

REVIEW

Making personalized prostate cancer medicine a reality: Challenges and opportunities in the re-establishment of gold standards

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Abstract: Prostate cancer is a serious multidimensional disorder that arises because of misrepresentation of signaling cascades and acquired resistance against apoptosis. It is progressively becoming more insurmountable because of rheostat like switching of oncogenic signaling in androgen dependent and androgen depleted microenvironment. Additionally, oncogenic fusion proteins have been explored in prostate cancer tissues thus adding another layer of complexity to the targeting of protein network in cancer cell and generate hurdles in the standardization of therapy. In this review we briefly describe identified oncogenic fusion transcripts in prostate cancer and suggest utilization of this biomarker for prostate cancer diagnosis alongwith standard PSA and immunohistochemistry analysis in Pakistan. We also provide overview of animal model studies to interpret the efficacy of vitamins.

Keywords: Tmprss2-erg, Prostate cancer, apoptosis.

INTRODUCTION

Multidimensional mechanisms of recurrent gene fusions have emerged as an additional layer of complexity and a major stumbling block in standardization of therapy. It is noteworthy that prostate cancer microenvironment consists of mixed cells and intriguingly fusion transcript positive cells have a differential response and aberrant activities. The gene and proteome network of fusion positive prostate cancer cells represent altogether a disrupted stoichiometric ratio of transcriptional corepressors and coactivators. Surprisingly, emerging lines of evidence indicate that there are varieties of subset of proteins which are directly involved in androgen-regulated transcription and wired into an AR centric transcriptional network via a spectrum of distal enhancers and/or proximal promoters. Based on the rapidly increasing challenges in multipronged approaches and finding the drugs with minimal off target effects, efforts are relentlessly ongoing to introduce alternatives to standard treatments for prostate cancer that offer comparable or better oncological efficacy. In this review we bring to limelight the current patterns and examples of

translating this information into therapy-guiding knowledge, and list the challenges that will need to be overcome before the existing knowledge can be fully exploited to get a step closer to personalized medicine.

Oncogenic Fusion transcripts have emerged as a hallmark feature involving the ETS genes in prostate carcinogenesis. These characteristic and well established gene fusions, which involve the juxtapositioning of the 5'-UTR of androgen-regulated genes with the ETS family genes, are documented in most prostate cancers. The ETS genes involved include ERG, ETV1, ETV4 and ETV5 (Tomlins *et al.*, 2005; Tomlins *et al.*, 2006; Tomlins *et al.*, 2007). In line with this notion, Transmembrane protease, serine 2 (TMPRSS2)-ERG Oncogenic fusion transcripts are the most frequent, with a prevalence of 36-78% in PSA screened surgical cohorts consisting of prostate cancer patients. Keeping in view the overlapping aspects between oestrogen and androgen signalling, it was described that androgen could induce chromosomal movements and bring together the gene fusion partners, thus promoting the genesis/induction of genomic rearrangements. It is undeniable that, treatment of LNCaP cells with the androgen receptor ligand dihydrotestosterone (DHT) initiates intrachromosomal

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proximity between TMPRSS2 and ERG and also interchromosomal proximity between TMPRSS2 and ETV. There are some other major determinants which are contributory to genesis of genomic rearrangements like nuclear myosin i- and actin-dependent mechanism mediates the chromosomal interactions induced by oestrogen and androgen signalling (Helgeson *et al.*, 2008; Mani *et al.*, 2009; Lin *et al.*, 2009).

Tumor markers and related assays for detection in prostate cancer

It is well appreciated information that serum PSA test still is the most important biomarker for the detection and follow-up of prostate cancer. However, several studies of both serum and urine-based prostate cancer biomarker candidates have been documented. Being non-invasive, urine-based tests might be appropriate for clinical screening purpose as well as for prediction and to gain prognostic information. Therefore it is beyond doubt that RNA-based urine biomarkers are by far the most developed. The PCA3 test, the TMPRSS2-ERG fusion gene, transcript expression levels of GOLPH2, SPINK1 and their multiplex PCR based assays have been subject of many studies showing encouraging results (Roobol *et al.* 2011).

It is a prominent feature of metastatic prostate cancers that they have a high prevalence of TMPRSS2-ERG gene fusion along with a frequent copy number increase of ERG gene. Therefore, characterization of the TMPRSS2-ERG gene fusion may be utilized to determine the prostatic origin of metastasis Xiao *et al.* (2011).

Probability to develop prostate cancer (PCA) varies among the prostate zones, with the peripheral zone (PZ) more susceptible to tumorigenesis than the transitional zone (TZ). Besides, ETS members markedly expressed in PCA are already overexpressed in the normal PZ, signifying that these mediators play a part in the development and progression of PCA Shaikhibrahim *et al.* (2012).

Furthermore additional studies also demonstrated that urine TMPRSS2:ERG, in combination with urine PCA3, enhanced the utility of serum PSA for predicting prostate cancer risk and clinically relevant cancer on biopsy Tomlins *et al.* (2011).

AR expression is noticeably higher in ERG-positive cancers. The selective expression in AR levels between ERG-positive and -negative cancers indicates a systematic difference in potential response to hormonal therapy Minner *et al.* (2011).

Mounting evidence pinpointed the fact that ERG assessment by immunohistochemistry may be useful for characterizing ERG status in prostate cancer as compared

to FISH in a large cohort of prostatectomy patients Falzarano *et al.* (2011).

CDKN2A, GATA3, CREBBP, ITGA2, NBL1 and TGM4 were noticeably down-regulated in the prostate carcinoma glands compared to the related normal glands, whereas TFF3, TMPRSS2 and ERG were considerably up-regulated Shaikhibrahim *et al.* (2011).

Accumulating findings verified the fact that TMPRSS2-ERG fusion was not prognostic for recurrence after retropubic radical prostatectomy for clinically localized prostate cancer, however men with ERG gene copy number gain without fusion were twice more susceptible to recurrence Toubaji *et al.* (2011).

It has substantially been established that approximately half of all prostatectomies harbour ERG rearrangements. However, the frequency and prevalence in incidentally diagnosed prostate cancer cohorts was lesser, even if multifocality was considered. Accordingly, zonal origin and cohort design are important for analysis of the clinical implications of ERG rearrangements Braun *et al.* (2011).

ERG immunohistochemical expression has a high accuracy for identifying and characterizing TMPRSS2-ERG fusion status. ERG immunohistochemistry may put forward an accurate, simpler, and less expensive substitute for evaluation of ERG fusion status in PCa than FISH Chaux *et al.* (2011).

On a similar note, P63/ERG double immunostain combines the high sensitivity of P63 and the high specificity of ERG and may be potentially helpful and valuable in the characterization of difficult prostate biopsies (Yaskiv *et al.*, 2011, Kirby *et al.*, 2012).

Therapeutic interventions for prostate cancer

Current findings advocate that a systemic delivery of 212Pb-trastuzumab could be a useful modality for management of advanced human prostate cancer Tan *et al.*, 2012. Clinicals trials verified that Denosumab a fully human anti-RANKL monoclonal antibody was better than zoledronic acid and denosumab (120 mg every 4 weeks) notably increased bone metastasis-free survival (von Moos *et al.*, 2012, Fizazi *et al.*, 2011, Smith *et al.*, 2012).

Attempts for visualization of smaller lesions have recently been made and pretargeting prostate cancer with BombsCx or BombsFCx enabled fast delivery of high particular radioactivity (111)In- or (99m)Tc-labeled polymer-drug conjugates resulted in visualization of lesions smaller than 1-2 mm in diameter within 3 h Patil *et al.*, 2012. In addition, radionuclide molecular imaging of HER2 expression in disseminated PC is useful in the categorization of patients who are probable responders to HER2 targeting therapy. Therefore, radiolabeled ABY-

025 Affibody molecule displayed considerable contrast in imaging of HER2-expressing PC xenografts than radiolabeled trastuzumab (Malmberg *et al.*, 2011).

Lately, N-terminal epitope-targeted mouse and a C-terminal epitope-targeted rabbit monoclonal anti-ERG antibody (ERG-MAbs) are undergoing trials for the detection of the ERG protein. Of significance, both ERG antibodies were able to detect the ERG expression in lymph node and distant PCa metastases (Braun *et al.*, 2012). Recently, a humanized monoclonal antibody targeting CTLA-4, CP-675,206 (tremelimumab), in combination with androgen deprivation using an antiandrogen is in phase I trial (McNeel *et al.*, 2011).

Abiraterone acetate (AA) is an androgen biosynthesis inhibitor that is documented to prolong life in patients with castration-resistant prostate cancer (CRPC) previously treated with chemotherapeutic interventions. AA treatment results in repression of prostate-specific antigen (PSA) in some patients and no declines in others, indicating the presence of molecular determinants of sensitivity in tumors. Molecular profiles of circulating tumor cells (CTCs) with a methodically valid assay confirmed the occurrence of the prostate cancer-specific TMPRSS2-ERG fusion but did not predict for responsiveness to AA treatment (Danila *et al.*, 2011).

Cytarabine at doses of 0.25-1g/m² at 21-day intervals is ineffective for men with castration resistant prostate cancer (Dhani *et al.*, 2012). Abiraterone acetate is documented to sustain suppression of testosterone in both blood and bone marrow aspirate to less than picograms-per-milliliter levels (Efstathiou *et al.*, 2011).

TRAIL as an anticancer agent

TRAIL has emerged as a paradigm in cancer therapy because of minimal toxicity and off target effects. It attaches to its respective receptors, death receptors which initiate intracellular signaling and resultant signalosome consequently triggers cell death either by an extrinsic or intrinsic pathway. The death receptors are displayed on cell surface. However there is an opposing set of receptors termed as decoy receptors which inhibit TRAIL mediated signaling because of absence of cytoplasmic domains. In prostate carcinogenesis, either death receptors are internalized and degraded or decoy receptors outnumber death receptors and regulate inhibition of TRAIL mediated signaling. In addition because of mutations or down-regulation of pro-apoptotic proteins or over-expression of anti-apoptotic proteins, lesser cell surface appearance of death receptors and drastic increase in decoy receptors on cell surface severely disturb threshold stoichiometry for apoptosis. In the following section we will discuss a range of approaches to overcome the refractoriness against TRAIL of prostate cancer cells emphasizing increased appearance of death receptors on cell surface and inhibition of anti-apoptotic proteins.

Emerging findings indicated that tunicamycin, an endoplasmic reticulum stress inducer potentiated TRAIL-induced apoptosis in human prostate cancer cells. Tunicamycin and TRAIL mediated synergistic induction of apoptosis in prostate cancer cells. Proof of concept elucidated that tunicamycin promoted TRAIL-induced apoptosis by the upregulation of death receptor (DR)4 and DR5 and the downregulation of cellular inhibitor of apoptosis 2 (cIAP2) Jung *et al.*, 2012. Saquinavir (Sa-NO) exceptionally sensitized LNCaP cells to TRAIL (Mojic *et al.*, 2012). Likewise, orlistat triggered the expression of DR 5, which is one of the TRAIL receptors, at both the mRNA and protein levels (Fujiwara *et al.*, 2012).

In an attempt to increase contact time of lymphocytes with tumor cells and thereby of TRAIL with its death receptors, lymphocytes were inter-connected to the CD3 arm of bispecific antibody EpCAMxCD3, to direct the lymphocytes to tumor cells positive for the cancer stem cell marker EpCAM/ESA. Combination of TRAIL-lymphocytes with EpCAMxCD3 counteracted tumorigenesis by augmenting antiapoptotic and antiproliferative signaling (Groth *et al.*, 2012). Consistent with same understanding potassium channel K(V)10.1 is another attractive target because this surface protein is not detected in normal tissue but is expressed in approximately 70% of tumors. Recently, a research group designed a single-chain antibody against an extracellular region of K(V)10.1 (scFv62) and fused it to the human soluble TRAIL. The K(V)10.1-specific scFv62 antibody - TRAIL fusion protein triggered apoptosis exclusively in K(V)10.1-positive cancer cells, but neither in non-tumor cells, nor in K(V)10.1 deficient tumor cells (Hartung *et al.*, 2011). Further steps were made for effective tumor combination therapy. In line with this perspective, PEG-TRAIL (dual agent) were microencapsulated into poly (lactic-co-glycolic acid) (PLGA) microspheres using a double-emulsion solvent extraction method. Strikingly, dual agent microspheres offer a promising means of delivering chemotherapeutic drugs and PEG-TRAIL to tumor sites (Jiang *et al.*, 2011).

It is meaningful that identification of a number of FDA-approved drugs as TRAIL sensitizers can increase chemotherapeutic options for combination treatments in prostate cancer. Particularly, mitoxantrone and mithramycin verified significant synergy with TRAIL and led to repression of cancer cell viability at concentrations lower than 1 μ M (Taylor *et al.*, 2011).

RU486 (Mifepristone) has been acknowledged as antiprogesterone and antiglucocorticoid agent. Convincingly, RU486 initiated TRAIL-mediated apoptosis through suppression of Bcl-2 and c-FLIP(L) (Min *et al.*, 2012).

Vitamins and Prostate cancer

Additional animal model studies indicated that athymic male nude mice bearing PC-3 human PCa xenografts received diets containing soy or calcitriol injections, or a combination of dietary soy and calcitriol and results indicated that combination treatments resulted in significantly better tumor inhibitory activity than either agent alone. Laboratory methodologies indicated that combinatorial approach enhanced calcitriol activity in regulating target gene expression, including greater up-regulation of anti-proliferative (p21, IGFBP-3) and pro-apoptotic (Bax) genes, increased inhibition of anti-apoptotic (Bcl-2) and cell cycle promoting (cyclin D1) genes, and suppression of prostaglandin (PG) synthesis and signaling (COX-2, 15-PGDH, PG receptors) (Wang *et al.*, 2012).

A latest study underscored the effect of dietary vitamin D and calcium on the growth of human androgen-insensitive prostate tumor in an athymic mouse model. It was demonstrated that the normal calcium - vitamin D-deficient group had highest tumor growth thus suggested an important role of dietary vitamin D as a preventive agent in androgen-insensitive PC (Ray *et al.*, 2012).

Effects of α - and γ -tocopherol on the cell cycle, uncontrolled cellular proliferation and differentiation, were investigated in prostate PC-3 tumor cell line. While drawing a parallel, more significant growth inhibitory activity for γ -tocopherol was recorded as compared to α -tocopherol. Flow cytometry study of α - and γ -tocopherol-treated prostate carcinoma PC3 cells displayed limited progression into the S-phase. This effect, predominantly noticeable for γ -tocopherol, was connected with an up-regulation and increased activity of transglutaminase 2 (TG2), a reduced DNA synthesis and a remarkable decline in levels of cyclin D1 and cyclin E. Activation of TG2 reveals the fact that γ -tocopherol has an evident differentiative capacity on PC3 cells, resulting in an increased expression of TG2, and reduced cyclin D1 and cyclin E levels, thus influencing cell cycle progression (Torricelli *et al.*, 2012).

Effectiveness of a mixed-tocotrienol diet against prostate tumorigenesis in the transgenic adenocarcinoma mouse prostate (TRAMP) mouse model was explored recently. Findings emphasized the fact that mixed tocotrienols significantly reduced the levels of high-grade neoplastic lesions as compared to the positive controls. This gradual decline in levels of high-grade neoplastic lesions was found to be connected with upregulated expression of proapoptotic proteins BAD and cleaved caspase-3 and cell cycle regulatory proteins cyclin dependent kinase inhibitors p21 and p27. Contrary to this, the expression of cyclins A and E were found down regulated in mixed-tocotrienol treated groups (Barve *et al.*, 2010). Another documentation recently assessed Alpha-tocopheryloxy

acetic acid (α -TEA) safety and pharmacokinetics after repeat dosing in a preclinical murine model. There was no mortality, and no clinical signs of toxicity in any of the α -TEA doses tested were observed (Hahn *et al.*, 2012).

In accordance with the understanding that dietary folate is essential in all tissues to maintain several metabolite pools and cellular proliferation. Findings of a study indicated that, mild dietary folate depletion arrested prostate carcinogenesis in 25 of 26 transgenic adenoma of the mouse prostate (TRAMP) mice, in which tumor progression is prostate-specific and characteristically aggressive (Bistulfi *et al.*, 2011).

It was also observed that incidence of prostate cancer was significantly decreased in the Lycopene fed transgenic adenocarcinoma of the mouse prostate (TRAMP) mice group relative to the control group. Additionally, oxidative DNA damage was significantly suppressed in the livers of mice fed lycopene diets relative to the control group (Konijeti *et al.*, 2010).

Translational oncology and personalized medicine

To detect gene fusion status in prostate cancer, fluorescence in situ hybridization (FISH) is the method of choice. However, with passage of time more research groups were interested in developing useful and valuable detection methods. In agreement with this approach, an unavoidable need to develop most sensitive and valuable detection method, impelled researchers to opt the best available tool. FISH has some disadvantages and therefore chromogenic in situ hybridization, which uses organic chromogens, and enzymatic metallography silver in situ hybridization have currently been appraised as capable bright-field alternatives. Detailed investigations of the protocol indicate that compared with chromogenic in situ hybridization, silver in situ hybridization signals are very distinct and better-quality with regard to signal clarity and resolution, but the method excludes multicolor protocols. Based on the ERG break-apart FISH assay, a research group established a dual-color ERG break-apart assay using combined chromogenic in situ hybridization and silver in situ hybridization (CS-ISH) and developed a comparative analysis of the findings with those obtained by FISH. The findings underlined the fact that the ERG rearrangement status can unswervingly be assessed by CS-ISH. In addition, the CS-ISH technique combines the correctness and accuracy of FISH with the easiness of bright-field microscopy (Braun *et al.*, 2012).

It is evident that various assays cannot distinguish between apoptotic and viable DTCs/CTCs. However a recently designed assay, a novel ELISPOT assay (designated 'EPISPOT') detected proteins secreted/released/shed from single epithelial cancer cells. Using this assay in prostate cancer it was revealed that significant fraction of CTCs secreted fibroblast growth

factor-2 (FGF2), a known stem cell growth factor Alix (Panabières 2012).

It is now obvious that each metastatic site may contain a specific subpopulation of the original metastatic tumor capable of growing at that site. In line with this aspect, fluorescent orthotopic prostate cancer model (PC-3-GFP) model was used for immunomagnetic capture of CTC. These PC-3-GFP cells were isolated from diverse metastatic sites, grown *in vitro* and consequently examined under fluorescence microscopy. More specifically, differential morphology was compared of primary tumor cells, CTC and disseminated (DTC) from multiple metastatic sites, from nude mice with orthotopic PC-3-GFP. The cultured captured CTC and DTC from various organs displayed differential morphologies. The results highlighted the fact that extensive tumor heterogeneity that could account for the widely different behavior of cancer cells in a single tumor (Bobek *et al.*, 2012).

Likewise, quantifying exfoliated PCTCs may provide as an indicator for the clinical management of prostate carcinogenesis, isolating and removing of PCTCs could counteract prostate cancer metastasis, and culturing and characterizing captured PCTCs could aid the development of personalized treatment options. Chemoaffinity capture of pre-targeted prostate cancer cells with magnetic beads can provide an efficient tool for the detection of metastatic prostate cancer (Wu *et al.*, 2012).

It has recently been explored that prostate tumor invasion is triggered by autoimmunoreactions induced focal basal cell layer disruptions (FBCLD) that differentially facilitate monoclonal proliferation of the overlying progenitors or of a biologically more aggressive cell clone. Evidence indicated that circulating chromogranin-A (CgA) levels correlated with tumor progression and the status of hormone refractoriness. Distribution of CgA-positive cells was observed in epithelial structures with FBCLD that revealed more than 5- and 7-fold lower expression of miR-146a and miR-146b-5p than their CgA-negative counterparts. It was interpreted that focal basal cell layer disruptions and the reduction or loss of miR-146a and miR-146b-5p correlated with prostate tumor invasion and hormone refractoriness (Man *et al.*, 2011).

The undeniable role of recently designed assays to detect, isolate and analyze CTCs allows a direct comparison of specific protein expression levels found in patient CTCs to cell lines. A non-enrichment CTC detection assay enables to evaluate cytometric features and relative expression levels of cytokeratin (CK) and AR by indirect immunofluorescence from prostate cancer patients against the prostate cancer cell line LNCaP (Lazar *et al.*, 2012).

miRNA's are currently being evaluated for suitability as potential biomarker of therapeutic response in prostate cancer (CaP) patients. Among these, miR-141 had the highest correlation with temporal changes of PSA as results of current studies have determined that circulating microRNA (miRNA) miR-141 is detected in plasma of patients with CaP (Gonzales *et al.*, 2011).

The effects of chemotherapy on circulating cell-free DNA (cfDNA) composition in relation to investigational whole-body measurement of tumor activity were evaluated by fluorine-18 fluorocholine (FCH) positron emission tomography/computed tomography (PET/CT) in hormone-refractory prostate cancer (Kwee *et al.*, 2012).

Moreover recently, analysis of circulating tumor cells from castration resistant metastatic prostate cancer indicated multiple copy number aberrations. The isolation protocol of CTCs, involved immunomagnetic enrichment followed by fluorescence activated cell sorting (IE/FACS) (Magbanua *et al.*, 2012).

It has recently been suggested that multiple marker consideration is helpful as most of the false-negative results of the PCA3 test are corrected by TMPRSS2:ERG (57%) and the combination of both have a superior sensitivity for PCa diagnosis (Robert *et al.*, 2012).

Docetaxel-based chemotherapy (DBC) has proved to be less effective in the clinical management of castration-resistant prostate cancer (CRPC) patients. Therefore for further investigation a phase II study of personalized peptide vaccine (PPV) for DBC-resistant CRPC patients was conducted. It was observed that elevated IL-6 levels before vaccination was an unfavorable factor for overall survival of DBC-resistant CRPC patients. It was suggested that control of elevated IL-6 by combined therapy might be helpful for a better clinical outcome (Noguchi *et al.*, 2012). It was also reported that personalized peptide vaccine (PPV) therapy in combination with leutenizing hormone-releasing hormone (LH-RH) analog and estramustine phosphate in certain cases was safe and induced both immune responses and clinical responses for metastatic castration-resistant prostate cancer (CRPC) patients (Noguchi *et al.*, 2007). Moreover, personalized peptide vaccination monotherapy also appeared to be safe and capable of inducing peptide-specific immune responses and clinical responses in CRPC patients (Uemura *et al.*, 2010). Personalized peptide vaccination (PPV) has been evaluated for efficacy in combination with chemotherapeutic agents like estramustine phosphate (EMP) in prostate cancer patients. It was recorded that PPV plus low-dose EMP was well tolerated exclusive of major adverse effects and with increased levels of IgG and cytotoxic-T cell responses to the vaccinated peptides (Noguchi *et al.*, 2010). A phase I study of personalized peptide vaccination using 14 kinds

of vaccine in combination with low-dose estramustine in HLA-A24-positive prostate cancer patients that provided notable results (Noguchi *et al.*, 2011).

It is important to mention that Human Proteome Organization, HUPO has recently launched the Human Proteome Project (HPP) that will map the organization of proteins on specific chromosomes, on a chromosome-by-chromosome basis utilizing the SRM technology platform. In line with this approach, a research group presented data on prostate cancer studies that provided a variety of PSA isoforms characterized by high-resolution separation interfaced to mass spectrometry (Rezeli *et al.*, 2011).

Diagnostic platforms providing biomarkers that are highly predictive for diagnosing, monitoring, and stratifying cancer patients are key approaches and methods in the development of personalized medicine. It has recently been explored that tumor cells transfer (mutant) RNA into blood platelets *in vitro* and *in vivo*. Blood platelets isolated from glioma contained the cancer-associated RNA biomarker EGFRvIII. Blood platelets isolated from prostate cancer patients contained the cancer-associated RNA biomarker PCA3. Since platelets are easily accessible and isolated, they may provide an attractive window of opportunity for the companion diagnostics of cancer (Nilsson *et al.*, 2011).

Likewise, Molecular imaging with promise of personalized medicine can offer patient-specific knowledge noninvasively, thus enabling treatment to be tailored to the particular biological hallmark features of both the disease and the patient. Molecular imaging technique utilizing DO3A-CH(2)CO-G-4-aminobenzoyl-Q-W-A-V-G-H-L-M-NH(2) (AMBA) in PC-3 prostate tumor-bearing SCID mice indicated that (111)In-AMBA is a safe, prospective molecular image-guided diagnostic agent for human GRPR-positive tumors (Ho *et al.*, 2011).

It is important to specify that tools such as the Comprehensive Geriatric Assessment (CGA) can aid estimate remaining life expectancy and can help predict treatment-related morbidity and mortality in older men. Application of CGA in older men with PCa is imperative to design individualize and optimize treatment strategies (Sajid *et al.*, 2011).

Many researchers are presently focusing on circulating tumor cells (CTC) in peripheral blood, and mounting evidence describes associations of CTC in patients with metastatic cancer and worse prognosis. However, data has emerged that currently used detection methods lack sensitivity or specificity to identify or characterize all CTC, particularly those that have lost characteristic epithelial features.

There are some recent advancement with reference to development of a method to predict and enhance the individual response to immunotherapy by using personalized mathematical models, constructed in the early phase of treatment. This particular approach included an iterative real-time in-treatment evaluation of patient-specific parameters from the accruing clinical data, construction of personalized models and their validation of proof of concept, model-based simulation of subsequent response to ongoing therapy, and suggestion of potentially more effective patient-specific modified treatment (Kogan *et al.*, 2012).

Interestingly, efforts are being made to identify drug candidates against prostate cancer by searching for inverse correlations between the aberrant gene expression levels in human cancer tissue and the most perturbed expression levels induced by bioactive compounds. This function-based strategy nonetheless broadens the search space for the efficient drugs with remarkable hit rate and has remarkable application for the personalized medicine (Shigemizu *et al.*, 2012).

CONCLUSION

It is understandable that prostate cancer is a multidimensional disorder that has intra tumor heterogeneity that offers stumbling blocks in the standardization of therapy. The therapeutic regimens used have off target effects which further complicate the cancer aggressiveness. It is therefore important to explore drugs having minimal toxicity and off target effects. Although numerous compounds have been tested in preclinical models and there are encouraging results but because of resistant prostate cancer proteome, it is significant to have a detailed snapshot of oncoproteins for an effective targeting.

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