1

# Biomarkers of Aggressiveness in Prostate Cancer

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## 1. Introduction

Although significant progress in the investigation of prostate cancer biomarkers, some men are overdiagnosed with indolent prostate cancer while others die from aggressive disease diagnosed too late. The introduction of PSA (Prostate Specific Antigen) in clinical practice has resulted in early detection and reduced mortality from prostate cancer (Schroder et al., 2009). Despite its great utility for prostate cancer detection and prognostication, PSA as a single test has several limitations. Prostate cancer screening remains thus controversial, because of the risk of overdiagnosis reduced mortality and overtreatment and the inability to detect a significant proportion of aggressive tumors. To extend the limited information provided by PSA testing, other biomarkers that could discriminate between indolent from aggressive cancers are therefore an absolute must. Despite numerous studies of biomarker candidates have been presented the last decade, the identification of the most aggressive subsets of this disease is still not possible. This review will cover last years development in this area and highlight the most promising biomarkers in prostate cancer, which have been divided into three groups; protein-based, DNA-based and RNA-based markers.

## 2. Protein biomarkers

### 2.1 Prostate Stem Cell Antigen (PSCA)

PSCA (Prostate Stem Cell Antigen) is a membrane glycoprotein with 30% homology to stem cell antigen type 2 (SCA-2), an immature lymphocyte cell surface marker. Like SCA-2, PSCA is attached to the membrane by a GPI anchor which can be cleaved by a phospholipase. Because of its homology with SCA-2, PSCA was named inaccurately since it is not a marker for stem cells nor is it uniquely expressed in the prostate (Saeki et al., 2010). Initially, PSCA was identified as a tumor antigen overexpressed in the prostate (Reiter et al., 1998), and subsequent studies have revealed that it is also up-regulated in other cancers including bladder and pancreas. PSCA has been proposed as a promising tumor marker of diagnostic and prognosis, as well as a potential therapeutic target for patients with metastatic prostate cancer. PSCA expression indeed increases with high gleason score, advanced stage and bone metastasis (Gu et al., 2000; Han et al., 2004; Lam et al., 2005; Zhigang & Wenlv, 2004). The levels of PSCA are also amplified in the prostate intraepithelial neoplasia (PIN) lesions that

subsequently progressed to cancer compared to those that did not progress (Zhigang & Wenlu, 2007). PSCA might also represent a useful marker for metastasis detection as almost 95% of lymph nodes and bone samples with metastasis have been found positive for PSCA expression (Ananias et al., 2009). It was originally observed that PSCA mRNA bearing cells circulating in peripheral blood were identified at higher rates in prostate cancer patients with extraprostatic disease (Hara et al., 2002). The presence of *PSCA* transcripts in the peripheral blood has found to be a significant predictor of biochemical recurrence after prostatectomy in high-risk prostate cancer (Joung et al., 2010). Of note, PSCA has also been investigated as a potential target for tumor-targeted immunotherapy and for suppression by anti-PSCA antibody in animals. Further evaluation of PSCA as a clinical prostate cancer marker of aggressiveness needs to be validated.

### 2.2 Prostate Secretory Protein 94 (PSP94)

The ELISA dosage of β-microseminoprotein (MSP) ou PSP94 (Prostate Secretory Protein of 94 amino acids) – one of three predominant proteins secreted by the human prostate gland (Lilja & Abrahamsson, 1988) – could be potentially interesting. In a case-control study of 1,212 men with no previous history of prostate cancer, Nam et al. found that patients with low PSP94 levels had a high probability for having prostate cancer diagnosed at biopsy (Nam et al., 2006). The authors also suggested that those cancers that maintain PSP94 expression tend to be well differentiated and less aggressive, as reported in previous immunohistochemistry studies (Abrahamsson et al., 1988). In serum, PSP94 can be complexed with PSPBP (PSP-binding protein), a glycoprotein of 50 kDa sharing significant identity with the CRISP (cystein-rich seccretory protein) family of proteins (Reeves et al., 2005). In a study comprising 185 patients, it was showed that PSPBP is negatively associated with recurrence after radical prostatectomy (Reeves et al., 2006). On the contrary, PSP94 immunohistochemistry performed on 59 radical prostatectomy specimens was associated with worsened survival outcomes (Girvan et al., 2005). Another immunohistochemistry study conducted on 945 patients found a high expression of PSP94 in tumor cells patients to be associated with a longer time to postprostatectomy biochemical recurrence (Bjartell et al., 2007) in agreement with serum studies. Further studies will be needed to determine whether PSP94 and its binding protein represent novel prognostic factors in the clinic.

However, it is interesting to note that genome-wide association studies identified several SNPs in a region on chromosome 10 that harbors the *PSP94* gene (Eeles et al., 2008; Thomas et al., 2008). Its location and the strength of the association raises the possibility that this SNP may be causally related to disease risk, but resequencing and further analyses will be needed clarify the functional basis of this association.

### 2.3 Early Prostate Cancer Antigens ECPA and ECPA-2

ECPA and ECPA-2 (Early Prostate Cancer Antigens) are nuclear matrix proteins those alterations are commonly associated with prostate cancer (Getzenberg et al., 1991; Lakshmanan et al., 1998). Initially, immunohistochemical studies on men with negative biopsies who were ultimately found to have prostate cancer could identify individuals as much as 5 years earlier than the current diagnostic (Dhir et al., 2004). ECPA positivity was hypothesized to be an early event in disease progression, as there was no correlation between ECPA staining and Gleason grade or pT stage (Uetsuki et al., 2005). In 2005, an ECPA-based ELISA showed 92% sensitivity and 94% specificity in prostate cancer detection

in patients undergoing radical prostatectomy, however only 46 blood samples were examined (Paul et al., 2005). ELISA used for initial serum EPCA measurement in 112 men with isolated high-grade prostatic intraepithelial neoplasia (HGPIN), showed a significantly higher serum ECPA level in isolated HGPIN patients with subsequent cancer than those without cancer (Zhao & Zeng, 2010). Pretreatment serum EPCA levels were also determined with an ELISA in 77 patients with clinically localized prostate cancer who underwent radical prostatectomy and 51 patients with locally advanced or metastatic disease who received primary androgen deprivation therapy, and were correlated with clinicopathological variables and disease progression. Patients with locally advanced and metastatic prostate cancer had significantly higher serum EPCA level than those with clinically localized disease. These data suggest that EPCA level correlates significantly with the poor prognosis, showing prediction potential for prostate cancer progression (Zhao et al., 2011). Unrelated to the original ECPA, the nuclear protein ECPA-2 was recently described (Leman et al., 2007). Carried out on 385 blood samples, the ECPA-2 ELISA was able to differentiate between men with and without prostate cancer with 92% specificity and 94% sensitivity, whereas the specificity of PSA was only 65% in the same population (Leman et al., 2007). More importantly, in contrast to PSA, ECPA-2 is able to discriminate men with non-organ-confined prostate cancer from those with organ-confined diseases. Although additional validation studies are needed to show the performance of ECPA-2 in a more representative population, these results lend support to the development of a more accurate blood-based assay to identify aggressive prostate cancer.

### 2.4 uPA/uPAR

A wealth of reports suggest a key role for the urokinase-type plasminogen activator and its receptor (uPA/uPAR) in invasion and metastatic dissemination (Duffy, 2004). uPA is is a member of the serine protease family synthetized and secreted as a pro-enzyme, whose activation is markedly accelerated upon binding with high affinity to specific membrane-bound or soluble cell surface uPAR. Once activated, the uPA/uPAR system efficiently converts plasminogen into plasmin, a protease which then modulates extracellular matrix degradation, tumor cell invasion and growth factor activation (Duffy, 2004). In prostate cancer, overexpression of uPA and uPAR (transcripts and proteins) have been reported in tumor tissues suggesting that both proteins could be associated with tumor progression. Immunohistochemical studies have shown an incremental increase in uPA/uPAR expression from benign epithelium to primary organ-confined prostate cancer, to disease extending beyond the prostate capsule, and to bone metastases (Cozzi et al., 2006; Gavrilov et al., 2001; Pulukuri et al., 2007; Usher et al., 2005). In addition, overexpression of uPA and its inhibitor PAI-1 are associated with aggressive prostate cancer recurrence in men treated with radical prostatectomy (Gupta et al., 2009). Elevated circulating levels of uPA and/or uPAR have been associated with advanced prostate cancer and bone metastases (Hienert et al., 1988a; Hienert et al., 1988b; Miyake et al., 1999). Shariat et al. have recently reported that plasma levels of uPA and uPAR are not only higher in men with prostate cancer than in healthy controls, but decrease significantly after prostatectomy (suggesting that direct local production by malignant cells significantly contributes to increased uPA and uPAR circulating levels of these markers in patients), then increase with disease progression (Shariat et al., 2007). Of note, higher preoperative uPA and uPAR were both significantly associated with shorter progression PSA doubling times, failure to respond to salvage local

radiation therapy, and /or development of distant metastases (Shariat et al., 2007). Larger studies are needed to validate the promising role of uPA and uPAR as biomarkers of aggressive prostate cancer.

## 3. DNA biomarkers

### 3.1 Epigenetic markers

Epigenetic alterations, i.e., alterations in gene expression without changes in the DNA sequence, include global genomic hypomethylation, promoter hypermethylation of CpG islands and loss of imprinting. The most common somatic genome alteration during prostate cancer development appears to be the hypermethylation in the regulatory region of certain genes, most commonly in the promoter of the π-class glutathione-*S*-transferase (*GSTP1*) gene (Lee et al., 1994). GSTP1 is a member of a large family of glutathione transferases that protect DNA from free radicals (Hayes & Strange, 1995). Men with a positive preoperative serum analysis for *GSTP1* CpG island hypermethylation were at significant risk to experience PSA recurrence within the first several years following radical prostatectomy (Bastian et al., 2005). A high frequency of *GSTP1* methylation in the urine of men with high-stage cancer was also recently reported (Woodson et al., 2008). Other candidate genes have been examined for hypermethylation along with *GSTP1*. A recent study suggested that men with advanced prostate cancer and biochemical recurrence experience a significant increase in promoter hypermethylation between initial diagnosis (first blood analysis) and time to progression (second blood analysis) in the four genes with the highest methylation frequencies (*GSTP1*, *APC*, *RAR*β2 and *RASSF1*α) in prostate cancer patients compared to age-matched controls (Roupret et al., 2008). This study suggests that multiple gene methylation analysis in circulating cell DNA could be a good biomarker for early detection of prostate cancer recurrence.

### 3.2 Gene fusion proteins

Based on a bioinformatics strategy Tomlins et al. described for the first time in prostate cancer a series of genetic rearrangements between the 5'-untranslated region of TMPRSS2 (21q22) and some members of the ETS family of transcription factors, such as ERG (21q22), ETV1 (7p21) and ETV4 (17q21), which have important roles in several oncogenic pathways (Tomlins et al., 2005). Approximatively 50% of prostate cancers from serum PSA-screened cohorts harbor recurrent gene fusions (Kumar-Sinha et al., 2008), which can be detected by fluorescent *in situ* hybridisation (FISH). Conflicting results have been reported regarding the prognosis value of prostate cancer harboring TMPRESS2:ERG gene fusions. Earlier studies reported associations with high stage, metastasis, and prostate cancer-specific death (Attard et al., 2008; Demichelis et al., 2007; Nam et al., 2007), but more recent reports found no association with outcome (Gopalan et al., 2009; Leinonen et al., 2010; Mehra et al., 2007), an association with favorable outcome (Saramaki et al., 2008), or a similar percentage of TMPRSS2:ERG gene fusion in minute and nonminute adenocarcinomas (Albadine et al., 2009), all suggesting its lack of value as a marker of aggressive prostate cancer. The analysis of the relationship between TMPRSS2:ERG fusion and morphological features of prostate cancer has produced diverging results. Most studies have found no statistically significant association between TMPRSS2:ERG rearrangement and Gleason score, while some have demonstrated an association with either higher (Attard et al., 2008; Demichelis et al., 2007)

or lower Gleason scores (Fine et al., 2010; Gopalan et al., 2009). Taken together, it seems like the TMPRSS2:ERG fusion gene is an early event related to development of prostate cancer rather than a marker for progressive disease. Of note, the TMPRSSE:ERG fusion has potential for noninvasive prognosis of prostate cancer. Although RNA-based urinary tests demonstrate in general a high specificity and sensitivity to detect prostate cancer, no significant relationship was found between the presence of fusion transcripts and Gleason score or clinical stage (Hessels et al., 2007; Rice et al., 2010).

### 3.3 Loss of heterozygosity

The loss of heterozygosity (LOH) is a frequent genetic alteration in prostate cancer, in particular on chromosome arms 7q, 8p, 10q, 12p, 13q, 16q, 17q and 18q (Dong, 2006). Studies on chromosomal deletions of 8p22 by fluorescence in situ hybridization technique revealed 8p22 deletion to be the strongest parameter to predict disease progression in patients undergoing surgery (Matsuyama et al., 2001). If some LOH have been shown to be associated with early stages of prostate cancer (Lu & Hano, 2008), others seem to indicate the presence of tumor suppressor genes whose inactivation is correlated with aggressive and metastatic tumors (Dong et al., 2000; Kibel et al., 2000; Matsuyama et al., 2007). A recent study reported the development of a noninvasive method to detect early stages of prostate cancer using LOH analysis of 7q31, 8p22, 12p13, 13q14, 16q23.2 and 18q21. Indeed LOH could be found in cells from urine obtained by prostatic massage (Thuret et al., 2005). In patients who underwent radical prostatectomy, LOH was confirmed from the prostatic tissue with a concordance of 86%. This noninvasive approach warrants further investigation to bring pronostic information on prostate cancer aggressiveness.

## 4. RNA biomarkers

### 4.1 PCA3

PCA3 (formerly known as DD3) is a non-coding RNA very prostate specific (Bussemakers et al., 1999; de Kok et al., 2002). PCA3 mRNA levels can be measured in the urine specimens and several studies have shown that the PCA3 score is superior to serum PSA for predicting biopsy outcome (Groskopf et al., 2006; Haese et al., 2008; van Gils et al., 2007). The relationship between PCA3 score and parameters of cancer aggressiveness has also been studied and differ. Some studies report a positive relationship between PCA3 scores and parameters of more serious disease (Nakanishi et al., 2008; Whitman et al., 2008), while other studies could not find such a relationship (Hessels et al., 2010). Further studies are requested to evaluate the potential of PCA3 testing as prognostic test for prostate cancer.

### 4.2 AMACR

α-methylacyl-CoA racemase (AMACR) is a catalyst in the peroximal beta-oxidation of branched chain fatty acids found in dietary sources (Wanders et al., 2001), such as red meat and dairy products, the consumption of which has been associated with increased prostate cancer risks (Hsing & Chokkalingam, 2006). AMACR has been identified as a potential biomarker based on its overexpression in localized prostate cancer as compared to benign prostate epithelium (Luo et al., 2002; Rhodes et al., 2002; Rubin et al., 2002). In fact, immunostaining for AMACR is commonly performed in prostate biopsies to help distinguish benign from malignant tissue. Of note, AMACR expression was found consistently lower both at the transcriptional (cDNA expression arrays and RT-PCR) and at

the protein level (immunohistochemistry and western-blot) in metastatic prostate cancer compared to localized prostate cancer (Kuefer et al., 2002; Rubin et al., 2004). An association between low AMACR protein expression at diagnosis and an increased risk of biochemical recurrence and fatal prostate cancer was reported in patients diagnosed with a localized prostate cancer who underwent radical prostatectomy or not (Rubin et al., 2005). Recent findings from the same group confirmed that down-regulation of AMACR expression is associated with poorer outcomes in a cohort of 920 men diagnosed with prostate cancer. However the lack of statistical significance suggests that tumor AMACR expression at diagnosis is not a useful prognostic biomarker for lethal disease after treatment (Barry et al., 2011). Although AMACR protein can been detected in urine by western-blot, its concentration is low in serum, making the development of a serum test difficult (Rogers et al., 2004). Circulating concentrations of AMACR mRNA in urine or serum quantified by RT-PCR have been found elevated in patients but these pilot studies are limited to small series (Zehentner et al., 2006; Zielie et al., 2004).

### 4.3 MicroRNAs

MicroRNAs are small RNAs found to regulate mRNA function by modulating both mRNA stability and the translation of mRNA into protein. Their expression is commonly altered in solid tumors and multiple microRNAs have been shown to have oncogenic properties or act like tumor suppressor genes. Besides their therapeutic potential, microRNAs hold unique characteristics that herald them as ideal tumor markers including their stability and ease of detection (Heneghan et al., 2010). Despite the large body of work that has been published to date, only limited information is available regarding the expression levels of specific microRNAs in relation to the aggressiveness of prostate cancer. Taking advantage of the stability of tumor-derived microRNAs in circulating blood, Mitchell and co-workers found a remarkably higher level of miR-141 (46-fold increase) in a patients with metastatic prostate cancer compared to healthy control men (Mitchell et al., 2008). The first evidence of a possible prognostic relevance of microRNAs in prostate cancer was obtained from a study examining the tissue expression of 40 patients undergoing prostatectomy. The increased expression of miR-135b and miR-194 was associated with biochemical recurrence within 2 years of surgery (Tong et al., 2009). Another study, conducted on matched tumor and adjacent normal tissues obtained from 76 patients, found that high expression of miR-96 was associated with cancer recurrence after radical prostatectomy, and that prognostic information was confirmed by an independent tumor sample set from 79 pateints (Schaefer et al., 2010). The miR-221 expression is also progressively reduced in aggressive prostate cancer and metastasis and predicts clinical recurrence in patients (n=92) undergoing radical prostatectomy (Spahn et al., 2010). More recently, miR-143 and miR-145 were identified as being associated with bone metastasis of prostate cancer and involved in the regulation of epithelial-mesenchymal transition (Peng et al., 2011). Interestingly, the loss of miR-101 expression during cancer progression in human tumors has been associated with overexpression of histone methytransferase EZH2 (enhancer of zeste homolog 2) (Varambally et al., 2008). Amounts of both EZH2 mRNA and EZH2 protein are increased in metastatic prostate cancer; in addition, clinically localized prostate cancers that express higher concentrations of EZH2 show a poorer prognosis (Varambally et al., 2002). In cancer cell lines, the expression and function of EZH2 are inhibited by miR-101 (Varambally et al., 2008).

Thus, dysregulated expression of EZH2 may be involved in the progression of prostate cancer, and miR101 might represent a marker that distinguishes indolent prostate cancer from those at risk of lethal progression

## 5. Other potential biomarkers

### 5.1 Metabolomics

Metabolite profiling or metabolomics, the analysis of endogenous metabolites in a biological system was recently suggested to be a promising approach to identify novel metabolites or their changes (Fredolini et al., 2010). In practice, however, analysis of the metabolome is complex because of the large range of detectable metabolites. By screening 110 samples from men's urine and blood and 42 tissue samples, Chinnaiyan and collaborators recently identified 1,126 metabolites. They identified 87 that distinguish normal prostate from prostate cancer, then narrowed down the list to 6 whose levels were higher in samples linked to localized prostate cancer and higher still in metastatic disease (Sreekumar et al., 2009). Sarcosine, an *N*-methyl derivative of the amino acid glycine, was identified as a differential metabolite that was highly increased during prostate cancer progression to metastasis. Surprisingly, the authors also provided evidence using cell cultures for a functional role of sarcosine in promoting invasive properties in these cells, whereas lowering the level of the enzyme producing sarcosine reduces invasiveness (Sreekumar et al., 2009). The potential role of urinary was reevaluated in another study, which showed that sarcosine in urine after digital rectal examination fails as a marker in prostate cancer detection and identification of aggressive tumors (Jentzmik et al., 2010). In addition to this work, the same group showed no correlation with sarcosine level in tissues and tumor stage, tumor grade or biochemical recurrence in 92 samples obtained after radical prostatectomy (Jentzmik et al., 2011). Although the lack of metastatic tissue samples was a limitation, this study establishes that sarcosine measurement in prostate tissue is not suitable to predict cancer aggressiveness or biochemical progress.

### 5.2 Disseminated tumor cells

The shedding of tumor cells into the circulation is a necessary condition for metastasis dissemination and the clinical relevance of the detection of disseminated tumors cells (DTCs) in bone marrow (the most prominent metastatic site in prostate and breast cancer) or in peripheral blood of patients free of apparent metastasis in under investigation. So far, only large breast cancer studies have confirmed the independent prognostic value of the bone marrow status (Berg et al., 2007). Recent studies have demonstrated an association between DTCs in bone marrow at diagnosis of nonmetastastic prostate cancer (Berg et al., 2007; Kollermann et al., 2008). Although a DTC-positive bone marrow status was associated with grading and increased risk of metastasis, the study by Berg et al. on 266 patients did not find a correlation of DTC detection and survival (Berg et al., 2007). In contrast, Köllermann et al. demonstrated the prognostic relevance of DTCs in bone marrow patients with clinically localized prostate cancer submitted to neo-adjuvant hormonal therapy followed by radical prostatectomy and a median follow-up of 44 months (Kollermann et al., 2008). This study is the first one on a large series of patients with sufficient long follow-up to clearly demonstrate an adverse prognostic effect of the presence of DTCs at the time of initial diagnostic.

| Markers | Strategy of Detection | Comments |
|---|---|---|
| PSCA | RT-PCR (blood),<br>Protein expression (tissue) | Potential therapeutic target |
| PSP94 | ELISA (blood),<br>Protein expression (tissue) | One of the major secretory proteins of the prostate gland |
| ECPA/ECPA-2 | ELISA (blood),<br>Protein expression (tissue) | |
| uPA/uPAR | ELISA (blood),<br>Protein expression (tissue) | uPAR expression in DTCs (bone marrow, peripheral blood),<br>Potential therapeutic target |
| Epigenetic markers (eg. GSTP1) | Methylation specific PCR (blood, urine) | Potential Multiplex test with other urine biomarkers |
| Gene fusion proteins (eg. TMPRSS2 :ERG) | RT-PCR (urine)<br>FISH (tissue) | Potential Multiplex test with other urine biomarkers |
| Loss of heterozygoty | PCR (blood, urine) | |
| PCA3 | Transcription-mediated amplification assay (urine) | Potential Multiplex test with other urine biomarkers |
| AMACR | RT-PCR (blood, urine)<br>Protein expression (tissue) | Potential Multiplex test with other urine biomarkers,<br>Potential therapeutic target |
| MicroRNAs | RT-PCR (blood, urine, tissue) | Potential therapeutic targets |
| Metabolomics | Profiling (urine, blood) | |
| Disseminated Tumor Cells | Enumeration (blood, bone marrow) | |

Table 1. Potential biomarkers and their strategy of detection

Despite bone marrow analysis provides important information, peripheral blood studies are more acceptable in the clinical management than invasive BM aspirations. However, identification of circulating tumor cells (DTCs) require extremely sensitive analytical methods that are usually combined with enrichment procedures. Although promising results from patients with advanced stages demonstrate the value of CTCs technology (currently evaluated and validated in clinical trials as a predictor and surrogate endpoint of

treatment response), studies on patients at earlier stages are hampered by the low CTC counts. A recent study from Haber and collaborators shows that tumor cells obtained from the blood of cancer patients were monitored before and after surgery, most circulating cells rapidly declined shortly after surgery while others persisted months thereafter, suggesting that postoperative CTCs might derive from preestablished non prostatic sites of disease that continue to shed CTCs into the circulation (Stott et al., 2010). If confirmed, these observations support the potential application of CTC monitoring as a marker of invasive localized disease before the establishment of viable metastatic lesions.

## 6. Conclusion

We have here attempted to give some examples of potential DNA-based, RNA-based and protein-based markers of aggressiveness in prostate cancer. Comparisons between studies are often difficult because of some inconsistencies between study cohorts, collection methods and handling of samples. It is unlikely that a single biomarker (evaluated on conventional approach looking at a single molecular predictor significantly up- or down-regulated) will provide the information requested to tell how aggressive a diagnosed prostate cancer is. New research methods (proteomics, metabolomics…) are also emerging, and high-throughput technologies will facilitate biomarker discovery. Therefore, future advances in this field will probably have to integrate proteomics, transcriptomics and multiplex approaches and identify combinations of multiple biomarkers in order to improve the characterization of aggressive prostate cancers.

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## 8. References

Abrahamsson, P.A.; Lilja, H.; Falkmer, S.& Wadstrom, L.B. (1988). Immunohistochemical distribution of the three predominant secretory proteins in the parenchyma of hyperplastic and neoplastic prostate glands. Prostate, Vol.12, No.1, pp.39-46, ISSN 0270-4137

Albadine, R.; Latour, M.; Toubaji, A.; Haffner, M.; Isaacs, W.B.; E, A.P.; Meeker, A.K.; Demarzo, A.M.; Epstein, J.I.& Netto, G.J. (2009). TMPRSS2-ERG gene fusion status in minute (minimal) prostatic adenocarcinoma. Mod Pathol, Vol.22, No.11, (Nov), pp.1415-1422, ISSN 1530-0285

Ananias, H.J.; van den Heuvel, M.C.; Helfrich, W.& de Jong, I.J. (2009). Expression of the gastrin-releasing peptide receptor, the prostate stem cell antigen and the prostate-specific membrane antigen in lymph node and bone metastases of prostate cancer. Prostate, Vol.69, No.10, (Jul 1), pp.1101-1108, ISSN 1097-0045

Attard, G.; Clark, J.; Ambroisine, L.; Fisher, G.; Kovacs, G.; Flohr, P.; Berney, D.; Foster, C.S.; Fletcher, A.; Gerald, W.L.; Moller, H.; Reuter, V.; De Bono, J.S.; Scardino, P.; Cuzick, J.& Cooper, C.S. (2008). Duplication of the fusion of TMPRSS2 to ERG sequences

identifies fatal human prostate cancer. Oncogene, Vol.27, No.3, (Jan 10), pp.253-263, ISSN 1476-5594

Barry, M.; Dhillon, P.K.; Stampfer, M.J.; Perner, S.; Ma, J.; Giovannucci, E.; Kurth, T.; Mucci, L.A.& Rubin, M.A. (2011). alpha-Methylacyl-CoA racemase expression and lethal prostate cancer in the Physicians' Health Study and Health Professionals Follow-up Study. Prostate, (Jun 28), ISSN 1097-0045

Bastian, P.J.; Palapattu, G.S.; Lin, X.; Yegnasubramanian, S.; Mangold, L.A.; Trock, B.; Eisenberger, M.A.; Partin, A.W.& Nelson, W.G. (2005). Preoperative serum DNA GSTP1 CpG island hypermethylation and the risk of early prostate-specific antigen recurrence following radical prostatectomy. Clin Cancer Res, Vol.11, No.11, (Jun 1), pp.4037-4043, ISSN 1078-0432

Berg, A.; Berner, A.; Lilleby, W.; Bruland, O.S.; Fossa, S.D.; Nesland, J.M.& Kvalheim, G. (2007). Impact of disseminated tumor cells in bone marrow at diagnosis in patients with nonmetastatic prostate cancer treated by definitive radiotherapy. Int J Cancer, Vol.120, No.8, (Apr 15), pp.1603-1609, ISSN 0020-7136

Bjartell, A.S.; Al-Ahmadie, H.; Serio, A.M.; Eastham, J.A.; Eggener, S.E.; Fine, S.W.; Udby, L.; Gerald, W.L.; Vickers, A.J.; Lilja, H.; Reuter, V.E.& Scardino, P.T. (2007). Association of cysteine-rich secretory protein 3 and beta-microseminoprotein with outcome after radical prostatectomy. Clin Cancer Res, Vol.13, No.14, (Jul 15), pp.4130-4138, ISSN 1078-0432

Bussemakers, M.J.; van Bokhoven, A.; Verhaegh, G.W.; Smit, F.P.; Karthaus, H.F.; Schalken, J.A.; Debruyne, F.M.; Ru, N.& Isaacs, W.B. (1999). DD3: a new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Res, Vol.59, No.23, (Dec 1), pp.5975-5979, ISSN 0008-5472

Cozzi, P.J.; Wang, J.; Delprado, W.; Madigan, M.C.; Fairy, S.; Russell, P.J.& Li, Y. (2006). Evaluation of urokinase plasminogen activator and its receptor in different grades of human prostate cancer. Hum Pathol, Vol.37, No.11, (Nov), pp.1442-1451, ISSN 0046-8177

de Kok, J.B.; Verhaegh, G.W.; Roelofs, R.W.; Hessels, D.; Kiemeney, L.A.; Aalders, T.W.; Swinkels, D.W.& Schalken, J.A. (2002). DD3(PCA3), a very sensitive and specific marker to detect prostate tumors. Cancer Res, Vol.62, No.9, (May 1), pp.2695-2698, ISSN 0008-5472

Demichelis, F.; Fall, K.; Perner, S.; Andren, O.; Schmidt, F.; Setlur, S.R.; Hoshida, Y.; Mosquera, J.M.; Pawitan, Y.; Lee, C.; Adami, H.O.; Mucci, L.A.; Kantoff, P.W.; Andersson, S.O.; Chinnaiyan, A.M.; Johansson, J.E.& Rubin, M.A. (2007). TMPRSS2:ERG gene fusion associated with lethal prostate cancer in a watchful waiting cohort. Oncogene, Vol.26, No.31, (Jul 5), pp.4596-4599, ISSN 0950-9232

Dhir, R.; Vietmeier, B.; Arlotti, J.; Acquafondata, M.; Landsittel, D.; Masterson, R.& Getzenberg, R.H. (2004). Early identification of individuals with prostate cancer in negative biopsies. J Urol, Vol.171, No.4, (Apr), pp.1419-1423, ISSN 0022-5347

Dong, J.T. (2006). Prevalent mutations in prostate cancer. J Cell Biochem, Vol.97, No.3, (Feb 15), pp.433-447, ISSN 0730-2312

Dong, J.T.; Chen, C.; Stultz, B.G.; Isaacs, J.T.& Frierson, H.F., Jr. (2000). Deletion at 13q21 is associated with aggressive prostate cancers. Cancer Res, Vol.60, No.14, (Jul 15), pp.3880-3883, ISSN 0008-5472

Duffy, M.J. (2004). The urokinase plasminogen activator system: role in malignancy. Curr Pharm Des, Vol.10, No.1, pp.39-49, ISSN 1381-6128

Eeles, R.A.; Kote-Jarai, Z.; Giles, G.G.; Olama, A.A.; Guy, M.; Jugurnauth, S.K.; Mulholland, S.; Leongamornlert, D.A.; Edwards, S.M.; Morrison, J.; Field, H.I.; Southey, M.C.; Severi, G.; Donovan, J.L.; Hamdy, F.C.; Dearnaley, D.P.; Muir, K.R.; Smith, C.; Bagnato, M.; Ardern-Jones, A.T.; Hall, A.L.; O'Brien, L.T.; Gehr-Swain, B.N.; Wilkinson, R.A.; Cox, A.; Lewis, S.; Brown, P.M.; Jhavar, S.G.; Tymrakiewicz, M.; Lophatananon, A.; Bryant, S.L.; Horwich, A.; Huddart, R.A.; Khoo, V.S.; Parker, C.C.; Woodhouse, C.J.; Thompson, A.; Christmas, T.; Ogden, C.; Fisher, C.; Jamieson, C.; Cooper, C.S.; English, D.R.; Hopper, J.L.; Neal, D.E.& Easton, D.F. (2008). Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet, Vol.40, No.3, (Mar), pp.316-321, ISSN 1546-1718

Fine, S.W.; Gopalan, A.; Leversha, M.A.; Al-Ahmadie, H.A.; Tickoo, S.K.; Zhou, Q.; Satagopan, J.M.; Scardino, P.T.; Gerald, W.L.& Reuter, V.E. (2010). TMPRSS2-ERG gene fusion is associated with low Gleason scores and not with high-grade morphological features. *Mod Pathol*, Vol.23, No.10, (Oct), pp.1325-1333, ISSN 1530-0285

Fredolini, C.; Liotta, L.A.& Petricoin, E.F. (2010). Application of proteomic technologies for prostate cancer detection, prognosis, and tailored therapy. *Crit Rev Clin Lab Sci*, Vol.47, No.3, (May-Jun), pp.125-138, ISSN 1040-8363

Gavrilov, D.; Kenzior, O.; Evans, M.; Calaluce, R.& Folk, W.R. (2001). Expression of urokinase plasminogen activator and receptor in conjunction with the ets family and AP-1 complex transcription factors in high grade prostate cancers. *Eur J Cancer*, Vol.37, No.8, (May), pp.1033-1040, ISSN 0959-8049

Getzenberg, R.H.; Pienta, K.J.; Huang, E.Y.& Coffey, D.S. (1991). Identification of nuclear matrix proteins in the cancer and normal rat prostate. *Cancer Res*, Vol.51, No.24, (Dec 15), pp.6514-6520, ISSN 0008-5472

Girvan, A.R.; Chang, P.; van Huizen, I.; Moussa, M.; Xuan, J.W.; Stitt, L.; Chin, J.L.; Yamasaki, Y.& Izawa, J.I. (2005). Increased intratumoral expression of prostate secretory protein of 94 amino acids predicts for worse disease recurrence and progression after radical prostatectomy in patients with prostate cancer. *Urology*, Vol.65, No.4, (Apr), pp.719-723, ISSN 1527-9995

Gopalan, A.; Leversha, M.A.; Satagopan, J.M.; Zhou, Q.; Al-Ahmadie, H.A.; Fine, S.W.; Eastham, J.A.; Scardino, P.T.; Scher, H.I.; Tickoo, S.K.; Reuter, V.E.& Gerald, W.L. (2009). TMPRSS2-ERG gene fusion is not associated with outcome in patients treated by prostatectomy. *Cancer Res*, Vol.69, No.4, (Feb 15), pp.1400-1406, ISSN 1538-7445

Groskopf, J.; Aubin, S.M.; Deras, I.L.; Blase, A.; Bodrug, S.; Clark, C.; Brentano, S.; Mathis, J.; Pham, J.; Meyer, T.; Cass, M.; Hodge, P.; Macairan, M.L.; Marks, L.S.& Rittenhouse, H. (2006). APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem*, Vol.52, No.6, (Jun), pp.1089-1095, ISSN 0009-9147

Gu, Z.; Thomas, G.; Yamashiro, J.; Shintaku, I.P.; Dorey, F.; Raitano, A.; Witte, O.N.; Said, J.W.; Loda, M.& Reiter, R.E. (2000). Prostate stem cell antigen (PSCA) expression increases with high gleason score, advanced stage and bone metastasis in prostate cancer. *Oncogene*, Vol.19, No.10, (Mar 2), pp.1288-1296, ISSN 0950-9232

Gupta, A.; Lotan, Y.; Ashfaq, R.; Roehrborn, C.G.; Raj, G.V.; Aragaki, C.C.; Montorsi, F.& Shariat, S.F. (2009). Predictive value of the differential expression of the urokinase plasminogen activation axis in radical prostatectomy patients. *Eur Urol*, Vol.55, No.5, (May), pp.1124-1133, ISSN 1873-7560

Haese, A.; de la Taille, A.; van Poppel, H.; Marberger, M.; Stenzl, A.; Mulders, P.F.; Huland, H.; Abbou, C.C.; Remzi, M.; Tinzl, M.; Feyerabend, S.; Stillebroer, A.B.; van Gils, M.P.& Schalken, J.A. (2008). Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. *Eur Urol*, Vol.54, No.5, (Nov), pp.1081-1088, ISSN 0302-2838

Han, K.R.; Seligson, D.B.; Liu, X.; Horvath, S.; Shintaku, P.I.; Thomas, G.V.; Said, J.W.& Reiter, R.E. (2004). Prostate stem cell antigen expression is associated with gleason score, seminal vesicle invasion and capsular invasion in prostate cancer. *J Urol*, Vol.171, No.3, (Mar), pp.1117-1121, ISSN 0022-5347

Hara, N.; Kasahara, T.; Kawasaki, T.; Bilim, V.; Obara, K.; Takahashi, K.& Tomita, Y. (2002). Reverse transcription-polymerase chain reaction detection of prostate-specific antigen, prostate-specific membrane antigen, and prostate stem cell antigen in one milliliter of peripheral blood: value for the staging of prostate cancer. *Clin Cancer Res*, Vol.8, No.6, (Jun), pp.1794-1799, ISSN 1078-0432

Hayes, J.D.& Strange, R.C. (1995). Potential contribution of the glutathione S-transferase supergene family to resistance to oxidative stress. *Free Radic Res*, Vol.22, No.3, (Mar), pp.193-207, ISSN 1071-5762

Heneghan, H.M.; Miller, N.& Kerin, M.J. (2010). MiRNAs as biomarkers and therapeutic targets in cancer. *Curr Opin Pharmacol*, Vol.10, No.5, (Oct), pp.543-550, ISSN 1471-4973

Hessels, D.; Smit, F.P.; Verhaegh, G.W.; Witjes, J.A.; Cornel, E.B.& Schalken, J.A. (2007). Detection of TMPRSS2-ERG fusion transcripts and prostate cancer antigen 3 in urinary sediments may improve diagnosis of prostate cancer. *Clin Cancer Res*, Vol.13, No.17, (Sep 1), pp.5103-5108, ISSN 1078-0432

Hessels, D.; van Gils, M.P.; van Hooij, O.; Jannink, S.A.; Witjes, J.A.; Verhaegh, G.W.& Schalken, J.A. (2010). Predictive value of PCA3 in urinary sediments in determining clinico-pathological characteristics of prostate cancer. *Prostate*, Vol.70, No.1, (Jan 1), pp.10-16, ISSN 1097-0045

Hienert, G.; Kirchheimer, J.C.; Christ, G.; Pfluger, H.& Binder, B.R. (1988a). Plasma urokinase-type plasminogen activator correlates to bone scintigraphy in prostatic carcinoma. *Eur Urol*, Vol.15, No.3-4, pp.256-258, ISSN 0302-2838

Hienert, G.; Kirchheimer, J.C.; Pfluger, H.& Binder, B.R. (1988b). Urokinase-type plasminogen activator as a marker for the formation of distant metastases in prostatic carcinomas. *J Urol*, Vol.140, No.6, (Dec), pp.1466-1469, ISSN 0022-5347

Hsing, A.W.& Chokkalingam, A.P. (2006). Prostate cancer epidemiology. *Front Biosci*, Vol.11, pp.1388-1413, ISSN 1093-4715

Jentzmik, F.; Stephan, C.; Lein, M.; Miller, K.; Kamlage, B.; Bethan, B.; Kristiansen, G.& Jung, K. (2011). Sarcosine in prostate cancer tissue is not a differential metabolite for prostate cancer aggressiveness and biochemical progression. *J Urol*, Vol.185, No.2, (Feb), pp.706-711, ISSN 1527-3792

Jentzmik, F.; Stephan, C.; Miller, K.; Schrader, M.; Erbersdobler, A.; Kristiansen, G.; Lein, M.& Jung, K. (2010). Sarcosine in urine after digital rectal examination fails as a

marker in prostate cancer detection and identification of aggressive tumours. *Eur Urol*, Vol.58, No.1, (Jul), pp.12-18; discussion 20-11, ISSN 1873-7560

Joung, J.Y.; Cho, K.S.; Kim, J.E.; Seo, H.K.; Chung, J.; Park, W.S.; Choi, M.K.& Lee, K.H. (2010). Prostate stem cell antigen mRNA in peripheral blood as a potential predictor of biochemical recurrence in high-risk prostate cancer. *J Surg Onco*l, Vol.101, No.2, (Feb 1), pp.145-148, ISSN 1096-9098

Kibel, A.S.; Faith, D.A.; Bova, G.S.& Isaacs, W.B. (2000). Loss of heterozygosity at 12P12-13 in primary and metastatic prostate adenocarcinoma. *J Urol*, Vol.164, No.1, (Jul), pp.192-196, ISSN 0022-5347

Kollermann, J.; Weikert, S.; Schostak, M.; Kempkensteffen, C.; Kleinschmidt, K.; Rau, T.& Pantel, K. (2008). Prognostic significance of disseminated tumor cells in the bone marrow of prostate cancer patients treated with neoadjuvant hormone treatment. *J Clin Oncol*, Vol.26, No.30, (Oct 20), pp.4928-4933, ISSN 1527-7755

Kuefer, R.; Varambally, S.; Zhou, M.; Lucas, P.C.; Loeffler, M.; Wolter, H.; Mattfeldt, T.; Hautmann, R.E.; Gschwend, J.E.; Barrette, T.R.; Dunn, R.L.; Chinnaiyan, A.M.& Rubin, M.A. (2002). alpha-Methylacyl-CoA racemase: expression levels of this novel cancer biomarker depend on tumor differentiation. *Am J Pathol*, Vol.161, No.3, (Sep), pp.841-848, ISSN 0002-9440

Kumar-Sinha, C.; Tomlins, S.A.& Chinnaiyan, A.M. (2008). Recurrent gene fusions in prostate cancer. *Nat Rev Cancer*, Vol.8, No.7, (Jul), pp.497-511, ISSN 1474-1768

Lakshmanan, Y.; Subong, E.N.& Partin, A.W. (1998). Differential nuclear matrix protein expression in prostate cancers: correlation with pathologic stage. J Urol, Vol.159, No.4, (Apr), pp.1354-1358, 0022-5347 (Print)

Lam, J.S.; Yamashiro, J.; Shintaku, I.P.; Vessella, R.L.; Jenkins, R.B.; Horvath, S.; Said, J.W.& Reiter, R.E. (2005). Prostate stem cell antigen is overexpressed in prostate cancer metastases. Clin Cancer Res, Vol.11, No.7, (Apr 1), pp.2591-2596, 1078-0432 (Print)

Lee, W.H.; Morton, R.A.; Epstein, J.I.; Brooks, J.D.; Campbell, P.A.; Bova, G.S.; Hsieh, W.S.; Isaacs, W.B.& Nelson, W.G. (1994). Cytidine methylation of regulatory sequences near the pi-class glutathione S-transferase gene accompanies human prostatic carcinogenesis. *Proc Natl Acad Sci U S A*, Vol.91, No.24, (Nov 22), pp.11733-11737, ISSN 0027-8424

Leinonen, K.A.; Tolonen, T.T.; Bracken, H.; Stenman, U.H.; Tammela, T.L.; Saramaki, O.R.& Visakorpi, T. (2010). Association of SPINK1 expression and TMPRSS2:ERG fusion with prognosis in endocrine-treated prostate cancer. *Clin Cancer Res*, Vol.16, No.10, (May 15), pp.2845-2851, ISSN 1078-0432

Leman, E.S.; Cannon, G.W.; Trock, B.J.; Sokoll, L.J.; Chan, D.W.; Mangold, L.; Partin, A.W.& Getzenberg, R.H. (2007). EPCA-2: a highly specific serum marker for prostate cancer. *Urology*, Vol.69, No.4, (Apr), pp.714-720, ISSN 1527-9995

Lilja, H.& Abrahamsson, P.A. (1988). Three predominant proteins secreted by the human prostate gland. *Prostate*, Vol.12, No.1, pp.29-38, ISSN 0270-4137

Lu, T.& Hano, H. (2008). Deletion at chromosome arms 6q16-22 and 10q22.3-23.1 associated with initiation of prostate cancer. *Prostate Cancer Prostatic Dis*, Vol.11, No.4, pp.357-361, ISSN 1476-5608

Luo, J.; Zha, S.; Gage, W.R.; Dunn, T.A.; Hicks, J.L.; Bennett, C.J.; Ewing, C.M.; Platz, E.A.; Ferdinandusse, S.; Wanders, R.J.; Trent, J.M.; Isaacs, W.B.& De Marzo, A.M. (2002).

Alpha-methylacyl-CoA racemase: a new molecular marker for prostate cancer. *Cancer Res*, Vol.62, No.8, (Apr 15), pp.2220-2226, ISSN 0008-5472

Matsuyama, H.; Oba, K.; Matsuda, K.; Yoshihiro, S.; Tsukamoto, M.; Kinjo, M.; Sagiyama, K.; Takei, M.; Yamaguchi, A.; Sasaki, K.& Naito, K. (2007). Haploinsufficiency of 8p22 may influence cancer-specific survival in prostate cancer. *Cancer Genet Cytogenet*, Vol.174, No.1, (Apr 1), pp.24-34, ISSN 0165-4608

Matsuyama, H.; Pan, Y.; Oba, K.; Yoshihiro, S.; Matsuda, K.; Hagarth, L.; Kudren, D.; Naito, K.; Bergerheim, U.S.& Ekman, P. (2001). Deletions on chromosome 8p22 may predict disease progression as well as pathological staging in prostate cancer. *Clin Cancer Res*, Vol.7, No.10, (Oct), pp.3139-3143, ISSN 1078-0432

Mehra, R.; Tomlins, S.A.; Shen, R.; Nadeem, O.; Wang, L.; Wei, J.T.; Pienta, K.J.; Ghosh, D.; Rubin, M.A.; Chinnaiyan, A.M.& Shah, R.B. (2007). Comprehensive assessment of TMPRSS2 and ETS family gene aberrations in clinically localized prostate cancer. *Mod Pathol*, Vol.20, No.5, (May), pp.538-544, ISSN 0893-3952

Mitchell, P.S.; Parkin, R.K.; Kroh, E.M.; Fritz, B.R.; Wyman, S.K.; Pogosova-Agadjanyan, E.L.; Peterson, A.; Noteboom, J.; O'Briant, K.C.; Allen, A.; Lin, D.W.; Urban, N.; Drescher, C.W.; Knudsen, B.S.; Stirewalt, D.L.; Gentleman, R.; Vessella, R.L.; Nelson, P.S.; Martin, D.B.& Tewari, M. (2008). Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci U S A*, Vol.105, No.30, (Jul 29), pp.10513-10518, ISSN 1091-6490

Miyake, H.; Hara, I.; Yamanaka, K.; Gohji, K.; Arakawa, S.& Kamidono, S. (1999). Elevation of serum levels of urokinase-type plasminogen activator and its receptor is associated with disease progression and prognosis in patients with prostate cancer. *Prostate*, Vol.39, No.2, (May), pp.123-129, ISSN 0270-4137

Nakanishi, H.; Groskopf, J.; Fritsche, H.A.; Bhadkamkar, V.; Blase, A.; Kumar, S.V.; Davis, J.W.; Troncoso, P.; Rittenhouse, H.& Babaian, R.J. (2008). PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance. *J Urol*, Vol.179, No.5, (May), pp.1804-1809; discussion 1809-1810, ISSN 1527-3792

Nam, R.K.; Reeves, J.R.; Toi, A.; Dulude, H.; Trachtenberg, J.; Emami, M.; Daigneault, L.; Panchal, C.; Sugar, L.; Jewett, M.A.& Narod, S.A. (2006). A novel serum marker, total prostate secretory protein of 94 amino acids, improves prostate cancer detection and helps identify high grade cancers at diagnosis. *J Urol*, Vol.175, No.4, (Apr), pp.1291-1297, ISSN 0022-5347

Nam, R.K.; Sugar, L.; Yang, W.; Srivastava, S.; Klotz, L.H.; Yang, L.Y.; Stanimirovic, A.; Encioiu, E.; Neill, M.; Loblaw, D.A.; Trachtenberg, J.; Narod, S.A.& Seth, A. (2007). Expression of the TMPRSS2:ERG fusion gene predicts cancer recurrence after surgery for localised prostate cancer. *Br J Cancer*, Vol.97, No.12, (Dec 17), pp.1690-1695, ISSN 0007-0920

Paul, B.; Dhir, R.; Landsittel, D.; Hitchens, M.R.& Getzenberg, R.H. (2005). Detection of prostate cancer with a blood-based assay for early prostate cancer antigen. *Cancer Res*, Vol.65, No.10, (May 15), pp.4097-4100, ISSN 0008-5472

Peng, X.; Guo, W.; Liu, T.; Wang, X.; Tu, X.; Xiong, D.; Chen, S.; Lai, Y.; Du, H.; Chen, G.; Liu, G.; Tang, Y.; Huang, S.& Zou, X. (2011). Identification of miRs-143 and -145 that Is Associated with Bone Metastasis of Prostate Cancer and Involved in the Regulation of EMT. *PLoS One*, Vol.6, No.5, pp.e20341, ISSN 1932-6203

Pulukuri, S.M.; Estes, N.; Patel, J.& Rao, J.S. (2007). Demethylation-linked activation of urokinase plasminogen activator is involved in progression of prostate cancer. *Cancer Res*, Vol.67, No.3, (Feb 1), pp.930-939, ISSN 0008-5472

Reeves, J.R.; Dulude, H.; Panchal, C.; Daigneault, L.& Ramnani, D.M. (2006). Prognostic value of prostate secretory protein of 94 amino acids and its binding protein after radical prostatectomy. *Clin Cancer Res*, Vol.12, No.20 Pt 1, (Oct 15), pp.6018-6022, ISSN 1078-0432

Reeves, J.R.; Xuan, J.W.; Arfanis, K.; Morin, C.; Garde, S.V.; Ruiz, M.T.; Wisniewski, J.; Panchal, C.& Tanner, J.E. (2005). Identification, purification and characterization of a novel human blood protein with binding affinity for prostate secretory protein of 94 amino acids. *Biochem J*, Vol.385, No.Pt 1, (Jan 1), pp.105-114, ISSN 1470-8728

Reiter, R.E.; Gu, Z.; Watabe, T.; Thomas, G.; Szigeti, K.; Davis, E.; Wahl, M.; Nisitani, S.; Yamashiro, J.; Le Beau, M.M.; Loda, M.& Witte, O.N. (1998). Prostate stem cell antigen: a cell surface marker overexpressed in prostate cancer. *Proc Natl Acad Sci U S A*, Vol.95, No.4, (Feb 17), pp.1735-1740, ISSN 0027-8424

Rhodes, D.R.; Barrette, T.R.; Rubin, M.A.; Ghosh, D.& Chinnaiyan, A.M. (2002). Meta-analysis of microarrays: interstudy validation of gene expression profiles reveals pathway dysregulation in prostate cancer. *Cancer Res*, Vol.62, No.15, (Aug 1), pp.4427-4433, ISSN 0008-5472

Rice, K.R.; Chen, Y.; Ali, A.; Whitman, E.J.; Blase, A.; Ibrahim, M.; Elsamanoudi, S.; Brassell, S.; Furusato, B.; Stingle, N.; Sesterhenn, I.A.; Petrovics, G.; Miick, S.; Rittenhouse, H.; Groskopf, J.; McLeod, D.G.& Srivastava, S. (2010). Evaluation of the ETS-related gene mRNA in urine for the detection of prostate cancer. *Clin Cancer Res*, Vol.16, No.5, (Mar 1), pp.1572-1576, ISSN 1078-0432

Rogers, C.G.; Yan, G.; Zha, S.; Gonzalgo, M.L.; Isaacs, W.B.; Luo, J.; De Marzo, A.M.; Nelson, W.G.& Pavlovich, C.P. (2004). Prostate cancer detection on urinalysis for alpha methylacyl coenzyme a racemase protein. *J Urol*, Vol.172, No.4 Pt 1, (Oct), pp.1501-1503, ISSN 0022-5347

Roupret, M.; Hupertan, V.; Catto, J.W.; Yates, D.R.; Rehman, I.; Proctor, L.M.; Phillips, J.; Meuth, M.; Cussenot, O.& Hamdy, F.C. (2008). Promoter hypermethylation in circulating blood cells identifies prostate cancer progression. *Int J Cance*r, Vol.122, No.4, (Feb 15), pp.952-956, ISSN 1097-0215

Rubin, M.A.; Bismar, T.A.; Andren, O.; Mucci, L.; Kim, R.; Shen, R.; Ghosh, D.; Wei, J.T.; Chinnaiyan, A.M.; Adami, H.O.; Kantoff, P.W.& Johansson, J.E. (2005). Decreased alpha-methylacyl CoA racemase expression in localized prostate cancer is associated with an increased rate of biochemical recurrence and cancer-specific death. *Cancer Epidemiol Biomarkers Prev*, Vol.14, No.6, (Jun), pp.1424-1432, ISSN 1055-9965

Rubin, M.A.; Zerkowski, M.P.; Camp, R.L.; Kuefer, R.; Hofer, M.D.; Chinnaiyan, A.M.& Rimm, D.L. (2004). Quantitative determination of expression of the prostate cancer protein alpha-methylacyl-CoA racemase using automated quantitative analysis (AQUA): a novel paradigm for automated and continuous biomarker measurements. *Am J Pathol*, Vol.164, No.3, (Mar), pp.831-840, ISSN 0002-9440

Rubin, M.A.; Zhou, M.; Dhanasekaran, S.M.; Varambally, S.; Barrette, T.R.; Sanda, M.G.; Pienta, K.J.; Ghosh, D.& Chinnaiyan, A.M. (2002). alpha-Methylacyl coenzyme A

racemase as a tissue biomarker for prostate cancer. *JAMA*, Vol.287, No.13, (Apr 3), pp.1662-1670, ISSN 0098-7484

Saeki, N.; Gu, J.; Yoshida, T.& Wu, X. (2010). Prostate stem cell antigen: a Jekyll and Hyde molecule? *Clin Cancer Res*, Vol.16, No.14, (Jul 15), pp.3533-3538, ISSN 1078-0432

Saramaki, O.R.; Harjula, A.E.; Martikainen, P.M.; Vessella, R.L.; Tammela, T.L.& Visakorpi, T. (2008). TMPRSS2:ERG fusion identifies a subgroup of prostate cancers with a favorable prognosis. *Clin Cancer Res*, Vol.14, No.11, (Jun 1), pp.3395-3400, ISSN 1078-0432

Schaefer, A.; Jung, M.; Mollenkopf, H.J.; Wagner, I.; Stephan, C.; Jentzmik, F.; Miller, K.; Lein, M.; Kristiansen, G.& Jung, K. (2010). Diagnostic and prognostic implications of microRNA profiling in prostate carcinoma. *Int J Cancer*, Vol.126, No.5, (Mar 1), pp.1166-1176, ISSN 1097-0215

Schroder, F.H.; Hugosson, J.; Roobol, M.J.; Tammela, T.L.; Ciatto, S.; Nelen, V.; Kwiatkowski, M.; Lujan, M.; Lilja, H.; Zappa, M.; Denis, L.J.; Recker, F.; Berenguer, A.; Maattanen, L.; Bangma, C.H.; Aus, G.; Villers, A.; Rebillard, X.; van der Kwast, T.; Blijenberg, B.G.; Moss, S.M.; de Koning, H.J.& Auvinen, A. (2009). Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*, Vol.360, No.13, (Mar 26), pp.1320-1328, ISSN 1533-4406

Shariat, S.F.; Roehrborn, C.G.; McConnell, J.D.; Park, S.; Alam, N.; Wheeler, T.M.& Slawin, K.M. (2007). Association of the circulating levels of the urokinase system of plasminogen activation with the presence of prostate cancer and invasion, progression, and metastasis. *J Clin Oncol*, Vol.25, No.4, (Feb 1), pp.349-355, ISSN 1527-7755

Spahn, M.; Kneitz, S.; Scholz, C.J.; Stenger, N.; Rudiger, T.; Strobel, P.; Riedmiller, H.& Kneitz, B. (2010). Expression of microRNA-221 is progressively reduced in aggressive prostate cancer and metastasis and predicts clinical recurrence. *Int J Cancer*, Vol.127, No.2, (Jul 15), pp.394-403, ISSN 1097-0215

Sreekumar, A.; Poisson, L.M.; Rajendiran, T.M.; Khan, A.P.; Cao, Q.; Yu, J.; Laxman, B.; Mehra, R.; Lonigro, R.J.; Li, Y.; Nyati, M.K.; Ahsan, A.; Kalyana-Sundaram, S.; Han, B.; Cao, X.; Byun, J.; Omenn, G.S.; Ghosh, D.; Pennathur, S.; Alexander, D.C.; Berger, A.; Shuster, J.R.; Wei, J.T.; Varambally, S.; Beecher, C.& Chinnaiyan, A.M. (2009). Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression. *Nature*, Vol.457, No.7231, (Feb 12), pp.910-914, ISSN 1476-4687

Stott, S.L.; Lee, R.J.; Nagrath, S.; Yu, M.; Miyamoto, D.T.; Ulkus, L.; Inserra, E.J.; Ulman, M.; Springer, S.; Nakamura, Z.; Moore, A.L.; Tsukrov, D.I.; Kempner, M.E.; Dahl, D.M.; Wu, C.L.; Iafrate, A.J.; Smith, M.R.; Tompkins, R.G.; Sequist, L.V.; Toner, M.; Haber, D.A.& Maheswaran, S. (2010). Isolation and characterization of circulating tumor cells from patients with localized and metastatic prostate cancer. *Sci Transl Med*, Vol.2, No.25, (Mar 31), pp.25ra23, ISSN 1946-6242

Thomas, G.; Jacobs, K.B.; Yeager, M.; Kraft, P.; Wacholder, S.; Orr, N.; Yu, K.; Chatterjee, N.; Welch, R.; Hutchinson, A.; Crenshaw, A.; Cancel-Tassin, G.; Staats, B.J.; Wang, Z.; Gonzalez-Bosquet, J.; Fang, J.; Deng, X.; Berndt, S.I.; Calle, E.E.; Feigelson, H.S.; Thun, M.J.; Rodriguez, C.; Albanes, D.; Virtamo, J.; Weinstein, S.; Schumacher, F.R.; Giovannucci, E.; Willett, W.C.; Cussenot, O.; Valeri, A.; Andriole, G.L.; Crawford, E.D.; Tucker, M.; Gerhard, D.S.; Fraumeni, J.F., Jr.; Hoover, R.; Hayes, R.B.; Hunter,

D.J.& Chanock, S.J. (2008). Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet*, Vol.40, No.3, (Mar), pp.310-315, ISSN 1546-1718

Thuret, R.; Chantrel-Groussard, K.; Azzouzi, A.R.; Villette, J.M.; Guimard, S.; Teillac, P.; Berthon, P.; Houlgatte, A.; Latil, A.& Cussenot, O. (2005). Clinical relevance of genetic instability in prostatic cells obtained by prostatic massage in early prostate cancer. *Br J Cancer*, Vol.92, No.2, (Jan 31), pp.236-240, ISSN 0007-0920

Tomlins, S.A.; Rhodes, D.R.; Perner, S.; Dhanasekaran, S.M.; Mehra, R.; Sun, X.W.; Varambally, S.; Cao, X.; Tchinda, J.; Kuefer, R.; Lee, C.; Montie, J.E.; Shah, R.B.; Pienta, K.J.; Rubin, M.A.& Chinnaiyan, A.M. (2005). Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science*, Vol.310, No.5748, (Oct 28), pp.644-648, ISSN 1095-9203

Tong, A.W.; Fulgham, P.; Jay, C.; Chen, P.; Khalil, I.; Liu, S.; Senzer, N.; Eklund, A.C.; Han, J.& Nemunaitis, J. (2009). MicroRNA profile analysis of human prostate cancers. *Cancer Gene Ther*, Vol.16, No.3, (Mar), pp.206-216, ISSN 1476-5500

Uetsuki, H.; Tsunemori, H.; Taoka, R.; Haba, R.; Ishikawa, M.& Kakehi, Y. (2005). Expression of a novel biomarker, EPCA, in adenocarcinomas and precancerous lesions in the prostate. *J Urol*, Vol.174, No.2, (Aug), pp.514-518, ISSN 0022-5347

Usher, P.A.; Thomsen, O.F.; Iversen, P.; Johnsen, M.; Brunner, N.; Hoyer-Hansen, G.; Andreasen, P.; Dano, K.& Nielsen, B.S. (2005). Expression of urokinase plasminogen activator, its receptor and type-1 inhibitor in malignant and benign prostate tissue. *Int J Cancer*, Vol.113, No.6, (Mar 1), pp.870-880, ISSN 0020-7136

van Gils, M.P.; Hessels, D.; van Hooij, O.; Jannink, S.A.; Peelen, W.P.; Hanssen, S.L.; Witjes, J.A.; Cornel, E.B.; Karthaus, H.F.; Smits, G.A.; Dijkman, G.A.; Mulders, P.F.& Schalken, J.A. (2007). The time-resolved fluorescence-based PCA3 test on urinary sediments after digital rectal examination; a Dutch multicenter validation of the diagnostic performance. *Clin Cancer Res*, Vol.13, No.3, (Feb 1), pp.939-943, ISSN 1078-0432

Varambally, S.; Cao, Q.; Mani, R.S.; Shankar, S.; Wang, X.; Ateeq, B.; Laxman, B.; Cao, X.; Jing, X.; Ramnarayanan, K.; Brenner, J.C.; Yu, J.; Kim, J.H.; Han, B.; Tan, P.; Kumar-Sinha, C.; Lonigro, R.J.; Palanisamy, N.; Maher, C.A.& Chinnaiyan, A.M. (2008). Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. *Science*, Vol.322, No.5908, (Dec 12), pp.1695-1699, ISSN 1095-9203

Varambally, S.; Dhanasekaran, S.M.; Zhou, M.; Barrette, T.R.; Kumar-Sinha, C.; Sanda, M.G.; Ghosh, D.; Pienta, K.J.; Sewalt, R.G.; Otte, A.P.; Rubin, M.A.& Chinnaiyan, A.M. (2002). The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature*, Vol.419, No.6907, (Oct 10), pp.624-629, ISSN 0028-0836

Wanders, R.J.; Vreken, P.; Ferdinandusse, S.; Jansen, G.A.; Waterham, H.R.; van Roermund, C.W.& Van Grunsven, E.G. (2001). Peroxisomal fatty acid alpha- and beta-oxidation in humans: enzymology, peroxisomal metabolite transporters and peroxisomal diseases. *Biochem Soc Trans*, Vol.29, No.Pt 2, (May), pp.250-267, ISSN 0300-5127

Whitman, E.J.; Groskopf, J.; Ali, A.; Chen, Y.; Blase, A.; Furusato, B.; Petrovics, G.; Ibrahim, M.; Elsamanoudi, S.; Cullen, J.; Sesterhenn, I.A.; Brassell, S.; Rittenhouse, H.; Srivastava, S.& McLeod, D.G. (2008). PCA3 score before radical prostatectomy predicts extracapsular extension and tumor volume. *J Urol*, Vol.180, No.5, (Nov), pp.1975-1978; discussion 1978-1979, ISSN 1527-3792

Woodson, K.; O'Reilly, K.J.; Hanson, J.C.; Nelson, D.; Walk, E.L.& Tangrea, J.A. (2008). The usefulness of the detection of GSTP1 methylation in urine as a biomarker in the diagnosis of prostate cancer. *J Urol*, Vol.179, No.2, (Feb), pp.508-511; discussion 511-502, ISSN 1527-3792

Zehentner, B.K.; Secrist, H.; Zhang, X.; Hayes, D.C.; Ostenson, R.; Goodman, G.; Xu, J.; Kiviat, M.; Kiviat, N.; Persing, D.H.& Houghton, R.L. (2006). Detection of alpha-methylacyl-coenzyme-A racemase transcripts in blood and urine samples of prostate cancer patients. *Mol Diagn Ther*, Vol.10, No.6, pp.397-403, ISSN 1177-1062

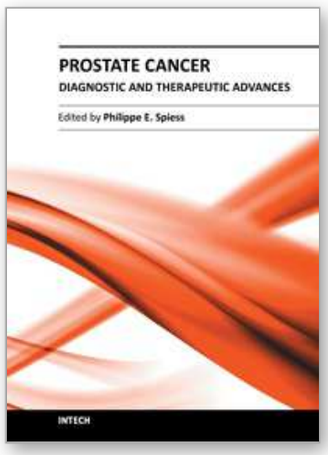
Zhao, Z.; Ma, W.; Zeng, G.; Qi, D.; Ou, L.& Liang, Y. (2011). Serum Early Prostate Cancer Antigen (EPCA) Level and Its Association with Disease Progression in Prostate Cancer in a Chinese Population. *PLoS One*, Vol.6, No.5, pp.e19284, ISSN 1932-6203

Zhao, Z.& Zeng, G. (2010). Increased serum level of early prostate cancer antigen is associated with subsequent cancer risk in men with high-grade prostatic intraepithelial neoplasia. *Endocr Relat Cancer*, Vol.17, No.2, (Jun), pp.505-512, ISSN 1479-6821

Zhigang, Z.& Wenlu, S. (2007). Prostate stem cell antigen (PSCA) mRNA expression in prostatic intraepithelial neoplasia: implications for the development of prostate cancer. *Prostate*, Vol.67, No.11, (Aug 1), pp.1143-1151, ISSN 0270-4137

Zhigang, Z.& Wenlv, S. (2004). Prostate stem cell antigen (PSCA) expression in human prostate cancer tissues and its potential role in prostate carcinogenesis and progression of prostate cancer. *World J Surg Oncol*, Vol.2, pp.13, ISSN 1477-7819

Zielie, P.J.; Mobley, J.A.; Ebb, R.G.; Jiang, Z.; Blute, R.D.& Ho, S.M. (2004). A novel diagnostic test for prostate cancer emerges from the determination of alpha-methylacyl-coenzyme a racemase in prostatic secretions. *J Urol*, Vol.172, No.3, (Sep), pp.1130-1133, ISSN 0022-5347

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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book , readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade.This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.




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