemo-resistance. Lukacs et al., 2010 concluded that Bmi-1 is a crucial regulator of self-renewal in adult prostate cells and plays important roles in prostate cancer initiation and progression. The expression of BMI1 levels are higher in malignant than in normal prostatic tissues, and there is significant increase in the expression as the disease progresses from low-grade to high-grade, with higher Gleason scores. Further, it was found to be a potential candidate as a dual biomarker (serum and biopsy) for the diagnosis and prognosis of prostate cancer in Caucasian and African-American men, that would probably perform better than PSA (Siddique & Saleem, 2013). PTC596 of PTC Therapeutics is an orally active small molecule drug candidate in Phase 1. It targets tumor stem cell populations by reducing the function, activity and amount of BMI1.

NETO2 (Neuropilin and tolloid-like protein 2) is a predicted transmembrane protein containing two extracellular CUB domains followed by a low-density lipoprotein class A (LDLa) domain. It also has an intracellular FXNPXY-like motif, which has been shown in other proteins to be essential for the internalization of clathrin coated pits during endocytosis. This gene encodes a predicted transmembrane protein containing two extracellular CUB domains followed by a low-density lipoprotein class A (LDLa) domain. It also has an intracellular FXNPXY-like motif, which has been shown in other proteins to be essential for the internalization of clathrin coated pits during endocytosis. Alternatively spliced transcript variants have been observed, but they have not been fully characterized. NETO2 is a KCC2 interacting protein, found to be required for neuronal Cl^- regulation in hippocampal neurons (Ivakine et al., 2013). NETO2 was observed to be frequently upregulated at both the mRNA and protein levels in colorectal cancer and to correlate with tumor progression and poor prognosis. Upregulation of NETO2 mRNA was also observed in renal, lung, and cervical carcinomas (Hu et al., 2015).

In Silenseed, application of the LODER (LOcal Drug EluteR) platform for prolonged delivery of RNAi drugs, targeting HSP90, BMI1 and NETO2 in in-vitro and in-vivo experiments, yielded strong halting of cell proliferation and tumor suppression results. These results have demonstrated the potential in applying such a technology to potent drug candidates for prostate cancer.

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